HEALTHY LIFESTYLE IN SECONDARY CARDIOVASCULAR DISEASE PREVENTION

DIETARY PATTERNS, PHYSICAL ACTIVITY, AND THEIR LONG-TERM BENEFITS

NADIA E. BONEKAMP

Healthy lifestyle in secondary cardiovascular disease prevention

Dietary patterns, physical activity, and their long-term benefits

Nadia Elisabeth Bonekamp

Provided by thesis specialist Ridderprint, ridderprint.nl

ISBN: 978-94-6483-867-1
Cover & layout: Marilou Maes | persoonlijkproefschrift.nl
Printing: Ridderprint

Healthy lifestyle in secondary cardiovascular disease prevention

Dietary patterns, physical activity, and their long-term benefits

Gezonde levensstijl in de secundaire preventie van hart- en vaatziekten

Voeding, lichamelijke activiteit en hun langetermijnvoordelen

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 4 april 2024 des middags te 12.15 uur

door

Nadia Elisabeth Bonekamp

geboren op 5 juli 1995
te Leiderdorp

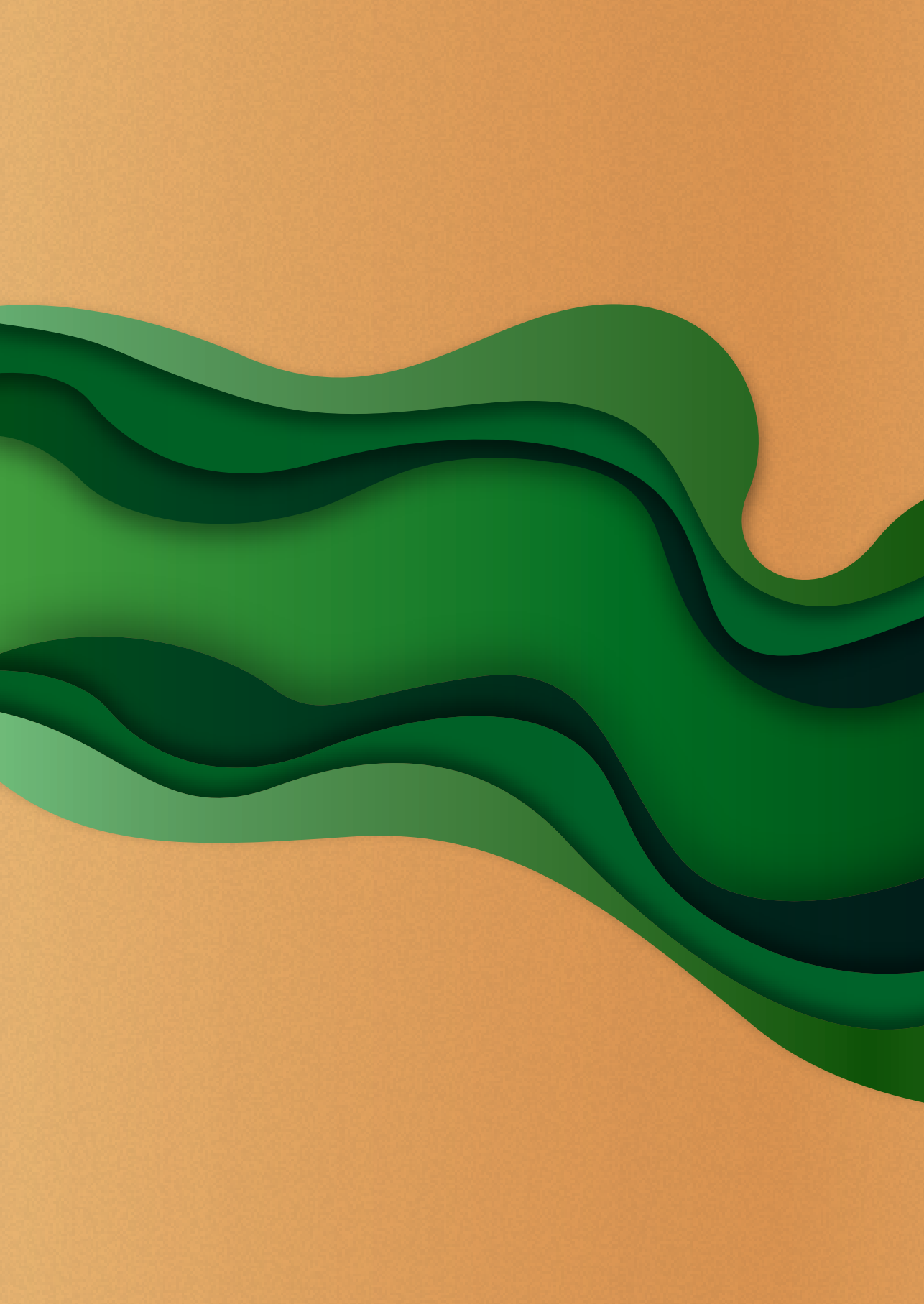
Promotoren:
Prof. dr. F.L.J. Visseren
Prof. dr. J.M. Geleijnse

Copromotor:
Dr. C. Koopal

Beoordelingscommissie:
Prof. dr. O.H. Franco Duran
Prof. dr. ir. E. Kampman
Prof. dr. L.J. Kappelle (voorzitter)
Prof. dr. M. Meine
Prof. dr. W.M.M. Verschuren

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

TABLE OF CONTENTS



CHAPTER 1

GENERAL INTRODUCTION

Despite considerable achievements of modern medicine, cardiovascular disease (CVD) continues to be the worldwide leading cause of morbidity and mortality.[1,2] While significant advances have been made in pharmacological treatments, there is a growing recognition of the crucial role that healthy lifestyle plays in prevention and treatment of CVD and type 2 diabetes (T2D).[3–6] International guidelines on prevention and treatment of CVD and T2D recommend not smoking, adopting a healthy diet, maintaining a healthy body weight, avoiding a sedentary lifestyle, achieving 150-300 min/wk moderate-intensity or 75-150 min/wk vigorous-intensity physical activity, and avoiding psychological stress as measures to attenuate cardiovascular risk factors and to lower the risk of (recurrent) cardiovascular events (Table 1).[5-8]

However, scientific evidence describing the relationship between healthy lifestyle behaviour and cardiovascular outcomes is largely derived from observational studies performed in apparently healthy populations without manifest CVD. Whether these results translate to patients with a history of CVD, remains largely unknown. Patients with CVD frequently receive medications that can potentially limit the effectiveness of lifestyle interventions, because their effect is partly mediated by the same risk factors (e.g. blood pressure). Furthermore, these medications could limit patients' ability to adhere to lifestyle recommendations (e.g. beta-blockers) and potential adverse effects of recommended lifestyle behaviours may be more pronounced in patients with manifest CVD (e.g. arrhythmia triggered by vigorous exercise). Therefore, this thesis examines the role of a healthy lifestyle, more specifically healthy diet and physical activity, in CVD prevention in patients with a history of CVD or T2D.

HEALTHY DIET

Food is essential for survival. A healthy diet should provide adequate energy intake, foods and nutrients to sustain a healthy life and prevent nutritional deficiencies. However, in developed countries, nutritional deficiencies are seldom a problem. We live in a world of easily available, energy-dense, nutrient-poor foods, which has resulted in a concerning epidemic of overconsumption and obesity. In Europe and the United States, the number of people who are overweight or obese has surpassed the number of people living with a healthy body weight.[9,10] This unsettling trend has far-reaching consequences. Unhealthy dietary habits are taking their toll on population health: 30-40% of cardiovascular deaths are attributable to unhealthy dietary habits[11,12] and

one in five premature deaths could be prevented with lifelong adherence to a healthy diet.[11] Unhealthy dietary habits are estimated to contribute to 8 million deaths and 188 million disability-adjusted life years annually.[1]

Unhealthy diet as a risk factor for developing cardiovascular disease

Observational studies have shown that unhealthy dietary habits are associated with an increased risk of developing CVD and with increased levels of traditional cardiovascular risk factors including body weight, systolic blood pressure and low-density lipoprotein cholesterol (LDL-C).[13,14] Excessive intake of calories, especially from diets low in fibre and high in sugary foods and beverages, plays a central role in the development of obesity.[15] People with unhealthy dietary habits have higher systolic blood pressure than those with healthy dietary habits. Specifically, high sodium and low potassium intake are important contributors to inadequate blood pressure control.[16] Dietary patterns with high saturated fat and *trans*-fatty acids content have been shown to result in modest but meaningful increases in LDL-C levels.[17–19] Some extreme diets, such as a carnivore diet devoid of plant-based food items, can even result in LDL-C levels that are within a familial hypercholesterolemia range.[20]

Unhealthy dietary habits also negatively affect other CVD risk factors, such as insulin resistance and low-grade inflammation.[21–23] Diets rich in refined sugars and red meat trigger a cascade of obesity and metabolic dysfunction that culminates in increased insulin resistance.[22] Dysfunctional adipose tissue generates a chronic state of low-grade inflammation through increased production of proinflammatory adipokines like interleukin-6 and tumor necrosis factor-alpha.[24] These high circulating levels of proinflammatory cytokines and adipokines could ultimately lead to metabolic syndrome, characterized by abdominal obesity, hypertension, impaired glucose tolerance and dyslipidemia. Metabolic syndrome has been associated with nearly twofold increased risk of developing cardiovascular disease.[25,26]

Many studies studied food items in isolation and have shown adverse associations with cardiovascular event risk for some, such as red meats and sugar-sweetened beverages and protective associations for others such as fruits and legumes.[27] Studying single food groups or nutrients is a useful tool for answering etiologic questions in nutritional epidemiology. However, food items are not consumed in isolation, but in meals with a myriad of possible combinations with other food items. Translating the complex interplay between food and CVD into actionable advise is, unfortunately,

not as simple as eating "*an apple a day*", which has been investigated and debunked to "*keep the doctor away*".[28] It may therefore be more suitable and better reflective of disease risk to study complete dietary patterns instead.[29] Several dietary patterns, such as a Mediterranean and plant-based diets, have been associated in observational studies with 15 to 30% reductions in relative risk of acute myocardial infarction, stroke, cardiovascular mortality and all-cause mortality.[30–33] Efficacy of dietary interventions to reduce cardiovascular event risk has rarely been assessed in randomized clinical trials. The majority of clinical trials on dietary interventions evaluated short-term effects on cardiovascular risk factors. Based on such studies it is difficult to select an optimal dietary pattern for secondary CVD prevention, especially given the magnitude of dietary patterns available which have not directly been compared in head-to-head trial. Furthermore, although multiple studies have extensively investigated the physiological and metabolic effects of dietary pattern interventions, their relative contributions as mediators of the effect of diet on clinical outcomes warrants further exploration.

Healthy diet as a treatment strategy for cardiovascular disease

Lifestyle optimization is a first-line guideline recommendation for patients with established CVD and this includes promoting adherence to a healthy dietary pattern (Table 1).[5,6] Dietary pattern interventions have been shown to effectively mitigate cardiovascular risk factors.[17,34] The Dietary Approaches to Stop Hypertension (DASH) diet, a dietary pattern with a strong emphasis on fruits, vegetables, whole grains, lean meats and sodium reduction, effectively reduced systolic blood pressure by up to 11.5 mmHg and body weight by 1.5 kg in hypertensive patients.[35,36] Interventions with a plant-based diet lowered LDL-C by mean of 0.3 mmol/l (range –1.4 to -0.1 mmol/l).[37] These trials provide an important clue to the potential for adopting a healthy diet in CVD prevention. However, relatively little is known about the added value of such interventions on top of blood pressure- and lipid-lowering medications. Moreover, it is unclear to what extent these reductions in cardiovascular risk factors would translate to reductions in risk of cardiovascular events and to what extent the health effects of dietary patterns are mediated by these factors.

In the 1950s, a talented researcher named Ancel Keys first studied the relationship between the Mediterranean diet and coronary heart disease.[38] Ever since this diet has sparked enormous research interest. The Mediterranean diet has stood the test of time and has repeatedly emerged as the optimal dietary pattern for CVD prevention.[39] Mediterranean-style diets put a strong emphasis on replacing saturated fats with

mono- and polyunsaturated fatty acids, intake of fresh fruits, vegetables and legumes and limited intake of animal products. Several randomized trials have assessed the effectiveness of a Mediterranean diet intervention for prevention of (recurrent) cardiovascular events in both primary and secondary CVD prevention populations. In the 1990's, the Lyon Diet Heart study compared a Mediterranean-type diet to a typical Western-style diet in 604 patients with coronary artery disease (CAD) and found a 70% reduction in risk of the composite cardiovascular and mortality endpoint.[40,41] The landmark PREDIMED (Prevención con Dieta Mediterránea) compared the efficacy of a Mediterranean diet supplemented with either extra-virgin olive oil or nuts to a low-fat diet in 7,447 patients at high risk of developing CVD and found protective hazard ratios of 0.69 (95%CI 0.53-0.91) and 0.72 (95%CI 0.54-0.95) for the two Mediterranean diets, respectively.[42] Finally, the recent CORDIOPREV trial showed that a Mediterranean diet was superior to a low-fat diet in CAD patients. This trial demonstrated a relative risk reduction of 28% (95%CI 4-46%) from the Mediterranean diet after a median follow-up of 7 years.[43] Together, these trials support international guideline recommendations for using a Mediterranean diet as a treatment option in both primary and secondary CVD prevention.[5–7]

PHYSICAL ACTIVITY

Physical activity is a crucial pillar of human well-being. However, in an era marked by technological advances and modern conveniences, physical inactivity has emerged as a prevalent concern in developed nations. The ubiquity of sedentary behaviours, compounded by an environment that facilitates minimal exertion, has given rise to a concerning pandemic of physical inactivity.[44] In Europe, one in three adults does not meet guideline-recommended physical activity levels[45] and in the USA a staggering 80% of adults is classified as physically inactive.[46] Physical inactivity is an important risk factor for a range of non-communicable diseases, including CVD. Low physical activity levels are estimated to contribute to 8.6 million life years lost and 16 million disability-adjusted life years annually.[1]

Physical activity classifications

'Physical activity' is a broad concept that may be challenging to capture into a single metric. Several classifications have been proposed to categorize it, for example based on the domain in which the activity is performed. Occupational physical

activity encompasses all physical activity at work, while leisure-time physical activity encompasses all activities outside the workplace, such as exercise, transportation and recreation. Additionally, physical activity is often classified based on its physiological characteristics into two primary categories: aerobic exercise and resistance training. Aerobic exercise involves continuous repetitive movements that elevate heart rate and increase oxygen consumption. Resistance, or muscle-strengthening, training involves exerting force against a resistance and results in increased muscle strength, size and endurance.

Physical activity can be expressed in type, frequency, intensity and duration. The frequency, duration and intensity dimensions can be captured into a single metric, physical activity volume. Physical activity intensity is commonly expressed as Metabolic Equivalent of Task (MET): a MET of 1 equates to the energy expenditure in complete rest.[47] High-intensity activities necessitate greater oxygen consumption and consequently receive higher MET values. To arrive at physical activity volume, the MET value can be multiplied by duration and frequency of the activity. Standard MET values are available for a wide spectrum of physical activities.[48] CVD prevention guidelines recommend engaging in 150-300 minutes moderate-intensity physical activity (MET value 3-6) or 75-150 minutes vigorous-intensity activity (MET value ≥6) per week.[5–7,45] Both recommendations correspond to a physical activity volume of 7.5 to 15 METh/wk. A limitation of assessing physical activity in a combined metric such as exercise volume, is that optimal physical activity intensity, duration and type remain largely unknown in patients with CVD.

Physical inactivity as a risk factor for developing cardiovascular disease

In primary prevention populations, higher leisure-time physical activity levels have consequently been associated with a myriad of health benefits including a decreased susceptibility to various forms of cancer,[49–51] and diminished occurrence of cardiovascular disease.[45,51–53] These associations appear to have clear dose-response relationship without an apparent minimum threshold for benefits to manifest.[53–56] Remarkably, even for a modest daily step count of 4,000 steps/day, the potential to reduce cardiovascular and all-cause mortality risk has been demonstated.[54] When an active lifestyle is adopted later in life, this change is still associated with a remarkable 45% relative risk reduction in (cardiovascular) mortality risk in observational studies,[57] underscoring the encouraging premise that it is truly never too late to start moving.[58]

While the health benefits of leisure-time physical activity are well documented, there have been conflicting reports on the health effects of occupational physical activity. In general population studies, higher occupational physical activity levels have been associated with reduced risk of T2D and cancer, but with increased risk of cardiovascular events and all-cause mortality even after extensive adjustment for confounding.[59,60] This so-called "*physical activity paradox*" between leisure-time and occupational physical activity has prompted inquiries into potential explanations. Plausible rationales include residual confounding, the low-intensity and repetitive nature of occupational physical activity, compounded by limited time for post-work recovery.[61] The generalizability of these paradoxical findings to patients with a history of cardiovascular disease remains unclear.

Physical activity as a treatment strategy for cardiovascular disease

In a multitude of smaller-scale clinical trials with limited follow-up time, physical activity has exhibited pronounced efficacy in attenuating cardiovascular risk factors, including LDL-cholesterol[62] and blood pressure,[63] and in improving cardiorespiratory fitness.[64,65] Increased physical activity inherently results in heightened energy expenditure and increases in muscle mass, which contributes to weight loss,[66] improved insulin sensitivity[67] and reduced systemic inflammations levels.[68] Although multiple studies have extensively investigated these physiological and metabolic effects of leisure-time physical activity, their relative contributions as mediators of the effect of physical activity on clinical outcomes warrants further exploration. It is unclear which mediators are most important to effectively reduce the risk of cardiovascular events. Notably, no long-term cardiovascular outcomes trial has been performed to directly assess the efficacy of physical activity interventions in primary or secondary CVD prevention.

IMPLEMENTING LIFESTYLE IN CLINICAL CVD MANAGEMENT

Despite the well-established evidence supporting the positive impact of lifestyle changes, it proves difficult to get individuals to adopt and maintain these habits. The EUROASPIRE V survey showed that a vast majority of patients with CVD is not compliant with guideline recommendations on smoking, weight loss and physical activity.[69] Remarkably, almost half of patients with obesity or an inactive lifestyle also reported never having received any counselling to improve these factors.[69] This

daunting gap between scientific evidence and clinical practice highlights the urgent need for comprehensive healthcare strategies that prioritize effective communication and personalized guidance to improve lifestyle habits for patients with established CVD in the era of evidence-based medicine.

Challenges in implementing healthy lifestyle habits

Implementing lifestyle changes in clinical practice presents various challenges for healthcare providers and patients alike. Factors such as patient motivation, physicians' time constraints, access to resources, and cultural influences can significantly impact the success of lifestyle interventions.[70] Important determinants of long-term adherence to lifestyle interventions include early weight loss, better baseline mood, male sex and older age.[71] Understanding these determinants is crucial for developing effective strategies to overcome barriers and promote lasting behaviour change.

The 2023 European Association of Preventive Cardiology (EAPC) consensus statement on Promotion of healthy nutrition in primary and secondary cardiovascular disease prevention puts a strong emphasis on the use of e-technology to improve nutritional assessment and dietary interventions.[72] Currently, there are very few of such online tools available to provide evidence-based and personalized estimates for the long-term benefits of lifestyle interventions.

Individualized lifetime benefits from lifestyle interventions

Improving comprehension of the personalized benefits arising from lifestyle interventions could significantly enhance patient motivation. A general population modelling study showed that a sustained change from a Western-style diet to a healthier diet could result in more than 10 years gained in life expectancy. These benefits were larger when the healthy diet was initiated at a younger age.[73]

Personalized risk prediction has become standard-of-care in primary and secondary CVD prevention and is recommended by international guidelines.[5] Several prediction models are available for predicting 10-year and lifetime risk of cardiovascular events based on individual patient characteristics for specific patient groups, such as those with CVD risk factors, T2D or established CVD.[74–77] A compelling aspect of these models is that they allow for estimating absolute lifetime benefit (in additional life years free of CVD) attainable through initiation of preventive treatment. This feature is an important tool in the shared decision-making progress and could bolster patients'

adherence to preventive treatment over prolonged periods. It would be very useful to combine these models with treatment effects from interventions aimed at improving lifestyle behaviours. Currently available models only assess the impact of smoking cessation as a lifestyle intervention and do not allow for estimating lifetime benefit from a dietary or physical activity intervention.

Economic evaluation of lifestyle interventions

As a result of improvement in clinical care for CVD patients over the last decades, the number of patients with chronic CVD continues to rise.[78] Although the improved health outcomes are applaudable, they are accompanied by large costs. Health care costs are expected to increase by 1% in both the European Union and the United States of America each year.[79,80] As healthcare systems strive to optimize resource allocation and prioritize cost-effective interventions, economic evaluations of lifestyle interventions become increasingly pertinent. It is therefore important to explore the economic aspects of implementing healthy lifestyle habits in the management of CVD. Previous cost-effectiveness analyses indicated that lifestyle interventions are cost effective in primary CVD prevention, and are likely to be even more cost-effective in populations at higher CVD risk,[81] while costs for new pharmacological treatments are relatively high compared to lifestyle interventions.[82–84] By assessing the cost-effectiveness and potential savings associated with lifestyle interventions, policymakers and healthcare providers can make informed decisions about allocating resources for preventative measures and long-term CVD management.

THESIS OBJECTIVES

This thesis uses a multitude of methodologies in order to explore the role of a healthy diet and physical activity in the management of patients with clinically manifest CVD. The objectives of this thesis are:

I. To explore the relationship between different dietary patterns and cardiovascular outcomes in people with a history of CVD and/or type 2 diabetes.
II. To evaluate the role of different types of physical activity in the occurrence of health outcomes in patients with established CVD.
III. To estimate the potential long-term benefit from healthy dietary habits and physical activity levels in the clinical management of patients with established CVD.

Thesis outline

PART I focuses on the relationship between different dietary patterns and cardiovascular outcomes in patients with cardiovascular disease or type 2 diabetes. **Chapter 2** describes the dietary intake of CVD patients and their compliance with current dietary guidelines. **Chapters 3** and **4** use a network meta-analysis approach to pool evidence from clinical trials on the effectiveness of dietary pattern interventions on cardiovascular risk factors in patients with established CVD and people with T2D. **Chapter 5** explores to what extent the effect of healthy dietary patterns is mediated through traditional cardiovascular risk factors. In **chapter 6** a target trial designed to assess the effect of a DASH diet on cardiovascular outcomes in CVD patients is emulated in observational data.

PART II explores the relationship of different types of physical activity with health outcomes in patients with established CVD. In **chapter 7**, the relationship between health outcomes and leisure-time physical activity on the one hand, and occupational physical activity on the other hand, is assessed. **Chapter 8** assesses the associations between exercise volume, type and intensity and risk of cardiovascular events and (cardiovascular) death, as well as the extent to which these relationships are mediated through cardiovascular risk factors.

PART III aims to bring together different healthy lifestyle behaviours and to assess the long-term benefits of healthy dietary and physical activity habits in the clinical management of CVD patients. **Chapter 9** examines the effect long-term change in multiple lifestyle factors, including smoking, alcohol consumption, body composition and physical activity, on (cardiovascular) mortality and incident diabetes risk. In **chapter 10**, individualized lifetime benefit of compliance with a Mediterranean diet and guideline-recommended physical activity levels is estimated in patients with established CVD. In **chapter 11**, the cost-effectiveness of treatment with a Mediterranean diet intervention and a physical activity intervention in the context of secondary CVD prevention is investigated.

The main findings of this thesis are discussed in **chapter 12**.

TABLE 1 Healthy lifestyle recommendations in international CVD guidelines[5–7]

Smoking
Stop smoking
Diet
Adopt a more plant- and less animal-based food pattern
Saturated fatty acids should account for <10% of total energy intake, through replacement by PUFAs, MUFAs, and carbohydrates from whole grains
Trans unsaturated fatty acids should be minimized as far as possible, with none from processed foods
<5 g total salt intake per day
30–45 g of fibre of per day, preferably from wholegrains
≥200 g of fruit per day (≥2–3 servings)
≥200 g of vegetables per day (≥2–3 servings)
Red meat should be reduced to a maximum of 350 – 500 g a week, in particular processed meat should be minimized
Fish is recommended 1–2 times per week, in particular fatty fish
30 g unsalted nuts per day
Consumption of alcohol should be limited to a maximum of 100 g per week
Sugar-sweetened beverages, such as soft drinks and fruit juices, must be discouraged
Plant-based dietary patterns and hypocaloric Mediterranean diets are recommended for ASCVD prevention and weight loss
Physical activity
Strive for at least 150-300 min a week moderate-intensity or 75-150 min a week vigorous intensity aerobic physical activity
Adults who cannot perform 150 min/wk of moderate intensity physical activity, should stay as active as possible
Reduce sedentary time
Perform resistance exercise on 2 or more days a week

Adapted from: 2021 ESC CVD prevention [5], 2019 AHA primary CVD prevention[7] and 2023 ACC/AHA chronic coronary disease guidelines[6]
MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid.

REFERENCES

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982–3021.
2. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet [Internet]. 2017 Sep 16;390(10100):1211–59.
3. Kromhout D, Menotti A, Kesteloot H, Sans S. Prevention of coronary heart disease by diet and lifestyle evidence from prospective cross-cultural, cohort, and intervention studies. Vol. 105, Circulation. 2002. p. 893–8.
4. Fernández D, Brotons C, Moral I, Bulc M, Afonso M, Akan H, et al. Lifestyle behaviours in patients with established cardiovascular diseases: A European observational study. BMC Fam Pract. 2019 Nov 26;20(1).
5. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J [Internet]. 2021 Aug 30;(00):1–111.
6. Virani SS, Newby LK, Arnold S V., Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation [Internet]. 2023 Jul 20;
7. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;74(10):e177–232.
8. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J. 2023 Aug 25;
9. Li M, Gong W, Wang S, Li Z. Trends in body mass index, overweight and obesity among adults in the USA, the NHANES from 2003 to 2018: a repeat cross-sectional survey. BMJ Open. 2022 Dec 16;12(12):e065425.
10. WHO European Regional Obesity Report 2022. Copenhagen; 2022.
11. Meier T, Gräfe K, Senn F, Sur P, Stangl GI, Dawczynski C, et al. Cardiovascular mortality attributable to dietary risk factors in 51 countries in the WHO European Region from 1990 to 2016: a systematic analysis of the Global Burden of Disease Study. Eur J Epidemiol. 2019 Jan 14;34(1):37–55.
12. Ezzati M, Vander Hoorn S, Rodgers A, Lopez AD, Mathers CD, Murray CJ. Estimates of global and regional potential health gains from reducing multiple major risk factors. The Lancet. 2003 Jul;362(9380):271–80.

13. Dai H, Much AA, Maor E, Asher E, Younis A, Xu Y, et al. Global, regional, and national burden of ischaemic heart disease and its attributable risk factors, 1990–2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes. 2020;1–11.

14. Yu E, Malik VS, Hu FB. Cardiovascular Disease Prevention by Diet Modification: JACC Health Promotion Series. J Am Coll Cardiol. 2018;72(8):914–26.

15. Hassapidou M, Vlassopoulos A, Kalliostra M, Govers E, Mulrooney H, Ells L, et al. European Association for the Study of Obesity Position Statement on Medical Nutrition Therapy for the Management of Overweight and Obesity in Adults Developed in Collaboration with the European Federation of the Associations of Dietitians. Obes Facts. 2023;16(1):11–28.

16. Filippini T, Malavolti M, Whelton PK, Naska A, Orsini N, Vinceti M. Blood Pressure Effects of Sodium Reduction. Circulation. 2021 Apr 20;143(16):1542–67.

17. Ge L, Sadeghirad B, Ball GDC, Da Costa BR, Hitchcock CL, Svendrovski A, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: Systematic review and network meta-analysis of randomised trials. The BMJ. 2020;369.

18. Kahleova H, Salas-Salvadó J, Rahelić D, Kendall CW, Rembert E, Sievenpiper JL. Dietary Patterns and Cardiometabolic Outcomes in Diabetes: A Summary of Systematic Reviews and Meta-Analyses. Nutrients. 2019 Sep 13;11(9):2209.

19. Chiavaroli L, Nishi SK, Khan TA, Braunstein CR, Glenn AJ, Mejia SB, et al. Portfolio Dietary Pattern and Cardiovascular Disease: A Systematic Review and Meta-analysis of Controlled Trials. Vol. 61, Progress in Cardiovascular Diseases. W.B. Saunders; 2018. p. 43–53.

20. Houttu V, Grefhorst A, Cohn DM, Levels JHM, Roeters van Lennep J, Stroes ESG, et al. Severe Dyslipidemia Mimicking Familial Hypercholesterolemia Induced by High-Fat, Low-Carbohydrate Diets: A Critical Review. Vol. 15, Nutrients. MDPI; 2023.

21. Anderson AL, Harris TB, Tylavsky FA, Perry SE, Houston DK, Lee JS, et al. Dietary patterns, insulin sensitivity and inflammation in older adults. Eur J Clin Nutr. 2012 Jan 14;66(1):18–24.

22. Martins FO, Conde S V. Impact of Diet Composition on Insulin Resistance. Nutrients. 2022 Sep 9;14(18):3716.

23. Hart MJ, Torres SJ, McNaughton SA, Milte CM. Dietary patterns and associations with biomarkers of inflammation in adults: a systematic review of observational studies. Nutr J. 2021 Dec 12;20(1):24.

24. Hajer GR, van Haeften TW, Visseren FLJ. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J. 2008 Dec 2;29(24):2959–71.

25. Galassi A, Reynolds K, He J. Metabolic Syndrome and Risk of Cardiovascular Disease: A Meta-Analysis. Am J Med. 2006 Oct;119(10):812–9.

26. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The Metabolic Syndrome and Cardiovascular Risk. J Am Coll Cardiol. 2010 Sep;56(14):1113–32.

27. Schwingshackl L, Schwedhelm C, Hoffmann G, Lampousi AM, Knüppel S, Iqbal K, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies ,. Am J Clin Nutr. 2017 Jun;105(6):1462–73.

28. Davis MA, Bynum JPW, Sirovich BE. Association Between Apple Consumption and Physician Visits. JAMA Intern Med. 2015 May 1;175(5):777.

29. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol [Internet]. 2002 Feb;13(1):3–9.

30. Gan ZH, Cheong HC, Tu YK, Kuo PH. Association between Plant-Based Dietary Patterns and Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. Nutrients. 2021 Nov 5;13(11):3952.

31. Grosso G, Marventano S, Yang J, Micek A, Pajak A, Scalfi L, et al. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: Are individual components equal? Crit Rev Food Sci Nutr. 2017 Oct 13;57(15):3218–32.

32. Rodríguez-Monforte M, Flores-Mateo G, Sánchez E. Dietary patterns and CVD: a systematic review and meta-analysis of observational studies. British Journal of Nutrition. 2015 Nov 14;114(9):1341–59.

33. Lichtenstein AH, Appel LJ, Vadiveloo M, Hu FB, Kris-Etherton PM, Rebholz CM, et al. 2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association. Circulation. 2021 Dec 7;144(23).

34. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ. Dietary Patterns and Blood Pressure in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Advances in Nutrition. 2016 Jan;7(1):76–89.

35. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. New England Journal of Medicine [Internet]. 2001 Jan 4;344(1):3–10. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM200101043440101

36. Soltani S, Shirani F, Chitsazi MJ, Salehi-Abargouei A. The effect of dietary approaches to stop hypertension (DASH) diet on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Obesity Reviews. 2016 May;17(5):442–54.

37. Koch CA, Kjeldsen EW, Frikke-Schmidt R. Vegetarian or vegan diets and blood lipids: a meta-analysis of randomized trials. Eur Heart J. 2023 Jul 21;44(28):2609–22.

38. KEYS A, MIENOTTI A, KARVONEN MJ, ARAVANIS C, BLACKBURN H, BUZINA R, et al. THE DIET AND 15-YEAR DEATH RATE IN THE SEVEN COUNTRIES STUDY. Am J Epidemiol. 1986 Dec;124(6):903–15.

39. Karam G, Agarwal A, Sadeghirad B, Jalink M, Hitchcock CL, Ge L, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. BMJ. 2023;

40. de Lorgeril M, Renaud S, Salen P, Monjaud I, Mamelle N, Martin JL, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. The Lancet [Internet]. 1994 Jun;343(8911):1454–9.

41. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779–85.

42. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. New England Journal of Medicine [Internet]. 2018 Jun 21;378(25):e34. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1800389
43. Delgado-lista J, Alcala-diaz JF, Torres-peña JD, Quintana-navarro GM, Fuentes F, Garcia-rios A, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet. 2022;399:1876–85.
44. World Health Organization. Global status report on physical activity 2022. Geneva; 2022.
45. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54(24):1451–62.
46. Center for Disease Control and Prevention. Physical Activity [Internet]. 2023 [cited 2023 Aug 9]. Available from: https://www.cdc.gov/physicalactivity/index.html
47. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol. 1990 Aug;13(8):555–65.
48. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32(9 SUPPL.).
49. Rezende LFM de, Sá TH de, Markozannes G, Rey-López JP, Lee IM, Tsilidis KK, et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770000 cancer cases. Br J Sports Med. 2018 Jul;52(13):826–33.
50. Hermelink R, Leitzmann MF, Markozannes G, Tsilidis K, Pukrop T, Berger F, et al. Sedentary behavior and cancer–an umbrella review and meta-analysis. Eur J Epidemiol. 2022 May 25;37(5):447–60.
51. Garcia L, Pearce M, Abbas A, Mok A, Strain T, Ali S, et al. Non-occupational physical activity and risk of cardiovascular disease, cancer and mortality outcomes: a dose–response meta-analysis of large prospective studies. Br J Sports Med. 2023 Aug;57(15):979–89.
52. Valenzuela PL, Ruilope LM, Santos-Lozano A, Wilhelm M, Kränkel N, Fiuza-Luces C, et al. Exercise benefits in cardiovascular diseases: from mechanisms to clinical implementation. Eur Heart J. 2023 Jun 1;44(21):1874–89.
53. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: Systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. Br Med J. 2016;354:i3857.
54. Banach M, Lewek J, Surma S, Penson PE, Sahebkar A, Martin SS, et al. The association between daily step count and all-cause and cardiovascular mortality: a meta-analysis. Eur J Prev Cardiol. 2023 Aug 9;
55. Geidl W, Schlesinger S, Mino E, Miranda L, Pfeifer K. Dose–response relationship between physical activity and mortality in adults with noncommunicable diseases: a systematic review and meta-analysis of prospective observational studies. International Journal of Behavioral Nutrition and Physical Activity. 2020 Dec 26;17(1):109.

56. Ekelund U, Tarp J, Steene-Johannessen J, Hansen BH, Jefferis B, Fagerland MW, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality : systematic review and harmonised meta-analysis. Br Med J. 2019;366:14570.

57. Gonzalez-Jaramillo N, Wilhelm M, Arango-Rivas AM, Gonzalez-Jaramillo V, Mesa-Vieira C, Minder B, et al. Systematic Review of Physical Activity Trajectories and Mortality in Patients With Coronary Artery Disease. J Am Coll Cardiol [Internet]. 2022 May;79(17):1690–700.

58. Moholdt T, Skarpsno ES, Moe B, Nilsen TIL. It is never too late to start: adherence to physical activity recommendations for 11–22 years and risk of all-cause and cardiovascular disease mortality. The HUNT Study. Br J Sports Med. 2021 Jul;55(13):743–50.

59. Cillekens B, Lang M, van Mechelen W, Verhagen E, Huysmans MA, Holtermann A, et al. How does occupational physical activity influence health? An umbrella review of 23 health outcomes across 158 observational studies. Br J Sports Med [Internet]. 2020 Dec 25;54(24):1474–81.

60. Holtermann A, Schnohr P, Nordestgaard BG, Marott JL. The physical activity paradox in cardiovascular disease and all-cause mortality: The contemporary Copenhagen General Population Study with 104 046 adults. Eur Heart J. 2021;42(15):1499–511.

61. Holtermann A, Krause N, van der Beek AJ, Straker L. The physical activity paradox: six reasons why occupational physical activity (OPA) does not confer the cardiovascular health benefits that leisure time physical activity does. Br J Sports Med [Internet]. 2018 Feb;52(3):149–50. Available from: https://bjsm.bmj.com/lookup/doi/10.1136/bjsports-2017-097965

62. Albarrati AM, Alghamdi MSM, Nazer RI, Alkorashy MM, Alshowier N, Gale N. Effectiveness of low to moderate physical exercise training on the level of low-density lipoproteins: A systematic review. Biomed Res Int. 2018;2018.

63. Naci H, Salcher-Konrad M, Dias S, Blum MR, Sahoo SA, Nunan D, et al. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure. Br J Sports Med [Internet]. 2019 Jul;53(14):859–69. Available from: https://bjsm.bmj.com/lookup/doi/10.1136/bjsports-2018-099921

64. Franklin BA, Eijsvogels TMH, Pandey A, Quindry J, Toth PP. Physical activity, cardiorespiratory fitness, and cardiovascular health: A clinical practice statement of the American Society for Preventive Cardiology Part I: Bioenergetics, contemporary physical activity recommendations, benefits, risks, extreme exercise regimens, potential maladaptations. Am J Prev Cardiol. 2022 Dec;12:100424.

65. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2015;4(7):1–28.

66. van Baak MA, Hul G, Astrup A, Saris WH. Physical Activity, Weight Loss, and Weight Maintenance in the DiOGenes Multicenter Trial. Front Nutr. 2021 Jun 30;8.

67. Nystoriak MA, Bhatnagar A. Cardiovascular Effects and Benefits of Exercise. Front Cardiovasc Med [Internet]. 2018 Sep 28;5(September):1–11. Available from: https://www.frontiersin.org/article/10.3389/fcvm.2018.00135/full

68. Cerqueira É, Marinho DA, Neiva HP, Lourenço O. Inflammatory Effects of High and Moderate Intensity Exercise—A Systematic Review. Front Physiol. 2020;10(January):1–14.

69. Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol. 2019 May 1;26(8):824–35.

70. Hardcastle SJ, Hancox J, Hattar A, Maxwell-Smith C, Thøgersen-Ntoumani C, Hagger MS. Motivating the unmotivated: how can health behavior be changed in those unwilling to change? Front Psychol [Internet]. 2015 Jun 16;6(June):1–4. Available from: http://journal.frontiersin.org/Article/10.3389/fpsyg.2015.00835/abstract

71. Burgess E, Hassmén P, Pumpa KL. Determinants of adherence to lifestyle intervention in adults with obesity: a systematic review. Clin Obes. 2017 Jun;7(3):123–35.

72. Vassiliou VS, Tsampasian V, Abreu A, Kurpas D, Cavarretta E, O'Flaherty M, et al. Promotion of healthy nutrition in primary and secondary cardiovascular disease prevention: a clinical consensus statement from the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2023 Jun 1;30(8):696–706.

73. Fadnes LT, Økland JM, Haaland ØA, Johansson KA. Estimating impact of food choices on life expectancy: A modeling study. PLoS Med. 2022;19(2):1–17.

74. Hageman S, Pennells L, Ojeda F, Kaptoge S, Kuulasmaa K, de Vries T, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021 Jul 1;42(25):2439–54.

75. de Vries TI, Cooney MT, Selmer RM, Hageman SHJ, Pennells LA, Wood A, et al. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021 Jul 1;42(25):2455–67.

76. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB, Massaro JM, et al. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: The SMART-REACH model. J Am Heart Assoc. 2018;7(16).

77. Østergaard HB, Hageman SHJ, Read SH, Taylor O, Pennells L, Kaptoge S, et al. Estimating individual lifetime risk of incident cardiovascular events in adults with Type 2 diabetes: an update and geographical calibration of the DIAbetes Lifetime perspective model (DIAL2). Eur J Prev Cardiol. 2023 Jan 11;30(1):61–9.

78. Li Y, Cao G ying, Jing W zhan, Liu J, Liu M. Global trends and regional differences in incidence and mortality of cardiovascular disease, 1990–2019: findings from 2019 global burden of disease study. Eur J Prev Cardiol. 2023 Feb 14;30(3):276–86.

79. Goryakin Y, Thiébaut SP, Cortaredona S, Lerouge MA, Cecchini M, Feigl AB, et al. Assessing the future medical cost burden for the European health systems under alternative exposure-to-risks scenarios. PLoS One. 2020 Sep 11;15(9):e0238565.

80. McCullough J Mac, Speer M, Magnan S, Fielding JE, Kindig D, Teutsch SM. Reduction in US Health Care Spending Required to Meet the Institute of Medicine's 2030 Target. Am J Public Health. 2020 Dec;110(12):1735–40.

81. Smith L, Atherly A, Campbell J, Flattery N, Coronel S, Krantz M. Cost-effectiveness of a statewide public health intervention to reduce cardiovascular disease risk. BMC Public Health. 2019 Dec 6;19(1):1234.

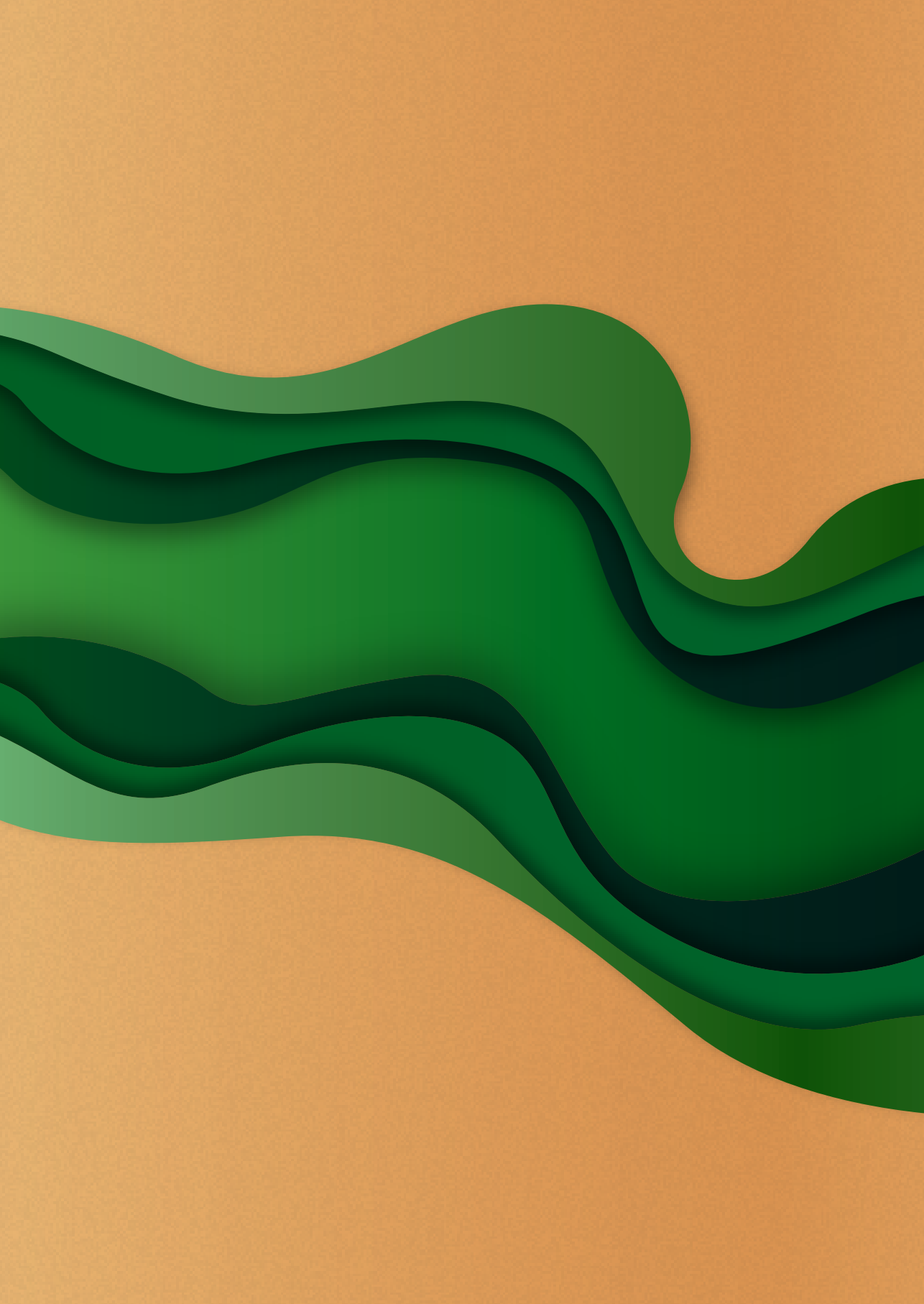
82. Michaeli DT, Michaeli JC, Boch T, Michaeli T. Cost-effectiveness of cholesterol-lowering drugs for secondary cardiovascular prevention in the UK: ezetimibe, evolocumab, and alirocumab. Eur Heart J. 2022 Oct 3;43(Supplement_2).

83. Petersohn S, Pouwels X, Ramaekers B, ten Cate-Hoek A, Joore M. Rivaroxaban plus aspirin for the prevention of ischaemic events in patients with cardiovascular disease: a cost-effectiveness study. Eur J Prev Cardiol. 2020 Sep 1;27(13):1354–65.

84. Li X, Hoogenveen R, El Alili M, Knies S, Wang J, Beulens JWJ, et al. Cost-Effectiveness of SGLT2 Inhibitors in a Real-World Population: A MICADO Model-Based Analysis Using Routine Data from a GP Registry. Pharmacoeconomics. 2023 Jun 10;

PART I

DIETARY PATTERNS FOR PATIENTS WITH ESTABLISHED CVD OR TYPE 2 DIABETES



CHAPTER 2

DIETARY HABITS AND COMPLIANCE WITH DIETARY GUIDELINES IN PATIENTS WITH ESTABLISHED CARDIOVASCULAR DISEASE

Nadia E. Bonekamp
Johanna M. Geleijnse
Yvonne T. van der Schouw
Jannick A.N. Dorresteijn
Manon G. van der Meer
Ynte M. Ruigrok
Martin Teraa
Frank L.J. Visseren
Charlotte Koopal

on behalf of the UCC-SMART study group

In revision

ABSTRACT

Background

Unhealthy dietary habits are an important risk factor for cardiovascular disease (CVD) and adopting a healthy diet is a central recommendation in CVD prevention. This study assessed the dietary habits of patients with established CVD, their compliance to dietary guidelines, and the relationship between guideline-compliance and recurrent cardiovascular event risk.

Methods

2,656 patients with established CVD from the Utrecht Cardiovascular Cohort-Secondary Manifestations of ARTerial disease (UCC-SMART) prospective cohort study, were included between 1996 and 2022. Data on dietary intake was retrospectively collected for all participants in December 2022 using a 160-item food frequency questionnaire. Compliance with dietary guidelines was quantified using an amended version of the Dutch Healthy Diet 2015 (DHD-15) index (range: 0-135). Cox proportional hazard models were used to quantify the relationship with cardiovascular events (stroke and myocardial infarction).

Results

Among 2,656 CVD patients (77% male, mean age 59 ±9 years), median energy intake was 1,922 [IQR: 1,536-2,351] kcal/day. The median DHD-15 index was 81.7 [IQR 71.2-92.0], with high compliance scores for recommendations on legumes and fish, and low scores for recommendations on whole grains, red meat, processed meat, and dairy. A higher DHD-15 score was associated with lower stroke risk (HR 0.78, 95%CI 0.66-0.92 per 10-point increase) but not with myocardial infarction.

Conclusion

Compliance with dietary guidelines was suboptimal in patients with established CVD. High compliance was associated with a clinically significant reduction in stroke risk in patients with established CVD, emphasizing the importance of dietary counseling.

INTRODUCTION

Healthy dietary habits are central in the prevention of cardiovascular disease (CVD).[1–4] An unhealthy diet significantly increases risk of developing non-communicable diseases like CVD, diabetes and cancer.[1,5,6] In 2015, the Dutch Health Council presented guidelines on healthy dietary habits for the Netherlands.[7] In 2023, the Dutch Health Council introduced updated diet recommendations, specifically targeted to patients with established CVD.[8] Both sets of guidelines include a general recommendation to adopt a more plant-based dietary pattern and provide specific recommendations on a range of food groups. Similarly, in the 2021 ESC Cardiovascular Prevention Guidelines a plant-based diet is advised in high-risk patients.[2] The Dutch Healthy Diet index 2015 (DHD15 index) was developed to measure compliance with the current Dutch dietary guidelines.[9] Previous research has shown that DHD-15 scores ranged between 50-70 (out of maximum 150) in the Dutch general population, and that higher compliance is associated with lower levels of cardiovascular risk factors, cardiovascular events, incident type 2 diabetes, cancer and depressive symptoms.[10–14]

The relationship between healthy diet and cardiovascular outcomes has extensively been studied in apparently healthy populations [15–18] and several dietary patterns have been associated with reduced risk of developing CVD. For instance, a high compliance with the American dietary guidelines has been associated with significant morbidity and mortality benefits.[19,20] Unfortunately, few cohorts comprising patients in whom CVD is clinically manifest, have collected detailed and up-to-date information on dietary intake. As a result, the relationship between compliance with dietary guideline recommendations and recurrent cardiovascular events has not extensively been studied and evidence on the dietary habits of these patients and the relationship between these habits and clinical outcomes is scarce. A meta-analysis on older dietary studies in patients with coronary artery disease suggested that the existing evidence was insufficient to provide a reliable estimate of the impact of diet on CVD patients' prognosis. However, based on the available data, this meta-analysis estimated a potential effect of approximately 45% relative risk reduction.[21] Further research on dietary habits of patients with CVD could help improve targeted dietary guidance for patients with established CVD and lead to better clinical outcomes.

The objective of the present study is to describe the dietary habits of patients with established CVD and to assess the degree of compliance with guideline-recommended

healthy diets. Additionally, the study aims to quantify the relation between compliance with the guideline-recommended healthy diet and recurrent cardiovascular events in patients with clinically manifest CVD.

METHODS

Study population

The Utrecht Cardiovascular Cohort - Secondary Manifestations of Arterial Disease (UCC-SMART) study is a single-center, ongoing prospective cohort that includes patients aged 18 to 79 years with cardiovascular risk factors or established CVD. In December 2022 all 10,072 UCC-SMART participants who were still alive and actively participating in follow-up were invited to complete a food frequency questionnaire (FFQ) (Figure 1, Figure S1). In total, 4,496 participants completed the FFQ, resulting in an overall response rate of 45%. The current analysis was limited to patients included between December 1996 and December 2022 with established CVD at baseline for whom plausible dietary intake data was available (N = 2,656). Established CVD was defined as a history of coronary artery disease (CAD), cerebrovascular disease (CeVD), peripheral arterial disease (PAD) or abdominal aortic aneurysm (AAA) (Table S1). The UCC-SMART study has been approved by the local Medical Ethics Committee (reference number 22-088), with all participants providing written informed consent. Details on the UCC-SMART study have been published previously.[22,23]

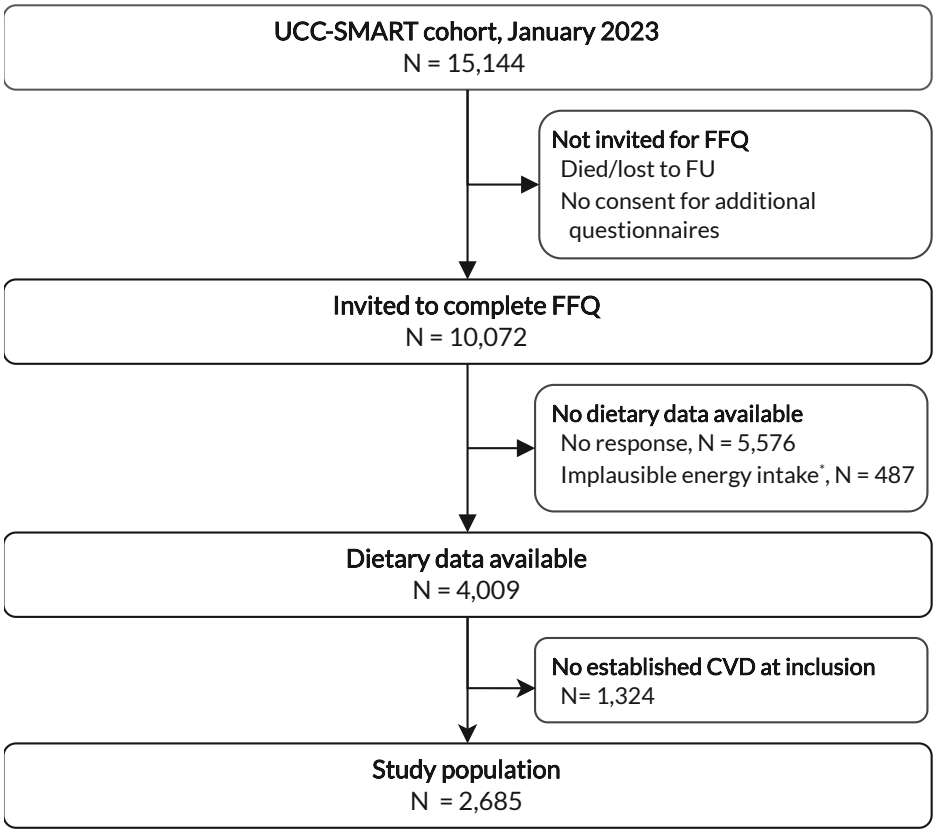
Dietary assessment

Data on dietary intake were collected at a different moment than the baseline covariates. Information on dietary habits using an FFQ was retrospectively collected in December 2022. Participants were sent an invitation letter to fill out the FFQ using a specially designed online tool (FFQ-TOOL). In case participants did not prepare their own meals, they were encouraged to complete the FFQ with the help of a spouse, family member or caregiver. A reminder was sent six weeks after the original invitation to those who had not completed the FFQ.

Dietary intake was assessed with the FFQ-NL 1.0, a web-based, 160-item questionnaire specifically designed for the Dutch population.[24] The questionnaire comprises questions on frequency and consumed amounts with a reference period of one year. FFQ-NL1.0 has good agreement with 24-hour dietary recalls on total energy

intake and macronutrients, with low levels of bias in the mean values. Moreover, it has a comparable performance to other FFQs.[24,25] Intakes of energy, macronutrients, and micronutrients were obtained by linking the reported consumption data with the Dutch Food Composition Database.[26] To address potential under- or overreporting of dietary intake, patients with implausible energy intake (< 500 kcal or > 3,500 kcal)[27,28] were excluded from the analysis resulting in the exclusion of 487 individuals (11% of all responses).

FIGURE 1 Flowchart of patient selection and dietary data collection



Flowchart representing dietary data collection in the UCC-SMART cohort. Plausible energy intake levels were defined as a daily caloric intake ≥ 500 kcal and ≤ 3,500 kcal.
FFQ: food frequency questionnaire, UCC-SMART: Utrecht Cardiovascular Cohort – Second Manifestations of ARTerial disease.

Compliance with dietary guidelines

The DHD-15 index was used to evaluate compliance with the Dutch dietary guidelines, based on the Dutch Health Council's recommendations on healthy dietary habits.[9] The Health Council's recommendations are targeted to the Dutch population, but show extensive overlap with current international dietary guidelines for CVD prevention (Table S2).[2,3] Recent updated guidelines specifically targeted to patients with CVD or type 2 diabetes, showed very few deviations from the general recommendations. [8,29] The DHD-15 index is a validated dietary index that scores intake for 15 food groups or nutrients, awarding a continuous score between 0 and 10 for each item based on target intake levels, with an overall score ranging from 0 to 150. In the current study, two components (3b wholegrain to refined grain ratio (5 points); and 10 use of filtered coffee (10 points) were not assessed in the current study because the required information is not captured in FFQ-NL 1.0, resulting in a maximum DHD-15 index score of 135 in this analysis.

Covariate assessment

Information on all non-dietary covariates was collected at inclusion in the UCC-SMART cohort. At this time, all participants completed a standardized questionnaire that included questions on age, sex, education, lifestyle behaviors, medical history, cardiovascular risk factors and medication use. Education level was classified as low, low-middle, middle-high, and high. Smoking status was self-reported and classified as never, former, or current. All patients underwent anthropomorphic measurements, physical examination, and laboratory measurements. Anthropometric measurements were taken with patients wearing light clothing and no shoes, and body mass index (BMI) was calculated by dividing body mass by height squared. Blood pressure was measured automatically, in triplicate with a 30-second interval, and the mean value of three measurements was used as systolic and diastolic blood pressure. Total cholesterol, high density lipoprotein cholesterol and triglyceride levels were measured in fasting venous blood. LDL-cholesterol levels were calculated using the Friedewald formula.[30] Physical activity was self-reported and assessed using a validated ranking questionnaire that included additional questions on type and duration of exercise.[31] Total physical activity volume in metabolic equivalent of task hours per week (METh/wk) were calculated based on the MET value for the reported activity from the Compendium of Physical Activity.[32]

Clinical outcomes

The endpoint in the explorative survival analysis was a composite of incident myocardial infarction (MI) and stroke. Myocardial infarction and stroke were separately assessed as secondary endpoints. Detailed endpoint definitions are provided in Table S3. Data on clinical endpoints was collected through annual follow-up questionnaires on vital status and occurrence of cardiovascular events from the time of inclusion until January 2022. When participants reported an event, the relevant medical information was obtained from the treating physician. The final categorization of the type of event was made independently by three physicians from the UCC-SMART endpoint committee.[23]

Data analyses

Baseline characteristics and reported dietary intake were described as mean ± standard deviation, median [interquartile range (IQR)] and number (percentage), as appropriate, stratified for history of CVD and for BMI group (< 25, 25-30 or ≥25 kg/m^2). Cox proportional hazard models were used to assess the relationship between quartiles of DHD-15 index and non-fatal stroke and non-fatal MI and a composite of these outcomes. Model 1 adjusted for age and sex. Model 2, the main model, additionally adjusted for daily energy intake, education level, smoking status and physical activity level. Finally, model 3 further adjusted for variables that could be both confounders or intermediates: BMI, systolic blood pressure, LDL-cholesterol, fasting triglycerides, and hs-CRP. Restricted cubic splines were used to assess the relationship between DHD-15 as a continuous variable with the outcomes. The proportional hazard assumption was checked by visual inspection of Schoenfeld residuals and was not violated.

Sensitivity analyses were conducted to evaluate the potential impact of participation bias in the collection of dietary intake data. Baseline characteristics for responders and non-responders were compared and standardized mean differences (SMD) were calculated. As a sensitivity analysis, dietary data were imputed for patients that did not respond to the FFQ using multiple imputation. In this imputed dataset, the Cox regression models were repeated. A subgroup analysis was conducted in patients with less than five years between the dietary intake questionnaire and collection of patients characteristics, anthropometrics, and laboratory testing. Finally, the relationship between quartiles of DHD-15 index and non-fatal stroke and non-fatal MI and a composite of these outcomes was assessed using logistic regression models adjusted for all confounders in model 2 to assess whether the collection of dietary data after outcome collection could have affected the results.

Missing data were imputed with single imputation using predictive mean matching. Missingness was highest for education (18%) and LDL-cholesterol (3%). All statistical analyses were performed using R statistical software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Study population

Table 1 presents the baseline characteristics of participants that completed the FFQ and reported a plausible energy intake (N = 2,656). Mean age was 59 ±9 years and the majority were men (77%). CAD was the most prevalent CVD manifestation (N = 1,697, 63%). Of all patients 79% used lipid-lowering medication and 78% used antihypertensive medication. Compared with non-responders, participants who completed the FFQ had a higher education level and a healthier cardiovascular risk profile, as they were less likely to be current smokers (19% *vs* 27%), had lower systolic blood pressure (133 ±21 *vs* 139 ±22 mmHg) and lower LDL-cholesterol levels (2.3 IQR 1.8-3.0 *vs* 2.8, IQR 2.2-3.7 mmol/l). Physical activity, body mass index and hs-CRP levels were similar across responders and non-responders (Table S4).

Participants with less than five years between the collection of dietary intakes in 2022 and the other patient characteristics at baseline (N = 719) were older compared to the main analysis (Table S5). However, across healthy dietary compliance quartiles, a similar pattern of patients with a better compliance being more frequently female and having a more favourable cardiovascular risk profile (less smoking, more physical activity, lower BMI, and more favourable lipid profile) between the subgroup and the main analysis was observed (Table S5).

TABLE 1 Patient characteristics of the UCC-SMART cohort

		Guideline diet adherence score			
	Overall	Quartile 1 [30.8,71.2]	Quartile 2 (71.2,81.7]	Quartile 3 (81.7,92.1]	Quartile 4 (92.1,129]
	N = 2,656	N = 664	N = 664	N = 664	N = 664
Male, N (%)	2,071 (77)	554 (83)	531 (80)	512 (77)	474 (71)
Age, *year*	59.3 ±9.4	58.5 ±9.5	59.0 ±9.4	59.8 ±9.4	60.1 ±9.1
Education level, N (%)					
Low	367 (14)	110 (17)	104 (16)	81 (12)	72 (11)
Low-middle	914 (34)	258 (39)	228 (34)	231 (35)	197 (30)
Middle-high	1,224 (46)	256 (39)	287 (43)	325 (49)	356 (54)
High	151 (6)	40 (6)	45 (7)	27 (4)	39 (6)
CAD, N (%)	1,697 (63)	449 (68)	482 (73)	484 (73)	474 (71)
CeVD, N (%)	518 (19)	186 (28)	150 (23)	141 (21)	173 (26)
Diabetes, N (%)	307 (11)	69 (10)	83 (13)	87 (13)	68 (10)
Smoking status, N (%)					
Never	788 (29)	158 (24)	179 (27)	200 (30)	251 (38)
Former	1,366 (51)	335 (51)	347 (52)	351 (53)	333 (50)
Current	502 (19)	171 (26)	138 (21)	113 (17)	80 (12)
Physical activity, *METh/wk*	42 [24-68]	37 [21-65]	41 [21-68]	43 [25-65]	44 [27-71]
Body mass index, *kg/m²*	26.8 ±5.6	27.5 ±9.0	26.9 ±3.8	26.7 ±3.7	26 ±4.3
Systolic BP, *mmHg*	133 ±18	134 ±17	134 ±20	134 ±18	132 ±18
Total cholesterol, *mmol/L*	4.2 [3.6-5.0]	4.3 [3.6-5.1]	4.3 [3.6-5.1]	4.2 [3.6-5.1]	4.2 [3.6-4.9]
HDL-cholesterol, *mmol/L*	1.2 [1.0-1.4]	1.2 [1.0-1.4]	1.2 [1.0-1.4]	1.2 [1.0-1.4]	1.2 [1.0-1.5]
LDL-cholesterol, *mmol/L*	2.3 [1.8-3.0]	2.4 [1.9-3.1]	2.3 [1.8-3.0]	2.3 [1.9-3.0]	2.3 [1.8-2.9]
CRP, *mg/L*	1.6 [0.8-3.2]	1.5 [0.8-3.3]	1.7 [0.9-3.4]	1.7 [0.9-3.4]	1.3 [0.7-2.9]
Lipid-lowering therapy (%)	2,131 (79)	517 (78)	541 (82)	536 (81)	537 (81)
BP-lowering therapy (%)	2,105 (78)	501 (76)	547 (82)	535 (81)	522 (79)

Baseline characteristics of UCC-SMART participants. Data are presented as number (percentage), mean ± standard deviation or median [interquartile range]. CVD: cardiovascular disease, CAD: coronary artery disease, CeVD: cerebrovascular disease, , BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, CRP: C reactive protein, NA: not applicable.

Dietary intake

The daily intake for macronutrients, micronutrients and food groups in the UCC-SMART cohort is presented in Table 2. Median energy intake was 1,922 [IQR 1,536-2,351] kcal. The median macronutrient intake consisted of 193 [IQR 147-239] g/day of carbohydrates, 21 [IQR 16-27] g/day of protein, and 27 [IQR 20-35] g/day of fatty acids (37% saturated fatty acids, SFA). Total energy intake was highest in participants with CAD and multiple CVD manifestations (1955, IQR 1570-2362 and 1938, IQR 1570-2478 kcal/day, respectively) and lowest in those with CeVD (1844, IQR 1417-2268 kcal/day) and PAD/AAA (1861, IQR 1436-2284 kcal/day). Fruit and vegetable intake were highest in patients with multiple CVD manifestations (118, IQR 37-225 and 108, IQR: 62-178 g/day, respectively) and lowest in PAD/AAA patients (99, IQR 24-222 and 102, IQR 43-154 g/day, respectively). Participants with multiple CVD manifestations consumed the largest amounts of red meat (95 g/day). PAD/AAA patients and those with multiple CVD manifestations consumed significantly more alcoholic beverages than those with CAD or CeVD (Table 2).

CVD patients with a BMI ≥ 30 kg/m^2 reported a lower total energy intake compared with those with a BMI < 25 kg/m^2 (1847, IQR 1432-2357 kcal/day *vs*. 1944, IQR 1548-2344 kcal/day). Reported intake of fruits, vegetables, wholegrains, nuts, legumes, and tea was lower in overweight and obese patients compared with those with a healthy BMI (Table S6). Overweight and obese patients reported a high intake of fatty acids, red and processed meat, and coffee.

TABLE 2 Daily nutrient intake in the UCC-SMART cohort, stratified for type of manifest cardiovascular disease.

		CVD manifestation			
	Overall N = 2,656	**CAD N = 1,697**	**CeVD N = 518**	**PAD/AAA N = 215**	**Multiple N = 226**
Nutrient intake (/day)					
Total energy intake, *kcal*	1922 [1536-2351]	1955 [1570-2362]	1844 [1417-2268]	1861 [1436-2284]	1938 [1570-2478]
Carbohydrate					
gram	193 [147-239]	196 [152-241]	183 [134-233]	178 [133-227]	196 [151-248]
E%	40 [36-45]	41 [36-45]	40 [36-44]	39 [35-44]	40 [35-45]
Mono- and disaccharides, *g*	81 [57-107]	81 [59-108]	78 [55-106]	74 [49- 98]	83 [57-109]
Polysaccharides, *g*	75 [58-97]	109 [84-140]	100 [75-131]	102 [73-132]	107 [82-137]
Total fat					
gram	27 [20-35]	76 [60-98]	73 [54-94]	74 [51-96]	76 [62-98]
E%	36 [33-40]	36 [33-40]	36 [33-40]	36 [32-41]	36 [32-40]
SFA, *g*	26 [20-34]	27 [21-35]	26 [18-36]	26 [19-34]	28 [22-35]
MUFA, *g*	15 [11-20]	27 [20-34]	25 [19-32]	26 [17-33]	27 [21-35]
PUFA, m*g*	210 [155-283]	15 [11-20]	14 [11-19]	14 [10-19]	15 [11-21]
Cholesterol, *mg*	79 [63-97]	212 [156-281]	203 [145-280]	199 [150-278]	220 [164-304]
Protein					
gram	21 [16-27]	80 [64-97]	76 [59-95]	73 [58-92]	78 [63-102]
E%	16 [15-18]	16 [15-18]	16 [14-18]	16 [14-19]	16 [15-19]
Dietary fiber, *g*	21 [16-27]	21 [17-27]	20 [15-26]	19 [14-24]	21 [17-27]
Food groups (/day)					
Vegetables, *g*	106 [57-166]	107 [60-167]	103 [47-164]	102 [43-154]	108 [62-178]
Fruit, *g*	117 [48-230]	118 [50-231]	120 [41-229]	99 [24-222]	118 [37-225]
Wholegrain, *g*	29 [0-75]	31 [0-84]	27 [0-72]	18 [0-67]	23 [0-71]
Pulses and legumes, *g*					

TABLE 2 (Continued)

		CVD manifestation			
	Overall N = 2,656	**CAD** N = 1,697	**CeVD** N = 518	**PAD/AAA** N = 215	**Multiple** N = 226
Consumers, *N (%)*	2,561 (95)	1,635 (96)	506 (98)	200 (93)	220 (97)
Intake among consumers, *g*	22 [11-42]	22 [11-42]	17 [7-35]	22 [11-51]	17 [11-35]
Nuts					
Consumers, *N (%)*	2,415 (90)	1,554 (92)	471 (91)	186 (87)	204 (90)
Intake among consumers, *g*	8 [3-21]	9 [3-21]	8 [3-20]	7 [2-19]	7 [2-18]
Dairy, *g*	271 [145-430]	287 [160-440]	245 [109-416]	239 [145-398]	274 [129-437]
Fish, *g*					
Consumers, *N (%)*	2,540 (95)	1,663 (98)	490 (95)	207 (96)	210 (93)
Intake among consumers, *g*	20 [11-34]	20 [11-34]	9 [11-34]	19 [11-32]	21 [11-40]
Meat					
Red meat, *g*	76 [44-116]	78 [46-118]	67 [37-104]	74 [42-109]	85 [44-131]
White meat, *g*	18 [7-36]	18 [7-36]	18 [7-36]	16 [6-36]	15 [7-36]
Processed meat	25 [10-45]	26 [11-46]	19 [7-40]	26 [11-48]	29 [14-49]
Tea, *g*	170 [3-340]	170 [7-340]	170 [3-510]	99 [0-510]	146 [3-510]
Coffee, *g*	420 [280-561]	420 [280-560]	361 [140-560]	420 [280-560]	420 [280-560]
Alcoholic beverages, *g*					
Consumers, *N (%)*	2,221 (83)	1,438 (85)	425 (82)	181 (84)	177 (78)
Intake among consumers, *g*	117 [36-255]	118 [37-246]	108 [34-240]	115 [37-306]	153 [37-313]

Daily dietary intake of (macro)nutrients and food groups, stratified for presence of established cardiovascular disease at inclusion in the cohort. SFA: saturated fatty acids, MUFA: monounsaturated fatty acids, PUFA: poly unsaturated fatty acids

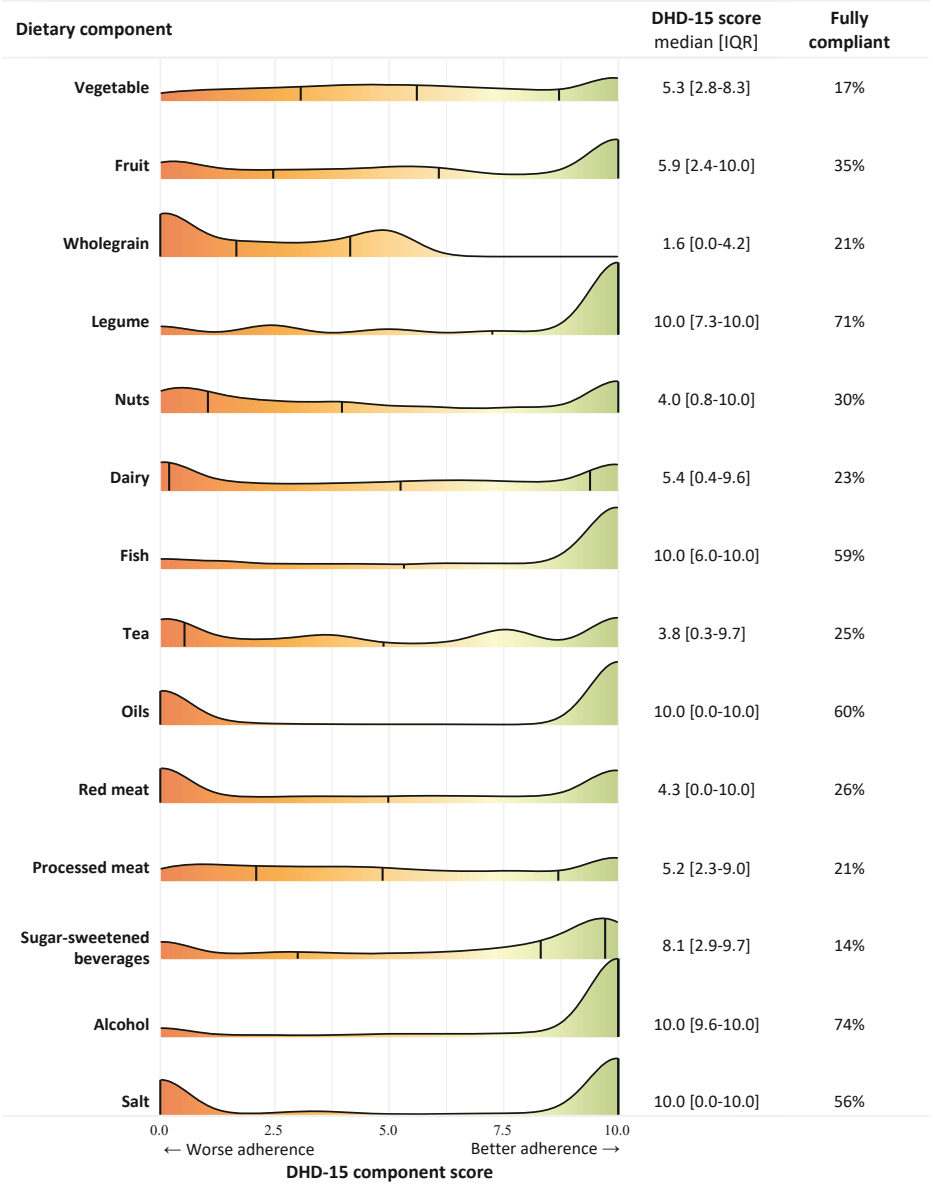
Compliance with dietary guidelines

The median DHD-15 index was 81.7 [IQR 71.2-92.0] and ranged between 30.8 and 129.4. The compliance scores for legume, vegetable oil, alcohol, and salt intake were the highest, with over 50% of the population meeting the target intake for these components (Figure 2). Compliance was lowest for the whole grain component, with a median score of 1.6 [IQR 0.0-4.2] out of a maximum of 5. Patients with established CVD also had poor-moderate compliance with the nuts and dairy components but with large variation across the population, with a median score of 4.0 [IQR 0.8-10.0] and 5.4 [IQR 0.4-9.6], respectively. DHD-15 component scores for red and processed meat were 4.3 [IQR 0-10] and 5.2 [IQR 2.3-9.0], respectively. Compliance with the healthy diet guidelines did not differ across subgroups of patients with different manifestations of CVD (Table 2).

Relationship between DHD-15 index and cardiovascular events

During a median follow-up of 8.7 [IQR: 4.1-13.7], a total of 211 cardiovascular events occurred. The multivariable-adjusted relationship between DHD-15 index and major cardiovascular events were approximately linear (Figure 3). DHD-15 score was not significantly associated with the composite cardiovascular event endpoint and incident myocardial infarction (HR 0.93, 95%CI 0.85-1.01 and 0.98, 95%CI 0.88-1.08 per 10-point increase, respectively). A higher DHD-15 score was associated with incident stroke (HR 0.78, 95%CI 0.66-0.92 per 10-point increase in DHD-15 index, Figure 3C). Table 3 presents HRs for cardiovascular events, myocardial infarction and stroke across DHD-15 index quartiles. In these analyses, a statistically significant relationship with stroke was observed for the third and fourth DHD-15 index quartile (HR 0.44, 95%CI 0.20-0.95 and HR 0.32, 95%CI 0.13-0.80, respectively). In a sensitivity analysis with imputed dietary intakes for non-responders, HRs for cardiovascular events were similar in size and direction (Table S7). A sensitivity analysis using logistic regression instead of cox regression to assess the relationship between DHD-15 index and cardiovascular outcomes yielded odds ratios that were similar in size and direction to those found in the Cox regressions (Table S8).

FIGURE 2 Compliance with the Dutch dietary guidelines (DHD-15 score)



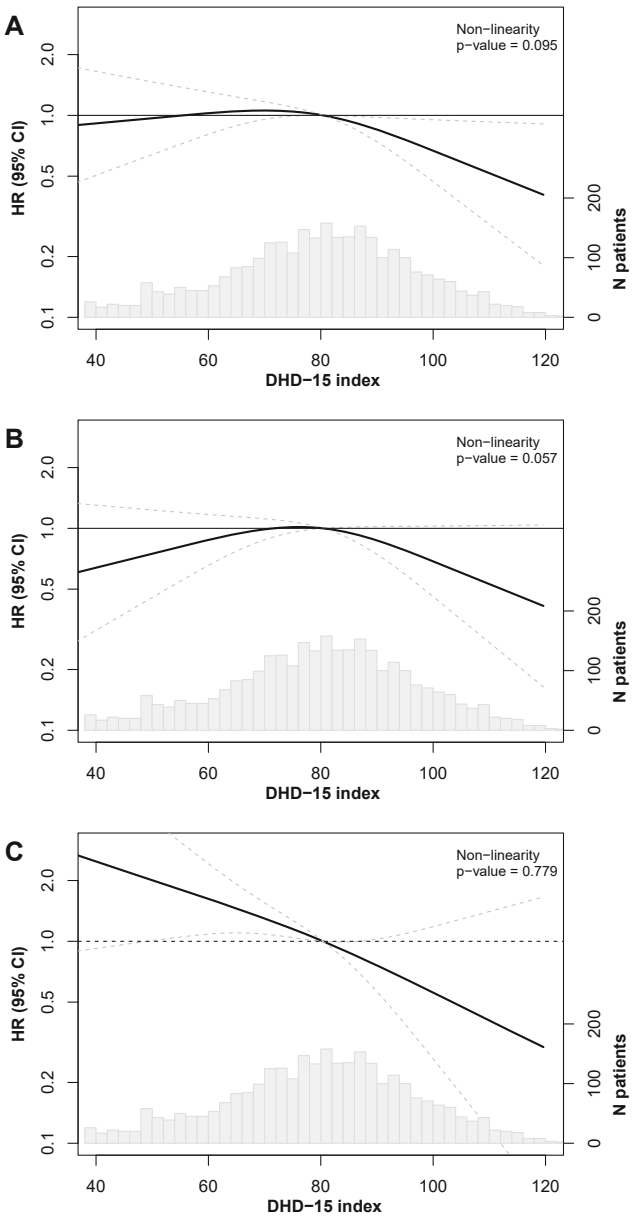
Distribution and median scores for the individual components of the DHD-15 index. Vertical dashes signify the quartiles. Fully compliant was defined as a score of 10, except for wholegrain intake where a score of 5 was fully compliant. SSB: Sugar-sweetened beverages, CVD: cardiovascular disease, DHD-15: Dutch health diet-15 index.

TABLE 3 Relationship between DHD-15 quartiles and cardiovascular events

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
	30-69	69-80	80-91	91-129
Cardiovascular events				
N events	64	69	42	36
Follow-up (py)	6,563	6,173	5,966	5,388
Model 1	*Reference*	1.14 (0.81-1.60)	0.72 (0.48-1.06)	0.70 (0.47-1.06)
Model 2	*Reference*	1.15 (0.82-1.62)	0.72 (0.49-1.07)	0.73 (0.48-1.11)
Model 3	*Reference*	1.17 (0.83-1.65)	0.73 (0.50-1.09)	0.77 (0.51-1.17)
Myocardial infarction				
N events	46	52	33	30
Follow-up (py)	6,693	6,276	6,013	5,435
Model 1	*Reference*	1.20 (0.81-1.78)	0.79 (0.51-1.24)	0.84 (0.53-1.33)
Model 2	*Reference*	1.21 (0.82-1.81)	0.80 (0.51-1.25)	0.88 (0.55-1.41)
Model 3	*Reference*	1.25 (0.84-1.86)	0.82 (0.52-1.28)	0.94 (0.59-1.51)
Stroke				
N events	23	18	9	6
Follow-up (py)	6,851	6,507	6,160	5,558
Model 1	*Reference*	0.83 (0.45-1.53)	0.44 (0.20-0.95)	0.32 (0.13-0.78)
Model 2	*Reference*	0.83 (0.45-1.54)	0.44 (0.20-0.95)	0.32 (0.13-0.80)
Model 3	*Reference*	0.79 (0.42-1.47)	0.42 (0.20-0.92)	0.30 (0.12-0.74)

Model 1 adjusted for age and sex. Model 2 for model 1 + daily energy intake, education level, smoking status and physical activity level. Model 3 adjusted Model 2 + BMI, systolic blood pressure, LDL-cholesterol, triglycerides, and CRP.

FIGURE 3 Continuous relationship between compliance with the Dutch dietary guidelines and risk of cardiovascular events



Continuous associations between compliance with the Dutch Healthy Diet 2015 guidelines and risk of recurrent cardiovascular events (**A**), non-fatal myocardial infarction (**B**) or non-fatal stroke (**C**). The grey bars represent a histogram of the DHD-15 scores. HR: hazard ratio, DHD-15: Dutch Healthy Diet 2015.

DISCUSSION

This study described the dietary intake and compliance with dietary guidelines in a large cohort of patients with established CVD. Overall, the reported dietary habits indicated a suboptimal compliance with dietary recommendations, especially concerning nuts, whole grains, fruits, and vegetables. An inverse relationship between a healthy diet index and stroke risk was observed. Importantly, clinically relevant risk reductions were only observed for patients with a high compliance score, which indicates that patients should be encouraged to follow all recommendations.

Although compliance with dietary guidelines was suboptimal in the UCC-SMART cohort, it exceeded scores reported in previous studies among apparently healthy individuals , which reported mean DHD-15 scores of about 70.[9,12] A potential explanation for these findings is that people with a history of CVD are more likely to receive active counselling on healthy dietary habits. This is reflected by the fact that legume, vegetable oil, alcohol and salt intake had the highest compliance scores, and all these components are explicitly part of CVD prevention guidelines.[2,3] Social desirability bias may have resulted in overreporting on these specific food items, which could also (partially) explain the observed high compliance with dietary guidelines in this population with established CVD.

Dietary habits in the general Dutch population are periodically assessed in the Dutch National Food Consumption Survey (DNFCS).[33] A comparison of data from adults in the 2012-2016 DNFCS revealed that the total energy intake of patients in UCC-SMART with established CVD was lower than that of the general population (1,905 kcal/day versus 2,200 kcal/day). The energy contributions of macronutrients were similar to the general population (15E% protein, 40-45E% carbohydrate and 35-40E% fatty acids). Patients with established CVD reported a higher intake of fruits, pulses and nuts compared to the general population. Moreover, it is noteworthy that the intake of red meat and especially processed meat in the UCC-SMART cohort was lower compared with the average intake in the Dutch population (73 vs 81 gram/day and 23 vs 55 gram/day),[33] possibly because guidelines for CVD management recommend a reduction in red meat consumption.[3] The observed differences in dietary intake between patients with CVD and the general population may be due to counselling on dietary habits after a cardiovascular event, but other potential explanations include the contribution of specific dietary habits to the development of cardiovascular disease,

differences in proportion male and female and the different methods used for dietary assessment (FFQ vs dietary recall with telephone interviews).

Few cohorts have assessed the dietary habits of patients with established CVD, and the available studies mainly focus on patients with CAD.[34–36] Similar to CVD patients in the current study, patients with a history of MI in the Dutch Alpha Omega Cohort, consumed relatively more healthy food items than unhealthy food items.[36] In this Alpha Omega cohort, better compliance with dietary guidelines was associated with reduced risk of all-cause and cardiovascular mortality.[36] A pooled analysis of MI-survivors in the Nurses' Health Study and the Health Professionals Follow-up Study found that patients had the highest compliance scores for guidelines on trans fatty acid and long-chain ω-3 fatty acid intake, which might be comparable to the high DHD-15 score for the oil component observed in the present study. However, compliance with guidelines on nuts, whole grains, and fruit and vegetable intake was poor, as was also observed in the UCC-SMART cohort.[35]

Similar to previous studies on the relationship between dietary habits and cardiovascular events, the present analyses support the recommendations in dietary guidelines and show that a healthy diet is associated with clinically relevant reductions in cardiovascular event risk[19,20]. In the current analysis, healthy dietary habits were strongly related with stroke risk, with almost 25% relative risk reduction per 10-point increase in DHD-15 score. To our knowledge, the association between stroke risk and compliance with dietary guidelines has not previously been studied in secondary prevention populations, but in apparently healthy populations a higher score for the Healthy Eating Index (measure for compliance with the *Dietary guidelines for Americans*[37]) was associated with significant reductions in stroke risk. In the PREDIMED trial on the Mediterranean diet, which emphasizes vegetable, fruit, legume, nuts, and vegetable oil intake, stoke risk was reduced by 45% compared to a low-fat diet.[38]

Potential mechanisms through which healthy diet may reduce cardiovascular event risk include reduction of cardiovascular risk factors (*e.g.* blood pressure, LDL-cholesterol), preventing obesity and its sequalae, or provision of cardioprotective nutrients like omega-3 fatty acids, potassium, fiber, and polyphenols. Furthermore, a high DHD-15 score may also be indicative of an overall healthier lifestyle because lifestyle components are often interrelated, although the current analyses were adjusted for such factors (smoking, physical activity, smoking, and education level). Some of these

mechanisms may have a different, strengthened or ameliorated effects in patients with established CVD compared with the general population, partly due to medication use and differences in baseline risk.

Strengths and limitations

Strengths of this study include the large sample size, the use of a validated dietary assessment tool, and the inclusion of individuals with different types of CVD. The UCC-SMART cohort includes a comprehensive vascular screening and high-quality data for a wide range of cardiovascular risk factors and outcomes. Addition of a dietary assessment opens opportunities to gain new insights in the role of dietary habits in the development and management of CVD.

Study limitations also need to be considered. In the current analysis, dietary intake was not assessed simultaneously with other patient characteristics, which complicates correlation of dietary habits to baseline measurements and might have diluted the relationship between dietary intake and clinical outcomes, because patients might have improved their diet after suffering from a CVD event. Previous studies have shown that dietary habits are relatively stable over time and that FFQs show good reproducibility over a period of at least five years.[39] In a subgroup of patients with less than five years between data collection on patient characteristics and dietary intake data, a similar pattern regarding distribution of patient characteristics was found. Furthermore, dietary intake was assessed after a recurrent cardiovascular event occurred, which might have led to reverse causality in the relationship between healthy diet and cardiovascular events (*i.e.* patients with a cardiovascular event adopt a healthy diet because the event occurred). This could have resulted in an underestimation of the association between healthy dietary habits and cardiovascular events. However, because all patients had established CVD at the time of inclusion, it is unlikely that they will have changed their dietary habits significantly after a recurrent event.

Using an FFQ for dietary assessment relies on self-report, is best suited for ranking intakes instead of estimating absolute intakes and may be affected by factors such as recall limitations, complexity of an individual's diet, or social desirability bias. However, the FFQ-NL 1.0 used in this study was validated in the Dutch population against 24-hour dietary recalls and showed good performance.[24,25] Moreover, the use of an FFQ is cost-efficient and widely accepted in epidemiological studies. In the FFQ-NL 1.0 there was no detailed information on whole grains and coffee preparation available, which

prevented these two components of the DHD-15 index from being fully assessed. This may have resulted in reduced contrast between those with a healthier diet and those with an unhealthy diet and could partly explain why no statistically significant relationship with the myocardial infarction risk was observed.

Another potential limitation of the retrospective collection of dietary assessments is selection bias, as only patients who survived and could complete the questionnaire accurately were included in the study. Comparison of patient characteristics for responders and non-responders of the FFQ indicated that responders were younger and had a slightly more favourable cardiovascular risk profile. Patients with a healthy lifestyle are more eager or better able to complete an FFQ. For the current analysis, this means that the presented dietary intakes may be overly optimistic because patients with unhealthier dietary intakes are not included in this study. Nevertheless, selection bias is unlikely to affect the analyses on the relation between dietary habits and cardiovascular risk because there is still ample distribution in the variables to assure adequate contrast for association analyses. Furthermore, the detailed data collection in the UCC-SMART cohort allows for thorough adjustment of confounders that explain the differences between the responders and non-responders.

CONCLUSION

In conclusion, in a large cohort of patients with established CVD, overall compliance with dietary guidelines was suboptimal. Patients had high compliance scores for recommendations on legume, liquid fats, and salt intake, but low compliance scores for whole grain, dairy and red meat intake. Even in this CVD population receiving extensive pharmacological treatment for cardiovascular risk factors, a guideline-compliant diet was associated with a lower stroke risk. These findings emphasize the importance of promoting healthy dietary habits among patients with established CVD and indicate the need for additional focus on food items where compliance scores were low. By prioritizing and addressing these areas of improvement, long-term cardiovascular health outcomes may be improved for this highly prevalent and very high-risk patient population.

REFERENCES

1. Dai H, Much AA, Maor E, Asher E, Younis A, Xu Y, et al. Global, regional, and national burden of ischaemic heart disease and its attributable risk factors, 1990–2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes. 2020;1–11.
2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J [Internet]. 2021 Aug 30;(00):1–111.
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;74(10):e177–232.
4. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, a. J Am Coll Cardiol. 2014;64(18):1929–49.
5. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982–3021.
6. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet [Internet]. 2017 Sep 16;390(10100):1211–59.
7. Health Council of the Netherlands. Guidelines for a healthy diet 2015. The Hague: Health Council of the Netherlands. 2015;
8. Health Council of the Netherlands. Dutch dietary guidelines for people with atherosclerotic cardiovascular disease. The Hague; 2023.
9. Looman M, Feskens EJM, Rijk M De, Meijboom S, Biesbroek S, Temme EHM, et al. Development and evaluation of the Dutch Healthy Diet index 2015. 2017;20(13):2289–99.
10. Gianfredi V, Koster A, Odone A, Amerio A, Signorelli C, Schaper NC, et al. Associations of Dietary Patterns with Incident Depression: The Maastricht Study. Nutrients. 2021 Mar 23;13(3).
11. Lee L Van, Geelen A, Jong JCK de, Witteman JCM, Hofman A, Vonk N, et al. Adherence to the Dutch dietary guidelines is inversely associated with 20-year mortality in a large prospective cohort study. 2016;(July 2015):262–8.
12. den Braver NR, Rutters F, van der Spek ALJK, Ibi D, Looman M, Geelen A, et al. Adherence to a food group-based dietary guideline and incidence of prediabetes and type 2 diabetes. Eur J Nutr [Internet]. 2020 Aug;59(5):2159–69.
13. Struijk EA, May AM, Beulens JWJ, Fransen HP, De Wit GA, Boer JMA, et al. Adherence to the Dutch Guidelines for a Healthy Diet and cancer risk in the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort. Public Health Nutr. 2013 Feb 18;17(11):2546–53.

14. Voortman T, Kiefte-de Jong JC, Ikram MA, Stricker BH, van Rooij FJA, Lahousse L, et al. Adherence to the 2015 Dutch dietary guidelines and risk of non-communicable diseases and mortality in the Rotterdam Study. Eur J Epidemiol. 2017 Nov 1;32(11):993–1005.

15. Baart AM, Brouwer-brolsma EM, Perenboom CWM, de Vries JHM, Feskens EJM. Dietary intake in the lifelines cohort study: Baseline results from the flower food frequency questionnaire among 59,982 participants. Nutrients. 2022 Jan 1;14(1).

16. Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S. The Prospective Urban Rural Epidemiology (PURE) study: Examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. Am Heart J. 2009 Jul;158(1):1-7.e1.

17. Gao M, Jebb SA, Aveyard P, Ambrosini GL, Perez-Cornago A, Carter J, et al. Associations between dietary patterns and the incidence of total and fatal cardiovascular disease and all-cause mortality in 116,806 individuals from the UK Biobank: a prospective cohort study. BMC Med. 2021 Dec 1;19(1).

18. Chen TC, Clark J, Riddles MK, Mohadjer LK, Fakhouri THI. National Health and Nutrition Examination Survey, 2015-2018: Sample Design and Estimation Procedures. Vital Health Stat 2. 2020 Apr;(184):1–35.

19. Shan Z, Li Y, Baden MY, Bhupathiraju SN, Wang DD, Sun Q, et al. Association Between Healthy Eating Patterns and Risk of Cardiovascular Disease. JAMA Intern Med. 2020 Aug 1;180(8):1090.

20. Zhong VW, Ning H, Van Horn L, Carnethon MR, Wilkins JT, Lloyd-Jones DM, et al. Diet Quality and Long-Term Absolute Risks for Incident Cardiovascular Disease and Mortality. Am J Med. 2021 Apr;134(4):490-498.e24.

21. Iestra JA, Kromhout D, van der Schouw YT, Grobbee DE, Boshuizen HC, van Staveren WA. Effect Size Estimates of Lifestyle and Dietary Changes on All-Cause Mortality in Coronary Artery Disease Patients. Circulation. 2005 Aug 9;112(6):924–34.

22. Simons PCG, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol [Internet]. 1999 Oct;15(9):773–81.

23. Castelijns MC, Helmink MAG, Hageman SHJ, Asselbergs FW, de Borst GJ, Bots ML, et al. Cohort profile: the Utrecht Cardiovascular Cohort-Second Manifestations of Arterial Disease (UCC-SMART) Study-an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands. BMJ Open. 2023 Feb 20;13(2):e066952.

24. Sluik D, Geelen A, De Vries JHM, Eussen SJPM, Brants HAM, Meijboom S, et al. A national FFQ for the Netherlands (the FFQ-NL 1.0): Validation of a comprehensive FFQ for adults. British Journal of Nutrition. 2016;116(5):913–23.

25. Eussen SJPM, Van Dongen MCJM, Wijckmans NEG, Meijboom S, Brants HAM, De Vries JHM, et al. A national FFQ for the Netherlands (the FFQ-NL1.0): Development and compatibility with existing Dutch FFQs. Public Health Nutr. 2018;21(12):2221–9.

26. Dutch Nutrition Center. Dutch Food Composition Table 2006 NEVO-table. The Hague, The Netherlands; 2006.

27. Rhee JJ, Sampson L, Cho E, Hughes MD, Hu FB, Willett WC. Comparison of methods to account for implausible reporting of energy intake in epidemiologic studies. Am J Epidemiol. 2015 Feb 15;181(4):225–33.

28. Banna JC, McCrory MA, Fialkowski MK, Boushey C. Examining Plausibility of Self-Reported Energy Intake Data: Considerations for Method Selection. Front Nutr. 2017 Sep 25;4.

29. Health Council of the Netherlands. Dutch dietary guidelines for people with type 2 diabetes. The Hague; 2021.

30. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972 Jun;18(6):499–502.

31. Pols MA, Peeters PH, Ocké MC, Slimani N, Bueno-de-Mesquita HB, Collette HJ. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol [Internet]. 1997 Feb 1;26 Suppl 1(90001):S181-9.

32. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32(9 SUPPL.).

33. van Rossum CTM, Buurma-Rethans EJM, Dinnissen CS, Beukers MH, Brants HAM, Dekkers ALM, et al. The diet of the Dutch. Results of the Dutch National Food Consumption Survey 2012-2016. Bilthoven, The Netherlands; 2020.

34. Dehghan M, Mente A, Teo KK, Gao P, Sleight P, Dagenais G, et al. Epidemiology and Prevention Relationship Between Healthy Diet and Risk of Cardiovascular Disease Among Patients on Drug Therapies for Secondary Prevention A Prospective Cohort Study of 31 546 High-Risk Individuals From 40 Countries DPhil; on Behalf of the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET)/Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND) Trial Investigators. 2012;

35. Li S, Chiuve SE, Flint A, Pai JK, Forman JP, Hu FB, et al. Better diet quality and decreased mortality among myocardial infarction survivors. JAMA Intern Med. 2013 Oct 28;173(19):1808–18.

36. Sijtsma FPC, Soedamah-Muthu SS, De Goede J, Oude Griep LM, Geleijnse JM, Giltay EJ, et al. Healthy eating and lower mortality risk in a large cohort of cardiac patients who received state-of-the-art drug treatment1-3. American Journal of Clinical Nutrition. 2015 Dec 1;102(6):1527–33.

37. U.S. Department of Agriculture, U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th Edition. 2020 Dec.

38. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med [Internet]. 2018 Jun 21;378(25):e34.

39. Goldbohm RA, van 't Veer P, van den Brandt PA, van 't Hof MA, Brants HA, Sturmans F, et al. Reproducibility of a food frequency questionnaire and stability of dietary habits determined from five annually repeated measurements. Eur J Clin Nutr. 1995 Jun;49(6):420–9.

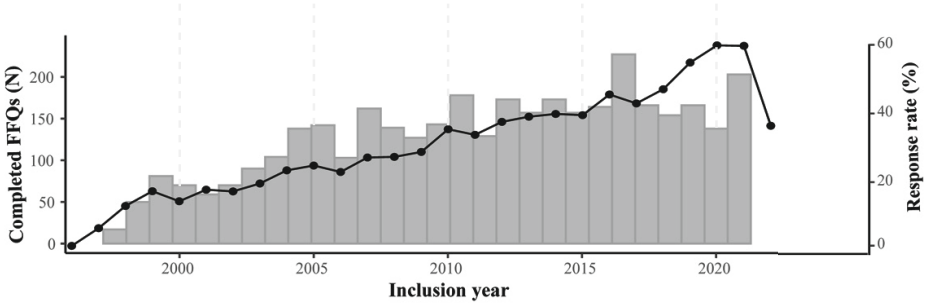
SUPPLEMENTAL MATERIAL

TABLE S1 Definitions of established CVD in the UCC-SMART study

CVD manifestation	Definition
Established CVD	Coronary artery disease, cerebrovascular disease and/or peripheral artery disease as defined below upon inclusion in the cohort.
Coronary artery disease	History of myocardial infarction (STEMI, nSTEMI), coronary syndrome requiring PCI or CABG.
Cerebrovascular disease	History of transient ischemic attack, cerebral infarction, subarachnoid hemorrhage, carotid artery stenosis or ischemic retinal syndrome.
Peripheral artery disease	Renal artery stenosis, peripheral arterial disease Fontaine classification II or higher.
Abdominal aortic aneurysm	Ultrasound confirmed local dilatation of abdominal aorta with anterior-posterior diameter ≥3 cm and/or distal-proximal ratio of >1,5

CVD: cardiovascular disease, STEMI: ST-elevation myocardial infarction, nSTEMI: non-ST-elevation myocardial infarction, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Grafting

FIGURE S1 Schematic representation of collection of dietary data in the UCC-SMART cohort



This figure illustrates the response rate to invitations for completing an online FFQ among UCC-SMART study participants who remained in active follow-up as of December 2022. The grey bars indicate the absolute number of FFQ responses with plausible energy intake and the black line represents the response rate relative to the year of initial inclusion in the UCC-SMART study. All FFQ responses were gathered between December 2022 and January 2023, while all other covariates were collected at the time of inclusion in the cohort. Abbreviations**:** FFQ: food frequency questionnaire, UCC-SMART: Utrecht Cardiovascular Cohort – Second Manifestations of ARTerial disease.

TABLE S2 Comparison of Dutch dietary guidelines to international dietary guidelines for CVD prevention and management.

Component	Dutch Health council guidelines[7]	ESC CVD prevention guidelines[2]	ACC/AHA CVD prevention guidelines[3]
Vegetable	Eat at least 200 g of vegetables daily	≥200 g of fruit per day (≥ 2-3 servings)	A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended.
Fruit	Eat at least 200 g of fruit daily	≥200 g of vegetables per day (≥ 2-3 servings)	A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended.
Wholegrains	Eat at least 90 g of wholegrain products daily and replace refined cereal products by wholegrain products	30-45 g of fibre per day, preferably from wholegrains	A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended. It is reasonable to minimize the intake of processed meats, refined carbohydrates and sweetened beverages.
Legumes	Eat at least 10 g of legumes daily	*No specific recommendation*	A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended.
Nuts	Eat at least 15 g of nuts daily	30 g unsalted nuts per day	A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended.
Dairy	Eat between 300-450 g dairy daily	*No specific recommendation*	*No specific recommendation*
Fish	Eat at least 15 g fish daily	1-2 servings per week, in particular fatty fish	A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended.
Tea	Drink at least 450 grams black or green tea/day	*No specific recommendation*	*No specific recommendation*
Fats and oil	No consumption of butter hard margarines or cooking fats OR Ratio of liquid to solid cooking fats ≥ 13	Saturated fatty acids should account for <10% of total energy intake, through replacement by PUFAs, MUFAs, and carbohydrates from wholegrains. Trans unsaturated fatty acids should be minimized as far as possible, with none from processed foods	Replacement of saturated fat with dietary MUFA and PUFA can be beneficial. A diet containing reduced amounts of cholesterol and sodium can be beneficial. The intake of *trans* fats should be avoided.
Coffee	No or only filtered coffee consumption	*No specific recommendation*	*No specific recommendation*

TABLE S2 (Continued)

Component	Dutch Health council guidelines[7]	ESC CVD prevention guidelines[2]	ACC/AHA CVD prevention guidelines[3]
Red meat	Eat less than 45 g red meat per day	Red meat should be reduced to a maximum of 350-500 g/week (50-71 g/day)	*No specific recommendation*
Processed meat	Do not eat processed meat	In particular processed meat should be minimized	It is reasonable to minimize the intake of processed meats, refined carbohydrates and sweetened beverages.
Sweetened beverages	Drink no sugar-sweetened beverages or fruit juice	Sugar-sweetened beverages, such as soft drinks and fruit juices, must be discouraged	It is reasonable to minimize the intake of processed meats, refined carbohydrates and sweetened beverages.
Alcohol	Drink less than 10 g alcohol per day	Consumption of alcohol should be limited to a maximum of 100 g/week (14 g/day)	In individuals who drink alcohol, reduce alcohol to: Men: ≤2 drinks daily, Women: ≤1 drink daily. 1 standard drink contains roughly 14 g of alcohol.
Salt	Consume less than 1.9 g sodium/day	<5 g total salt intake per day	A diet containing reduced amounts of cholesterol and sodium can be beneficial.

Comparison of Dutch Healthy diet guidelines to current international dietary guidelines for CVD prevention. **Abbreviations**: MUFA: monounsaturated fatty acid. PUFA: polyunsaturated fatty acid

TABLE S3 Endpoint definitions

Endpoint	Definition
Combined vascular endpoint	Composite of myocardial infarction and stroke
Myocardial infarction	*STEMI* Acute chest pain with persistent (>20 minutes) ST-elevation *NSTEMI* Acute chest pain without ST-elevation, with elevated troponin *Intervention-related myocardial infarction* New Q wave and elevated troponin <7 days after any intervention (for PCI >3x, for CABG >5x) *Probable myocardial infarction* Typical pain, persistent STT-changes, no documented course of cardiac enzymes
Stroke	*Ischemic stroke* >24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale and new (haemorrhagic) infarction on CT or MRI <2 weeks after stroke *Cerebral haemorrhage* Cerebral haemorrhage confirmed with CT, MRI or surgery *Subarachnoid haemorrhage* Subarachnoid haemorrhage confirmed with CT, MRI or surgery *Stroke - Type not determined* >24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale, but no brain imaging performed

All endpoints in the UCC-SMART cohort are adjudicated independently by three study physicians. Detailed information on endpoint definitions has been published previously.[23]

TABLE S4 Baseline characteristics of responders and non-responders to dietary questionnaire

	FFQ responders	FFQ non-responders	SMD
	N = 2,656	N = 6,063	
Male, N (%)	2,071 (77)	3584 (59)	0.205
Age, *year*	59.3 ±9.4	53.6 ±12.6	0.256
Education			0.238
Low	367 (14)	1057 (17)	
Low - Middle	914 (34)	2225 (37)	
Middle - High	1,224 (46)	2257 (37)	
High	151 (6)	524 (9)	
CAD	1,697 (63)	1,862 (31)	
CeVD	518 (19)	797 (13)	
Diabetes, N (%)	307 (11)	952 (16)	
Smoking status, N (%)			0.275
Never	788 (29)	1970 (33)	
Former	1,366 (51)	2429 (40)	
Current	502 (19)	1654 (27)	
Physical activity, *METh/wk*	42 [24-68]	37 [19-64]	0.012
Body mass index, kg/m^2	26.8 ±5.6	27.2 ±4.6	0.103
Systolic BP, *mmHg*	133 ±18	139 ±22	0.102
Total cholesterol, *mmol/L*	4.2 [3.6-5.0]	4.8 [4.1-5.8]	0.194
HDL-cholesterol, *mmol/L*	1.2 [1.0-1.4]	1.2 [1-1.5]	0.019
LDL-cholesterol, *mmol/L*	2.3 [1.8-3.0]	2.8 [2.2-3.7]	0.172
CRP, *mg/L*	1.6 [0.8-3.2]	1.9 [0.9-4]	0.066
Lipid-lowering therapy (%)	2,131 (79)	3275 (54)	0.187
BP-lowering therapy (%)	2,105 (78)	3922 (65)	0.114

Baseline characteristics of UCC-SMART participants that were invited to report their dietary habits, stratified for participants that plausibly completed the FFQ and participants that did not respond or reported implausible daily energy intake. SMDs were calculated to compare baseline characteristics across these groups. CVD: cardiovascular disease, CAD: coronary artery disease, CeVD: cerebrovascular disease, BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, CRP: C reactive protein, SMD: standardized mean difference.

TABLE S5 Patients characteristics for patients with less that five years between collection of patient characteristics and dietary intake data (N = 791)

	Overall	Guideline diet adherence score			
		Quartile 1 [30.8,71.2]	Quartile 2 (71.2,81.7]	Quartile 3 (81.7,92.1]	Quartile 4 (92.1,129]
	N = 791	N = 163	N = 179	N = 211	N = 238
Male, N (%)	601 (76)	139 (85)	140 (78)	159 (75)	163 (69)
Age, *year*	64.0 ±9.0	64.0 ±9.7	64.6 ±8.2	63.8 ±9.5	63.7 ±8.6
CAD, N (%)	633 (80)	128 (79)	143 (80)	167 (79)	195 (82)
CeVD, N (%)	151 (19)	41 (25)	35 (20)	34 (16)	41 (17)
Diabetes, N (%)	171 (22)	28 (17)	48 (27)	48 (23)	47 (20)
Smoking status, N (%)					
Never	257 (33)	46 (28)	57 (32)	63 (30)	91 (38)
Former	450 (57)	92 (56)	101 (57)	131 (62)	126 (53)
Current	84 (11)	25 (15)	21 (12)	17 (8)	21 (9)
Physical activity, *METh/wk*	39 [23-63]	36 [23-72]	37 [21-61]	41 [23-58]	41 [25-62]
Body mass index, *kg/m²*	26.8 ±4	27.3 ±4.4	27.3 ±3.8	26.8 ±3.8	26.2 ±4.1
Systolic BP, *mmHg*	132 ±17	133 ±16	133 ±19	133 ±17	131 ±17
Total cholesterol, *mmol/L*	3.9 [3.3-4.5]	3.9 [3.4-4.5]	3.9 [3.3-4.6]	3.9 [3.3-4.6]	3.7 [3.2-4.5]
HDL-cholesterol, *mmol/L*	1.2 [1.0-1.4]	1.2 [1.0-1.4]	1.2 [1.0-1.4]	1.2 [1.0-1.3]	1.2 [1.0-1.5]
LDL-cholesterol, *mmol/L*	2.0 [1.6-2.5]	2.1 [1.7-2.5]	2.0 [1.6-2.6]	2.0 [1.6-2.6]	2.0 [1.5-2.4]
CRP, *mg/L*	2.0 [1.0-4.0]	1.7 [1.0-3.0]	2.6 [1.0-5.0]	2.0 [1.0-4.0]	1.8 [0.9-3.3]

Baseline characteristics are presented as number (percentage), mean ± standard deviation or median [interquartile range].
CVD: cardiovascular disease, CAD: coronary artery disease, CeVD: cerebrovascular disease, BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, CRP: C reactive protein

TABLE S6 Daily nutrient intake in the UCC-SMART cohort, stratified for BMI categories and presence of manifest cardiovascular disease

	BMI < 25 kg/m² (N = 914)	**BMI 25-30 kg/m²** (N = 1,291)	**BMI >30 kg/m²** (N = 451)
Total energy intake, *kcal*	1944 [1548-2344]	1914 [1453-2351]	1847 [1432-2357]
Carbohydrate, *g*	199 [151-240]	182 [141-234]	180 [134-227]
Total fat, *g*	75 [58-96]	77 [57-96]	77 [57-100]
Protein, *g*	77 [63-95]	79 [63-98]	81 [61-100]
Dietary fiber, *g*	22 [17-28]	21 [16-27]	19 [14-25]
Alcohol, *g*	7 [1-17]	4 [0-17]	3 [0-16]
Sodium, *g*	2 [0-10]	2 [0-14]	1 [0-7]
Vegetables, *g*	119 [62-187]	121 [71-183]	95 [47-159]
Fruit, *g*	127 [62-241]	134 [50-229]	108 [31-226]
Wholegrain, *g*	35 [0-85]	30 [0-71]	24 [0-71]
Pulses and legumes, *g*			
Consumers, *N (%)*	858 (94)	1190 (92)	398 (88)
Intake among consumers, *g*	21.8 [10.9-43.5]	21.8 [10.9-35.1]	16.9 [9.7-35.1]
Nuts			
Consumers, *N (%)*	816 (89)	1,125 (87)	376 (83)
Intake among consumers, *g*	10.6 [3.5=21.6]	7.0 [2.9-18.4]	5.8 [2.0-18.0]
Dairy, *g*	265 [139-434]	259 [150-434]	265 [141-426]
Fish, *g*			
Consumers, *N (%)*	840 (92)	1,193 (92)	406 (90)
Intake among consumers, *g*	19.9 [11.4-35.2]	19.9 [1.3-33.2]	21.0 [11.3-34.8]
Meat			
Red meat, *g*	66 [34-102]	74 [43-113]	89 [57-132]
White meat, *g*	14 [7-29]	21 [11-42]	21 [9-44]
Processed meat	20.3 [7.3-40.0]	27.7 [13.6-46.4]	33.0 [16.6-56.8]
Tea, *g*	340 [31-510]	170 [13.6-340]	146.2 [3.4-340.0]
Coffee, *g*	420 [81-561]	420 [81-561]	420 [81-561]
Alcoholic beverages, *g*			
Consumers, *N (%)*	740 (81)	1,053 (82)	339 (75)
Intake among consumers, *g*	121.6 [41.0-244]	117.6 [36-250]	88.4 [21.6-28]

Daily dietary intake of (macro)nutrients and food groups, stratified for presence of established cardiovascular disease at inclusion in the cohort. SFA: saturated fatty acids, MUFA: monounsaturated fatty acids, PUFA: poly unsaturated fatty acids

TABLE S7 Relationship between DHD-15 quartiles and cardiovascular events in the full UCC-SMART cohort, with imputed dietary intake for non-responders to the FFQ

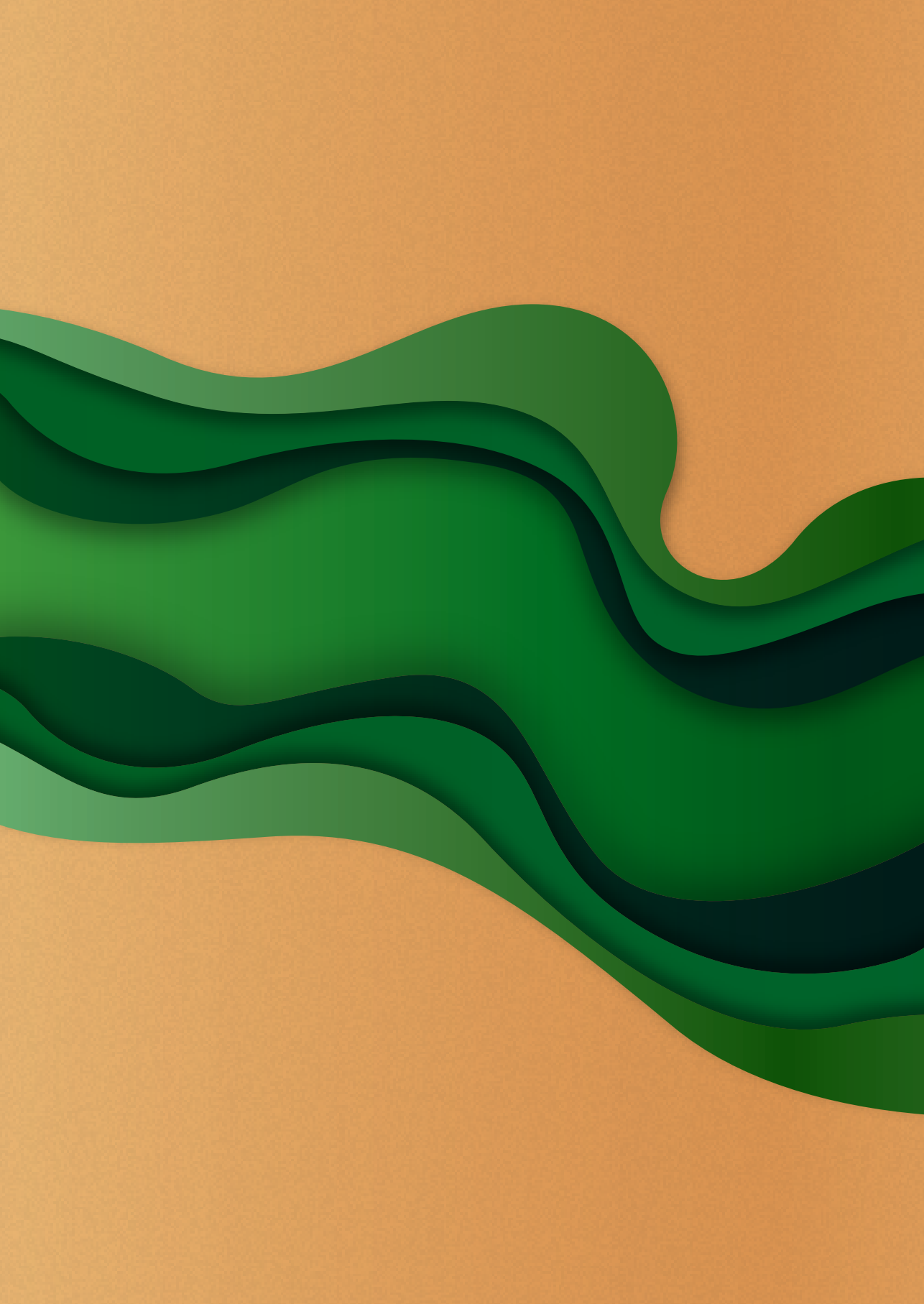
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
	30-69	69-80	80-91	91-129
Cardiovascular events				
Model 1	*Reference*	1.21 (0.86-1.70)	0.74 (0.50-1.09)	0.66 (0.43-0.99)
Model 2	*Reference*	1.20 (0.86-1.70)	0.73 (0.50-1.08)	0.67 (0.44-1.01)
Model 3	*Reference*	1.19 (0.79-1.80)	0.72 (0.44-1.16)	0.69 (0.42-1.14)
Myocardial infarction				
Model 1	*Reference*	1.31 (0.88-1.96)	0.84 (0.53-1.31)	0.79 (0.50-1.26)
Model 2	*Reference*	1.30 (0.87-1.95)	0.83 (0.53-1.31)	0.81 (0.51-1.29)
Model 3	*Reference*	1.22 (0.75-1.98)	0.72 (0.41-1.27)	0.82 (0.47-1.44)
Stroke				
Model 1	*Reference*	0.80 (0.43-1.49)	0.41 (0.19-0.90)	0.29 (0.12-0.71)
Model 2	*Reference*	0.81 (0.43-1.49)	0.42 (0.19-0.90)	0.29 (0.12-0.71)
Model 3	*Reference*	0.87 (0.41-1.84)	0.57 (0.24-1.34)	0.34 (0.12-0.95)

Model 1 adjusted for age and sex. Model 2 for model 1 + daily energy intake, education level, smoking status and physical activity level. Model 3 adjusted Model 2 + BMI, systolic blood pressure, LDL-cholesterol, triglycerides, and CRP.

TABLE S8 Association between DHD-15 quartiles and cardiovascular events, estimated using logistic regression

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Cardiovascular events				
Model 1	*Reference*	1.13 (0.79-1.62)	0.69 (0.46-1.04)	0.63 (0.41-0.95)
Model 2	*Reference*	1.18 (0.81-1.71)	0.74 (0.48-1.12)	0.70 (0.45-1.09)
Model 3	*Reference*	1.19 (0.82-1.73)	0.73 (0.48-1.12)	0.74 (0.47-1.15)
Myocardial infarction				
Model 1	*Reference*	1.18 (0.78-1.79)	0.77 (0.48-1.22)	0.75 (0.46-1.20)
Model 2	*Reference*	1.31 (0.85-2.03)	0.88 (0.54-1.42)	0.91 (0.55-1.51)
Model 3	*Reference*	1.34 (0.87-2.07)	0.88 (0.54-1.43)	0.98 (0.59-1.62)
Stroke				
Model 1	*Reference*	0.82 (0.43-1.52)	0.42 (0.18-0.88)	0.29 (0.10-0.67)
Model 2	*Reference*	0.74 (0.38-1.39)	0.37 (0.16-0.79)	0.26 (0.09-0.62)
Model 3	*Reference*	0.71 (0.37-1.34)	0.36 (0.15-0.77)	0.25 (0.09-0.59)

Model 1 adjusted for age and sex. Model 2 for model 1 + daily energy intake, education level, smoking status and physical activity level. Model 3 adjusted Model 2 + BMI, systolic blood pressure, LDL-cholesterol, triglycerides, and CRP.



CHAPTER 3

DIET IN SECONDARY PREVENTION: THE EFFECT OF DIETARY PATTERNS ON CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH CARDIOVASCULAR DISEASE

A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Nadia E. Bonekamp
Esther Cruijsen
Johanna M. Geleijnse
Renate M. Winkels
Frank L.J. Visseren
Pamela B. Morris
Charlotte Koopal

Nutrition journal, accepted for publication

ABSTRACT

Background

Improving dietary habits is a first-line recommendation for patients with cardiovascular disease (CVD). It is unclear which dietary pattern most effectively lowers cardiovascular risk factors and what the short- and long-term effects are. Therefore, this network meta-analysis compared the effects of popular dietary patterns on cardiovascular risk factors in patients with established CVD.

Methods

A systematic search of PubMed, Embase, the Cochrane library, SCOPUS and Web of Science was conducted up to 1 April 2023. Randomized controlled trials (RCTs) comparing the effect of popular dietary patterns (Mediterranean, moderate carbohydrate, low glycemic index, low-fat and minimal dietary intervention) on cardiovascular risk factors (body weight, systolic blood pressure, lipids) in CVD populations were selected. A random-effects network meta-analysis was performed.

Results

Seventeen RCTs comprising 6,331 participants were included. The moderate carbohydrate diet had the most beneficial effect on body weight (-4.6 kg, , 95%CrI -25.1; 15.8) and systolic blood pressure (-7.0 mmHg 95%CrI -16.8; 2.7) compared to minimal intervention. None of the included dietary patterns had a favourable effect on low-density lipoprotein cholesterol. After 12 months, the effects were attenuated compared to those at <6 months.

Conclusions

In this network meta-analysis of 17 randomized trials, potentially clinically relevant effects of dietary interventions on CV risk factors were observed, but there was considerable uncertainty due to study heterogeneity, low adherence, or actual diminished effects in the medically treated CVD population. It was not possible to select optimal dietary patterns for secondary CVD prevention. Given recent clinical trials demonstrating the potential of dietary patterns to significantly reduce cardiovascular event risk, it is likely that these effects are effectuated through alternative physiological pathways.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity worldwide, despite declining CVD mortality rates as a result of advances in diagnosis and management[1,2]. Consequently, an increasingly large group of patients with established CVD is at risk of recurrent cardiovascular events. The impact of a healthy diet on CVD risk is hypothesized to be multifaceted, acting either as a direct and autonomous protective factor or by favourably influencing cardiovascular risk factors, such as low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP)[3]. Embracing a healthy lifestyle, including healthy dietary habits, constitutes a central step in the primary and secondary prevention of CVD, an approach unanimously advocated by major CVD prevention guidelines. [3,4]

Previous meta-analyses have shown conflicting results on the effects of dietary intervention on markers of CVD, and the evidence is especially limited in patients with established CVD[5,6]. Current treatment guidelines for CVD patients either provide dietary recommendations that are largely extrapolated from primary prevention populations or stress the need for further research[4,7,8]. Current guideline recommendations focus on specific food groups and nutrients rather than on dietary patterns.[4,7] Focusing on dietary patterns may improve patients' understanding of dietary recommendations and more adequately capture the effects of diet-related health benefits[9]. Unfortunately, the plethora of overlapping dietary patterns complicates identification of the best dietary pattern for patients with established CVD because it would require a multitude of randomized trials.

The aim of this study was to address this problem by comparing all the available randomized controlled trials on the effect of dietary patterns on cardiovascular risk factors in patients with CVD in a network meta-analysis. This approach made it possible to provide an effect estimate even when dietary pattern interventions had never been compared in a head-to-head clinical trial.

METHODS

This systematic review and network meta-analysis was prospectively registered in the PROSPERO registry for systematic reviews (CRD42021233632).

Literature search and data extraction

A systematic literature search was performed on PubMed, Embase, the Cochrane Library, SCOPUS and Web of Science from data inception until 31 January 2022. The search was updated to cover a time range up to 1 April 2023 to ensure completeness of the results. Search terms included terms and synonyms for diet, dietary patterns, different types of CVD and RCTs. The complete search string is presented in Supplementary appendix 1.

RCTs that were performed in an adult population with established CVD (defined as a history of myocardial infarction, coronary revascularization, ischemic or haemorrhagic stroke, or peripheral arterial disease) were included. Studies were eligible if they studied the effect of an entire dietary pattern compared to an alternative dietary pattern or to a minimal dietary intervention. Changes in at least one cardiovascular risk factor over a period of at least 12 weeks should be reported as a primary or secondary endpoint. RCTs that investigated only specific food groups (*e.g.*, fruits or eggs) or specific nutrients were excluded. Studies with interventions that encompassed other components unrelated to diet, such as medication of supervised exercise, were only included if these components were applied equally to the intervention and control group (*i.e.*, both groups should receive the same medication). Eligibility was independently assessed by two authors (NEB, EC), and conflicting interpretations were resolved by consensus after inclusion of a third reviewer.

Data on study design, study population, intervention and control diet and outcomes were extracted independently by two authors (NEB, EC) using a standardized report form. Critical appraisal of the included records was independently performed by two authors (NEB, EC) using the Cochrane Risk of Bias 2 tool[10].

Dietary pattern categories

Dietary interventions were categorized into predefined dietary pattern categories:

- Mediterranean diet: a dietary pattern rich in whole grains, green vegetables, fruits, fish, lean meat and plant-based oils.

- Low-fat diet: ≤30% of total energy intake from fat.
- Moderate carbohydrate diet: 30-60% of energy from carbohydrates and 10-20% of energy from protein.
- Low glycemic index (GI) diet
- Minimal dietary intervention: no changes in dietary pattern or intervention limited to pamphlet with dietary advice.

If two dietary patterns from one study were assigned to the same diet category, the findings from this study were excluded from the quantitative synthesis.

Statistical analyses

The primary outcomes were short-term changes in body weight, SBP and LDL-C levels. Secondary outcomes were long-term changes in these three measures and short- and long-term changes in body mass index (BMI), total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride and C-reactive protein (CRP) levels. Short-term was defined as the measurement closest to 6 months after initiation of the dietary intervention (range 3-11 months), and long-term was defined as the first measurement at least 12 months after the start of the dietary intervention (range 12-18 months).

For each outcome, the mean change from baseline and corresponding standard deviation (SD) were extracted from the study paper. If other measures were reported (*e.g.*, standard error or means at baseline and after intervention), the mean change and SD were calculated in accordance with the Cochrane Handbook[11].

A network meta-analysis was performed to pool the available evidence. Bayesian hierarchical effect models were used to calculate a network estimate of the absolute change in cardiovascular risk factors. These estimates are presented as the effect of one diet *vs* another diet for all available comparisons. The transitivity assumption of the network meta-analysis was assessed based on study characteristics.

For each outcome, a network plot was made of the studies providing evidence, and a random-effects network meta-analysis with a Bayesian framework was calculated in a Monte Carlo Markov Chain simulation (4 chains, 5000 burn-in iterations, 100,000 iterations).[12,13] The convergence of the model was checked and confirmed by visual inspection of Gelman-Rubin-Brooks plots. Model fit was checked using the deviance information criterion and the posterior mean residual deviance compared to the

number of data points[14]. Heterogeneity of the results was assessed using the I^2 statistic. The consistency assumption was checked by performing node-splitting analyses to compare direct and indirect evidence and by calculating a p value for inconsistency.

Uncertainty surrounding the model estimates was reflected by 95% credible intervals (95% CrI) obtained from the 2.5th and 97.5th percentile values of the simulations. Ranking of the different dietary patterns was assessed in each iteration and presented as median ranking (2.5th – 97th percentile). The hierarchy of the different dietary patterns was summarized in the surface under the cumulative ranking curve (SUCRA)[15].

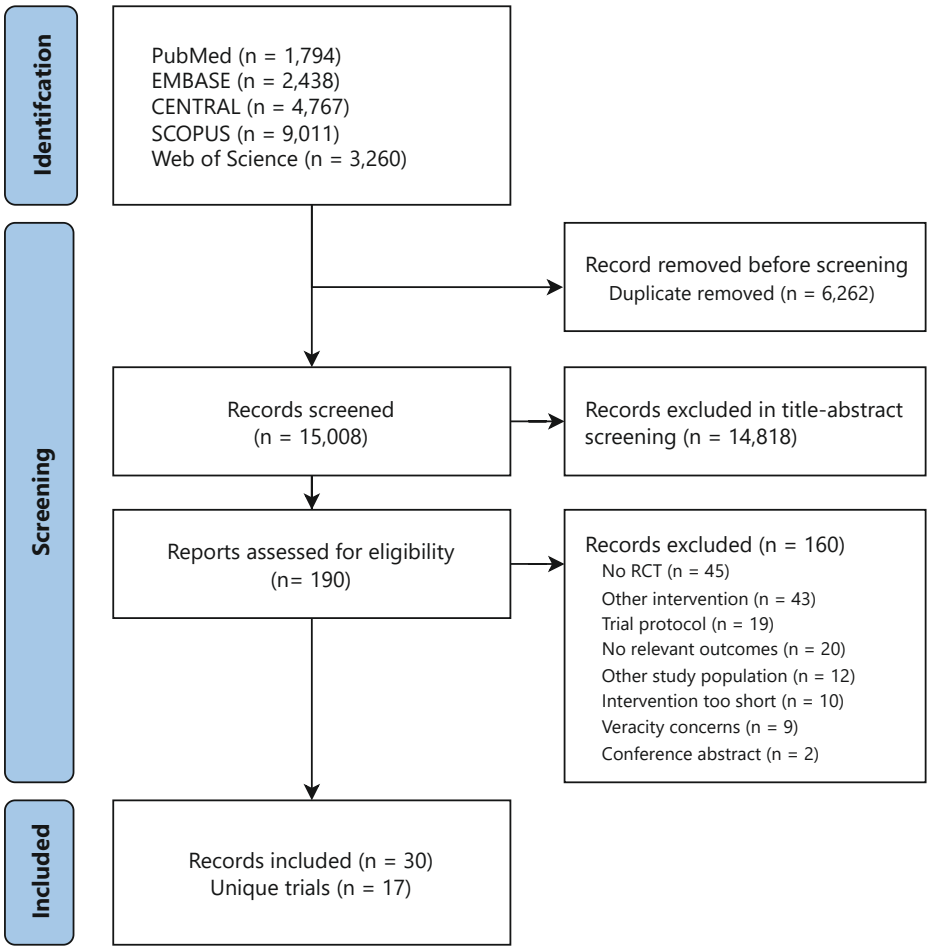
Sensitivity analyses were run to assess the effects of certain assumptions on the network estimates of the primary outcomes. A sensitivity analysis limited to studies published in or after the year 2000 was performed because results from older studies may not be generalizable to contemporary practice, as many pharmacotherapeutical interventions (*e.g.*, statins, blood pressure-lowering medication and platelet aggregation inhibitors) were not yet as commonly or intensively prescribed at that time. A second sensitivity analysis was performed including only studies that reported data for both the short- and long-term endpoints. The aim of this analysis was to assess whether the observed effects would be retained over a longer time span in the same population. A sensitivity analysis was limited to studies that assessed the effects of dietary interventions in CAD populations only (N = 15) and a final sensitivity analysis was conducted where all studies with a high risk of bias were excluded. All statistical analyses were performed using R version 4.0.4 (R Core Team, Vienna, Austria) with the gemtc package[16].

RESULTS

Systematic literature search

The systematic literature search yielded a total of 15,008 unique publications, of which, after title and abstract screening, 190 full text records were assessed for eligibility. Ultimately, 30 records [17-46] reporting on 17 unique RCTs were included (Figure 1). Two RCTs (Singh et al[44,45] and von Haehling et al[46]) were excluded from the quantitative synthesis because both the intervention and control diets from these studies were classified into the same dietary category.

FIGURE 1 PRISMA flow diagram of study selection



This flow diagram shows the process used to identify relevant records for the network meta-analysis. The systematic literature search was performed from database inception to 1 April 2023. RCT: Randomized controlled trial

TABLE 1 Eligible study description and baseline study population characteristics

Reference	Year	N	Intervention	Control	Follow-up (wk)	CVD type	Age (yr)	Female (%)	BMI (kg/m²)	SBP (mmHg)	LDL-C (mmol/l)	LLT (%)	AHT (%)
Ball[17]	1965	264	Low-fat	No intervention	*159*	CAD	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Oslo Diet Heart study[18,19]	1970	412	Moderate carb	No intervention	250	CAD	*NR*	0	*NR*	*NR*	*NR*	*NR*	*NR*
Brown[20,21]	1984	50	Moderate carb	Low-fat	52	PAD	62	26	*NR*	*NR*	4.0	*NR*	*NR*
Lyon Heart study[22–24]	1994	605	Mediterranean	No intervention	117	CAD	54	9	*NR*	*120*	*4.5*	*NR*	62
Huh[25]	1996	14	Low-fat	No intervention	52	CAD	59	14	24.3	*NR*	*3.6*	*NR*	*NR*
Aquilani[26]	1999	126	Low-fat	Moderate carb	26	CAD	57	0	*NR*	*NR*	4.6	*NR*	*NR*
Sondergaard[27]	2003	131	Mediterranean	No intervention	52	CAD	63	30	26.6	*NR*	4.0	*NR*	*NR*
Frost[28]	2004	55	Low GI	No intervention	12	CAD	62	13	27.8	NR	NR	73	25
Lindeberg[29,30]	2007	29	Low-fat	Mediterranean	12	CAD	61	0	29.5	NR	NR	90	NR
THIS-DIET trial[31]	2008	101	Mediterranean	Low-fat	104	CAD	58	26	*NR*	120	2.4	82	>88
Weber[32]	2012	124	Moderate carb	Mediterranean	12	CAD	63	34	29.9	128	NR	87	90
AUSMED study[33–35]	2018	65	Mediterranean	Low-fat	52	CAD	62	16	*NR*	137	1.9	89	*NR*
BALANCE[36–38]	2019	2,521	Moderate carb	Low-fat	182	Multiple	63	42	*NR*	*NR*	*NR*	*NR*	*NR*
DISCO-CT study[39]	2019	81	Moderate carb	No intervention	26	CAD	60	38	29	NR	NR	69	69
CORDIOPREV[40–43]	2020	805	Mediterranean	Low-fat	52	CAD	60	8	31	NR	2.3	86	63
Eligible records not included in quantitative synthesis													
Singh[44,45]	1992	406	Moderate carb	Moderate carb	36	CAD	51	10	27	*133*	*4.4*	*NR*	*NR*
Von Haehling[46]	2013	524	Moderate carb	Moderate carb	26	CAD	68	26	*NR*	138	3.4	58	*NR*

Characteristics of included studies. Study population characteristics refer to the entire study population (both intervention and control groups) before treatment initiation and are presented as mean (age, BMI, SBP and LDL-C) or proportion of the entire population (sex, LLT and AHT)
CVD: cardiovascular disease, BMI: Body mass index, Moderate carb: moderate carbohydrate, CAD: coronary artery disease, PAD: peripheral arterial disease, SBP: systolic blood pressure, LDL-C: Low-density lipoprotein cholesterol. NR: not reported. N=number of included patients. Additional information on study population and intervention and reference diet are provided in table S2

Study characteristics and risk of bias assessment

Table 1 summarizes the main study characteristics of the 17 included RCTs. Additional information on the study design, population and dietary pattern interventions is presented in Table S1. Studies were published between 1965 and 2020 and comprised a total of 6,331 participants. Sixteen studies included patients with a history of coronary artery disease, and one included patients with a history of peripheral arterial disease. The median age was 61 (interquartile range (IQR) 57-62) years, and the median percentage of female participants was 17% (IQR 8-30%, range 0-61%). The use of antihypertensive and/or lipid-lowering therapy increased with more recent publications, with median percentages of 76% (IQR 53-90%) and 86% (IQR 73-87%), respectively, in studies published before and after 2000. No detailed information was available on the type of blood-pressure or lipid-lowering medications study participants used.

The risk of bias assessment yielded a judgment of *some concerns* for the majority of the included studies, with only two records judged to be at low risk of bias (Figure S1). This risk of bias was mostly attributable to the fact that participants could not be blinded to treatment allocation and to the unavailability of pre-published study protocols available for older studies.

Effects of dietary patterns on cardiovascular risk factors

Figures 2, S2 and S3 show the networks of eligible studies for the primary and secondary outcomes. Compared to the minimal change diet, the moderate carbohydrate diet showed the largest reductions in body weight (-4.6 kg, 95%CrI-25.1;15.8) and SBP (-7.0 mmHg, 95%CI -16.8; 2.7), while increasing LDL-C (0.6 mmol/L, 95%CrI -0.4; 1.4). None of the dietary patterns lowered LDL-C compared to a minimal dietary intervention. The results for all pairwise comparisons can be found in Figure S5. The moderate carbohydrate pattern had the best ranking for body weight and SBP, and the low GI diet ranked best for LDL-C (Figure S6). None of the dietary patterns had a statistically significant short-term effect on body weight, BMI, SBP or LDL-C (Figure 3/Figure S4).

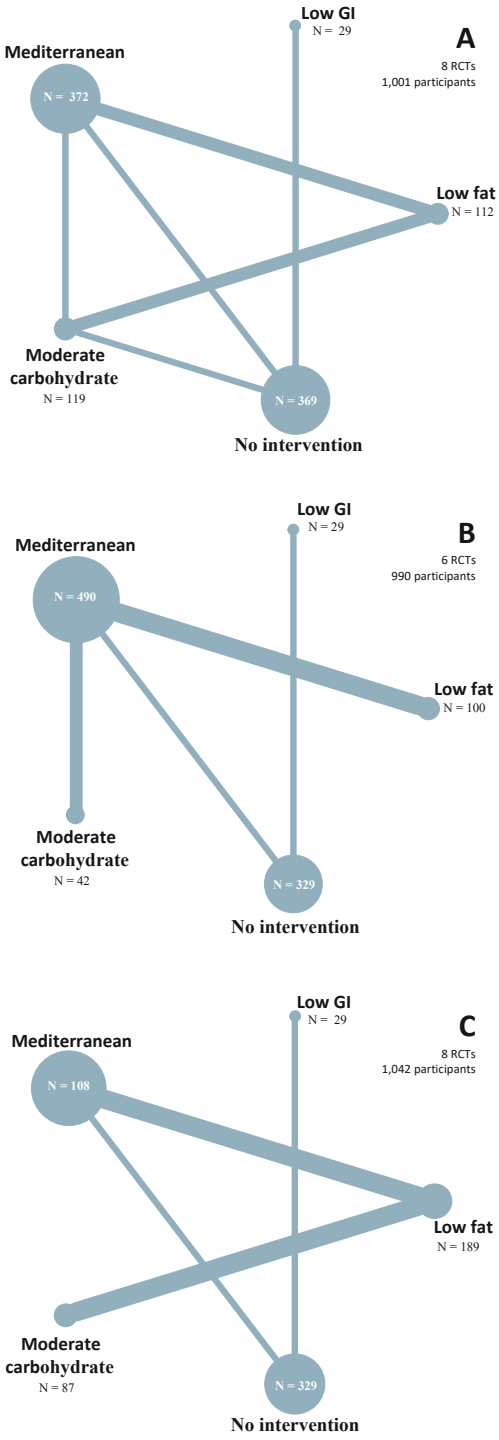
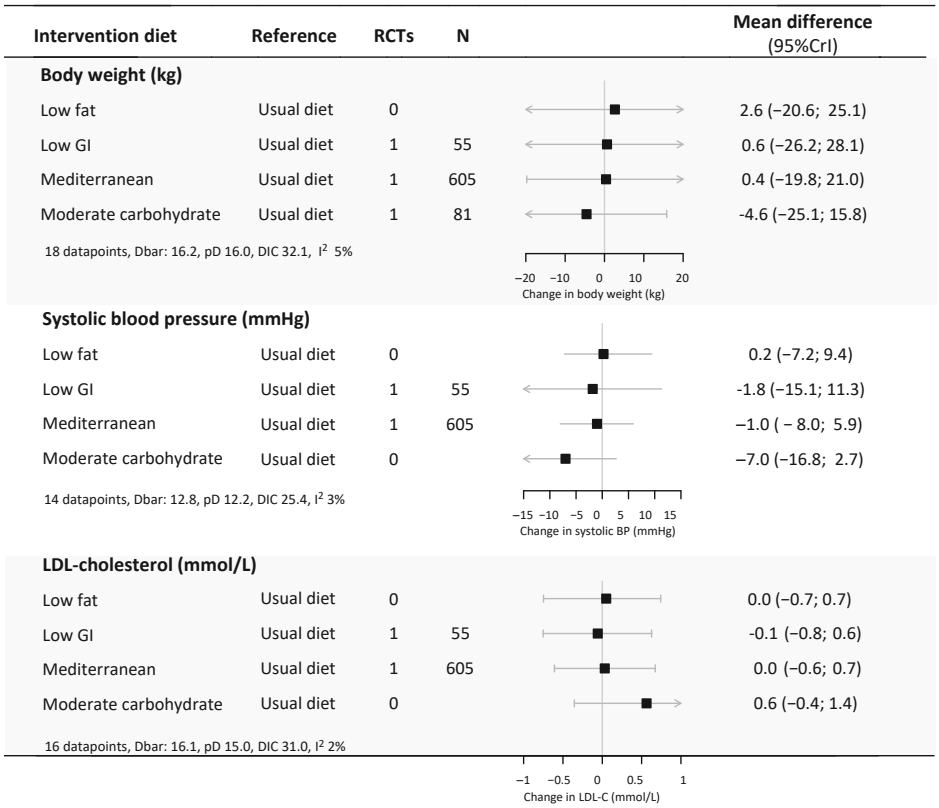


FIGURE 2 Network plots for body weight (A), systolic blood pressure (B) and LDL-cholesterol (C) after 6 months.

For each endpoint, the number of clinical trials assessing the endpoint and number of participants are presented. The node sizes represent the number of participants randomized to a dietary pattern, and edge thickness is proportionate to the number of trials with a direct comparison between two dietary patterns. Abbreviations: RCT: randomized controlled trial, GI: glycemic index.

FIGURE 3 Short-term effects of dietary patterns on body weight, SBP and LDL cholesterol

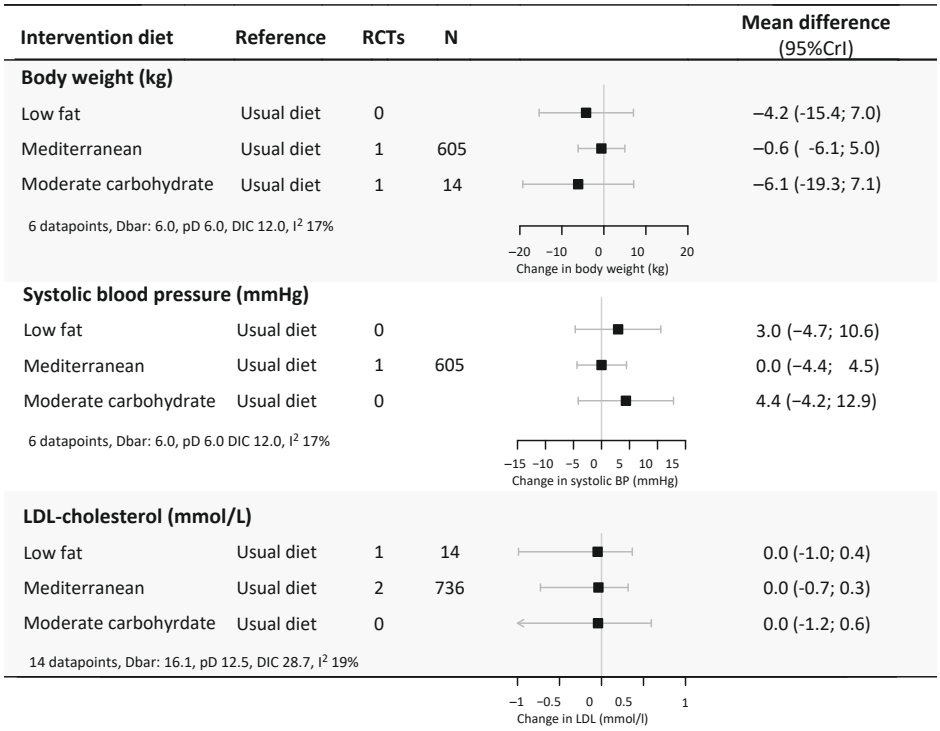


This figure shows the network estimates for the 6-month difference in effect on body weight, systolic blood pressure and LDL cholesterol levels for all possible pairwise dietary comparisons. The first column shows the intervention diet and the second column shows the reference diet. The column 'Direct comparisons' presents the number of trials in which a diet was directly compared to another diet, and the 'N' column presents the total number of participants included in these trials. Zero direct comparisons mean that the presented network estimate is based on indirect evidence alone. Abbreviations: RCT: randomized controlled trial, CI: credible interval, Moderate carb: moderate carbohydrate, SBP: systolic blood pressure, LDL-C: low-density lipoprotein cholesterol

At >12 months, the moderate carbohydrate and low-fat diets resulted in a decrease in body weight (-6.1 kg (95%CrI-19.3;7.1) and -4.2 kg (95%CrI 15.4;7.0), respectively) and an increase in SBP (4.4 mmHg (95%CrI -4.2;12.9) and 3.0 mmHg (95%CrI -4.7;10.6), respectively) compared to minimal dietary intervention. The results for all pairwise comparisons and corresponding rankings are presented in Figures S5 and S6. No statistically significant long-term (>12 months) differences were observed with all head-to-head comparisons (Figure 4). Figure S5 shows the corresponding ranking of the different treatments.

For the secondary outcomes, the low-fat diet had the most beneficial effect on total cholesterol (-0.6 mmol/l, 95%CrI -1.4; 0.3, Figure S5). The low GI diet decreased triglycerides the most (-0.3 mmol/l, 95%CrI -1.2; 0.6). A low-fat diet reduced CRP compared to a Mediterranean diet (-0.3 mg/L, 95%CrI -1.4;0.6), but only one study was available. None of the effects on secondary outcomes was statistically significant for the short or long term (Figure S4).

FIGURE 4 Long-term effects of dietary patterns on body weight, SBP and LDL cholesterol



This figure shows the network estimates for the 12-month difference in effect on body weight, systolic blood pressure and LDL cholesterol levels for all possible pairwise dietary comparisons. The first column shows the intervention diet and the second column shows the reference diet. The column 'Direct comparisons' presents the number of trials in which a diet was directly compared to another diet, and the 'N' column presents the total number of participants included in these clinical trials. Zero direct comparisons mean that the presented network estimate is based on indirect evidence alone. Abbreviations: RCT: randomized controlled trial, CI: credible interval, Moderate carb: moderate carbohydrate, SBP: systolic blood pressure, LDL-C: low-density lipoprotein cholesterol.

Sensitivity analyses

After excluding studies published before 2000, the effects on body weight, SBP and LDL-C were comparable to those found in the complete dataset (Figure S6). Only three RCTs published after 2000 reported an effect on LDL-C levels, and the results were similar to those of the RCTs published before 2000. The tendency toward an increasing effect of a moderate carbohydrate diet on LDL-C was not seen in this sensitivity analysis.

In networks comprising only studies that reported on both short- and long-term effects, overall, the results were similar. However, the low-fat diet showed a tendency to decrease body weight and increase SBP, both in the short and long term. In particular, the short-term effect of a low-fat diet on body weight was larger than that in the main analysis (Figure S7). In this subset, LDL-C levels were similar in both the long and short term, although they were closer to zero in the long term (Figure S7). Sensitivity analysis limited to patients with CAD or excluding studies with a high risk of bias yielded non-statistically significant results, similar to the main analysis (Figure S8, Figure S9).

DISCUSSION

In this systematic review and network meta-analysis of 17 RCTs comprising 6,331 patients with established CVD, no significant effect on cardiovascular risk factors was found for interventions with a low-fat, Mediterranean, low GI or moderate carbohydrate dietary pattern compared to a minimal dietary intervention in patients with CVD.

This study is the first network meta-analysis on dietary patterns in patients with CVD. However, similar analyses have been performed in populations at high risk of CVD. These studies showed similar effect estimates for different CVD risk factors, albeit with smaller confidence intervals and more statistically significant findings.[47,48] One network meta-analysis in overweight and obese populations showed that low carbohydrate, low-fat and moderate macronutrient diets were associated with clinically relevant and statistically significant reductions in body weight up to -4.6 kg and blood pressure up to -5.0 mmHg compared to the usual diet[47]. Our study showed similar short-term effects for the moderate carbohydrate pattern on SBP, but not body weight, and smaller effects for other dietary patterns. Another network meta-analysis in patients

with type 2 diabetes showed that the Mediterranean diet was effective in reducing body weight and LDL cholesterol, but no effect of other dietary patterns was found.[49]

There are multiple potential explanations for the wide credibility intervals around the effects of dietary patterns on CVD risk factors. First, it is conceivable that the effect of diet is smaller in CVD populations than in patients without CVD because the administration of lipid-lowering and antihypertensive medications to CVD patients might limit the potential influence of dietary interventions on lipid and blood pressure profiles.

Second, the quantity and quality of the available evidence might be insufficient to find a statistically significant effect. Fifteen of 17 included studies were judged as 'some concerns' in the risk of bias assessment, specifically stemming from the inability to blind participants to the intervention. This may have inadvertently led patients in the control groups to adopt certain components of the intervention in the intervention group, which leads to an underestimation of the effect. Additionally, the number of trials available for this network meta-analysis may have been too small to show statistically significant evidence. For example, although we found similar effects of a moderate carbohydrate dietary pattern on SBP as studies in persons without CVD,[47] our results had wide credibility intervals and were therefore not statistically significant.

A third explanation for the absence of an effect might be rooted in low adherence to the dietary patterns in the included trials. Although the majority of the included RCTs did not explicitly measure or report adherence to the dietary pattern intervention, it is reasonable to assume that adherence decreased over time. Low compliance rates are a major issue, especially in long-term dietary trials, where a significant proportion of participants return to their original dietary pattern[48] if not regularly counseled[50]. Therefore, strategies to increase adherence may be more important for obtaining meaningful cardiovascular benefits than the specific macronutrient composition of the dietary pattern itself.

Fourth, amelioration of traditional risk factors probably does not capture the full effect of dietary interventions on cardiovascular event risk. Alternative pathways could be low-grade inflammation, lipid composition and vascular function. Moreover, the cumulative effect of small improvements in individual risk factors may translate into a more considerable decrease in overall CVD risk. Further research is needed

to elucidate the mediating pathways between dietary pattern interventions and cardiovascular risk reduction.

The findings of the current study stand in contrast with previous observational and experimental studies on the relationship between dietary patterns and occurrence of cardiovascular events, especially on the Mediterranean diet.[51] Long-term randomized controlled trials such as the Lyon diet heart study, the PREDIMED study and the CORDIOPREV trial demonstrated a beneficial effect of a Mediterranean diet compared to low-fat diets in both primary and secondary CVD prevention populations and resulted in 30-50% relative risk reduction of (recurrent) cardiovascular events.[24,43,52] Interestingly the CORDIOPREV trial found non-significant changes in intermediate endpoints such as weight, LDL-cholesterol and systolic blood pressure.[43] The present study also suggests that the beneficial effects of dietary patterns may not primarily be achieved through reduction of such traditional cardiovascular risk factor levels. While the diets included in this analysis have different macronutrient distributions, generally they all recommend sufficient fruit and vegetable intake and consumption of fish and other products rich in unsaturated fatty acids. These dietary components are known to mitigate systemic inflammation, offering a plausible explanation for the discordance between the current findings and those of previous long-term studies.[53] Moreover, the emphasis on home-cooked, whole-food items within nearly all dietary patterns in this network meta-analysis could elucidate why none outperformed the others. In contrast, diets rich in ultra-processed foods, characterized by low nutritional value and elevated sodium and trans-fatty acid content, have been associated with an increased risk of cardiovascular disease.[54,55]

For the implementation of dietary interventions in the clinical management of CVD patients, a shift towards assessing their impact on cardiovascular event risk is recommended, as opposed to focusing solely on cardiovascular risk factor levels. The current analysis underscores that efficacy with regard to these endpoints does not directly align with efficacy on cardiovascular event risk. Furthermore, in patients with established CVD, the inclusion of non-traditional cardiovascular risk factors such as CRP as trial outcomes in dietary pattern trials should be considered as these could provide more informative insights into efficacy concerning cardiovascular event risk.[43]

Strengths of this study include the systematic literature search and the selection of only RCTs to limit the impact of bias. Moreover, network meta-analysis techniques

allowed for combining direct and indirect evidence, which increases power and enables comparison of interventions that have not been directly compared in an RCT. Finally, a wide range of cardiovascular risk factors was examined. Study limitations include that some outcome measures had to be manually calculated because not all included studies reported their outcomes as the mean differences, and these calculations may be less accurate. We used strict selection criteria in the systematic literature search to ensure applicability of the results to our target population, but as a result, few studies met the eligibility criteria, leading to wide credibility intervals. Furthermore, the limited number of studies prevented extensive sensitivity and subgroup analysis, such as analyses to assess the impact of sex, concomitant use of medication or the type of counselling provided in the included trials. Ethnic background may affect the metabolic response to dietary intervention,[56] but the majority of studies included in this analysis (13 out of 17) were conducted in European and North American countries and ethnicity was rarely reported. This may limit the generalizability of the findings to populations in other countries. Finally, the included studies showed considerable heterogeneity in study characteristics, such as sex distribution and medication use, and the limited number of RCTs prevented adjustment for such sources of heterogeneity. However, careful node-splitting analyses gave no indication that the consistency assumption was violated, meaning that the heterogeneity between different RCTs did not result in conflicts between direct and indirect evidence.

To solidify the role of dietary counselling in clinical care for patients with established CVD, further research is necessary to adequately assess the effect of dietary patterns and their mediating pathways in preventing CVD outcomes in patients with CVD. Another point of interest should be how to improve long-term adherence to a healthy dietary pattern.

CONCLUSION

In this network meta-analysis of 17 randomized trials, there was not one single best dietary pattern, and long-term effects were attenuated. The nonsignificant findings might be explained by inadequate sample size, diminished dietary effects in CVD populations, low adherence, or mediation by other pathways. To answer this question, more randomized trials are needed that focus on the protective effects of diet on CVD outcomes in CVD populations.

REFERENCES

1. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 Nov 10;392(10159):1736–88.
2. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: A report from the American Heart Association. Circulation. 2020. 139–596 p.
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;74(10):e177–232.
4. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J [Internet]. 2021 Sep 7;42(34):3227–337.
5. Doughty KN, Del Pilar NX, Audette A, Katz DL. Lifestyle Medicine and the Management of Cardiovascular Disease. Curr Cardiol Rep. 2017;19(11).
6. Rees K, Takeda A, Martin N, Ellis L, Wijesekara D, Vepa A, et al. Mediterranean-Style Diet for the Primary and Secondary Prevention of Cardiovascular Disease: A Cochrane Review. Glob Heart. 2020;15(1):56.
7. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, a. J Am Coll Cardiol. 2014;64(18):1929–49.
8. Virani SS, Newby LK, Arnold S V., Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation [Internet]. 2023 Jul 20;
9. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol [Internet]. 2002 Feb;13(1):3–9.
10. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. The BMJ. 2019;366:1–8.
11. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 [Internet]. Cochrane. 2020 [cited 2020 Nov 19]. Available from: www.training.cochrane.org/handbook.
12. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med. 2002;21(16):2313–24.
13. Salanti G, Higgins JPT, Ades AE, Ioannidis JPA. Evaluation of networks of randomized trials. Stat Methods Med Res. 2008;17(3):279–301.

14. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010;29(7–8):935–44.

15. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. J Clin Epidemiol. 2011;64(2):163–71.

16. van Valkenhoef G, Kuiper J. gemtc: Network Meta-Analysis Using Bayesian Methods. 2020.

17. A Research Committee. LOW-FAT DIET IN MYOCARDIAL INFARCTION. The Lancet [Internet]. 1965 Sep 11;286(7411):501–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4158171

18. Leren P. The effect of plasma-cholesterol-lowering diet in male survivors of myocardial infarction. A controlled clinical trial. Bull N Y Acad Med. 1968 Aug;44(8):1012–20.

19. Leren P. The Oslo diet-heart study. Eleven-year report. Circulation [Internet]. 1970 Nov;42(5):935–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/5477261

20. Hutchinson K, Oberle K, Crockford P, Grace M, Whyte L, Gee M, et al. Effects of dietary manipulation on vascular status of patients with peripheral vascular disease. JAMA. 1983 Jun;249(24):3326–30.

21. Brown GD, Whyte L, Gee MI, Crockford PM, Grace M, Oberle K, et al. Effects of two "lipid-lowering" diets on plasma lipid levels of patients with peripheral vascular disease. J Am Diet Assoc [Internet]. 1984 May;84(5):546–50.

22. de Lorgeril M, Renaud S, Salen P, Monjaud I, Mamelle N, Martin JL, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. The Lancet [Internet]. 1994 Jun;343(8911):1454–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673694925801

23. Renaud S, De Lorgeril M, Delaye J, Guidollet J, Jacquard F, Mamelle N, et al. Cretan Mediterranean diet for prevention of coronary heart disease. American Journal of Clinical Nutrition. 1995;61(6 SUPPL.).

24. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779–85.

25. Huh KB, Lee HC, Cho SY, Lee JH, Song YD. The role of insulin resistance in Korean patients with coronary atherosclerosis. Diabetes. 1996;45(3 SUPPL.):59–61.

26. Aquilani R, Tramarin R, Pedretti RFE, Bertolotti G, Sommaruga M, Mariani P, et al. Despite good compliance, very low fat diet alone does not achieve recommended cholesterol goals in outpatients with coronary heart disease. Eur Heart J. 1999;20(14):1020–9.

27. Søndergaard E, Møller JE, Egstrup K. Effect of dietary intervention and lipid-lowering treatment on brachial vasoreactivity in patients with ischemic heart disease and hypercholesterolemia. Am Heart J [Internet]. 2003 May;145(5):E19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12766751

28. Frost GS, Brynes AE, Bovill-Taylor C, Dornhorst A. A prospective randomised trial to determine the efficacy of a low glycaemic index diet given in addition to healthy eating and weight loss advice in patients with coronary heart disease. Eur J Clin Nutr. 2004 Jan;58(1):121–7.

29. Lindeberg S, Jönsson T, Granfeldt Y, Borgstrand E, Soffman J, Sjöström K, et al. A Palaeolithic diet improves glucose tolerance more than a Mediterranean-like diet in individuals with ischaemic heart disease. Diabetologia. 2007;50(9):1795–807.

30. Jönsson T, Granfeldt Y, Erlanson-Albertsson C, Ahrén B, Lindeberg S. A paleolithic diet is more satiating per calorie than a mediterranean-like diet in individuals with ischemic heart disease. Nutr Metab (Lond) [Internet]. 2010;7. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L51176845&from=export

31. Tuttle KR, Shuler LA, Packard DP, Milton JE, Daratha KB, Bibus DM, et al. Comparison of Low-Fat Versus Mediterranean-Style Dietary Intervention After First Myocardial Infarction. American Journal of Cardiology. 2008;101(11):1523–30.

32. Weber B, Galante AP, Bersch-Ferreira AC, Torreglosa CR, Carvalho VO, Victor E da S, et al. Effects of Brazilian Cardioprotective Diet Program on risk factors in patients with coronary heart disease: A Brazilian Cardioprotective Diet randomized pilot trial. Clinics. 2012;67(12):1407–14.

33. Mayr HL, Thomas CJ, Tierney AC, Kucianski T, George ES, Ruiz-Canela M, et al. Randomization to 6-month Mediterranean diet compared with a low-fat diet leads to improvement in Dietary Inflammatory Index scores in patients with coronary heart disease: the AUSMED Heart Trial. Nutrition Research [Internet]. 2018;55:94–107. Available from: https://doi.org/10.1016/j.nutres.2018.04.006

34. Mayr HL, Itsiopoulos C, Tierney AC, Kucianski T, Radcliffe J, Garg M, et al. Ad libitum Mediterranean diet reduces subcutaneous but not visceral fat in patients with coronary heart disease: A randomised controlled pilot study. Clin Nutr ESPEN. 2019 Aug;32:61–9.

35. Mayr HL, Tierney AC, Kucianski T, Thomas CJ, Itsiopoulos C. Australian patients with coronary heart disease achieve high adherence to 6-month Mediterranean diet intervention: preliminary results of the AUSMED Heart Trial. Nutrition. 2019 May;61:21–31.

36. Weber B, Bersch-Ferreira ÂC, Torreglosa CR, Marcadenti A, Lara ES, da Silva JT, et al. Implementation of a Brazilian Cardioprotective Nutritional (BALANCE) Program for improvement on quality of diet and secondary prevention of cardiovascular events: A randomized, multicenter trial. Am Heart J. 2019 Sep;215:187–97.

37. Bersch-Ferreira AC, Hall WL, Santos RHN, Torreglosa CR, Sampaio G, Tereza da Silva J, et al. The effect of the a regional cardioprotective nutritional program on inflammatory biomarkers and metabolic risk factors in secondary prevention for cardiovascular disease, a randomised trial. Clin Nutr. 2021 Jun;40(6):3828–35.

38. Coura AGL, Arruda Neta A da CP de, Lima RLFC de, Bersch-Ferreira ÂC, Weber B, Vianna RP de T. Tracking of Dietary Patterns in the Secondary Prevention of Cardiovascular Disease after a Nutritional Intervention Program—A Randomized Clinical Trial. Nutrients. 2022 Nov 1;14(22).

39. Makarewicz-Wujec M, Henzel J, Kruk M, Kępka C, Wardziak Ł, Trochimiuk P, et al. DASH diet decreases CXCL4 plasma concentration in patients diagnosed with coronary atherosclerotic lesions. Nutrition, Metabolism and Cardiovascular Diseases. 2020;30(1):56–9.

40. Roncero-Ramos I, Rangel-Zuñiga OA, Lopez-Moreno J, Alcala-Diaz JF, Perez-Martinez P, Jimenez-Lucena R, et al. Mediterranean Diet, Glucose Homeostasis, and Inflammasome Genetic Variants: The CORDIOPREV Study. Mol Nutr Food Res. 2018 May;62(9):e1700960.

41. Yubero-Serrano EM, Fernandez-Gandara C, Garcia-Rios A, Rangel-Zuñiga OA, Gutierrez-Mariscal FM, Torres-Peña JD, et al. Mediterranean diet and endothelial function in patients with coronary heart disease: An analysis of the CORDIOPREV randomized controlled trial. Rahimi K, editor. PLoS Med [Internet]. 2020 Sep 9;17(9):e1003282. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2008016195&from=export

42. Podadera-Herreros A, Alcala-Diaz JF, Gutierrez-Mariscal FM, Jimenez-Torres J, Cruz-Ares S de la, Arenas-de Larriva AP, et al. Long-term consumption of a mediterranean diet or a low-fat diet on kidney function in coronary heart disease patients: The CORDIOPREV randomized controlled trial. Clinical Nutrition. 2022 Feb 1;41(2):552–9.

43. Delgado-lista J, Alcala-diaz JF, Torres-peña JD, Quintana-navarro GM, Fuentes F, Garcia-rios A, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet. 2022;399:1876–85.

44. Singh RB, Ghosh S, Singh R. Effects on serum lipids of adding fruits and vegetables to prudent diet in the Indian Experiment of Infarct Survival (IEIS). Cardiology. 1992;80(3–4):283–93.

45. Singh RB, Rastogi SS, Niaz MA, Ghosh S, Singh R, Gupta S. Effect of fat-modified and fruit- and vegetable-enriched diets on blood lipids in the Indian Diet Heart Study. Am J Cardiol. 1992 Oct 1;70(9):869–74.

46. von Haehling S, Stellos K, Qusar N, Gawaz M, Bigalke B. Weight reduction in patients with coronary artery disease: comparison of Traditional Tibetan Medicine and Western diet. Int J Cardiol. 2013 Sep 30;168(2):1509–15.

47. Ge L, Sadeghirad B, Ball GDC, Da Costa BR, Hitchcock CL, Svendrovski A, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: Systematic review and network meta-analysis of randomised trials. The BMJ. 2020;369.

48. Bonekamp NE, van Damme I, Geleijnse JM, Winkels RM, Visseren FLJ, Morris PB, et al. Effect of Dietary Patterns on Cardiovascular Risk Factors in People with Type 2 Diabetes. A Systematic Review and Network Meta-Analysis. Diabetes Res Clin Pract. 2022 Dec;110207.

49. Pan B, Wu Y, Yang Q, Ge L, Gao C, Xun Y, et al. The impact of major dietary patterns on glycemic control, cardiovascular risk factors, and weight loss in patients with type 2 diabetes: A network meta-analysis. J Evid Based Med. 2019;12(1):29–39.

50. Vilaro MJ, Staub D, Xu C, Mathews AE. Theory-Based Interventions for Long-Term Adherence to Improvements in Diet Quality: An In-depth Review. Am J Lifestyle Med. 2016;10(6):369–76.

51. Karam G, Agarwal A, Sadeghirad B, Jalink M, Hitchcock CL, Ge L, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. BMJ. 2023;

52. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med [Internet]. 2018 Jun 21;378(25):e34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29897866

53. Stromsnes K, Correas AG, Lehmann J, Gambini J, Olaso-Gonzalez G. Anti-Inflammatory Properties of Diet: Role in Healthy Aging. Biomedicines. 2021 Jul 30;9(8):922.

54. Juul F, Vaidean G, Lin Y, Deierlein AL, Parekh N. Ultra-Processed Foods and Incident Cardiovascular Disease in the Framingham Offspring Study. J Am Coll Cardiol. 2021 Mar;77(12):1520–31.

55. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Méjean C, Andrianasolo RM, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). BMJ. 2019 May 29;l1451.

56. Thomas J. Nutrition intervention in ethnic minority groups. Proceedings of the Nutrition Society. 2002 Nov 5;61(4):559–67.

SUPPLEMENTAL MATERIAL

Supplementary appendix 1 Search strategy

The presented search string was used in PubMED from database inception until April 1, 2023. The same search string was used in EMBASE, The Cochrane library, Web of Science and SCOPUS after alterations were made to meet their respective search engines.

("alkaline"[Title/Abstract] OR "atkins"[Title/Abstract] OR "biggest loser"[Title/Abstract] OR "bulletproof"[Title/Abstract] OR ("DART"[Title/Abstract] OR "Reinfarction trial"[Title/Abstract]) OR ("DASH"[Title/Abstract] OR "Dietary approach to stop hypertension"[Title/Abstract]) OR "drinking man*"[Title/Abstract] OR "Dukan"[Title/Abstract] OR "Engine"[Title/Abstract] OR ("F-plan"[Title/Abstract] OR "F2"[Title/Abstract]) OR "Fertility diet"[Title/Abstract] OR "FODMAP"[Title/Abstract] OR "Hamptons"[Title/Abstract] OR "High Protein"[Title/Abstract] OR "HMR"[Title/Abstract] OR "Jenny Craig"[Title/Abstract] OR "keto*"[Title/Abstract] OR "LEARN"[Title/Abstract] OR ("low carb*"[Title/Abstract] OR "carbohydrate restr*"[Title/Abstract] OR "restricted carb*"[Title/Abstract]) OR ("low fat"[Title/Abstract] OR "fat free"[Title/Abstract] OR "fat restrict*"[Title/Abstract] OR ("restrict*"[All Fields] AND "lipid"[Title/Abstract])) OR "low glycemic index"[Title/Abstract] OR ("low salt"[Title/Abstract] OR "low sodium"[Title/Abstract] OR "salt restrict*"[Title/Abstract] OR "saltless"[Title/Abstract] OR "sodium free"[Title/Abstract]) OR "Mayo clinic diet"[Title/Abstract] OR "McDougal"[Title/Abstract] OR "Mediterranean"[Title/Abstract] OR "MIND"[Title/Abstract] OR "Nordic diet"[Title/Abstract] OR "Nutrisystem"[Title/Abstract] OR "Ornish"[Title/Abstract] OR "Okinawa"[Title/Abstract] OR "Optavia"[Title/Abstract] OR "paleo*"[Title/Abstract] OR "Pioppi"[Title/Abstract] OR "Plant-based"[Title/Abstract] OR "Portfolio diet"[Title/Abstract] OR "Pritikin"[Title/Abstract] OR "Protein power"[Title/Abstract] OR "Rosedale"[Title/Abstract] OR "Rosemary Conley"[Title/Abstract] OR "Salisbury"[Title/Abstract] OR "Scarsdale"[Title/Abstract] OR "slimming world"[Title/Abstract] OR "South beach"[Title/Abstract] OR "Stillmann"[Title/Abstract] OR "Sugar busters"[Title/Abstract] OR ("TLC"[Title/Abstract] OR "Therapeutic lifestyle changes"[Title/Abstract]) OR "Vegetarian"[Title/Abstract] OR "vegan"[Title/Abstract] OR "Volumetrics"[Title/Abstract] OR "Western diet"[Title/Abstract] OR ("weight watcher*"[Title/Abstract] OR "weightwatcher*"[Title/Abstract]) OR "ZONE"[Title/Abstract] OR "American Heart Association"[Title/Abstract] OR "Cardiac diet"[Title/

Abstract] OR "Cardioprotective"[Title/Abstract] OR "Dietary guidelines"[Title/Abstract] OR "Dietary index"[Title/Abstract] OR "eating pattern*"[Title/Abstract] OR "eating plan*"[Title/Abstract] OR "Guidance"[Title/Abstract] OR "Healthy diet index"[Title/Abstract] OR "Healthy diet score"[Title/Abstract] OR "Nutrition therapy"[Title/Abstract] OR "Nutritional therapy"[Title/Abstract] OR "Prudent diet"[Title/Abstract] OR "Usual diet"[Title/Abstract]) AND ("diet"[MeSH Terms] OR "diet*"[Title/Abstract] OR "nutrition*"[Title/Abstract]) AND ("coronary disease"[Title/Abstract] OR "coronary heart disease"[Title/Abstract] OR "coronary artery disease"[Title/Abstract] OR "ischemic heart disease"[Title/Abstract] OR "myocardial infarction"[Title/Abstract] OR "angina"[Title/Abstract] OR "cardiac arrest"[Title/Abstract] OR "PCI"[Title/Abstract] OR "CABG"[Title/Abstract] OR "Percutaneous coronary intervention"[Title/Abstract] OR "coronary artery bypass graft"[Title/Abstract] OR ("cerebrovascular disease"[Title/Abstract] OR "stroke"[Title/Abstract] OR "cerebral haemorrhage"[Title/Abstract] OR "cerebrovascular accident"[Title/Abstract]) OR ("peripheral arterial disease"[Title/Abstract] OR "peripheral artery disease"[Title/Abstract]) OR ("AAA"[Title/Abstract] OR "abdominal aortic aneurysm"[Title/Abstract]) OR ("cardiovascular disease"[Title/Abstract] OR "CVD"[Title/Abstract] OR "vascular diseases"[MeSH Terms])) AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR

"randomized controlled trial"[Title/Abstract] OR "Clinical trial"[Title/Abstract])

TABLE S1 Baseline characteristics of studies included in the systematic review and network meta-analysis

				Intervention diet		Reference diet		
Study	**Population**	**Country**	**Study follow-up (weeks)**	**Description**	**Behavioral support**	**Description**	**Behavioral support**	**Sources of funding**
Ball, 1965	264 males, <65 y, recently recovered from first MI	United Kingdom	159	Reduced fat. Low-fat dietary regimen with <40 g fat / day. Reduced caloric intake for overweight patients.	NR	Usual diet. Reduced caloric intake for overweight patients.	NR	Supported by the research committee of the North West Regional Hospital Board and by the Medical Research Council.
Oslo Diet Heart study, 1970	412 males, 30- 64 y with first MI 1-2 prior inclusion.	Norway	260	Moderate carb. Cholesterol lowering diet low in animal fats and dietary cholesterol, rich in vegetable oil.	NR	Usual diet.	NR	NR
Brown, 1984	50 patients (26% female) with confirmed PAD of the lower extremities, symptoms of intermittent claudication, nonexistent or stable CHD and no insulin requirement.	Canada	52	Moderate carb. Low cholesterol, modified fat American Heart Association Hyperlipidemia Diet C. Individualized to achieve optimal weight. Limit alcohol as much as possible and restrict salt intake	4 days of intense training with a relative in small group sessions.	Reduced fat. High fiber, low cholesterol, very low fat diet based on the Pritikin maintenance diet. Individualized to achieve optimal weight. Limit alcohol as much as possible and restrict salt intake.	4 days of intense training with a relative in small group sessions.	Supported by the Medical Services Research Foundation of Alberta and the Special Services and Research Committee, University of Alberta Hospital, Edmonton, Alberta, Canada.
Lyon Heart study, 1994	605 patients (9.3% female), <70 y with MI < 6 months prior inclusion.	France	117	Mediterranean. Increased bread, root and green vegetables, fish. Less meat (beef, lamb, and pork to be replaced with poultry), no day without fruit. Butter and cream to be replaced with provided margarine. Moderate alcohol consumption in the form of wine was allowed.	1 h dietary counselling session by cardiologist and dietician. Reinforced after 8 weeks, then annually.	Usual diet. No dietary advice apart from that of hospital dieticians or attending physicians.	NR	Supported by grants from INSERM (Reseau Clinique), Ministry of Research (Aliments 2000 and 2002), CNAMTS, CETIOM, and ONIDOL, Astra-Calve BSN, and the Fondation pour la Recherche Medicale.

TABLE S1 (Continued)

Study	Population	Country	Study follow-up (weeks)	Intervention diet		Reference diet		Sources of funding
				Description	Behavioral support	Description	Behavioral support	
Huh, 1996	14 patients (16% female) with angiographically documented CAD.	South Korea	52	Reduced fat. Low-fat, low-cholesterol diet. Fat <10% of daily caloric intake, cholesterol <50 mg/d. Caloric restriction. Instructed to eliminate alcohol intake.	NR	Usual diet. Asked not to make dietary or lifestyle changes.	NR	
Aquilani, 1999	126 males with coronary heart disease and serum LDL-c above 3.37 mmol/L.	Italy	26	Reduced fat. Hypocaloric diet with energy intake equal to their resting energy expenditure. Wine consumption was optimal with 200 ml / d limit.	NR	Moderate carb. National Cholesterol Education Program (NCEP) Step 2. Hypocaloric diet with energy intake equal to their resting energy expenditure. Wine consumption was optimal with 200 ml / d limit.	NR	NR
Sondergaard, 2003	131 patients (30% female), 18-80 y with documented IHD (recent MI or unstable angina pectoris or stable angina pectoris and serum cholesterol ≥5 mmol/L.	Denmark	52	Mediterranean. Advice to eat ≥600 g of fruits and vegetables, modify fat intake from meat and dairy, eat fatty fish ≥1x per week, plenty of bread and cereals. Replace refined, hard animal margarine with vegetable oils.	Dietary advice by MSc in clinical nutrition. Advice based on 24-h recall.	Usual diet. Leaflet on healthy heart diet.	Single visit to dietician, not included in the study.	Supported by AstraZeneca

TABLE S1 (Continued)

				Intervention diet		Reference diet		
Study	**Population**	**Country**	**Study follow-up (weeks)**	**Description**	**Behavioral support**	**Description**	**Behavioral support**	**Sources of funding**
Frost, 2004	55 volunteers, aged between 30-70 years with a history of myocardial infarction, unstable angina or angiographically proved CAD.	United Kingdom	12	Healthy eating advice with weight loss advice if indicated and the use of at least one LGI food (<85 reference to white bread) at each meal.	One-to one counselling supported with regular visits and telephone calls.	Healthy dietary pattern based on the guidelines advocated by the COMA panel (1994). Target energy intake: 50% carbohydrate and 35% from fat.	One-to one counselling supported with regular visits and telephone calls.	NR
Lindeberg, 2007	29 males with WC > 94 cm and increased blood glucose. One of following conditions: acute coronary syndrome, history of MI, PCI or CABG or angiographically diagnosed coronary stenosis.	Sweden	12	Reduced fat. Paleolithic diet based on lean meat, fish, fruits, leafy and cruciferous vegetables, root vegetables (restricted amounts of potatoes), eggs and nuts. Advised not to consume >1 glass of wine. Avoid beer.	NR	Mediterranean. Consensus diet based on whole-grain cereals, low-fat dairy products, potatoes, legumes, vegetables, fruits, fatty fish and fats rich in monounsaturated fatty acids. Advised not to consume >1 glass of wine.	NR	Study was funded by Region Skåne and Lund University.
THIS-DIET trial, 2008	101 patients (26% female) <6 weeks after first MI.	United States of America	104	Mediterranean. Reduce saturated fat calories ≤7% and cholesterol to ≤200 mg/day and increase omega-3 fatty acids and mono-unsaturated fatty acids. Recommended increased intake of fruit, vegetables and whole grains with an emphasis on cold-water fish (3-5 times / wk) and oils from olives, canola and soybeans. Caloric restriction for patients with BMI > 25.	Individual counselling sessions. 6 different group sessions focused on behavioral modification and practical aspects of the assigned diets.	Reduced fat. Reduce saturated fat calories ≤7% and cholesterol to ≤200 mg/day. Recommended increased intake of fruit, vegetables and whole grains. Caloric restriction for patients with BMI > 25	6 different group sessions focused on behavioral modification and practical aspects of the assigned diets.	Supported by a Nutrition Grant from the Washington State Attorney General Vitamins Settlement Fund and intramural or in-kind support from the investigator's sponsoring institutions, The Heart Institute Spokane and Providence Medical Research Center, Sacred Heart Medical Center, Spokane, Washington, and Deaconess Medical Center, Spokane, Washington.

TABLE S1 (Continued)

				Intervention diet		Reference diet		
Study	**Population**	**Country**	**Study follow-up (weeks)**	**Description**	**Behavioral support**	**Description**	**Behavioral support**	**Sources of funding**
Weber, 2012	122 patients (34% female) with established or previous atherothrombotic CVD and at least one additional risk factor.	Brazil	182	Moderate carb. Brazilian cardioprotective diet. Avoid high energy dense food. Culturally accepted diet. Caloric restriction for patients with BMI > 25. 2000 mg/d of sodium was recommended	Weekly training sessions with dieticians.	Mediterranean. Usual diet with Mediterranean components. Caloric restriction for patients with BMI > 25. 2000 mg/d of sodium was recommended	Weekly training sessions	Funded by the Brazilian Ministry of Health (Programma Hospitais de Excelencia a Serviço do SUS).
AUSMED Heart study, 2018	56 adult patients (16% female) with CHD (acute MI, angina pectoris with documented CAD, CABG or PCI.	Australia	52	Mediterranean. Daily intake of extra virgin olive oil, nuts, vegetables, fruit and wholegrain cereals, regular intakes of legumes, fish and yogurt and limited intake of commercial sweets or pastries and red or processed meat. Moderation of poultry, eggs and feta cheese. For participants choosing to consume alcohol, red wine was suggested to drink in moderation (1-2 glasses /d) with meals.	3 face-to-face counselling sessions and 5 telephone counselling sessions.	Reduced fat. Daily intake of grains and cereals (mostly whole grains, 5-7 servings /day), vegetables (5-6 servings /day), fruit (2 servings / day), high-protein foods (2-3 servings /day) and low-fat dairy (2 servings /day.	3 face-to-face counselling sessions and 5 telephone counselling sessions.	This work was supported by La Trobe University (Understanding Disease RFA Start-Up Grant, 2013, the Australian Government Research Training Program Scholarship and a Northern Health PhD Scholarship and the United States National Institute for Diabetes, Digestive and Kidney Diseases (grant no. R44DK103377).
BALANCE, 2019	2534 Patients, aged 45 years or older with established CVD (CAD, CeVD or PAD)	Brazil	182 (median follow-up)	Macronutrient intake: 50%- 60% of energy from carbohydrates, 10%-15% from proteins, 25%-35% from total fat. A cookbook of regional Brazilian modified recipes (o reduce SFA, dietary cholesterol, and sodium concentration) was also devised and given to the participants as an educational tool.	Individual sessions with a registered dietitian every 6 months for 2 years.	Dietary pattern in accordance with current guidelines for CVD	Folder with foods that should be preferred or avoided	Funded by Hospital do Coração (HCor) as part of the "Hospitais de Excelência a Serviço do SUS (PROADI-SUS)" Program, in partnership with the Brazilian Ministry of Health

TABLE S1 (Continued)

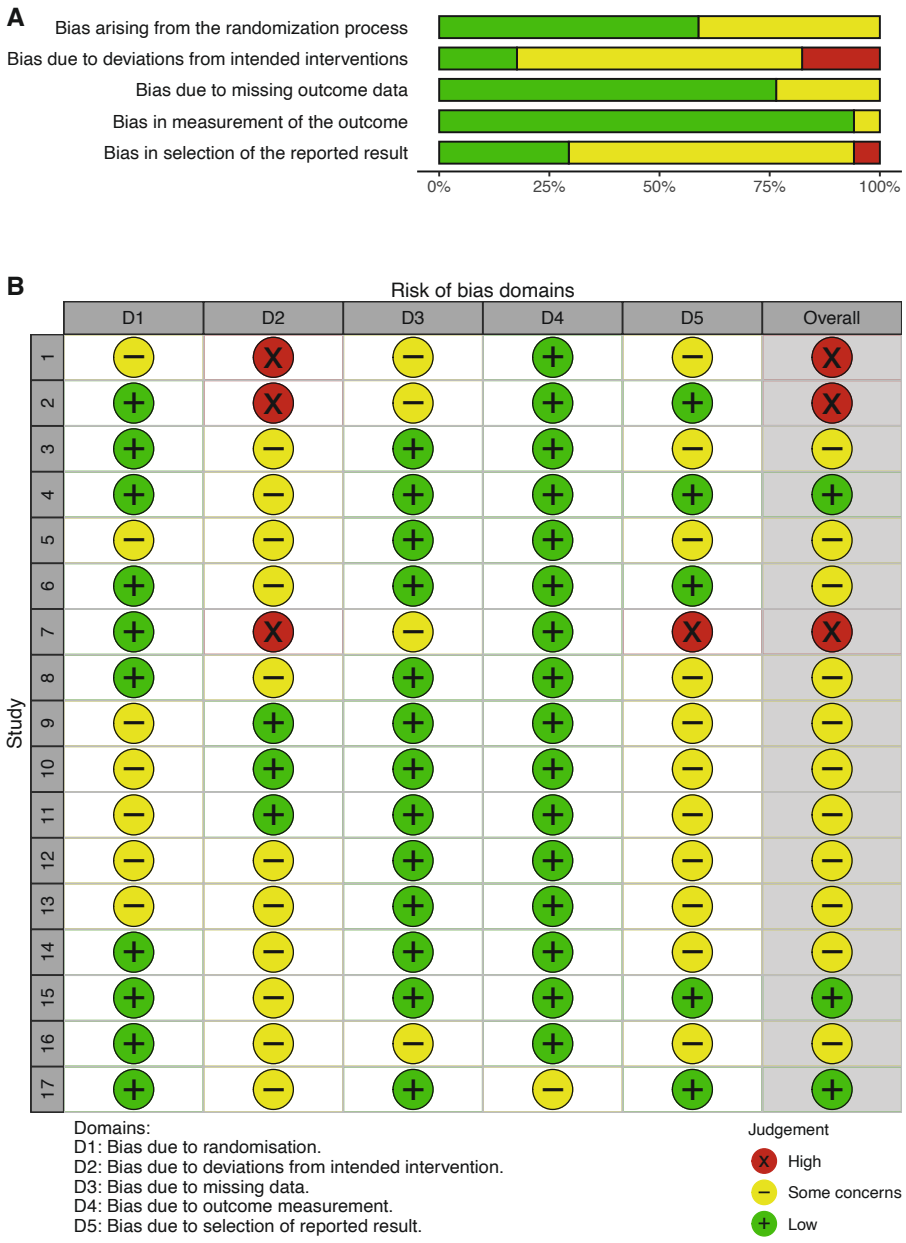
				Intervention diet		Reference diet		
Study	**Population**	**Country**	**Study follow-up (weeks)**	**Description**	**Behavioral support**	**Description**	**Behavioral support**	**Sources of funding**
DISCO-CT study, 2019	91 patients (38% female) with stable coronary artery disease	Poland	26	DASH is focused on reduced sodium intake.	Six dietary counselling sessions within 6 months	Standard of care in accordance with the 2013 ESC Guidelines on the Management of Stable Coronary Artery Disease. No specific dietary counseling.	NR	This work was supported by a grant (2.15/III/15) from the Institute of Cardiology in Warsaw, Poland.
CORDIOPREV, 2020	805 patients (8% female) aged 20-75 with established CHD, without clinical events in <6 months	Spain	52	Mediterranean. Mediterranean diet, abundant use of virgin olive oil, vegetables, fresh fruit, legumes, fish, fresh nuts and seeds, reduction in meat, avoid additional fats.	Intensive dietary counselling. Personal interviews at baseline and at 6 months. Group education sessions 4x per year.	Reduced fat. Low fat diet, recommended by the National Cholesterol Education program and the AHA.	Intensive dietary counselling. Personal interviews at baseline and at 6 months. Group education sessions 4x per year.	The CORDIOPREV study was supported by the Fundacion Patrimonio Comunal Olivarero, Consejerı´a de Economı´a, Innovacio´n, Ciencia y Empleo and Ministerio de Ciencia e Innovacio´n, integrated into the framework ofthe National Plan For Scientific Research,Technological evelopment and Innovation 2013-2016, co-financed by the Instituto de Salud Carlos III (ISCIII) of Spain and also by the Directorate General for Assessment and Promotion of Research and the EU's European Regional Development Fund (FEDER). It was also partly supported by the U.S. Department of Agriculture (

TABLE S1 (Continued)

				Intervention diet		Reference diet		
Study	**Population**	**Country**	**Study follow-up (weeks)**	**Description**	**Behavioral support**	**Description**	**Behavioral support**	**Sources of funding**
Von Haehling, 2013	524 patients (26% female) with manifest CAD and MBS	Germany	26	Moderate carb. Tibetan diet, high-protein, and vitamin-rich food, preferably cooked and warm food.	Personal dietary and behavioral advice according to assigned diet.	Moderate carb. AHA prudent Western diet, balanced carbohydrate, low-fat, dietary fiber food, fresh fruit and vegetables (steamed or raw), polyunsaturated fatty acids.	Personal dietary and behavioral advice according to assigned diet. one calls	The study was supported by the German Cardiac Society (DGK) molecular imaging of atherosclerotic plaques' and in part by Klinische Forschergruppe KFO274 — 'Platelets, Molecular Mechanisms and Translational Medicine'
Singh, 1992	406 patients (10% female) with acute MI, possible acute MI or unstable AP.	India	52	Moderate carb. AHA healthy heart diet + additional fruits, vegetables, pulses, nuts. Mainly vegetarian diet with eggs 4-5 times / week and meat 1-2 times / wk.	Dietary advice was regularly enforced	Moderate carb. AHA healthy heart diet. Mainly vegetarian diet with eggs 4-5 times / week and meat 1-2 times / wk	Left to usual care after initial advice.	NR

AHA = American Heart Association, AP = Angina pectoris, BMI = Body mass index, CABG = Coronary artery bypass graft, CAD = Coronary artery disease, carb = Carbohydrate, CETIOM = Centre Technique Interprofessionnel des oléagineux Métropolitains, CHD = Coronary heart disease, CNAMTS = French National Health Insurance Fund for Salaried Workers, COMA = Committee on Medical Aspects of Food and Nutrition Policy, CVD = Cardiovascular disease, DASH = Dietary approaches to stop hypertension, ESC = European Society of Cardiology, IHD = Ischemic heart disease, INSERM = Institut national de la santé et de la recherche médicale, LDL = Low-density lipoprotein, LGI = Low glycemic index, MBS = Metabolic syndrome, MI = myocardial infarction, MSc = Master of science, NR = Not reported, ONIDOL = Organisation Nationale Interprofessionnelle des Oléagineux , PAD = Peripheral arterial disease, PCI = Percutaneous Coronary Intervention, SFA = Saturated fatty acid

FIGURE S1 Risk of Bias assessment



Risk of bias was determined using the Cochrane risk of Bias 2 tool. Study numbers refer to: 1: Aquilani 1999, 2: AUSMED Heart study, 3: Ball 1965, 4. BALANCE, 5: Brown 1984, 6: CORDIOPREV trial, 7 DISCO-CT trial, 8: Frost, 2004, 9: Huh 1997, 10: Lindeberg 2007, 11: Lyon Heart study, 12: Oslo diet heart trial, 13: Sondergaard 2003, 14: THIS-DIET trial, 15: Weber 2012, 16: Singh 2013, 17: Von Haehling 2013.

FIGURE S2 Network plots for short-term outcomes

For each endpoint, the number of clinical trials assessing the endpoint and number of participants are presented. The node sizes represent the number of participants randomized to a dietary pattern, and edge thickness is proportionate to the number of trials with a direct comparison between two dietary patterns. RCT: randomized controlled trial, GI: glycemic index, carb: carbohydrate, HDL: high-density lipoprotein

Figure S2a Body mass index

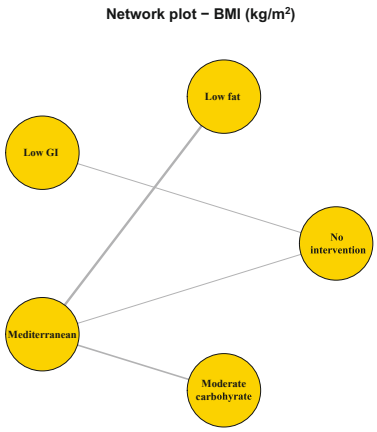


Figure S2b Total cholesterol

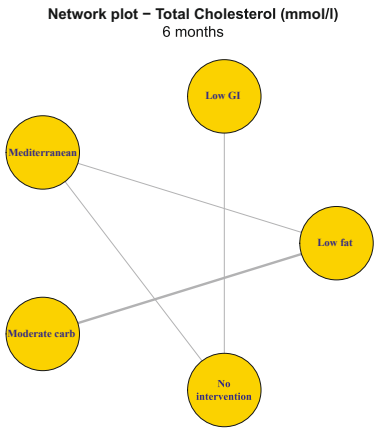


Figure S2c HDL-cholesterol

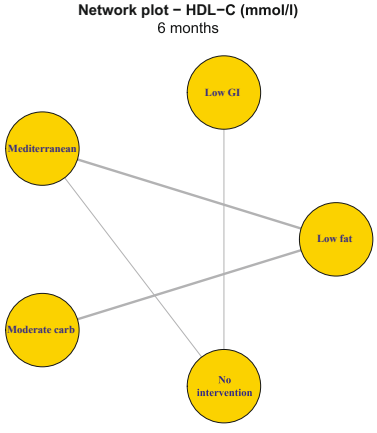


Figure S2d Triglycerides

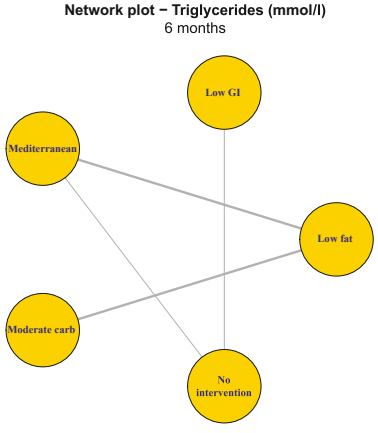


Figure S2e C reactive protein

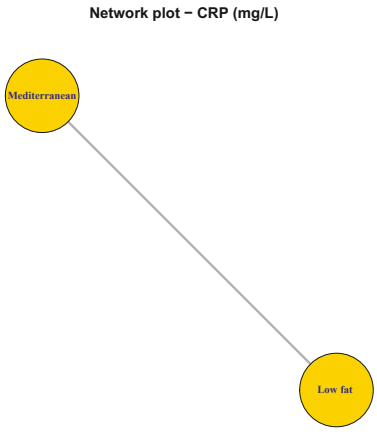


FIGURE S3 Network plots for long-term outcomes

For each endpoint, the number of clinical trials assessing the endpoint and number of participants are presented. The node sizes represent the number of participants randomized to a dietary pattern, and edge thickness is proportionate to the number of trials with a direct comparison between two dietary patterns. RCT: randomized controlled trial, GI: glycemic index, carb: carbohydrate, HDL: high-density lipoprotein

Figure S3a Body weight

Figure S3b Body mass index

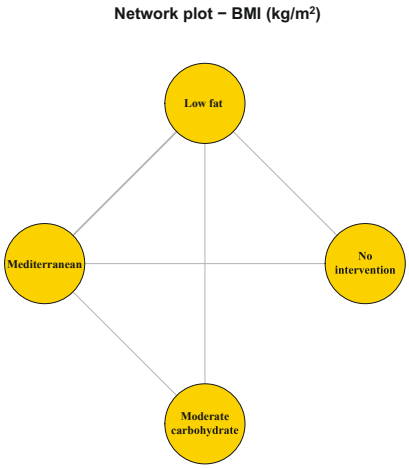


Figure S3c Systolic blood pressure

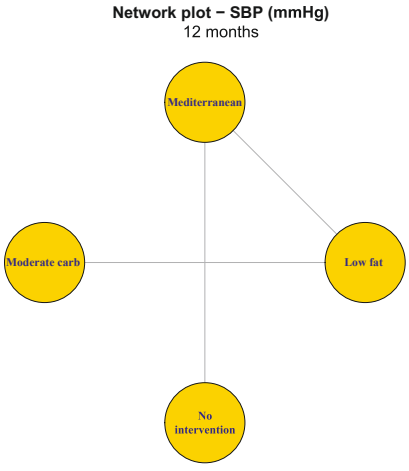


Figure S3d Total Cholesterol

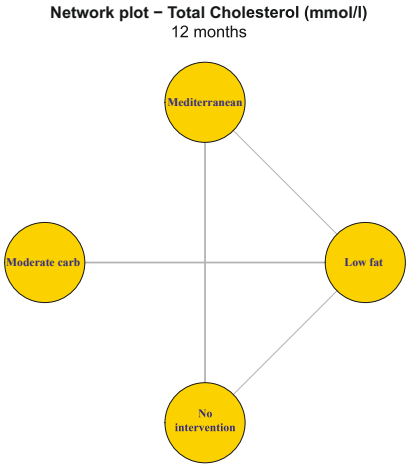


Figure S3e LDL-Cholesterol

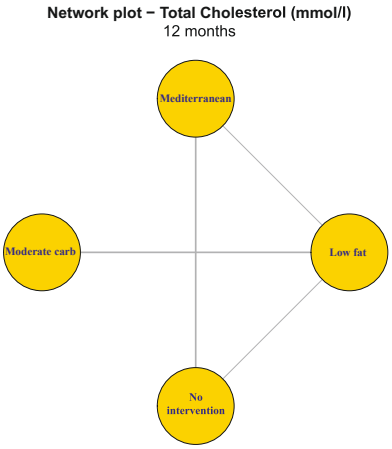


Figure S3f HDL-cholesterol

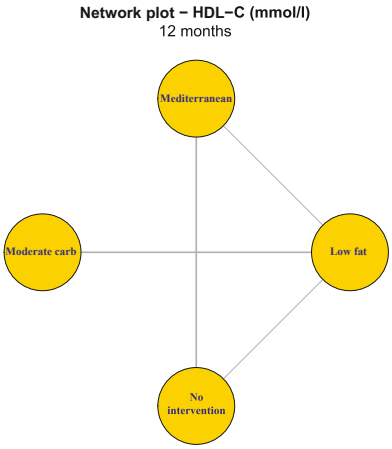


Figure S3g Triglycerides

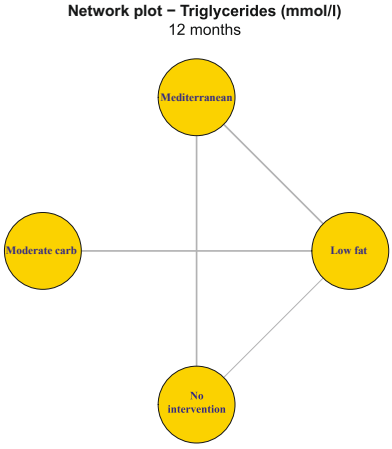


FIGURE S4 League tables of the network estimates for the short- and long- term effects of dietary pattern on cardiovascular risk factors

Values correspond to the mean difference in reduction and corresponding 95% credibility interval in the outcomes for the dietary pattern in the column compared to the dietary pattern in the row. Values below and left of the dietary patterns represent changes at 6 months after diet initiation and values above and right of the dietary patterns represent changes at least 12 months after diet initiation. Carb: carbohydrate, GI: glycemic index, LDL: low-density lipoprotein, 95%CrI: 95% Credibility interval

FIGURE S4a Mean differences in body weight (kg)

		Mean difference (95%CrI) after 12 months			
Mean difference after 6 months (95% CrI)	**Low fat**	*NA*	3.6 (-8.9, 16.1)	-1.9 (-8.8, 5.0)	4.2 (-7.0, 15.4)
	1.9 (-34.1, 37.3)	**Low GI**	NA	NA	NA
	2.2 (-13.5, 17.7)	0.3 (-33.6, 34.3)	**Mediterranean**	-5.5 (-19.7, 8.6)	0.6 (-5.0, 6.1)
	7.2 (-8.4, 22.8)	5.4 (-28.2, 39.4)	5.0 (-11.7, 21.7)	**Moderate carb**	6.1 (-7.1, 19.3)
	2.6 (-20.6, 25.1)	0.6 (-26.2, 28.1)	0.4 (-19.8, 21.0)	-4.6 (-25.1, 15.8)	**No intervention**

FIGURE S4b Mean differences in body mass index (kg/m^2)

		Mean difference (95%CrI) after 12 months			
Mean difference after 6 months (95% CrI)	**Low fat**	*NA*	-0.1 (-0.8; 0.5)	-0.1 (-0.9; 0.7)	0.4 (-0.6; 1.4)
	-0.5 (-2.9; 2.0)	**Low GI**	*NA*	*NA*	*NA*
	0.0 (-1.0; 0.9)	0.4 (-1.9; 2.7)	**Mediterranean**	0 (-1.0; 1.0)	0.5 (-0.3; 1.3)
	0.4 (-2.0; 2.9)	0.8 (-2.4; 4.2)	0.4 (-1.8; 2.7)	**Moderate carb**	0.5 (-0.7; 1.7)
	-0.2 (-1.6; 1.3)	0.3 (-1.8; 2.4)	-0.1 (-1.2; 1.0)	-0.5 (-3.1; 2.0)	**No intervention**

FIGURE S4c Mean differences in systolic blood pressure (mmHg)

		Mean difference (95%CrI) after 12 months			
Mean difference after 6 months (95% CrI)	**Low fat**	*NA*	-3.0 (-9.2, 3.3)	1.4 (-2.6, 5.3)	-3.0 (-10.6, 4.7)
	2.3 (-12.6, 18.2)	**Low GI**	*NA*	*NA*	*NA*
	1.2 (-2.5, 6.8)	-0.9 (-15.6, 13.9)	**Mediterranean n**	4.4 (-3.0, 11.6)	0.0 (-4.5, 4.4)
	7.4 (-0.3, 16.3)	5.1 (-11.2, 21.6)	6.0 (-0.9, 13.0)	**Moderate carb**	-4.4 (-12.9, 4.2)
	0.2 (-7.2, 9.4)	-1.8 (-15.1, 11.3)	-1.0 (-8.0, 5.9)	-7.0 (-16.8, 2.7)	**No intervention**

FIGURE S4d Mean differences in total cholesterol (mmol/l)

		Mean difference (95%CrI) after 12 months			
Mean difference after 6 months (95% CrI)	**Low fat**	*NA*	0.2 (-0.6, 1.5)	0.0 (-0.9, 1.0)	0.3 (-0.4, 1.8)
	-0.5 (-1.6, 0.7)	**Low GI**	*NA*	*NA*	*NA*
	-0.4 (-1.1, 0.3)	0.0 (-0.8, 0.9)	**Mediterranean**	-0.1 (-1.8, 1.0)	0.0 (-0.6, 1.0)
	-0.1 (-0.5, 0.3)	0.3 (-0.8, 1.5)	0.3 (-0.5, 1.1)	**Moderate carb**	0.2 (-0.8, 2.1)
	-0.6 (-1.4, 0.3)	0.0 (-0.8, 0.6)	-0.1 (-0.7, 0.4)	-0.4 (-1.4, 0.5)	**No intervention**

FIGURE S4e Mean differences in low density lipoprotein-cholesterol (mmol/l)

		Mean difference (95%CrI) after 12 months			
Mean difference after 6 months (95% CrI)	**Low fat**	NA	0.0 (-0.4, 0.7)	0.0 (-0.6, 0.6)	0.0 (-0.4, 1.0)
	0.1 (-1.0, 1.1)	**Low GI**	NA	NA	NA
	0.0 (-0.4, 0.3)	0.0 (-1.0, 0.8)	**Mediterranean**	0.0 (-0.9, 0.7)	0.0 (-0.3, 0.7)
	-0.5 (-0.9, 0.0)	-0.6 (-1.6, 0.5)	-0.5 (-1.0, 0.1)	**Moderate carb**	0.0 (-0.6, 1.2)
	0.0 (-0.7, 0.7)	0.0 (-0.8, 0.6)	0.0 (-0.6, 0.7)	0.6 (-0.4, 1.4)	**No intervention**

FIGURE S4f Mean differences in high density lipoprotein-cholesterol (mmol/l)

		Mean difference (95%CrI) after 12 months			
Mean difference after 6 months (95% CrI)	**Low fat**	NA	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.1 (0.0, 0.1)
	0.0 (-0.3, 0.2)	**Low GI**	NA	NA	NA
	0.0 (-0.1, 0.1)	0.0 (-0.2, 0.2)	**Mediterranean**	0.0 (-0.1, 0.1)	0.0 (0.0, 0.1)
	0.1 (-0.0, 0.2)	0.1 (-0.2, 0.4)	0.1 (0.0, 0.2)	**Moderate carb**	0.0 (-0.1, 0.1)
	0.0 (-0.2, 0.1)	0.0 (-0.2, 0.1)	0.0 (-0.2, 0.1)	-0.1 (-0.3, 0.1)	**No intervention**

FIGURE S4g Mean differences in triglycerides (mmol/l)

		Mean difference (95%CrI) after 12 months			
Mean difference after 6 months (95% CrI)	**Low fat**	*NA*	-0.1 (-0.7, 0.4)	0.0 (-0.5, 0.9)	-0.0 (-0.7, 0.7)
	0.5 (-1.7, 2.7)	**Low GI**	*NA*	*NA*	*NA*
	0.2 (-0.3, 0.7)	-0.3 (-2.5, 1.9)	**Mediterranean**	0.2 (-0.6, 1.2)	0.1 (-0.4, 0.7)
	-0.2 (-0.7, 0.3)	-0.7 (-3.0, 1.6)	-0.4 (-1.1, 0.3)	**Moderate carb**	-0.1 (-1.1, 0.8)
	0.2 (-1.8, 2.3)	-0.3 (-1.2, 0.6)	0.0 (-2.0, 2.0)	0.5 (-1.7, 2.6)	**No intervention**

FIGURE S4h Mean differences in triglycerides (mmol/l)

		Mean difference (95%CrI) after 12 months			
Mean difference after 6 months (95% CrI)	**Low fat**	*NA*	*NA*	*NA*	*NA*
	NA	**Low GI**	*NA*	*NA*	*NA*
	0.3 (-0.6, 1.4)	*NA*	**Mediterranean**	*NA*	*NA*
	NA	*NA*	*NA*	**Moderate carb**	*NA*
	NA	*NA*	*NA*	*NA*	**No intervention**

FIGURE S5 Short term effects SUCRA values for all outcomes

Figures represent the ranking of the different dietary patterns for the corresponding outcome. A higher ranking means that a dietary pattern is more likely to affect the outcome favourably, which was defined as reduction for all outcomes but HDL-cholesterol (where increase is the favourable outcome). Surface under the cumulative ranking curve (SUCRA) summarizes the probability of being the best treatment option into one number, with a value ranging between 0 and 1. A higher SUCRA values indicates that a treatment option performs better than alternatives, but effect size is not taken into account. SUCRA: Surface under the cumulative ranking curve, 95%CrI: 95% credibility interval

FIGURE S5A Body weight - 6 months

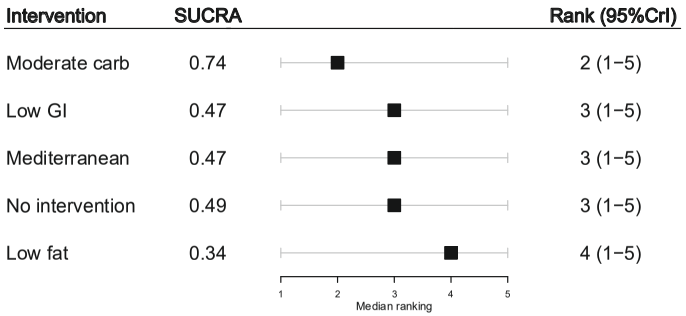


FIGURE S5B Body weight - 12 months

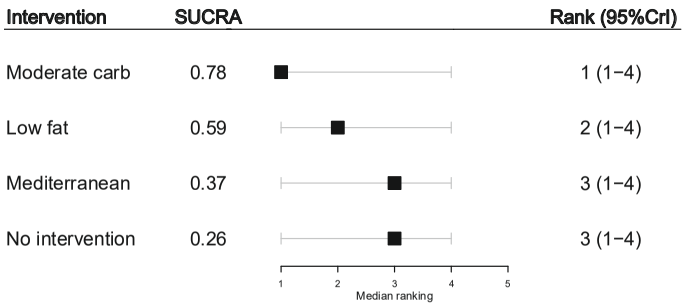


FIGURE S5C Body mass index - 6 months

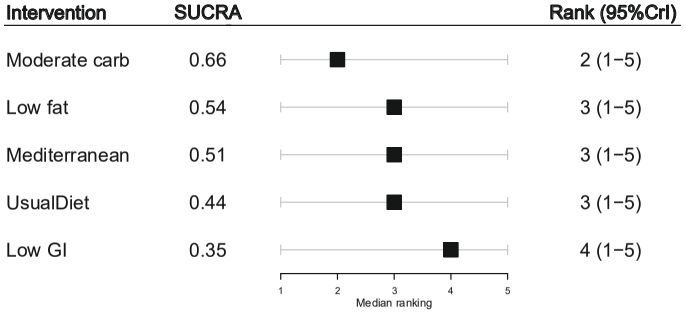


FIGURE S5D Body mass index - 12 months

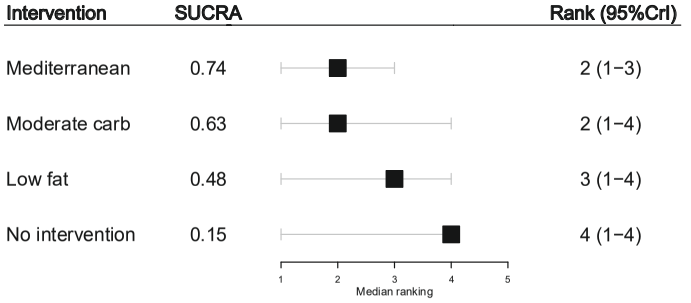


FIGURE S5E Systolic blood pressure - 6 months

Intervention	SUCRA	Rank (95%CrI)
Moderate carb	0.9	1 (1–4)
Low GI	0.51	2 (1–5)
Mediterranean	0.49	3 (2–5)
Low fat	0.27	4 (2–5)
No intervention	0.33	4 (2–5)

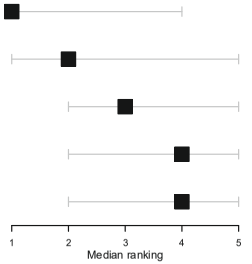


FIGURE S5F Systolic blood pressure - 12 months

Intervention	SUCRA	Rank (95%CrI)
Mediterranean	0.74	2 (1–4)
No intervention	0.72	2 (1–4)
Low fat	0.4	3 (1–4)
Moderate carb	0.14	4 (1–4)

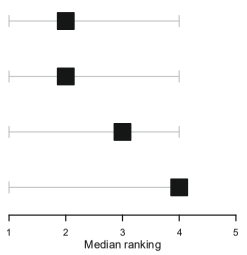


FIGURE S5G Total cholesterol - 6 months

Intervention	SUCRA	Rank (95%CrI)
Low fat	0.84	1 (1–4)
Moderate carb	0.65	2 (1–5)
Mediterranean	0.40	3 (1–5)
Low GI	0.38	4 (1–5)
No intervention	0.22	4 (1–5)

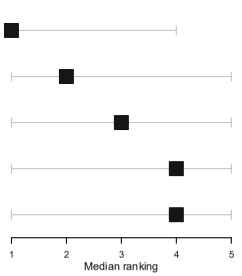


FIGURE S5H Total cholesterol - 12 months

Intervention	SUCRA	Rank (95%CrI)
Low fat	0.68	2 (1–4)
Moderate carb	0.64	2 (1–4)
Mediterranean	0.42	3 (1–4)
No intervention	0.27	4 (1–4)

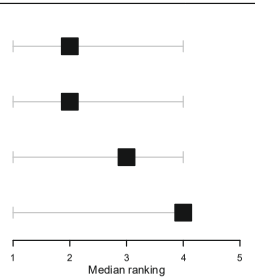


FIGURE S5I LDL-cholesterol - 6 months

Intervention	SUCRA	Rank (95%CrI)
Low GI	0.66	2 (1–5)
No intervention	0.61	2 (1–5)
Low fat	0.57	3 (1–4)
Mediterranean	0.59	3 (1–4)
Moderate carb	0.06	5 (3–5)

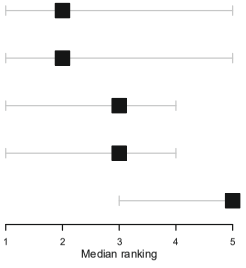


FIGURE S5J LDL-cholesterol - 12 months

Intervention	SUCRA	Rank (95%CrI)
Low fat	0.54	2 (1–4)
Moderate carb	0.54	2 (1–4)
Mediterranean	0.51	3 (1–4)
No intervention	0.4	3 (1–4)

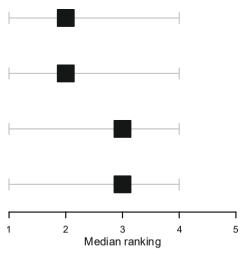


FIGURE S5K HDL-cholesterol - 6 months

Intervention	SUCRA	Rank (95%CrI)
No intervention	0.77	2 (1–4)
Low fat	0.48	3 (1–5)
Low GI	0.55	3 (1–5)
Mediterranean	0.59	3 (1–4)
Moderate carb	0.11	5 (2–5)

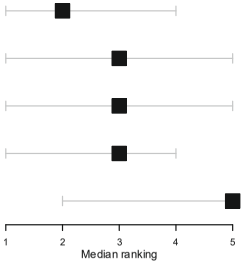


FIGURE S5L HDL-cholesterol - 12 months

Intervention	SUCRA	Rank (95%CrI)
No intervention	0.86	1 (1–4)
Mediterranean	0.58	2 (1–4)
Moderate carb	0.37	3 (1–4)
Low fat	0.20	4 (2–4)

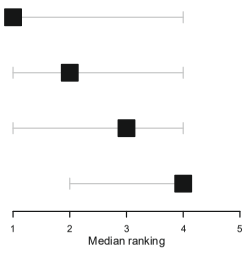


FIGURE S5M Triglycerides - 6 months

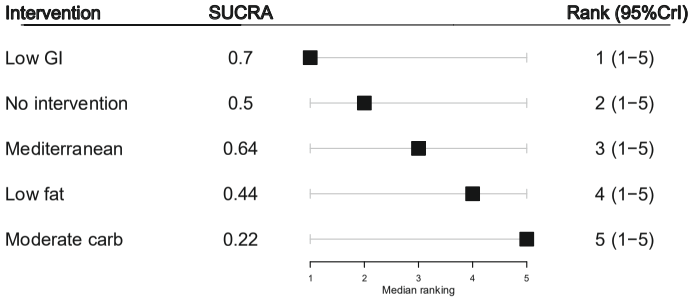


FIGURE S5N Triglycerides - 12 months

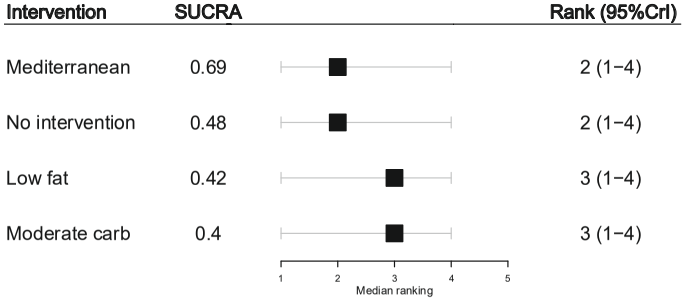


FIGURE S5O C reactive protein - 6 months

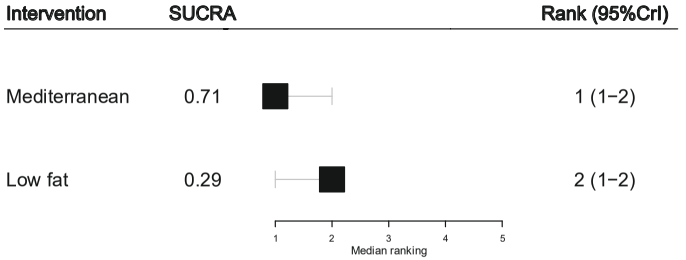


FIGURE S5P C reactive protein - 12 months

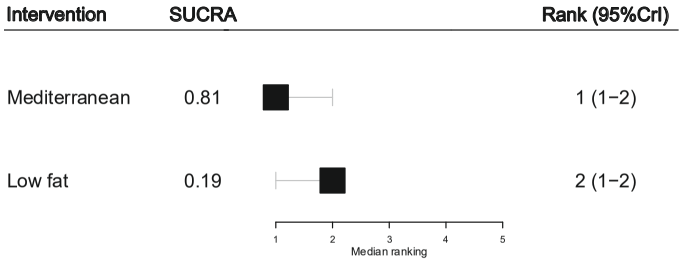
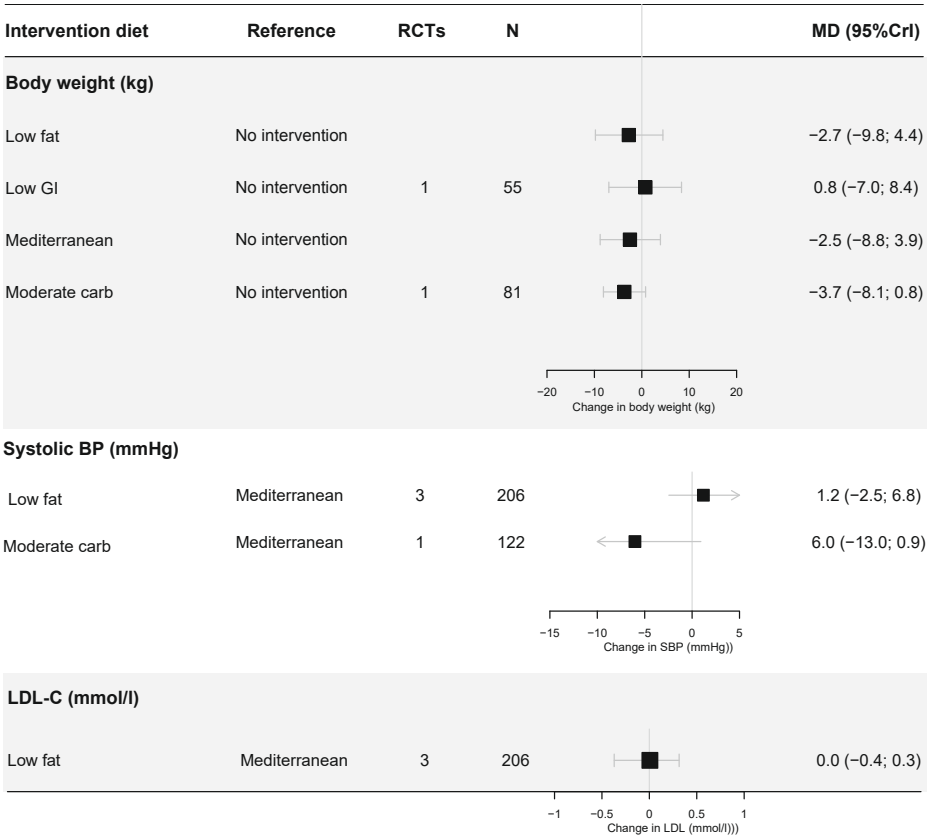
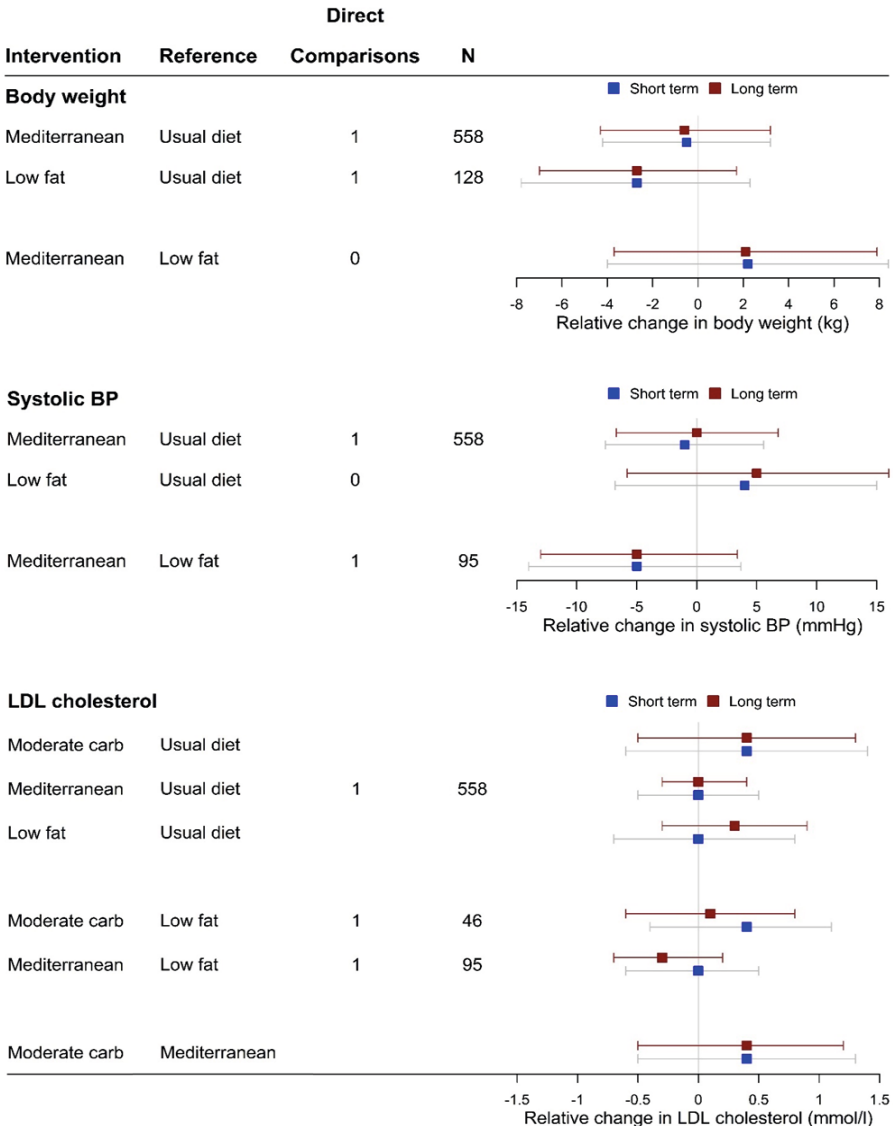


FIGURE S6 Sensitivity analysis: 6-month effects on body weight, systolic blood pressure and LDL-C in studies published in or after 2000



This table presents network estimates for the relative effects on primary outcomes based on studies published from the year 2000 onwards.. The column 'Direct comparisons' present the number of time a comparison was trialed and the 'N' column presents the total number of participants included in these clinical trials. Zero direct comparisons means that the presented network estimate is based on indirect evidence only. Abbreviations: SBP: systolic blood pressure, LDL-C: low-density lipoprotein cholesterol

FIGURE S7 Sensitivity analysis: Comparison of short- and long term effects on primary outcomes



This table presents network estimates for the relative effects on primary outcomes based on studies that reported both short- and long-term effects. The short- and long-term effects are presented alongside each other. The column 'Direct comparisons' present the number of time a comparison was trialed and the 'N' column presents the total number of participants included in these clinical trials. Zero direct comparisons means that the presented network estimate is based on indirect evidence only. BP: blood pressure, LDL: low-density lipoprotein, moderate carb: moderate carbohydrate.

FIGURE S8 Sensitivity analysis - League tables for 6-month change in body weight, systolic blood pressure and LDL-cholesterol limited to CAD patients

Values correspond to the mean difference in reduction and corresponding 95% credibility interval in the outcomes for the dietary pattern in the column compared to the dietary pattern in the row. Carb: carbohydrate, GI: glycemic index, LDL: low-density lipoprotein, 95%CrI: 95% Credibility interval

FIGURE S8a Body weight (kg)

Mean difference after 6 months (95% CrI)

Low fat				
1.8 (-1.5; 5.8)	**Low GI**			
-0.7 (-8.0; 6.6)	-2.6 (-10.8; 5.5)	**Mediterranean**		
1.2 (-1.6; 4.5)	-0.6 (-3.3; 1.9)	2.0 (-5.9; 10.0)	**Moderate carb**	
2.8 (-0.3; 5.8)	0.9 (-2.3; 3.6)	3.5 (-4.4; 11.4)	1.5 (-1.4; 4.1)	**No intervention**

FIGURE S8b Systolic blood pressure (mmHg)

Mean difference after 6 months (95% CrI)

Low fat				
0.8 (-42.5; 43.7)	**Low GI**			
1.8 (-57.6; 60.2)	0.8 (-71.7; 75.7)	**Mediterranean**		
1.4 (-41.0; 43.8)	0.8 (-9.1; 10.9)	-0.1 (-74.3; 72.2)	**Moderate carb**	
8.2 (-54.8; 73.4)	7.7 (-40.4; 57.8)	6.6 (-80.3; 93.7)	6.8 (-40.0; 56.7)	**No intervention**

FIGURE S8c LDL-Cholesterol (mmol/l)

Mean difference after 6 months (95% CrI)

Low fat				
-0.1 (-3.8; 3.6)	**Low GI**			
0.1 (-1.9; 2.1)	0.2 (-4.0; 4.3)	**Mediterranean**		
0.0 (-3.6; 3.6)	0.1 (-0.6; 0.8)	-0.1 (-4.1; 4.0)	**Moderate carb**	
-0.7 (-4.5; 3.2)	-0.6 (-1.7; 0.6)	-0.7 (-5.0; 3.6)	-0.7 (-2.0; 0.7)	**No intervention**

FIGURE S9 Sensitivity analysis - League tables for 6-month change in body weight, systolic blood pressure and LDL-cholesterol after exclusion of studies judged to be at high risk of bias

Values correspond to the mean difference in reduction and corresponding 95% credibility interval in the outcomes for the dietary pattern in the column compared to the dietary pattern in the row. Carb: carbohydrate, GI: glycemic index, LDL: low-density lipoprotein, 95%CrI: 95% Credibility interval

FIGURE S9a Body weight (kg)

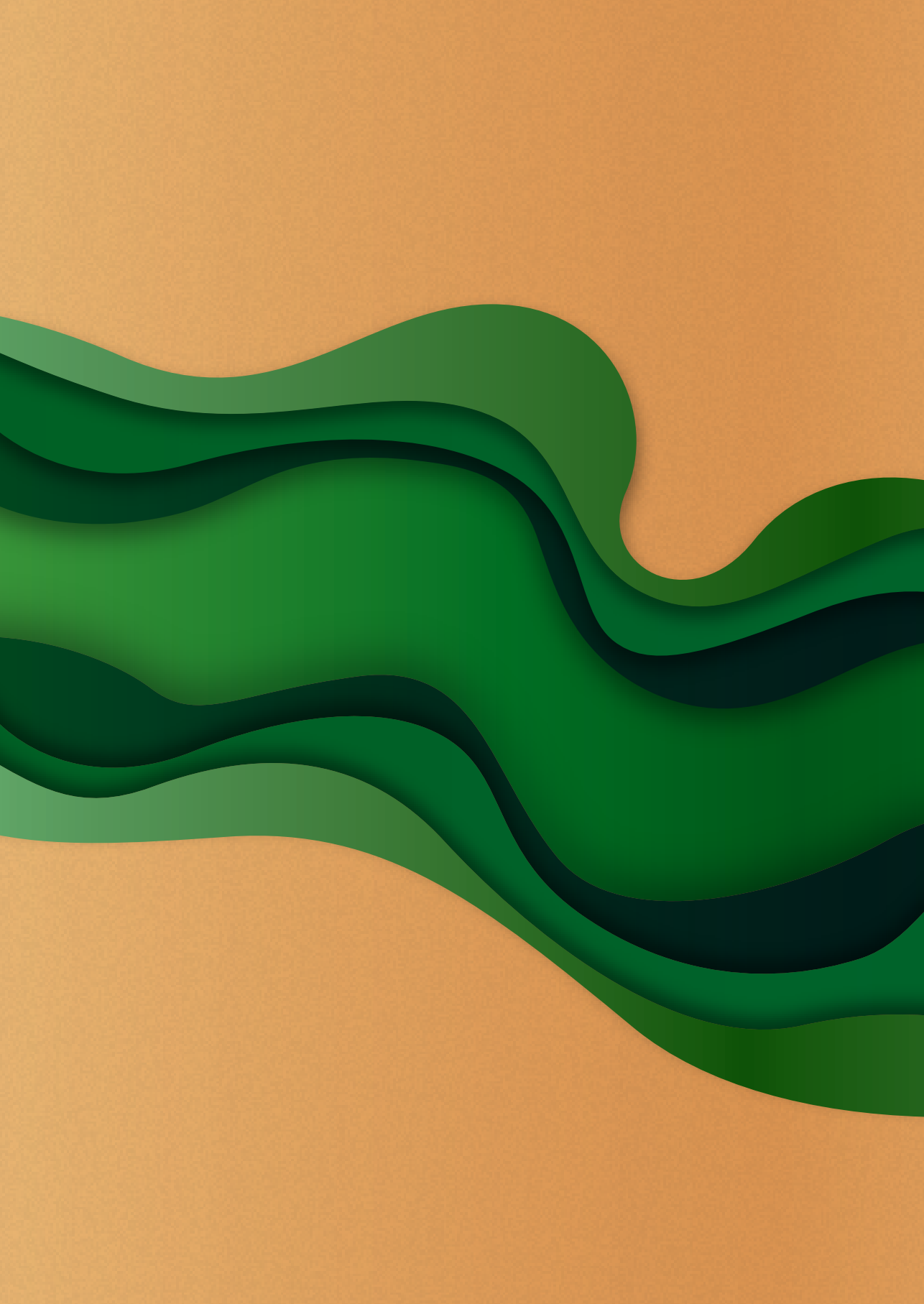
Mean difference after 6 months (95% CrI)					
	Low fat				
0.6 (-4.2; 5.5)	**Low GI**				
-0.6 (-7.4; 6.1)	-1.2 (-9.6; 7.0)	**Mediterranean**			
0.5 (-1.6; 2.7)	-0.1 (-4.5; 4.3)	1.1 (-5.9; 8.2)	**Moderate carb**		
1.7 (-1.6; 5.0)	1.1 (-4.0; 6.2)	1.1 (-5.9; 8.2)	1.2 (-1.3; 3.7)	**No intervention**	

FIGURE S9b Systolic blood pressure (mmHg)

Mean difference after 6 months (95% CrI)					
	Low fat				
-4.0 (-54.7; 45.8)	**Low GI**				
1.8 (-57.5; 62.1)	6.0 (-72.6; 83.8)	**Mediterranean**			
0.4 (-42.7; 42.3)	4.2 (-23.2; 31.5)	-1.7 (-73.9; 72.4)	**Moderate carb**		
7.6 (-55.9; 71.4)	11.9 (-43.8; 66.9)	5.7 (-80.4; 93.2)	7.4 (-40.9; 55.5)	**No intervention**	

FIGURE S9c LDL-Cholesterol (mmol/l)

Mean difference after 6 months (95% CrI)					
	Low fat				
0.3 (-3.5; 4.0)	**Low GI**				
0.1 (-1.8; 2.0)	-0.2 (-4.4; 4.0)	**Mediterranean**			
0.0 (-3.4; 3.4)	-0.3 (-1.7; 1.2)	-0.1 (-4.0; 3.9)	**Moderate carb**		
-0.1 (-4.9; 4.6)	-0.3 (-3.2; 2.5)	-0.2 (-5.3; 4.9)	-0.1 (-3.3; 3.0)	**No intervention**	



CHAPTER 4

EFFECT OF DIETARY PATTERNS ON CARDIOVASCULAR RISK FACTORS IN PEOPLE WITH TYPE 2 DIABETES

A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Nadia E. Bonekamp
Iris van Damme
Johanna M. Geleijnse
Renate M. Winkels
Frank L.J. Visseren
Pamela B. Morris
Charlotte Koopal

Diabetes Research and Clinical Practice, 2023 Jan;195:110207.

ABSTRACT

Aims

To identify the most effective dietary pattern for improving cardiovascular risk factors in people with type 2 diabetes.

Methods

PubMed, Embase, the Cochrane library, SCOPUS and Web of Science were systematically searched for randomized controlled trials comparing the effects of dietary patterns on body weight, blood pressure, HbA1c and lipids after 6 and 12 months. Treatment effects were synthesized using Bayesian network meta-analysis. Six-month changes in HbA1c, SBP and LDL-C were used to estimate relative risk reductions (RRR) for cardiovascular events.

Results

Seventy-three RCTs on eight different dietary patterns were included. All reduced body weight and HbA1c after 6 months, with the largest effects from the low carbohydrate (body weight -4.8 kg,95%credibility interval (95%CrI) -6.5;-3.2kg) and Mediterranean diet (HbA1c -1.0%, 95%CrI-15;-0.4% vs. usual diet). There were no significant 6-month blood pressure or lipid effects. Dietary patterns had non-statistically significant 12-months effects. The Mediterranean diet resulted in the largest expected RRR for cardiovascular events: -16% (95%CI-31;3.0) vs. usual diet.

Conclusions

In patients with type 2 diabetes, all dietary patterns outperformed usual diet in improving body weight and HbA1c after 6 months and clinically relevant cardiovascular risk reduction could be achieved. There was insufficient evidence to select one optimal dietary pattern.

INTRODUCTION

Type 2 diabetes is an important risk factor for cardiovascular disease (CVD) and mortality[1,2] and, with its prevalence expected to exceed 10% of the world population in 2030,[3] it imposes a major global health burden. Unhealthy dietary habits and obesity predispose for development of type 2 diabetes[4,5] and may have a detrimental effect on cardiovascular risk factors such as hypertension and dyslipidaemia.[6,7]

Healthy diet is a key recommendation in guidelines for the management of type 2 diabetes.[8,9] Weight loss achieved through hypocaloric diets and increased physical activity is widely recommended[8] and multiple dietary patterns (Mediterranean diet, low carbohydrate diet and plant-based diet), effectively improve glycemic control, systolic blood pressure (SBP) and low density lipoprotein (LDL) cholesterol levels.[10-13] However, it is unclear which of these dietary patterns most effectively improves glycemic control and cardiovascular risk factors and, ultimately, best prevents cardiovascular events and mortality in people with type 2 diabetes.

Ideally, evidence on effectiveness of different dietary patterns would be gathered by direct comparison in long-term randomized controlled trials (RCTs), but due to the large number of dietary patterns and time and financial constraints, this approach is not feasible. Network meta-analysis provides an alternative, because it uses the results from existing RCTs that directly compared two or more dietary patterns (direct evidence) to estimate the relative effects of two dietary patterns that have never been compared in a head-to-head RCT (indirect evidence).[14] Moreover, network meta-analysis may improve the precision of effect estimates from RCTs and traditional pairwise meta-analyses by combining direct and indirect evidence.[15]

The aim of this systematic literature review and network meta-analysis was to compare the effectiveness of multiple dietary patterns for improving glycemic control and reducing cardiovascular risk factors in people with type 2 diabetes. Moreover, the aim was to rank dietary patterns based on their effects on cardiovascular risk factors and identify the optimal dietary pattern. Additionally, an estimate of the effects of dietary patterns on risk of cardiovascular events compared to no dietary intervention was made based on their effect on cardiovascular risk factors as found in the network meta-analysis.

MATERIAL AND METHODS

This systematic review and network meta-analysis was prospectively registered in the PROSPERO registry (CRD42021233287).

Systematic literature search and data extraction

A systematic literature search was performed from database initiation up to 31 January 2022 in PubMED, EMBASE, the Cochrane Library, Scopus and Web of Science, using search terms for diet and dietary patterns, type 2 diabetes and RCTs (Supplemental Appendix 1). RCTs comparing a dietary pattern with an alternative pattern or with no dietary intervention for at least 12 weeks in a adults with type 2 diabetes were included. RCTs with multiple lifestyle interventions, not restricted to diet, were eligible when non-dietary components were applied universally (e.g. both groups received the same exercise program, Table S1). The definition of type 2 diabetes was accepted from the eligible RCTs, to avoid exclusion of relevant records due to unreported data required for a specific type 2 diabetes definition. Two authors (NEB, IVD) independently performed title and abstract screening followed by full-text review of relevant articles. Discrepancies were resolved by consensus after inclusion of a third reviewer.

Data on study design, population, intervention characteristics and outcome measures were independently extracted by two authors (NEB, IVD) using a standardized report form. Included records were critically appraised using the Cochrane Risk of Bias 2 tool.[16]

Dietary pattern categories

Interventions were categorized as one of eight pre-defined dietary patterns (Table S2):

- Low glycemic index (GI) diet: focusing on food items with a low GI and high fiber content
- Mediterranean diet: rich in whole grains, green vegetables, fruits, fish, lean meat and plant-based oils
- Plant-based diet: vegan or vegetarian diet
- High protein diet: ≥25% of total energy (E%) from protein
- Low carbohydrate diet: <30E% from carbohydrates
- Low fat diet: <30E% from fat
- Moderate carbohydrate diet: >45E% from carbohydrates, >30E% from fat and <25E% from protein
- No dietary intervention: usual diet or one-time dietary advice from treating physician without behavioural support

Categorization was based on details provided in the included articles. When a dietary intervention could be classified as either a low GI, Mediterranean or plant-based diet, this classification was preferred over the classification based on macronutrient distribution of the diet.

Outcomes

Outcome data were divided into two time points: 6 months for measurements taken after 12 weeks and before 12 months, and 12 months for measurements taken more than 12 months after diet initiation. The data available to assess other time points was insufficient or too heterogeneous to meet the assumptions underlying a network meta-analysis and were therefore not quantitatively synthesized. The primary outcomes were difference in 6-month change in body weight, glycosylated hemoglobin (HbA1c), SBP and LDL-cholesterol between different dietary patterns. Secondary outcomes were the 12-month change in these parameters and the 6- and 12-month change in high-density lipoprotein (HDL) cholesterol, triglyceride and C-reactive protein (CRP) levels.

When available, the mean difference from baseline and corresponding standard deviation (SD) were used in the analysis. If relevant outcomes were reported as other measures (e.g. standard error), the mean difference and SD were calculated in accordance with the Cochrane Handbook.[17]

Statistical analyses

A random-effects network meta-analysis with a Bayesian framework was performed in a Monte Carlo Markov Chain simulation (4 chains, 5000 burn-in iterations, 100,000 iterations).[14,18] The transitivity assumption was evaluated by comparing characteristics of the eligible RCTs. Convergence of the model was assessed by visual inspection of trace plots and Gelman-Rubin-Brooks plots. Model fit was assessed by checking the ratio between number of data points in each model and the residual deviance of the posterior distribution. The consistency assumption was assessed by performing node-splitting analyses to compare direct and indirect evidence. Imprecision of the model estimates was reflected by 95% credible intervals (95%CrI) obtained from the 2.5th and 97.5th percentile values of the simulations. Ranking probabilities were calculated for all outcomes and the hierarchy of the different dietary patterns was summarized using ranking plots and surface under the cumulative ranking curve (SUCRA).[19]

Changes in HbA1c, SBP and LDL-cholesterol at 6 months after diet initiation were used to estimate the relative risk reduction (RRR) in risk of major adverse cardiovascular events (MACE), in accordance with the methodology previously published by Berkelmans and colleagues.[20] For these analyses, the reference category was no dietary intervention. The following results from previously published meta-analyses were used to estimate the effect on MACE risk: 10 mmol/mol reduction in HbA1c associates with a hazard ratio (HR) of 0.91 (95%CI 0.84; 0.99),[21] 1 mmol/l reduction in plasma LDL-C with a HR of 0.78 (95%CI 0.76; 0.80),[22] and 10 mmHg reduction in systolic blood pressure with a HR of 0.80 (95%CI 0.77; 0.83).[23] A detailed description of the methodology for the calculation of MACE risk is provided in Supplemental Appendix 2.

Post-hoc sensitivity analyses were performed to explore the impact of potential sources of heterogeneity between the included studies. The first sensitivity analysis was limited to studies published from the year 2010 onwards. A second sensitivity analysis was limited to studies that selected patients with a baseline body mass index (BMI) ≥25 kg/m2, with the aim of exploring whether the effects of dietary patterns were different in overweight populations. In the final sensitivity analysis, all records that were judged to be at high risk of bias were excluded.

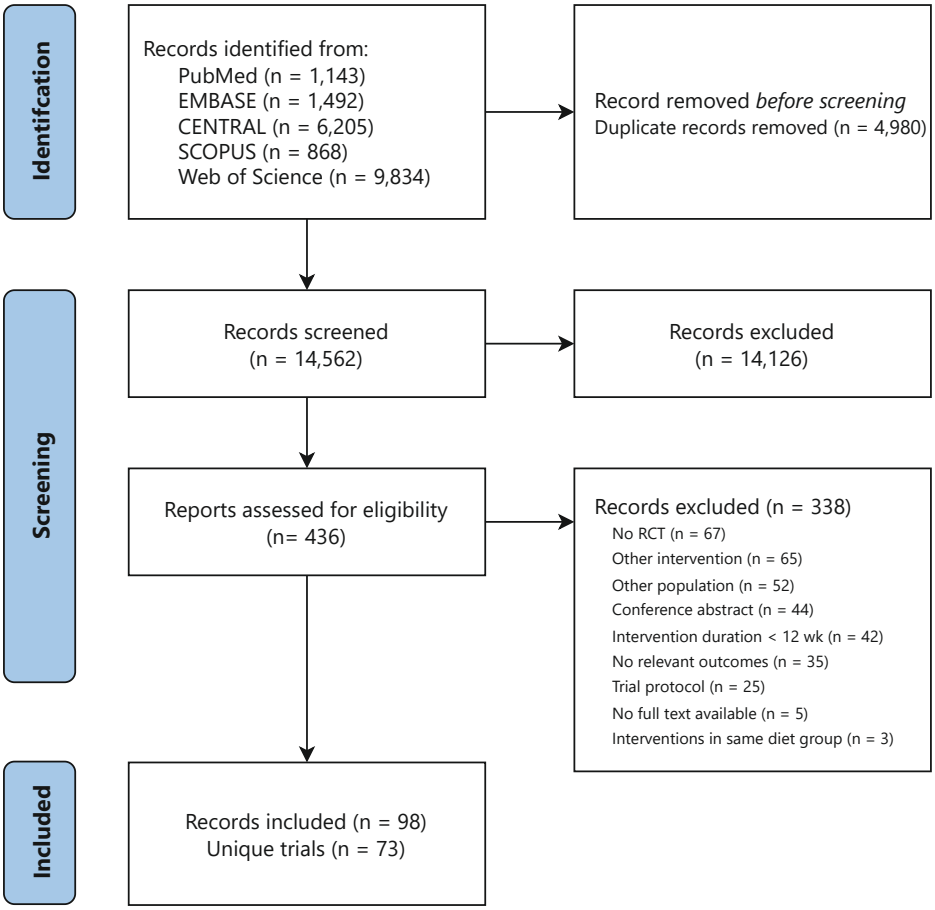
All statistical analyses were performed using R version 4.0.4 (R Core Team, Vienna, Austria) with the gemtc package.[24]

RESULTS

Article selection and risk of bias assessment

The search of five different databases yielded 14,563 unique records that were screened for eligibility and 98 records, reporting on 73 unique RCTs were included (Figure 1/ Table S3). The included studies were published between 1978 and 2022 and comprised a total of 5,753 participants. Study durations ranged from 12 weeks to 7 years, with a median of 26 weeks. Approximately half of participants were female, mean age was 58 ±5.7 years, mean BMI was 32.5 ±4.2 kg/m2 and median time since type 2 diabetes diagnosis was 9 [IQR 7– 10] years. Details on achieved caloric intake was available for 43 trials, of which 27 (63%) reported a similar or lower energy intake in the intervention group.

FIGURE 1 Study selection flowchart



This flow diagram shows the process used to identify relevant records for the network meta-analysis. The systematic literature search was performed from database inception to 31 January 2022. Abbreviations: RCT: Randomized controlled trial

Funding and conflict-of-interest information was fully available for 50 of the included RCTs (68%) of whom 31 trials reported having received funding from governmental or academic sources alone and no potential conflicts of interest (Table S4). Industry sponsoring, or lack thereof, was not reported for studies on the Mediterranean diet, and reported most frequently for RCTs assessing the effectiveness of the high protein (N = 6, 55%) and plant-based dietary patterns (N = 4, 50%, Table S4). Twenty-four studies (35%) were judged to be at high risk of bias (Figure S1). Risk of bias mainly arose

because participants could not be blinded to the dietary intervention, and because older RCTs often did not have a pre-published protocol.

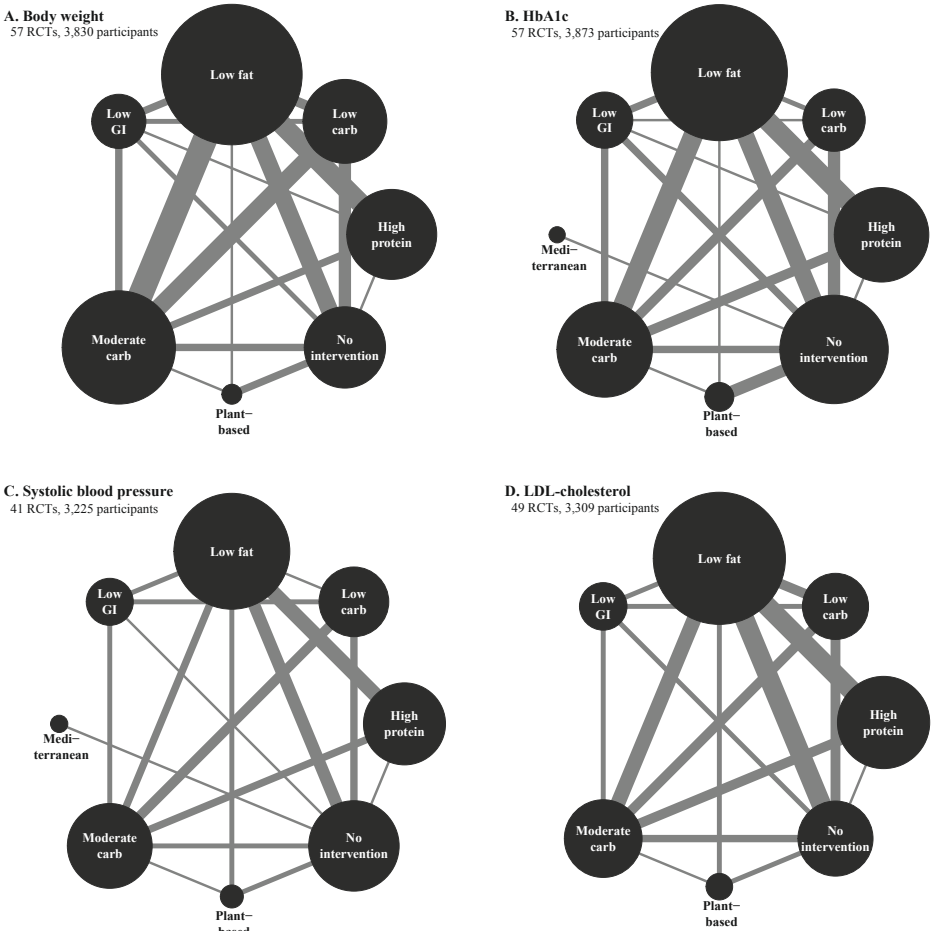
Diet categories and network

Network plots showing the number of direct comparisons between dietary patterns for each outcome are presented in Figures 2 and S2. Most participants were randomized to either low-fat diet (N=1,478), moderate carbohydrate diet (N=1,011) or no dietary intervention (N=969). The most frequent direct comparison was moderate carbohydrate vs. low fat diet (13 RCTs), followed by low carbohydrate vs. moderate carbohydrate and low fat vs. no dietary intervention (both reported in 9 RCTs).

6-month effects of dietary interventions on cardiovascular risk factors

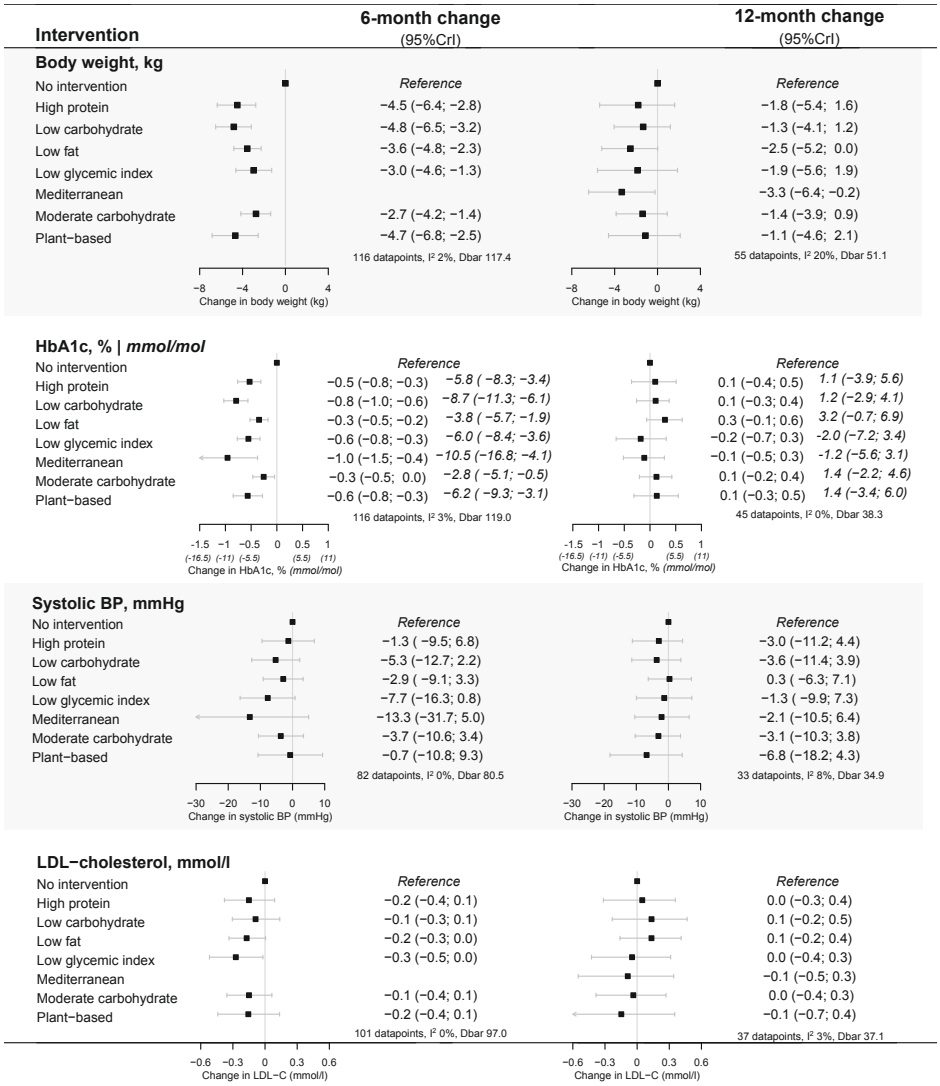
After 6 months, all dietary patterns were more effective in reducing body weight than no dietary intervention, with changes ranging between -4.8 and -2.7 kg (Figure 3). The largest reductions were achieved with the low carbohydrate diet (-4.8 kg, 95%CrI-6.5;-3.2) and plant-based diet (-4.7kg, 95%CrI-6.8; -2.5) compared to no dietary intervention. All dietary patterns resulted in statistically significant 6-month HbA1c reductions, ranging between –1.0% and -0.3% (-10.5 and -2.8 mmol/mol) compared to no dietary intervention. The largest reduction was achieved by the Mediterranean diet: -1.0%, 95%CrI-15.8;-0.4 (–10.5 mmol/mol, 95%CrI–16.8;–4.1 mmol/mol). For SBP there was a non-statistically significant trend towards reduction for all dietary patterns. The estimates for SBP reduction ranged between -13.3 and -0.7 mmHg, with the largest reduction being achieved by the Mediterranean diet (-13.3 mmHg, 95%CrI-31.7; 5.0). Six-month changes in LDL-cholesterol compared with no dietary intervention ranged between -0.3 and -0.1 mmol/l for all dietary patterns. A statistically significant LDL-cholesterol reduction was only observed for the low GI diet: -0.3 mmol/l (95%CrI -0.5; 0.0) compared with no dietary intervention. The studied dietary patterns had small, non-statistically significant, effects on HDL-cholesterol, triglycerides and CRP levels (Table S5).

FIGURE 2 Network plots of direct comparisons after 6 months



These network graphs show the direct comparisons between dietary interventions from head-to-head trials for the primary outcomes: (A) body weight, (B) HbA1c, (C) systolic blood pressure and (D) LDL-cholesterol after 6 months. The sizes of the dietary pattern nodes correspond to the number of participants randomized to that dietary pattern. The width of the edges between the nodes corresponds to the number of direct head-to-head comparisons. Carb: carbohydrate GI: glycemic index, RCT: randomized controlled trial.

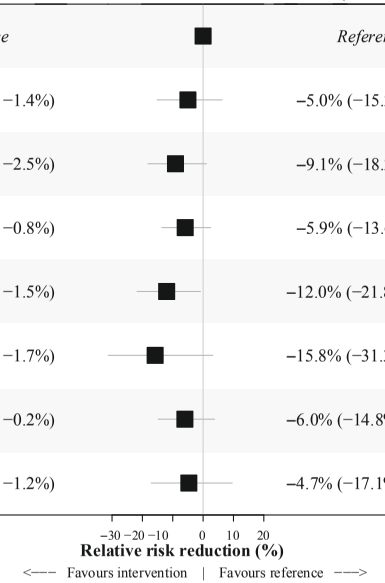
FIGURE 3 The effect of dietary patterns on body weight, HbA1c, systolic blood pressure and LDL-C at 6 and 12 months after diet initiation.



This figure presents the network estimates and 95% CrI for the 6 and 12 month relative change from baseline in body weight, HbA1c, systolic blood pressure and LDL-C compared to usual diet. For each outcome, measures of model fit are provided in the figure: number of data points used for the model, I2 and the posterior mean residual difference (Dbar). Changes in HbA1c as measured in % are presented in regular font and changes expressed in mmol/mol are presented in italic. Abbreviations: 95%CrI: 95% credibility interval, HbA1c – glycated hemoglobin, BP: Blood pressure, LDL-cholesterol: low-density lipoprotein cholesterol.

FIGURE 4 Estimated relative risk reductions for MACE achieved by dietary interventions compared to no intervention

Intervention	RRR (95%CI) based on changes in individual cardiovascular risk factors: Systolic BP	LDL−C	HbA1c	Combined relative risk reduction (95%CI)
No intervention	*Reference*	*Reference*	*Reference*	*Reference*
High protein	−1.3% (−8.8%; 6.8%)	−1.5% (−3.8%; 0.9%)	−2.3% (−3.4%; −1.4%)	−5.0% (−15.2%; 6.3%)
Low carbohydrate	−5.0% (−11.6%; 2.2%)	−0.9% (−3.1%; 1.4%)	−3.5% (−4.5%; −2.5%)	−9.1% (−18.2%; 1.1%)
Low fat	−2.8% (−8.5%; 3.2%)	−1.7% (−3.4%; 0.1%)	−1.5% (−2.3%; −0.8%)	−5.9% (−13.6%; 2.5%)
Low glycemic index	−7.2% (−14.6%; 0.8%)	−2.8% (−5.2%; −0.2%)	−2.4% (−3.4%; −1.5%)	−12.0% (−21.8%; −0.9%)
Mediterranean	−12.1% (−26.4%; 5.0%)	*Not available*	−4.2% (−6.7%; −1.7%)	−15.8% (−31.3%; 3.2%)
Moderate carbohydrate	−3.5% (−9.8%; 3.4%)	−1.5% (−3.6%; 0.7%)	−1.1% (−2.1%; −0.2%)	−6.0% (−14.8%; 3.8%)
Plant−based	−0.7% (−9.9%; 9.5%)	−1.6% (−4.4%; 1.4%)	−2.5% (−3.7%; −1.2%)	−4.7% (−17.1%; 9.6%)



This figure presents the estimated changes in relative risk of MACE that can be achieved by different dietary interventions compared to no dietary intervention. The relative risk reduction achieved by changes in systolic blood pressure, LDL cholesterol and HbA1c were calculated by multiplying the 6-month network estimates for these cardiovascular risk factors with hazard ratios that were previously published. Note: This approach may result in an underestimation of the association between dietary pattern interventions and risk of MACE because dietary effects may manifest through other biological mechanisms. * The estimate for the Mediterranean diet is based on changes in systolic blood pressure and HbA1c, because no direct or indirect estimate for the effect on LDL-cholesterol could be obtained from the network. Abbreviations: RRR: relative risk reduction 95%CI: 95% confidence interval, Systolic BP: systolic blood pressure, LDL-C: low density lipoprotein cholesterol, HbA1c: glycated haemoglobin, carb: carbohydrate

12-month effects of dietary patterns on cardiovascular risk factors

Twelve months after diet initiation, body weight reductions ranged between -3.3 and -1.1 kg compared with no dietary intervention, with the Mediterranean (-3.3 kg, 95%CrI-6.4;-0.2 kg) and low-fat diet (-2.5kg, 95%CrI-5.2;0.0) yielding the largest reductions. Twelve-month HbA1c changes were not statistically significant and ranged between -0.2 and 0.3% (-2.0 and 3.2 mmol/mol) compared to no dietary intervention. For SBP and LDL-cholesterol, these 12-month changes were not statistically significant, ranging from -6.8 to 0.3 mmHg and -0.1 to 0.1 mmol/l, respectively.

Ranking of dietary interventions

There was no dietary pattern that ranked best for all primary outcomes (Figure S4). The low carbohydrate diet ranked highest for body weight reduction, the Mediterranean diet for reducing HbA1c and SBP; and the low GI diet for reducing LDL-cholesterol. Usual diet performed worst for all primary outcomes. Ranking plots for the secondary outcomes are provided in Figure S5

Estimated relative reductions in MACE risk

Compared with no dietary intervention, all dietary patterns were estimated to reduce MACE risk. However, only the effect of the low GI diet was statistically significant (RRR – 12.0%, 95%CI -21.8;-0.9%) (Figure 4). The Mediterranean diet resulted in the largest RRR: -15.8% (95%CI-31.3;3.2%).

Sensitivity analyses

Results of studies published in or after 2010 (44/73 RCTs), were similar in size and direction to the main analysis with respect to the effects of dietary patterns on body weight, HbA1c, SBP, and LDL-cholesterol. For each outcome, the dietary pattern that resulted in the largest reduction was the same compared to the full analysis (Figure S6).

In studies excluding participants with BMI <25 kg/m2, all dietary patterns resulted in more weight loss compared with the main analysis (Figure S7). In this subgroup, the largest 6-month weight reduction was achieved by the high protein diet (-6.6 kg, 95%CrI-10.8;-2.2 kg). The effects of dietary patterns on HbA1c and LDL-cholesterol were similar in the overweight population. The effects of dietary patterns on SBP compared to no dietary intervention could not be estimated, because none of the studies in this subgroup used no dietary intervention as a reference group.

In the final sensitivity analysis, excluding all studies that were judged to be at high risk of bias (n = 23), the size and direction of the network estimates was similar compared with the main analysis (Figure S8).

DISCUSSION

This systematic review and network meta-analysis showed that dietary pattern interventions result in clinically relevant short-term reductions in body weight and HbA1c compared with no dietary intervention in people with type 2 diabetes. All effects were attenuated and not statistically significant after 12 months. When ranking dietary patterns there was no overall best option. However, for all primary outcomes, continuing usual diet was the worst option. Based on the 6-months results, dietary pattern interventions can reduce risk of MACE through their effect on CVD risk factors in patients with type 2 diabetes.

With regard to body weight, previous (network) meta-analyses have shown similar short- but not long-term weight loss.[25,26] A negative energy balance is the main driver for weight loss. Although the majority of comparisons between dietary patterns included in the present analyses were intended to be isocaloric, this intention was not always realized. In practice, participants that were randomized to a dietary intervention were more likely to reduce caloric intake than those that received no dietary intervention. The findings in the present study indicate that the studied dietary patterns have a similar effect on body weight and that all outperform no dietary intervention; a finding consistent with previous research.[27,28]

Similar to previous research,[10] the findings from this study indicate that dietary patterns reduce HbA1c, with the Mediterranean and low carbohydrate diets having the largest effects. These beneficial effects on HbA1c might be mediated through weight loss, which has been shown to reduce HbA1c[29] and even reverse type 2 diabetes.[30] In line with this, the short-term reductions in HbA1c lined up with the observed weight loss. The long-term effects on weight loss were smaller and no longer significant and, similarly, the effects on HbA1c were attenuated. Another mechanism through which diet can influence glycemic control is by reducing the quantity and improving the quality of carbohydrate intake.[31] Consumption of food items that are rich in high glycemic carbohydrates, result in fast and steep increases in blood glucose and insulin

levels, especially in patients with type 2 diabetes. Frequent consumption can aggravate hyperinsulinemia and strengthen the accompanying atherogenic response.[32] The low carbohydrate dietary intervention was associated with reductions in short-term body weight and HbA1c, and therefore, might be a good dietary option for patients with type 2 diabetes, although long-term effects remain unclear.

The SBP and LDL-cholesterol effects were non-significant at both 6 and 12 months for all dietary interventions. A previous meta-analysis of dietary RCTs found an overall statistically significant 4 mmHg SBP reduction compared with usual diet.[33] However, that study pooled the effects of different dietary interventions in one estimate, which leads to limited options for generalization. In our analysis, a tendency towards clinically relevant 6-month reductions in SBP up to 13 mmHg was observed, but with wide CrIs, indicating insufficient power. The most important dietary factor that affects SBP is sodium salt intake.[34] Data on sodium intake was not extracted and may partially explain the findings.

The small effects of diet on LDL-cholesterol levels have been shown before[26,35] and might be explained through pathophysiologic processes leading to dyslipidaemia. Genetic predisposition and low-grade inflammation are of large importance for LDL-cholesterol levels.[36] Moreover, dietary absorption and hepatic synthesis together determine serum cholesterol levels including LDL-cholesterol, and hepatic synthesis is negatively correlated to dietary adsorption.[37] Ultimately, these factors contribute to generally stable LDL-cholesterol levels that are minimally affected by dietary changes.

The present study shows that the effects of dietary patterns attenuate over time, a finding that has consistently been shown in dietary RCTs and meta-analyses.[10,26] A probable explanation is that adherence to prescribed dietary pattern decreases, while adherence is a strong predictor for a sustained future effects.[38] Our analyses are based on intention-to-treat results when available, meaning that the presented results are an average effect over adherent and non-adherent study participants. Especially in studies with a longer follow-up time, the proportion of non-adherent participants is expected to increase. It may be reasonable to expect larger long-term effects of the studied dietary patterns in patients that are compliant with the intervention throughout the entire follow-up period. Identifying such participants that are likely to adhere to a dietary intervention over time, is an interesting challenge for future research and may aid in targeting dietary interventions to patients that will benefit most.

To our knowledge there are no RCTs that have directly investigated the effect of dietary patterns on the occurrence of MACE in type 2 diabetes populations. Therefore, the network estimates of the effects on cardiovascular risk factors were used to calculate the expected MACE risk reduction compared to usual diet. The PREDIMED trial, performed in a population at high risk of CVD, previously showed that a Mediterranean diet reduced MACE risk by 31% (HR 0.69, 95%CI 0.53-0.91).[39] The CORDIORPEV trial in patients with coronary heart disease, showed that a Mediterranean diet compared to a low fat diet led to a reduction in the risk of cardiovascular events up to 28% (HR 0.72, 95%CI 0.54-0. 96).[40] The estimates for MACE risk reduction in the present study were smaller, probably because they were only based on changes in SBP, LDL-cholesterol and HbA1c. This approach therefore potentially underestimates benefits of dietary patterns when these are mediated through other mechanisms, such as inflammatory state, lipids and lipoprotein composition or quality of life.[41,42]

As recommended in type 2 diabetes guidelines, adopting a healthy diet is an important part of clinical management.[8,9] This network meta-analysis underlines this recommendation, by showing that dietary patterns improve body weight and cardiovascular risk factors and potentially confer reductions in MACE risk. Of the included dietary patterns, there was no pattern that outperformed the others with regard to body weight, HbA1c, LDL and SBP reduction. The similarities between the studied dietary patterns should be noted. For example, in many of the included interventions it was recommended to consume fiber-rich foods and whole grain products and to limit sugar-sweetened beverages. Therefore, physicians should probably advice patients to adopt a healthy diet that suits their personal preferences. As adherence to a dietary pattern determines the success of dietary change, we recommend guiding patients towards a healthier dietary pattern they can maintain in the long-term.

Study strengths include the systematic search and analysis according to a pre-published protocol. Network meta-analysis techniques allowed for combining direct and indirect evidence and estimating the relative effects of dietary interventions that had not been compared in RCTs. The use of a Bayesian rather than frequentist framework allows for better modelling of the assumptions in a network meta-analysis, and is preferred by health care authorities.[43] Finally, multiple relevant cardiovascular risk factors were included, and an estimation of MACE risk reduction was made for all dietary patterns, which enables direct translation to clinical practice.

Limitations of the study include that the available RCTs were of low or moderate quality, although sensitivity analyses showed that the results were not impacted by studies at high risk of bias. We did not perform a GRADE assessment,[44] due to its poor fit to nutrition research,[45] but this means that certainty of evidence was not assessed in our analysis. A significant proportion of the included studies did not disclose funding information or was funded by advocacy groups for specific dietary patterns, which might have affected the choice of reported outcomes. Moreover, the grouping of interventions into dietary patterns inherently leads to simplification and loss of contrast. The same limitation arises for combining outcomes into two time points. However, both were necessary steps to present the available evidence in a comprehensible way and to provide sufficient power. Furthermore, the results of the ranking analyses are sensitive to the decision threshold used to determine relative effectiveness.[46] and should therefore not be interpreted as definitive evidence that one dietary pattern is more effective than alternatives, but instead should be considered in light of the small differences in the estimated effect size. Our analyses focused on cardiovascular risk factors, but adverse effects, such as hypoglycemia or nutritional deficiencies, quality of life outcomes, adequacy of dietary patterns and patient dietary preferences are highly relevant for patients in deciding on the most optimal dietary pattern and should be evaluated in future research.

CONCLUSIONS

In conclusion, this systematic review and network meta-analysis showed that dietary patterns compared with no dietary intervention had beneficial effects on body weight and glycemic control in people with type 2 diabetes, especially in the first six months. These effects were attenuated and non-statistically significant after 12 months. Furthermore, the study shows that each included dietary pattern was preferable over no dietary intervention, with subtle differences between them but no particular dietary intervention being overall better than the others. Lastly, all dietary patterns resulted in reduced MACE risk mediated by their (short-term) effects on cardiovascular risk factors. These findings stress the importance of dietary interventions in the management of type 2 diabetes and their potential to reduce cardiovascular risk. There is a need to quantify the effects of dietary pattern interventions on the occurrence of cardiovascular events in a long-term randomized controlled trial. In the meantime, patients with T2DM should be advised to adopt a healthy diet, without a preference for any dietary pattern in particular.

REFERENCES

1. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet [Internet]. 2010 Jun;375(9733):2215–22. Available from: http://dx.doi.org/10.1016/S0140-6736(10)60484-9
2. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol [Internet]. 2018 Dec 8;17(1):83. Available from: https://doi.org/10.1186/s12933-018-0728-6
3. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract [Internet]. 2019;157:107843. Available from: https://doi.org/10.1016/j.diabres.2019.107843
4. Schnurr TM, Jakupović H, Carrasquilla GD, Ängquist L, Grarup N, Sørensen TIA, et al. Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study. Diabetologia. 2020;63(7):1324–32.
5. Narayan KMV, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on Lifetime Risk for Diabetes in the U.S. Diabetes Care [Internet]. 2007 Jun 1;30(6):1562–6. Available from: http://care.diabetesjournals.org/cgi/doi/10.2337/dc06-2544
6. Klop B, Elte JWF, Cabezas MC. Dyslipidemia in Obesity: Mechanisms and Potential Targets. Nutrients. 2013;5(4):1218–40.
7. Kotchen TA. Obesity-related hypertension: Epidemiology, pathophysiology, and clinical management. Am J Hypertens [Internet]. 2010;23(11):1170–8. Available from: http://dx.doi.org/10.1038/ajh.2010.172
8. American Association of Diabetes. ADA standards of diabetes care 2021. Vol. 44, Diabetes Care. 2021. p. S21–226.
9. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J [Internet]. 2021 Aug 30;(00):1–111. Available from: https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab484/6358713
10. Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. Eur J Epidemiol [Internet]. 2018;33(2):157–70. Available from: https://doi.org/10.1007/s10654-017-0352-x
11. Huo R, Du T, Xu Y, Xu W, Chen X, Sun K, et al. Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis. Eur J Clin Nutr [Internet]. 2015 Nov 5;69(11):1200–8. Available from: http://www.nature.com/articles/ejcn2014243
12. Korsmo-Haugen HK, Brurberg KG, Mann J, Aas AM. Carbohydrate quantity in the dietary management of type 2 diabetes: A systematic review and meta-analysis. Diabetes, Obes Metab. 2019;21(1):15–27.

13. Viguiliouk E, Kendall CW, Kahleová H, Rahelić D, Salas-Salvadó J, Choo VL, et al. Effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr [Internet]. 2019 Jun;38(3):1133–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0261561418302206

14. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med. 2002;21(16):2313–24.

15. Cooper NJ, Peters J, Lai MCW, Juni P, Wandel S, Palmer S, et al. How valuable are multiple treatment comparison methods in evidence-based health-care evaluation. Value Heal [Internet]. 2011;14(2):371–80. Available from: http://dx.doi.org/10.1016/j.jval.2010.09.001

16. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:1–8.

17. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 [Internet]. Cochrane. 2020 [cited 2020 Nov 19]. Available from: www.training.cochrane.org/handbook.

18. Salanti G, Higgins JPT, Ades AE, Ioannidis JPA. Evaluation of networks of randomized trials. Stat Methods Med Res. 2008;17(3):279–301.

19. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. J Clin Epidemiol [Internet]. 2011;64(2):163–71. Available from: http://dx.doi.org/10.1016/j.jclinepi.2010.03.016

20. Berkelmans GFN, Gudbjörnsdottir S, Visseren FLJ, Wild SH, Franzen S, Chalmers J, et al. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. Eur Heart J [Internet]. 2019 Sep 7;40(34):2899–906. Available from: https://academic.oup.com/eurheartj/article/40/34/2899/5281244

21. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. 2009;52(11):2288–98.

22. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet [Internet]. 2010;376(9753):1670–81. Available from: http://dx.doi.org/10.1016/S0140-6736(10)61350-5

23. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet [Internet]. 2016 Mar;387(10022):957–67. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673615012258

24. van Valkenhoef G, Kuiper J. gemtc: Network Meta-Analysis Using Bayesian Methods. 2020.

25. Johnston BC, Kanters S, Bandayrel K, Wu P, Naji F, Siemieniuk RA, et al. Comparison of Weight Loss Among Named Diet Programs in Overweight and Obese Adults A Meta-analysis. J Am Med Assoc. 2014;312(9):923–33.

26. Ge L, Sadeghirad B, Ball GDC, Da Costa BR, Hitchcock CL, Svendrovski A, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: Systematic review and network meta-analysis of randomised trials. BMJ. 2020;369.

27. Gardner CD, Trepanowski JF, Gobbo LC Del, Hauser ME, Rigdon J, Ioannidis JPA, et al. Effect of Low-Fat vs Low-Carbohydrate Diet on 12-Month Weight Loss in Overweight Adults and the Association With Genotype Pattern or Insulin Secretion The DIETFITS Randomized Clinical Trial. J Am Med Assoc. 2018;319(7):667–79.

28. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of Weight-Loss Diets with Different Compositions of Fat, Protein, and Carbohydrates. N Engl J Med. 2009;360(9):859–73.

29. Gummesson A, Nyman E, Knutsson M, Karpefors M. Effect of weight reduction on glycated haemoglobin in weight loss trials in patients with type 2 diabetes. Diabetes, Obes Metab [Internet]. 2017 Sep 22;19(9):1295–305. Available from: https://onlinelibrary.wiley.com/doi/10.1111/dom.12971

30. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and Type 2 Diabetes after Bariatric Surgery: Systematic Review and Meta-analysis. Am J Med [Internet]. 2009 Mar;122(3):248-256.e5. Available from: http://dx.doi.org/10.1016/j.amjmed.2008.09.041

31. Goldenberg JZ, Day A, Brinkworth GD, Sato J, Yamada S, Jönsson T, et al. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission : systematic review and meta-analysis of published and unpublished randomized trial data. BMJ. 2021;372:m4743.

32. O'Neill BJ. Effect of low-carbohydrate diets on cardiometabolic risk, insulin resistance, and metabolic syndrome. Curr Opin Endocrinol Diabetes Obes [Internet]. 2020 Oct;27(5):301–7. Available from: https://journals.lww.com/10.1097/MED.0000000000000569

33. Abbasnezhad A, Falahi E, Gonzalez MJ, Kavehi P, Fouladvand F, Choghakhori R. Effect of different dietary approaches compared with a regular diet on systolic and diastolic blood pressure in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract [Internet]. 2020;163:108108. Available from: https://doi.org/10.1016/j.diabres.2020.108108

34. Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary Sodium and Cardiovascular Disease Risk — Measurement Matters. N Engl J Med. 2016;375(6):580–6.

35. Neuenschwander M, Hoffmann G, Schwingshackl L, Schlesinger S. Impact of different dietary approaches on blood lipid control in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. Eur J Epidemiol [Internet]. 2019 Sep 14;34(9):837–52. Available from: http://link.springer.com/10.1007/s10654-019-00534-1

36. Paththinige CS, Sirisena ND, Dissanayake VHW. Genetic determinants of inherited susceptibility to hypercholesterolemia – a comprehensive literature review. Lipids Health Dis. 2017;16(103):1–22.

37. Lecerf J, De Lorgeril M. Review Article Dietary cholesterol : from physiology to cardiovascular risk. Br J Nutr. 2011;106:6–14.

38. Del Corral P, Bryan DR, Garvey WT, Gower BA, Hunter GR. Dietary adherence during weight loss predicts weight regain. Obesity [Internet]. 2011;19(6):1177–81. Available from: http://dx.doi.org/10.1038/oby.2010.298/nature06264

39. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013 Apr;368(14):1279–90.

40. Delgado-lista J, Alcala-diaz JF, Torres-peña JD, Quintana-navarro GM, Fuentes F, Garcia-rios A, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet. 2022;399:1876–85.

41. Prattichizzo F, Giuliani A, Matacchione G, Ramini D, Rita A, Maria B, et al. Prevalence of residual inflammatory risk and associated clinical variables in patients with type 2 diabetes. Diabetes Obes Metab. 2020;(April):1696–700.

42. Carson TL, Hidalgo B, Ard JD, Affuso O. Special Article Dietary Interventions and Quality of Life : A Systematic Review of the Literature. J Nutr Educ Behav [Internet]. 2014;46(2):90–101. Available from: http://dx.doi.org/10.1016/j.jneb.2013.09.005

43. Hong H, Carlin BP, Shamliyan TA, Wyman JF, Ramakrishnan R, Sainfort F, et al. Comparing Bayesian and Frequentist Approaches for Multiple Outcome Mixed Treatment Comparisons. Med Decis Mak [Internet]. 2013 Jul 2;33(5):702–14. Available from: http://journals.sagepub.com/doi/10.1177/0272989X13481110

44. Grading quality of evidence and strength of recommendations. BMJ [Internet]. 2004 Jun 19;328(7454):1490. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.328.7454.1490

45. Tobias DK, Wittenbecher C, Hu FB. Grading nutrition evidence: where to go from here? Am J Clin Nutr [Internet]. 2021 Jun 1;113(6):1385–7. Available from: https://academic.oup.com/ajcn/article/113/6/1385/6272430

46. Brignardello-Petersen R, Johnston BC, Jadad AR, Tomlinson G. Using decision thresholds for ranking treatments in network meta-analysis results in more informative rankings. J Clin Epidemiol [Internet]. 2018 Jun;98:62–9. Available from: https://doi.org/10.1016/j.jclinepi.2018.02.008

SUPPLEMENTAL MATERIAL

APPENDIX S1 Search strategy

This search string was used to search for relevant literature in the PubMED. Appropriate changes were made to adapt the search string to EMBASE, The Cochrane library, SCOPUS and Web of Science. The systematic literature search was performed on 31 March 2022.

("alkaline"[Title/Abstract] OR "atkins"[Title/Abstract] OR "biggest loser"[Title/Abstract] OR "bulletproof"[Title/Abstract] OR ("DART"[Title/Abstract] OR "Reinfarction trial"[Title/Abstract]) OR ("DASH"[Title/Abstract] OR "Dietary approach to stop hypertension"[Title/Abstract]) OR "drinking man*"[Title/Abstract] OR "Dukan"[Title/Abstract] OR "Engine"[Title/Abstract] OR ("F-plan"[Title/Abstract] OR "F2"[Title/Abstract]) OR "Fertility diet"[Title/Abstract] OR "FODMAP"[Title/Abstract] OR "Hamptons"[Title/Abstract] OR "High Protein"[Title/Abstract] OR "HMR"[Title/Abstract] OR "Jenny Craig"[Title/Abstract] OR "keto*"[Title/Abstract] OR "LEARN"[Title/Abstract] OR ("low carb*"[Title/Abstract] OR "carbohydrate restr*"[Title/Abstract] OR "restricted carb*"[Title/Abstract]) OR ("low fat"[Title/Abstract] OR "fat free"[Title/Abstract] OR "fat restrict*"[Title/Abstract] OR ("restrict*"[All Fields] AND "lipid"[Title/Abstract])) OR "low glycemic index"[Title/Abstract] OR ("low salt"[Title/Abstract] OR "low sodium"[Title/Abstract] OR "salt restrict*"[Title/Abstract] OR "saltless"[Title/Abstract] OR "sodium free"[Title/Abstract]) OR "Mayo clinic diet"[Title/Abstract] OR "McDougal"[Title/Abstract] OR "Mediterranean"[Title/Abstract] OR "MIND"[Title/Abstract] OR "Nordic diet"[Title/Abstract] OR "Nutrisystem"[Title/Abstract] OR "Ornish"[Title/Abstract] OR "Okinawa"[Title/Abstract] OR "Optavia"[Title/Abstract] OR "paleo*"[Title/Abstract] OR "Pioppi"[Title/Abstract] OR "Plant-based"[Title/Abstract] OR "Portfolio diet"[Title/Abstract] OR "Pritikin"[Title/Abstract] OR "Protein power"[Title/Abstract] OR "Rosedale"[Title/Abstract] OR "Rosemary Conley"[Title/Abstract] OR "Salisbury"[Title/Abstract] OR "Scarsdale"[Title/Abstract] OR "slimming world"[Title/Abstract] OR "South beach"[Title/Abstract] OR "Stillmann"[Title/Abstract] OR "Sugar busters"[Title/Abstract] OR ("TLC"[Title/Abstract] OR "Therapeutic lifestyle changes"[Title/Abstract]) OR "Vegetarian"[Title/Abstract] OR "vegan"[Title/Abstract] OR "Volumetrics"[Title/Abstract] OR "Western diet"[Title/Abstract] OR ("weight watcher*"[Title/Abstract] OR "weightwatcher*"[Title/Abstract]) OR "ZONE"[Title/Abstract] OR "American Heart Association"[Title/Abstract] OR "Cardiac diet"[Title/

Abstract] OR “Cardioprotective”[Title/Abstract] OR “Dietary guidelines”[Title/Abstract] OR “Dietary index”[Title/Abstract] OR “eating pattern*”[Title/Abstract] OR “eating plan*”[Title/Abstract] OR “Guidance”[Title/Abstract] OR “Healthy diet index”[Title/Abstract] OR “Healthy diet score”[Title/Abstract] OR “Nutrition therapy”[Title/Abstract] OR “Nutritional therapy”[Title/Abstract] OR “Prudent diet”[Title/Abstract] OR “Usual diet”[Title/Abstract]) AND (“diet”[MeSH Terms] OR “diet*”[Title/Abstract] OR “nutrition*”[Title/Abstract])

AND

((“diabetes”[Title/Abstract] OR “diabetes mellitus”[MeSH Terms]) NOT (“diabetes, gestational”[MeSH Terms] OR “gestational”[Title/Abstract] OR “pregnan*”[Title/Abstract] OR “gravidarum”[Title/Abstract]))

AND

(“randomized controlled trial”[Publication Type] OR “controlled clinical trial”[Publication Type] OR “randomized controlled trial”[Title/Abstract] OR “Clinical trial”[Title/Abstract])

TABLE S1 Eligibility criteria for inclusion in the systematic literature search

Inclusion criteria	Exclusion criteria
• Randomized controlled trial • Comparison between full dietary pattern and an alternative dietary pattern or usual diet • Population with type II diabetes mellitus • Reporting changes in one or more of: o Body weight o HbA1c o Systolic blood pressure o Lipid profile (LDL-C, HDL-C and/or triglycerides) o CRP • Minimum follow-up 12 weeks • Participants aged ≥18 years	• Dietary intervention consisting of one specific food group • Dietary interventions focused on timing of food consumption (*e.g.* intermittent fasting) • Interventions combining multiple lifestyle interventions such as diet and exercise* • Interventions combining diet and medication* • Interventions comparing diet against medication • Population of women with gestational diabetes

HbA1c: glycosylated haemoglobin, LDL-C: Low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, CRP: C reactive protein. * If non-diet components of the lifestyle intervention (e.g. smoking cessation, physical exercise programs) or medication were equal in the intervention and reference groups, trials were not excluded. Any differences in effects in these studies can be assumed to be the result of the differences in the dietary component of the interventions.

TABLE S2 Criteria for diet category classification

	Macronutrient distribution			
Diet group	E% Carb	E% Fat	E% Protein	**Other dietary characteristics**
High protein			>25	
Low carbohydate	<30			
Low fat diet		<30		
Low GI / High fiber				Intervention focusing on low glycemic index or load
Mediterranean diet				Fruit, vegetables, olive oil, legumes, cereals, fish, high MUFA/PUFA
Moderate carbohydrate	>45	>30	≤25	
Plant-based				Vegan or vegetarian dietary pattern: exclusion of meat and fish from the diet.
No dietary intervention				No or minimal dietary intervention: no additional dietary advice or counselling compared to usual care for diabetes patients. Interventions not extending a single counselling session by the treating physician or the provision of an instructional pamphlet.

This table shows the criteria that were used to classify the dietary interventions from the included randomized controlled trials into dietary patterns groups for the network meta-analysis. The name of a diet in an RCT did not necessarily directly correspond to the dietary pattern category in our analysis. To minimize heterogeneity these cut-off values were leading.

APPENDIX S2 Example calculation of MACE risk reduction achieved by dietary pattern interventions

Assumptions

- Estimates of the effects of reductions in HbA1c, LDL-cholesterol and systolic blood pressure were obtained from previously published meta-analyses:
    - A 10 mmol/l (0.91%) reduction in HbA1c results in a 9% relative risk reduction (HR 0.91, 95% 0.84-0.99)1.
    - A 1 mmol/l (38.67 mg/dl) reduction in LDL-cholesterol results in 22% relative risk reduction of 22% (HR 0.78, 95%CI 0.76; 0.80)2
    - A 10 mmHg reduction in systolic blood pressure results in 20% relative risk reduction (HR 0.80, 95%CI 0.77-0.83)3.
- Reductions in HbA1c, LDL-cholesterol and systolic blood pressure are linearly associated with MACE risk and the relative risk reduction is not influenced by the baseline value before dietary intervention. The effects of HbA1c, LDL-cholesterol and systolic blood pressure are independent

Example calculation

6 month network estimates for effect of the plant-based diet compared to no dietary intervention:

- HbA1c: - 0.6%, 95CrI -0.8; -0.3%, i.e. – 6.6 mmol/l, 95%CrI -8.7; -3.3 mmol
- LDL-cholesterol: -0.2 mmol/l, 95%CrI -0.4; 0.1 mmol/l
- Systolic blood pressure: - 0.7 mmHg, -10.8; 9.3 mmHg.

First, the effects of a dietary intervention on MACE risk, achieved through the modification of a single cardiovascular risk factor was calculated by multiplying the network estimate and corresponding upper and lower limits of the credibility interval with the treatment effects obtained from literature:

Risk factor	Mean	Lower 95%CrI	Upper 95%CrI	Estimated RRR
HbA1c	0.91^0.66 = 0.94	0.91^0.87 = 0.92	0.91^0.33 = 0.97	-6%, 95%CI-8; -3%
LDL-C	0.78^0.20 = 0.95	0.78^0.40 = 0.91	0.78^-0.10 = 1.03	-5%, 95%CI -9; +3%
Systolic BP	0.80^0.07 = 0.98	0.80^1.08 = 0.79	0.80^-0.93 = 1.23	-2%, 95%CI -21;+23%

Finally, to estimate the overall effect of a dietary intervention on relative MACE risk, the estimated hazard ratios for the different cardiovascular risk factors were multiplied. The upper and lower bounds for the 95% confidence interval were obtained

by multiplying the estimates for the upper and lower bound of the effects of the individual cardiovascular risk factors, respectively. Results are presented as relative risk reductions (RRR) to aid interpretability.

Combined estimate = 0.94 * 0.78 * 0.98 = 0.88 → Relative risk reduction: (1 – 0.88) * 100% = 12.0%

Lower bound = 0.92 * 0.91 * 0.79 = 0.66 → Lower bound RRR : (1 - 0.64) * 100% = 34.5%

Upper bound = 0.97 * 1.03 * 1.23 = 1.23 → Upper bound RRR: (1 - 1.23) * 100% = -22.9%

Overall estimate for relative MACE risk reduction achieved by plant-based diet vs. no intervention 12.0% (95%CI -22.9; 34.5%)

Note: Values were not rounded until the final step of the calculation. A RRR above zero favours the intervention diet.

TABLE S3 Characteristics of eligible randomized controlled trials

First author	Year	Country	FU time (wk)	N	Dietary pattern I	Dietary pattern II	Dietary pattern III	Intention isocaloric	Female (%)	Age (yr)	BMI (kg/m²)	T2D duration (yr)	Insulin dependent (%)	LLT (%)	AHT (%)
AlFaris[4]	2020	Saudi Arabia	13	26	Low fat	No intervention		No	100		37		0		
Asle Mohammadi Zadeh[5]	2018	Iran	24	33	Low carbohydrate	Low fat	No intervention	Yes	0	47	34	7	0		
Barnard[6,7]	2006	USA	74	99	Plant-based	Moderate carbohydrate		No	60	56	35	9	16	55	70
Barnard[8]	2019	USA	20	45	Plant-based	Low fat		No	53	61	34				
Brunerova[9]	2007	USA	12	27	Moderate carbohydrate	Low fat		Yes		53	34		0		
Bunner[10]	2015	USA	20	35	Plant-based	No intervention		Unknown	56	57	36	14	44		
Cai[11]	2017	China	26	130	Low GI	No intervention		Unknown	46	57		6	0		
Chen[12]	2020	Taiwan	78	92	Low carbohydrate	Low fat		No	61	64		10	16		
Coppell[13]	2010	New Zealand	26	93	Low fat	No intervention		Unknown	59	58		9	30	61	>60
Davis[14–16]	2009	USA	52	105	High protein	Moderate carbohydrate		Unknown	78	54	36		30	59	
de Bont[17]	1981	United Kingdom	26	137	Low fat	Moderate carbohydrate			100	55		7	2		
Dodson[18]	1984	United Kingdom	13	50	Low fat	Moderate carbohydrate		No	50	57	28	6	22		26
Durrer[19]	2021	Canada	12	188	Low carbohydrate	No intervention		No	54	58	36	10			
Dyson[20]	2007	United Kingdom	13	13	Low carbohydrate	No intervention		Unknown	70	54	35		0		
Elhayany[21]	2010	Israel	52	259	Mediterranean	Low GI	Moderate carbohydrate	Yes	48	55	31	6	0		
Esposito[22–25]	2009	Italy	208	215	Mediterranean	Low fat		Yes	51	52	30		0	14	24
Evangelista[26]	2009	USA	13	14	Low fat	No intervention		No	21	59	38		0		100
Evangelista[27]	2021	USA	76	13	High protein	Moderate carbohydrate		Yes	28	58					100
Fabricatore[28]	2011	USA	40	79	Low fat	Low GI			80	53	36				
Facchini[29]	2003	USA	210	191	Low fat	No intervention		No	47	59	28	10	50	8	>78

TABLE S3 (Continued)

First author	Year	Country	FU time (wk)	N	Dietary pattern I	Dietary pattern II	Dietary pattern III	Intention isocaloric	Female (%)	Age (yr)	BMI (kg/m²)	T2D duration (yr)	Insulin dependent (%)	LLT (%)	AHT (%)
Ferdowsian[30]	2010	United States	22	19	Plant-based	No intervention		Unknown	55						
Goday[31]	2016	Spain	17	89	High protein	Low fat		No	65	55	33		0		
Goldstein[32]	2011	Israel	52	52	Low carbohydrate	Moderate carbohydrate		No	52	56	33	8			
Gram-Kampmann[33]	2022	Denmark	26	71	Low carbohydrate	No intervention		Yes	56	57		5	7	1	>36
Guldbrand[34,35]	2012	Sweden	104	61	Low fat	Low carbohydrate		Yes	44	62	33	9	34		
Heilbronn[36]	1999	Australia	12	35	Low fat	Moderate carbohydrate	Moderate carbohydrate	Unknown	77	58	33	5	0	0	
Hockaday[37]	1978	United Kingdom	52	93	Moderate carbohydrate	Low fat		Yes	44	52					
Iqbal[38]	2010	USA	104	144	Low carbohydrate	Moderate carbohydrate		No	10	59	38		26	54	66
Itsiopoulos[39]	2009	Australia	24	27	Mediterranean	No intervention		No	41		31	6	11	26	48
Jesudason[4040,41]	2013	Australia	52	45	High protein	Moderate carbohydrate		Yes	22	61	36	10	18		>76
Jin[42]	2020	South Korea	12	60	Low carbohydrate	Moderate carbohydrate		Yes	48	62	24	14	0	70	37
Jonsson[43]	2009	Sweden	26	13	High protein	No intervention		Unknown	23	64	30	8	0	62	39
Kahleova[44-47]	2010	Czech Republic	78	74	Plant-based	No intervention		Yes	53		35		0	51	64
Kimura[48]	2018	Japan	12	48	Moderate carbohydrate	Low fat		Yes	67	65	25	12	0		
Krebs[49]	2012	New Zealand	104	419	High protein	Low fat		Yes	60	58	37	8	27	66	76
Larsen[50]	2011	Australia	52	99	Moderate carbohydrate	High protein		Yes	52	59		9	17		
Lasa[51]	2014	Spain	52	191	Mediterranean	Low fat		Unknown	60	67	30		0		
Lee[52]	2016	South Korea	12	93	Plant-based	Low fat		No	81	58	24	9	16	53	43
Li[53]	2022	China	12	60	Low carbohydrate	Low fat		Yes		37	29	0	0		
Liu[54]	2018	China	12	122	Low fat	High protein		Yes	50	50	21	31		0	

TABLE S3 (Continued)

First author	Year	Country	FU time (wk)	N	Dietary pattern I	Dietary pattern II	Dietary pattern III	Intention isocaloric	Female (%)	Age (yr)	BMI (kg/m^2)	T2D duration (yr)	Insulin dependent (%)	LLT (%)	AHT (%)
Lopez-Espinoza[55]	1984	United Kingdom	364	59	Low fat	Moderate carbohydrate		Yes	42	56	31	7	15		
Luger[56]	2013	Austria	12	44	Low fat	High protein		Yes	55	62	33	17	100	59	91
Ma[57]	2008	United States	52	40	Low GI	Moderate carbohydrate		Unknown	53	54	36	9	25	75	60
Metz[58]	2000	United States	52	119	Low fat	No intervention		Unknown	58	54	34		0		
Milne[59]	1994	New Zealand	72	64	Low fat	Low carbohydrate	No intervention	Yes	55	59	29	5	0		
Mishra[60]	2013	United States	18	43	Plant-based	No intervention		Yes	83	45	35				
Morris[61]	2020	United Kingdom	12	32	Low carbohydrate	No intervention		No	55	67	35	9	0		
Nicholson[62,63]	1999	United States	12	11	Plant-based	No intervention		No	45	54			18		
Parker[64,65]	2002	Australia	64	54	High protein	Low fat		Yes	65	61			7	42	47
Pascale[66]	1995	United States	52	31	Moderate carbohydrate	Low fat		Yes	100	57	36		0		
Pavithran[67]	2020	India	24	36	Low GI	No intervention		Unknown	42	52	27	7			
Pavithran[64]	2020	India	24	80	Low GI	No intervention		Unknown	35	53	27		38	58	53
Perna[68]	2019	Italy	12	17	Low carbohydrate	No intervention		Yes	65	64	31		0		
Pijls[69,70]	1999	The Netherlands	52	121	Moderate carbohydrate	No intervention		Unknown	39	64	28	7	3		0
Ren[71]	2020	China	12	45	Moderate carbohydrate	Low GI		Unknown	56	72	24	15	38		
Sato[72,73]	2017	Japan	72	62	Low carbohydrate	No intervention		No	23	59	27	14	30	69	43
Shai[74]	2008	Israel	12	46	Low fat	Low carbohydrate	Mediterranean	No	14	52	31			26	30
Struik[75]	2020	Australia	16	84	Moderate carbohydrate	Low carbohydrate		Yes	48	59	35	7			
Tay[76–83]	2015	Australia	104	115	Low carbohydrate	Low GI		Yes	43	58	35	7	10	62	66
Tsihlias[84]	2000	Canada	26	91	Low GI	Moderate carbohydrate	Low fat	Unknown	43	63	28		0	18	53

TABLE S3 (Continued)

First author	Year	Country	FU time (wk)	N	Dietary pattern I	Dietary pattern II	Dietary pattern III	Intention isocaloric	Female (%)	Age (yr)	BMI (kg/m^2)	T2D duration (yr)	Insulin dependent (%)	LLT (%)	AHT (%)
Visek[85]	2014	Czech Republic	12	20	Low GI	No intervention		Unknown	40	63	32	7	0		
Walker[63,86]	1995	Australia	12	24	Low fat	High protein		Yes	63	58	29		0		
Wang[87]	2018	China	12	49	Moderate carbohydrate	Low fat		Unknown	53	64	24			39	
Watson[88,89]	2016	Australia	24	61	Low fat	Low GI		Yes	46	54	34		66	56	51
Westman[90]	2008	USA	24	97	Low carbohydrate	Low GI		No	70	51	38				
Wolever[91–93]	2008	Canada	52	156	Low carbohydrate	Moderate carbohydrate	Low GI	Unknown	55	64	31		0	43	
Wycherley[94]	2010	Australia	16	31	Low fat	No intervention		Yes		55	35		0	35	43
Wycherley[95]	2016	Australia	52	115	Low carb	No intervention		Yes	43	58	34.6			62	66
Yamada[96]	2014	Japan	26	24	Moderate carbohydrate	No intervention		No	50	63	26	9	29		
Yusof[97]	2009	Malaysia	12	104	Low GI	Moderate carbohydrate		Unknown			27				
Zahedi[98]	2020	Iran	26	228	Mediterranean	No intervention		Unknown	77	57					
Zainordin[99]	2021	Malaysia	12	30	Low carbohydrate	Moderate carbohydrate		Unknown	40	57	31	11			

This table shows the main study characteristics for the studies that were included in the network meta-analysis and provides references to the published articles that were used to extract data from. The dietary patterns in this table are the dietary pattern groups that the dietary interventions from these trials were assigned to for our analyses. Abbreviations: T2DM: type 2 diabetes, mellitus, NIDDM: Non-insulin dependent diabetes mellitus, BMI: body mass index, eGFT: estmated glomerular filtration rate, UK: United Kingdom, USA: United states of America

TABLE S4 Funding and conflicts of interest

TABLE S4a Funding and conflicts of interest per dietary pattern

Dietary pattern	Total studies N	Funding from governmental or academic institutions, N (%)	Industry-sponsored or industry-related conflicts of interest, N (%)	Funding/COI unknown, N (%)
No intervention	29	12 (41)	10 (34)	8 (28)
High protein	11	4 (36)	6 (55)	1 (9)
Low carbohydrate	21	11 (52)	8 (38)	3 (14)
Low fat	34	21 (62)	11 (32)	6 (18)
Low glycemic index	14	6 (43)	5 (36)	4 (29)
Mediterranean	6	4 (67)	0 (0)	2 (33)
Moderate carbohydrate	28	13 (46)	8 (29)	10 (36)
Plant-based	8	4 (50)	4 (50)	2 (25)

Overview of sources of funding per dietary pattern. Percentages were calculated by dividing the number of studies receiving funding from a specific source by the total number of studies performed with that dietary pattern. Note: some studies received both industry- and governmental funding, meaning that percentages can add up to more than 100% in total. Abbreviations: COI – conflicts of interest.

TABLE S4b Funding and conflicts of interest per study

Information on funding for the reported study and authors' conflicts of interest were extracted from the full text record or publisher website.

First author	Year	Funding	Reported conflicts of interest
AlFaris[4]	2020	The King Abdul-Aziz City for Science and Technology (KACST), Riyadh, Saudi Arabia, Grant/Award Number: AT-10-12 (and -10-12 ط) Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fasttrack Research Funding Program.	Not reported.
Asle Mohammadi Zadeh[5]	2018	Faculty of Physical Education and Sports Sciences, Isfahan University, Iran.	Not reported
Barnard[6,7]	2006	Physicians Committee for Responsible Medicine.	Physicians Committee for Responsible Medicine
Barnard[8]	2019	The study was supported by grant R01 DK059362-01A2 from the National Institute of Diabetes and Digestive and Kidney Diseases and by the Diabetes Action Research and Education Foundation.	Physicians Committee for Responsible Medicine
Brunerova[9]	2007	VZ MSM 0021620814	Not reported
Bunner[10]	2015	Not reported	Physicians Committee for Responsible Medicine
Cai[11]	2017	Not reported	Not reported
Chen[12]	2020	National Taiwan University Hospital	None declared
Coppell[13]	2010	Health Research Council of New Zealand (06/352) and the Southern Trust, New Zealand	None declared
Davis[14–16]	2009	Robert C. Atkins Foundation and the Diabetes Research and Training Center (P60 DK020541) and by Clinical and Translational Science Award UL1 RR025750.	Bayer, Sanofi
de Bont[17]	1981	Not reported	Mr. A. de Bont was supported by a Royal Society fellowship as part of the European Science Exchange Programme of the Royal Society London and the 'Netherlands Organization for the Advancement of Pure Research'
Dodson[18]	1984	Not reported	Not reported
Durrer[19]	2021	Peer-reviewed funding was obtained from the Mitacs Accelerate program (Grant No. IT08605). Matching funds for the Mitacs Accelerate fellowship to C.D. were provided by industry partner Pharmasave Drugs (Pacific) Ltd. Further funding support was provided through salary support to J.P.L. from the Canadian Institutes for Health Research (MSH-141980) and the Michael Smith Foundation for Health Research (Scholar Award #16890). Food products were provided in-kind to pharmacies by Ideal Protein. The funding agencies did not influence the study design or manuscript writing	J.P.L. holds founder shares and advises for Metabolic Insights Inc., and is volunteer Chief Scientific Officer for the not-for-profit Institute for Personalized Therapeutic Nutrition S.M. is employed as Chief Executive Officer for the not-for-profit Institute for Personalized Therapeutic Nutrition. J.W. is a member of the Scientific Advisory Board, and has received travel support and speaker's honoraria, from Atkins Nutritionals Inc. J.D.J. is Chair of the Board for the Institute for Personalized Therapeutic Nutrition and receives no compensation. C.D., J.S., A.M.B., and K.G. have nothing to declare.
Dyson[20]	2007	funded by Medisense UK, Abbott Laboratories	DRM and PAD have received research funding from the Sugar Bureau. SB has no competing interests to declare.

TABLE S4b (Continued)

First author	Year	Funding	Reported conflicts of interest
Elhayany[21]	2010	Not reported	Not reported
Esposito[22–25]	2009	Second University of Naples	None disclosed
Evangelista[26]	2009	Intramural grant and by the University of California School of Nursing	None disclosed
Evangelista[27]	2021	Intramural grant and by the University of California School of Nursing	None disclosed
Fabricatore[28]	2011	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to Dr. Fabricatore. In addition, this project was supported by grant K24DK065018 from NIDDK to Dr. Wadden, by grant K24DK082730 from NIDDK to Dr. Ludwig, and by grant UL1 RR024134 from the National Center for Research Resources. Calorie guides were donated by Calorie King.	Dr. Fabricatore has received research funding from Merck, and has received consulting fees from Merck, Pfizer, and Allergan. Although he was employed full-time by the University of Pennsylvania when this study was conceivedand completed, Dr. Fabricatore is currently employed by Nutrisystem, Inc. Dr. Wadden has received research support from Novo Nordisk and serves on the Advisory Board of Novo Nordisk, Orexigen Therapeutics, and Vivus. Dr. Schwartz has received honoraria in the past year from Medtronic, Takeda, Novo Nordisk, Lilly, Merck, and Amylin for advisory board participation, and from Lilly, Amylin, Sanofi-Aventis, BMS/Astra-Zeneca, Novo Nordisk, Merck, and Takeda for speaker bureau participation.
Facchini[29]	2003	Not reported	Not reported
Ferdowsian[30]	2010	The study was funded by the Washington Center for Clinical Research	Not reported
Goday[31]	2016	The founding for the study as well as the DiaproKal Method products were provided by Pronokal Group., (Barcelona, Spain) free of charge to the patients. The funding source had no involvement in the study design, recruitment of patients, study interventions, the data collection or interpretation of the results. The investigators and representatives from Pronokal Group were responsible for the study design, protocol, statistical analysis plans, analysis and reporting of the results. Final responsibility for the decision to submit the manuscript for publication was made jointly by all author.	AG, DB, BM, ABC and FFC received advisory board fees and or research grants from Pronokal Protein Supplies Spain.
Goldstein[32]	2011	There were no study sponsors for this manuscript	No authors have conflicts of interest to disclose.
Gram-Kampmann[33]	2022	AP Møller Foundation; Danish Diabetes Academy funded by the Novo Nordisk Foundation; Novo Nordisk Fonden; Odense Universitetshospital; Overlæge Johan Boserup og Lise Boserups Legat; Region of Southern Denmark; Syddansk Universitet	The authors declare that there is no duality of interest associated with this manuscript.
Guldbrand[34,35]	2012	University Hospital of Linköping Research Funds, Linköping University, the County Council of Östergötland, and the Diabetes Research Centre of Linköping University	The authors declare that there is no duality of interest associated with this manuscript.
Heilbronn[36]	1999	Not reported	Not reported
Hockaday[37]	1978	British Diabetic Association and from the International Sugar Research Foundation	Not reported

TABLE S4b (Continued)

First author	Year	Funding	Reported conflicts of interest
Iqbal[38]	2010	VA Merit Review Entry Program	Not reported
Itsiopoulos[39]	2009	The National Health and Medical Research Council of Australia part-funded this study (Project # 124317)	Not reported
Jesudason[4040,41]	2013	Supported by an National Health and Medical Research Council Principal Research Fellowship (to PMC).	Not reported
Jin[42]	2020	Dr. Kitchen Corp., Seoul, Korea	The authors declare no conflict of interest.
Jonsson[43]	2009	The study was funded by Crafoordska stiftelsen, Region Skåne and Lund University.	The authors declare that they have no competing interests.
Kahleova[44-47]	2010	This work was supported by grant IGA MZCR NS/10534-3 from Ministry of Health, Prague, Czech Republic	Nothing to declare
Kimura[48]	2018	Not reported	None of the authors have any potential conflict of interest associated with this research.
Krebs[49]	2012	The Health Research Council of New Zealand (06/337).	The authors declare that there is no duality of interest associated with this manuscript.
Larsen[50]	2011	This study was funded by a nutritional research grant from Meat and Livestock Australia (MLA). J.E. Shaw is supported by NHMRC Fellowship 586623.	J. E. Shaw has received grants, honoraria and speakers' fees from: GlaxoSmithKline, Lilly Pharmaceuticals, Bristol Myers Squibb, Astra Zeneca, Pfizer, Merck Sharp and Dolme, and Novo Nordisk. N. Mann has received two nutrition grants from MLA in the last 5 years. The protocol and execution of the study was the responsibility of the investigators. MLA had no role in the study design, data collection, data analysis, data interpretation or the decision to submit this paper for publication.
Lasa[51]	2014	This study was funded by the Spanish Ministry of Health (PI1001407, AGL2009-130906-C02-02, AGL2010-22319-C03-02, G03/140, RD06/0045), by Carlos III Health Institute (PREDIMED; CIBERobn), by Public Health Division of the Department of Health of the Autonomous Government of Catalonia in collaboration with Merck Sharp & Dohme Laboratories, by the Government of the Basque Country (IT-572-13) and by the University of the Basque Country (EDUNANOTEK, UFI11/32).	The authors declare no conflict of interest.
Lee[52]	2016	This research was supported by the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare (A111716-1202-0000100), as well as the Korean Health Technology R&D Project, funded by the Ministry of Health and Welfare, Republic of Korea (HI13C0715 and HI11C1300).	The authors have declared that no competing interests exist.
Li[53]	2022	This work was supported by Putian Science and Technology Bureau, Fujian province, China. The funding agency was not involved in the design of the study, collection, analysis, and interpretation of data, or preparation of the manuscript.	The authors declare that they have no competing interests.

TABLE S4b (Continued)

First author	Year	Funding	Reported conflicts of interest
Liu[54]	2018	Supported by the National Natural Science Foundation of China (no. 81472973), Nutrition Science Foundation of BY-HEALTH (TY-20140101), and Sansun Life Sciences Foundation.	None of the authors declared a conflict of interest.
Lopez-Espinoza[55]	1984	This study was supported by the Simon Broome Heart Research Trust and the Oxford Diabetes Trust funding of the Sheikh Rashid Diabetes Unit.	Not reported
Luger[56]	2013	Not reported	None of the authors had a confl ict of interest in relation to this manuscript.
Ma[57]	2008	The project described was supported by grant 5 P30 DK032520 from the National Institute of Diabetes and Digestive and Kidney Diseases.	Not reported
Metz[58]	2000	Campbell's Center for Nutrition and Wellness, Campbell Soup Company, Camden, NJ	Not reported
Milne[59]	1994	This study was supported by a grant from the Health Research Council of New Zealand.	Not reported
Mishra[60]	2013	This research is supported by Physicians Committee for Responsible Medicine, 5100 Wisconsin Avenue, Suite 400, Washington, DC 20016.	Dr Neal Barnard gives lectures and writes books on the subject of plant-based diets and receives occasional honoraria and royalties therefrom. The remaining authors declare no conflict of interest.
Morris[61]	2020	This study was supported by the NIHR Oxford Biomedical Research Centre (BRC) and NIHR School for Primary Care Research (SPCR).	P. A. and S. A. J. have received research grant funding but no personal remuneration from commercial weight loss companies, but none of these companies have interests in the programme described here. C. B. is the author of The 8-week blood sugar diet recipe book and The Fast 800 recipe book, and part-owner of thefast800.com. P. D. is a member (unpaid) of the Joint SACN/ NHS England/Diabetes UK Working Group to review the evidence on lower carbohydrate diets compared with current government advice for adults with type 2 diabetes.
Nicholson[62,63]	1999	This research was supported by a grant from the Diabetes Action Research and Education Foundation, with additional funding from the Physicians Committee for Responsible Medicine.	Not reported
Parker[64,65]	2002	We gratefully acknowledge the support of Meadow Lea Foods for their financial contribution to this study.	Not reported
Pascale[66]	1995	This research was supported by the National Institutes of Health through the funding of the Obesity/Nutrition Research Center (NIDDK-46204) and through a research grant (NIDDK-29757). R.W.P. was supported by a Postdoctoral Fellowship from the HJ. Heinz Company.	Not reported
Pavithran[67]	2020	This research received no external funding.	The authors declare no conflict of interest.
Pavithran[64]	2020	This research received no external funding.	The authors declare no conflict of interest.
Perna[68]	2019	Deanship of Scientific Research, University of Bahrain (Project No. 19/2011).	None
Pijls[69,70]	1999	Not reported	Not reported
Ren[71]	2020	This research was funded by Suzhou Science and Technology Project, China (Grant number SYS2019026).	he authors declare no conflict of interest.

TABLE S4b (Continued)

First author	Year	Funding	Reported conflicts of interest
Sato[72,73]	2017	JS received funds from the Mishima Kaiun Memorial Foundation. http://www.mishima-kaiun.or.jp/.	I have read the journal's policy and the authors of this manuscript have the following competing interests: JS has received lecture fees from Novartis Pharmaceuticals, NovoNordisk Pharma, Sanofi, and Takeda Pharmaceutical Co. AK has received lecture fees from Kissei Pharma, Sanofi, and Takeda Pharmaceutical Co. YT has received lecture fees from Takeda Pharmaceutical Co., MSD, Eli Lilly, Kissei Pharma, and AstraZeneca. TM has received lecture fees from MSD, Takeda Pharmaceutical Co., and Eli Lilly. HW has received lecture fees from Asteras, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo Inc., Eli Lilly, Kissei Pharma, Kowa Pharmaceutical Co., Kyowa Hakko Kirin Co., MSD, Novartis Pharmaceuticals, Novo Nordisk Pharma, Ono Pharmaceutical Co., Mitsubishi Tanabe Pharma, Sanofi, Sanwakagaku Kenkyusho, and Takeda Pharmaceutical Co., and has received research funds from Asteras, AstraZeneca, Bristol- Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo Inc., Dainippon Sumitomo Pharma, Eli Lilly, Johnson and Johnson, Kissei Pharmaceutical Co., Kowa Pharmaceutical Co., Kyowa Hakko Kirin Co. MSD, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical Co., Novartis Pharmaceuticals, Novo Nordisk Pharma, Pfizer, Sanwakagaku Kenkyusho, Sanofi, and Takeda Pharmaceutical Co. All the other authors report no conflict of interest.
Shai[74]	2008	This work was supported by the funds from the Mishima Kaiun Memorial Foundation.	S has received lecture fees from Novartis Pharmaceuticals, Novo Nordisk Pharma, Sanofi, and Takeda Pharmaceutical Co. AK has received lecture fees from Kissei Pharma, Sanofi and Takeda Pharmaceutical Co. YT has received lecture fees from Takeda Pharmaceutical Co., MSD, Eli Lilly, Kissei Pharma and AstraZeneca. TMhas received lecture fees from MSD, Takeda Pharmaceutical Co., and Eli Lilly. YF has received lecture fees from Novartis Pharmaceuticals and Eli Lilly, research funds from Novartis Pharmaceuticals, MSD and Takeda Pharmaceutical Co. HW has received lecture fees from Asteras, Astrazeneca, Boehringer Ingelheim, Daiichi Sankyo Inc., Eli Lilly and Company, Kissei Pharmaceutical Co., Kowa Pharmaceutical CO., Kyowa Hakko Kirin Co., MSD, Novartis Pharmaceuticals, Novo Nordisk Pharma, Ono Pharmaceutical Co., Mitsubishi Tanabe Pharma, Sanofi-Aventis, Sanwakagaku Kenkyusho, and Takeda Pharmaceutical Co. and research funds from Asteras, Astrazeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo Inc., Dainippon Sumitomo Pharma, Eli Lilly, Johnson and Johnson, Kissei Pharmaceutical Co., Kowa Pharmaceutical Co., Kyowa Hakko Kirin Co. MSD, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical Novartis Pharmaceuticals, Novo Nordisk Pharma, Pfizer, Sanwakagaku Kenkyusho, Sanofi, and Takeda Pharmaceutical Co. All the other authors report no conflict of interest.
Struik[75]	2020	Supported by the Nuclear Research Center Negev (NRCN), the Dr. Robert C. and Veronica Atkins Research Foundation, and the S. Daniel Abraham International Center for Health and Nutrition, Ben-Gurion University, Israel.	No potential conflict of interest relevant to this article was reported.

TABLE S4b (Continued)

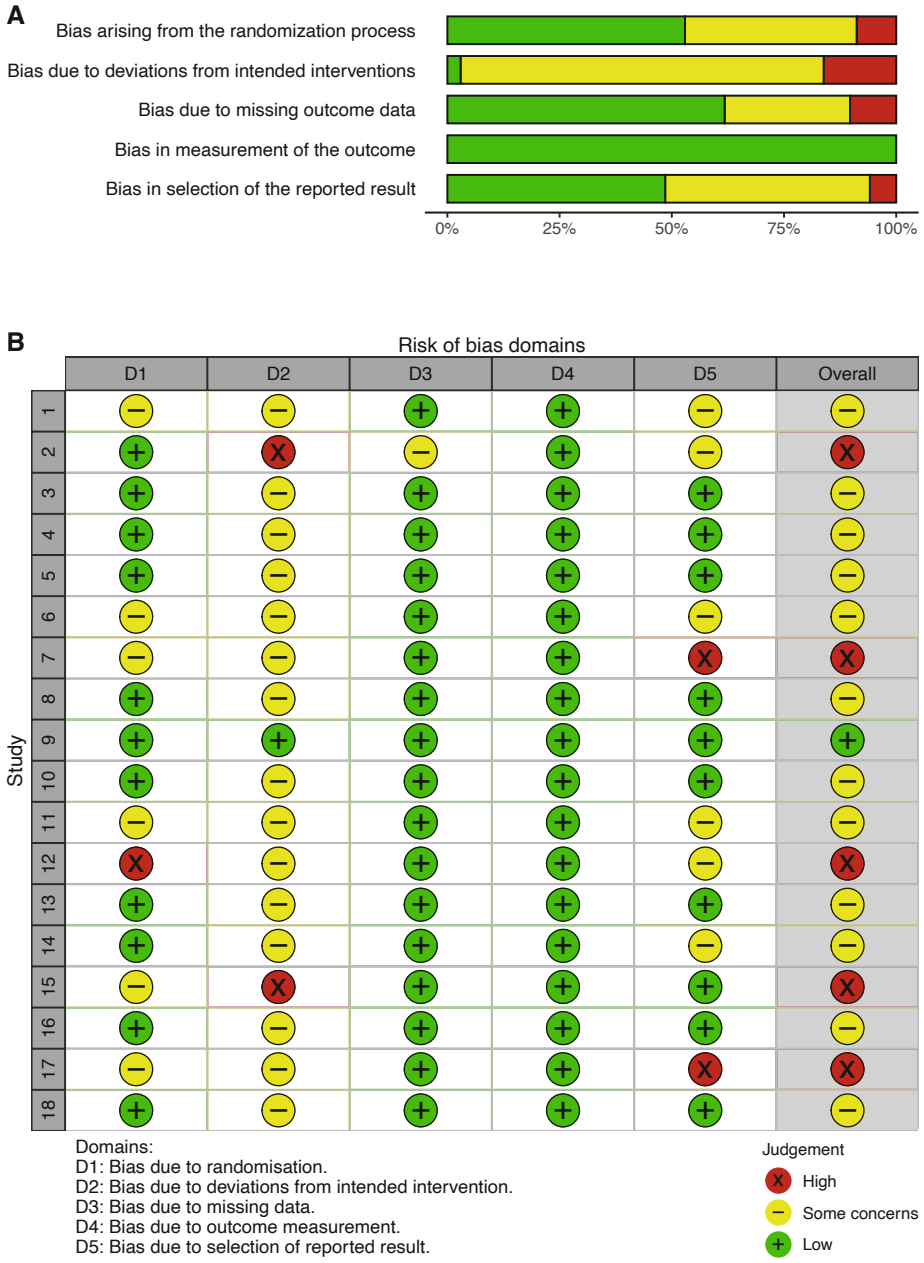
First author	Year	Funding	Reported conflicts of interest
Tay[76-83]	2015	This study was supported by National Health and Medical Research Council project grant 103415. J.T. was supported by a postgraduate research scholarship from the Agency for Science, Technology and Research (A*STAR). No sponsor or funding source had a role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.	No potential conflicts of interest relevant to this article were reported.
Tsihlias[84]	2000	Supported by the Kellogg Company and the Medical Research Council of Canada (grant no. UI-13990).	Not reported
Visek[85]	2014	This work was supported by research grant of the Medical Faculty in Pilsen, Charles University in Prague, MSM 0021620814.	None declared
Walker[63,86]	1995	This study was supported by a grant from Diabetes Australia. We are grateful for products supplied by the International Olive Oil Council and Meadow Lea Foods Australia.	Not reported
Wang[87]	2018	This study was supported by Suzhou Science and Technology Project, China (Grant number SYS201513).	The authors declare no conflict of interest
Watson[88,89]	2016	This study was funded by a grant from the Pork Co-operative Research Centre (Pork CRC), an Australian Government funding initiative. NAWis supported by a post-graduate research scholarship from the Pork CRC.	Not reported
Westman[90]	2008	Funding was provided by the Robert C. Atkins Foundation. Dr. Yancy was supported by a VA Health Services Research Career Development Award.	The authors declare that they have no competing interests.
Wolever[91-93]	2008	Supported by the Canadian Institutes of Health Research (CIHR-MCT-44205). Key foods were donated by Kellogg Canada Inc, Robin Hood (division of Smucker Foods of Canada Co), HJ Heinz Co, Italpasta Ltd, Uncle Ben's Rice (division of Mars Inc), Kraft Foods Inc, Dainty Foods Inc (division of MRRM Inc), the Almond Board of California, and the National Peanut Board.	TMSW is president and partowner of Glycemic Index Laboratories Inc, a contract research organization, and president and part-owner of Glycaemic Index Testing Inc, a corporation that provides services related to the measurement of the glycemic index of foods. He has received grant or research support from Cargill Inc and ILSI Europe; was a consultant for the US Potato Board; and received honoraria for consulting or speaking from the Dutch Sugar Bureau and Mars Inc. TMSW is co-author of a range of popular books on the glycemic index under the general title of The Glucose Revolution: Authoritative Guide to the Glycemic Index, published by Marlowe & Co (New York, NY) and the author of a scientific book entitled The Glycaemic Index: A Physiologic Classification of Dietary Carbohydrate, published by CABI (London, United Kingdom). None of the other authors had any personal or financial conflict of interest
Wycherley[94]	2010	This work was supported by a National Health and Medical Research Council project grant (103415).	The funding source had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

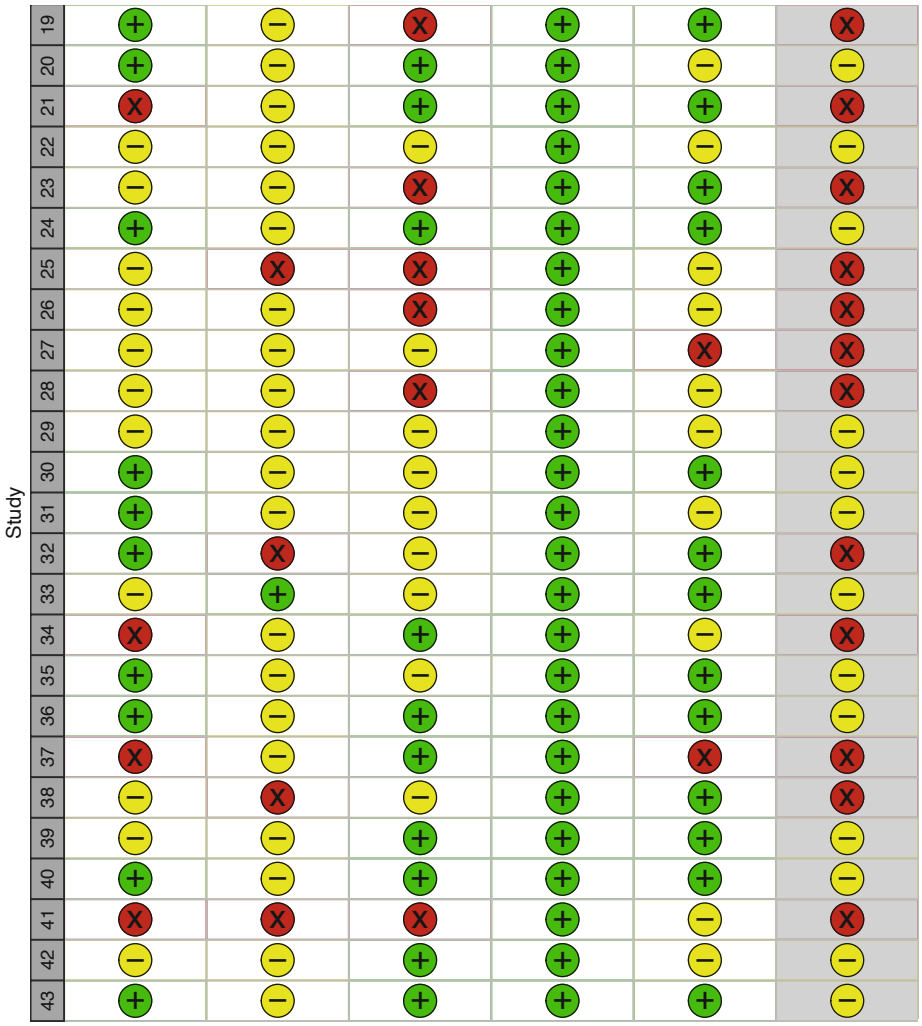
TABLE S4b (Continued)

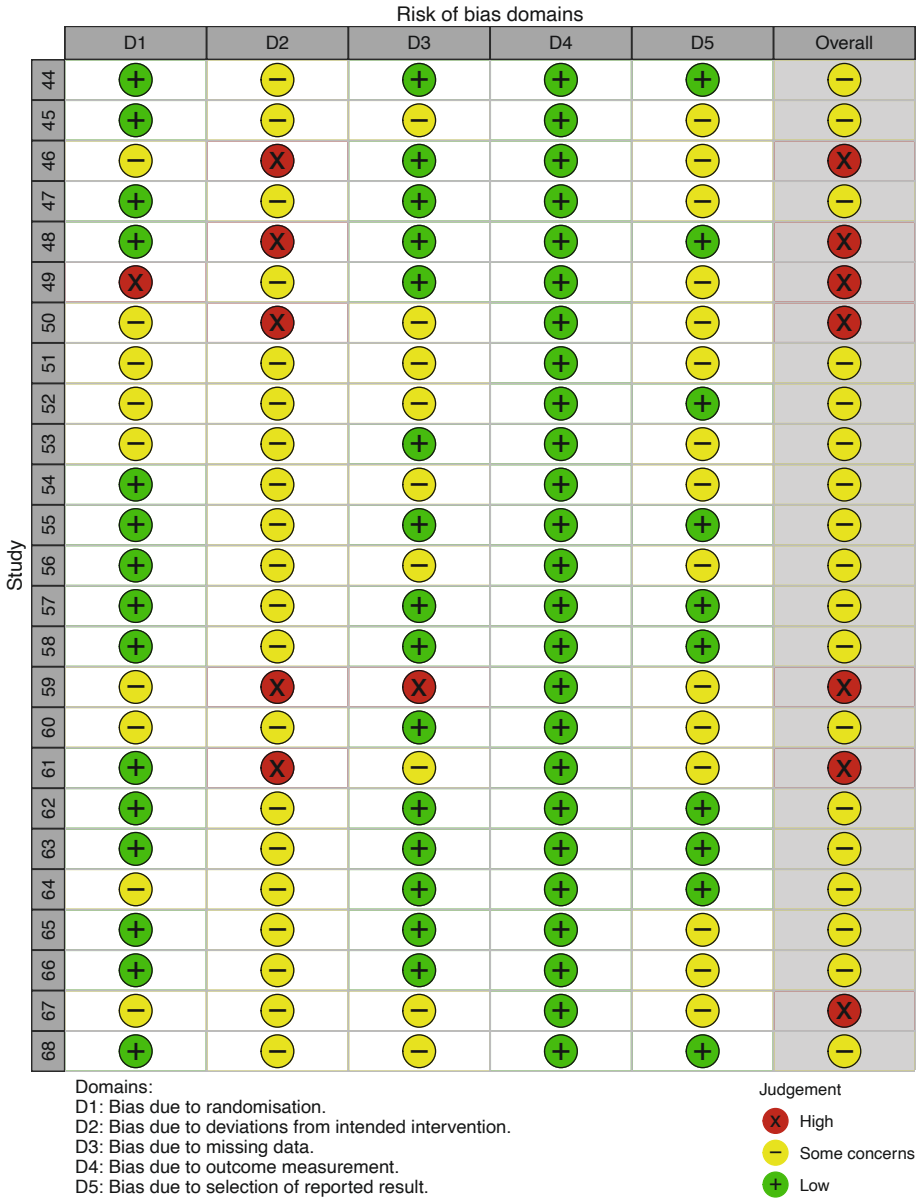
First author	Year	Funding	Reported conflicts of interest
Wycherley[95]	2016	This work was supported with project grants from the National Heart Foundation of Australia, the Diabetes Australia Research Trust, and the Pork Cooperative Research Centre. George Weston Foods donated foods for this study. None of the funding agencies played a role in the conception, design or conduct of the study, collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.	No potential conflicts of interest relevant to this article were reported.
Yamada[96]	2014	Not reported	The authors state that they have no Conflict of Interest (COI).
Yusof[97]	2009	Malaysian Endocrine & Metabolic Society (MEMS) for providing the research grant,	Not reported
Zahedi[98]	2020	Not reported	No potential conflicts of interest relevant to this article were reported.
Zainordin[99]	2021	RAG received partial research grants from the Malaysian Endocrine and Metabolic Society (MEMS)-LR1. NMI received partial research grant from the International Medical University (IMU)- IMU 418/2018. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.	The authors have declared that no competing interests exist.

Information on funding for the reported study and authors' conflicts of interest were extracted from the full text record or publisher website.

FIGURE S1 Risk of bias assessment (Cochrane risk of bias 2 tool)




Study
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.
Judgement
High
Some concerns
Low

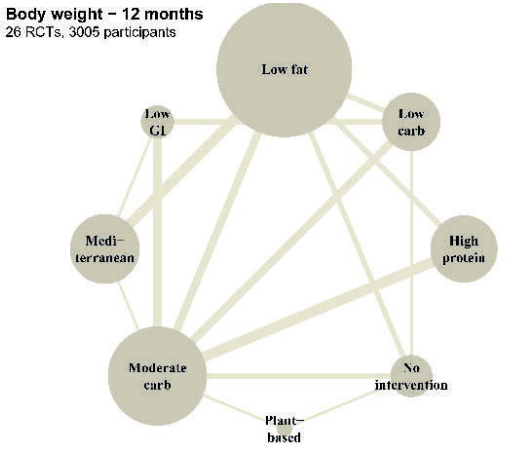


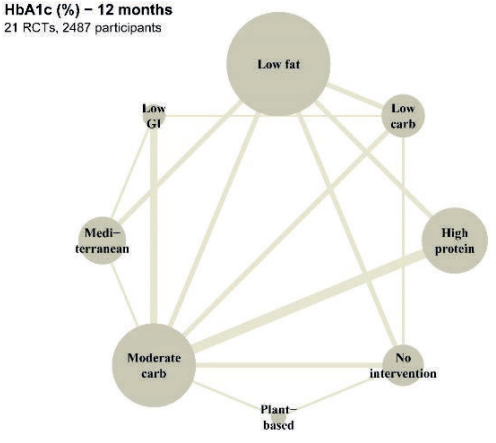
Risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Panel A shows a summary of the bias assessments per domain included in the tool. Panel B shows the risk of bias assessment for each domain and the overall risk of bias for each included study individually. Study numbers correspond to the following studies: 1: AlFaris, 2: Asle Mohammadi Zadeh, 3: Barnard 2006, 4: Barnard_2019, 5: Bunner, 6: Brunerova, 7: Cai 8: Chen, 9: Coppell, 10: Davis, 11: de Bont, 12: Dodson, 13: Durrer, 14: Dyson, 15: Elhayany, 16: Esposito, 17: Evangelista, 18: Evangelista, 19: Fabricatore, 20: Facchini, 21: Ferdowsian,22: Goday, 23: Goldstein, 24: Gram-Kampmann,25: Harvey, 26: Heilbronn, 27: Hockaday, 28: Iqbal,29: Itsiopoulos, 30: Jesudason, 31: Jin, 32: Jonsson, 33: Kahleova, 34: Kimura, 35: Krebs,

36: Larsen, 37: Lasa, 38: Lee, 39: Li, 40: Liu, 41: Lopez-Espinoza, 42: Luger, 43: Ma, 44: Maiorino, 45: Metz, 46: Milne, 47: Mishra, 48: Morris, 49: Nicholson, 50: Parker,51: Pascale, 52: Pavithran, 53: Perna, 54: Pijls, 55: Ren, 56: Sato, 57: Shai, 58: Tay, 59: Tsihlias, 60: Walker, 61: Wang, 62: Watson, 63: Wolever, 64: Wycherly, 65: Yamada, 66: Yusof, 67: Zahedi, 68: Zainordin.

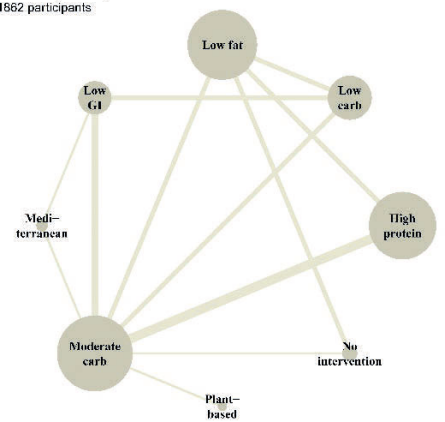
FIGURE S2 Network plots per outcome

These figures represent the networks of randomize controlled trials that were available for each outcome and time point. Node size respresents the number of study participants that were randomized to a dietary pattern and edge width represents the number of direct comparisons. The scale of nodes and edges is the same for all networks. Abbreviations: Carb – carbohydrate, GI – glycemic index, RCT – randomized controlled trial, LDL – low density lipoprotein, HDL – High density lipoprotein, HbA1c – glycated hemoglobin, CRP – C reactive protein.

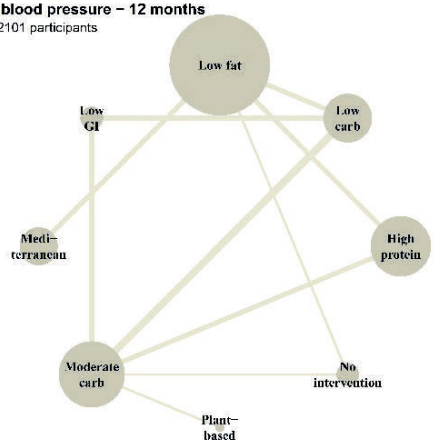




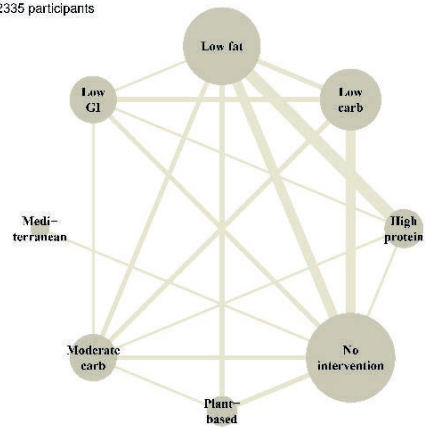
LDL cholesterol (mmol/l) – 12 months
17 RCTs, 1862 participants



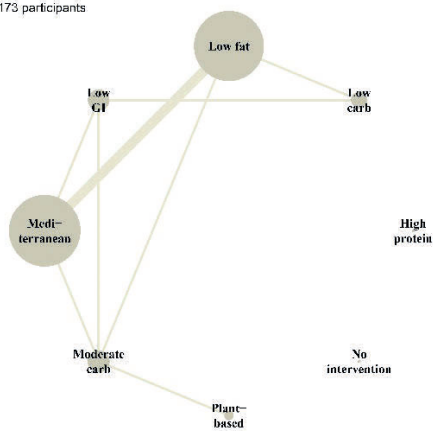
Systolic blood pressure – 12 months
16 RCTs, 2101 participants



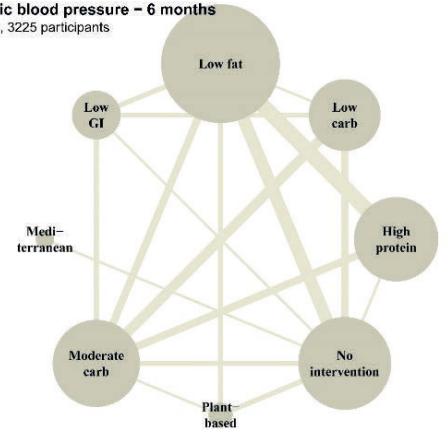
Body mass index – 6 months
36 RCTs, 2335 participants



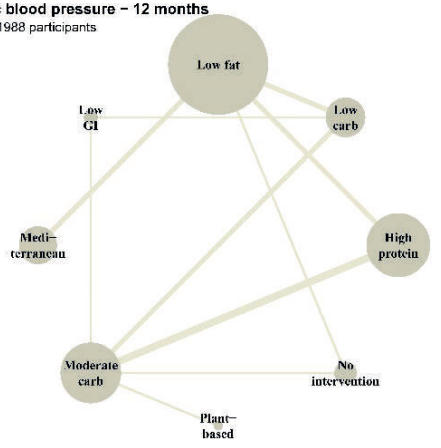
Body mass index – 12 months
9 RCTs, 1173 participants



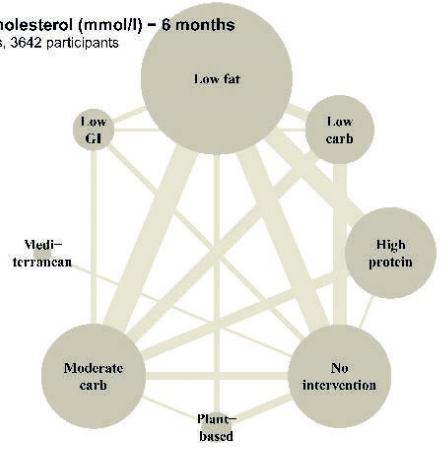
Diastolic blood pressure – 6 months
41 RCTs, 3225 participants



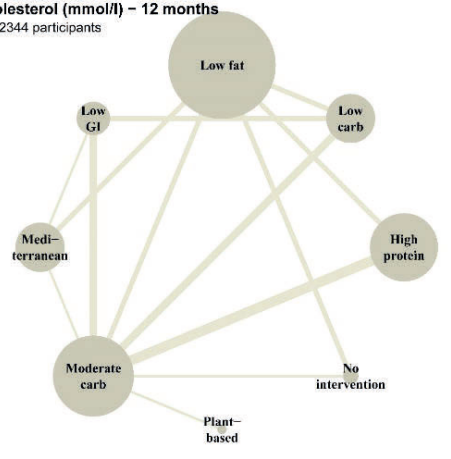
Diastolic blood pressure – 12 months
16 RCTs, 1988 participants



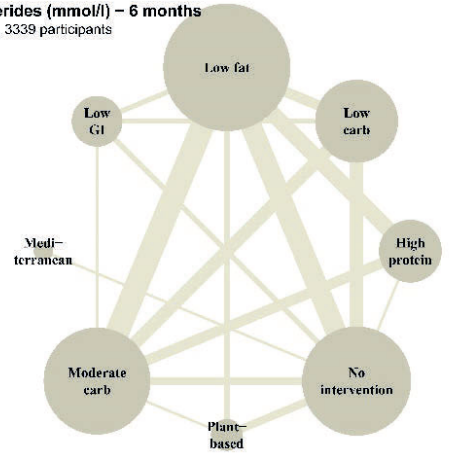
HDL cholesterol (mmol/l) – 6 months
54 RCTs, 3642 participants



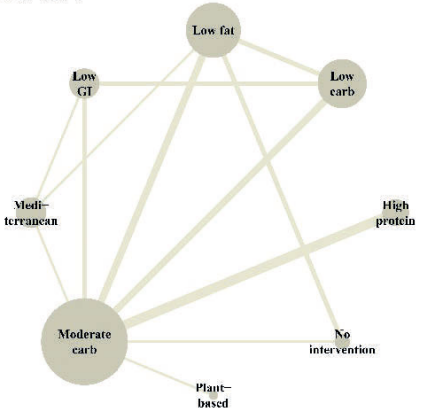
HDL cholesterol (mmol/l) – 12 months
20 RCTs, 2344 participants



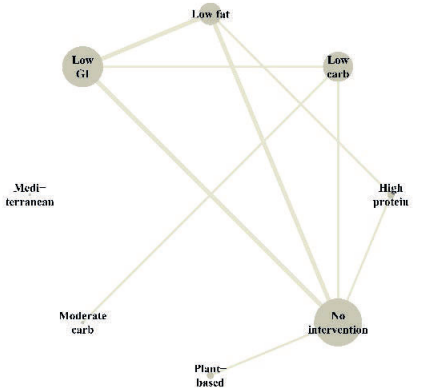
Triglycerides (mmol/l) – 6 months
53 RCTs, 3339 participants



Triglycerides (mmol/l) – 12 months
17 RCTs, 1709 participants



CRP – 6 months
12 RCTs, 896 participants



CRP – 12 months
5 RCTs, 802 participants

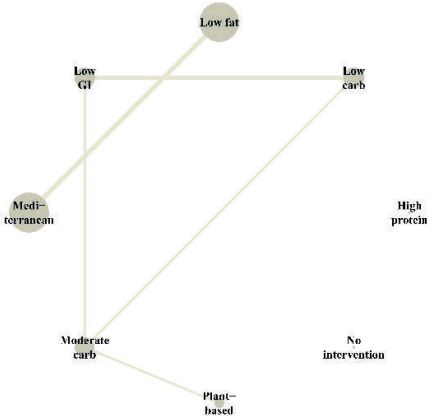


TABLE S5 League tables of mean differences in body weight, blood pressure, glucose regulation and lipids.

League tables present the network estimates for all possible pairwise in the networks for each outcome included in our analysis. The lower left half of each league table, below the names of the dietary patterns, presents the effect estimates after 6 months and the upper right half, above the names of the dietary patterns, presents the effect estimates after 12 months. In the league tables, each cell represents the mean difference and 95% credibility interval for the dietary pattern named in the column relative to the dietary pattern named in the row. For example, after 6 months a high protein diet results in -2.8 kg (95%CrI -6.4; 0.4) relative to a low carbohydrate diet and after 12 months a low carbohydrate diet result in an increase in body weight by 1.2 kg (95%CrI -4.7; 7.4) relative to a high protein dietary pattern. Abbreviations: NA – Not available.

TABLE S5a League table of network estimates of mean differences in body weight at 6 and 12 months after diet initiation.

Relative change in body weight after 12 months (kg)

Relative change in body weight after 6 months (kg)							
High protein	0.5 (-2.9; 3.9)	-0.7 (-3.8; 2.4)	-0.1 (-4.1; 4.1)	-1.5 (-4.9; 2)	0.4 (-2.4; 3.2)	0.7 (-3.7; 5)	1.8 (-1.6; 5.4)
0.3 (-1.8; 2.3)	**Low carbohydrate**	-1.2 (-3.7; 1.3)	-0.5 (-3.7; 2.7)	-2 (-4.9; 1)	-0.1 (-2.3; 2.2)	0.2 (-3.6; 4)	1.3 (-1.2; 4.1)
-0.9 (-2.4; 0.4)	-1.3 (-2.9; 0.4)	**Low fat**	0.7 (-2.8; 4.2)	-0.8 (-2.7; 1.2)	1.1 (-1.1; 3.3)	1.4 (-2.4; 5.2)	2.5 (0; 5.2)
-1.5 (-3.7; 0.5)	-1.9 (-3.8; 0)	-0.6 (-2.3; 1.1)	**Low glycemic index**	-1.5 (-5.1; 2.2)	0.5 (-2.9; 3.7)	0.7 (-3.9; 5.3)	1.9 (-1.9; 5.6)
NA	NA	NA	NA	**Mediterranean**	1.9 (-0.8; 4.6)	2.2 (-2; 6.3)	3.3 (0.2; 6.4)
-1.7 (-3.5; -0.1)	-2.1 (-3.5; -0.7)	-0.8 (-2.1; 0.5)	-0.2 (-2; 1.6)	NA	**Moderate carbohydrate**	0.3 (-3.1; 3.7)	1.4 (-0.9; 3.9)
0.2 (-2.4; 2.6)	-0.1 (-2.6; 2.3)	1.1 (-1; 3.3)	1.7 (-0.8; 4.3)	NA	1.9 (-0.3; 4.1)	**Plant-based**	1.1 (-2.1; 4.6)
-4.5 (-6.4; -2.8)	-4.8 (-6.5; -3.2)	-3.6 (-4.8; -2.3)	-3 (-4.6; -1.3)	NA	-2.7 (-4.2; -1.4)	-4.7 (-6.8; -2.5)	**No intervention**

TABLE S5b League table of network estimates of mean differences in body mass index at 6 and 12 months after diet initiation.

Relative change in BMI after 12 months (kg/m2)

Relative change in BMI after 6 months (kg/m2)							
High protein	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
0.3 (-1; 1.7)	**Low carbohydrate**	0.2 (-2.6; 2.8)	-0.5 (-3; 1.9)	-0.6 (-3.4; 2.1)	0.4 (-2.6; 3.4)	-0.1 (-4.2; 3.9)	*NA*
-0.8 (-1.7; 0.1)	-1.1 (-2.2; 0)	**Low fat**	-0.7 (-3; 1.8)	-0.8 (-2; 0.6)	0.2 (-1.9; 2.5)	-0.3 (-3.7; 3.3)	*NA*
-0.7 (-2.1; 0.7)	-0.9 (-2.1; 0.2)	0.1 (-1; 1.3)	**Low glycemic index**	-0.1 (-2.5; 2.2)	0.9 (-1.6; 3.4)	0.4 (-3.3; 4.1)	*NA*
-0.6 (-3.2; 1.9)	-0.9 (-3.4; 1.5)	0.2 (-2.2; 2.6)	0 (-2.4; 2.5)	**Mediterranean**	1 (-1.1; 3.2)	0.5 (-3; 4)	*NA*
-1.1 (-2.3; 0.2)	-1.4 (-2.4; -0.4)	-0.3 (-1.2; 0.7)	-0.4 (-1.6; 0.7)	-0.5 (-2.9; 2)	**Moderate carbohydrate**	-0.5 (-3.2; 2.2)	*NA*
-0.2 (-1.6; 1.1)	-0.5 (-1.9; 0.8)	0.6 (-0.5; 1.6)	0.4 (-0.9; 1.8)	0.4 (-2.1; 2.9)	0.8 (-0.3; 2)	**Plant-based**	*NA*
-1.8 (-3; -0.6)	-2.1 (-3.1; -1.1)	-1 (-1.9; -0.2)	-1.2 (-2.2; -0.1)	-1.2 (-3.5; 1)	-0.7 (-1.7; 0.2)	-1.6 (-2.6; -0.5)	**No intervention**

TABLE S5c League table of network estimates of mean differences in systolic blood pressure at 6 and 12 months after diet initiation.

Relative change in systolic BP after 6 months (mmHg) \ Relative change in systolic BP after 12 months (mmHg)							
High protein	-0.7 (-6.7; 6.1)	3.3 (-1.4; 9.1)	1.7 (-5.5; 9.7)	0.8 (-6; 8.8)	-0.1 (-5.5; 5.7)	-3.8 (-14.1; 7)	3 (-4.4; 11.2)
3.9 (-5.2; 13.1)	**Low carbohydrate**	4 (-1.2; 9.5)	2.3 (-3.2; 8.2)	1.5 (-5.8; 9.1)	0.5 (-4.7; 5.5)	-3.1 (-13.4; 6.9)	3.6 (-3.9; 11.4)
1.6 (-5; 8.1)	-2.4 (-10.1; 5.4)	**Low fat**	-1.6 (-8.9; 5.5)	-2.4 (-7.7; 2.7)	-3.4 (-9.4; 2)	-7.1 (-17.9; 3.1)	-0.3 (-7.1; 6.3)
6.4 (-3.3; 16.1)	2.5 (-5.9; 10.8)	4.8 (-3.4; 12.9)	**Low glycemic index**	-0.8 (-9.6; 8)	-1.8 (-8; 3.9)	-5.5 (-16.3; 4.9)	1.3 (-7.3; 9.9)
12 (-8.1; 32)	8.1 (-11.8; 27.9)	10.4 (-9; 29.9)	5.6 (-14.7; 25.7)	**Mediterranean**	-1 (-9; 6.3)	-4.7 (-16.7; 6.6)	2.1 (-6.4; 10.5)
2.3 (-5.4; 10)	-1.6 (-8.9; 5.6)	0.7 (-5.8; 7.3)	-4.1 (-12.2; 4)	-9.7 (-29.4; 9.9)	**Moderate carbohydrate**	-3.7 (-12.6; 5.1)	3.1 (-3.8; 10.3)
-0.6 (-11.9; 10.5)	-4.5 (-15.9; 6.7)	-2.2 (-11.9; 7.4)	-7 (-18.8; 4.7)	-12.5 (-33.5; 8.5)	-2.9 (-13.2; 7.3)	**Plant-based**	6.8 (-4.3; 18.2)
-1.3 (-9.5; 6.8)	-5.3 (-12.7; 2.2)	-2.9 (-9.1; 3.3)	-7.7 (-16.3; 0.8)	-13.3 (-31.7; 5)	-3.7 (-10.6; 3.4)	-0.7 (-10.8; 9.3)	**No intervention**

TABLE S5d League table of network estimates of mean differences in LDL-C at 6 and 12 months after diet initiation.

Relative change in LDL-cholesterol after 6 months (mmol/l) \ Relative change in LDL-cholesterol after 12 months (mmol/l)							
High protein	0.1 (-0.1; 0.3)	0.1 (-0.1; 0.3)	-0.1 (-0.3; 0.2)	-0.1 (-0.5; 0.2)	-0.1 (-0.2; 0.1)	-0.2 (-0.6; 0.2)	0 (-0.4; 0.3)
-0.1 (-0.3; 0.2)	**Low carbohydrate**	0 (-0.2; 0.2)	-0.2 (-0.4; 0)	-0.2 (-0.6; 0.1)	-0.2 (-0.4; 0)	-0.3 (-0.7; 0.2)	-0.1 (-0.5; 0.2)
0 (-0.2; 0.2)	0.1 (-0.1; 0.3)	**Low fat**	-0.2 (-0.4; 0.1)	-0.2 (-0.6; 0.1)	-0.2 (-0.4; 0)	-0.3 (-0.7; 0.2)	-0.1 (-0.4; 0.2)
0.1 (-0.2; 0.4)	0.2 (-0.1; 0.4)	0.1 (-0.1; 0.3)	**Low glycemic index**	0 (-0.4; 0.3)	0 (-0.2; 0.2)	-0.1 (-0.6; 0.3)	0 (-0.3; 0.4)
0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 0)	**Mediterranean**	0.1 (-0.3; 0.4)	-0.1 (-0.6; 0.4)	0.1 (-0.3; 0.5)
0 (-0.2; 0.2)	0.1 (-0.2; 0.3)	0 (-0.2; 0.2)	-0.1 (-0.4; 0.1)	0 (0; 0)	**Moderate carbohydrate**	-0.1 (-0.5; 0.3)	0 (-0.3; 0.4)
0 (-0.3; 0.3)	0.1 (-0.3; 0.4)	0 (-0.3; 0.3)	-0.1 (-0.5; 0.2)	0 (0; 0)	0 (-0.3; 0.3)	**Plant-based**	0.1 (-0.4; 0.7)
-0.2 (-0.4; 0.1)	-0.1 (-0.3; 0.1)	-0.2 (-0.3; 0)	-0.3 (-0.5; 0)	0 (0; 0)	-0.1 (-0.4; 0.1)	-0.2 (-0.4; 0.1)	**No intervention**

TABLE S5e League table of network estimates of mean differences in HDL-C at 6 and 12 months after diet initiation.

Relative change in HDL-cholesterol after 6 months (mmol/l) \ Relative change in HDL-cholesterol after 12 months (mmol/l)							
High protein	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.2; 0.2)	-0.1 (-0.2; 0.1)
-0.1 (-0.2; 0)	**Low carbohydrate**	-0.1 (-0.1; 0)	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.1; 0)	0 (-0.2; 0.1)	-0.1 (-0.2; 0)
0 (-0.1; 0.1)	0.1 (0; 0.2)	**Low fat**	0.1 (-0.1; 0.1)	0 (0; 0.1)	0 (-0.1; 0.1)	0 (-0.2; 0.2)	0 (-0.2; 0.1)
0 (-0.1; 0.2)	0.1 (0; 0.2)	0 (-0.1; 0.1)	**Low glycemic index**	0 (-0.1; 0.1)	0 (-0.1; 0)	0 (-0.2; 0.2)	-0.1 (-0.2; 0)
0.1 (-0.2; 0.3)	0.1 (-0.1; 0.4)	0.1 (-0.2; 0.3)	0 (-0.2; 0.3)	**Mediterranean**	0 (-0.1; 0.1)	0 (-0.2; 0.2)	-0.1 (-0.2; 0)
0 (-0.1; 0.1)	0.1 (0; 0.2)	0 (0; 0.1)	0 (-0.1; 0.1)	0 (-0.3; 0.2)	**Moderate carbohydrate**	0 (-0.2; 0.2)	-0.1 (-0.2; 0.1)
0.1 (0; 0.2)	0.2 (0; 0.3)	0.1 (0; 0.2)	0 (-0.1; 0.2)	0 (-0.2; 0.3)	0 (-0.1; 0.2)	**Plant-based**	-0.1 (-0.3; 0.1)
0 (-0.1; 0.1)	0.1 (0; 0.2)	0 (0; 0.1)	0 (-0.1; 0.1)	0 (-0.2; 0.2)	0 (-0.1; 0.1)	0 (-0.2; 0.1)	**No intervention**

TABLE S5f League table of network estimates of mean differences in triglycerides at 6 and 12 months after diet initiation.

Relative change in triglycerides after 6 months (mmol/l) \ Relative change in triglycerides after 12 months (mmol/l)							
High protein	-0.1 (-0.5; 0.3)	0.1 (-0.3; 0.6)	0.1 (-0.3; 0.6)	-0.1 (-0.6; 0.4)	0.2 (-0.1; 0.5)	-0.1 (-1; 0.8)	0.1 (-0.5; 0.8)
0.1 (-0.2; 0.3)	**Low carbohydrate**	0.2 (-0.1; 0.5)	0.2 (-0.1; 0.5)	0 (-0.4; 0.4)	0.3 (0; 0.6)	0 (-0.9; 0.9)	0.2 (-0.4; 0.8)
-0.1 (-0.3; 0)	-0.2 (-0.3; 0)	**Low fat**	0 (-0.4; 0.4)	-0.2 (-0.6; 0.2)	0.1 (-0.2; 0.4)	-0.2 (-1.1; 0.7)	0 (-0.5; 0.5)
-0.2 (-0.4; 0.1)	-0.2 (-0.4; 0)	-0.1 (-0.2; 0.1)	**Low glycemic index**	-0.2 (-0.6; 0.2)	0.1 (-0.2; 0.4)	-0.2 (-1.1; 0.7)	0 (-0.6; 0.6)
-0.5 (-0.9; -0.1)	-0.6 (-1; -0.2)	-0.4 (-0.8; 0)	-0.4 (-0.8; 0.1)	**Mediterranean**	0.3 (-0.1; 0.7)	0 (-0.9; 0.9)	0.2 (-0.4; 0.8)
-0.1 (-0.3; 0.1)	-0.2 (-0.3; 0)	0 (-0.2; 0.1)	0.1 (-0.1; 0.3)	0.4 (0; 0.8)	**Moderate carbohydrate**	-0.3 (-1.1; 0.5)	-0.1 (-0.7; 0.5)
-0.3 (-0.6; 0)	-0.4 (-0.6; -0.1)	-0.2 (-0.4; 0.1)	-0.1 (-0.4; 0.2)	0.2 (-0.2; 0.7)	-0.2 (-0.4; 0.1)	**Plant-based**	0.2 (-0.8; 1.2)
-0.4 (-0.6; -0.2)	-0.5 (-0.6; -0.3)	-0.3 (-0.5; -0.2)	-0.2 (-0.4; -0.1)	0.1 (-0.3; 0.5)	-0.3 (-0.5; -0.1)	-0.1 (-0.4; 0.1)	**No intervention**

TABLE S5g League table of network estimates of mean differences in HbA1c at 6 and 12 months after diet initiation.

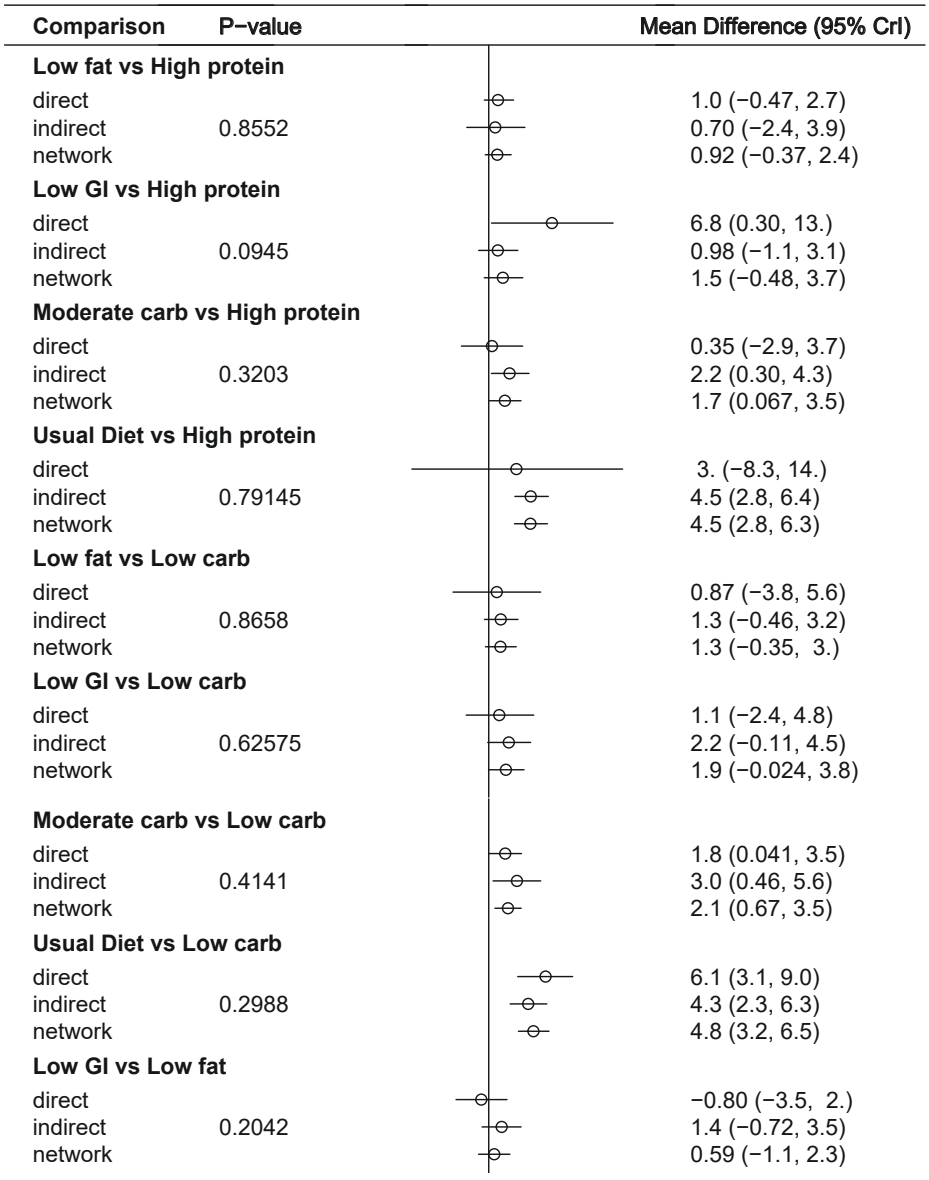
Relative change in HbA1c after 6 months (%) \ Relative change in HbA1c after 12 months (%)							
High protein	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.2; 0.2)	-0.1 (-0.2; 0.1)
0.3 (0; 0.5)	**Low carbohydrate**	-0.1 (-0.1; 0)	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0 (-0.1; 0)	0 (-0.2; 0.1)	-0.1 (-0.2; 0)
-0.2 (-0.4; 0)	-0.4 (-0.7; -0.2)	**Low fat**	0.1 (-0.1; 0.1)	0 (0; 0.1)	0 (-0.1; 0.1)	0 (-0.2; 0.2)	0 (-0.2; 0.1)
0 (-0.2; 0.3)	-0.2 (-0.5; 0)	0.2 (0; 0.4)	**Low glycemic index**	0 (-0.1; 0.1)	0 (-0.1; 0)	0 (-0.2; 0.2)	-0.1 (-0.2; 0)
0.4 (-0.2; 1)	0.2 (-0.5; 0.8)	0.6 (0; 1.2)	0.4 (-0.2; 1)	**Mediterranean**	0 (-0.1; 0.1)	0 (-0.2; 0.2)	-0.1 (-0.2; 0)
-0.3 (-0.5; -0.1)	-0.5 (-0.8; -0.3)	-0.1 (-0.3; 0.1)	-0.3 (-0.5; -0.1)	-0.7 (-1.3; -0.1)	**Moderate carbohydrate**	0 (-0.2; 0.2)	-0.1 (-0.2; 0.1)
0 (-0.3; 0.4)	-0.2 (-0.6; 0.1)	0.2 (-0.1; 0.5)	0 (-0.3; 0.4)	-0.4 (-1; 0.3)	0.3 (0; 0.6)	**Plant-based**	-0.1 (-0.3; 0.1)
-0.5 (-0.8; -0.3)	-0.8 (-1; -0.6)	-0.3 (-0.5; -0.2)	-0.6 (-0.8; -0.3)	-1 (-1.5; -0.4)	-0.3 (-0.5; 0)	-0.6 (-0.8; -0.3)	**No intervention**

TABLE S5h League table of network estimates of mean differences in C reactive protein at 6 months after diet initiation.

Relative change in CRP after 6 months (mg/l)							
High protein							
0 (-2.4; 2.3)	**Low carbohydrate**						
-0.1 (-2; 1.8)	-0.1 (-1.8; 1.8)	**Low fat**					
0.4 (-1.7; 2.3)	0.3 (-1.1; 1.9)	0.4 (-0.9; 1.7)	**Low glycemic index**				
NA	*NA*	*NA*	*NA*	**Mediterranean**			
-0.5 (-4.2; 2.9)	-0.6 (-3.2; 2)	-0.5 (-3.7; 2.6)	-0.9 (-4; 2)	*NA*	**Moderate carbohydrate**		
1.7 (-2.1; 5.4)	1.7 (-1.9; 5.4)	1.7 (-1.7; 5.3)	1.3 (-2.1; 4.9)	*NA*	2.2 (-2.2; 6.8)	**Plant-based**	
-0.7 (-2.5; 1.1)	-0.7 (-2.1; 1)	-0.6 (-1.8; 0.6)	-1.1 (-2.1; 0.1)	*NA*	-0.1 (-3.1; 3)	-2.3 (-5.7; 1)	**No intervention**

FIGURE S3 Consistency plots

FIGURE S3a Consistency plot – Change in body weight (kg) after 6 months



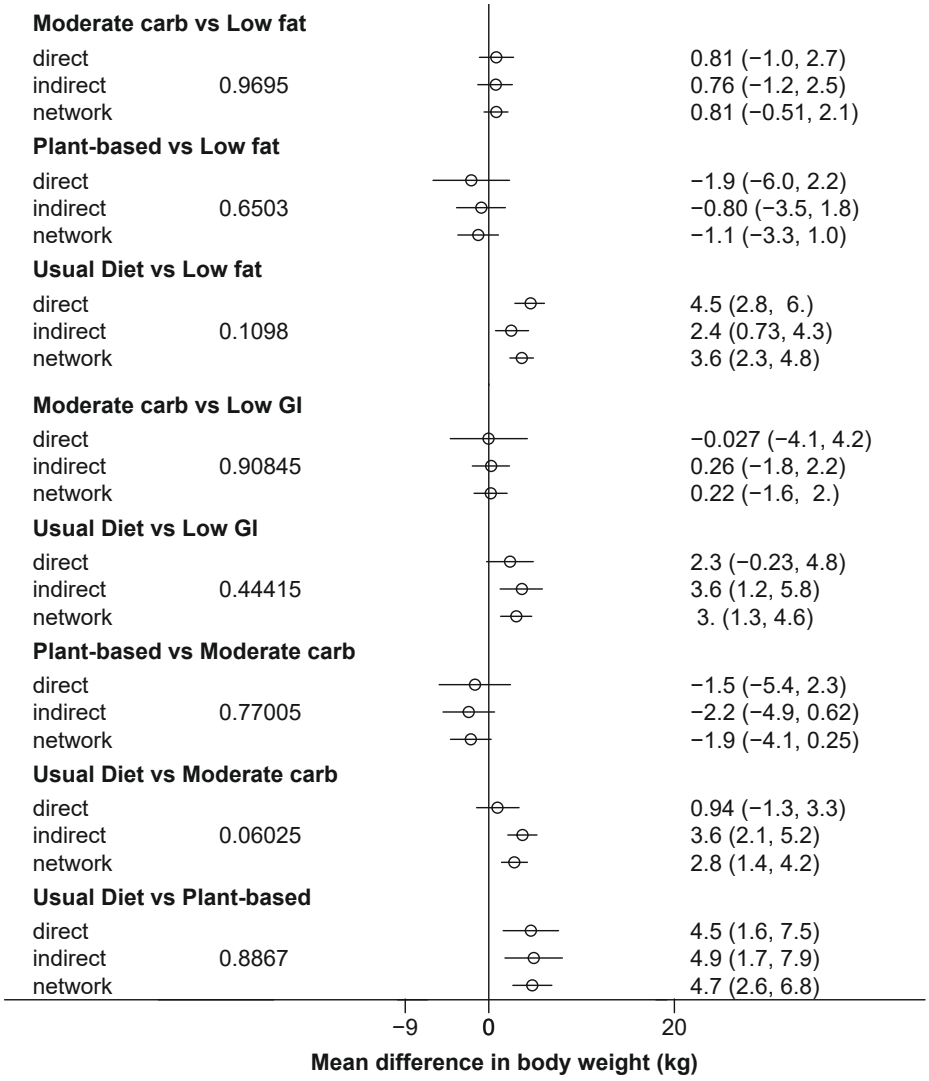
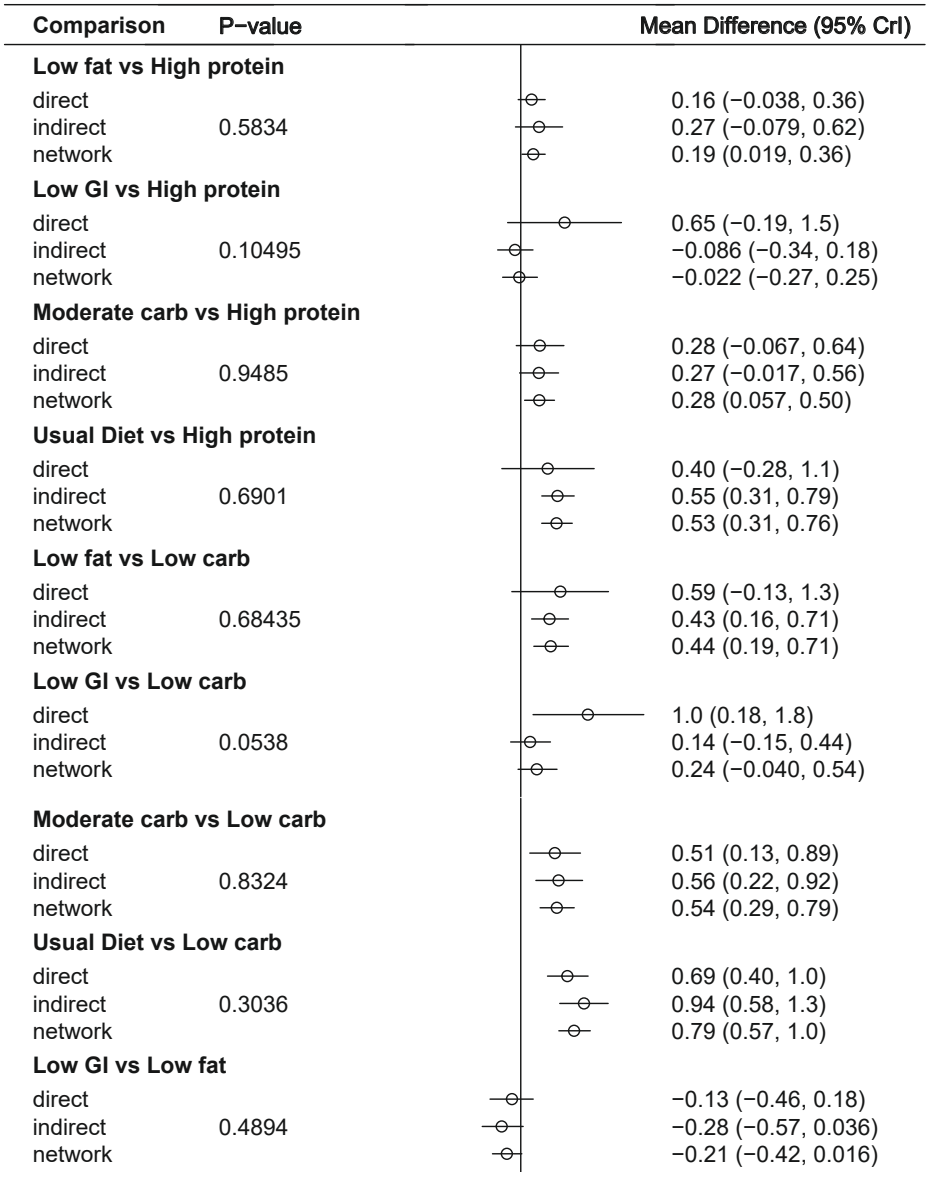

Moderate carb vs Low fat
direct
indirect 0.9695
network
0.81 (−1.0, 2.7)
0.76 (−1.2, 2.5)
0.81 (−0.51, 2.1)
Plant-based vs Low fat
direct
indirect 0.6503
network
−1.9 (−6.0, 2.2)
−0.80 (−3.5, 1.8)
−1.1 (−3.3, 1.0)
Usual Diet vs Low fat
direct
indirect 0.1098
network
4.5 (2.8, 6.)
2.4 (0.73, 4.3)
3.6 (2.3, 4.8)
Moderate carb vs Low GI
direct
indirect 0.90845
network
−0.027 (−4.1, 4.2)
0.26 (−1.8, 2.2)
0.22 (−1.6, 2.)
Usual Diet vs Low GI
direct
indirect 0.44415
network
2.3 (−0.23, 4.8)
3.6 (1.2, 5.8)
3. (1.3, 4.6)
Plant-based vs Moderate carb
direct
indirect 0.77005
network
−1.5 (−5.4, 2.3)
−2.2 (−4.9, 0.62)
−1.9 (−4.1, 0.25)
Usual Diet vs Moderate carb
direct
indirect 0.06025
network
0.94 (−1.3, 3.3)
3.6 (2.1, 5.2)
2.8 (1.4, 4.2)
Usual Diet vs Plant-based
direct
indirect 0.8867
network
4.5 (1.6, 7.5)
4.9 (1.7, 7.9)
4.7 (2.6, 6.8)
−9
0
20
Mean difference in body weight (kg)

FIGURE S3b Consistency plot – Change in HbA1c (%) after 6 months



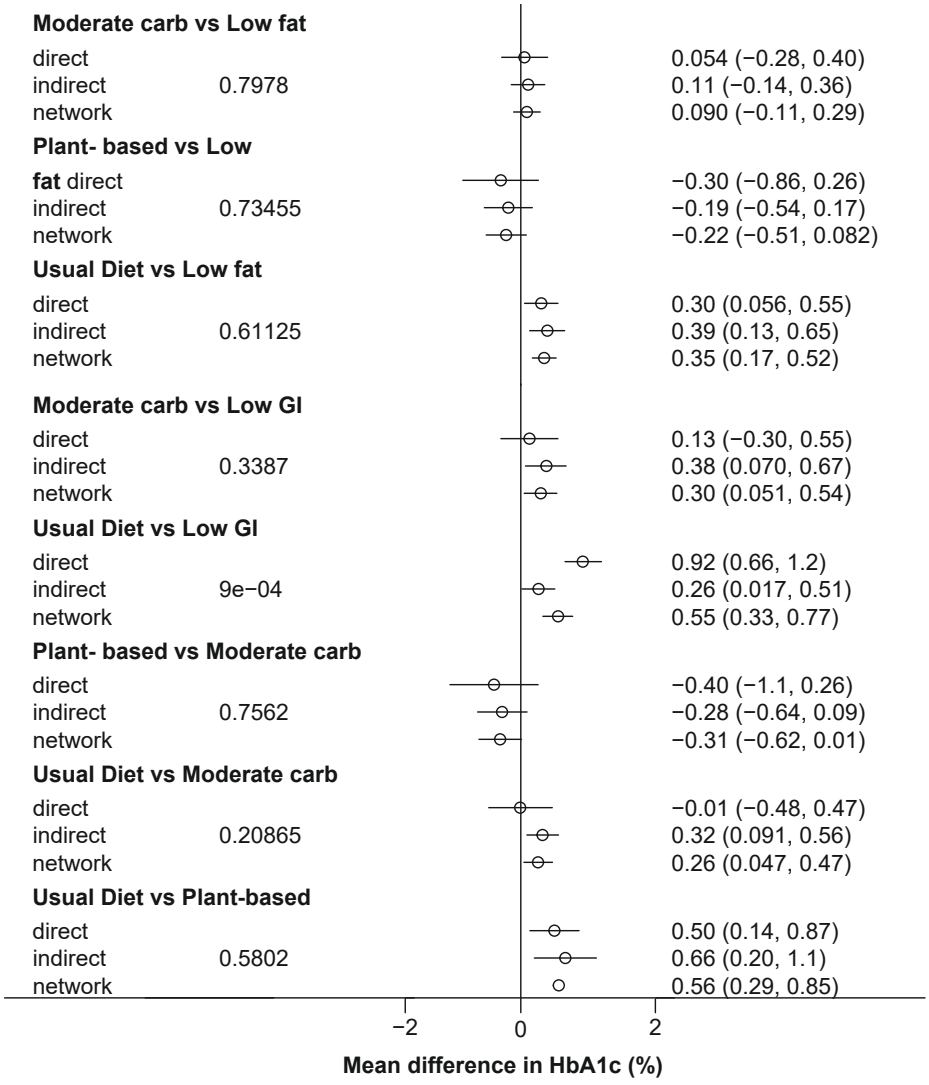
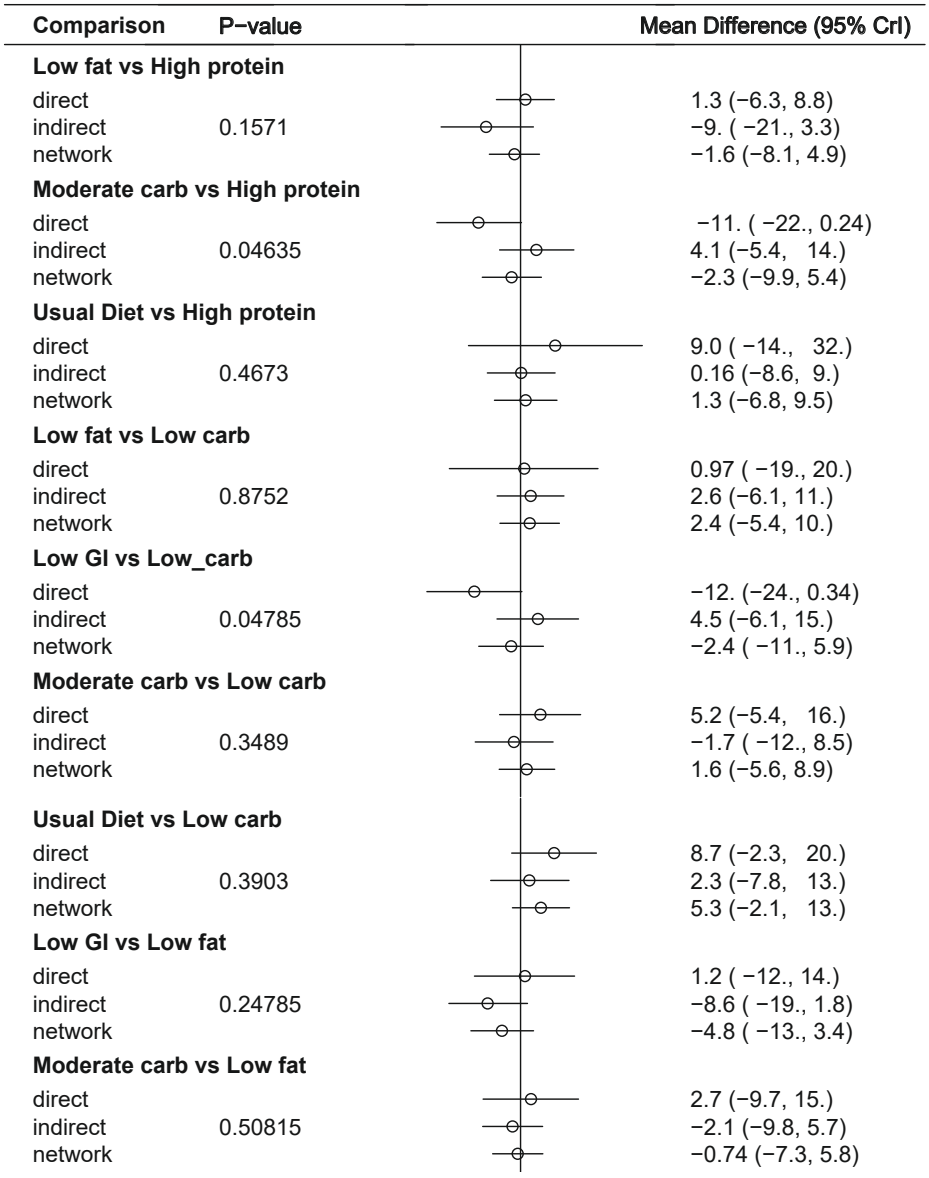

Moderate carb vs Low fat
direct
indirect 0.7978
network
0.054 (−0.28, 0.40)
0.11 (−0.14, 0.36)
0.090 (−0.11, 0.29)
Plant- based vs Low
fat direct
indirect 0.73455
network
−0.30 (−0.86, 0.26)
−0.19 (−0.54, 0.17)
−0.22 (−0.51, 0.082)
Usual Diet vs Low fat
direct
indirect 0.61125
network
0.30 (0.056, 0.55)
0.39 (0.13, 0.65)
0.35 (0.17, 0.52)
Moderate carb vs Low GI
direct
indirect 0.3387
network
0.13 (−0.30, 0.55)
0.38 (0.070, 0.67)
0.30 (0.051, 0.54)
Usual Diet vs Low GI
direct
indirect 9e−04
network
0.92 (0.66, 1.2)
0.26 (0.017, 0.51)
0.55 (0.33, 0.77)
Plant- based vs Moderate carb
direct
indirect 0.7562
network
−0.40 (−1.1, 0.26)
−0.28 (−0.64, 0.09)
−0.31 (−0.62, 0.01)
Usual Diet vs Moderate carb
direct
indirect 0.20865
network
−0.01 (−0.48, 0.47)
0.32 (0.091, 0.56)
0.26 (0.047, 0.47)
Usual Diet vs Plant-based
direct
indirect 0.5802
network
0.50 (0.14, 0.87)
0.66 (0.20, 1.1)
0.56 (0.29, 0.85)
−2
0
2
Mean difference in HbA1c (%)

FIGURE S3c Consistency plot – Change in systolic blood pressure (mmHg) after 6 months



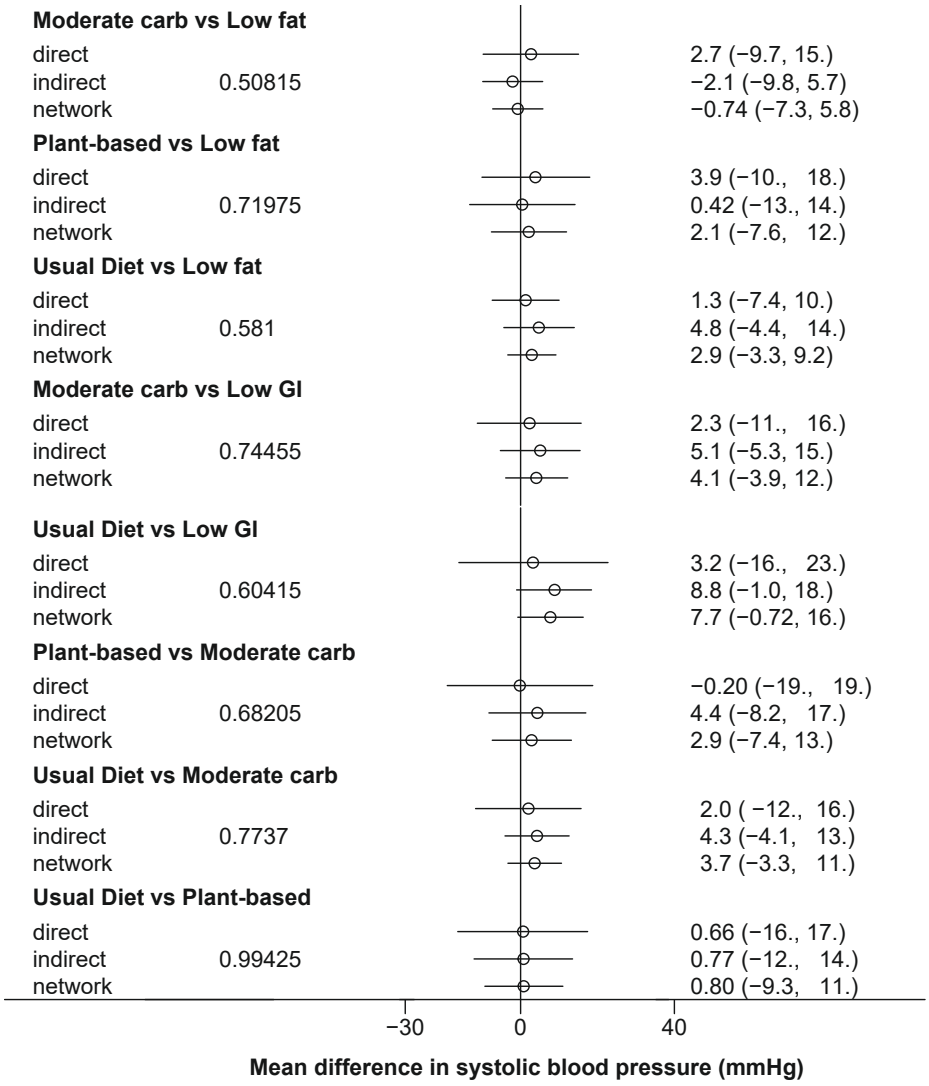
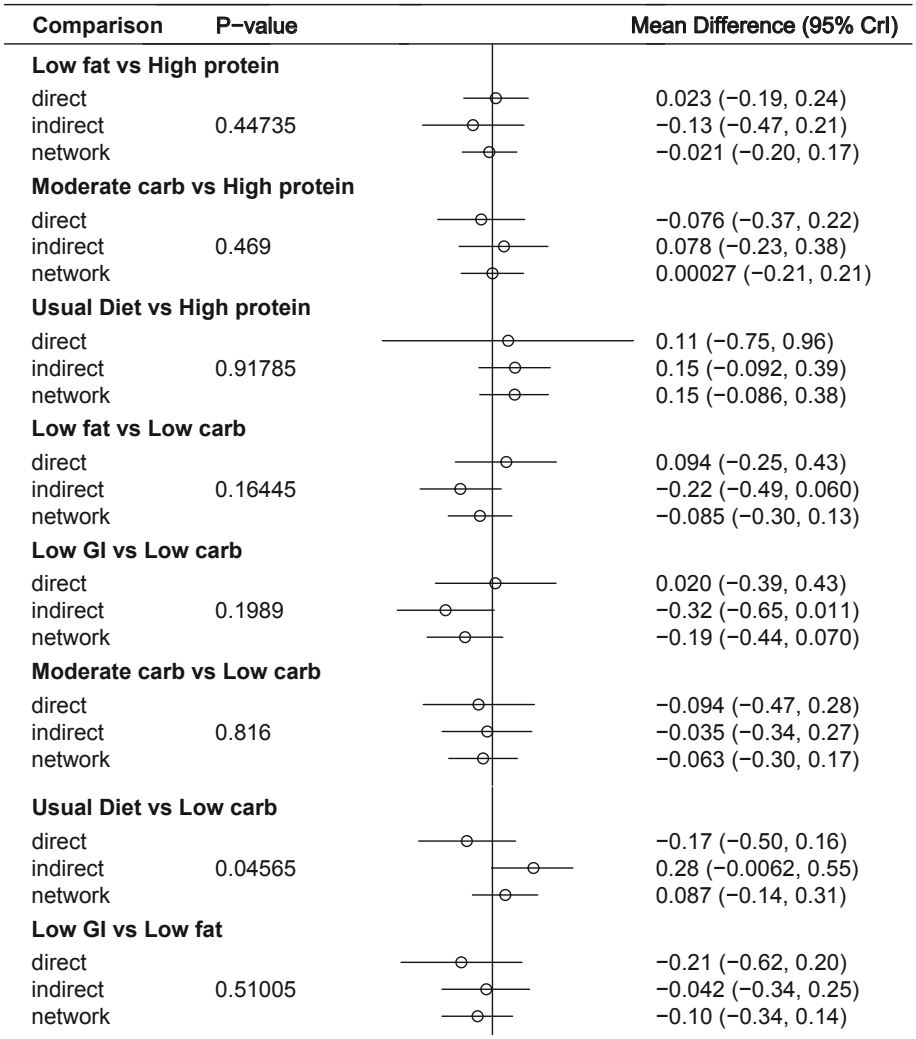

Moderate carb vs Low fat
direct
indirect 0.50815
network
2.7 (−9.7, 15.)
−2.1 (−9.8, 5.7)
−0.74 (−7.3, 5.8)
Plant-based vs Low fat
direct
indirect 0.71975
network
3.9 (−10., 18.)
0.42 (−13., 14.)
2.1 (−7.6, 12.)
Usual Diet vs Low fat
direct
indirect 0.581
network
1.3 (−7.4, 10.)
4.8 (−4.4, 14.)
2.9 (−3.3, 9.2)
Moderate carb vs Low GI
direct
indirect 0.74455
network
2.3 (−11., 16.)
5.1 (−5.3, 15.)
4.1 (−3.9, 12.)
Usual Diet vs Low GI
direct
indirect 0.60415
network
3.2 (−16., 23.)
8.8 (−1.0, 18.)
7.7 (−0.72, 16.)
Plant-based vs Moderate carb
direct
indirect 0.68205
network
−0.20 (−19., 19.)
4.4 (−8.2, 17.)
2.9 (−7.4, 13.)
Usual Diet vs Moderate carb
direct
indirect 0.7737
network
2.0 (−12., 16.)
4.3 (−4.1, 13.)
3.7 (−3.3, 11.)
Usual Diet vs Plant-based
direct
indirect 0.99425
network
0.66 (−16., 17.)
0.77 (−12., 14.)
0.80 (−9.3, 11.)
−30
0
40
Mean difference in systolic blood pressure (mmHg)

FIGURE S3d Consistency plot – Change in LDL-cholesterol (mmol/l) after 6 months



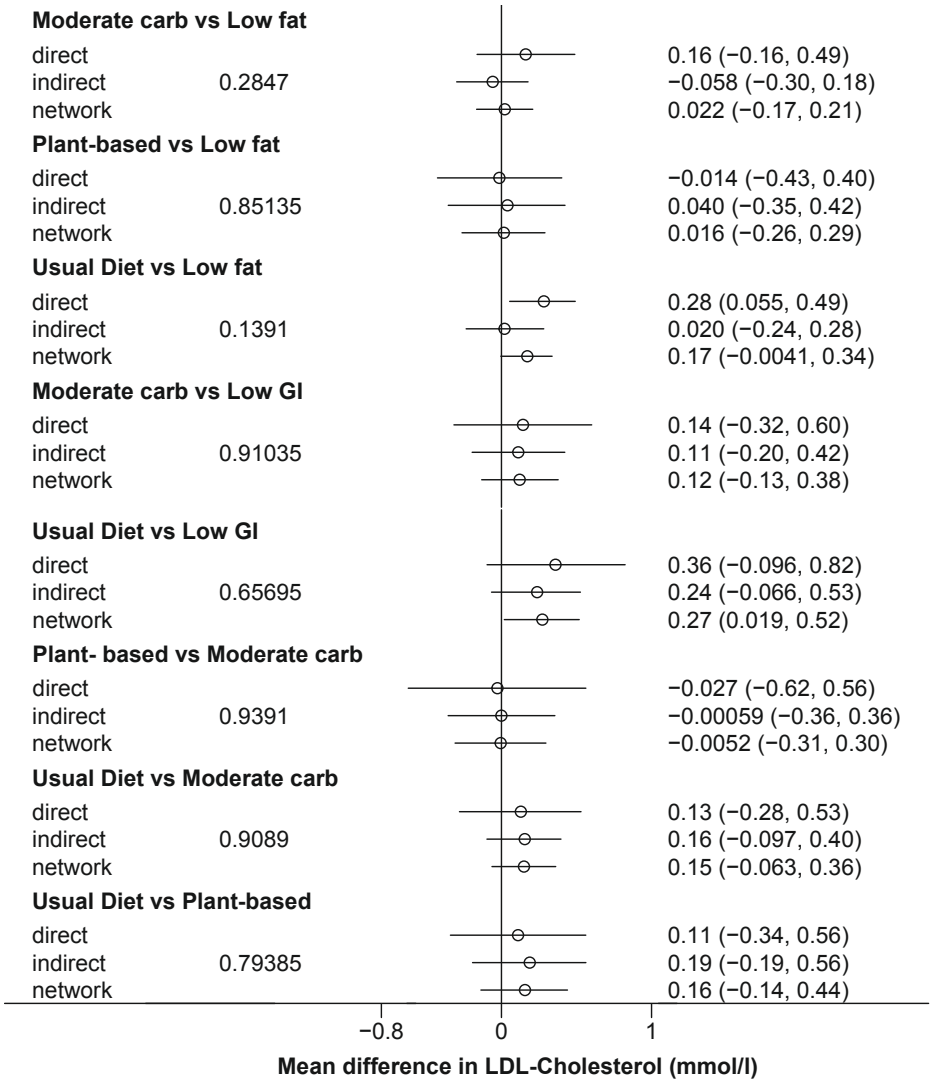
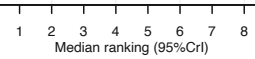

Moderate carb vs Low fat
direct
indirect 0.2847
network
0.16 (−0.16, 0.49)
−0.058 (−0.30, 0.18)
0.022 (−0.17, 0.21)
Plant-based vs Low fat
direct
indirect 0.85135
network
−0.014 (−0.43, 0.40)
0.040 (−0.35, 0.42)
0.016 (−0.26, 0.29)
Usual Diet vs Low fat
direct
indirect 0.1391
network
0.28 (0.055, 0.49)
0.020 (−0.24, 0.28)
0.17 (−0.0041, 0.34)
Moderate carb vs Low GI
direct
indirect 0.91035
network
0.14 (−0.32, 0.60)
0.11 (−0.20, 0.42)
0.12 (−0.13, 0.38)
Usual Diet vs Low GI
direct
indirect 0.65695
network
0.36 (−0.096, 0.82)
0.24 (−0.066, 0.53)
0.27 (0.019, 0.52)
Plant- based vs Moderate carb
direct
indirect 0.9391
network
−0.027 (−0.62, 0.56)
−0.00059 (−0.36, 0.36)
−0.0052 (−0.31, 0.30)
Usual Diet vs Moderate carb
direct
indirect 0.9089
network
0.13 (−0.28, 0.53)
0.16 (−0.097, 0.40)
0.15 (−0.063, 0.36)
Usual Diet vs Plant-based
direct
indirect 0.79385
network
0.11 (−0.34, 0.56)
0.19 (−0.19, 0.56)
0.16 (−0.14, 0.44)
−0.8
0
1
Mean difference in LDL-Cholesterol (mmol/l)

FIGURE S4 Ranking plots and SUCRA values for 6-month change in body weight, HbA1c, systolic blood pressure and LDL-cholesterol

Intervention	SUCRA	Rank (95%CrI)
Body weight		
Low carbohydrate	0.85	2 (1 – 2)
Plant–based	0.79	2 (1 – 3)
High–protein	0.77	2 (2 – 3)
Low fat	0.49	4 (4 – 5)
Low GI	0.34	5 (4 – 6)
Moderate carbohydrate	0.26	6 (5 – 6)
No intervention	0	7 (7 – 7)
HbA1c		
Mediterranean	0.91	1 (1 – 2)
Low carbohydrate	0.87	2 (1 – 2)
Plant–based	0.60	4 (3 – 5)
Low GI	0.59	4 (3 – 5)
High–protein	0.56	4 (3 – 5)
Low fat	0.28	6 (6 – 6)
Moderate carbohydrate	0.18	7 (7 – 7)
No intervention	0	8 (8 – 8)
Systolic BP		
Mediterranean	0.84	1 (1 – 2)
Low GI	0.78	2 (2 – 2)
Low carbohydrate	0.63	3 (2 – 5)
Moderate carbohydrate	0.50	4 (3 – 6)
Low fat	0.45	5 (4 – 6)
High–protein	0.31	6 (5 – 7)
Plant–based	0.30	7 (4– 8)
No intervention	0.19	7 (6 – 8)
LDL–cholesterol		
Low GI	0.85	1 (1 – 2)
Low fat	0.61	3 (2 – 4)
Plant–based	0.54	4 (2 – 6)
High–protein	0.53	4 (2 – 5)
Moderate carbohydrate	0.53	4 (3 – 5)
Low carbohydrate	0.34	5 (4 – 6)
No intervention	0.10	7 (6 – 7)



This figure shows the ranking of different dietary patterns and no dietary interventions in the networks for 6-month changes in body weight, HbA1c, systolic blood pressure and LDL-cholesterol. A lower rank (i.e. closer to 1) indicates that a dietary pattern outperforms the other dietary patterns in the majority of iterations of the Monte-Carlo Markov chain simulation. The SUCRA value represents the surface under the cumulative ranking curve for a dietary pattern. A SUCRA value ranges between 0 and 1 and a value closer to 1 indicates a higher probability of being among the best treatment options for a specific outcome.

FIGURE S5 Ranking plots and SUCRA values of different dietary interventions

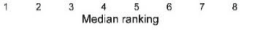
These ranking plots show the surface under the cumulative ranking curve (SUCRA) values for the dietary interventions included in the networks for each outcome. A SUCRA value ranges between 0 and 1 and a value of 1 indicates that an intervention has a higher probability of being among the best treatment options. In each of the 100,000 iterations of the Monte Carlo Markov Chain simulation, treatments can be ranked from best to worst, e.g. the intervention that results in the largest weight loss to the intervention that leads to the largest weight gain. These plots present the median ranking and corresponding interquartile range for each intervention for each outcome. A lower rank, *i.e.* closer to 1, indicates a better performance for that outcome. Carb: carbohydrate, GI: glycemic index, SUCRA: Surface under the cumulative ranking curve, IQR: interquartile range.

Body weight - 6 months

Intervention	SUCRA	Rank (95%CrI)
Low carb.	0.85	2 (1–2)
Plant-based	0.79	2 (1–3)
High protein	0.77	2 (2–3)
Low fat	0.49	4 (4–5)
Low GI	0.34	5 (4–6)
Moderate carb.	0.26	6 (5–6)
No intervention	0	7 (7–7)

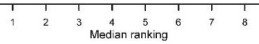
Body weight - 12 months

Intervention	SUCRA	Rank (IQR)
Mediterranean	0.87	1 (1–2)
Low fat	0.71	3 (2–4)
Low GI	0.54	4 (2–6)
High protein	0.53	4 (3–6)
Moderate carb.	0.43	5 (4–6)
Low carb.	0.42	5 (4–6)
Plant-based	0.39	6 (4–7)
No intervention	0.12	8 (7–8)



BMI - 6 months

Intervention	SUCRA	Rank (IQR)
Low carb.	0.88	2 (1−2)
High protein	0.77	2 (2−3)
Plant-based	0.67	3 (2−4)
Mediterranean	0.5	5 (2−7)
Low GI	0.48	5 (4−6)
Low fat	0.39	5 (5−6)
Moderate carb.	0.27	6 (5−7)
No intervention	0.03	8 (8−8)

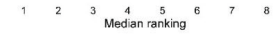


BMI - 12 months

Intervention	SUCRA	Rank (IQR)
Mediterranean	0.72	2 (1−3)
Low GI	0.66	2 (1−4)
Plant-based	0.5	4 (2−5)
Low carb.	0.45	4 (2−5)
Low fat	0.37	4 (3−5)
Moderate carb.	0.3	5 (4−6)

Systolic BP - 6 months

Intervention	SUCRA	Rank (IQR)
Mediterranean	0.84	1 (1−2)
Low GI	0.78	2 (2−3)
Low carb.	0.63	3 (2−5)
Moderate carb.	0.5	4 (3−6)
Low fat	0.45	5 (4−6)
High protein	0.31	6 (5−7)
Plant-based	0.3	7 (4−8)
No intervention	0.19	7 (6−8)

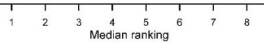


Systolic BP - 12 months

Intervention	SUCRA	Rank (IQR)
Plant-based	0.84	1 (1−3)
Low carb.	0.67	3 (2−4)
Moderate carb.	0.6	4 (3−5)
High protein	0.59	4 (2−5)
Mediterranean	0.49	5 (3−6)
Low GI	0.38	6 (4−7)
No intervention	0.26	7 (5−8)
Low fat	0.17	7 (6−8)

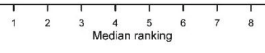
Diastolic BP - 6 months

Intervention	SUCRA	Rank (IQR)
Mediterranean	0.84	1 (1–2)
High protein	0.8	2 (2–3)
Low carb.	0.65	3 (2–4)
Low fat	0.62	4 (3–4)
Low GI	0.45	5 (4–6)
Plant-based	0.33	6 (5–7)
Moderate carb.	0.27	6 (6–7)
No intervention	0.03	8 (8–8)



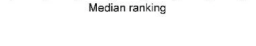
Diastolic BP - 12 months

Intervention	SUCRA	Rank (IQR)
Plant-based	0.71	2 (1–5)
High protein	0.69	3 (2–4)
Moderate carb.	0.6	4 (3–5)
Low carb.	0.59	4 (2–5)
Low GI	0.55	4 (2–6)
Mediterranean	0.47	5 (3–6)
Low fat	0.24	7 (6–7)
No intervention	0.16	8 (6–8)



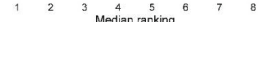
Total cholestrol - 6 months

Intervention	SUCRA	Rank (IQR)
Low GI	0.91	1 (1–2)
Low fat	0.7	3 (2–4)
High protein	0.66	3 (2–4)
Moderate carb.	0.45	5 (4–6)
Plant-based	0.42	5 (4–7)
Mediterranean	0.39	6 (3–8)
Low carb.	0.38	6 (4–6)
No intervention	0.08	8 (7–8)



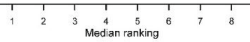
Total cholesterol - 12 months

Intervention	SUCRA	Rank (IQR)
Mediterranean	0.83	2 (1–3)
Plant-based	0.78	1 (1–3)
No intervention	0.57	3 (2–6)
Low GI	0.5	4 (3–6)
Moderate carb.	0.45	5 (4–6)
Low carb.	0.37	5 (4–7)
Low fat	0.3	6 (5–7)
High protein	0.2	7 (6–8)



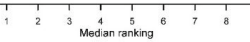
LDL-cholesterol - 6 months

Intervention	SUCRA	Rank (IQR)
Low GI	0.85	1 (1–2)
Low fat	0.61	3 (2–4)
Plant-based	0.54	4 (2–6)
High protein	0.53	4 (2–5)
Moderate carb.	0.53	4 (3–5)
Low carb.	0.34	5 (4–6)
No intervention	0.1	7 (6–7)



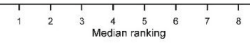
LDL-cholesterol - 12 months

Intervention	SUCRA	Rank (IQR)
Plant-based	0.76	2 (1–4)
Mediterranean	0.71	2 (1–4)
Low GI	0.64	3 (2–5)
Moderate carb.	0.64	4 (3–4)
No intervention	0.52	4 (2–6)
High protein	0.4	5 (4–6)
Low carb.	0.17	7 (6–8)
Low fat	0.16	7 (6–8)



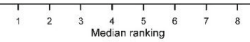
HDL-cholesterol - 6 months

Intervention	SUCRA	Rank (IQR)
Low carb.	0.95	1 (1–2)
High protein	0.65	3 (2–4)
Low fat	0.64	3 (3–4)
Moderate carb.	0.42	5 (4–6)
Low GI	0.38	6 (4–7)
Mediterranean	0.38	6 (2–8)
No intervention	0.38	5 (4–6)
Plant-based	0.19	7 (6–8)



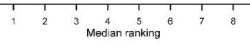
HDL-cholesterol - 12 months

Intervention	SUCRA	Rank (IQR)
Low carb.	0.74	2 (2–4)
Low GI	0.7	3 (2–4)
Mediterranean	0.68	3 (2–4)
High protein	0.56	4 (3–6)
Plant-based	0.48	5 (2–7)
Moderate carb.	0.38	5 (4–6)
Low fat	0.32	6 (5–7)
No intervention	0.14	8 (7–8)



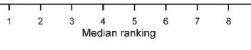
Triglycerides - 6 months

Intervention	SUCRA	Rank (IQR)
Low carb.	0.95	1 (1–2)
High protein	0.85	2 (1–2)
Low fat	0.62	4 (3–4)
Moderate carb.	0.61	4 (3–4)
Low GI	0.49	5 (4–5)
Plant-based	0.29	6 (6–6)
No intervention	0.13	7 (7–7)
Mediterranean	0.07	8 (7–8)



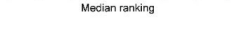
Triglycerides - 12 months

Intervention	SUCRA	Rank (IQR)
Low carb	0.77	2 (2–3)
Mediterranean	0.71	3 (2–4)
Plant-based	0.61	3 (1–7)
High protein	0.59	4 (2–5)
No intervention	0.41	5 (3–8)
Low GI	0.4	5 (4–6)
Low fat	0.36	6 (4–7)
Moderate carb	0.17	7 (6–8)



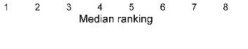
HbA1c - 6 months

Intervention	SUCRA	Rank (IQR)
Mediterranean	0.91	1 (1–2)
Low carb.	0.87	2 (1–2)
Plant-based	0.6	4 (3–5)
Low GI	0.59	4 (3–5)
High protein	0.56	4 (3–5)
Low fat	0.28	6 (6–6)
Moderate carb.	0.18	7 (7–7)
No intervention	0	8 (8–8)



HbA1c - 12 months

Intervention	SUCRA	Rank (IQR)
Low GI	0.84	1 (1–3)
Mediterranean	0.8	2 (1–3)
No intervention	0.63	3 (3–5)
High protein	0.44	5 (3–7)
Low carb.	0.43	5 (4–6)
Plant-based	0.39	6 (4–7)
Moderate carb.	0.37	5 (4–6)
Low fat	0.1	8 (7–8)



CRP - 6 months

Intervention	SUCRA	Rank (IQR)
Plant-based	0.84	1 (1−2)
Low GI	0.68	3 (2−4)
Low carb.	0.5	4 (3−5)
High protein	0.49	4 (2−6)
Low fat	0.47	4 (3−5)
Moderate carb.	0.34	6 (3−7)
No intervention	0.18	6 (5−7)

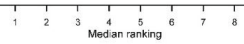
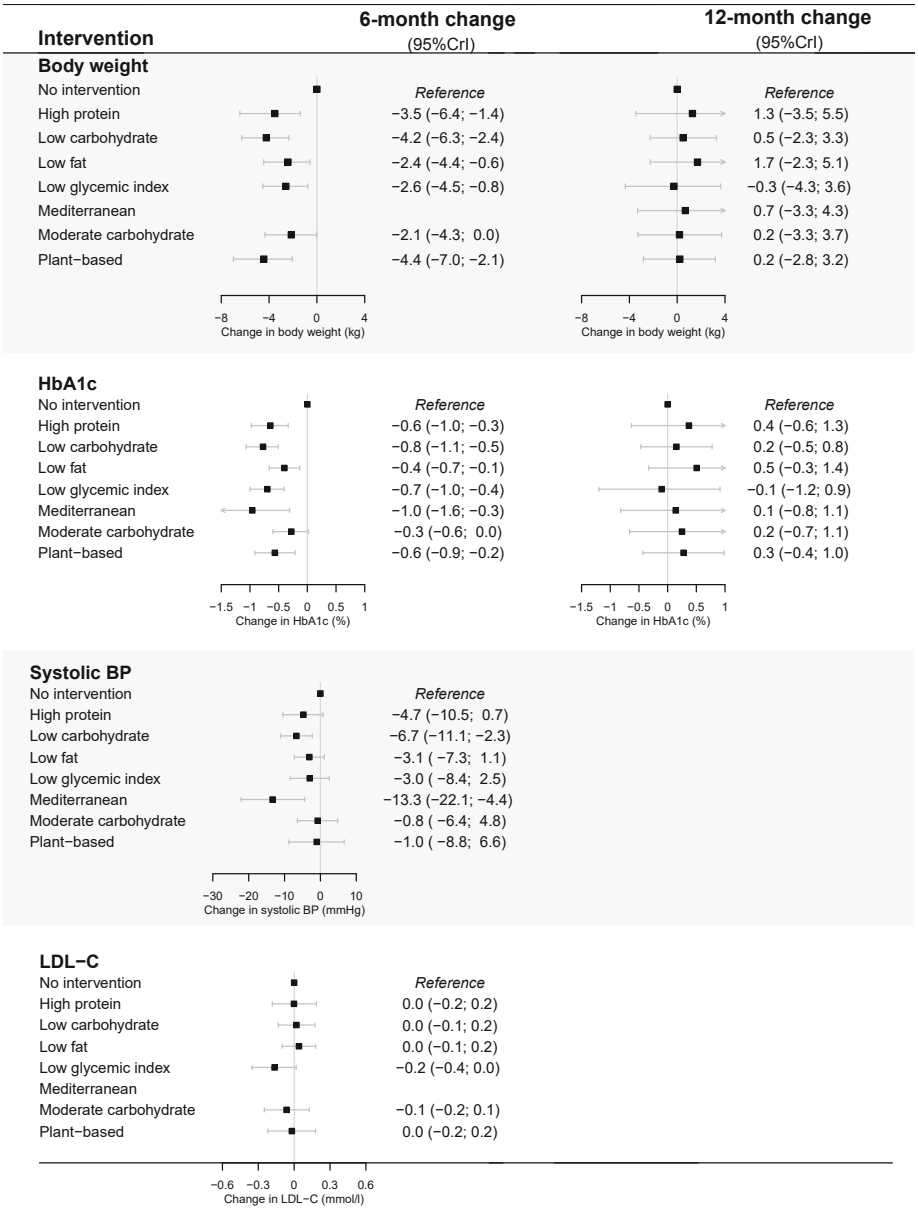
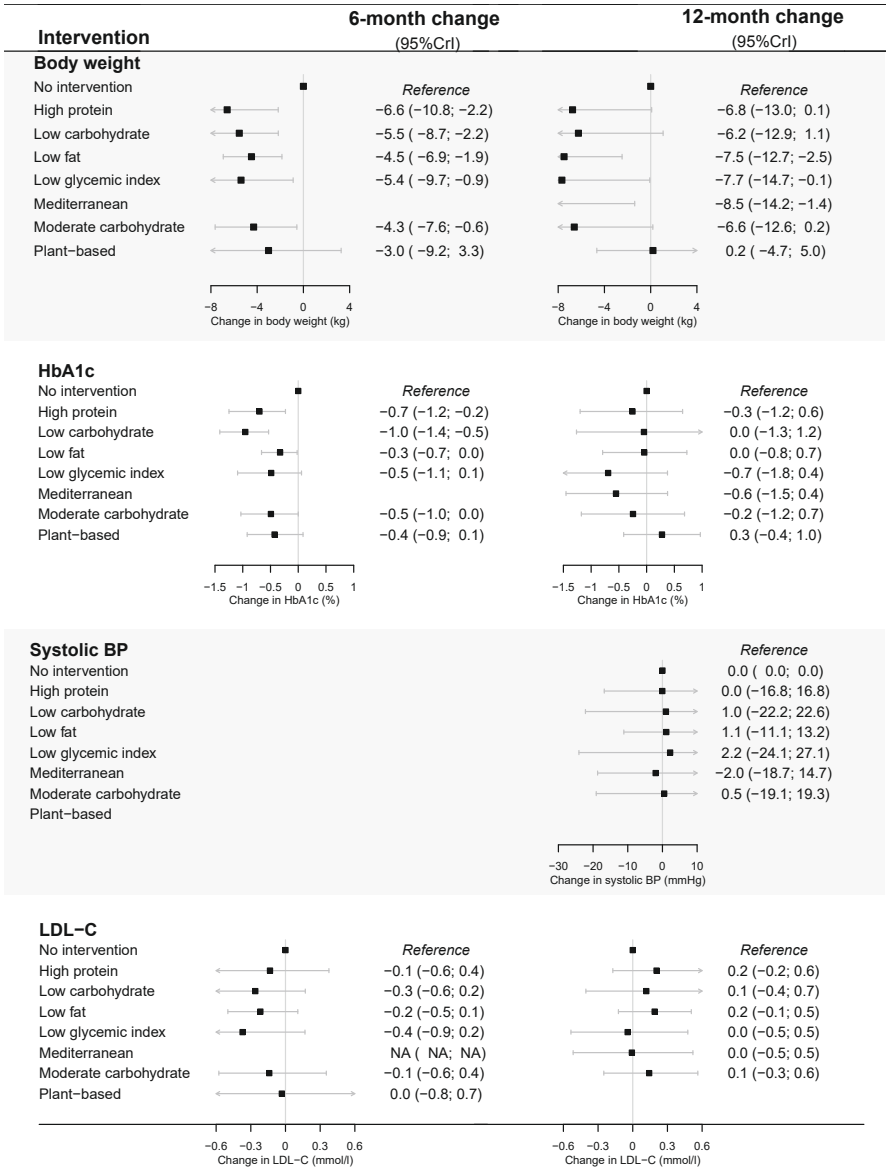


FIGURE S6 Sensitivity analysis limited to studies published in or after 2010



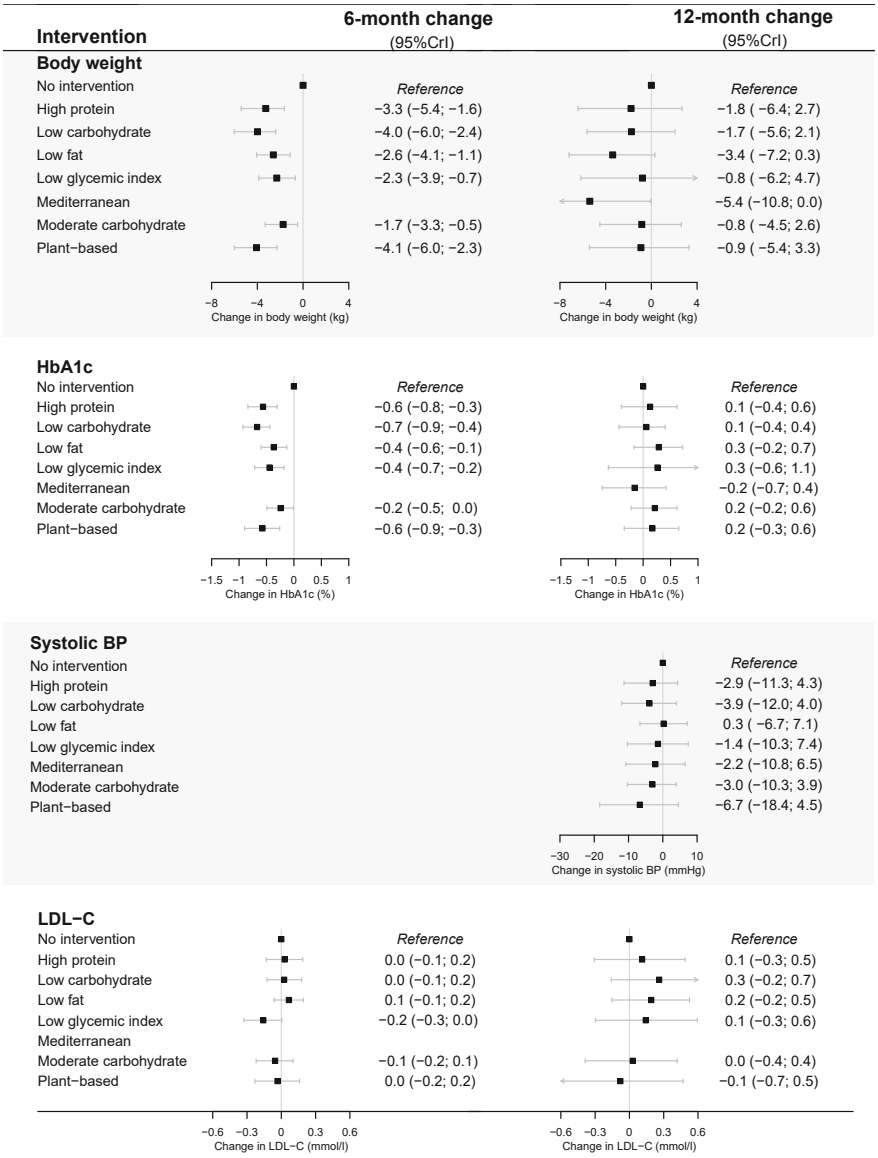
This figure shows the network estimates for the change in body weight, HbA1c, systolic blood pressure and low-density lipoprotein cholesterol relative to usual diet based on networks that were limited to studies published in or after the year 2010. The network for change in LDL-C and SBP after 12 months did not include any studies testing the effects of dietary interventions against no intervention and, therefore, results are not presented here. Abbreviations: 95%CrI: 95% credibility interval, HbA1c: glycated haemoglobin, BP: blood pressure, LDL-C: low-density lipoprotein cholesterol.

FIGURE S7 Sensitivity analysis limited to studies in overweight population



This figure shows the network estimates for the change in body weight, HbA1c, systolic blood pressure and low-density lipoprotein cholesterol relative to usual diet based on networks that were limited to studies that selected a population of people with type 2 diabetes mellitus and a body mass index ≥ 25 kg/m2 at baseline. The network for change in SBP after 6 months did not include any studies testing the effects of dietary interventions against no intervention and, therefore, results are not presented here. Abbreviations: 95%CrI: 95% credibility interval, HbA1c: glycated haemoglobin, BP: blood pressure, LDL-C: low-density lipoprotein cholesterol.

FIGURE S8 Sensitivity analysis in studies with a low or moderate risk of bias.



This figure shows the network estimates for the change in body weight, HbA1c, systolic blood pressure and low-density lipoprotein cholesterol relative to no dietary interventions based on networks excluded all studies that were at high risk of bias, according to the critical appraisal using the Cochrane RoB2 tool. The network for change in SBP after 6 months did not include any studies testing the effects of dietary interventions against no intervention and, therefore, results are not presented here. 95%CrI: 95% credibility interval, HbA1c: glycated haemoglobin, BP: blood pressure, LDL-C: low-density lipoprotein cholesterol.

SUPPLEMENTAL REFERENCES

1. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. 2009;52(11):2288-2298. doi:10.1007/s00125-009-1470-0
2. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-1681. doi:10.1016/S0140-6736(10)61350-5
3. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-967. doi:10.1016/S0140-6736(15)01225-8
4. AlFaris NA, Ba-Jaber AS. Effects of a low-energy diet with and without oat bran and olive oil supplements on body mass index, blood pressure, and serum lipids in diabetic women: A randomized controlled trial. Food Sci Nutr. 2020;8(7):3602-3609. doi:10.1002/fsn3.1642
5. Asle Mohammadi Zadeh M, Kargarfard M, Marandi SM, Habibi A. Diets along with interval training regimes improves inflammatory & anti-inflammatory condition in obesity with type 2 diabetes subjects. J Diabetes Metab Disord. 2018;17(2):253-267. doi:10.1007/s40200-018-0368-0
6. Barnard ND, Cohen J, Jenkins DJA, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care. 2006;29(8):1777-1783. doi:10.2337/dc06-0606
7. Barnard ND, Cohen J, Jenkins DJA, et al. A low-fat vegan diet and a conventional diabetes diet in the treatment of type 2 diabetes: A randomized, controlled, 74-wk clinical trial. Am J Clin Nutr. 2009;89(5):1588-1596. doi:10.3945/ajcn.2009.26736H
8. Barnard ND, Levin SM, Gloede L, Flores R. Turning the Waiting Room into a Classroom: Weekly Classes Using a Vegan or a Portion-Controlled Eating Plan Improve Diabetes Control in a Randomized Translational Study. J Acad Nutr Diet. 2018;118(6):1072-1079. doi:10.1016/j.jand.2017.11.017
9. Brunerova L, Smejkalova V, Potockova J, Andel M. A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and Type 2 diabetic patients. Published online 2007:533-540. doi:10.1111/j.1464-5491.2007.02104.x
10. Bunner AE, Wells CL, Gonzales J, Agarwal U, Bayat E, Barnard ND. A dietary intervention for chronic diabetic neuropathy pain: A randomized controlled pilot study. Nutr Diabetes. 2015;5(5):e158-6. doi:10.1038/nutd.2015.8
11. Cai X, Wang L, Wang X, Song L. Effect of high dietary fiber low glycemic index diet on intestinal flora, blood glucose and inflammatory response in T2DM patients. Biomed Res. 2017;28(21).
12. Chen CY, Huang WS, Chen HC, et al. Effect of a 90 g/day low-carbohydrate diet on glycaemic control, small, dense low-density lipoprotein and carotid intima-media thickness in type 2 diabetic patients: An 18-month randomised controlled trial. PLoS One. 2020;15(10):e0240158. doi:10.1371/journal.pone.0240158

13. Coppell KJ, Kataoka M, Williams SM, Chisholm AW, Vorgers SM, Mann JI. Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment - Lifestyle over and above drugs in diabetes (LOADD) study: Randomised controlled trial. BMJ. 2010;341(7766):237. doi:10.1136/bmj.c3337

14. Davis NJ, Tomuta N, Schechter C, et al. Comparative Study of the Effects of a 1-Year Dietary Intervention of a Low-Carbohydrate Diet Versus a Low-Fat Diet on Weight and Glycemic Control in Type 2 Diabetes. Diabetes Care. 2009;32(7):1147-1152. doi:10.2337/dc08-2108

15. Davis NJ, Crandall JP, Gajavelli S, et al. Differential effects of low-carbohydrate and low-fat diets on inflammation and endothelial function in diabetes. J Diabetes Complications. 2011;25(6):371-376. doi:10.1016/j.jdiacomp.2011.08.001

16. Davis NJ, Tomuta N, Isasi CR, Leung V, Wylie-Rosett J. Diabetes-specific Quality of Life After a Low-carbohydrate and Low-fat Dietary Intervention. Diabetes Educ. 2012;38(2):250-255. doi:10.1177/0145721711436132

17. de Bont AJ, Baker IA, St. Leger AS, et al. A randomised controlled trial of the effect of low fat diet advice on dietary response in insulin independent diabetic women. Diabetologia. 1981;21(6):529-533. doi:10.1007/BF00281543

18. Dodson PM, Pacy PJ, Bal P, Kubicki AJ, Fletcher RF, Taylor KG. A controlled trial of a high fibre, low fat and low sodium diet for mild hypertension in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1984;27(5):522-526. doi:10.1007/BF00290388

19. Durrer C, Mckelvey S, Singer J, et al. A randomized controlled trial of pharmacist-led therapeutic carbohydrate and energy restriction in type 2 diabetes. Nat Commun. 2021;(2021):1-8. doi:10.1038/s41467-021-25667-4

20. Dyson PA, Beatty S, Matthews DR. A low-carbohydrate diet is more effective in reducing body weight than healthy eating in both diabetic and non-diabetic subjects. Diabet Med. 2007;24(12):1430-1435. doi:10.1111/j.1464-5491.2007.02290.x

21. Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: A 1-year prospective randomized intervention study. Diabetes, Obes Metab. 2010;12(3):204-209. doi:10.1111/j.1463-1326.2009.01151.x

22. Esposito K, Ida Maiorino M, Ciotola M, et al. Effects of a mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: A randomized trial. Obstet Gynecol Surv. 2010;65(6):379-380. doi:10.1097/OGX.0b013e3181e5a159

23. Esposito K, Maiorino MI, Petrizzo M, Bellastella G, Giugliano D. The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: Follow-up of a randomized trial. Diabetes Care. 2014;37(7):1824-1830. doi:10.2337/dc13-2899

24. Maiorino MI, Bellastella G, Petrizzo M, et al. Effect of a Mediterranean diet on endothelial progenitor cells and carotid intima-media thickness in type 2 diabetes: Follow-up of a randomized trial. Eur J Prev Cardiol. 2017;24(4):399-408. doi:10.1177/2047487316676133

25. Maiorino MI, Bellastella G, Petrizzo M, Scappaticcio L, Giugliano D, Esposito K. Mediterranean diet cools down the inflammatory milieu in type 2 diabetes: the MÉDITA randomized controlled trial. Endocrine. 2016;54(3):634-641. doi:10.1007/s12020-016-0881-1

26. Evangelista LS, Heber D, Li Z, Bowerman S, Hamilton MA, Fonarow GC. Reduced Body Weight and Adiposity With a High-Protein Diet Improves Functional Status, Lipid Profiles, Glycemic Control, and Quality of Life in Patients With Heart Failure. J Cardiovasc Nurs. 2009;24(3):207-215. doi:10.1097/JCN.0b013e31819846b9

27. Evangelista LS, Jose MM, Sallam H, et al. High-protein vs. standard-protein diets in overweightand obese patients with heart failure and diabetes mellitus: findings of the Pro-HEART trial. ESC Hear Fail. 2021;8:1342-1348. doi:10.1002/ehf2.13213

28. Fabricatore AN, Wadden TA, Ebbeling CB, et al. Targeting dietary fat or glycemic load in the treatment of obesity and type 2 diabetes: A randomized controlled trial. Diabetes Res Clin Pract. 2011;92(1):37-45. doi:10.1016/j.diabres.2010.12.016

29. Facchini FS, Saylor KL. A low-iron-available, polyphenol-enriched, carbohydrate-restricted diet to slow progression of diabetic nephropathy. Diabetes. 2003;52(5):1204-1209. doi:10.2337/diabetes.52.5.1204

30. Ferdowsian HR, Barnard ND, Hoover VJ, et al. A multicomponent intervention reduces body weight and cardiovascular risk at a GEICO corporate site. Am J Heal Promot. 2010;24(6):384-387. doi:10.4278/ajhp.081027-QUAN-255

31. Goday A, Bellido D, Sajoux I, et al. Short-Term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. Nutr Diabetes. 2016;6(9):e230. doi:10.1038/nutd.2016.36

32. Goldstein T, Kark JD, Berry EM, Adler B, Ziv E, Raz I. The effect of a low carbohydrate energy-unrestricted diet on weight loss in obese type 2 diabetes patients - A randomized controlled trial. e-SPEN. 2011;6(4):e178-e186. doi:10.1016/j.eclnm.2011.04.003

33. Gram-kampmann EM, Hansen CD, Hugger MB, et al. Effects of a 6-month , low-carbohydrate diet on glycaemic control , body composition , and cardiovascular risk factors in patients with type 2 diabetes : An open-label randomized controlled trial. 2022;(October 2021):1-11. doi:10.1111/dom.14633

34. Guldbrand H, Dizdar B, Bunjaku B, et al. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia. 2012;55(8):2118-2127. doi:10.1007/s00125-012-2567-4

35. Guldbrand H, Lindström T, Dizdar B, et al. Randomization to a low-carbohydrate diet advice improves health related quality of life compared with a low-fat diet at similar weight-loss in Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2014;106(2):221-227. doi:10.1016/j.diabres.2014.08.032

36. Heilbronn LK, Noakes M, Clifton PM. Effect of energy restriction, weight loss, and diet composition on plasma lipids and glucose in patients with type 2 diabetes. Diabetes Care. 1999;22(6):889-895. doi:10.2337/diacare.22.6.889

37. Hockaday TDR, Hockaday JM, Mann JI, Turner RC. Prospective comparison of modified-fat–high-carbohydrate with standard low-carbohydrate dietary advice in the treatment of diabetes: one year follow-up study. Br J Nutr. 1978;39(2):357-362. doi:10.1079/bjn19780045

38. Iqbal N, Vetter ML, Moore RH, et al. Effects of a low-intensity intervention that prescribed a low-carbohydrate vs. a low-fat diet in obese, diabetic participants. Obesity. 2010;18(9):1733-1738. doi:10.1038/oby.2009.460

39. Itsiopoulos C, Brazionis L, Kaimakamis M, et al. Can the Mediterranean diet lower HbA1c in type 2 diabetes? Results from a randomized cross-over study. Nutr Metab Cardiovasc Dis. 2011;21(9):740-747. doi:10.1016/j.numecd.2010.03.005

40. Jesudason DR, Pedersen E, Clifton PM. Weight-loss diets in people with type 2 diabetes and renal disease: A randomized controlled trial of the effect of different dietary protein amounts. Am J Clin Nutr. 2013;98(2):494-501. doi:10.3945/ajcn.113.060889

41. Pedersen E, Jesudason DR, Clifton PM. High protein weight loss diets in obese subjects with type 2 diabetes mellitus. Nutr Metab Cardiovasc Dis. 2014;24(5):554-562. doi:10.1016/j.numecd.2013.11.003

42. Jin SM, Ahn J, Park J, Hur KY, Kim JH, Lee MK. East Asian diet-mimicking diet plan based on the Mediterranean diet and the Dietary Approaches to Stop Hypertension diet in adults with type 2 diabetes: A randomized controlled trial. J Diabetes Investig. 2021;12(3):357-364. doi:10.1111/jdi.13384

43. Jönsson T, Granfeldt Y, Ahrén B, et al. Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: A randomized cross-over pilot study. Cardiovasc Diabetol. 2009;8:1-14. doi:10.1186/1475-2840-8-35

44. Kahleova H, Matoulek M, Malinska H, et al. Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with Type2 diabetes. Diabet Med. 2011;28(5):549-559. doi:10.1111/j.1464-5491.2010.03209.x

45. Kahleová H, Hill M, Pelikánová T. Vegetarian vs. conventional diabetic diet - A 1-year follow-up. Cor Vasa. 2014;56(2):e140-e144. doi:10.1016/j.crvasa.2013.12.004

46. Kahleova H, Tonstad S, Rosmus J, et al. The effect of a vegetarian versus conventional hypocaloric diet on serum concentrations of persistent organic pollutants in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis. 2016;26(5):430-438. doi:10.1016/j.numecd.2016.01.008

47. Kahleova H, Klementova M, Herynek V, et al. The Effect of a Vegetarian vs Conventional Hypocaloric Diabetic Diet on Thigh Adipose Tissue Distribution in Subjects with Type 2 Diabetes: A Randomized Study. J Am Coll Nutr. 2017;36(5):364-369. doi:10.1080/07315724.2017.1302367

48. Kimura M, Kondo Y, Aoki K, et al. Correction: A Randomized Controlled Trial of a Mini Low-Carbohydrate Diet and an Energy-Controlled Diet Among Japanese Patients With Type 2 Diabetes. J Clin Med Res. 2018;10(6):531-534. doi:10.14740/jocmr3281wc1

49. Krebs JD, Elley CR, Parry-Strong A, et al. The Diabetes Excess Weight Loss (DEWL) Trial: A randomised controlled trial of high-protein versus high-carbohydrate diets over 2 years in type 2 diabetes. Diabetologia. 2012;55(4):905-914. doi:10.1007/s00125-012-2461-0

50. Larsen RN, Mann NJ, Maclean E, Shaw JE. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: A 12 month randomised controlled trial. Diabetologia. 2011;54(4):731-740. doi:10.1007/s00125-010-2027-y

51. Lasa A, Miranda J, Bulló M, et al. Comparative effect of two Mediterranean diets versus a low-fat diet on glycaemic control in individuals with type 2 diabetes. Eur J Clin Nutr. 2014;68(7):767-772. doi:10.1038/ejcn.2014.1

52. Lee YM, Kim SA, Lee IK, et al. Effect of a brown rice based vegan diet and conventional diabetic diet on glycemic control of patients with type 2 diabetes: A 12-week randomized clinical trial. PLoS One. 2016;11(6):1-14. doi:10.1371/journal.pone.0155918

53. Li S, Lin G, Chen J, et al. The effect of periodic ketogenic diet on newly diagnosed overweight or obese patients with type 2 diabetes. BMC Endocr Disord. Published online 2022:4-9. doi:10.1186/s12902-022-00947-2

54. Liu K, Wang B, Zhou R, et al. Effect of combined use of a low-carbohydrate, high-protein diet with omega-3 polyunsaturated fatty acid supplementation on glycemic control in newly diagnosed type 2 diabetes: A randomized, double-blind, parallel-controlled trial. Am J Clin Nutr. 2018;108(2):256-265. doi:10.1093/ajcn/nqy120

55. Lopez-Espinoza I, Howard-Williams J, Mann JI, Carter RD, Hockaday TDR. Fatty acid composition of platelet phospholipids in non-insulin-dependent diabetics randomized for dietary advice. Br J Nutr. 1984;52(1):41-47. doi:10.1079/bjn19840069

56. Luger M, Holstein B, Schindler K, Kruschitz R, Ludvik B. Feasibility and efficacy of an isocaloric high-protein vsstandard diet on insulin requirement, body weight and metabolic parameters in patients with type 2 diabetes on insulin therapy. Exp Clin Endocrinol Diabetes. 2013;121(5):286-294. doi:10.1055/s-0033-1341472

57. Ma Y, Olendzki BC, Merriam PA, et al. A randomized clinical trial comparing low-glycemic index versus ADA dietary education among individuals with type 2 diabetes. Nutrition. 2008;24(1):45-56. doi:10.1016/j.nut.2007.10.008

58. Metz JA, Stern JS, Kris-Etherton P, et al. A randomized trial of improved weight loss with a prepared meal plan in overweight and obese patients impact on cardiovascular risk reduction. Arch Intern Med. 2000;160(14):2150-2158. doi:10.1001/archinte.160.14.2150

59. Milne RM, Mann JI, Chisholm AW, Williams SM. Long-term comparison of three dietary prescriptions in the treatment of NIDDM. Diabetes Care. 1994;17(1):74-80. doi:10.2337/diacare.17.1.74

60. Mishra S, Xu J, Agarwal U, Gonzales J, Levin S, Barnard ND. A multicenter randomized controlled trial of a plant-based nutrition program to reduce body weight and cardiovascular risk in the corporate setting: The GEICO study. Eur J Clin Nutr. 2013;67(7):718-724. doi:10.1038/ejcn.2013.92

61. Morris E, Aveyard P, Dyson P, et al. A food-based, low-energy, low-carbohydrate diet for people with type 2 diabetes in primary care: A randomized controlled feasibility trial. Diabetes, Obes Metab. 2020;22(4):512-520. doi:10.1111/dom.13915

62. Nicholson AS, Sklar M, Barnard ND, Gore S, Sullivan R, Browning S. Toward improved management of NIDDM: A randomized, controlled, pilot intervention using a lowfat, vegetarian diet. Prev Med (Baltim). 1999;29(2):87-91. doi:10.1006/pmed.1999.0529

63. Walker Z, Sinclair J, Piers S, Nicholson C. Body fat distribution and non-insulin-dependent diabetes : com parison of a fi ber-rich. Published online 1996:254-260.

64. Parker B, Noakes M, Luscombe N, Clifton P. Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes. Diabetes Care. 2002;25(3):425-430. doi:10.2337/diacare.25.3.425

65. Brinkworth GD, Noakes M, Parker B, Foster P, Clifton PM. Long-term effects of advice to consume a high-protein, low-fat diet, rather than a conventional weight-loss diet, in obese adults with Type 2 diabetes: One-year follow-up of a randomised trial. Diabetologia. 2004;47(10):1677-1686. doi:10.1007/s00125-004-1511-7

66. Pascale RW, Wing RR, Butler BA, Mullen M, Bononi P. Effects of a Behavioral Weight Loss Program Stressing Calorie Restriction Versus Calorie Plus Fat Restriction in Obese Individuals With NIDDM or a Family History of Diabetes. Diabetes Care. 1995;18(9):1241-1248. doi:10.2337/diacare.18.9.1241

67. Pavithran N, Kumar H, Menon AS, Pillai GK, Sundaram KR, Ojo O. The Effect of a Low GI Diet on Truncal Fat Mass and Glycated Hemoglobin in South Indians with Type 2 Diabetes—A Single Centre Randomized Prospective Study. Nutrients. 2020;12(1):179. doi:10.3390/nu12010179

68. Perna S, Alalwan TA, Gozzer C, et al. Effectiveness of a hypocaloric and low-carbohydrate diet on visceral adipose tissue and glycemic control in overweight and obese patients with type 2 diabetes. Bahrain Med Bull. 2019;41(3):159-164.

69. Pijls LTJ, Vries H De, Donker AJM, Eijk JTM Van. The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus : a randomized trial. Published online 1999:1445-1453.

70. Pijls LTJ, Vries H De, Eijk J Van, Donker AJM. Protein restriction , glomerular filtration rate and albuminuria in patients with type 2 diabetes mellitus : a randomized trial. Published online 2002:1200-1207.

71. Ren M, Zhang H, Qi J, et al. An almond-based low carbohydrate diet improves depression and glycometabolism in patients with type 2 diabetes through modulating gut microbiota and glp-1: A randomized controlled trial. Nutrients. 2020;12(10):1-21. doi:10.3390/nu12103036

72. Sato J, Kanazawa A, Makita S, et al. A randomized controlled trial of 130 g/day low-carbohydrate diet in type 2 diabetes with poor glycemic control. Clin Nutr. 2017;36(4):992-1000. doi:10.1016/j.clnu.2016.07.003

73. Sato J, Kanazawa A, Hatae C, et al. One year follow-up after a randomized controlled trial of a 130 g/day low-carbohydrate diet in patients with type 2 diabetes mellitus and poor glycemic control. PLoS One. 2017;12(12):1-13. doi:10.1371/journal.pone.0188892

74. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. N Engl J Med. 2008;359(3):229-241. doi:10.1056/NEJMoa0708681

75. Struik NA, Brinkworth GD, Thompson CH, Buckley JD, Wittert G, Luscombe-Marsh ND. Very Low and Higher Carbohydrate Diets Promote Differential Appetite Responses in Adults with Type 2 Diabetes: A Randomized Trial. J Nutr. 2020;150(4):800-805. doi:10.1093/jn/nxz344

76. Tay J, Luscombe-Marsh ND, Thompson CH, et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: A randomized trial. Diabetes Care. 2014;37(11):2909-2918. doi:10.2337/dc14-0845

77. Tay J, Luscombe-Marsh ND, Thompson CH, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: A randomized trial. Am J Clin Nutr. 2015;102(4):780-790. doi:10.3945/ajcn.115.112581

78. Tay J, Thompson CH, Luscombe-Marsh ND, et al. Long-Term effects of a very low carbohydrate compared with a high carbohydrate diet on renal function in individuals with type 2 diabetes: A randomized trial. Med (United States). 2015;94(47):e2181. doi:10.1097/MD.0000000000002181

79. Brinkworth GD, Luscombe-Marsh ND, Thompson CH, et al. Long-term effects of very low-carbohydrate and high-carbohydrate weight-loss diets on psychological health in obese adults with type 2 diabetes: randomized controlled trial. J Intern Med. 2016;280(4):388-397. doi:10.1111/joim.12501

80. Wen-Harn P, Ying-Ho L, Wen-Ting Y, et al. Intake of potassium- and magnesium-enriched salt improves functional outcome after stroke: a randomized, multicenter, double-blind controlled trial. Am J Clin Nutr. 2017;106(5):1267-1273. doi:10.3945/ajcn.116.148536

81. Tay J, Thompson CH, Luscombe-Marsh ND, et al. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. Diabetes, Obes Metab. 2018;20(4):858-871. doi:10.1111/dom.13164

82. Tay J, Thompson CH, Luscombe-Marsh ND, et al. Nutritional adequacy of very low- and high-carbohydrate, low saturated fat diets in adults with type 2 diabetes: A secondary analysis of a 2-year randomised controlled trial. Diabetes Res Clin Pract. 2020;170. doi:10.1016/j.diabres.2020.108501

83. Kakoschke N, Zajac IT, Tay J, et al. Effects of very low - carbohydrate vs . high - carbohydrate weight loss diets on psychological health in adults with obesity and type 2 diabetes : a 2 - year randomized controlled trial. Eur J Nutr. 2021;60(8):4251-4262. doi:10.1007/s00394-021-02587-z

84. Tsihlias EB, Gibbs AL, McBurney MI, Wolever TMS. Comparison of high- and low-glycemic-index breakfast cereals with monounsaturated fat in the long-term dietary management of type 2 diabetes. Am J Clin Nutr. 2000;72(2):439-449. doi:10.1093/ajcn/72.2.439

85. Visek J, Lacigova S, Cechurova D, Rusavy Z. Comparison of a low-Glycemic index VS standard diabetic diet. Biomed Pap. 2014;158(1):112-116. doi:10.5507/bp.2012.103

86. Walker KZ, O'Dea K, Nicholson GC, Muir JG. Dietary composition, body weight, and NIDDM: Comparison of high-fiber, high-carbohydrate, and modified-fat diets. Diabetes Care. 1995;18(3):401-403. doi:10.2337/diacare.18.3.401

87. Wang LL, Wang Q, Hong Y, et al. The effect of low-carbohydrate diet on glycemic control in patients with type 2 diabetes mellitus. Nutrients. 2018;10(6). doi:10.3390/nu10060661

88. Watson N, Dyer K, Buckley J, et al. Effects of low-fat diets differing in protein and carbohydrate content on cardiometabolic risk factors during weight loss and weight maintenance in obese adults with type 2 diabetes. Nutrients. 2016;8(5). doi:10.3390/nu8050289

89. Watson NA, Dyer KA, Buckley JD, et al. Reductions in food cravings are similar with low-fat weight loss diets differing in protein and carbohydrate in overweight and obese adults with type 2 diabetes: A randomized clinical trial. Nutr Res. 2018;57:56-66. doi:10.1016/j.nutres.2018.05.005

90. Westman EC, Jr WSY, Mavropoulos JC, Marquart M, Mcduffie JR. Nutrition & Metabolism The effect of a low-carbohydrate , ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. 2008;9:1-9. doi:10.1186/1743-7075-5-36

91. Wolever TMS, Gibbs AL, Mehling C, et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: No effect on glycated hemoglobin but reduction in C-reactive protein. Am J Clin Nutr. 2008;87(1):114-125. doi:10.1093/ajcn/87.1.114

92. Wolever TMS, Mehling C, Chiasson JL, et al. Low glycaemic index diet and disposition index in type 2 diabetes (the Canadian trial of Carbohydrates in Diabetes): A randomised controlled trial. Diabetologia. 2008;51(9):1607-1615. doi:10.1007/s00125-008-1093-x

93. Wolever TMS, Gibbs AL, Chiasson J, et al. Altering source or amount of dietary carbohydrate has acute and chronic effects on postprandial glucose and triglycerides in type 2 diabetes : Canadian trial of Carbohydrates in Diabetes (CCD). Nutr Metab Cardiovasc Dis. 2013;23(3):227-234. doi:10.1016/j.numecd.2011.12.011

94. Wycherley TP, Noakes M, Clifton PM, Cleanthous X, Keogh JB, Brinkworth GD. A high-protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes. Diabetes Care. 2010;33(5):969-976. doi:10.2337/dc09-1974

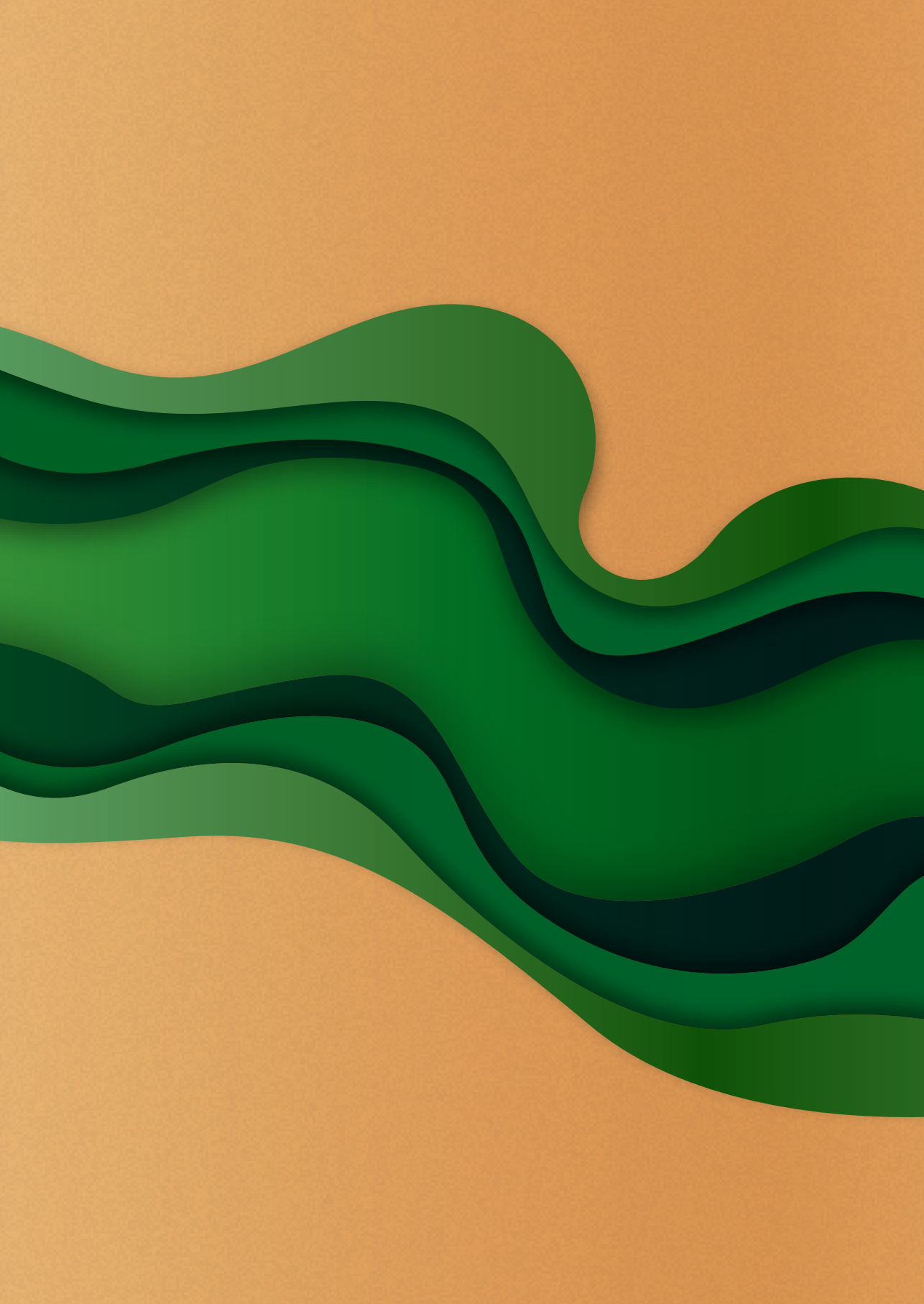
95. Wycherley TP, Thompson CH, Buckley JD, et al. Long-term effects of weight loss with a very-low carbohydrate, low saturated fat diet on flow mediated dilatation in patients with type 2 diabetes: A randomised controlled trial. Atherosclerosis. 2016;252:28-31. doi:10.1016/j.atherosclerosis.2016.07.908

96. Yamada Y, Uchida J, Izumi H, et al. A non-calorie-restricted low-carbohydrate diet is effective as an alternative therapy for patients with type 2 diabetes. Intern Med. 2014;53(1):13-19. doi:10.2169/internalmedicine.53.0861

97. Yusof BNM, Talib RA, Kamaruddin NA, Karim NA, Chinna K, Gilbertson H. A low-GI diet is associated with a short-term improvement of glycaemic control in Asian patients with type 2 diabetes. Diabetes, Obes Metab. 2009;11(4):387-396. doi:10.1111/j.1463-1326.2008.00984.x

98. Zahedi M, Akhlagh SA, Aboomardani M, Alipoor R, Hosseini SA, Shahmirzadi AR. Efficacy of mediterranean diet on blood biochemical factors in type II diabetic patients: A randomized controlled trial. Gazi Med J. 2021;31(4A):714-718.

99. Zainordin NA, Warman NAE, Mohamad AF, et al. Safety and efficacy of very low carbohydrate diet in patients with diabetic kidney disease — A randomized controlled trial. PLoS One. 2021;27:1-17. doi:10.1371/journal.pone.0258507



CHAPTER 5

RELATIONSHIP OF THE DASH AND MEDITERRANEAN DIET WITH RISK OF ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN PATIENTS WITH ESTABLISHED CVD

A MEDIATION ANALYSIS

Nadia E. Bonekamp
Esther Cruijsen
Frank L.J. Visseren
Charlotte Koopal
Johanna M. Geleijnse

Manuscript draft

ABSTRACT

Objective

To quantify the association between adherence scores for the Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean diet with (cardiovascular) mortality in drug-treated stable CVD patients and to assess to what extent these associations could be mediated by differences in baseline cardiovascular risk factor levels. Baseline body weight, systolic blood pressure, low-density lipoprotein cholesterol (LDL-C), triglycerides and C reactive protein (CRP) levels were assessed as potential mediators.

Methods

Data from 4,365 CVD patients (79% male, median age 69) with dietary data from the Alpha Omega Cohort was used. The relationship of DASH and Mediterranean diet scores with all-cause and cardiovascular mortality was assessed using multivariable-adjusted Cox proportional hazard models. A mediation analysis using a structural equation model was performed to quantify the proportion effect potentially mediated by baseline levels of body weight, systolic blood pressure, LDL-C, triglycerides, and high-sensitivity CRP.

Results

Over 12.4 years [IQR 8.8-13.8] of follow-up, 2,035 deaths and 903 cardiovascular deaths occurred. Overall compliance with the DASH and Mediterranean diet was poor and the relationships between these diet scores and (cardiovascular) mortality were small and not statistically significant. Of these associations, the included CVD risk factors mediated between 30-50% Differences in CRP level accounted for the largest proportion of the total association: 66% (95%CI 16.2; 122.2) of the total association of the DASH diet score and 28% (95%CI -8.1; 65.7) of the Mediterranean diet score.

Conclusion

In CVD patients who received advanced drug treatment, non-statistically significant associations of the DASH and Mediterranean diet scores with cardiovascular and all-cause mortality were mediated by low-grade systemic inflammation, rather than classical CVD risk factors

INTRODUCTION

Improving dietary habits is a first-line recommendation in the secondary prevention of cardiovascular disease (CVD).[1,2] Guidelines for the clinical management of CVD patients provide a set of recommendations on the intake levels of several food items that have been related to CVD risk, such as vegetables, legumes, fish, and meat.[1–4] However, these guidelines also recommend consideration of specific dietary patterns such as the Dietary Approaches to Stop Hypertension diet (DASH), a diet rich in fruit, vegetables, and low-fat dairy and with a strong emphasis on sodium reduction,[5,6] or a Mediterranean-style diet (a dietary pattern rich in plant-based, unsaturated fats, legumes and lean meats).[1,2,4,7]

The majority of randomized controlled trials (RCTs) assessing the efficacy of dietary patterns for reducing cardiovascular risk primarily focused on evaluating a range of cardiovascular risk factors. Notably, these studies have demonstrated that dietary patterns such as the DASH and Mediterranean diets have benefits in terms of lowering body weight and systolic blood pressure,[8] and a neutral impact on lipid levels.[8] In contrast, only a limited number of RCTs directly addressed the impact of dietary interventions on cardiovascular event risk. The existing research suggests a substantial potential of the Mediterranean diet for reducing cardiovascular risk in both primary and secondary prevention populations.[9–12]

Due to the logistical and financial challenges inherent to conducting long-term clinical trials to assess the effectiveness of dietary interventions, it is unlikely that all potentially heart-healthy diets will ever be assessed in a cardiovascular outcome trial. Instead, the majority of experimental research on dietary patterns relies on shorter-term trials that assess their efficacy for lowering cardiovascular risk factors, such as blood pressure and lipid levels. However, it remains largely unclear which and to what extent cardiovascular risk factors serve as mediators of the previously observed reduction of cardiovascular event risk.[10,12] Gaining further insight into the mediating pathways between dietary interventions and recurrent cardiovascular event risk, may improve translation of the results in shorter-term dietary trials to clinical CVD management and contribute to identifying the most effective dietary intervention for CVD patients.

The aim of the current study was to assess the relationship of theoretical compliance with a DASH diet and a Mediterranean-style diet with cardiovascular and all-cause

mortality in patients with a history of myocardial infarction (MI). Moreover, the objective was to assess to what extent these relationships were mediated by differences in baseline cardiovascular risk factor levels: body weight, systolic blood pressure, low-density lipoprotein (LDL) cholesterol, triglycerides, and C reactive protein (CRP) levels.

MATERIALS & METHODS

Study population

The Alpha Omega Cohort (AOC) is a prospective cohort study comprising patients aged 60-80 year with a history of MI within 10 years before inclusion in the study (between 2002 and 2006). The AOC was originally designed as an RCT where patients were randomized to either low-dose *omega*-3 fatty acid supplementation or placebo for a 40-month period. The trial had a neutral effect on cardiovascular event and mortality risk.[13] The AOC was approved by the Central Ethics committee (Haga Hospital) and by the Ethics committees of the participating hospitals. All participants provided written informed consent. For the current study, participants without dietary data or with an implausible energy intake were excluded (men: <800 kcal/day or > 8,000 kcal/day and women: <600 kcal/day or >6,000 kcal/day), resulting a study population of 4,365 patients.

Data collection

Upon inclusion in the AOC, participants completed a self-administered questionnaire on patient characteristics, medical history, medication use, and lifestyle behaviours. Furthermore, they underwent anthropometric and laboratory assessments. Smoking status was classified as never, former, or current smoking. Educational level was divided into four groups: elementary education or less, low education, moderate education, and high education. Body weight was measured according to a standardized protocol in light clothing without shoes. Blood pressure was measured twice with the patient in sitting position after a 10-minute rest using an automatic device (HEM-711, Omron) and then averaged. Serum lipids, plasma glucose and serum C-reactive protein (CRP) were analysed from non-fasting blood samples using standardized kits (Hitachi 912; Roche Diagnostics). Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula.[14]

Dietary assessment

Dietary intake was assessed using a 203-item food frequency questionnaire (FFQ).[15] Energy, macronutrient and micronutrient intake were calculated by linking the FFQ responses to the 2006 Dutch Food Composition Database.[16] Compliance to the Mediterranean diet and the DASH diet was quantified using diet-specific compliance scores (Table S1). For the DASH diet, the nutrient-based DASH dietary index proposed by Mellen *et al.*[17] was used. This diet index comprises nine components and for each item one point is awarded when the target intake level is reached; if only the intermediate target is reached, 0.5 point is awarded. Target intake levels were based on the target intake in the original DASH diet RCTs.[5,6]. The scores for the nine components were then summed, meaning that a total score ranging between 0 and 9 points can be achieved.

Compliance with a Mediterranean-style diet was assessed using the validated Mediterranean Diet Adherence screener (MEDAS) score, originally developed for the PREDIMED trial.[10,18] This score encompasses 14 food groups, and 1 point is awarded when a respondent is compliant with the recommendation for that item. No continuous or intermediate scores are awarded. In the AOC, no information was available on use of *sofrito* in daily cooking and therefore, this component was not included in the score. As a consequence, the total MEDAS score in these analyses ranged between 0 and 13 points. For the survival and mediation analyses, compliance with the DASH and Mediterranean diets was categorized into tertiles.

Outcome assessment

Primary endpoints for the current analysis were all-cause mortality and cardiovascular mortality. Cause of death was classified based on the International Classification of Diseases, 10th revision (ICD-10) coding. Cardiovascular mortality was defined as death from ischemic heart disease (ICD-10 codes I20-I25), cardiac arrest (I46), stroke (I60-I69), heart failure (I50), or undefined, sudden death (R96). Vital status was monitored through linkage with municipal registries. Cause of death was assessed in three phases:

1. Initially, during the Alpha Omega trial phase (2002-2009), data was obtained from the national mortality registry and patients' relatives. Additional information on cause of death was requested from the treating physician and a final judgement on the cause of death was made by an independent Endpoint Adjudication Committee.[13,19]

2. Between 2010 and 2013, information on primary and contributing causes of death were obtained from Statistics Netherlands (CBS).
3. From 2013 onwards, CBS provided only the primary cause of death. During this phase, treating physicians were asked to provide additional detailed information on cause of death (response rate 67%).

Person-time was calculated from date of inclusion in the AOC until the date of death or until the end of follow-up (December 31, 2018), whichever came first.

Data analyses

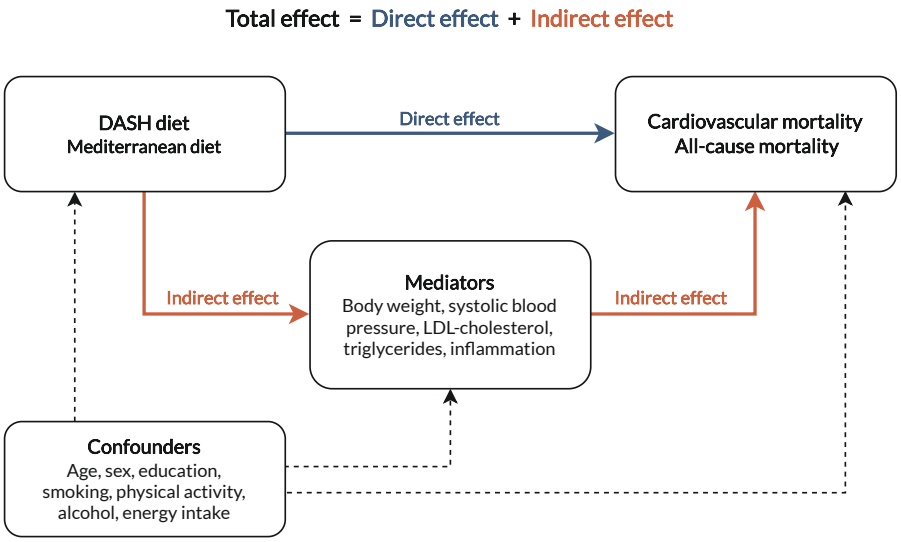
Baseline characteristics were described across tertiles of the DASH and Mediterranean diet scores as mean with standard deviation (SD), median and interquartile range (IQR) or absolute number and percentage, as appropriate. Cox proportional hazard models were used to estimate the relationship of tertiles of DASH and Mediterranean diet scores with all-cause and cardiovascular mortality. Stepwise adjustments were made for confounders. The first model adjusted for age and sex. In the second and main model, adjustments were made for age, sex, education level, physical activity level, smoking status, alcohol consumption and total energy intake. The proportional hazard assumption was assessed through visual inspection of Schoenfeld residuals. The continuous association between the two dietary adherence scores and all-cause mortality and cardiovascular mortality was assessed using restricted cubic splines with three knots.

Baseline levels of body weight, systolic blood pressure, LDL-cholesterol, triglycerides, and CRP were assessed as potential mediators of the relationship between the DASH and Mediterranean diet and (cardiovascular) mortality (Figure 1). These mediators were selected because they frequently serve as outcomes in dietary intervention studies and are theoretically plausible mediators in the association between diet and CVD outcomes. A mediation analysis was performed using marginal structural models in a counterfactual framework.[20–24] In this approach, weighted Cox proportional hazard model are used to separately estimate the effect of dietary patterns on the outcome through a potential mediator (the indirect effect) and the effect independent of the mediators of interest (direct effect). Indirect and direct effects are additive on the log-hazard scale and can be combined into an estimate of the total effect. The proportion mediated effect (PME) was calculated by dividing the indirect effect for a mediator by the total effect. 95% confidence intervals (95%CI) for total effect, direct effect, indirect

effect and PME were obtained by repeating the analyses in 1,000 bootstrapping samples using the percentile method. A detailed description of the statistical analysis is provided in Supplementary Appendix 1.

Models assessing one potential mediator at a time were performed to assess independence of the mediating pathways. The impact of reverse causation was assessed by running the Cox proportional hazard models after exclusion of the initial 1, 3, and 5 years of follow-up. Missing data was imputed using single imputation with predictive mean matching. All analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing).

FIGURE 1 Causal framework of the relationship between dietary patterns and all-cause and cardiovascular mortality



Graphic representation of the hypothesized relationships between dietary patterns and cardiovascular and all-cause mortality. Indirect effects represent the proportion of the total effect that is effectuated through change in the mediators. Adjustments were made for confounding in the determinant-outcome, determinant-mediator, and mediator-outcome relationships. DASH: dietary approaches to stop hypertension, LDL-cholesterol: low-density lipoprotein cholesterol

RESULTS

Study population

In total, 4,365 patients with a history of MI were included. Most participants were men (N = 3,432, 79%) and the median age at inclusion in the cohort was 69 years [IQR 64-73] (Table 1). Twenty percent of the population had T2D, and the mean BMI was 27.7 ± 3.8 kg/m^2. Sixty-seven percent reported having previously smoked and 16% was still smoking at inclusion in the cohort. Median leisure-time physical activity level was 23 METh/wk [IQR 11-45]. The majority of the study population was treated with blood pressure-lowering medication (90%), lipid-lowering medication (87%) and antithrombotic agents (98%).

Compliance with the DASH and Mediterranean diet

The median compliance score for the DASH diet was 3.0 [IQR: 2.0-4.0] out of a maximum score of 9 (Figure 2). Compared to the lowest DASH score tertile, patients in the highest DASH tertile had a similar age, but were more frequently female (32% *vs* 14%) and had a lower energy intake (1,697 kcal/day *vs* 2,049 kcal/day). Moreover, they were less frequently current smokers (11% *vs* 21%), had higher median physical activity levels (24 METh/wk *vs* 20 METh/wk) and had a higher mean systolic blood pressure (Table 1).

For the Mediterranean diet, the median compliance score was 3.0 [IQR 3.0-4.0] out of a maximum of 13 points (Figure 2). Patients within the highest Mediterranean compliance tertile were more frequently female (26% vs 17%), completed higher education (15% vs 11%), and less frequently were current smokers (13 vs 17%), compared with the lowest Mediterranean diet scores. Total energy intake was lower in patients in the highest Mediterranean diet score tertile, and a smaller proportion of energy intake was derived from (saturated) fatty acids (Table 1).

TABLE 1 Alpha Omega Cohort participants' characteristics stratified for DASH and Mediterranean compliance score tertiles (N = 4,365)

	DASH diet score			Mediterranean diet score		
Characteristic	1st Tertile 0 – 2.5	2nd Tertile 3.0 – 3.5	3rd Tertile 4.0 – 8.5	1st Tertile 0 – 2	2nd Tertile 3	3rd Tertile 4 – 7
	N = 1,462	*N = 1,719*	*N = 1,184*	*N = 1,020*	*N = 1,955*	*N = 1,390*
Patient characteristics						
Age, years	69 ±5.6	69 ±5.6	69 ±5.6	68.8 ±5.6	69 ±5.5	69.2 ±5.6
Male sex, n (%)	1255 (86)	1372 (80)	805 (68)	844 (83)	1557 (80)	1031 (74)
Education level, n (%)						
Elementary education	306 (21)	361 (21)	221 (19)	189 (19)	456 (23)	243 (18)
Lower education	540 (37)	592 (34)	436 (37)	405 (40)	715 (37)	448 (32)
Moderate education	450 (31)	543 (32)	380 (32)	311 (31)	572 (29)	490 (35)
Higher education	166 (11)	223 (13)	147 (12)	115 (11)	212 (11)	209 (15)
Type 2 diabetes, n (%)	284 (19)	333 (19)	266 (23)	198 (19)	409 (21)	276 (20)
Smoking status						
Never smoker, n (%)	182 (12)	270 (16)	270 (23)	161 (16)	291 (15)	270 (19)
Former smoker, n (%)	980 (67)	1170 (68)	780 (66)	687 (67)	1307 (67)	936 (67)
Current smoker, n (%)	300 (21)	279 (16)	134 (11)	172 (17)	357 (18)	184 (13)
Physical activity, METh/wk	20 [8-41]	24 [11-48]	24 [11-47]	21 [8-44]	21 [9-44]	25.5 [11-50]
Alcohol, units/wk	8.54 (9)	7.43 (8)	6.15 (7)	6.9 ±7.7	7.8 ±8.4	7.4 ±8
Body mass index, kg/m^2	27.7 ±3.7	27.7 ±3.8	27.9 ±4	27.9 ±3.8	27.7 ±3.8	27.7 ±3.8
Systolic BP, mmHg	141 ±21	142 ±22	143 ±22	142 ±21	142 ±22	142 ±22
Total cholesterol, mmol/l	4.6 [4.1-5.3]	4.6 [4-5.2.0]	4.7 [4.0-5.3]	4.6 [4.0-5.3]	4.7 [4.1-5.3]	4.6 [4.0-5.2]
HDL-cholesterol, mmol/l	1.2 [1.0-1.4]	1.2 [1.1-1.5]	1.2 [1.1-1.5]	1.2 [1.0-1.4]	1.2 [1.1-1.5]	1.3 [1.1-1.5]
LDL-cholesterol, mmol/l	2.5 [2.0-3.1]	2.5 [2.0-3.0]	2.5 [2.0-3.0]	2.5 [2.0-3.0]	2.5 [2.0-3.0]	2.5 [2.0-3.0]

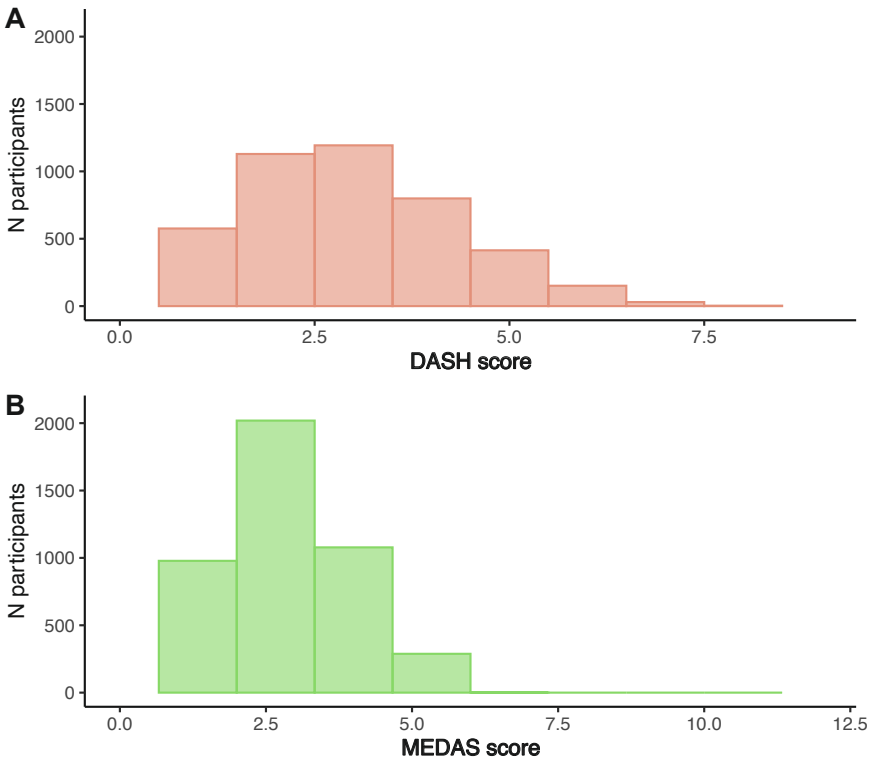
TABLE 1 (Continued)

Characteristic	DASH diet score			Mediterranean diet score		
	1st Tertile 0 – 2.5	2nd Tertile 3.0 – 3.5	3rd Tertile 4.0 – 8.5	1st Tertile 0 – 2	2nd Tertile 3	3rd Tertile 4 – 7
	N = 1,462	*N = 1,719*	*N = 1,184*	*N = 1,020*	*N = 1,955*	*N = 1,390*
Triglycerides, mmol/l*	1.7 [1.3-2.4]	1.6 [1.2-2.3]	1.7 [1.2-2.4]	1.7 [1.3-2.4]	1.7 [1.2-2.4]	1.6 [1.2-2.3]
C-reactive protein, mg/dl	1.9 [0.9-3.8]	1.6 [0.8-3.4]	1.6 [0.8-3.6]	1.8 [0.8-3.7]	1.7 [0.8-3.6]	1.6 [0.7-3.5]
Antithrombotic agent, n (%)	1424 (97)	1688 (98)	1154 (98)	1003 (98)	1903 (97)	1360 (98)
Antihypertensives, n (%)	1319 (90)	1539 (90)	1061 (90)	915 (90)	1760 (90)	1244 (90)
Lipid-lowering therapy, n (%)	1230 (84)	1497 (87)	1058 (89)	886 (87)	1683 (86)	1216 (88)
Dietary intake characteristics						
Energy intake, kcal/day	2049 [1716-2418]	1862 [1553-2196]	1697 [1416-2013]	2105 [1764-2463]	1841 [1541-2165]	1768 [1441-2124]
Carbohydrates						
Total intake, E%	43 [39-47]	47 [43-51]	52 [47-56]	47 [43-52]	46 [41-50]	48 [43-53]
Mono- and disaccharides, g	106 [78-139]	108 [79-143]	114 [85-147]	125 [99-158]	101 [75-134]	106 [79-141]
Fatty acids						
Total intake, E%	38 [34-42]	33 [30-37]	28 [24-31]	35 [31-39]	34 [30-39]	31 [27-36]
Saturated fatty acids, g	33 [27-42]	26 [21-32]	20 [16-25]	31 [25-40]	27 [21-34]	23 [17-30]
MUFA, g	29 [24-36]	24 [19-29]	18 [14-22]	27 [21-34]	24 [18-29]	22 [16-29]
PUFA, g	19 [14-25]	15 [12-20]	12 [9-15]	17 [13-23]	15 [12-20]	13 [10-19]
Protein						
Total intake, E%	14 [13-15]	15 [13-17]	16 [14-18]	14 [12-16]	15 [13-17]	15 [14-17]
Fiber, g	19 [15-23]	21 [16-25]	23 [18-28]	21 [17-25]	20 [16-25]	22 [17-27]

DASH: Dietary Approaches to Stop Hypertension, MEDAS: Mediterranean Diet Adherence Screener, BP: Blood pressure, HDL: High-density lipoprotein ,LDL: low-density lipoprotein, CRP: C reactive protein, MUFA: mono unsaturated fatty acid, PUFA: poly unsaturated fatty acid

* Non-fasting measurement

FIGURE 2 Distribution DASH and Mediterranean diet scores in the Alpha Omega cohort



Distribution of dietary compliance score for DASH diet **(A)** and Mediterranean diet **(B)**. DASH: Dietary Approaches to Stop Hypertension, MEDAS: Mediterranean diet Adherence Screener

Relationship of DASH and Mediterranean diet with risk of all-cause mortality and cardiovascular mortality

Over a median follow-up of 12.4 years [IQR 8.8-13.8], 2,023 deaths occurred of which 903 had a cardiovascular origin (Figure S1). There was a trend toward a lower risk of all-cause mortality for the highest vs the lowest tertile for the DASH diet (HR 0.92, 95%CI 0.82-1.03) and the Mediterranean diet (HR 0.94, 95%CI 0.83-1.06), but these relationships were not statistically significant (Table 2). For the cardiovascular mortality endpoint, the hazard ratio was 0.88, 95%CI 0.73-1.06 (third vs first tertile) for the DASH diet score and 1.00, 95%CI 0.84-1.19 for the Mediterranean diet. For both the DASH and Mediterranean diet, the continuous relation with the mortality endpoints was not statistically significant (Figure S2). Effect estimates did not change after exclusion of the first 1, 3, and 5 years of follow-up (Table S2).

TABLE 2 Associations of dietary pattern scores with cardiovascular and all-cause mortality in 4365 patients from the Alpha Omega Cohort

	DASH diet score*			**Mediterranean diet score†**		
	1st Tertile	2nd Tertile	3rd Tertile	1st Tertile	2nd Tertile	3rd Tertile
range	0–2.5	3.0-3.5	4.0–8.5	0-2	3	4-7
All-cause mortality						
Events/N	700/1,462	797/1,719	538/1,184	462/1,020	954/1,955	619/1,390
Follow-up time (py)	16,064	18,986	13,424	11,322	21,448	15,704
HR (95%CI), unadjusted	*Reference*	0.96 (0.87-1.06)	0.91 (0.81-1.02)	*Reference*	1.10 (0.99-1.23)	0.96 (0.85-1.09)
HR (95%CI), Model1	*Reference*	0.94 (0.85-1.04)	0.87 (0.77-0.97)	*Reference*	1.09 (0.97-1.22)	0.92 (0.82-1.04)
HR (95%CI), Model2	*Reference*	0.96 (0.87-1.07)	0.92 (0.82-1.03)	*Reference*	1.05 (0.93-1.17)	0.94 (0.83-1.06)
Cardiovascular mortality						
Events/N	307/1,462	340/1,719	256/1,184	211/1,020	429/1,955	263/1,390
Follow-up time (py)	16,064	18,986	13,424	11,322	21,448	15,704
HR (95%CI), unadjusted	Reference	0.93 (0.80-1.09)	0.99 (0.84-1.16)	*Reference*	1.08 (0.92-1.28)	0.90 (0.75-1.07)
HR (95%CI), Model 1	*Reference*	0.91 (0.78-1.06)	0.92 (0.78-1.09)	*Reference*	1.07 (0.91-1.26)	0.85 (0.71-1.02)
HR (95%CI), Model 2	*Reference*	0.94 (0.81-1.10)	1.00 (0.84-1.19)	*Reference*	1.06 (0.90-1.26)	0.88 (0.73-1.06)

In model 1 adjustments were made for age and sex. In Model 2, additional adjustments were made for education, smoking, alcohol consumption, physical activity, and total energy intake. DASH: Dietary Approaches to Stop Hypertension, py: person year, HR: hazard ratio, 95%CI: 95% confidence interval. * Nutrient-based DASH adherence score, based on Mellen et al[17]. † Food-group based Mediterranean diet adherence score, originally developed for the PREDIMED trial[18]

Mediation of the DASH and Mediterranean diet by cardiovascular risk factors

Table 3 presents the direct and indirect effects of compliance with DASH and Mediterranean diet, as well as the PME by the five included mediators. In the relationship between DASH diet score and all-cause mortality, 21.0% (95%CI -9.0; 52.1) of the total effect was mediated by the five mediators, with C reactive protein (PME 17.3%, 95%CI -2.0; 38.9) and systolic blood pressure (PME 5.1, 95%CI -5.1; 16.1) arising as the strongest mediators. In the relationship between DASH score and cardiovascular mortality, the total effect and direct effect had opposite signs (HR 1.03, 0.87-1.23 and HR 0.97, 95%CI 0.93, 1.01), meaning that changes in the included mediators attenuate the direct effect of compliance with DASH. Differences in C reactive protein and systolic blood pressure were the main mediators, accounting for a PME of -78.1% (95%CI -167.5; -2.0) and -23.5% (95%CI -58.0; 29.4), respectively.

In the relationship between Mediterranean diet score and all-cause mortality, 43% (95%CI -7.2; 95.0) was mediated by the five mediators (Table 3). Differences in C reactive protein levels stood out as the main mediator (PME 27.6%, 95%CI -8.1; 65.7), while differences in body mass index, LDL-cholesterol and triglycerides accounted for 3-5% of the total indirect effect. In the relationship between Mediterranean diet and cardiovascular mortality, 35% (95%CI 4.2; 70.3) was mediated by the five mediators, with C reactive protein again being the main mediator (PME 15.3%, 95%CI -3.4; 35.5). Baseline blood pressure levels were not a mediator for the relationship of Mediterranean diet with all-cause and cardiovascular mortality. In a sensitivity analysis assessing the five mediators separately, the PME by each of the mediators remained similar to the main analysis for both DASH and Mediterranean diet (Table S3).

TABLE 3 Mediation by cardiovascular risk factors of the relationship between DASH and Mediterranean diet scores and all-cause mortality and cardiovascular mortality in drug-treated CVD patients

	DASH diet*			Mediterranean diet*		
	1st Tertile	2nd Tertile	3rd Tertile	1stTertile	2nd Tertile	3rd Tertile
All-cause mortality						
Total effect, HR (95%CI)	*Reference*	0.97 (0.87; 1.07)	0.91 (0.81; 1.01)	*Reference*	1.07 (0.94; 1.19)	0.93 (0.82; 1.06)
Direct effect, HR (95%CI)	*Reference*	0.99 (0.89; 1.10)	0.93 (0.82; 1.03)	*Reference*	1.08 (0.96; 1.20)	0.96 (0.84; 1.10)
Indirect effect, HR (95%CI)	*Reference*	0.98 (0.96; 1.00)	0.98 (0.95; 1.01)	*Reference*	0.98 (0.96; 1.01)	0.97 (0.93; 1.01)
Total PME, %		62.6 (-13.2; 139.8)	21.0 (-9.0; 52.1)		-26.8 (-63.7; 10.9)	42.6 (-7.2; 95.0)
Proportion mediated by						
Body mass index, %		-8.6 (-37.8; 15.1)	-5.1 (-19.6; 7.6)		-4.0 (-21.0; 13.5)	6.6 (-15.1; 28.9)
Systolic blood pressure, %		3.4 (-23.8; 31.1)	5.1 (-5.1; 16.1)		-2.8 (-14.9; 8.6)	0.1 (-13.7; 15.0)
LDL-cholesterol, %		3.2 (-18.5; 28.1)	2.7 (-5.9; 12.9)		3.3 (-7.6; 15.9)	3.8 (-7.9; 16.5)
Triglycerides, %		-0.9 (-28.5; 26.6)	1.0 (-7.4; 10.7)		-1.1 (9.3; -11.7)	4.4 (-10.1; 19.6)
C-reactive protein, %		65.6 (16.2; 122.2)	17.3 (-2.0; 38.9)		-22.2 (-46.5; 1.9)	27.6 (-8.1; 65.7)
Cardiovascular mortality						
Total effect, HR (95%CI)	*Reference*	0.95 (0.80; 1.10)	1.03 (0.87; 1.23)	*Reference*	1.08 (0.91; 1.27)	0.87 (0.71; 1.04)
Direct effect, HR (95%CI)	*Reference*	0.98 (0.83; 1.13)	1.06 (0.89; 1.27)	*Reference*	1.12 (0.94; 1.32)	0.91 (0.75; 1.10)
Indirect effect, HR (95%CI)	*Reference*	0.97 (0.94; 1.00)	0.97 (0.93; 1.01)	*Reference*	0.97 (0.93; 1.00)	0.95 (0.90; 0.99)
Total PME, %		55.8 (0.8; 113.1)	-94.1 (-228.9; 36.7)		-43.3 (-2.6; -88.6)	35.3 (4.2; 70.3)

TABLE 3 (Continued)

	DASH diet*			Mediterranean diet†		
	1st Tertile	2nd Tertile	3rd Tertile	1stTertile	2nd Tertile	3rd Tertile
Proportion mediated by						
Body mass index, %		-3.9 (-28.8; 19.6)	18.3 (82.1; -35.2)		-11.6 (-35.2; 10.9)	10.4 (-5.7; 28.0)
Systolic blood pressure, %		3.0 (-18.5; 27.7)	-11.8 (-58.0; 29.4;)		-2.7 (-17.6; 11.1)	-0.1 (10.4; -10.6)
LDL-cholesterol, %		7.1 (-11.8; 28.4)	-23.5 (-84.2; 27.0)		2.5 (-12.2; 17.1)	4.9 (-4.6; 15.2)
Triglycerides, %		12.8 (-10.1; 41.0)	0.9 (-37.0; 40.0)		-6.7 (-22.0; 6.3)	4.8 (-7.9; 18.5)
C-reactive protein, %		36.8 (7.0; 73.1)	-78.1 (-167.5; -2.0;)		-24.8 (-52.8; -0.4)	15.3 (-3.4; 35.5)

Mediation analysis of the associations between tertiles of DASH and Mediterranean diet compliance scores and all-cause mortality and cardiovascular mortality. Total effect represents the full size of the association between the exposure and the health outcomes. The direct effect is the effect of the exposure that is effectuated through other paths than the included mediators. The indirect effect represents the effect size that is brought about through diet-related changes in the included mediators. The PME indicates the proportion of the overall effect that is mediated through the included mediators. A negative PME indicates that the sign of the total effect and the indirect effect are opposite. All models are adjusted for age, sex education, smoking, alcohol consumption, physical activity, and total energy intake. 95% CI, 95% confidence interval; HR, hazard ratio; LDL, low-density lipoprotein; PME, proportion mediated effect. * Nutrient-based DASH adherence score, based on Mellen et al[17]. † Food-group based Mediterranean diet adherence score, originally developed for the PREDIMED trial[18]

DISCUSSION

In this prospective cohort study of 4,365 patients with established CVD, no statistically significant relationship between DASH or Mediterranean diet scores and risk of all-cause mortality and cardiovascular mortality were found. Of these associations, approximately 30-50% of the total relationship appeared to be mediated by differences in baseline levels of five cardiovascular risk factors: body weight, systolic blood pressure, LDL-cholesterol, triglycerides, and systemic inflammation. Systemic inflammation, measured as hs-CRP, was a relatively strong mediator compared to other assessed risk factors, possibly because the other risk factors are influenced by drug treatment in clinical CVD management.

Previous observational studies on the association between compliance with the DASH diet and (cardiovascular) mortality has reported mixed results comprising neutral associations or 10-20% relative risk reductions. The findings of the current study are in line with this previous evidence.[25–27] However, the lack of a statistically significant association of Mediterranean diet with (cardiovascular) mortality is contradictory to previous observational and experimental evidence.[11,12,28] In the CORDIOPREV trial, an intervention targeted at the Mediterranean diet resulted in approximately 30% relative risk reductions of cardiovascular events compared to a low-fat diet, but in this trial patients received intensive counselling.[12] In meta-analyses of observational studies of both primary and secondary CVD prevention populations, a 10 to 30% relative risk reduction for cardiovascular events is reported for the highest vs lowest adherence groups.[7,29] Potential explanations for the weaker associations in the current study include the overall low compliance with the Mediterranean diet in the Alpha Omega cohort and high degree of concomitant medication use.

It is well-documented that adopting healthy dietary habits can effectively mitigate cardiovascular risk factors like blood pressure, LDL-cholesterol, and body weight.[8,30–32] However, the precise relationship between improved cardiovascular risk factors and prevention of actual cardiovascular events remains uncertain. For instance, the CORDIOPREV trial, which compared a Mediterranean diet to a low-fat diet in secondary CVD prevention, demonstrated minimal effects on intermediate risk factors. Strikingly, despite these modest effects, the Mediterranean diet intervention led to a substantial relative risk reduction in composite cardiovascular endpoints.[12,33] The

current study's results align with this pattern, underscoring that only part of the total effect can be attributed to traditional risk factors.

In the present study, there were no statistically significant associations between the DASH and Mediterranean diet score and mortality outcomes. In case of non-significant overall findings, performing a mediation analysis can be hypothesis-generating regarding explanations for the non-significant findings and can help gain new insight how a (dietary) exposure achieves its association with clinical outcomes.[34,35] For example, a mediation analysis can bring inconsistent mediation to light, which means that the direct effect (independent of the assessed mediators) has an opposite direction than the mediating effect.[35] In the current analyses inconsistent mediation was present in the association between the DASH diet and cardiovascular mortality.

Based on the findings of the current study, of the assessed traditional CVD risk factors, low-grade systemic inflammation appears to be an important mediator for both the DASH and Mediterranean diet. This finding aligns with prior research that has linked systemic inflammation to the positive effects of healthy diets on non-cardiovascular outcomes such as cognitive function and arthritis.[36,37] Additionally, CRP has previously been identified as a mediator of the benefits of other lifestyle behaviours, such as exercise.[24] Furthermore, dietary patterns with a high anti-inflammatory index have consistently demonstrated associations with decreased risks of cardiovascular events, cancer, and mortality in observational studies.[38,39] A previous analysis indicated that dietary patterns with a high anti-inflammatory potential reduce endothelial activation and vascular inflammation, which could possibly explain the central mediating role of systemic inflammation in lowering residual CVD risk in patients that receive optimal medical risk factor treatment.[40] Detailed future analyses could further illuminate if there truly is a beneficial inflammatory response to healthy dietary habits and to what extent such responses contribute to cardiovascular event risk.

Although the DASH diet has specifically been designed to '*stop hypertension*' and has previously been shown to lower systolic blood pressure levels by over 11 mmHg in hypertensive patients,[41] the current study indicated that blood pressure was not an important mediator in the relationship between DASH compliance and mortality outcomes. Furthermore, in patients in the highest DASH score tertile, systolic blood pressure was the highest. Potential explanations for this finding include that blood pressure-lowering effects of the DASH diet may be less pronounced in a CVD

population because of the high proportion of patients treated with blood pressure-lowering medication. Indication bias may be present, when hypertensive patients were more likely to be counselled on dietary habits that align with a DASH diet resulting in dilution of the observed effects. Finally, the DASH diet strongly relies on sodium restriction.[5,41] In this study, an FFQ was used to measure sodium intake, but this approach is not suitable to measure discretionary salt intake[42] and this may have led to misclassification of patients with a high discretionary salt use as being highly DASH compliant. As a result, a potential beneficial effect of the DASH diet might not have been detected in the current study.

It is important to acknowledge a substantial proportion of the observed associations between diet and mortality was not mediated by the included cardiovascular risk factors. Between 60 and 90% of the total effects in this study constituted a *direct effect*, meaning that these were effectuated independently of the included traditional CVD risk factors. Improved insulin sensitivity is a plausible alternative mediator as it is strongly related to cardiovascular outcomes [43] and can be beneficially affected by adopting a healthy diet.[44] It was not possible to explore the impact of insulin resistance as a mediator in the current analysis, as no fasting blood samples with glucose and/or insulin measures were available to calculate a measure of insulin sensitivity. Other alternative mediating pathways include effects on gut microbiota which influence cardiovascular outcomes or effects of micronutrients that were not assessed in the current analysis.

The current study yielded results that are hypothesis-generating for future research. The finding that systemic inflammation was a stronger mediator compared to the other four traditional risk factors, could provide an explanation for findings of recent RCTs, such as the CORDIOPREV trial, that demonstrated large protective effects on recurrent cardiovascular event rates, despite negligible effects on LDL-cholesterol and blood pressure levels.[12] Low-grade systemic inflammation remains a relatively underassessed outcome measure in dietary intervention trials but could potentially help identify the most heart-healthy diets, especially for drug-treated CVD patients. Future research could also help identify additional mediating factors, as the included mediators in the current analysis only accounted for a proportion of the overall effect. These insights hold value for clinical practice, because the majority of dietary intervention trials assess the effect of these interventions on intermediate endpoints, such as the cardiovascular risk factors that were assessed in this study. A better understanding of the mediating

role of such intermediate factors can be used to translate the findings of dietary intervention trials to cardiovascular event risk.

Strengths and limitations

Strengths of this study include the size of the study population, the rigorous collection of dietary intake data, and the long and detailed follow-up on vital status and cause of death. Study limitations include the need for categorization of continuous exposure and mediator variables. This approach was necessary for the counterfactual approach used in the mediation analysis, but categorization leads to a loss of contrast in the data and a loss of statistical power. Dietary habits were self-reported in an FFQ and are subject to social desirability bias. Residual sources of confounding should always be considered and, in the current analysis, residual confounding from difficult-to-measure variables such a social-economic position or frailty may affect the results. Finally, the exposure and mediator variables were measured at the same time and this cross-sectional assessment prevents drawing conclusions on the direction of a potential causal effect. However, based on the results of clinical trials on dietary interventions it is likely that dietary habits influenced mediator levels instead of the other way around.

CONCLUSION

In conclusion, small non-statistically significant associations between DASH and Mediterranean diet scores and all-cause and cardiovascular mortality were observed among drug-treated CVD patients. Systemic inflammation appeared to be an important mediator of these associations compared to other traditional cardiovascular risk factors. Improved insight in the mediating pathways of different dietary patterns may contribute to translating results of dietary trials reporting changes in cardiovascular risk factors to clinical outcomes or for developing personalized dietary counselling targeted at the individual risk profile of patients with established CVD.

REFERENCES

1. Virani SS, Newby LK, Arnold S V., Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation [Internet]. 2023 Jul 20; Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000001168
2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J [Internet]. 2021 Sep 7;42(34):3227–337. Available from: https://academic.oup.com/eurheartj/article/42/34/3227/6358713
3. Health Council of the Netherlands. Dutch dietary guidelines for people with atherosclerotic cardiovascular disease. The Hague; 2023.
4. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J. 2023 Aug 25;
5. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of Weight-Loss Diets with Different Compositions of Fat, Protein, and Carbohydrates. New England Journal of Medicine [Internet]. 2009 Feb 26;360(9):859–73. Available from: http://www.nejm.org/doi/10.1056/NEJMoa0804748
6. Appel LJ, Miller ER 3rd, Jee SH, Stolzenberg-Solomon R, Lin PH, Erlinger T, et al. Effect of dietary patterns on serum homocysteine: results of a randomized, controlled feeding study. Circulation. 2000 Aug;102(8):852–7.
7. Rees K, Takeda A, Martin N, Ellis L, Wijesekara D, Vepa A, et al. Mediterranean-style diet for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2019 Mar 13;2019(3).
8. Ge L, Sadeghirad B, Ball GDC, Da Costa BR, Hitchcock CL, Svendrovski A, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: Systematic review and network meta-analysis of randomised trials. The BMJ. 2020;369.
9. Karam G, Agarwal A, Sadeghirad B, Jalink M, Hitchcock CL, Ge L, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. BMJ. 2023;
10. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. New England Journal of Medicine [Internet]. 2018 Jun 21;378(25):e34. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1800389
11. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779–85.

12. Delgado-lista J, Alcala-diaz JF, Torres-peña JD, Quintana-navarro GM, Fuentes F, Garcia-rios A, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet. 2022;399:1876–85.

13. Kromhout D, Giltay EJ, Geleijnse JM. n–3 Fatty Acids and Cardiovascular Events after Myocardial Infarction. New England Journal of Medicine [Internet]. 2010 Nov 18;363(21):2015–26. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1003603

14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem [Internet]. 1972 Jun;18(6):499–502. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4337382

15. Feunekes GI, Van Staveren WA, De Vries JH, Burema J, Hautvast JG. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. Am J Clin Nutr [Internet]. 1993 Oct 1;58(4):489–96. Available from: https://academic.oup.com/ajcn/article/58/4/489/4716022

16. Dutch Nutrition Center. Dutch Food Composition Table 2006 NEVO-table. The Hague, The Netherlands; 2006.

17. Mellen PB, Gao SK, Vitolins MZ, Goff DC. Deteriorating Dietary Habits Among Adults With Hypertension. Arch Intern Med. 2008;168(3):308.

18. García-Conesa MT, Philippou E, Pafilas C, Massaro M, Quarta S, Andrade V, et al. Exploring the Validity of the 14-Item Mediterranean Diet Adherence Screener (MEDAS): A Cross-National Study in Seven European Countries around the Mediterranean Region. Nutrients [Internet]. 2020 Sep 27;12(10):2960. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32992649

19. Geleijnse JM, Giltay EJ, Schouten EG, de Goede J, Griep LMO, Teitsma-Jansen AM, et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: Design and baseline characteristics of the Alpha Omega Trial. Am Heart J [Internet]. 2010 Apr;159(4):539-546.e2. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002870310000748

20. VanderWeele TJ. Marginal Structural Models for the Estimation of Direct and Indirect Effects. Epidemiology [Internet]. 2009 Jan;20(1):18–26. Available from: https://journals.lww.com/00001648-200901000-00006

21. VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. Annu Rev Public Health. 2016 Mar 18;37(1):17–32.

22. Hong G. Ratio of Mediator Probability Weighting for Estimating Natural Direct and Indirect Effects. Proceedings of the American Statistical Association, Biometrics Section. 2010;2401–15.

23. Lange T, Vansteelandt S, Bekaert M. A Simple Unified Approach for Estimating Natural Direct and Indirect Effects. Am J Epidemiol. 2012;176(3):190–5.

24. Bonekamp NE, May AM, Halle M, Dorresteijn JAN, van der Meer MG, Ruigrok YM, et al. Physical exercise volume, type and intensity and risk of all-cause mortality and cardiovascular events in patients with cardiovascular disease: A mediation analysis. European Heart Journal Open. 2023 Jun 13;

25. Bonekamp NE, Cruijsen E, Visseren FLJ, van der Schouw YT, Geleijnse JM, Koopal C. Compliance with the DASH diet and risk of all-cause and cardiovascular mortality in patients with myocardial infarction. Clinical Nutrition. 2023 Aug;42(8):1418–26.

26. Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L. Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases-Incidence: A systematic review and meta-analysis on observational prospective studies. Nutrition [Internet]. 2013;29(4):611–8. Available from: http://dx.doi.org/10.1016/j.nut.2012.12.018

27. Bertoia ML, Triche EW, Michaud DS, Baylin A, Hogan JW, Neuhouser ML, et al. Mediterranean and Dietary Approaches to Stop Hypertension dietary patterns and risk of sudden cardiac death in postmenopausal women. Am J Clin Nutr [Internet]. 2014 Feb 1;99(2):344–51. Available from: https://academic.oup.com/ajcn/article/99/2/344/4571484

28. Rees K, Takeda A, Martin N, Ellis L, Wijesekara D, Vepa A, et al. Mediterranean-Style Diet for the Primary and Secondary Prevention of Cardiovascular Disease: A Cochrane Review. Glob Heart. 2020;15(1):56.

29. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur J Clin Nutr. 2018 Jan 10;72(1):30–43.

30. Schwingshackl L, Hoffmann G. Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis. Nutr J. 2013 Dec 15;12(1):48.

31. Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on Health Outcomes of a Mediterranean Diet With No Restriction on Fat Intake. Ann Intern Med. 2016 Oct 4;165(7):491.

32. Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. British Journal of Nutrition. 2015 Jan 14;113(1):1–15.

33. Yubero-Serrano EM, Fernandez-Gandara C, Garcia-Rios A, Rangel-Zuñiga OA, Gutierrez-Mariscal FM, Torres-Peña JD, et al. Mediterranean diet and endothelial function in patients with coronary heart disease: An analysis of the CORDIOPREV randomized controlled trial. Rahimi K, editor. PLoS Med [Internet]. 2020 Sep 9;17(9):e1003282. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2008016195&from=export

34. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation Analysis. Annu Rev Psychol. 2007 Jan 1;58(1):593–614.

35. O'Rourke HP, MacKinnon DP. Reasons for Testing Mediation in the Absence of an Intervention Effect: A Research Imperative in Prevention and Intervention Research. J Stud Alcohol Drugs. 2018 Mar;79(2):171–81.

36. Shi H, Schweren LJS, ter Horst R, Bloemendaal M, van Rooij D, Vasquez AA, et al. Low-grade inflammation as mediator between diet and behavioral disinhibition: A UK Biobank study. Brain Behav Immun. 2022 Nov;106:100–10.

37. Runhaar J, Beavers D, Miller G, Nicklas B, Loeser R, Bierma-Zeinstra S, et al. Inflammatory cytokines mediate the effects of diet and exercise on pain and function in knee osteoarthritis, independent of BMI. Osteoarthritis Cartilage. 2019 Apr;27:S453.

38. Shivappa N, Godos J, Hébert J, Wirth M, Piuri G, Speciani A, et al. Dietary Inflammatory Index and Cardiovascular Risk and Mortality—A Meta-Analysis. Nutrients. 2018 Feb 12;10(2):200.

39. Liu FH, Liu C, Gong TT, Gao S, Sun H, Jiang YT, et al. Dietary Inflammatory Index and Health Outcomes: An Umbrella Review of Systematic Review and Meta-Analyses of Observational Studies. Front Nutr. 2021 May 19;8.

40. Li J, Lee DH, Hu J, Tabung FK, Li Y, Bhupathiraju SN, et al. Dietary Inflammatory Potential and Risk of Cardiovascular Disease Among Men and Women in the U.S. J Am Coll Cardiol. 2020 Nov;76(19):2181–93.

41. Leblanc V, Hudon AM, Royer MM, Corneau L, Dodin S, Bégin C, et al. Differences between men and women in dietary intakes and metabolic profile in response to a 12-week nutritional intervention promoting the Mediterranean diet. J Nutr Sci. 2015 Apr 13;4:e13.

42. Santos-Marcos JA, Haro C, Vega-Rojas A, Alcala-Diaz JF, Molina-Abril H, Leon-Acuña A, et al. Sex Differences in the Gut Microbiota as Potential Determinants of Gender Predisposition to Disease. Mol Nutr Food Res. 2019 Apr 13;63(7):1800870.

43. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. New England Journal of Medicine [Internet]. 2001 Jan 4;344(1):3–10. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM200101043440101

44. McLean RM, Farmer VL, Nettleton A, Cameron CM, Cook NR, Campbell NRC. Assessment of dietary sodium intake using a food frequency questionnaire and 24-hour urinary sodium excretion: a systematic literature review. The Journal of Clinical Hypertension. 2017 Dec;19(12):1214–30.

45. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol. 2018 Dec 31;17(1):122.

46. Adeva-Andany MM, González-Lucán M, Fernández-Fernández C, Carneiro-Freire N, Seco-Filgueira M, Pedre-Piñeiro AM. Effect of diet composition on insulin sensitivity in humans. Clin Nutr ESPEN. 2019 Oct;33:29–38.

SUPPLEMENTAL MATERIAL

Supplemental appendix 1 Supplemental methods

Statistical analyses

The mediation analysis in this study was based on an approach described by VanderWeele *et al* (2009), Hong *et al* (2010) and Lange *et al* (2012) and used marginal structural models within a counterfactual frame work.[1-4] This model allows for estimating a direct, indirect and total effects within a survival context and for taking confounding in the exposure-mediator, mediator-outcome and exposure-outcome relationship into account.

The mediation was first applied to each potential mediator separately to assess if the causal paths were independent of other mediators. For the main analyses, the five mediators were combined into a single model to estimate the overall indirect and direct effects. The mediation analysis was executed by following the steps below:

1. Fit multinomial logistic regression models to condition the mediator on the exposure and to adjust for confounding in the exposure-mediator relationship.
2. Create new dataset by replicating the original data with addition of a new variable: *exposure1**. In the first replication, *exposure1** takes the value for the exposure that was observed. In the second replication, *exposure1** takes the counterfactual value (*i.e.* if the patient was adherent, the new value will be non-adherent).
3. This procedure is repeated five times (because there are five potential mediators) and yields pseudo-population that will be used for the subsequent analyses.
4. The multinomial logistic regression models from the first step are used to predict the probability the value that was observed for a mediator given *exposure**. This procedure was repeated to obtain a probability for each mediator included in the analysis. Weights for each participant in the pseudo-population are calculated by multiplying the five probabilities.
5. Ratio of mediator probability weighting on the combined probability is applied to ensure balance of the covariates in the pseudo-population. Through this weighting procedure adjustment for confounding in the exposure-mediator and the mediator-outcome relation can be achieved.
6. Weighted Cox proportional hazard models including only the direct and indirect effects and confounders in the exposure-outcome relation are used to estimate each effect. This step yields the estimate for the direct and indirect effect.

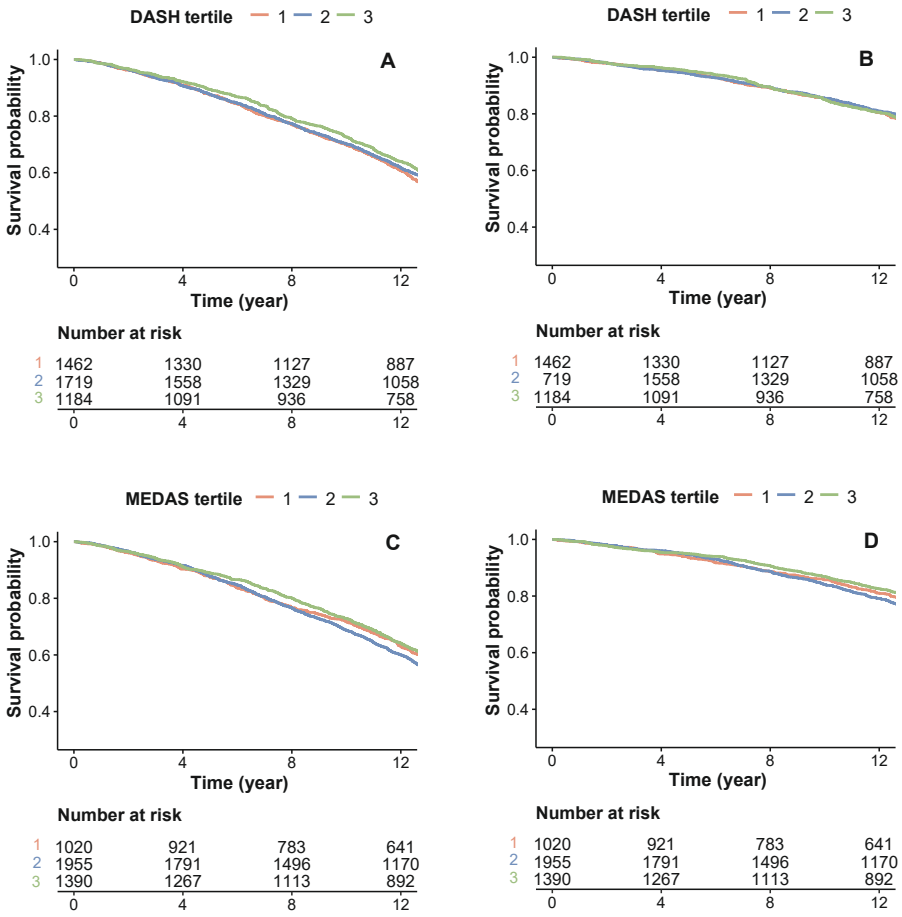
7. Direct and indirect effects are additive on the log(hazard) scale. To calculate the proportion mediated effect (PME), the indirect effect of each mediator is divided by the total effect on the log(hazard) scale.

Bootstrapping was used to obtain 95% confidence intervals for the direct effects, indirect effects and PMEs. The entire procedure was repeated in 1,000 bootstrap samples and the 2.5th and 97.5th percentiles of the distributions for each estimand were set as the lower and upper bounds of the confidence intervals.

Operationalization of potential mediating factors

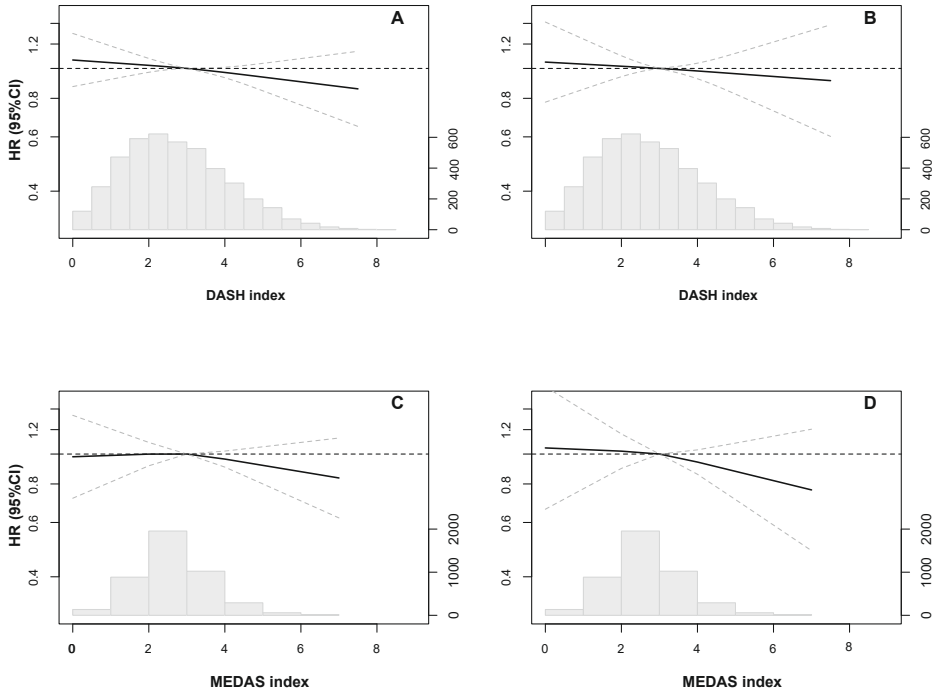
Mediator	Operationalization in the Alpha Omega cohort
Body mass index	Body mass index was calculated by dividing body weight in kg by height squared. Quintile cut-offs (kg/m^2): 24.8, 26.5, 28.2, 30.5
Systolic blood pressure	Blood pressure was measured twice with the patient in sitting position and after a 10-minute rest using an automatic device (HEM-711, Omron) and then averaged. Quintile cut-offs (mmHg): 124, 136, 146, 160
LDL-cholesterol	LDL-cholesterol levels estimated using the Friedewald formula. Quintile cut-offs (mmol/l): 1.9, 2.3, 2.7, 3.2
Triglycerides	Non-fasting triglyceride levels Quintile cut-offs (mmol/l): 1.1, 1.5, 1.9, 2.5
C-reactive protein	C-reactive protein (CRP) was selected as a measure for systemic inflammation. A CRP value > 20 mg/L was considered to be indicative of an ongoing inflammatory process and therefore not to be representative of low-grade inflammation. To handle these values, CRP values > 20 mg/L were set as missing and included in the imputation. Quintile cut-offs (mg/L): 0.7, 1.2, 2.3, 4.3

FIGURE S1 Kaplan Meier curves stratified for DASH and Mediterranean diet compliance tertile.



Survival curves for all-cause mortality and cardiovascular mortality stratified for DASH compliance tertiles (panels **A** and **B**) and survival curves for all-cause mortality and cardiovascular mortality stratified for Mediterranean diet compliance tertiles (panels **C** and **D**). MEDAS: Mediterranean diet Adherence Screener, DASH: Dietary Approaches to Stop Hypertension

FIGURE S2 Restricted cubic splines depicting the relation between compliance with the DASH and Mediterranean diet and risk of all-cause and cardiovascular mortality.



Panels A and **B** show the relationship between compliance with the DASH diet and all-cause mortality (A) and cardiovascular mortality (B). **Panels C** and **D** show the relationship between compliance with the Mediterranean diet and all-cause mortality (C) and cardiovascular mortality (D). The solid black line indicates the estimated hazard ratio and the dotted grey lines indicate the limits of the 95% confidence interval Models were adjusted for age, sex, education, smoking status, physical activity level, alcohol consumption and total daily energy intake (model 2). . The histogram included in the panels describes the distribution of the DASH and Mediterranean diet adherences scores in the Alpha Omega cohort.

TABLE S1 Mediterranean diet and DASH diet compliance scores

Food group	Mediterranean diet MEDAS score[20]	DASH diet Mellen's DASH index[19]
Fruits	• ≥ 3 pieces of fruit per day	
Vegetables	• ≥ 2 servings (200g) of vegetables per day' • ≥ 2 dishes with a sauce of tomato, garlic, onion or leek sautéed in olive oil per week	
Legumes	• ≥ 3 servings (150g) of pulses per week	
Nuts	• ≥ 3 servings (30g) of nuts per week	
Meat	• < 1 serving (100-150g) red meat, hamburger, or sausage per day • Prefers chicken, turkey or rabbit over red meat	
Fish	• ≥ 3 servings (100-150g fish, 200g seafood) fish or seafood per week	
Sweets	• < 2 times commercial pastry per week	
Non-alcoholic drinks	• < 1 carbonated and/or sugar-sweetened beverages per day	
Alcoholic drinks	• ≥ 7 cups wine per week	
Fatty acids	• Olive oil as the principal source of fat for cooking • ≥ 4 tbsp olive oil per day • < 1 serving (12g) butter, margarine, or cream per day	• Saturated fat: • Target: < 6 E%, • Intermediate target: < 11 E% • Total fat: • Target: <27 E%, • Intermediate target: < 32 E% • Cholesterol: • Target < 150 mg/day, Intermediate target: < 225 mg/day
Protein		• Target: >18 E%, Intermediate target: > 16.5 E%
Fiber		• Target < 150 mg/day, Intermediate target: < 225 mg/day
Magnesium		• Target: > 500 mg/day • Intermediate target: > 332 mg/day
Calcium		• Target > 1,240 mg/day, Intermediate target: > 844 mg/day
Potassium		• Target: > 4,700 mg/day, Intermediate target: >3,221 mg/day
Sodium		• Target < 2400 mg/day, • Intermediate target: <2,700 mg/day

In the MEDAS score, 1 point is awarded if participants reach the target intake. If not, no points are awarded. For the DASH diet index, 1 point is awarded if patients reach the target intake, 0.5 point is awarded if the intermediate intake level is reached. No points are awarded when participants do not at least comply with the intermediate intake level. MEDAS: Mediterranean diet Adherence Screener, DASH: Dietary Approaches to Stop Hypertension

TABLE S2 Sensitivity analysis – Reverse causation

	DASH diet			Mediterranean diet		
	1st Tertile	2nd Tertile	3rd Tertile	1st Tertile	2nd Tertile	3rd Tertile
range	0–2.5	3.0-3.5	4.0–8.5	0-2	3	4-7
All-cause mortality						
Main analysis	*Reference*	0.96 (0.87-1.07)	0.92 (0.82-1.03)	*Reference*	1.10 (0.99-1.23)	0.96 (0.85-1.09)
1 year	*Reference*	0.96 (0.86-1.07)	0.91 (0.81-1.03)	*Reference*	1.05 (0.94-1.18)	0.93 (0.83-1.06)
3 years	*Reference*	0.94 (0.85-1.06)	0.92 (0.81-1.04)	*Reference*	1.07 (0.95-1.21)	0.94 (0.83-1.08)
5 years	*Reference*	0.93 (0.83-1.05)	0.92 (0.80-1.05)	*Reference*	1.09 (0.96-1.25)	0.95 (0.82-1.09)
Cardiovascular mortality						
Main analysis	*Reference*	0.94 (0.81-1.10)	1.00 (0.84-1.19)	*Reference*	1.08 (0.92-1.28)	0.90 (0.75-1.07)
1 year	*Reference*	0.96 (0.82-1.12)	1.01 (0.85-1.21)	*Reference*	1.08 (0.90-1.28)	0.89 (0.74-1.08)
3 years	*Reference*	0.91 (0.76-1.08)	1.00 (0.83-1.20)	*Reference*	1.07 (0.89-1.28)	0.83 (0.68-1.01)
5 years	*Reference*	0.89 (0.74-1.07)	1.00 (0.81-1.21)	*Reference*	1.16 (0.95-1.41)	0.90 (0.72-1.13)

Assessment of reverse causation by removing the first 1, 3, and 5 years of follow-up after inclusion in the AOC. All presented hazard ratios are adjusted for age, sex, education, smoking status, physical activity level, alcohol consumption and total daily energy intake (model 2). DHD-15: Dutch Healthy Diet 2015, DASH: Dietary Approaches to Stop Hypertension, py: person year HR: hazard ratio, 95%CI: 95% confidence interval

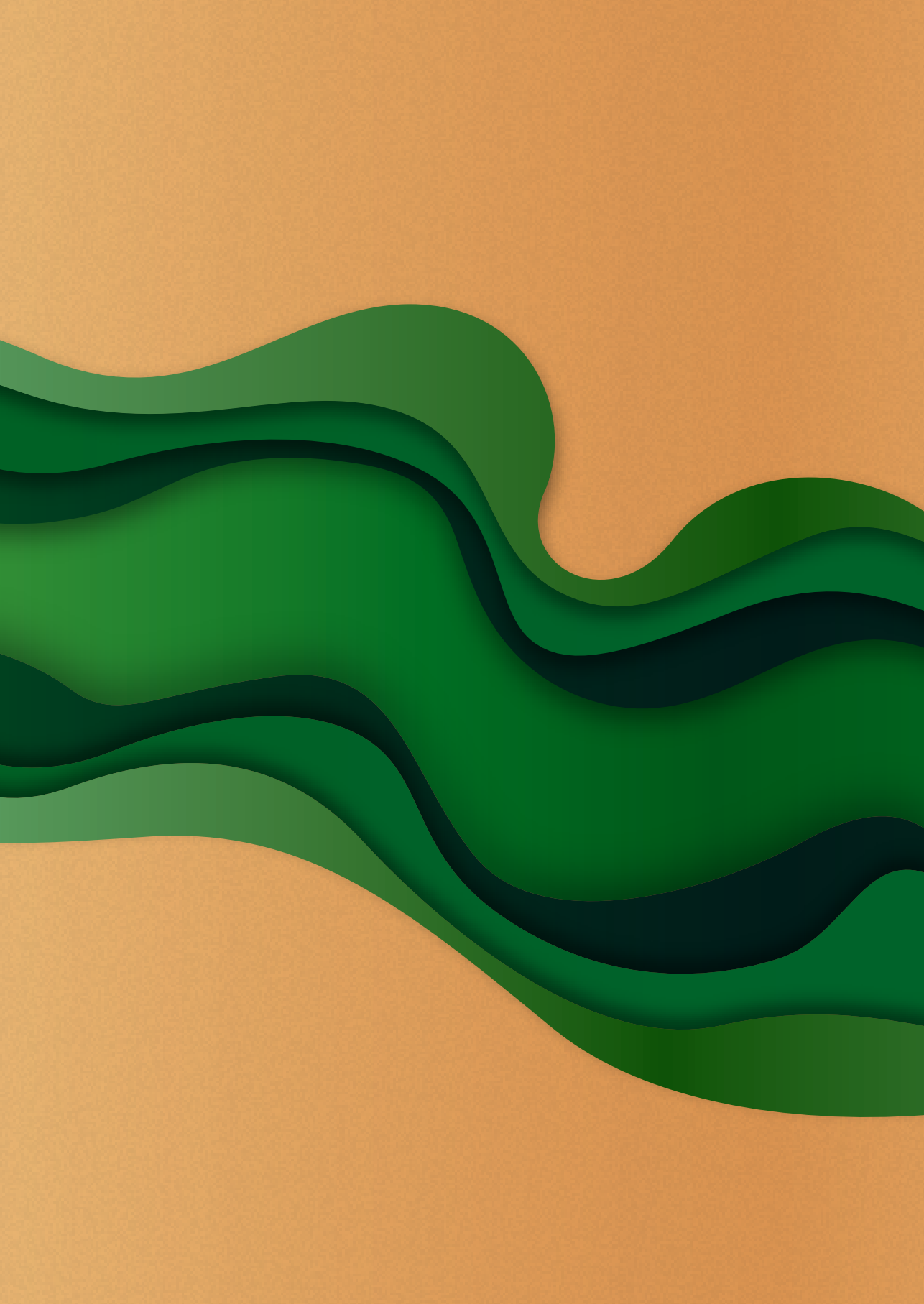
TABLE S3 Sensitivity analysis – Proportion of effect mediated by a single mediator

	DASH diet		Mediterranean diet	
	2nd tertile	3rd tertile	2nd tertile	3rd tertile
All-cause mortality				
Body mass index, %	-7.4 (-103.2; 136.1)	-4.7 (-59.1; 36.7)	-5.3 (-116.8; 87.6)	8 (-48.9; 80.5)
Systolic blood pressure, %	2.4 (-81.4; 92.9)	4.0 (-34.4; 49.3)	-3.4 (-61.8; 61.8)	-0.5 (-43.1; 46.1)
LDL-cholesterol, %	2.5 (-100.7; 75.8)	2.3 (-20.9; 59.1)	3.6 (-39.5; 94.8)	3.5 (-37.5; 34.4)
Triglycerides, %	-0.8 (-75; 96.1)	0.8 (-35.4; 25.5)	-1 (-47.3; 52.1)	5 (-58.5; 38.8)
C-reactive protein, %	58.5 (-485.5; 551.4)	16.9 (-72.5; 167.6)	-24.8 (-318.6; 527)	28.5 (-173.9; 242)
Cardiovascular mortality				
Body mass index, %	-3.2 (-87.6; 57.8)	18.2 (-143.2; 137.5)	-13.9 (-260.9; 233)	11.4 (-49.6; 113.3)
Systolic blood pressure, %	2.2 (-45; 75.2)	-6.9 (-70; 67.7)	-3.1 (-137.9; 67.3)	-0.4 (-33.7; 20.2)
LDL-cholesterol, %	7.3 (-97.4; 69.5)	-20.7 (-142.3; 137.3)	3.5 (-84.7; 91.2)	4.5 (-25.7; 40.5)
Triglycerides, %	12.3 (-172.2; 140.9)	1.7 (-106.8; 81.2)	-7.5 (-102; 131.5)	5.2 (-20.3; 50.1)
C-reactive protein, %	34 (-283; 269.9)	-84.7 (-345.3; 458.4)	-27.9 (-499.5; 347.6)	15.6 (-66.5; 138.1)

Proportions mediated effect in mediation analyses assessing one mediator at a time. All models were adjusted for age, sex, education, smoking, physical activity level, alcohol consumption and total energy intake. Negative proportion mediated effect indicates that the sign of the total effect and the indirect effect mediated by a mediator are opposite, e.g. the total relations between the 2nd Mediterranean diet tertile and all-cause mortality is harmful (HR > 1.00) but the indirect effect mediated by BMI is protective (indirect HR <1.00). DASH: Dietary Approaches to Stop Hypertension, LDL: Low-density lipoprotein

SUPPLEMENTAL REFERENCES

1. VanderWeele TJ. Marginal Structural Models for the Estimation of Direct and Indirect Effects. Epidemiology [Internet]. 2009 Jan;20(1):18–26.
2. VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. Annu Rev Public Health. 2016 Mar 18;37(1):17–32.
3. Hong G. Ratio of Mediator Probability Weighting for Estimating Natural Direct and Indirect Effects. Proceedings of the American Statistical Association, Biometrics Section. 2010;2401–15.
4. Lange T, Vansteelandt S, Bekaert M. A Simple Unified Approach for Estimating Natural Direct and Indirect Effects. Am J Epidemiol. 2012;176(3):190–5.



CHAPTER 6

COMPLIANCE WITH THE DASH DIET AND RISK OF ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN PATIENTS WITH MYOCARDIAL INFARCTION

A TARGET TRIAL EMULATION IN OBSERVATIONAL DATA

Nadia E. Bonekamp
Esther Cruijsen
Frank L.J. Visseren
Yvonne T. van der Schouw
Johanna M. Geleijnse
Charlotte Koopal

Clinical Nutrition, 2023 Aug;42(8):1418-1426

ABSTRACT

Aims

The Dietary Approaches to Stop Hypertension (DASH) diet has been shown to effectively reduce blood pressure and body weight, but its effectiveness for reducing (cardiovascular) mortality rates has never been assessed in a clinical trial. Causal effects of dietary interventions are difficult to measure, due to practical limitations of randomized controlled diet trials. Target trial emulation can be used to improve causal inference in observational data. The aim of this study was to emulate a target trial assessing the relationship between compliance with the DASH diet and cardiovascular and all-cause mortality risk in patients with established CVD.

Methods

Using data from the Alpha Omega Cohort, we emulated a DASH diet trial in patients with a history of myocardial infarction (MI). Inverse probability of treatment weighting (IPTW) was used to balance confounders over DASH-compliant and non-DASH-compliant participants. Hazard ratios (HRs) were estimated with IPT-weighted Cox models.

Results

Of 4,365 patients (79% male, median age 69 years, >80% treated with lipid- and blood pressure-lowering medication), 598 were classified as DASH-compliant (compliance score ≥5 out of 9). During a median follow-up of 12.4 years, 2,035 deaths occurred of which 903 (44%) were of cardiovascular origin. DASH compliance was not associated with all-cause mortality (HR 0.92, 95%CI 0.0.80-1.06) and cardiovascular mortality (HR 0.90, 95%CI 0.72-1.11).

Conclusions

In an emulated target trial on the DASH diet in the Alpha Omega cohort no relation was found between DASH compliance and risk of all-cause and cardiovascular mortality in patients with a history of MI. The DASH diet's effects may have been modified in this population by concomitant use of blood pressure-lowering medications.

INTRODUCTION

Cardiovascular disease (CVD) is the worldwide leading cause of mortality and inflicts a large morbidity burden.[1] Unhealthy dietary habits are a major modifiable risk factor for developing CVD, both independently as well as through a harmful effects on cardiovascular risk factors like blood pressure and low-density lipoprotein cholesterol (LDL-C) levels.[2,3]

The Dietary Approaches to Stop Hypertension (DASH) diet is a dietary pattern rich in fruits, vegetables, whole grains, low-fat dairy products and with a focus on plant-based rather than animal protein.[4,5] DASH was originally developed for blood pressure management in people with hypertension, but is nowadays more widely recommended for populations with (high risk of) CVD.[6-8] Although the benefits of the DASH diet with regards to blood pressure and body weight reduction are well established,[9-11] there have been no long-term clinical trials that assessed the effects of the DASH diet on risk of (recurrent) cardiovascular events or mortality. In general, randomized controlled trials investigating the long-term effects of dietary interventions on hard clinical endpoints are lacking.

Observational studies on the long-term effects of adhering to the DASH diet have reported mixed results, with some studies showing neutral associations with risk of cardiovascular events and mortality,[12-15] while others found protective associations with CVD, cancer and all-cause mortality.[16-21] These studies were performed in the general population or populations at high cardiovascular risk, but not in patients with established CVD. The health consequences of adhering to a DASH diet may be different in a CVD population due to a higher absolute risk of cardiovascular events, a different distribution of cardiovascular risk factors and more prevalent use of lipid-lowering and blood pressure-lowering medications.

Current knowledge about the long-term effects of dietary patterns, such as the DASH diet, on health outcomes is largely based on observational studies, because randomized trials are often considered unpractical, unethical and too costly.[22] Using observational data to estimate causal effects of dietary interventions is subject to bias from selection, information, reverse causation, confounding and confounding by indication.[23,24] Target trial emulation is an increasingly popular methodology that can be used to approximate causal effects in observational data.[25-28] By first designing a

target trial that would answer the clinical question and then emulating that trial in observational data, potential sources of bias come to light and can be addressed in the design of the observational study. As a result, the results are more directly applicable in clinical practice.[25-28]

The aim of this study was to emulate a clinical trial that assesses the long-term relation compliance with the DASH dietary pattern and risk of cardiovascular and all-cause mortality in patients with a history of myocardial infarction (MI).

MATERIAL AND METHODS

Target trial

In brief, the target trial would be a single-blind, randomized controlled trial that would include adults with stable coronary artery disease after having experienced an acute MI. To qualify for participation, the qualifying MI needed to be ascertained by the treating physician based on anginal chest pain, typical changes on the electrocardiogram and/or myocardial enzymes and to have occurred between 6 months and 2 years before inclusion in the trial. All participants need to be 18 years or older and able to give written informed consent.

Eligible participants would be randomized in a 1:1 ratio to the intervention or the control diet. The dietary intervention would be known to participants and their dietary counsellors, but not to investigators assessing or analysing outcome data (investigator-blinded study). The primary outcome of the target trial would be time to cardiovascular death and all-cause death. Table 1 summarizes the design of the target trial and its emulation in the observational data set.

Trial interventions

Participants of the target trial would be randomly assigned to one of two dietary strategies, which they would be expected to maintain for the duration of the study.

1. No intervention. Participants are expected to have received counselling on healthy dietary habits as part of routine clinical care for MI patients. Participants in this control group receive no additional counselling or support on their dietary habits.[7,8]

2. The DASH dietary intervention. A dietary intervention based the DASH intervention arm of previous trials.[4,5,29] This intervention comprises nutritional counselling sessions on a dietary pattern emphasizing fruits, vegetables, whole-grains and low-fat dairy products in lieu of red meats and refined carbohydrates. Participants will be provided with recipes, week menus and shopping lists that are in line with the DASH diet. Food items will not be provided.

Causal contrast and statistical analysis

The primary outcome, difference in risk of cardiovascular mortality and all-cause mortality, would be assessed using the log-rank test in Kaplan Meier survival analyses. The primary causal contrast of interest would be the intention-to-treat effect, comparing the (cardiovascular) mortality risks of the DASH intervention group to care-as-usual. A per-protocol analysis would be performed as a secondary outcome. Per-protocol analyses may be a useful addition in this setting, especially because of the high attrition rates in dietary intervention trials.[30]

TABLE 1 Target trial protocol and emulation in the Alpha Omega Cohort.

	Target trial	**Emulated trial in observational data**
Aim	To estimate the effect of an intervention to improve compliance with the DASH diet on risk of cardiovascular and all-cause mortality in patients with a history of myocardial infarction.	To estimate the effect of compliance with the DASH diet on risk of cardiovascular and all-cause mortality in patients with a history of myocardial infarction.
Eligibility criteria	Male or female (aged 18 years or older). Stable coronary artery disease after having experienced myocardial infarction, defined based on anginal chest pain, typical changes on the electrocardiogram and/or myocardial enzymes. Myocardial infarction should have occurred within 6 months and 2 years before inclusion in the trial. Able to provide written informed consent	Patients, aged 60-80, with a history of myocardial infarction within 10 years of inclusion. Additionally, patients that reported implausible energy intake on a food frequency questionnaire at baseline were excluded.

TABLE 1 (Continued)

	Target trial	Emulated trial in observational data
Sample size	A total of 497 deaths would be needed to detect a hazard ratio of 0.80, with two-sided α of 0.05 and 80% power. This requires a total sample size of 1,212 patients, equally distributed over the intervention and control group. The sample size calculation was based on the following assumptions: – 1:1 randomization ratio – Expected effect: HR 0.80 – Two-sided α 0.05, power 80%[21]) – Accrual period: 2 years – Trial duration: 10 years – Incidence rate control group: 0.069 deaths/person year (median survival 10 years). – Loss to follow-up during the study period: 20% Sample size calculation was based on estimation on the log-rank test.[55]	The same number of events would be required in the observational data if the exposure and control groups were of equal size. After IPTW, intervention and control groups had a size of 596.65 and 3767.17 (1:6.3). For this ratio, a total of 1052 deaths would need to be observed; or a total sample size of 2,279. Due to the observational design of the study and the determination of endpoints through linking of the data with municipal registries, the loss to follow-up and censoring rates are lower in the observational study. In the emulated trial this was assumed to be 0%. Note: For the observed effect size of HR 0.90, a sample size of 9,768 would be required for an α of 0.05 and power 80%.
Dietary strategies	DASH, as described and trialled previously by Appel *et al*[4]) and Sacks *et al*[5]).	We assumed that dietary intake reported in baseline food frequency questionnaires adequately represented the dietary intake during the study period. We assessed compliance with the DASH diet using a score developed by Mellen *et al*[37] based on the intake target from the original DASH trials[4,5]). We defined a score of ≥5 out of 9 as compliant to DASH. In the target trial the DASH diet would be adopted at the start of the trial. In the emulated trial, the moment of DASH initiation is unknown, but likely to be (long) before inclusion in the observational cohort.

TABLE 1 (Continued)

	Target trial	**Emulated trial in observational data**
Assignment	Patients are randomly assigned 1:1 to either the intervention or comparator diet.	Randomization not possible, instead was emulated with inverse probability of treatment weighting (IPTW). A propensity score for complying with the DASH diet was constructed using logistic regression models with adjustment for age, sex, education level, smoking status, alcohol consumption, physical activity and creatinine. After IPTW the DASH-compliant and non-compliant groups were balanced in a 1:6.3 ratio.
Outcome	Follow-up starts at inclusion in the trial and ends at death or loss to follow-up, whichever comes first. Intended trial duration would be 10 years.	Follow-up starts at inclusion in the study and ends at death, loss to follow-up, or December 31st, 2018 (the end of follow-up for the Alpha Omega Cohort), whichever comes first A sensitivity analysis with follow-up cut off after 10 years was run to mimic the 10 years follow-up of the target trial.
Follow-up	(Cardiovascular) death after inclusion in the trial	Same
Causal contrast	Intention-to-treat effect	Observational analogue of a per-protocol effect. Intervention strategies cannot be assigned in observational data. It is only possible to present the causal contrast between people that comply with the intervention and those who do not, balanced for observed confounders.
Statistical analysis	Intention-to-treat analysis: unadjusted Cox proportional hazard models to estimate relative risk reductions with the DASH diet.	Unadjusted Cox proportional hazard models in the IPTW pseudo-population to estimate relative risk reductions with compliance with the DASH diet.

DASH: Dietary approaches to stop hypertension, IPTW: inverse probability of treatment weighting

Target trial emulation in observational data

Study population

For the target trial emulation, data from the Alpha Omega Cohort was used. This is a prospective cohort study, comprising adults aged 60-80 years who experienced a MI within ten years before inclusion (2002-2006). During early follow-up, patients were randomized to low-dose supplementation of omega-3 fatty acids or placebo for approximately 40 months, which resulted in no effect on cardiovascular events and all-cause mortality.[31] Therefore randomization was ignored, and the Alpha Omega Cohort was treated like an observational cohort study. Follow-up for cause-specific mortality continued and is still ongoing. The study was approved by the research ethics committee and all participants gave written informed consent. Details on study design and eligibility criteria have been published previously.[31,32]

For the present study, patients with missing FFQ data or implausible energy intake (total energy intake <800 kcal/day or >8,000 kcal/day for men and <600 kcal/day or >6,000 kcal/day for women) were excluded (n = 19, 0.4%), leaving a total of 4,365 patients with a history of MI.

At baseline, all participants completed a health questionnaire, physical examination and laboratory measurements. Physical activity was assessed using the validated Physical Activity Scale for the Elderly.[33] Blood pressure was measured two times using an automated device (HEM-711; Omron); the average of the two measurements was used in the analyses. Serum lipids were determined from non-fasting blood and analysed by an automated analyser (Hitachi 912; Roche Diagnostics).

Dietary intake was assessed using a 203-item food frequency questionnaire (FFQ).[34] The FFQ assessed food and beverage intake over the last month before inclusion. Sodium intake was assessed from food items only and did not include discretionary salt use. Trained dietitians checked all responses and additional data was obtained when responses were missing or unclear. Energy and nutrient intake were calculated by linking the FFQ responses to the Dutch Food Composition Database (2006).[35]

Cardiovascular deaths were coded in accordance with the International Classification of Disease coding, tenth revision (ICD-10)[36] and comprised the following codes: I20-I25, I46, R96, I50 and I60-I69. Data on vital status was obtained through linkage of the Alpha Omega Cohort to municipal registries from baseline through December

2018. Causes of death were obtained from the national mortality registry (Statistics Netherlands, CBS). From 2013, the CBS only provided the primary cause of death and therefore treating physicians were asked to complete an additional cause-of-death questionnaire (response rate 67%).

Modifications to the trial protocol

Eligibility criteria of the observational data were age between 60 and 80 years at the moment of inclusion, which is stricter than the inclusion criterion of an age >18 years in the target trial. Conversely, patients with a MI within the past 10 years were eligible for the Alpha Omega study, which was broader than the time restriction in the target trial. This restriction on time since qualifying event was loosened in the target trial emulation, to maintain sufficient statistical power.

Randomization to the control diet or the dietary intervention could not be applied to patients in the observational dataset. Compliance with the DASH diet was therefore quantified using a DASH diet compliance index proposed by Mellen and colleagues.[37] This diet index comprises nine components: saturated fat, total fat, protein, cholesterol, fibre, magnesium, calcium, potassium and sodium. For each component, a target intake (indexed to total daily energy intake) was proposed based on the target intakes from the two original DASH trials.[4,5] Respondents received 1 point when they achieved the target intake for a DASH component; when only the intermediate target was reached, 0.5 point was awarded. The scores for the nine components were then summed, meaning that a total score ranging between 0 and 9 points could be achieved. Supplemental table S1 shows the targets and intermediate targets for the nine DASH components.

In the current study, patients were classified with a DASH compliance greater or equal to 5 out of 9 as DASH-compliant. To emulate randomization, a pseudo-population with balanced distribution of confounding factors over the intervention and comparator groups was created, using inverse probability of treatment weighting (IPTW).

Statistical analysis

Continuous baseline characteristics were presented as mean with standard deviation or median with interquartile range, as appropriate. Categorical baseline characteristics were presented as number with percentage.

Real-world compliance with medical treatments or lifestyle behaviours is often motivated by underlying medical conditions, that are also associated with clinical outcomes: i.e. confounding by indication.[38] Propensity score (PS) methods, including IPTW, have been suggested as a statistical method to deal with confounding by indication in observational studies.[39-41] A PS was constructed to predict the probability of being DASH-compliant using multivariable logistic regression adjusted for the a priori identified confounders: age, sex, education level, smoking status, alcohol consumption, leisure-time physical activity and serum creatinine level. A pseudo-population was created using IPTW, where patients that were DASH-compliant received a weight of 1/PS and patients that were not DASH-compliant received a weight of 1/(1-PS). IPT weights were stabilized to prevent the impact of outliers. After IPTW, balance was assessed by calculating standardized mean differences (SMD) in baseline characteristics and SMD values < 0.10 were accepted as indicative of achieved balance between the intervention and comparator group.[42] The relation of compliance with the DASH diet with cardiovascular mortality and all-cause mortality risk was assessed using the Kaplan Meier method. Weighted Cox proportional hazard models with time-on-study as a time axis were used to obtain hazard ratios (HRs) for all-cause and cardiovascular mortality in the pseudo-population. Schoenfeld residuals were visually assessed to check the proportional hazard assumption. The IPT-weighted models are presented as the main findings, but explorative adjustments were made for the covariates included in the PS estimation and for covariates that could be either confounder or intermediates, i.e. type 2 diabetes, body mass index, systolic blood pressure, LDL-C and high-sensitivity C reactive protein (hs-CRP) levels.

Missing data was imputed with single imputation using predictive mean matching. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using R statistical software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Subgroup analyses and sensitivity analyses

Sensitivity analyses with DASH compliance defined as a score ≥2, ≥3, ≥4 and ≥6 were performed to assess the impact of the choice of compliance cut-off. A new PS was estimated for each cut-off and HRs were estimated after IPTW. The IPT-weighted analyses were also repeated in subgroups of patients not currently using any blood-pressure lowering agents (N = 446) and a subgroup of patients not using renin-

angiotensin system inhibitors (RASi, N = 3,372) to assess potential effect modification by the use of these medications and the DASH diet.

Sodium intake is difficult to assess using FFQs and might be underestimated. Therefore, a sensitivity analysis excluding the sodium criterion from Mellen's proposed DASH compliance scores was performed. In this sensitivity analysis a DASH score ≥4/8 instead of ≥5/9 was defined as DASH compliant. Unweighted, multivariable adjusted Cox proportional hazard models were run as a sensitivity analysis to explore differences in the estimates compared to IPTW, one comparing DASH compliance (score ≥5/9) to non-compliance and one comparing quintiles of the DASH compliance scores.

RESULTS

Baseline characteristics

Table 2 shows the baseline characteristics of 4,365 post-MI patients included in the present analysis. Median age was 69 [IQR 64 -73] years and the majority of the cohort was male (N = 3,432, 79%). Upon inclusion in the cohort, the median time since the classifying MI was 3.7 years. Over 85% of the cohort was treated with lipid- and/or blood pressure-lowering medications.

DASH compliance scores in the cohort ranged between 0 and 8.5 out of a maximum score of 9, with a median of 3.0 [IQR 2.0-4.0] (Figure S1). DASH compliance scores were higher for women compared with men, but followed similar distributions across strata of age, education, smoking status, alcohol consumption and physical activity level (Figure S1). When focusing on individual components of the DASH compliance score, compliance was high for the fibre and potassium targets, with over 70% of the cohort reaching at least the intermediate intake target level for these components. Compliance was lowest for protein and saturated fat intake, with 73% of the participants not even reaching the intermediate intake target (Figure S2).

TABLE 2 Baseline characteristics of the Alpha Omega cohort – overall and stratified for DASH compliance, before and after IPTW

		Study population before IPTW			Pseudo-population after IPTW		
	Full cohort	Not DASH-compliant	DASH-compliant	SMD	Not DASH-compliant	DASH-compliant	SMD
N	4365	3767	598		3767.17	596.65	
Age, *year*	69 [64-73]	69 [64-73]	69 [65-74]	0.062	69 [64-73]	69 [65-73]	0.025
Male sex, *N (%)*	3432 (79)	3071 (82)	361 (60)	0.479	2961.6 (79)	468 (78)	0.004
Education, *N (%)*				0.036			0.016
Low	888 (20)	773 (21)	115 (19)		767.0 (20)	124.4 (21)	
Lower-Middle	1566 (36)	1345 (36)	221 (37)		1350.4 (36)	213.0 (36)	
Middle-High	1376 (32)	1188 (32)	188 (31)		1187.9 (32)	185.0 (31)	
High	535 (12)	461 (12)	74 (12)		461.8 (12)	74.3 (13)	
Diabetes mellitus, *N (%)*	883 (20)	744 (20)	139 (23)	0.085			0.089
Smoking status, *N (%)*				0.326			0.009
Never	723 (17)	570 (15)	153 (26)		623.7 (17)	98.3 (17)	
Former, quit > 10 years ago	767 (18)	656 (17)	111 (19)		662.5 (18)	105.3 (18)	
Former, quit ≤ 10 years ago	2162 (50)	1885 (50)	277 (46)		1865.7 (50)	297.4 (50)	
Current	713 (16)	656 (17)	57 (10)		615.3 (16)	95.7 (16)	
Alcohol consumption, *glasses/wk*	5 [2-12]	6 [2-12]	4 [1-9]	0.297	5 [2-12]	5 [2-12]	0.016
Physical activity level, *METh/wk*	23 [11-45]	23 [11-45]	24 [11-47]	0.037	23 [10-45]	24 [11-45]	0.009
Body mass index, *kg/m2*	27.7 ±3.8	27.7 ±3.8	28.1 ±3.9	0.091	27.7 ±3.8	28 ±3.8	0.065
Waist circumference, *cm*	102 ±10	102 ±10	101 ±11	0.156	102 ±10	102 ±11	0.008
Systolic blood pressure, *mmHg*	142 ±22	142 ±22	143 ±21	0.036	142 ±22	143 ±21	0.055
Diastolic blood pressure, *mmHg*	80 ±11	80 ±11	80 ±11	0.068	80 ±11	80 ±11	0.003

TABLE 2 (Continued)

	Full cohort	Study population before IPTW			Pseudo-population after IPTW		
		Not DASH-compliant	DASH-compliant	SMD	Not DASH-compliant	DASH-compliant	SMD
Total cholesterol, *mmol/L**	4.6 [4.0-5.3]	4.6 [4.0-5.3]	4.7 [4.0-5.3]	0.047	4.6 [4.0-5.3]	4.6 [4.0-5.3]	0.015
Triglycerides, *mmol/L**	1.7 [1.2-2.3]	1.7 [1.2-2.3]	1.7 [1.2-2.3]	0.015	1.7 [1.2-2.3]	1.7 [1.2-2.3]	0.003
HDL-cholesterol, *mmol/L**	1.2 [1.0-1.5]	1.2 [1.0-1.5]	1.3 [1.1-1.5]	0.099	1.2 [1.1-1.5]	1.2 [1.0-1.5]	0.016
LDL-cholesterol, *mmol/L**	2.5 [2.0-3.0]	2.5 [2.0-3.0]	2.5 [2.0-3.0]	0.008	2.5 [2.0-3.0]	2.5 [2.0-3.0]	0.015
Creatinine, *μmol/L*	86 [75-99]	86 [75-99]	83 [72-96]	0.171	86 [75-99]	86 [75-98]	0.011
High sensitivity CRP, *mg/L*	1.7 [0.8-3.8]	1.7 [0.8-3.8]	1.7 [0.8-3.7]	0.069	1.7 [0.8-3.8]	1.7 [0.8-3.7]	0.047

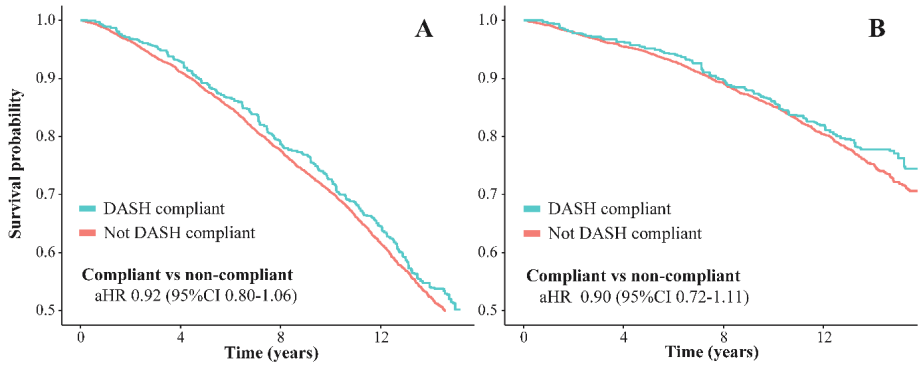
Baseline characteristics of the overall Alpha Omega cohort and stratified for DASH compliance, defined as a score ≥5/9, before and after IPTW.IPTW was based on a propensity score adjusted for, sex, education, smoking, alcohol consumption and creatinine. Data are presented as N (%) for categorical variables and as mean ±standard deviation or median [interquartile range] for continuous variables. * Non-fasting measurements. DASH: Dietary approaches to stop hypertension, HDL: High density lipoprotein, LDL: Low density lipoprotein, CRP: C reactive protein., IPTW: inverse probability of treatment weighting, SMD: standardized mean difference

Five hundred ninety-eight participants (14%) had a DASH compliance score ≥5 and were classified as DASH-compliant. Patients that were DASH-compliant were similar in age, history of diabetes, physical activity level and education levels compared with those that were not. However, DASH-compliant patients were more frequently female (40% vs 18%) and less frequently smokers (10% vs 17%). SMD values in the unadjusted data indicated that the DASH-compliant and non-compliant groups were not balanced (Table 2). After IPTW was applied, the baseline characteristics and potential confounding covariates were balanced over the DASH-compliant and non-compliant groups (Table 2, Figure S3).

Relation with cardiovascular mortality and all-cause mortality

During a median follow-up of 12.4 years, 2,035 deaths occurred of which 903 (44%) were of cardiovascular origin. Figure 1 shows IPT-weighted Kaplan Meier curves for all-cause mortality and cardiovascular mortality. DASH compliance showed no association with all-cause mortality (HR 0.92, 95%CI 0.80-1.06) and cardiovascular mortality (HR 0.90, 95%CI 0.72-1.11). Further adjustments for potential confounders and intermediate factors did not affect the estimates (Table 3)

FIGURE 1 IPT-weighted Kaplan Meier curves for all-cause mortality and cardiovascular mortality



Propensity score-matched Kaplan Meier curves for all-cause mortality (A) and cardiovascular mortality (B). The presented hazard ratios are based on IPT-weighted Cox proportional hazard models. 95%CI: 95% Confidence Interval, HR –Hazard Ratio, DASH: Dietary Approaches to Stop Hypertension

TABLE 3 IPTW estimates for the effect of DASH compliance on the risk of all-cause and cardiovascular mortality

	All-cause mortality		Cardiovascular mortality	
	Not DASH-compliant	DASH-compliant	Not DASH-compliant	DASH-compliant
Crude	*Reference*	0.92 (0.80-1.06)	*Reference*	0.90 (0.72-1.11)
Model 1	*Reference*	0.89 (0.77-1.03)	*Reference*	0.88 (0.70-1.09)
Model 2	*Reference*	0.89 (0.77-1.02)	*Reference*	0.87 (0.70-1.08)

IPT-weighted hazard ratios for compliance with the DASH-diet and risk of all-cause mortality and cardiovascular mortality. The crude model included no covariates but was IPT-weighted. Model 1 adjusted for the confounders included in the propensity score model: age, sex, education, smoking and alcohol consumption. Model 2 was further adjusted for body mass index, systolic blood pressure, LDL-cholesterol and type 2 diabetes. DASH: Dietary approaches to stop hypertension

In a sensitivity analysis using multivariable adjusted Cox proportional hazard models, instead of IPT-weighted Cox models, the direction and size of the relations between DASH compliance and all-cause and cause-specific mortality were similar to the main analyses (HR 0.92, 95%CI 0.80-1.05 and HR 0.88, 95%CI 0.72-1.08 respectively (Table 4).

TABLE 4 Sensitivity analysis – Effect estimates based on multi-variable adjusted Cox regression models

	All-cause mortality		Cardiovascular mortality	
	Not DASH-compliant	DASH-compliant	Not DASH-compliant	DASH-compliant
Events/N	1,774/3,767	261/598	789/3,767	114/598
FU (py)	41,583	6,891	41,583	6,891
Crude	*Reference*	0.87 (0.77-0.99)	*Reference*	0.86 (0.71-1.04)
Model 1	*Reference*	0.92 (0.80-1.05)	*Reference*	0.88 (0.72-1.08)
Model 2	*Reference*	0.91 (0.80-1.04)	*Reference*	0.88 (0.72-1.07)

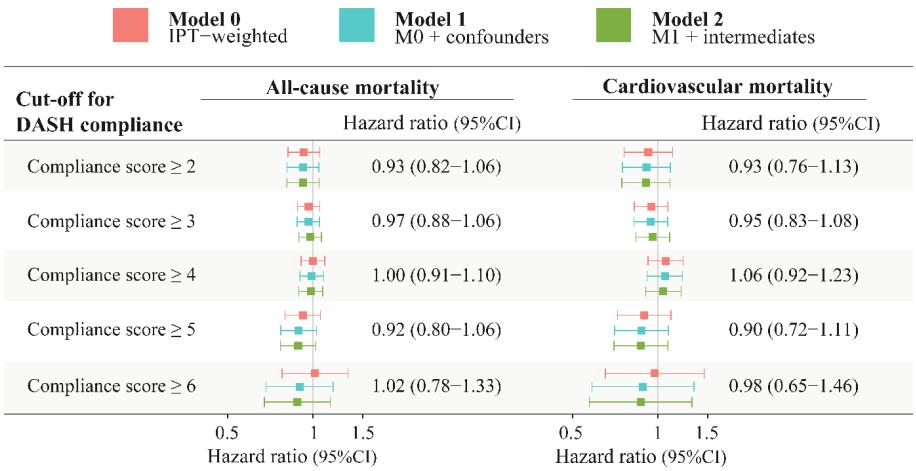
Hazard ratios for compliance with the DASH-diet and risk of all-cause mortality and cardiovascular mortality estimated using multivariable-adjusted Cox Proportional Hazard models. Model 1 adjusted for the confounders included in the propensity score model: age, sex, education, smoking, alcohol consumption, physical activity and creatinine. Model 2 further adjusted for body mass index, systolic blood pressure, LDL-cholesterol and type 2 diabetes. DASH: Dietary approaches to stop hypertension, py: person year

Figure 2 shows the IPT-weighted and multivariable adjusted HRs for different cut-off values for DASH compliance. IPTW was successful for the alternative cut-off values, and balance of baseline characteristics (SMDs <0.10) was achieved at each threshold (data not shown). Both lower (≥2, ≥3, ≥4 of 9) and higher (≥6 of 9) cut-off values for DASH compliance were not related with a significantly reduced risk of all-cause and

cardiovascular mortality. In sensitivity analyses assessing DASH compliance in quintiles of the compliance distribution, there was no indication of a dose-response relation between DASH compliance score and all-cause or cardiovascular mortality (Figure S4).

To more closely mimic the target trial, a sensitivity analysis was performed limiting the follow-up to 10 years, after which patients that were still alive were censored. In this analysis, the incidence rates for all-cause mortality and cardiovascular mortality did not differ according to DASH compliance status (all-cause mortality: 3.4/100 py for non-DASH compliant versus 2.9/100 py for DASH-compliant patients and cardiovascular mortality: 1.6/100 py vs. 1.4/100 py, respectively. Table S2).

FIGURE 2 IPT-weighted hazard ratios for alternative cut-offs for DASH compliance



This figure shows the estimated hazard ratio for all-cause and cardiovascular mortality for alternative cut-offs for DASH compliance. For all included cut-offs, patients with a score greater or equal to the cut-off value are compared with patients below the threshold. The presented numerical hazard ratios are IPT-weighted; a new propensity score was calculated for each cut-off value. The forest plot shows the IPT-weighted hazard ratio, model 1 is a hazard ratio that was further adjusted for confounders: age, sex, education, smoking and alcohol consumption. Model 2 was additionally adjusted for body mass index, systolic blood pressure, LDL-cholesterol and type 2 diabetes (potential confounders or intermediates). IPT: inverse probability of treatment, 95%CI: 95% confidence interval. In an IPT-weighted sensitivity analysis that negated the sodium component of the DASH compliance score, similar HRs were found compared to the main analysis (Table S2). In hypothesis-generating analyses of patients not using any blood pressure-lowering agents (N = 446), a protective association of DASH compliance and all-cause mortality (HR 0.85, 95%CI 0.45-1.63) and cardiovascular mortality (HR 0.36-1.12) was found (Table S2). In patients not using any RASi a smaller but still protective association was found (Table S2).

DISCUSSION

In this study, a target trial was emulated to assess of the relationship between DASH compliance and risk of (cardiovascular) mortality in an observational cohort of patients with a history of MI. Adhering to the DASH diet was not related with reduction in cardiovascular and all-cause mortality risk in a population with established CVD. This absence of a beneficial relationship may in part be explained by a high proportion of patients using blood-pressure lowering agents which interfere with the working mechanisms of the DASH diet.

It is not possible to compare the findings of the present study to experimental study data, as no such long-term RCT on the clinical effects of DASH has ever been performed in a population with CVD, or any other population. A meta-analysis of observational studies in apparently healthy patients reported a pooled estimate of 20% relative risk reduction for both all-cause and cardiovascular mortality when comparing the highest to lowest DASH compliance categories.[21] Effect estimates in the present study were smaller, probably due to smaller contrast between the DASH-compliant and non-compliant participants or because the meta-analysis did not include secondary prevention populations. Overall, the findings in the current study are in line with existing literature that shows that compliance with the DASH diet has a small, if any, effect on cardiovascular and all-cause mortality risk.[12-21]

Previous short-term RCTs in populations at high cardiovascular risk, found that DASH effectively reduces body weight[11,43] and blood pressure[5,9,44], and observational studies in these populations indicate that DASH also has a beneficial association with cardiovascular and mortality outcomes, possibly through amelioration of cardiovascular risk factors.[16–21] However, body weight reduction and blood pressure-lowering effects were not observed in the present study. DASH has been hypothesized to reduce blood pressure through reduced sodium intake, additional natriuretic effects,[45] and inhibition of RAS which induces a blood pressure-lowering response.[46,47] The blood pressure-lowering potential of DASH in the study population will likely have been limited because a vast majority of the Alpha Omega Cohort, was treated with blood-pressure lowering agents, some of which also interact with RAS. This hypothesis is supported by the larger benefits observed in subgroups of patients not using any blood pressure-lowering agents or RASi specifically. These findings suggest that the use of such agents may attenuate the effects of the DASH diet.

Overall, the target trial emulation was successful. Important design components of the target trial that could not directly be emulated in the observational study were age of the study population and time since the qualifying MI. As a result, the emulated trial comprised an older population with a relatively long time since the qualifying event. This may have resulted in an attenuated relation between DASH compliance and (cardiovascular) mortality, because the benefits of dietary changes likely take a few years to fully manifest and may therefore be more pronounced in younger populations.[48] Furthermore, people were not actively instructed to adopt a DASH diet, but instead they were naturally compliant to the diet. Previous studies suggest that DASH's blood pressure-lowering effects manifest quickly, even as soon as one or two weeks after diet initiation, and remain stable afterwards.[4,49,50] The observation that the HRs for DASH compliance in the present study were not statistically significant might have been due to insufficient statistical power, as a post hoc power calculation indicated that approximately 10,000 participants would have been required to detect a statistically significant result for a HR of 0.90.

Strengths and limitations

Strengths of the current study include the extensive range of available baseline characteristics which were systematically collected. Linkage with mortality registries prevented loss to follow-up and limited the chance of selection bias introduced by informative censoring.[27,51,52] This study is the first target trial emulation to assess the long-term relation of DASH compliance with (cardiovascular) mortality risk. Using target trial has resulted in a well-defined study population, which improves applicability of the findings to external populations. Moreover, using IPTW is a recommended statistical approach to handle confounding by indication,[39-41] and yielded a well-balanced distribution of confounders over the intervention and reference group.

Study limitations need to be considered. The current study did not actively randomize patients to be DASH-compliant or non-DASH compliant and is remains observational research. Using trial emulation and IPTW techniques, does not resolve all biases that are inherent to observational research, such as unmeasured confounding, model misspecification and measurement bias. In these analyses, no adjustments could be made for variables that were not measured, but which might have affected the findings (e.g. frailty and functional status). For the determination of dietary intake, we relied on self-report in an FFQ, which, although validated in a Dutch population,[34] is sensitive to measurement and reporting errors. Reduction of sodium intake is an important

aspect of the DASH diet, but it is notoriously difficult to validly estimate using an FFQ.[53] Estimated sodium intake was relatively low in this cohort compared with the Dutch population but could have been underestimated.[54] Misclassification of sodium intake could have diluted the observed associations with compliance with DASH, but a sensitivity analysis excluding the sodium criterion yielded highly similar results to the main analysis. Dichotomization of the DASH compliance score into compliant and non-compliant categories is likely to have resulted in loss of contrast and an underestimation of the true effect size of a DASH intervention. However, in an analysis of DASH compliance quintiles, no indication for a dose-response relation was found.

Using explicit trial emulation and IPTW reduced the risk of biases and increased transparency of the findings but did not eradicate all biases that accompany observational data when answering etiologic questions. Ideally, a long-term RCT would be performed to assess the benefits of the DASH diet in an experimental setting. As it is unlikely that such a trial will ever be performed, the present study provides an important clue that the DASH diet is unlikely to have large beneficial effects in patients with established CVD.

CONCLUSION

In conclusion, this target trial emulation assessing the relationship between compliance with the DASH diet and all-cause and cardiovascular mortality found no association between compliance with the DASH diet and reductions in risks of all-cause and cardiovascular death. This survival benefits effectuated by the DASH diet can partly be explained by the high proportion of CVD patients treated with blood-pressure lowering medications that modify the effect of the DASH diet.

REFERENCES

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol 2020;76:2982–3021. https://doi.org/10.1016/j.jacc.2020.11.010.
2. Dai H, Much AA, Maor E, Asher E, Younis A, Xu Y, et al. Global, regional, and national burden of ischaemic heart disease and its attributable risk factors, 1990–2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes 2020:1–11. https://doi.org/10.1093/ehjqcco/qcaa076.
3. Yu E, Malik VS, Hu FB. Cardiovascular Disease Prevention by Diet Modification: JACC Health Promotion Series. J Am Coll Cardiol 2018;72:914–26. https://doi.org/10.1016/j.jacc.2018.02.085.
4. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A Clinical Trial of the Effects of Dietary Patterns on Blood Pressure. New England Journal of Medicine 1997;336:1117–24. https://doi.org/10.1056/NEJM199704173361601.
5. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. New England Journal of Medicine 2001;344:3–10. https://doi.org/10.1056/NEJM200101043440101.
6. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. Circulation 2012;126:e354-471. https://doi.org/10.1161/CIR.0b013e318277d6a0.
7. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140:e596–646. https://doi.org/10.1161/CIR.0000000000000678.
8. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021:1–111. https://doi.org/10.1093/eurheartj/ehab484.
9. Abbasnezhad A, Falahi E, Gonzalez MJ, Kavehi P, Fouladvand F, Choghakhori R. Effect of different dietary approaches compared with a regular diet on systolic and diastolic blood pressure in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract 2020;163:108108. https://doi.org/10.1016/j.diabres.2020.108108.
10. Gay HC, Rao SG, Vaccarino V, Ali MK. Effects of different dietary interventions on blood pressure: Systematic review and meta-analysis of randomized controlled trials. Hypertension 2016;67:733–9. https://doi.org/10.1161/HYPERTENSIONAHA.115.06853.
11. Soltani S, Shirani F, Chitsazi MJ, Salehi-Abargouei A. The effect of dietary approaches to stop hypertension (DASH) diet on weight and body composition in adults: A systematic review and meta-analysis of randomized controlled clinical trials. Obesity Reviews 2016;17:442–54. https://doi.org/10.1111/obr.12391.

12. Fitzgerald KC, Chiuve SE, Buring JE, Ridker PM, Glynn RJ. Comparison of associations of adherence to a Dietary Approaches to Stop Hypertension (DASH)-style diet with risks of cardiovascular disease and venous thromboembolism. Journal of Thrombosis and Haemostasis 2012;10:189–98. https://doi.org/10.1111/j.1538-7836.2011.04588.x.

13. Wang JS, Liu WJ, Lee CL. Associations of Adherence to the DASH Diet and the Mediterranean Diet With All-Cause Mortality in Subjects With Various Glucose Regulation States. Front Nutr 2022;9:1–9. https://doi.org/10.3389/fnut.2022.828792.

14. Bertoia ML, Triche EW, Michaud DS, Baylin A, Hogan JW, Neuhouser ML, et al. Mediterranean and Dietary Approaches to Stop Hypertension dietary patterns and risk of sudden cardiac death in postmenopausal women. Am J Clin Nutr 2014;99:344–51. https://doi.org/10.3945/ajcn.112.056135.

15. Bathrellou E, Kontogianni MD, Chrysanthopoulou E, Georgousopoulou E, Chrysohoou C, Pitsavos C, et al. Adherence to a DASH-style diet and cardiovascular disease risk: The 10-year follow-up of the ATTICA study. Nutr Health 2019;25:225–30. https://doi.org/10.1177/0260106019862995.

16. Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L. Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases-Incidence: A systematic review and meta-analysis on observational prospective studies. Nutrition 2013;29:611–8. https://doi.org/10.1016/j.nut.2012.12.018.

17. Hu J-R, Wu Y, Sacks FM, Appel LJ, Miller Iii ER, Young JH, et al. Effects of carbohydrate quality and amount on plasma lactate: Results from the OmniCarb trial. BMJ Open Diabetes Res Care 2020;8.

18. Struijk EA, May AM, Wezenbeek NLW, Fransen HP, Soedamah-Muthu SS, Geelen A, et al. Adherence to dietary guidelines and cardiovascular disease risk in the EPIC-NL cohort. Int J Cardiol 2014;176:354–9. https://doi.org/10.1016/j.ijcard.2014.07.017.

19. Talaei M, Koh WP, Yuan JM, van Dam RM. DASH Dietary Pattern, Mediation by Mineral Intakes, and the Risk of Coronary Artery Disease and Stroke Mortality. J Am Heart Assoc 2019;8. https://doi.org/10.1161/JAHA.118.011054.

20. Mertens E, Markey O, Geleijnse JM, Lovegrove JA, Givens DI. Adherence to a healthy diet in relation to cardiovascular incidence and risk markers: evidence from the Caerphilly Prospective Study. Eur J Nutr 2018;57:1245–58. https://doi.org/10.1007/s00394-017-1408-0.

21. Schwingshackl L, Hoffmann G. Diet Quality as Assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension Score, and Health Outcomes: A Systematic Review and Meta-Analysis of Cohort Studies. J Acad Nutr Diet 2015;115:780-800.e5. https://doi.org/10.1016/j.jand.2014.12.009.

22. Satija A, Stampfer MJ, Rimm EB, Willett W, Hu FB. Perspective: Are large, simple trials the solution for nutrition research? Advances in Nutrition 2018;9:378–87. https://doi.org/10.1093/ADVANCES/NMY030.

23. Ioannidis JPA. The Challenge of Reforming Nutritional Epidemiologic Research. JAMA 2018;320:969. https://doi.org/10.1001/jama.2018.11025.

24. Freedman LS, Schatzkin A, Midthune D, Kipnis V. Dealing with dietary measurement error in nutritional cohort studies. J Natl Cancer Inst 2011;103:1086–92. https://doi.org/10.1093/jnci/djr189.

25. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available: Table 1. Am J Epidemiol 2016;183:758–64. https://doi.org/10.1093/aje/kwv254.

26. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016;79:70–5. https://doi.org/10.1016/j.jclinepi.2016.04.014.

27. Tobias DK, Lajous M. What would the trial be? Emulating randomized dietary intervention trials to estimate causal effects with observational data. Am J Clin Nutr 2021;114:416–7. https://doi.org/10.1093/ajcn/nqab169.

28. Matthews AA, Danaei G, Islam N, Kurth T. Target trial emulation: applying principles of randomised trials to observational studies. BMJ 2022:e071108. https://doi.org/10.1136/bmj-2022-071108.

29. Svetkey LP, Sacks FM, Obarzanek E, Vollmer WM, Appel LJ, Lin PH, et al. The DASH Diet, Sodium Intake and Blood Pressure Trial (DASH-sodium): rationale and design. DASH-Sodium Collaborative Research Group. J Am Diet Assoc 1999;99:S96-104. https://doi.org/10.1016/s0002-8223(99)00423-x.

30. Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. New England Journal of Medicine 2017;377:1391–8. https://doi.org/10.1056/NEJMsm1605385.

31. Kromhout D, Giltay EJ, Geleijnse JM. n–3 Fatty Acids and Cardiovascular Events after Myocardial Infarction. New 2015;363:2015–26.

32. Geleijnse JM, Giltay EJ, Schouten EG, de Goede J, Griep LMO, Teitsma-Jansen AM, et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: Design and baseline characteristics of the Alpha Omega Trial. Am Heart J 2010;159:539-546.e2. https://doi.org/10.1016/j.ahj.2009.12.033.

33. Schuit AJ, Schouten EG, Westerterp KR, Saris WHM. Validity of the physical activity scale for the elderly (PASE): According to energy expenditure assessed by the doubly labeled water method. J Clin Epidemiol 1997;50:541–6. https://doi.org/10.1016/S0895-4356(97)00010-3.

34. Feunekes GI, Van Staveren WA, De Vries JH, Burema J, Hautvast JG. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. Am J Clin Nutr 1993;58:489–96. https://doi.org/10.1093/ajcn/58.4.489.

35. Dutch Nutrition Center. Dutch Food Composition Table 2006 NEVO-table. The Hague, The Netherlands: 2006.

36. World Health Organization. ICD-10 : international statistical classification of diseases and related health problems : tenth revision n.d.

37. Mellen PB, Gao SK, Vitolins MZ, Goff DC. Deteriorating Dietary Habits Among Adults With Hypertension. Arch Intern Med 2008;168:308. https://doi.org/10.1001/archinternmed.2007.119.

38. Psaty BM, Koepsell TD, Lin D, Weiss NS, Siscovick DS, Rosendaal FR, et al. Assessment and Control for Confounding by Indication in Observational Studies. J Am Geriatr Soc 1999;47:749–54. https://doi.org/10.1111/j.1532-5415.1999.tb01603.x.

39. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55. https://doi.org/10.1093/biomet/70.1.41.

40. Brookhart MA, Wyss R, Layton JB, Stürmer T. Propensity score methods for confounding control in nonexperimental research. Circ Cardiovasc Qual Outcomes 2013;6:604–11. https://doi.org/10.1161/CIRCOUTCOMES.113.000359.

41. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med 2014;275:570–80. https://doi.org/10.1111/joim.12197.

42. Franklin JM, Rassen JA, Ackermann D, Bartels DB, Schneeweiss S. Metrics for covariate balance in cohort studies of causal effects. Stat Med 2014;33:1685–99. https://doi.org/10.1002/sim.6058.

43. Ge L, Sadeghirad B, Ball GDC, Da Costa BR, Hitchcock CL, Svendrovski A, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: Systematic review and network meta-analysis of randomised trials. The BMJ 2020;369. https://doi.org/10.1136/bmj.m696.

44. Filippou CD, Tsioufis CP, Thomopoulos CG, Mihas CC, Dimitriadis KS, Sotiropoulou LI, et al. Dietary Approaches to Stop Hypertension (DASH) Diet and Blood Pressure Reduction in Adults with and without Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Advances in Nutrition 2020;11:1150–60. https://doi.org/10.1093/advances/nmaa041.

45. Akita S, Sacks FM, Svetkey LP, Conlin PR, Kimura G. Effects of the Dietary Approaches to Stop Hypertension (DASH) Diet on the Pressure-Natriuresis Relationship. Hypertension 2003;42:8–13. https://doi.org/10.1161/01.HYP.0000074668.08704.6E.

46. Lin P-H, Allen JD, Li Y-J, Yu M, Lien LF, Svetkey LP. Blood Pressure-Lowering Mechanisms of the DASH Dietary Pattern. J Nutr Metab 2012;2012:1–10. https://doi.org/10.1155/2012/472396.

47. Maris SA, Williams JS, Sun B, Brown S, Mitchell GF, Conlin PR. Interactions of the DASH Diet with the Renin-Angiotensin-Aldosterone System. Curr Dev Nutr 2019;3. https://doi.org/10.1093/cdn/nzz091.

48. Capewell S, O'Flaherty M. Can dietary changes rapidly decrease cardiovascular mortality rates? Eur Heart J 2011;32:1187–9. https://doi.org/10.1093/eurheartj/ehr049.

49. Lin P-H, Ginty F, Appel LJ, Aickin M, Bohannon A, Garnero P, et al. The DASH diet and sodium reduction improve markers of bone turnover and calcium metabolism in adults. J Nutr 2003;133:3130–6. https://doi.org/10.1093/jn/133.10.3130.

50. Juraschek SP, Woodward M, Sacks FM, Carey VJ, Miller ER, Appel LJ. Time Course of Change in Blood Pressure From Sodium Reduction and the DASH Diet. Hypertension 2017;70:923–9. https://doi.org/10.1161/HYPERTENSIONAHA.117.10017.

51. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016;79:70–5. https://doi.org/10.1016/j.jclinepi.2016.04.014.

52. Chiu Y-H, Chavarro JE, Dickerman BA, Manson JE, Mukamal KJ, Rexrode KM, et al. Estimating the effect of nutritional interventions using observational data: the American Heart Association's 2020 Dietary Goals and mortality. Am J Clin Nutr 2021;114:690–703. https://doi.org/10.1093/ajcn/nqab100.

53. McLean RM, Farmer VL, Nettleton A, Cameron CM, Cook NR, Campbell NRC. Assessment of dietary sodium intake using a food frequency questionnaire and 24-hour urinary sodium excretion: a systematic literature review. The Journal of Clinical Hypertension 2017;19:1214–30. https://doi.org/10.1111/jch.13148.

54. Verkaik-Kloosterman J, Dekkers ALM, de Borst MH, Bakker SJL. Estimation of the salt intake distribution of Dutch kidney transplant recipients using 24-h urinary sodium excretion: the potential of external within-person variance. Am J Clin Nutr 2019;110:641–51. https://doi.org/10.1093/ajcn/nqz134.

55. Moore DF. Sample Size Determination for Survival Studies BT - Applied Survival Analysis Using R. In: Moore DF, editor., Cham: Springer International Publishing; 2016, p. 157–75. https://doi.org/10.1007/978-3-319-31245-3_11.

SUPPLEMENTAL MATERIAL

TABLE S1 DASH compliance score targets

Diet component	**DASH score target** (1 point)	**Intermediate target** (0.5 point)
Saturated fat	<6% total energy	11% total energy
Total fat	<27% total energy	32% total energy
Protein	>18.0% total energy	16.5% total energy
Cholesterol	<71.4 mg/1,000 kcal	107.1 mg/1,000 kcal
Fiber	>14.8 g/1,000 kcal	9.5 g/1,000 kcal
Magnesium	>238 mg/1,000 kcal	158 mg/1,000 kcal
Calcium	>590 mg/1,000 kcal	402 mg/1,000 kcal
Potassium	>2,238 mg/1,000 kcal	1,534 mg/1,000 kcal
Sodium*	<1,143 mg/1,000 kcal	1,286 mg/1,000 kcal

DASH compliance score as proposed by Mellen and colleagues.(37) The score was based on the target nutrient intakes from the original DASH trials assuming a daily energy intake of 2,100 kcal. The total compliance score ranges between 0 and 9. Abbreviations: DASH: Dietary Approaches to Stop Hypertension. * This criterion was negated in a sensitivity analysis.

TABLE S2 Sensitivity analyses

TABLE S2a Follow-up cut off after 10 years

	All-cause mortality		**Cardiovascular mortality**	
	Not DASH-compliant	DASH-compliant	Not DASH-compliant	DASH-compliant
N events/N	1,122/3,767	155/598	513/3,767	73/598
Follow-up (py)	32,729	5,337	32,729	5,337
Incidence rate /100py	3.4	2.9	1.6	1.4
10-year event risk	30%	26%	14%	12%
Crude	*Reference*	0.91 (0.76-1.09)	*Reference*	0.93 (0.71-1.20)
Model 1	*Reference*	0.90 (0.75-1.08)	*Reference*	0.92 (0.70-1.20)
Model 2	*Reference*	0.88 (0.73-1.06)	*Reference*	0.91 (0.70-1.19)

TABLE S2b DASH compliance without sodium component (compliant defined as a score 4/8)

	All-cause mortality		Cardiovascular mortality	
	Not DASH-compliant	DASH-compliant	Not DASH-compliant	DASH-compliant
N events/N	1,880/4,017	155/348	833/4,017	70/348
Follow-up (py)	44,496	3,978	44,496	3,978
Crude	*Reference*	0.97 (0.79-1.18)	*Reference*	0.98 (0.73-1.30)
Model 1	*Reference*	0.93 (0.76-1.13)	*Reference*	0.94 (0.71-1.25)
Model 2	*Reference*	0.88 (0.72-1.08)	*Reference*	0.92 (0.69-1.24)

TABLE S2c Subgroup of patients not using any antihypertensive medication (N = 446)

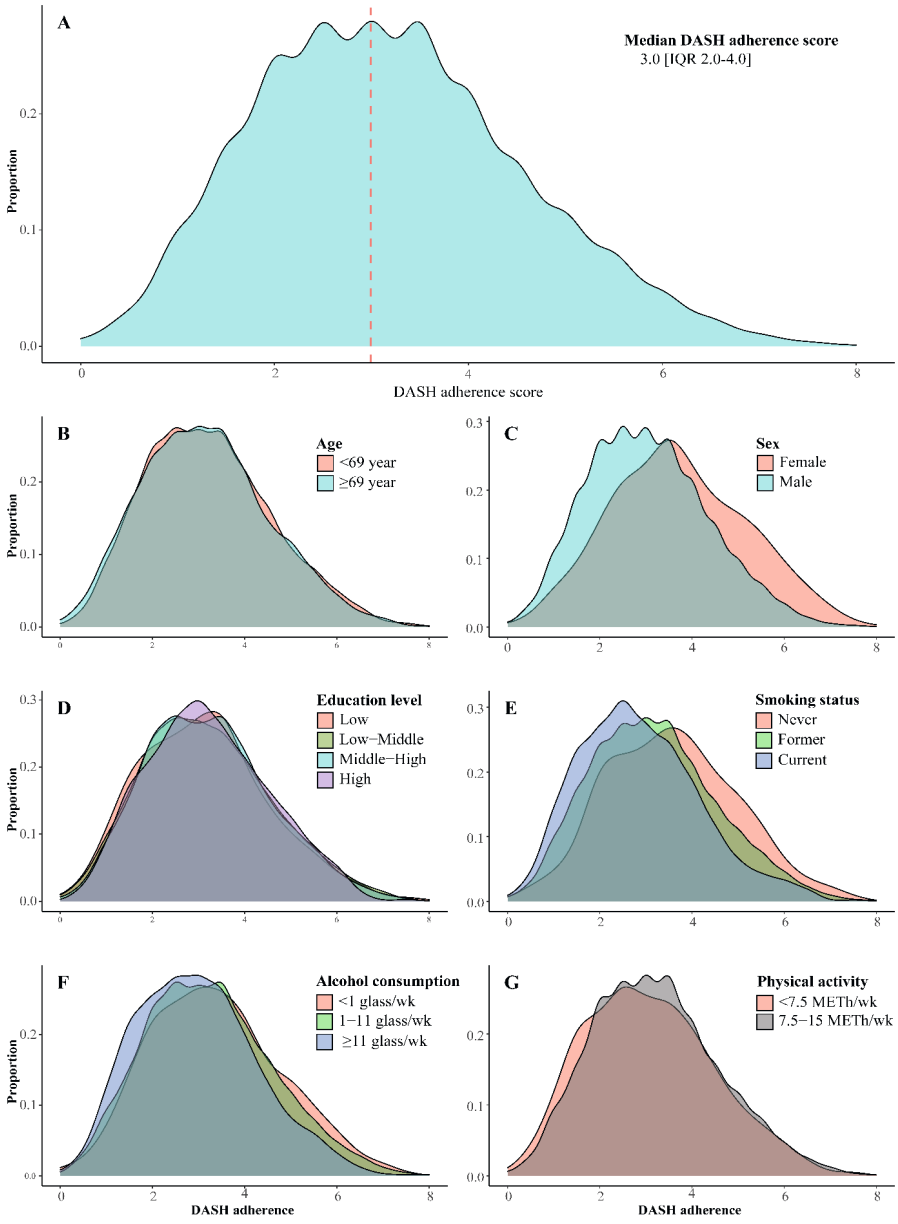
	All-cause mortality		Cardiovascular mortality	
	Not DASH-compliant	DASH-compliant	Not DASH-compliant	DASH-compliant
N events/N	181/387	17/59	70/387	5/59
Follow-up (py)	4,486	775	4,486	775
Crude	*Reference*	0.85 (0.45-1.63)	*Reference*	0.36 (0.12-1.12)
Model 1	*Reference*	0.70 (0.42-1.19)	*Reference*	0.31 (0.09-1.04)
Model 2	*Reference*	0.54 (0.28-1.01)	*Reference*	0.29 (0.08-1.07)

TABLE S2d Subgroup of patients not using RAS-inhibitors (N = 3,372)

	All-cause mortality		Cardiovascular mortality	
	Not DASH-compliant	DASH-compliant	Not DASH-compliant	DASH-compliant
N events/N	733/1,634	104/257	293/1,634	37/257
Follow-up (py)	18,430	3,032	18,430	3,032
Crude	*Reference*	0.90 (0.71-1.14)	*Reference*	0.79 (0.54-1.16)
Model 1	*Reference*	0.86 (0.68-1.09)	*Reference*	0.76 (0.52-1.12)
Model 2	*Reference*	0.83 (0.64-1.06)	*Reference*	0.76 (0.51-1.12)

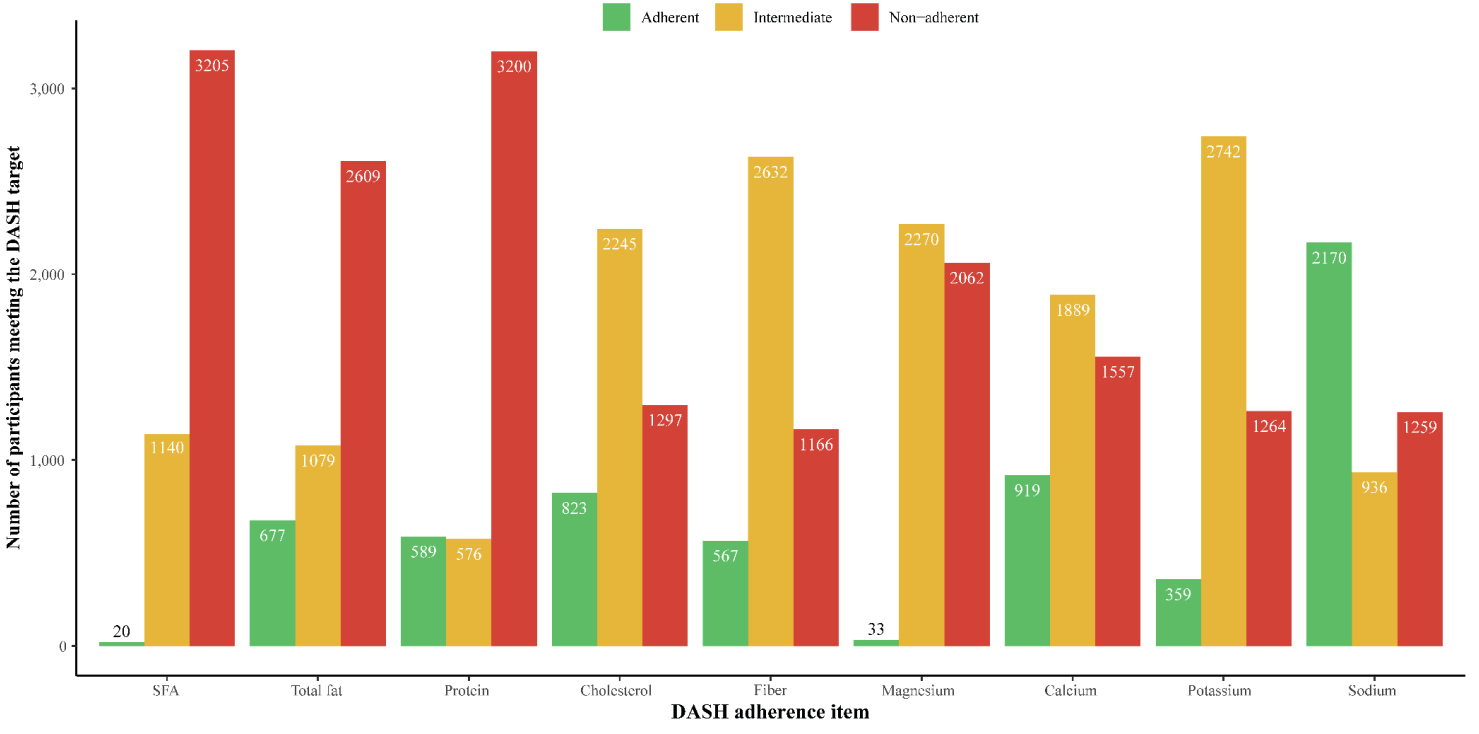
Hazard ratios for compliance to the DASH-diet and risk of all-cause mortality and cardiovascular mortality estimated using multivariable-adjusted Cox Proportional Hazard models. DASH compliance was defined as a score equal to 5 or greater out of maximum 9. In the sensitivity analysis excluding the sodium intake criterion (Table S2b), a score greater or equal to 4 out of maximum 8 was defined as DASH compliant. All models were inverse probability of treatment weighted, with propensity scores estimated in the relevant subgroups. Additional adjustments were made in two steps: Model 1 adjusted for the confounders included in the propensity score model: age, sex, education, smoking, alcohol consumption, physical activity and creatinine. Model 2 further adjusted for body mass index, systolic blood pressure, LDL-cholesterol and type 2 diabetes. DASH: Dietary approaches to stop hypertension, py: person year

FIGURE S1 Distribution of DASH compliance scores



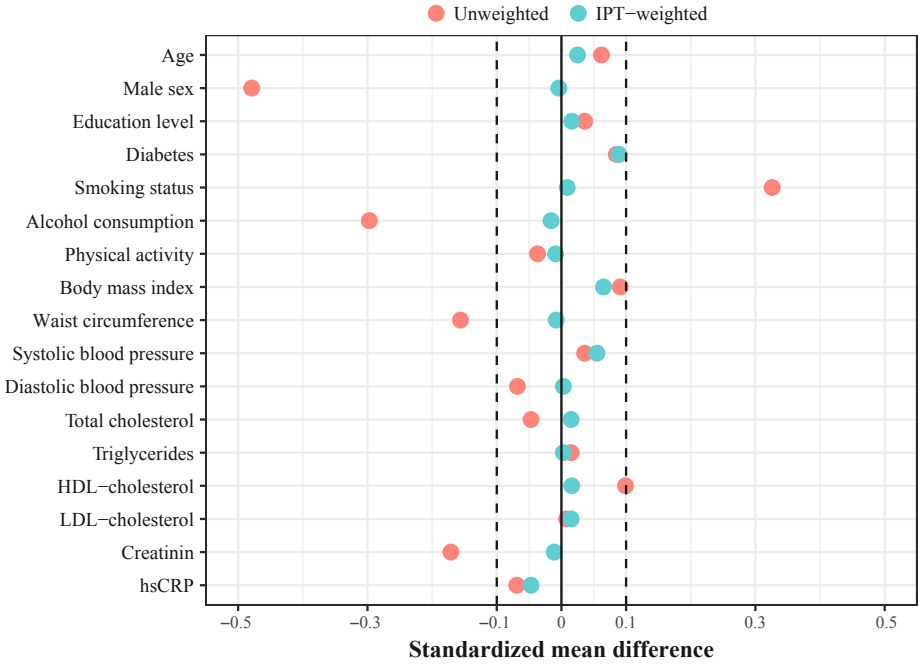
Distribution of the DASH compliance score in the study population, overall (A) and stratified for the covariates in the propensity score model: age (B), sex (C), education level (D), smoking status (E), alcohol consumption (F) and physical activity level (G).. The red dashed line indicates the median DASH compliance score of 3.0. DASH: Dietary Approaches to Stop Hypertension, IQR: interquartile range, METh/wk: Metabolic equivalent of task hours/wk.

FIGURE S2 Number of Alpha Omega Cohort participants reaching DASH target levels



Number of participants meeting each DASH compliance component as defined by Mellen et al.(37) Targets for each of the nine components are presented in Supplemental Table 1 . DASH: Dietary approaches to stop hypertension, SFA: Saturated fatty acid.

FIGURE S3 Balance plot of confounding factors before and after IPTW



Balance of patient characteristics before (unadjusted) and after (adjusted) inverse probability of treatment weighting. A SMD < 0.10 was accepted as the cut-off for a balanced distribution. HDL: high density lipoprotein, LDL: low-density lipoprotein, hsCRP: high sensitivity lipoprotein

FIGURE S4 Analysis of DASH compliance in quintiles

FIGURE S4a Association between DASH compliance quintiles and all-cause mortality

DASH quintile	events/N	Follow-up (py)	Hazard Ratio (95%CI)
Quintile 1	563/1,180	12,981	*Reference*
Quintile 2	292/595	6,453	1.01 (0.87−1.16)
Quintile 3	537/1,193	13,246	0.95 (0.84−1.07)
Quintile 4	382/799	8,903	1.02 (0.89−1.16)
Quintile 5	261/598	6,891	0.91 (0.78−1.06)

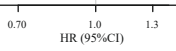
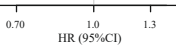


FIGURE S4b Association between DASH compliance quintiles and cardiovascular mortality

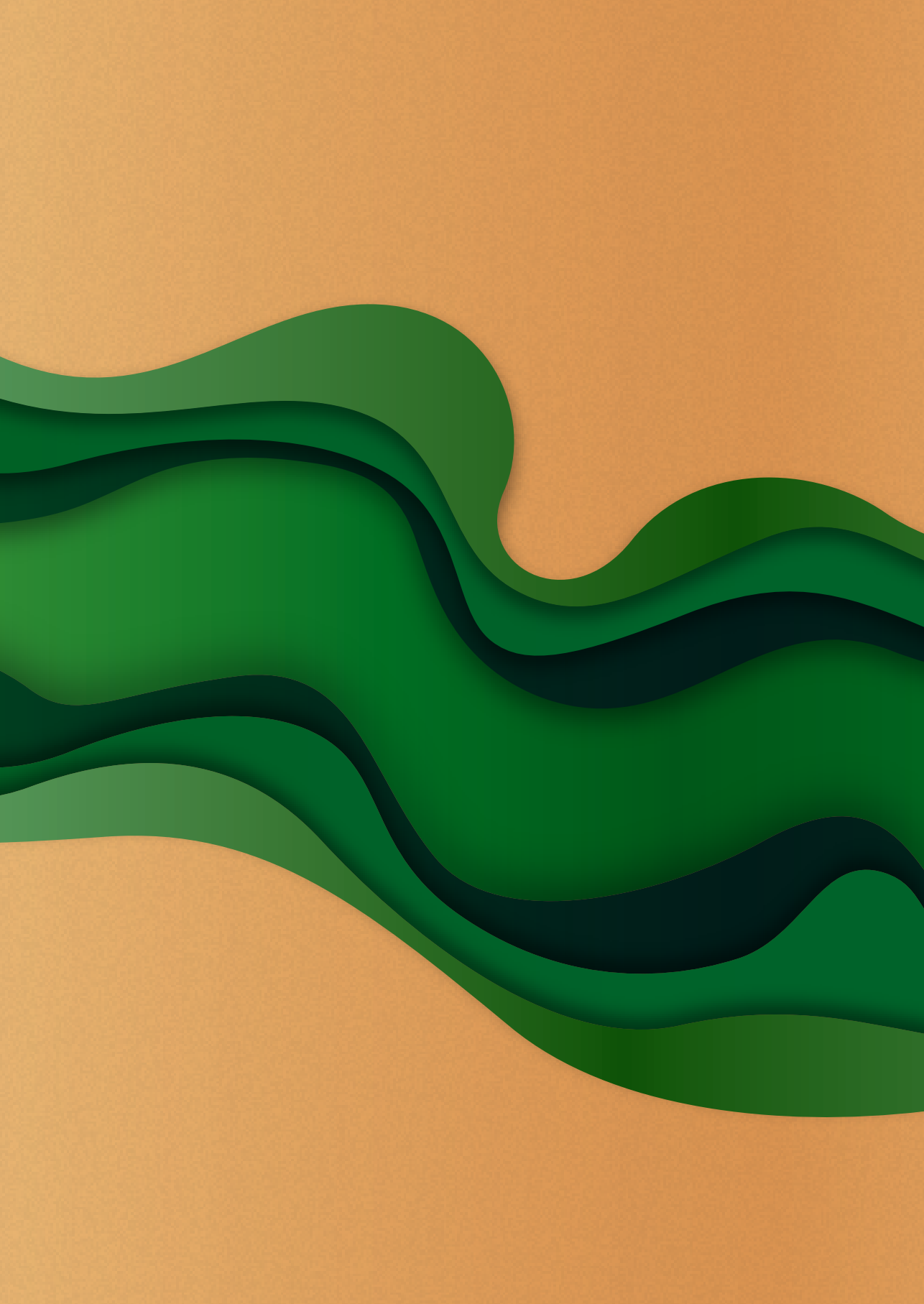
DASH quintile	events/N	Follow-up (py)	Hazard Ratio (95%CI)
Quintile 1	244/1,180	12,981	*Reference*
Quintile 2	137/595	6,453	1.05 (0.85−1.30)
Quintile 3	222/1,193	13,246	0.89 (0.74−1.07)
Quintile 4	186/799	8,903	1.11 (0.92−1.35)
Quintile 5	114/598	6,891	0.88 (0.70−1.10)



Hazard ratios for quintiles of compliance scores to the DASH-diet and risk of all-cause mortality (Figure S4a) and cardiovascular mortality (Figure S4b) estimated using multivariable-adjusted Cox Proportional Hazard models. These estimates were adjusted for age, sex, education, smoking, alcohol consumption, physical activity and creatinine levels. Inverse probability of treatment weighting was not applied in these analyses. DASH: Dietary approaches to stop hypertension, py: person year

PART II

PHYSICAL ACTIVITY FOR PATIENTS WITH ESTABLISHED CVD



CHAPTER 7

LEISURE-TIME AND OCCUPATIONAL PHYSICAL ACTIVITY AND HEALTH OUTCOMES IN CARDIOVASCULAR DISEASE

Nadia E. Bonekamp
Frank L.J. Visseren
Ynte M. Ruigrok
Maarten J.M. Cramer
Gert Jan de Borst
Anne M. May
Charlotte Koopal

on behalf of the UCC-SMART study group

Heart, 2023 Apr 12;109(9):686-694.

ABSTRACT

Objective

In healthy populations, leisure-time physical activity (LTPA) improves health outcomes, while, paradoxically, occupational physical activity (OPA) is associated with detrimental health effects. This study aimed to investigate the associations of LTPA and OPA with mortality, cardiovascular events, and type 2 diabetes (T2D) in patients with cardiovascular disease (CVD).

Methods

In 7,058 CVD outpatients (age 61 ±10 years, 75% male) from the prospective Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART) cohort, Cox models were used to quantify the associations between self-reported LTPA and OPA and all-cause mortality, cardiovascular events, and T2D.

Results

Over 8.6 years [IQR: 4.6-12.5] of follow-up, 1,088 vascular events, 1,254 deaths, and 447 incident T2D cases occurred. The top LTPA quarter had a lower risk of all-cause mortality (HR 0.63, 95%CI0.54-0.74), recurrent cardiovascular events (HR 0.72, 95%CI0.60-0.84) and incident T2D (HR 0.71, 95%CI0.55-0.93), compared to the lowest quarter. The continuous LTPA associations were reverse J-shaped for all-cause mortality and vascular events and linear for T2D. OPA (heavy manual *vs* sedentary) showed a trend towards an increased risk of all-cause mortality (HR 1.08, 95%CI0.86-1.35), cardiovascular events (HR 1.15, 95%CI0.91-1.45), and T2D (HR 1.04, 95%CI0.72-1.50). The detrimental effects of higher OPA were more pronounced in men, never-smokers, people with higher education and active employment.

Conclusions

In CVD patients, LTPA was associated with lower risk of all-cause mortality, recurrent cardiovascular events and incident T2D. In contrast, OPA seemed to increase the risk of these outcomes. These findings support the existence of a physical activity paradox in patients with CVD.

KEY MESSAGES

What is already known

In apparently healthy populations, leisure-time physical activity and occupational physical activity have opposite health effects: while leisure-time physical activity is associated with reduced risk of all-cause mortality and cardiovascular events, occupational physical activity increases these risks. This physical activity paradox may be more pronounced in patients with cardiovascular disease, due to pathophysiological changes after cardiovascular events.

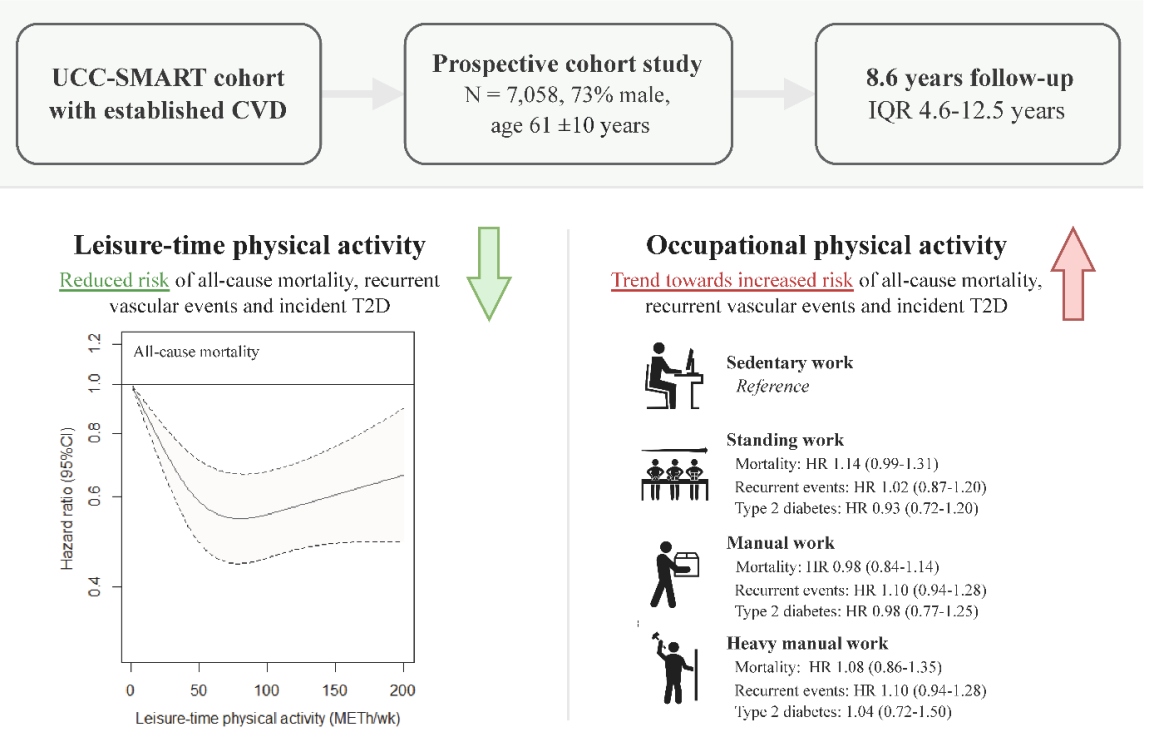
What this study adds

This study shows that leisure-time physical activity has a strong protective association with all-cause mortality (HR 0.63, 95%CI 0.54-0.74), cardiovascular events (HR 0.72, 95%C I0.60-0.84) and type 2 diabetes risk (HR 0.71, 95%CI0.55-0.93) in patients with cardiovascular disease, while physical activity at work might be associated with unfavourable health effects in this population (hazard ratios around 1.10 with 95%CI including 1.00, for the three outcomes)

How this study might affect research, practice or policy

This study shows that physical activity at work does not provide similar health benefits as leisure-time physical activity and may even have harmful effects for patients with cardiovascular disease. For clinical practice, our results indicate that physical activity at work should not be regarded as a substitute for physical activity in leisure-time.

CENTRAL FIGURE



CVD: Cardiovascular disease, IQR: interquartile range, UCC-SMART: Utrecht Cardiovascular cohort-Second Manifestations of Arterial disease, T2D: Type 2 diabetes, HR: hazard ratio, METh/wk: Metabolic equivalent of task hours per week.

INTRODUCTION

Physical activity has extensively been shown to reduce the risk of cardiovascular disease (CVD) in apparently healthy individuals[1] and is a key recommendation in guidelines for CVD prevention and treatment.[2,3] Physical activity's benefits result from reducing inflammation and improving cardiorespiratory fitness[4,5] as well as attenuation of traditional cardiovascular risk factors such as systolic blood pressure and lipid profile.[6,7]

Physical activity can be categorized into occupational physical activity (OPA), comprising all work-related activity, and leisure-time physical activity (LTPA), comprising all activity outside the workspace, such as sport and transport-related activities like walking. In apparently healthy populations, higher LTPA confers relative risk reductions for all-cause mortality (up to 35%)[8]; CVD (up to 55%)[9]; and type 2 diabetes (T2D) (up to 30%).[9,10] In contrast, increased OPA does not unequivocally show such benefits, with some studies even indicating that more physically demanding OPA increases CVD risk, especially in men.[11-14] This contradiction in the effects of LTPA and OPA has been called the physical activity paradox.[12]

LTPA and OPA may affect patients with CVD differently than patients from the general population. LTPA is commonly regarded as beneficial for atherosclerotic plaque stability, but OPA has been associated with an increased rate of plaque progression.[15,16] Evidence from subgroup analyses of observational studies indicates that LTPA reduces CVD and all-cause mortality risk in patients with a history of CVD.[17,18] On the other hand, CVD subgroups in observational studies on OPA show that physically demanding OPA might be associated with an increased risk of cardiovascular events and mortality and even show that higher LTPA could have a detrimental effect in CVD patients with physically demanding OPA.[16]

In this study, we investigated the associations between LTPA and OPA and risk of all-cause mortality, recurrent cardiovascular events, and incident T2D in patients with a history of CVD.

METHODS

Study population

Data were used from the Utrecht Cardiovascular Cohort - Secondary Manifestations of Arterial Disease (UCC-SMART) study, an ongoing single-center prospective cohort comprising patients aged 18 to 79 years with cardiovascular risk factors or established CVD.[19] The UCC-SMART study was approved by the local Medical Ethics Committee (reference number 22-088) and all participants gave written informed consent. For the current study, data was used from 7,058 patients, included in the cohort between January 2002 and December 2019 with established coronary artery disease, peripheral artery disease (PAD), or cerebrovascular disease (CeVD) at inclusion in the cohort. Analyses on T2D incidence were limited to participants without T2D at baseline (N = 5,765, Figure S1).

Baseline measurements

Upon inclusion in the UCC-SMART cohort, participants completed a standardized questionnaire on medical history, cardiovascular risk factors and medication use. Patients underwent physical examination and laboratory measurements were performed.

LTPA and OPA were self-reported in the baseline questionnaire. LTPA was defined as activity from sports, walking, cycling and gardening and was assessed using validated ranking physical activity questionnaire[20] with an additional question on sport activity. LTPA was expressed as Metabolic Equivalent of Task hours per week (METh/wk). METh/wk combines intensity and duration of the activity by multiplying the reported weekly hours of physical activity with activity-specific MET intensity obtained from the Compendium of Physical Activity.[21] To exemplify: a participant who walks (estimated at 3.5 MET) 2 hours per week would perform (2 x 3.5 =) 7.0 METh/week. OPA was quantified using a question with four intensity levels that assessed the physical activity intensity during participants' last active employment. These four levels were: predominantly sedentary work, standing work, manual work and heavy manual work.

Clinical outcomes

Participants were sent biannual follow-up questionnaires on vital status and the occurrence of cardiovascular events. When participants reported an event, additional information was obtained from the treating physician or hospital. The endpoint

classification was made independently by three physicians in accordance with previously published definitions.[19]

The primary outcomes were all-cause mortality, recurrent cardiovascular events, and incident T2D. Recurrent cardiovascular events were a composite of non-fatal myocardial infarction (MI), non-fatal stroke and cardiovascular mortality. The individual components of the vascular composite endpoint were assessed as secondary endpoints.

Data analyses

Baseline characteristics were reported stratified for quarters of the LTPA distribution and OPA categories. Categorical variables were presented as frequencies with percentages and continuous variables as means with standard deviation or medians with interquartile range (IQR). Multivariable adjusted Cox models with time-on-study as time-scale were used to estimate the associations for LTPA and OPA. Patients that were lost to follow-up (N = 446, 6%) were censored on the last day their status was known. The proportional hazard assumption was checked by visual inspection of Schoenfeld residuals. Model 1 adjusted for age and sex. Model 2 adjusted for model 1, smoking status, number of pack years and alcohol use. Model 3, the main model, additionally adjusted for education level and employment status. In model 4, further adjustments were made for variables that could be either confounders or intermediates: T2D, body mass index (BMI), systolic blood pressure and low-density lipoprotein cholesterol (LDL-C). The models for LTPA and OPA were not mutually adjusted for each other. The associations of LTPA as a continuous variable were assessed using restricted cubic splines with three knots in Cox models adjusted for the covariates in model 3.

Interplay between LTPA and OPA was assessed by comparing the effect of different combinations of LTPA and OPA against a common reference (*i.e.* LTPA quarter 1 and sedentary OPA). Sex, age, education, employment status, type of pre-existing CVD, presence of metabolic syndrome, BMI, systolic blood pressure and LDL-C levels were assessed as potential effect modifiers. Effect modification was tested by introducing multiplicative interaction terms into the Cox models. Bonferroni correction was used to account for multiple testing. Subgroup analyses based on strata of sex, smoking status and employment status were run. To assess the impact of reverse causation, the primary analyses were repeated with removal of the first 1, 3 and 5 years of follow-up.

Missing data on LTPA (1%), OPA (7%), education (33%), metabolic syndrome (1%), smoking status (1%), alcohol consumption (1%) and LDL-C levels (7%) were imputed with single imputation using predictive mean matching. A complete-case analysis was run to assess the robustness of the imputation. All statistical analyses were performed using R statistical software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The central figure summarizes the study design and key findings.

Baseline characteristics

Patients with higher levels of LTPA were more frequently men (top *vs* lowest LTPA quarter, 77% *vs* 69%), more often had a history of coronary artery disease (68% *vs* 60%), were less likely to smoke (24% *vs* 35%) and reported more physically demanding OPA (35% (heavy) manual OPA *vs* 28%, Table 1). Patients with more physically demanding OPA had lower education levels, were more frequently smokers and had a higher BMI (Table S1). Participants with active employment were younger than those who were not actively employed, but otherwise had similar distributions of baseline characteristics.

TABLE 1 Baseline characteristics stratified for LTPA

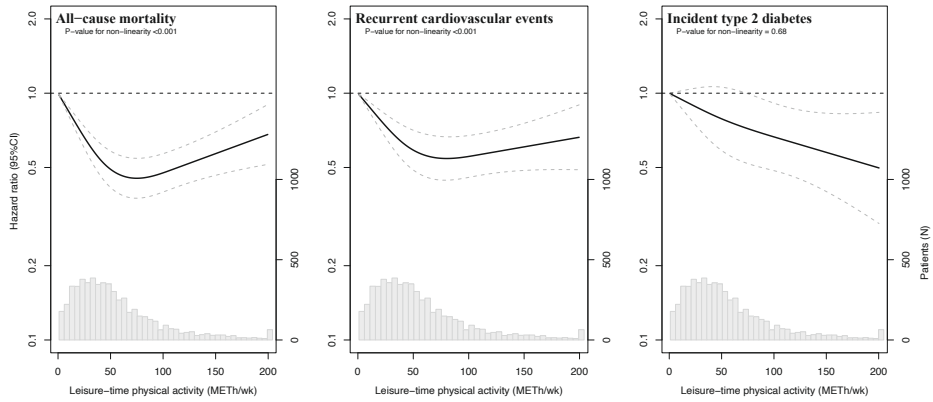
		Leisure-time physical activity level			
		Quarter 1	**Quarter 2**	**Quarter 3**	**Quarter 4**
	Overall	0-24 METh/wk	24-43 METh/wk	43-71 METh/wk	71-356 METh/wk
Characteristic	*N = 7058*	*N = 1765*	*N = 1767*	*N = 1763*	*N = 1763*
Male sex	5144 (73)	1214 (69)	1268 (72)	1299 (74)	1363 (77)
Age (years)	61 ±10	60 ±11	60 ±10	60 ±10	61 ±10
Occupational physical activity					
Sedentary	3558 (50)	914 (52)	979 (55)	940 (53)	725 (41)
Standing	1449 (21)	345 (20)	346 (20)	356 (20)	402 (23)
Manual work	1605 (23)	394 (22)	364 (21)	377 (21)	470 (27)
Heavy manual work	446 (6)	112 (6)	78 (4)	90 (5)	166 (9)
Education					
Low	1927 (27)	551 (31)	450 (26)	445 (25)	481 (27)
Middle	3008 (43)	761 (43)	726 (41)	730 (41)	791 (45)
High	2123 (30)	453 (26)	591 (33)	588 (33)	491 (28)
History of CAD	4551 (65)	1062 (60)	1124 (64)	1167 (66)	1198 (68)
History of CeVD	2053 (29)	544 (31)	552 (31)	477 (27)	480 (27)
History of PAD	1003 (14)	342 (19)	251 (14)	214 (12)	196 (11)
History of AAA	481 (7)	154 (9)	114 (7)	97 (6)	116 (7)
Multiple types of pre-existing CVD	923 (13)	303 (17)	244 (14)	171 (10)	205 (12)
Diabetes mellitus	1210 (17)	389 (22)	323 (18)	247 (14)	251 (14)
Metabolic syndrome	3624 (51)	1066 (60)	906 (51)	828 (47)	824 (47)

TABLE 1 (Continued)

		Leisure-time physical activity level			
		Quarter 1	**Quarter 2**	**Quarter 3**	**Quarter 4**
	Overall	0-24 METh/wk	24-43 METh/wk	43-71 METh/wk	71-356 METh/wk
Characteristic	*N = 7058*	*N = 1765*	*N = 1767*	*N = 1763*	*N = 1763*
Current smoking	1921 (27)	618 (35)	468 (27)	411 (23)	424 (24)
Alcohol consumption	5111 (72)	1118 (63)	1336 (76)	1344 (76)	1313 (75)
Body mass index (kg/m2)	27.1 ±4.2	27.7 ±4.5	27 ±4.4	26.8 ±3.9	26.8 ±3.8
<25 kg/m2	2274 (32)	481 (27)	576 (33)	613 (35)	604 (34)
25-30 kg/m2	3313 (47)	800 (45)	837 (47)	832 (47)	844 (48)
>30 kg/m2	1471 (21)	484 (27)	354 (20)	318 (18)	315 (18)
Systolic blood pressure (mmHg)	138 ±20	139 ±21	138 ±21	137 ±19	138 ±19
Total cholesterol (mmol/l)	4.4 [3.8-5.2]	4.5 [3.8-5.3]	4.4 [3.7-5.1]	4.3 [3.7-5.2]	4.4 [3.8-5.2]
LDL cholesterol (mmol/l)	2.5 [1.9-3.1]	2.5 [1.9-3.1]	2.4 [1.9-3.1]	2.4 [1.9-3.1]	2.5 [2.0-3.1]
HDL cholesterol (mmol/l)	1.2 [1.0-1.5]	1.2 [1.0-1.4]	1.2 [1.0-1.5]	1.2 [1.0-1.5]	1.2 [1.0-1.5]
Antihypertensive medication	5495 (78)	1382 (78)	1367 (77)	1380 (78)	1366 (78)
Lipid-lowering treatment	5501 (78)	1313 (74)	1379 (78)	1433 (81)	1376 (78)

Data are presented as number (%), mean ±standard deviation or median [interquartile range] as appropriate. Abbreviations: METh/wk: Metabolic equivalent of task hours per week, CAD: coronary artery disease, CeVD: cerebrovascular disease, PAD: peripheral artery disease, AAA: abdominal aortic aneurysm, CVD: Cardiovascular disease, LDL: low density lipoprotein, HDL: high density lipoprotein.

FIGURE 1 Continuous association between leisure-time physical activity and risk of all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes



Associations between continuous leisure-time physical and all-cause mortality (A), recurrent vascular events (B), and incident type 2 diabetes (C). Hazard ratios are adjusted for age, sex, smoking status, pack years, alcohol consumption, education and current employment (model 3). The histograms inside the figures represent the number of study participants that achieved a certain leisure-time physical activity level. METh/wk: Metabolic equivalent of task hours per week. 95%CI: 95% confidence interval

Association between leisure-time physical activity and risk of all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes

Over a follow-up of 8.6 years [IQR: 4.6-12.5 years], 1,254 patients (18%) died and 1,088 patients (15%) experienced a recurrent cardiovascular event. Incident T2D was diagnosed in 447 participants (8%). For all-cause mortality and recurrent cardiovascular events, LTPA showed a reverse J-shaped association and the association with incident T2D risk was approximately linear (Figure 1). Compared to the lowest LTPA quarter, participants in the highest quarter had a lower risk of all-cause mortality (HR 0.63, 95%CI 0.54-0.74), recurrent cardiovascular events (HR 0.72, 95%CI 0.60-0.84) and incident T2D (HR 0.72, 95%CI 0.55-0.93, Table 2). The decreased risk of recurrent cardiovascular events was driven by cardiovascular mortality (HR 0.54, 95%CI 0.42-0.69, LTPA Q4 vs Q1) and non-fatal stroke (HR 0.87, 95%CI 0.64-1.17, Figure S2/Table S2). LTPA was associated with a slightly increased risk of non-fatal MI (HR 1.06 95%CI 0.91-1.24, Figure S2/Table S2).

TABLE 2 Association between leisure-time physical activity and all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes

	Leisure-time physical activity level, HR (95%CI)			
	Quarter 1	**Quarter 2**	**Quarter 3**	**Quarter 4**
All-cause mortality				
Events/N total	434/1,746	434/1,740	255/1,732	262/1,739
Follow-up (py)	15,007	15,392	15,218	15,214
Model 1	*Reference*	0.66 (0.57-0.77)	0.55 (0.47-0.65)	0.55 (0.47-0.65)
Model 2	*Reference*	0.73 (0.63-0.85)	0.63 (0.54-0.73)	0.64 (0.54-0.73)
Model 3	*Reference*	0.73 (0.63-0.85)	0.63 (0.54-0.74)	0.63 (0.54-0.74)
Model 4	*Reference*	0.74 (0.64-0.86)	0.65 (0.55-0.76)	0.66 (0.56-0.77)
Recurrent vascular events				
Events/N total	342/1,746	342/1,740	221/1,732	244/1,739
Follow-up (py)	14,023	14,427	14,455	14,356
Model 1	*Reference*	0.78 (0.67-0.91)	0.60 (0.51-0.71)	0.65 (0.55-0.77)
Model 2	*Reference*	0.84 (0.72-0.99)	0.67 (0.56-0.79)	0.72 (0.61-0.84)
Model 3	*Reference*	0.85 (0.72-0.99)	0.67 (0.56-0.79)	0.72 (0.60-0.84)
Model 4	*Reference*	0.86 (0.74-1.01)	0.69 (0.58-0.82)	0.74 (0.62-0.87)
Type 2 diabetes				
Events/N total	139/1,447	139/1,445	106/1,437	93/1,436
Follow-up (py)	11,894	12,046	11,815	11,921
Model 1	*Reference*	0.77 (0.60-0.98)	0.76 (0.58-0.97)	0.65 (0.50-0.84)
Model 2	*Reference*	0.84 (0.65-1.09)	0.85 (0.66-1.10)	0.72 (0.55-0.94)
Model 3	*Reference*	0.86 (0.67-1.11)	0.86 (0.66-1.11)	0.71 (0.55-0.93)
Model 4	*Reference*	0.91 (0.71-1.18)	0.96 (0.74-1.25)	0.79 (0.61-1.04)

Multivariable adjusted hazard ratios and 95% confidence intervals. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for: smoking, packyears, alcohol use. Model 3 additionally adjusted for education level and current employment. Model 4 was adjusted for model 3 and history of T2D, body mass index, systolic blood pressure and low-density lipoprotein cholesterol. Abbreviations: Py: Person years. Model 3 was used as the main outcome.

Association between occupational physical activity and risk of all-cause mortality, recurrent cardiovascular events and incident type 2 diabetes

For all-cause mortality and recurrent cardiovascular events, there was an increased risk in the groups with higher OPA (HR 1.08, 95%CI 0.86-1.35 and HR 1.15, 95%CI 0.91-1.45 respectively, heavy manual *vs* sedentary, Table 3). Standing work conferred an increased risk of all-cause mortality (HR 1.14, 95%0.99-1.31 *vs* sedentary) and manual

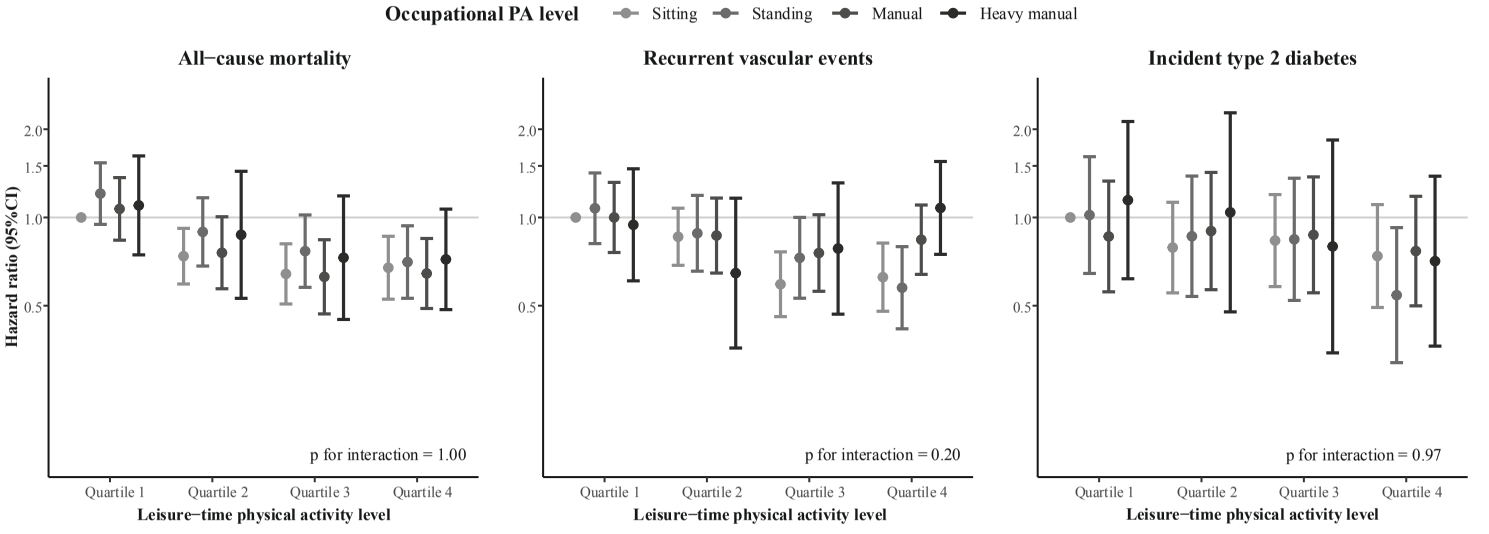
work conferred an increased risk of recurrent cardiovascular events (HR 1.10, 95%CI 0.94-1.28 *vs* sedentary). Heavy manual work was associated with a higher non-fatal stroke risk (HR 1.66, 95%CI 1.10-2.50 *vs* sedentary, Table S2). OPA was not associated with incident T2D (Table 3).

TABLE 3 Association between occupational physical activity and all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes

	Occupational physical activity level, HR (95%CI)			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Events/N total	540/3,558	307/1,449	313/1,605	94/446
Follow-up (py)	29,482	12,713	14,804	3,831
Model 1	Reference	1.21 (1.05-1.39)	1.07 (0.92-1.24)	1.20 (0.97-1.50)
Model 2	Reference	1.16 (1.01-1.34)	0.99 (0.86-1.16)	1.12 (0.90-1.40)
Model 3	Reference	1.14 (0.99-1.31)	0.98 (0.84-1.14)	1.08 (0.86-1.35)
Model 4	Reference	1.13 (0.98-1.30)	0.97 (0.83-1.12)	1.09 (0.87-1.36)
Recurrent vascular events				
Events/N total	486/3,558	231/1,449	284/1,605	87/446
Follow-up (py)	27,980	11,969	13,806	3,506
Model 1	Reference	1.10 (0.94-1.29)	1.22 (1.05-1.43)	1.34 (1.07-1.68)
Model 2	Reference	1.04 (0.89-1.22)	1.13 (0.96-1.32)	1.21 (0.96-1.53)
Model 3	Reference	1.02 (0.87-1.20)	1.10 (0.94-1.28)	1.15 (0.91-1.45)
Model 4	Reference	1.01 (0.86-1.18)	1.08 (0.92-1.26)	1.15 (0.91-1.46)
Type 2 diabetes				
Events/N total	214/2,948	87/1163	111/1287	35/367
Follow-up (py)	23,514	9747	11411	3004
Model 1	Reference	1.01 (0.79-1.31)	1.14 (0.90-1.44)	1.25 (0.87-1.79)
Model 2	Reference	0.97 (0.76-1.25)	1.06 (0.84-1.35)	1.15 (0.81-1.66)
Model 3	Reference	0.93 (0.72-1.20)	0.98 (0.77-1.25)	1.04 (0.72-1.50)
Model 4	Reference	0.92 (0.71-1.18)	0.97 (0.76-1.25)	0.91 (0.63-1.32)

Multivariable adjusted hazard ratios and 95% confidence intervals. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for: smoking, packyears, alcohol use. Model 3 additionally adjusted for education level and current employment. Model 4 was adjusted for model 3 and history of T2D, body mass index, systolic blood pressure and low-density lipoprotein cholesterol. Abbreviations: Py: Person years. Model 3 was used as the main outcome.

FIGURE 2 Interaction between leisure-time and occupational physical activity on the risk of all-cause mortality recurrent vascular events, and incident type 2 diabetes.



Hazard ratios assessing the interaction between LTPA and OPA level in the association with all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. These figures show the hazard ratios for each combination of leisure-time and OPA level with the least active (quarter 1 leisure-time and sedentary OPA) as reference category. Models were adjusted for age, sex, smoking, pack years, alcohol consumption, education and current employment (model 3). Numeric values for the presented hazard ratios are included in Table S3. PA level: physical activity level, 95%CI: 95% confidence interval

Effect modification

Figure 2 shows the interaction between LTPA and OPA. For all-cause mortality and T2D, higher levels of LTPA were associated with a lower risk regardless of OPA level. For recurrent cardiovascular events, the protective association of LTPA was not present in participants with (heavy) manual work. When looking at the different components of recurrent vascular events, this effect modification of (heavy) manual OPA on LTPA was most pronounced in the associations with non-fatal MI and stroke (Figure S3).

Figure 3 shows the associations between LTPA and OPA across strata of potential effect modifiers. LTPA was strongly associated with risk reductions in patients with multiple CVD types and PAD, but had smaller effects in patients with a history of coronary disease, CeVD or abdominal aortic aneurysm. Across age strata, the association between LTPA and recurrent vascular events was stronger for patients aged 60 or older.

The associations of OPA with all-cause mortality and recurrent events differed across sex-strata, with a protective association of heavy manual OPA in women and a detrimental effect in men (Figure 3A/B). Similarly, the associations differed across strata of pre-existing CVD type: protective associations were found for people with PAD and harmful associations were found for people with CeVD. For patients with multiple CVD manifestations, higher OPA was associated with reduced risk of recurrent cardiovascular events, HR 0.58 (95%CI 0.33-1.00), while there was no association for patients with a single CVD type. The associations for OPA were stronger for people with a higher education level, with a recurrent events HR of 1.48 (95%CI 0.52-4.23) for heavy manual work in highly educated participants compared to a HR of 1.10 (95%CI 0.88-1.88) in participants with a lower education.

Subgroup and sensitivity analyses

In never-smokers, higher LTPA was associated with a lower risk of all-cause mortality and recurrent cardiovascular events compared to the full population, with HR 0.56 (95%CI0.38-0.83) for all-cause mortality and HR 0.45 (95%CI0.29-0.71) for recurrent vascular events (Table S4). Conversely, OPA seemed to be associated with increased risk of the primary outcomes in never-smokers (*e.g.* incident T2D HR 1.87, 95%CI 1.04-3.37 for manual vs. sedentary OPA).

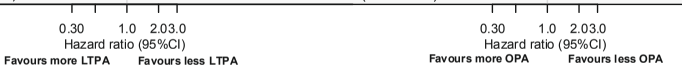
FIGURE 3 Potential effect modifiers in the association between leisure-time and occupational physical activity and clinical endpoints.

FIGURE 3a Effect modification in association with all-cause mortality

			Leisure-time physical activity *Q4 vs. Q1*		Occupational physical activity *heavy manual vs. sitting*	
Variable	**events/N**	**Follow-up (persyr)**	**HR (95%CI)**	**P for interaction**	**HR (95%CI)**	**P for interaction**
All	1,254/7,058	60,831	0.63 (0.54−0.74)		1.08 (0.86−1.35)	
Sex						
Female	302/1,914	16,851	0.66 (0.47−0.93)	0.03	0.66 (0.24−1.81)	0.08
Male	952/5,144	43,979	0.63 (0.53−0.75)		1.10 (0.87−1.39)	
Age						
<60 years	307/3,191	29,984	0.64 (0.46−0.89)	0.46	0.85 (0.53−1.38)	0.71
=60 years	947/3,867	30,847	0.64 (0.53−0.77)		1.14 (0.88−1.47)	
Education level						
Low	454/1,927	17,519	0.68 (0.52−0.88)	0.79	1.03 (0.73−1.46)	0.22
Middle	526/3,008	26,904	0.59 (0.46−0.74)		1.10 (0.79−1.52)	
High	274/2,123	16,407	0.65 (0.46−0.92)		1.89 (0.87−4.07)	
Occupation status						
Not working	904/3,580	30,155	0.62 (0.51−0.74)	<0.01	1.07 (0.83−1.39)	<0.01
Working	350/3,478	30,676	0.67 (0.50−0.90)		1.04 (0.66−1.62)	
Type of pre−existing CVD						
CAD	529/3,788	32,849	0.82 (0.64−1.04)	0.34	0.92 (0.65−1.32)	0.68
CeVD	223/1,542	13,530	0.80 (0.55−1.15)		1.68 (0.93−3.06)	
PAD	144/618	5,731	0.58 (0.35−0.96)		1.17 (0.59−2.32)	
AAA	57/187	1,566	0.90 (0.41−1.97)		1.23 (0.33−4.52)	
Multiple	301/923	7,154	0.47 (0.33−0.67)		0.94 (0.63−1.41)	
Metabolic syndrome						
No MetS	537/3,434	30,456	0.66 (0.52−0.84)	0.80	1.14 (0.80−1.63)	0.78
MetS	717/3,624	30,375	0.65 (0.53−0.80)		1.02 (0.76−1.36)	
BMI						
<25 kg/m2	426/2,274	19,618	0.57 (0.43−0.76)	0.03	1.41 (0.92−2.17)	0.01
25−30 kg/m2	550/3,313	28,876	0.69 (0.55−0.88)		0.92 (0.65−1.30)	
=30 kg/m2	278/1,471	12,336	0.63 (0.45−0.88)		1.04 (0.68−1.59)	
Systolic blood pressure						
< 140 mmHg	563/4,086	33,976	0.62 (0.49−0.78)	0.94	1.02 (0.74−1.42)	0.08
=140 mmHg	691/2,972	26,855	0.66 (0.53−0.81)		1.13 (0.83−1.54)	
LDL cholesterol						
< 3.0 mmol/l	850/5,063	42,719	0.64 (0.53−0.77)	0.40	0.98 (0.74−1.31)	0.19
=3.0 mmol/l	404/1,995	18,112	0.63 (0.47−0.83)		1.30 (0.90−1.87)	

FIGURE 3b Effect modification in association with recurrent cardiovascular events

Variable	events/N	Follow-up (persyr)	Leisure-time physical activity *Q4 vs. Q1* HR (95%CI)	P for interaction	Occupational physical activity *heavy manual vs. sitting* HR (95%CI)	P for interaction
All	1,088/7,058	57,262	0.71 (0.60−0.84)		1.15 (0.91−1.45)	
Sex						
Female	238/1,914	16,017	0.69 (0.47−1.01)	<0.01	0.78 (0.28−2.15)	<0.01
Male	850/5,144	41,244	0.74 (0.61−0.89)		1.20 (0.94−1.53)	
Age						
<60 years	377/3,191	28,273	0.85 (0.64−1.13)	0.14	1.29 (0.88−1.88)	0.53
=60 years	711/3,867	28,989	0.67 (0.54−0.82)		1.03 (0.76−1.39)	
Education level						
Low	375/1,927	16,237	0.70 (0.53−0.93)	0.30	0.78 (0.52−1.18)	0.03
Middle	472/3,008	25,341	0.73 (0.57−0.94)		1.42 (1.04−1.95)	
High	241/2,123	15,683	0.72 (0.50−1.06)		2.38 (1.10−5.16)	
Occupation status						
Not working	675/3,580	28,102	0.68 (0.55−0.84)	0.01	0.97 (0.72−1.32)	0.03
Working	413/3,478	29,159	0.80 (0.60−1.05)		1.50 (1.04−2.17)	
Type of pre−existing CVD						
CAD	532/3,788	30,992	0.84 (0.66−1.07)	0.08	1.27 (0.92−1.75)	<0.01
CeVD	180/1,542	12,849	0.73 (0.49−1.09)		2.43 (1.40−4.21)	
PAD	87/618	5,447	0.48 (0.25−0.93)		0.71 (0.25−2.06)	
AAA	41/187	1,470	0.58 (0.22−1.52)		2.19 (0.54−8.92)	
Multiple	248/923	6,503	0.74 (0.52−1.05)		0.58 (0.33−1.00)	
Metabolic syndrome						
No MetS	463/3,434	28,923	0.73 (0.56−0.94)	0.45	1.25 (0.86−1.83)	0.66
MetS	625/3,624	28,338	0.74 (0.60−0.92)		1.06 (0.78−1.43)	
BMI						
<25 kg/m2	325/2,274	18,648	0.83 (0.60−1.13)	0.36	1.17 (0.69−1.98)	0.10
25−30 kg/m2	525/3,313	27,042	0.66 (0.52−0.84)		1.37 (0.99−1.89)	
=30 kg/m2	238/1,471	11,571	0.76 (0.54−1.07)		0.75 (0.47−1.18)	
Systolic blood pressure						
< 140 mmHg	529/4,086	32,162	0.75 (0.59−0.95)	0.96	1.07 (0.77−1.50)	0.10
=140 mmHg	559/2,972	25,099	0.68 (0.54−0.86)		1.23 (0.89−1.71)	
LDL cholesterol						
< 3.0 mmol/l	746/5,063	40,286	0.75 (0.61−0.91)	0.03	1.08 (0.81−1.44)	0.58
=3.0 mmol/l	342/1,995	16,976	0.63 (0.46−0.87)		1.34 (0.90−2.00)	



← Association between the highest vs. lowest quarter of LTPA and heavy manual OPA vs. sedentary OPA and all-cause mortality and recurrent cardiovascular events, stratified for potential effect modifiers. Hazard ratios are adjusted for age, sex, smoking status, pack years, alcohol consumption, education and active employment (model 3). After Bonferroni correction for multiple testing a p-value <0.001 (<0.05/36 tests) was considered statistically significant. HR: hazard ratio, 95%CI: 95% confidence interval, CVD: cardiovascular disease, CAD: coronary artery disease, CeVD: cerebrovascular disease, PAD: peripheral artery disease, AAA: abdominal aortic aneurysm, BMI: body mass index, LDL: low-density lipoprotein.

In actively employed participants (N=3,478), OPA was more strongly associated with detrimental health effects compared to unemployed or retired participants, especially for recurrent vascular events (HR 1.30, 95%CI 1.01-1.67 for heavy manual *vs* sedentary, Table S5). The harmful health effects of OPA were more pronounced in men (Tables S6a-d).

To address potential reverse causality, sensitivity analyses were performed excluding participants who experienced an outcome within 1, 3 or 5 years after inclusion and the results were similar in size and direction to main analysis (Figure S4). A complete-case analysis resulted in associations that were similar in size and direction to the main analysis (data not shown).

DISCUSSION

In patients with established CVD, higher levels of LTPA were associated with a lower risk of all-cause mortality, recurrent cardiovascular events and incident T2D. In contrast, OPA, especially standing and manual work, was associated with an increased risk of all-cause mortality and recurrent cardiovascular events, notably in men, actively employed participants, patients with a history of CeVD and non-smokers. Furthermore, the beneficial effects of LTPA were attenuated in patients with (heavy) manual work. These findings suggest that the physical activity paradox also manifests in patients with established CVD.

The health benefits of increasing LTPA are widely accepted in healthy populations and supported by multiple prospective cohort studies.[8-10] In patients with established CVD, studies show that people with the highest LTPA level have up to 50% lower risk of all-cause mortality and 35% lower risk of recurrent CVD events which is in line with the findings in our study.[17,18] In the present study, the association between LTPA

and cardiovascular and mortality risk had a reverse J-shape, meaning that a level of LTPA exists beyond which additional activity no longer confers further risk reduction. This finding is in line with previous studies in apparently healthy populations[8] and with findings in two cohorts of patients with CVD.[17,18] Potential explanations for the plateauing and even reversal of the beneficial effects of LTPA at higher levels include atherosclerotic plaque rupture during vigorous exercise or triggering of arrhythmias in scarred myocardial tissue.[22,23]

Interestingly, LTPA was protective of cardiovascular mortality and non-fatal stroke but was associated with an increase in non-fatal MI risk. A potential explanation for these contrasting associations is that LTPA does not reduce the number of events, but prevents events from being fatal by limiting the ischemic damage incurred to heart muscle. Mechanisms for this process include improved blood flow, vasodilation and angiogenesis in coronary arteries.[24,25] These adaptations could reduce infarct size and infarction-reperfusion injury after a recurrent cardiovascular event.

The associations of LTPA and OPA with T2D have not extensively been studied in a CVD populations, but in apparently healthy populations, a linear association with LTPA was observed.[10] Potential explanations for the protective effect of LTPA on T2D, include weight loss and increased insulin sensitivity through upregulation of GLUT4 transporters in skeletal muscles.[10,26] In the present study, OPA was not associated with T2D risk. Possible explanations for this lack of effect include that OPA is associated with other lifestyle factors that increase the risk of T2D (*e.g.* unhealthy diet) or that the low-intensity, repetitive character of OPA puts less strain on skeletal muscles and therefore does not result in upregulation of GLUT-4.

In apparently healthy populations, higher OPA levels have been associated with up to 50% increased risk of mortality and CVD.[12] In the present study, higher OPA levels were associated with risk increases of approximately 10%, which is in line with previous evidence from exploratory analyses in CVD subgroups.[16] A possible explanation for this difference in effect size could be that UCC-SMART participants with CVD were around retirement age while OPA conferred stronger harmful effects in a subgroup of actively employed participants. Furthermore, the results could have been affected by index-event bias.

Although standing work is commonly thought of as health-promoting, this idea might not hold for patients with established CVD.[27] Our results showed that standing OPA was associated with increased risk of all-cause and cardiovascular mortality and non-fatal stroke. The hemodynamic effects of prolonged standing may lead to blood pooling in the extremities, increased pulse pressure and vascular turbulence, ultimately increasing risk of cardiovascular, specifically cerebrovascular, events.[15]

An explanation for the contrasting health effects of LTPA and OPA should be sought in the differing characteristics of the physical activity types.[28] LTPA usually has a higher intensity and shorter duration, while OPA requires low-intensity repetitive movements with short recovery times. Therefore, it has been hypothesized that OPA does not lead to the cardiovascular benefits and improved cardiorespiratory fitness that can be achieved with LTPA and instead has unhealthy effects, such as increased 24-hour heart rate, systolic blood pressure and systemic inflammation.[28]

Another explanation for the finding that OPA does not improve health outcomes, might be residual confounding. Manual work is associated with heavier smoking habits and unhealthy diet. Furthermore, people with manual work have has a higher chance of exposure to toxic environmental factors and more frequently do shift work which is independently associated with increased CVD risk.[29] In the current analyses, attempts were made to account for socioeconomic status by adjusting for education level, and the estimated HR decreased slightly toward the null. In studies with more extensive adjustment for socioeconomic factors, the detrimental health effects of OPA were still upheld.[12] In never-smokers, the detrimental associations of OPA were also found, indicating that residual confounding from smoking status did not bias the main findings. Ultimately, it is difficult to disentangle the effect of OPA itself from the effects of other (lifestyle) factors that often accompany it. Further research is needed to better understand the effects of physically demanding work so specific OPA recommendations can be implemented in guidelines.

Strengths of our study include its size, prospective design, comprehensive data collection and low rate of loss-to-follow-up. Study limitations include that OPA level was assessed at baseline only, while the majority of the study population was no longer actively employed at that time. This may have diluted the overall effect estimates for OPA, as a sensitivity analysis in actively employed patients yielded stronger associations. Moreover, the physical activity questionnaire was only validated for

ranking participants from lowest to highest LTPA level and, therefore, it was impossible to estimate an optimal LTPA level. Furthermore, LTPA and OPA were based on self-reporting, which may lead to optimistic estimates due to social desirability bias. There is, however, no reason to assume the extent of over-reporting differs between low and high levels of LTPA, which means that ranking of individuals will remain unaffected. OPA estimates may have been biased by a healthy workers effect, an important form of selection bias in occupational epidemiology research, because unhealthy people are more likely to switch to less physically demanding occupations.[30] As a result, the associations for the more physically demanding OPA categories could have been biased towards the null.

In conclusion, in patients with established CVD, higher LTPA was associated with a lower risk of all-cause mortality, recurrent cardiovascular events and incident T2D, but this relationship was not observed for higher OPA levels. These findings support the existence of a *physical activity paradox* in patients with established CVD, because they show that while LTPA is beneficial, physically demanding OPA may have harmful effects. Health care providers should be aware of these potentially harmful effects of OPA and OPA should therefore not be regarded as a substitute for LTPA.

REFERENCES

1 Bull FC, Al-Ansari SS, Biddle S, *et al.* World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54:1451–62. doi:10.1136/bjsports-2020-102955

2 Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;:1–111. doi:10.1093/eurheartj/ehab484

3 Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140:e596–646. doi:10.1161/CIR.0000000000000678

4 Cerqueira É, Marinho DA, Neiva HP, et al. Inflammatory Effects of High and Moderate Intensity Exercise—A Systematic Review. Front Physiol 2020;10:1–14. doi:10.3389/fphys.2019.01550

5 Pinckard K, Baskin KK, Stanford KI. Effects of Exercise to Improve Cardiovascular Health. Front Cardiovasc Med 2019;6:1–12. doi:10.3389/fcvm.2019.00069

6 Whelton SP, Chin A, Xin X, et al. Effect of Aerobic Exercise on Blood Pressure. Ann Intern Med 2002;136:493. doi:10.7326/0003-4819-136-7-200204020-00006

7 Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. Lipids Health Dis 2017;16:132. doi:10.1186/s12944-017-0515-5

8 Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality : systematic review and harmonised meta-analysis. Br Med J 2019;366:14570. doi:10.1136/bmj.l4570

9 Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: Systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. Br Med J 2016;354:i3857. doi:10.1136/bmj.i3857

10 Aune D, Norat T, Leitzmann M, et al. Physical activity and the risk of type 2 diabetes: A systematic review and dose-response meta-analysis. Eur J Epidemiol 2015;30:529–42. doi:10.1007/s10654-015-0056-z

11 Cillekens B, Lang M, van Mechelen W, et al. How does occupational physical activity influence health? An umbrella review of 23 health outcomes across 158 observational studies. Br J Sports Med 2020;54:1474–81. doi:10.1136/bjsports-2020-102587

12 Holtermann A, Schnohr P, Nordestgaard BG, et al. The physical activity paradox in cardiovascular disease and all-cause mortality: The contemporary Copenhagen General Population Study with 104 046 adults. Eur Heart J 2021;42:1499–511. doi:10.1093/eurheartj/ehab087

13 Martinez Gomez D, Coenen P, Celis-Morales C, et al. Lifetime high occupational physical activity and total and cause-specific mortality among 320 000 adults in the NIH-AARP study: a cohort study. Occup Environ Med 2021;:oemed-2021-107393. doi:10.1136/oemed-2021-107393

14 Coenen P, Huysmans MA, Holtermann A, et al. Do highly physically active workers die early ? A systematic review with meta-analysis of data from 193 696 participants. Br J Sports Med 2018;52:1320–6. doi:10.1136/bjsports-2017-098540

15 Krause N, Lynch J, Kaplan GA, et al. Standing at work and progression of carotid atherosclerosis. Scand J Work Environ Health 2000;26:227–36. doi:10.5271/sjweh.536

16 Krause N, Brand RJ, Kaplan GA, et al. Occupational physical activity, energy expenditure and 11-year progression of carotid atherosclerosis. Scand J Work Environ Health 2007;33:405–24. doi:10.5271/sjweh.1171

17 Mons U, Hahmann H, Brenner H. A reverse J-shaped association of leisure time physical activity with prognosis in patients with stable coronary heart disease: Evidence from a large cohort with repeated measurements. Heart 2014;100:1043–9. doi:10.1136/heartjnl-2013-305242

18 Stewart RAH, Held C, Hadziosmanovic N, et al. Physical Activity and Mortality in Patients With Stable Coronary Heart Disease. J Am Coll Cardiol 2017;70:1689–700. doi:10.1016/j.jacc.2017.08.017

19 Simons PCG, Algra A, van de Laak MF, et al. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol 1999;15:773–81. doi:10.1023/a:1007621514757

20 Pols MA, Peeters PH, Ocké MC, et al. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol 1997;26 Suppl 1:S181-9. doi:10.1093/ije/26.suppl_1.s181

21 Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32. doi:10.1097/00005768-200009001-00009

22 Mittleman MA, Maclure M, Tofler GH, et al. Triggering of Acute Myocardial Infarction by Heavy Physical Exertion -- Protection against Triggering by Regular Exertion. N Engl J Med 1993;329:1677–83. doi:10.1056/NEJM199312023292301

23 Albert CM, Mittleman MA, Chae CU, et al. Triggering of Sudden Death from Cardiac Causes by Vigorous Exertion. N Engl J Med 2000;343:1355–61. doi:10.1056/NEJM200011093431902

24 Hambrecht R, Wolf A, Gielen S, et al. Effect of Exercise on Coronary Endothelial Function in Patients with Coronary Artery Disease. N Engl J Med 2000;342:454–60. doi:10.1056/NEJM200002173420702

25 Olver TD, Ferguson BS, Laughlin MH. Molecular Mechanisms for Exercise Training-Induced Changes in Vascular Structure and Function. Prog Mol Biol Transl Sci 2015;135:227–57. doi:10.1016/bs.pmbts.2015.07.017

26 Stanford KI, Goodyear LJ. Exercise regulation of adipose tissue. Adipocyte 2016;5:153–62. doi:10.1080/21623945.2016.1191307

27 Rempel D, Krause N. Do Sit–Stand Workstations Improve Cardiovascular Health? J Occup Environ Med 2018;60:e319–20. doi:10.1097/JOM.0000000000001351

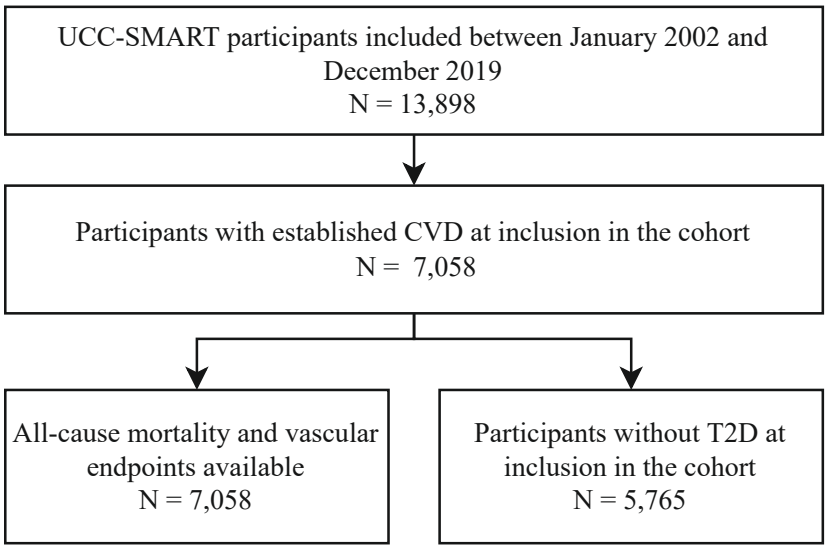
28 Holtermann A, Krause N, van der Beek AJ, et al. The physical activity paradox: six reasons why occupational physical activity (OPA) does not confer the cardiovascular health benefits that leisure time physical activity does. Br J Sports Med 2018;52:149–50. doi:10.1136/bjsports-2017-097965

29 Vyas M V., Garg AX, Iansavichus A V., et al. Shift work and vascular events: systematic review and meta-analysis. BMJ 2012;345:e4800–e4800. doi:10.1136/bmj.e4800

30 Pearce N, Checkoway H, Kriebel D. Bias in occupational epidemiology studies. Occup Environ Med 2007;64:562–8. doi:10.1136/oem.2006.026690

SUPPLEMENTAL MATERIAL

FIGURE S1 Flowchart UCC-SMART participants selection



Flowchart describing the criteria used to create the datasets used in the analyses of the association between physical activity levels and different outcomes. All datasets were limited to participants included from January 2002 onwards, because a new questionnaire for physical activity level was introduced then. All datasets were limited to participants with established cardiovascular disease at baseline. Data on all-cause mortality, cause-specific mortality and recurrent cardiovascular events was available for all participants. The analysis for incident type 2 diabetes was limited to participants without diabetes at baseline.

TABLE S1 Baseline characteristics of UCC-SMART participants stratified for OPA

	Not working				Working			
	Sedentary	**Standing**	**Manual**	**Heavy manual**	**Sedentary**	**Standing**	**Manual**	**Heavy manual**
Characteristic	*N = 1600*	*N = 808*	*N = 924*	*N = 248*	*N = 1958*	*N = 641*	*N = 681*	*N = 198*
Male sex	1282 (80)	532 (66)	417 (45)	227 (92)	1626 (83)	434 (68)	440 (65)	186 (94)
Age (years)	66 ±9	66 ±9	65 ±9	65 ±9	55 ±9	56 ±9	57 ±9	56 ±10
Leisure-time physical activity								
Quartile 1	405 (25)	206 (26)	247 (27)	72 (29)	509 (26)	139 (22)	147 (22)	40 (20)
Quartile 2	430 (27)	202 (25)	219 (24)	49 (20)	549 (28)	144 (23)	145 (21)	29 (15)
Quartile 3	405 (25)	192 (24)	229 (25)	52 (21)	535 (27)	164 (26)	148 (22)	38 (19)
Quartile 4	360 (23)	208 (26)	229 (25)	75 (30)	365 (19)	194 (30)	241 (35)	91 (46)
Education								
Low	434 (27)	271 (34)	362 (39)	115 (46)	338 (17)	170 (27)	183 (27)	54 (27)
Middle	548 (34)	334 (41)	485 (53)	119 (48)	702 (36)	280 (44)	412 (61)	128 (65)
High	618 (39)	203 (25)	77 (8)	14 (6)	918 (47)	191 (30)	86 (13)	16 (8)
History of CAD	1084 (68)	502 (62)	582 (63)	182 (73)	1253 (64)	402 (63)	400 (59)	146 (74)
History of CeVD	454 (28)	254 (31)	287 (31)	67 (27)	538 (28)	190 (30)	217 (32)	46 (23)
History of PAD	225 (14)	140 (17)	129 (14)	44 (18)	276 (14)	82 (13)	94 (14)	13 (7)
History of AAA	148 (9)	61 (8)	66 (7)	32 (13)	92 (5)	28 (4)	42 (6)	12 (6)
Multiple CVD manifestations	275 (17)	130 (16)	123 (13)	66 (27)	189 (10)	54 (8)	67 (10)	19 (10)
Diabetes mellitus	351 (22)	159 (20)	202 (22)	55 (22)	243 (12)	97 (15)	84 (12)	19 (10)
Metabolic syndrome	835 (52)	404 (50)	547 (59)	155 (63)	920 (47)	320 (50)	335 (49)	108 (55)
Current smoking	333 (21)	193 (24)	240 (26)	78 (32)	543 (28)	217 (34)	245 (36)	72 (36)

TABLE S1 (Continued)

	Not working				Working			
	Sedentary	**Standing**	**Manual**	**Heavy manual**	**Sedentary**	**Standing**	**Manual**	**Heavy manual**
Characteristic	*N = 1600*	*N = 808*	*N = 924*	*N = 248*	*N = 1958*	*N = 641*	*N = 681*	*N = 198*
Alcohol consumption	1236 (77)	547 (68)	547 (59)	152 (61)	1590 (81)	461 (72)	456 (67)	122 (62)
Body mass index (kg/m2)	26.85 (4)	26.89 (4)	27.34 (4)	28.29 (4)	26.89 (4)	26.93 (4)	27.21 (4)	28.42 (5)
<25 kg/m2	546 (34)	284 (35)	279 (30)	46 (19)	634 (32)	229 (36)	214 (31)	42 (21)
25-30 kg/m2	754 (47)	347 (43)	432 (47)	129 (52)	962 (49)	279 (44)	312 (46)	98 (50)
>30 kg/m2	300 (19)	177 (22)	213 (23)	73 (29)	362 (19)	133 (21)	155 (23)	58 (29)
Systolic BP (mmHg)	139 ±20	142 ±21	143 ±22	140 ±21	134 ±19	136 ±20	138 ±20	135 ±19
LDL cholesterol (mmol/l)	2.4 [1.9-3.0]	2.5 [1.9-3.1]	2.4 [2.0-3.1]	2.5 [1.9-3.1]	2.4 [1.9-3.1]	2.5 [2.0-3.3]	2.6 [2.0-3.2]	2.5 [2.0-3.2]
Antihypertensive medication	1314 (82)	649 (80)	749 (81)	211 (85)	1448 (74)	473 (74)	487 (72)	164 (83)
Lipid-lowering treatment	1252 (78)	618 (77)	727 (79)	209 (84)	1543 (79)	497 (78)	497 (73)	158 (80)

Data are presented as number (%), mean ±standard deviation or median [interquartile range] as appropriate. Abbreviations: METh/wk: Metabolic equivalent of task hours per week, CAD: coronary artery disease, CeVD: cerebrovascular disease, PAD: peripheral artery disease, AAA: abdominal aortic aneurysm, LDL: low density lipoprotein, HDL: high density lipoprotein.

TABLE S2 Hazard ratios for non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality

TABLE S2a Specific vascular outcomes and LTPA

	Leisure-time physical activity level			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
Non-fatal myocardial infarction				
Events/N total	325/1,765	322/1,767	345/1,763	357/1,763
Follow-up (py)	13,030	13,196	13,013	12,832
Model 1	*Reference*	0.97 (0.83-1.13)	1.03 (0.89-1.20)	1.06 (0.91-1.23)
Model 2	*Reference*	1.00 (0.86-1.17)	1.07 (0.92-1.25)	1.06 (0.91-1.24)
Model 3	*Reference*	1.03 (0.88-1.21)	1.12 (0.96-1.30)	1.12 (0.96-1.30)
Non-fatal stroke				
Events/N total	96/1,765	87/1,767	57/1,763	82/1,763
Follow-up (py)	14,592	14,992	14,946	14,912
Model 1	*Reference*	0.87 (0.65-1.16)	0.57 (0.41-0.79)	0.81 (0.60-1.09)
Model 2	*Reference*	0.93 (0.69-1.24)	0.62 (0.44-0.86)	0.87 (0.64-1.17)
Model 3	*Reference*	0.92 (0.69-1.23)	0.61 (0.44-0.86)	0.86 (0.64-1.16)
Cardiovascular mortality				
Events/N total	187/1,765	133/1,767	103/1,763	101/1,763
Follow-up (py)	15,007	15,392	15,218	15,214
Model 1	*Reference*	0.68 (0.54-0.84)	0.52 (0.41-0.66)	0.49 (0.38-0.62)
Model 2	*Reference*	0.73 (0.59-0.92)	0.57 (0.45-0.72)	0.54 (0.42-0.69)
Model 3	*Reference*	0.76 (0.61-0.96)	0.61 (0.48-0.78)	0.58 (0.45-0.74)

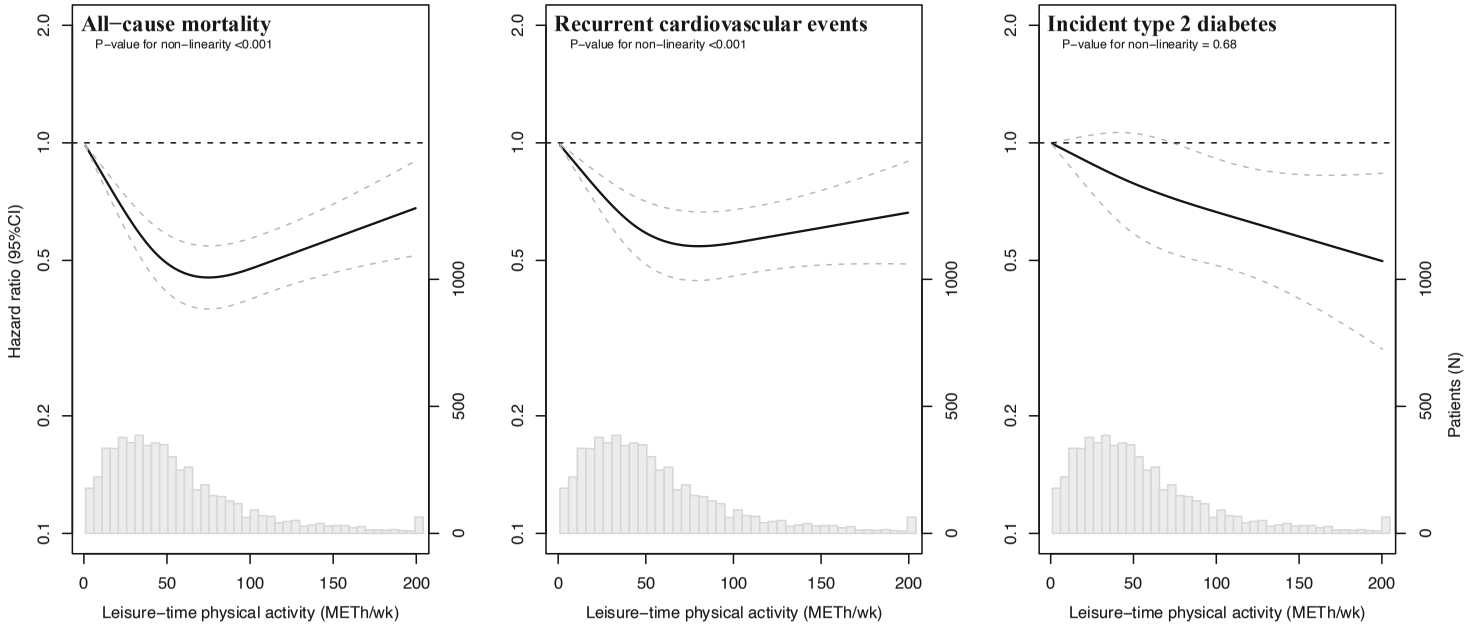
Hazard ratios and corresponding 95% confidence intervals for non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, packyears, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels. Abbreviations: py: person year

TABLE S2b Specific vascular outcomes and OPA

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
Non-fatal myocardial infarction				
Events/N total	662/3,558	258/1,449	321/1,605	108/446
Follow-up (py)	25,331	10,994	12,578	3,170
Model 1	*Reference*	0.97 (0.84-1.13)	1.16 (1.01-1.33)	1.22 (0.99-1.49)
Model 2	*Reference*	0.92 (0.80-1.07)	1.06 (0.92-1.22)	1.07 (0.87-1.32)
Model 3	*Reference*	0.92 (0.79-1.06)	1.05 (0.91-1.21)	1.05 (0.85-1.29)
Non-fatal stroke				
Events/N total	127/3,558	74/1449	91/1,605	30/446
Follow-up (py)	28,934	12415	14,394	3,699
Model 1	*Reference*	1.31 (0.98-1.75)	1.40 (1.05-1.85)	1.77 (1.19-2.64)
Model 2	*Reference*	1.27 (0.95-1.70)	1.35 (1.01-1.81)	1.66 (1.10-2.50)
Model 3	*Reference*	1.25 (0.93-1.68)	1.34 (1.00-1.79)	1.74 (1.15-2.63)
Cardiovascular mortality				
Events/N total	233/3,558	131/1,449	125/1,605	35/446
Follow-up (py)	29,482	12,713	14,804	3,831
Model 1	*Reference*	1.22 (0.98-1.51)	1.04 (0.83-1.31)	1.03 (0.72-1.46)
Model 2	*Reference*	1.14 (0.92-1.42)	0.93 (0.74-1.17)	0.90 (0.62-1.29)
Model 3	*Reference*	1.12 (0.90-1.39)	0.91 (0.72-1.15)	0.89 (0.62-1.28)

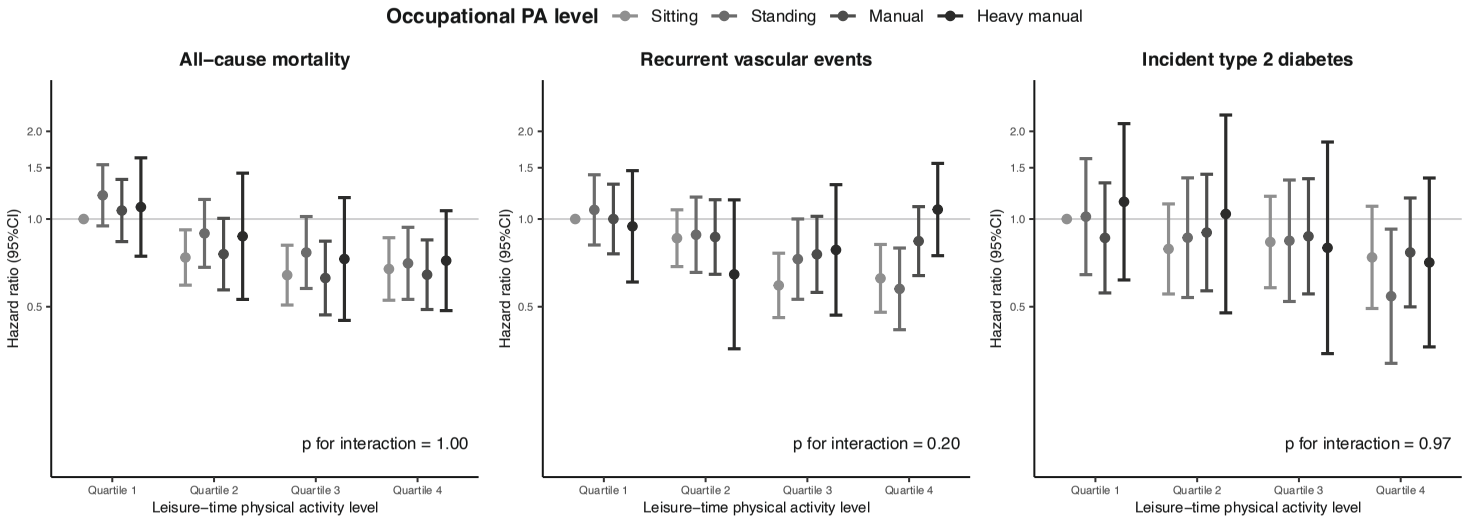
Hazard ratios and corresponding 95% confidence intervals for non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, packyears, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels.
Abbreviations: py: person year.

FIGURE S2 Continuous association between leisure-time physical activity and non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality



Hazard ratios are adjusted for age, sex, smoking status, pack years, alcohol consumption, education and current employment (model 3). The histograms inside the figures represent the number of study participants that achieved a certain leisure-time physical activity level. METh/wk: Metabolic equivalent of task hours per week. 95%CI: 95% confidence interval

FIGURE S3 Interaction between LTPA and OPA on the risk of all-cause mortality recurrent vascular events, and incident T2D.



Hazard ratios assessing the interaction between LTPA and OPA level in the association with the individual components of the combined vascular endpoint: non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. These figures show the hazard ratios for each combination of leisure-time and OPA level with the least active (quartile 1 leisure-time and sedentary OPA) as reference category. Models were adjusted for age, sex, smoking, packyears, alcohol consumption, education and current employment. 95%CI: 95% confidence interval, Mi: myocardial infarction.

TABLE S3 Hazard ratios for interplay between LTPA and OPA

TABLE S3a All-cause mortality

		Leisure-time physical activity, HR (95%CI)			
		Quarter 1	Quarter 2	Quarter 3	Quarter 4
Occupational PA	Sedentary	*Reference*	0.74 (0.59-0.92)	0.64 (0.51-0.81)	0.67 (0.53-0.86)
	Standing	1.21 (0.95-1.54)	0.89 (0.68-1.17)	0.77 (0.58-1.02)	0.70 (0.53-0.94)
	Manual	1.07 (0.84-1.37)	0.76 (0.57-1.01)	0.63 (0.47-0.84)	0.64 (0.49-0.85)
	Heavy manual	1.10 (0.75-1.62)	0.87 (0.53-1.44)	0.73 (0.45-1.18)	0.72 (0.48-1.07)

TABLE S3b Recurrent vascular events

		Leisure-time physical activity, HR (95%CI)			
		Quarter 1	Quarter 2	Quarter 3	Quarter 4
Occupational PA	Sedentary	*Reference*	0.86 (0.69-1.08)	0.59 (0.46-0.76)	0.63 (0.48-0.82)
	Standing	1.07 (0.81-1.42)	0.88 (0.66-1.19)	0.73 (0.53-1.00)	0.58 (0.42-0.8)
	Manual	1.00 (0.76-1.32)	0.87 (0.65-1.16)	0.76 (0.56-1.02)	0.84 (0.64-1.1)
	Heavy manual	0.94 (0.61-1.47)	0.65 (0.36-1.16)	0.78 (0.47-1.31)	1.08 (0.75-1.55)

TABLE S3c Incident type 2 diabetes

		Leisure-time physical activity, HR (95%CI)			
		Quarter 1	Quarter 2	Quarter 3	Quarter 4
Occupational PA	Sedentary	*Reference*	0.79 (0.55-1.13)	0.83 (0.58-1.20)	0.74 (0.49-1.11)
	Standing	1.02 (0.64-1.61)	0.86 (0.54-1.38)	0.84 (0.52-1.36)	0.54 (0.32-0.92)
	Manual	0.86 (0.56-1.33)	0.90 (0.57-1.42)	0.87 (0.55-1.38)	0.77 (0.50-1.18)
	Heavy manual	1.15 (0.62-2.13)	1.04 (0.48-2.28)	0.80 (0.35-1.84)	0.71 (0.36-1.38)

Hazard ratios assessing the interaction between LTPA and OPA level in the association with all-cause mortality, recurrent vascular events and incident type 2 diabetes. All presented hazard ratios are relative to people with sedentary OPA and LTPA quarter 1. Models were adjusted for age, sex, smoking, pack years, alcohol consumption, education and current employment. 95%CI: 95% confidence interval, HR: hazard ratio

FIGURE S4 Associations with start of follow-up after 1, 3 and 5 years after inclusion

Outcome	Start Follow-up	Events/N	Follow−up (pers.yr)	LTPA Q4 *vs.*Q1	Hazard ratio (95%CI)	OPA Heavy manual vs sedentary	Hazard ratio (95%CI)
Mortality	All	1254/7058	60831		0.61 (0.52−0.71)		1.09 (0.87−1.37)
	1 year	1199/6702	60629		0.61 (0.52−0.72)		1.11 (0.89−1.40)
	3 year	1040/5957	59105		0.63 (0.53−0.74)		1.09 (0.85−1.40)
	5 year	847/5136	55813		0.62 (0.52−0.75)		1.10 (0.83−1.45)
Combined vascular endpoint	All	1088/7058	57262		0.71 (0.60−0.83)		1.16 (0.92−1.47)
	1 year	952/6599	57019		0.68 (0.57−0.82)		1.09 (0.84−1.41)
	3 year	775/5759	55327		0.69 (0.57−0.84)		1.02 (0.76−1.37)
	5 year	600/4870	51763		0.71 (0.57−0.89)		0.97 (0.69−1.36)
Diabetes	All	447/5765	47676		0.68 (0.52−0.89)		1.04 (0.72−1.50)
	1 year	423/5460	47507		0.69 (0.52−0.90)		1.09 (0.75−1.58)
	3 year	312/4782	46114		0.71 (0.52−0.97)		1.12 (0.73−1.72)
	5 year	219/4045	43164		0.64 (0.43−0.95)		1.09 (0.65−1.85)

Hazard ratios for all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes with the full dataset and with datasets that exclude participants with an event in the first 1, 3 or 5 years after inclusion. The presented estimates were adjusted for the covariates included in model 3. These figures show the hazard ratio for the highest quartile *vs.* these lowest quartile of leisure-time physical activity and the highest level of occupational physical activity (heavy manual work) *vs.* sedentary. FU: follow-up, pers.yr: person year, 95%CI: 95% confidence interval, LTPA: leisure-time physical activity, OPA: Occupational physical activity.

TABLE S4 Hazard ratios for LTPA and OPA in patients that never smoked

TABLE S4a Hazard ratios for different levels of LTPA in never-smokers.

	Leisure-time physical activity level			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
All-cause mortality				
Events/N total	64/374	50/426	33/441	44/447
Follow-up (py)	2910	3620	3675	3783
Model 1	*Reference*	0.66 (0.45-0.96)	0.48 (0.31-0.74)	0.55 (0.37-0.81)
Model 2	*Reference*	0.66 (0.45-0.96)	0.50 (0.33-0.77)	0.56 (0.38-0.83)
Model 3	*Reference*	0.72 (0.49-1.05)	0.55 (0.36-0.85)	0.66 (0.44-0.98)
Combined vascular endpoint				
Events/N total	57/374	50/426	29/441	50/447
Follow-up (py)	2722	3453	3550	3596
Model 1	*Reference*	0.71 (0.49-1.04)	0.42 (0.27-0.66)	0.68 (0.46-0.99)
Model 2	*Reference*	0.74 (0.50-1.08)	0.45 (0.29-0.71)	0.45 (0.29-0.71)
Model 3	*Reference*	0.77 (0.52-1.13)	0.47 (0.30-0.75)	0.46 (0.28-0.73)
Type 2 diabetes				
Events/N total	24/363	15/408	21/434	19/442
Follow-up (py)	2428	2847	2969	3084
Model 1	*Reference*	0.54 (0.28-1.04)	0.73 (0.40-1.31)	0.62 (0.34-1.14)
Model 2	*Reference*	0.62 (0.32-1.19)	0.83 (0.46-1.52)	0.67 (0.36-1.23)
Model 3	*Reference*	0.66 (0.34-1.29)	0.94 (0.51-1.72)	0.80 (0.43-1.48)

Sensitivity analysis limited to SMART participants that reported they had never smoked (N = 1688). This table shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, packyears, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels. * The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. Abbreviations: py: person year.

TABLE S4b Hazard ratios for different levels of OPA in never-smokers.

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Events/N total	73/869	40/329	63/393	15/97
Follow-up (py)	6661	2942	3486	898
Model 1	*Reference*	0.98 (0.66-1.45)	1.24 (0.84-1.82)	1.01 (0.58-1.76)
Model 2	*Reference*	0.97 (0.65-1.44)	1.27 (0.85-1.89)	1.04 (0.58-1.86)
Model 3	*Reference*	0.93 (0.62-1.38)	1.26 (0.84-1.87)	1.03 (0.58-1.86)
Combined vascular endpoint				
Events/N total	73/869	39/329	58/393	16/97
Follow-up (py)	6408	2789	3279	845
Model 1	*Reference*	1.10 (0.74-1.64)	1.31 (0.89-1.93)	1.44 (0.83-2.47)
Model 2	*Reference*	1.02 (0.68-1.52)	1.20 (0.81-1.79)	1.20 (0.81-1.79)
Model 3	*Reference*	0.99 (0.66-1.48)	1.18 (0.79-1.77)	1.26 (0.72-2.21)
Type 2 diabetes				
Events/N total	32/752	11/271	30/306	6/84
Follow-up (py)	5603	2400	2579	744
Model 1	*Reference*	0.77 (0.38-1.55)	1.94 (1.11-3.37)	1.29 (0.53-3.09)
Model 2	*Reference*	0.76 (0.37-1.54)	1.87 (1.04-3.37)	1.17 (0.47-2.92)
Model 3	*Reference*	0.74 (0.36-1.50)	1.85 (1.01-3.36)	1.04 (0.41-2.58)

Sensitivity analysis limited to SMART participants that reported they had never smoked (N = 1688). This table shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels. * The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. Abbreviations: py: person year.

TABLE S5 Hazard ratios for OPA stratified for employment status at inclusion in the UCC-SMART cohort

TABLE S5a Hazard ratios for OPA among actively employed UCC-SMART participants

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Events/N total	166/1958	77/641	84/681	23/198
Follow-up (py)	16696	5811	6425	1744
Model 1	*Reference*	1.22 (0.93-1.61)	1.09 (0.83-1.43)	1.13 (0.73-1.74)
Model 2	*Reference*	1.13 (0.86-1.49)	0.95 (0.72-1.26)	1.04 (0.66-1.62)
Model 3	*Reference*	1.11 (0.84-1.46)	0.98 (0.74-1.29)	1.13 (0.72-1.77)
Combined vascular endpoint				
Events/N total	198/1958	73/641	106/681	36/198
Follow-up (py)	15987	5563	6021	1588
Model 1	Reference	1.12 (0.85-1.47)	1.50 (1.18-1.90)	1.65 (1.15-2.35)
Model 2	Reference	1.03 (0.79-1.36)	1.30 (1.01-1.67)	1.30 (1.01-1.67)
Model 3	Reference	1.01 (0.77-1.33)	1.29 (1.01-1.66)	1.54 (1.06-2.23)
Type 2 diabetes				
Events/N total	127/1704	43/539	45/591	18/174
Follow-up (py)	13861	4620	5396	1445
Model 1	*Reference*	1.09 (0.77-1.55)	0.97 (0.69-1.37)	1.26 (0.77-2.07)
Model 2	*Reference*	0.99 (0.70-1.41)	0.81 (0.57-1.16)	1.13 (0.68-1.89)
Model 3	*Reference*	0.98 (0.69-1.40)	0.84 (0.59-1.21)	1.01 (0.61-1.69)

Sensitivity analysis limited to SMART participants that reported they had active employment at the moment of inclusion in the cohort (n = 3,478). This table shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, pack years, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels. * The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. py: person year

TABLE S5b Hazard ratios for OPA among UCC-SMART participants without active employment

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Events/N total	374/1600	230/808	229/924	71/248
Follow-up (py)	12786	6902	8380	2087
Model 1	*Reference*	1.17 (0.99-1.38)	1.04 (0.87-1.24)	1.19 (0.92-1.53)
Model 2	*Reference*	1.14 (0.96-1.34)	0.98 (0.82-1.17)	1.07 (0.83-1.39)
Model 3	*Reference*	1.13 (0.95-1.33)	0.97 (0.81-1.15)	1.07 (0.83-1.39)
Combined vascular endpoint				
Events/N total	288/1600	158/808	178/924	51/248
Follow-up (py)	11993	6405	7786	1918
Model 1	*Reference*	1.05 (0.87-1.28)	1.03 (0.85-1.26)	1.13 (0.84-1.53)
Model 2	*Reference*	1.01 (0.83-1.22)	0.96 (0.78-1.18)	0.96 (0.78-1.18)
Model 3	*Reference*	1.00 (0.82-1.22)	0.95 (0.78-1.17)	0.98 (0.72-1.34)
Type 2 diabetes				
Events/N total	87/1244	44/624	66/696	17/193
Follow-up (py)	9653	5127	6015	1559
Model 1	*Reference*	0.96 (0.67-1.39)	1.24 (0.88-1.73)	1.20 (0.71-2.01)
Model 2	*Reference*	0.91 (0.63-1.31)	1.11 (0.79-1.56)	1.00 (0.59-1.69)
Model 3	*Reference*	0.88 (0.61-1.28)	1.06 (0.75-1.50)	0.85 (0.50-1.45)

Sensitivity analysis limited to SMART participants that reported they were not actively employed at the moment of inclusion in the cohort (n = 3,580). This table shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, pack years, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels. * The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality. py: person year

TABLE S6 Hazard ratios for LTPA and OPA stratified for sex

TABLE S6a Hazard ratios for LTPA in female UCC-SMART participants

	Leisure-time physical activity level			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
All-cause mortality				
Model 1	*Reference*	0.56 (0.42-0.75)	0.49 (0.36-0.67)	0.48 (0.34-0.67)
Model 2	*Reference*	0.59 (0.44-0.79)	0.51 (0.37-0.70)	0.54 (0.39-0.75)
Model 3	*Reference*	0.61 (0.45-0.82)	0.55 (0.40-0.75)	0.57 (0.41-0.80)
Combined vascular endpoint				
Model 1	*Reference*	0.67 (0.48-0.93)	0.57 (0.40-0.81)	0.54 (0.37-0.78)
Model 2	*Reference*	0.68 (0.49-0.94)	0.60 (0.42-0.86)	0.58 (0.40-0.84)
Model 3	*Reference*	0.73 (0.53-1.02)	0.68 (0.47-0.97)	0.64 (0.44-0.93)
Type 2 diabetes				
Model 1	*Reference*	0.74 (0.44-1.26)	1.06 (0.65-1.72)	0.82 (0.47-1.42)
Model 2	*Reference*	0.76 (0.45-1.28)	1.08 (0.66-1.77)	0.83 (0.48-1.43)
Model 3	*Reference*	0.83 (0.49-1.41)	1.18 (0.72-1.92)	0.91 (0.52-1.58)

TABLE S6b Hazard ratios for OPA in female UCC-SMART participants

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Model 1	*Reference*	1.35 (0.98-1.86)	1.54 (1.16-2.05)	1.11 (0.41-3.04)
Model 2	*Reference*	1.16 (0.84-1.61)	1.10 (0.82-1.47)	0.78 (0.28-2.14)
Model 3	*Reference*	1.11 (0.80-1.54)	1.03 (0.76-1.38)	0.71 (0.26-1.94)
Combined vascular endpoint				
Model 1	*Reference*	1.19 (0.83-1.71)	1.44 (1.05-1.96)	1.32 (0.48-3.63)
Model 2	*Reference*	1.07 (0.74-1.53)	1.07 (0.78-1.47)	1.01 (0.37-2.78)
Model 3	*Reference*	0.98 (0.69-1.41)	0.92 (0.66-1.27)	0.83 (0.30-2.29)
Type 2 diabetes				
Model 1	*Reference*	0.68 (0.38-1.20)	1.29 (0.84-1.97)	1.71 (0.53-5.57)
Model 2	*Reference*	0.65 (0.37-1.15)	1.17 (0.76-1.82)	1.58 (0.48-5.15)
Model 3	*Reference*	0.60 (0.34-1.06)	0.98 (0.63-1.53)	1.17 (0.36-3.86)

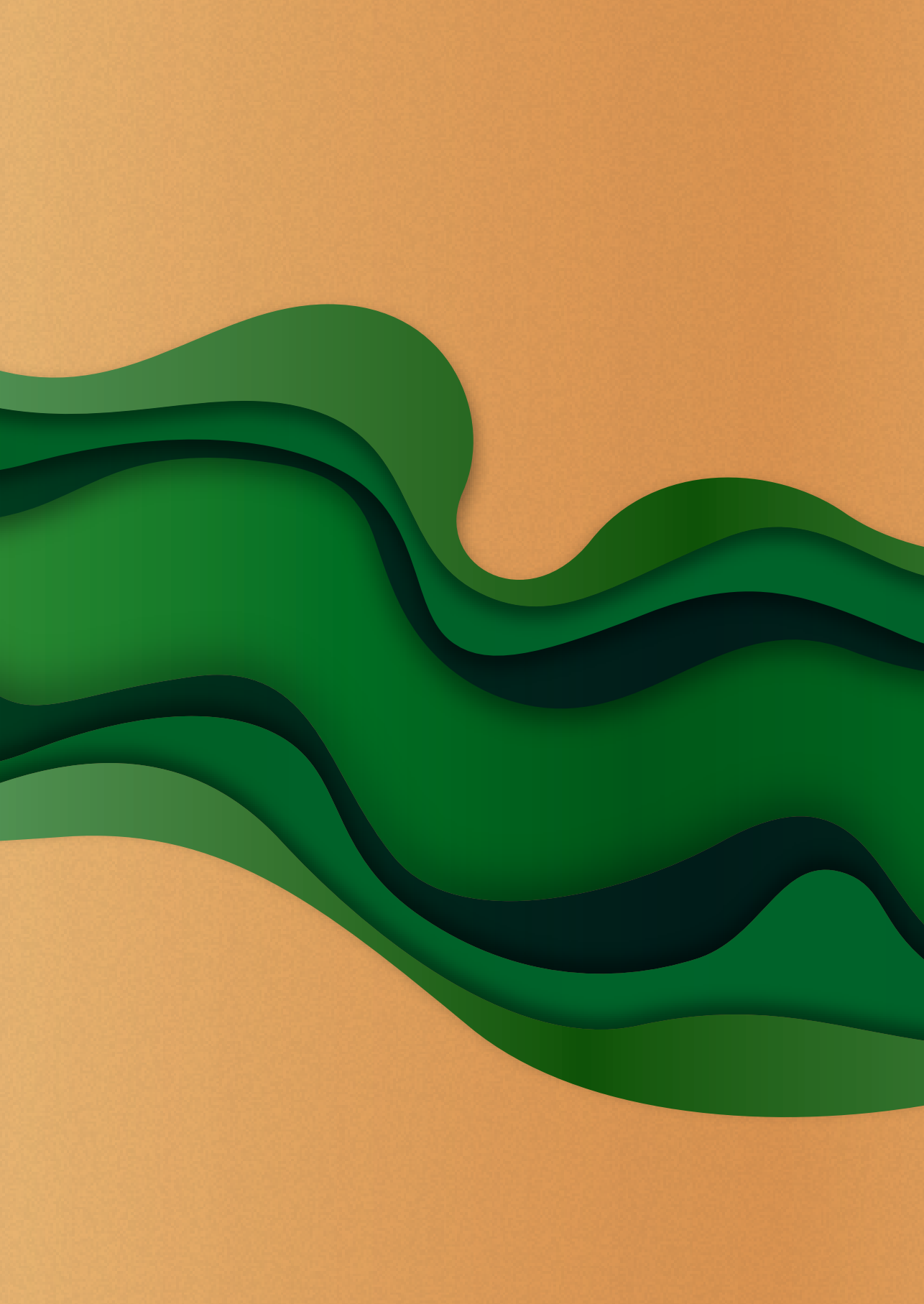
TABLE S6c Hazard ratios for LTPA in male UCC-SMART participants

	Leisure-time physical activity level			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
All-cause mortality				
Model 1	*Reference*	0.72 (0.60-0.85)	0.60 (0.51-0.72)	0.62 (0.52-0.74)
Model 2	*Reference*	0.68 (0.58-0.81)	0.57 (0.47-0.68)	0.56 (0.47-0.66)
Model 3	*Reference*	0.70 (0.59-0.83)	0.58 (0.48-0.69)	0.56 (0.47-0.66)
Combined vascular endpoint				
Model 1	*Reference*	0.84 (0.70-1.00)	0.63 (0.52-0.77)	0.72 (0.60-0.87)
Model 2	*Reference*	0.82 (0.68-0.98)	0.61 (0.51-0.74)	0.69 (0.57-0.83)
Model 3	*Reference*	0.85 (0.71-1.01)	0.63 (0.52-0.77)	0.69 (0.58-0.83)
Type 2 diabetes				
Model 1	*Reference*	0.77 (0.58-1.02)	0.67 (0.50-0.90)	0.60 (0.45-0.81)
Model 2	*Reference*	0.77 (0.58-1.02)	0.67 (0.50-0.90)	0.60 (0.45-0.82)
Model 3	*Reference*	0.81 (0.61-1.08)	0.70 (0.52-0.95)	0.61 (0.45-0.82)

TABLE S6d Hazard ratios for OPA in male UCC-SMART participants

	Occupational physical activity level			
	Sedentary	**Standing**	**Manual**	**Heavy manual**
All-cause mortality				
Model 1	*Reference*	1.37 (1.17-1.61)	1.04 (0.87-1.25)	1.29 (1.03-1.62)
Model 2	*Reference*	1.22 (1.04-1.43)	1.05 (0.87-1.25)	1.23 (0.98-1.54)
Model 3	*Reference*	1.17 (0.99-1.37)	0.97 (0.80-1.16)	1.11 (0.88-1.39)
Combined vascular endpoint				
Model 1	*Reference*	1.17 (0.98-1.40)	1.26 (1.05-1.50)	1.37 (1.09-1.74)
Model 2	*Reference*	1.01 (0.92-1.32)	1.25 (1.04-1.49)	1.36 (1.08-1.72)
Model 3	*Reference*	1.05 (0.88-1.26)	1.15 (0.96-1.39)	1.20 (0.94-1.53)
Type 2 diabetes				
Model 1	*Reference*	1.17 (0.89-1.54)	1.03 (0.77-1.38)	1.22 (0.84-1.78)
Model 2	*Reference*	1.18 (0.89-1.56)	1.03 (0.77-1.38)	1.22 (0.84-1.78)
Model 3	*Reference*	1.11 (0.84-1.47)	0.91 (0.67-1.23)	1.05 (0.71-1.55)

Sensitivity analyses stratified for sex. These tables shows hazard ratios and corresponding 95% confidence intervals all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes. In Model 1 adjustments were made for age and sex. In Model 2 adjustments were made for Model 1 + smoking status, pack years, alcohol consumption, and education. In Model 3 adjustments were made for Model 2 + diabetes mellitus, body mass index, systolic blood pressure and LDL-cholesterol levels. * The combined vascular endpoints was a composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality.



CHAPTER 8

PHYSICAL EXERCISE VOLUME, TYPE AND INTENSITY AND RISK OF ALL-CAUSE MORTALITY AND CARDIOVASCULAR EVENTS IN PATIENTS WITH CARDIOVASCULAR DISEASE

A MEDIATION ANALYSIS

Nadia E. Bonekamp
Anne M. May
Martin Halle
Jannick A.N. Dorresteijn
Manon G. van der Meer
Ynte M. Ruigrok
Gert-Jan de Borst
Johanna M. Geleijnse
Frank L.J. Visseren
Charlotte Koopal

on behalf of the UCC-SMART study group

European Heart Journal Open, 2023 Jun 13;3(3):oead057.

ABSTRACT

Aims

To estimate the relation between physical exercise volume, type and intensity with all-cause mortality and recurrent vascular events in patients with cardiovascular disease (CVD), and to quantify to what extent traditional cardiovascular risk factors mediate these relations.

Methods

In the prospective UCC-SMART cohort (N=8,660), the associations of clinical endpoints and physical exercise volume (metabolic equivalent of task hours per week, METh/wk), type (endurance vs endurance + resistance) and intensity (moderate vs vigorous) were estimated using multivariable-adjusted Cox models. The proportion mediated effect (PME) through body mass index, systolic blood pressure, low-density lipoprotein cholesterol, insulin sensitivity and systemic inflammation was assessed using structural equation models.

Results

Sixty-one percent of patients (73% male, age 61±10 years), reported that they did not exercise. Over a median follow-up of 9.5 years [IQR 5.1-14.0], 2,256 deaths and 1,828 recurrent vascular events occurred. The association between exercise volume had a reverse J-shape with a nadir at 29 (95%CI 24-29) METh/wk, corresponding with a HR 0.56 (95%CI 0.48-0.64) for all-cause mortality and HR 0.63 (95%CI 0.55-0.73) for recurrent vascular events compared with no exercise. Up to 38% (95%CI 24-61) of the association was mediated through the assessed risk factors of which insulin sensitivity (PME up to 12%, 95%CI 5-25) and systemic inflammation (PME up to 18%, 95%CI 9-37) were the most important.

Conclusion

Regular physical exercise is significantly related with reduced risk of all-cause mortality and recurrent vascular events in patients with CVD. The exercise benefits are mainly mediated through systemic inflammation and insulin resistance.

LAY SUMMARY

People that have previously experienced cardiovascular events, like a heart attack or stroke, are at lower risk of a recurrent event or mortality when they regularly perform physical exercise because exercise beneficially affect cardiovascular risk factors.

- Time spent on exercise is the most important determinant of exercise benefits; similar cardiovascular benefits can be achieved with different exercise types and intensities. It is important to choose an exercise modality that suits a personal preferences and abilities, as any level of exercise is better than no exercise.
- For a large part, exercise benefits come about through beneficial modification of cardiovascular risk factors, most importantly inflammation and insulin sensitivity.

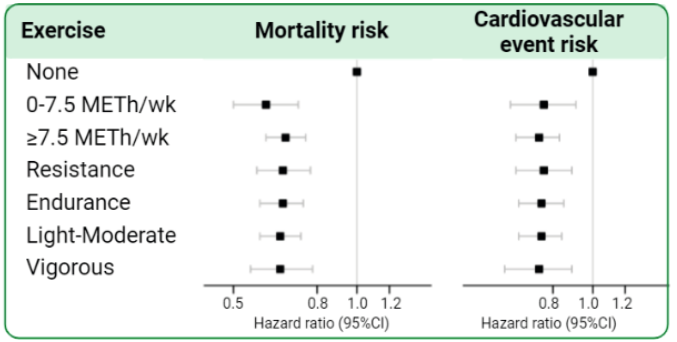
GRAPHICAL ABSTRACT

Physical exercise volume, type and intensity and risk of all-cause mortality and cardiovascular events in patients with cardiovascular disease: A mediation analysis

Objective: To quantify the relation between exercise type, volume and intensity and cardiovascular event risk and to what extent this is mediated through cardiovascular risk factors.

Methods

- UCC SMART cohort, N = 8,660
- 9.5 years follow-up
- Cox proportional hazard models
- Mediation analysis using structural equation models



Proportion of total exercise effects mediated through cardiovascular risk factors: Up to 38% (95%CI 24-61)

Conclusion

- Exercise reduces risk of all-cause mortality and recurrent cardiovascular events
- Different exercise types and intensities result in similar benefits
- Systemic inflammation and insulin resistance are the most important mediators

95%CI – 95% confidence intervals, UCC-SMART: Utrecht Cardiovascular Cohort – Second Manifestations of ARTerial disease

INTRODUCTION

Physical exercise is a key component of a healthy lifestyle, and has consistently been associated with reduced rates of all-cause mortality and cardiovascular disease (CVD).[1–3] Performing regular exercise is a central recommendation in international guidelines for CVD management, which distinguish between exercise type, *e.g.* resistance or endurance training, and intensity.[4,5] Resistance training predominantly has musculoskeletal benefits and reduces risk of CVD and some types of cancer; it is specifically recommended for improving physical functioning and glycemic control.[6–8] Endurance exercise effectively improves cardiorespiratory fitness, reduces subcutaneous fat mass and lowers CVD risk.[9,10] However, the optimal exercise volume, type and intensity are unknown for patients with CVD.[11]

Exercise has been shown to attenuate traditional CVD risk factors,[12–15] reduce systemic inflammation,[16,17] increase insulin sensitivity[18,19], and improve cardiorespiratory fitness.[20] However, the relative contributions of these mediating pathways are unclear and it is unknown if mediators differ across exercise types and intensities. Better understanding of the causal pathway between exercise and cardiovascular events may help inform patients with CVD about the most beneficial way to exercise.

We aimed to quantify the relation between exercise volume, type and intensity and risk of all-cause mortality and recurrent vascular events in patients with a history of CVD. Furthermore, we aimed to quantify to whichnadir extent the effects of exercise are mediated through body mass index (BMI), insulin resistance, systemic inflammation, systolic blood pressure (SBP) and low-density lipoprotein-cholesterol (LDL-C).

METHODS

Study population

The Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART) study is a single-centre prospective cohort study that comprises patients at high risk of or with established CVD. Details on study design have been published previously.[21] The local Medical Ethics Review Committee approved the study, and all participants gave written informed consent.

For the present study, data was used from 8,660 participants with established CVD at inclusion in the cohort. Participants were included between 1996 and 2019 and history of CVD was defined as either coronary artery disease, cerebrovascular disease, peripheral artery disease, or abdominal aortic aneurysm.

Baseline measurements and determination of exercise volume, intensity and type

All participants completed a baseline health questionnaire, and underwent a physical examination and laboratory testing. Physical activity was self-reported and assessed using the validated EPIC physical activity questionnaire with additional questions on type and duration of exercise.[22] The EPIC questionnaire showed moderate-high agreement with 3-day activity diaries especially in men (Spearman correlation coefficients between 0.32 and 0.81).[22] Detailed information on exercise was available, *i.e.* the exact sports activity that a participant participated in and the number of hours spent on that activity each week. Metabolic equivalent of task (MET) values for the reported exercise activities were calculated according to the Compendium of Physical Activity.[23] Exercise is commonly defined as planned, structured and goal-oriented activity, which best translates to sport-related physical activity in the UCC-SMART study.[24] For this analysis, exercise was assessed in three ways: exercise volume, exercise type and exercise intensity.

1. Exercise volume was defined as the average intensity of exercise (the MET value) times weekly hours spent on exercise and was measured in METh/wk. It was analysed both continuously and categorically in three groups: (a) no exercise, (b) >0 and <7.5 METh/wk and (c) ≥7.5 METh/wk. This 7.5 METh/wk cut-off was based on guideline–recommended exercise volume and corresponds to 150 minutes/week of moderate intensity exercise or 75 minutes/week of vigorous exercise[4,5]
2. Exercise intensity was based on the MET-value of the exercise and was assessed categorically in three groups: (a) no exercise, (b) light-moderate intensity exercise with a MET value between 0 and 6, and, (c) vigorous intensity with a MET value ≥6.
3. Exercise type was determined by classifying the reported exercise activity as either (a) no exercise, (b) resistance training or (c) combined endurance-resistance training, based on the classification proposed by the Dutch National Institute of Public Health and the Environment.[25]

Outcome measurement

The primary outcomes were all-cause mortality and recurrent vascular events, a composite of non-fatal myocardial infarction, non-fatal stroke and, cardiovascular mortality. These components were assessed as secondary outcomes. Outcomes were assessed in biannual follow-up questionnaires, and requesting additional information from the treating physician for all reported events. Three independent physicians made the final endpoint adjudication based on pre-published definitions.[21]

Statistical analysis

Baseline characteristics were presented as frequencies with percentages for categorical variables and as means with standard deviation or median with interquartile range (IQR) for continuous variables. Cox proportional hazard models with time-on study as the time scale, were used to estimate the relations of exercise volume, intensity and type with the outcomes. Model 1 adjusted for age and sex. Model 2, the main model, additionally adjusted for smoking status, pack years, alcohol consumption and education level. Model 3 further adjusted for covariates that could be either intermediates or confounders: SBP, LDL-C, type 2 diabetes (T2D) and BMI. To model the association with exercise volume as a continuous variable, Cox models with restricted cubic splines with three knots were selected based on Akaike information criterion (AIC). The nadir exercise volume and corresponding 95% confidence intervals (95%CIs) were obtained in 1,000 bootstrap samples.

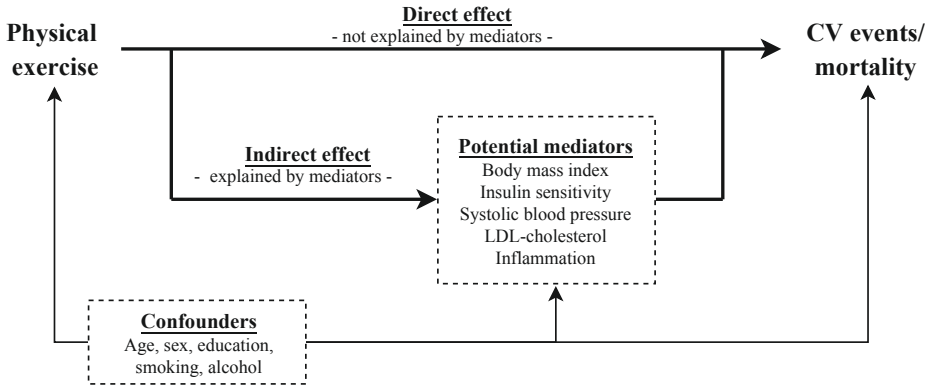
Mediation analysis was performed with marginal structural models in a counterfactual framework.[26–28] Potential mediators were selected based on previous etiologic research: BMI, SBP, systemic inflammation, insulin resistance and LDL-C (Figure 1). To ensure stability of the models, the exposure was dichotomized and mediators were categorized into sex-specific quintiles. A weighted Cox regression model was used to estimate the total, direct and indirect effect and the proportion mediated effect (PME). The 95%CIs for these estimates were obtained in 1,000 bootstrap samples. A detailed methodology is provided in *Supplemental appendix 1*.

The mediation analysis was repeated in subgroups based on sex, metabolic syndrome (MetS) and a low-grade inflammatory state (defined as CRP level between 2 and 10 mg/l). In a subgroup of people without type 2 diabetes, the mediation analysis was repeated using HOMA-IR for insulin resistance. To check robustness of the total effect estimates from these mediation analyses, subgroup analyses were repeated

using traditional Cox proportion hazard models adjusted for age, sex, education, smoking, number of pack years and alcohol consumption. To assess independence of the mediating pathways, PMEs were estimated in models including one mediator at a time. To assess the impact of reverse confounding, the analyses were repeated in subsets with follow-up commencing after 1, 3 and 5 year after inclusion.

Missing data on education (22.7%), SBP (0.1%), smoking status and pack years (0.1%), alcohol consumption (0.3%), BMI (0.1%), serum triglycerides (0.1%) and C-reactive protein (2.3%) were imputed with single imputation using predictive mean matching. All statistical analyses were performed using R statistical software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

FIGURE 1 Path diagram of the relation between physical exercise and cardiovascular events and all-cause mortality



Causal path diagram of the relation between physical exercise and cardiovascular events and all-cause mortality. Abbreviations – CV: cardiovascular, LDL: low-density lipoprotein

RESULTS

Baseline characteristics

The majority (61%) of participants reported that they did not exercise (Table 1). Compared with these non-exercisers, people who exercised more frequently had higher levels of education (38% *vs* 19%), were less frequently smokers (20% vs 36%) and less frequently had T2D (12% *vs* 20%).

TABLE 1 Baseline characteristics stratified for exercise volume, type, and intensity

		Exercise volume		Exercise type		Exercise intensity*	
	No exercise	>0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance-endurance	Light to moderate	Vigorous
	N = 5,266	*N = 724*	*N = 2,670*	*N = 1,020*	*N = 2,374*	*N = 2,470*	*N = 897*
Male (%)	3,830 (73)	449 (62)	2,097 (79)	732 (72)	1,814 (76)	1,828 (74)	701 (78)
Age, years	61.2 ±10	59.8 ±10	59.4 ±10	60.9 ±10	58.9 ±10	60 ±10	58 ±10
Education level (%)							
Low	1,816 (35)	201 (28)	557 (21)	231 (23)	527 (22)	559 (23)	192 (21)
Middle	2,460 (47)	309 (43)	1,033 (39)	425 (42)	917 (38)	1,002 (41)	330 (37)
High	990 (19)	214 (30)	1,080 (40)	364 (36)	930 (39)	909 (37)	375 (42)
Total leisure-time PA, METh/wk	26 [10 - 51]	30 [16-49]	55 [36-83]	52 [31 - 84]	49 [3 - 75]	48 [30-75]	56 [36-84]
Sports-related PA, METh/wk	*NA*	5 [4-6]	18 [12-28]	14 [8 - 25]	15 [9 - 24]	13 [8-22]	21 [14-32]
History of CAD (%)	3,120 (59)	460 (64)	1,748 (66)	689 (68)	1519 (64)	1,611 (65)	580 (65)
History of CeVD (%)	1,599 (30)	220 (30)	741 (28)	283 (28)	678 (29)	719 (29)	239 (27)
History of PAD (%)	1,091 (21)	69 (13)	325 (12)	123 (12)	298 (13)	300 (12)	111 (12)
History of AAA (%)	502 (10)	51 (7)	160 (6)	69 (7)	142 (6)	153 (6)	55 (6)
Multiple CVD manifestations	917 (17)	92 (13)	273 (10)	125 (12)	240 (10)	285 (12)	75 (8)
Type 2 diabetes (%)	1,058 (20)	99 (14)	318 (12)	117 (12)	300 (13)	346 (14)	66 (7)
Metabolic syndrome (%)	3,037 (58)	357 (49)	1,153 (43)	475 (47)	1,035 (44)	1,143 (46)	353 (39)
Smoking (%)							
Never	992 (19)	195 (27)	763 (29)	325 (32)	633 (27)	680 (28)	273 (30)
Former	2,376 (45)	342 (47)	1,383 (52)	519 (51)	1,206 (51)	518 (21)	183 (20)
Current	1,898 (36)	187 (26)	524 (20)	176 (17)	535 (23)	1,272 (52)	441 (49)

TABLE 1 (Continued)

		Exercise volume		Exercise type		Exercise intensity*	
	No exercise	>0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance-endurance	Light to moderate	Vigorous
Body mass index (%)							
<25 kg/m^2	1681 (32)	256 (35)	958 (36)	345 (34)	633 (27)	857 (35)	344 (38)
25-30 kg/m^2	2453 (47)	338 (47)	1304 (49)	495 (49)	535 (23)	1196 (48)	437 (49)
≥30 kg/m^2	1132 (22)	130 (18)	408 (15)	180 (18)	1206 (51)	417 (17)	116 (19)
Systolic BP, mmHg	140 ±21	137 ±20	137 ±19	138 ±20	136 ±19	137 ±20	136 ±19
Diastolic BP, mmHg	81 ±11	80 ±11	81 ±11	80 ±12	81 ±11	81 ±11	81 ±10
Total cholesterol, mmol/l	4.7 [4.0 - 5.6]	4.6 [3.9-5.5]	4.5 [3.8-5.3]	4.6 [3.9 - 5.4]	4.5 [3.8 - 5.3]	4.5 [3.8-5.4]	4.5 [3.8-5.3]
LDL cholesterol, mmol/l	2.7 [2.1 - 3.5]	2.6 [2-3.4]	2.5 [2.0-3.3]	2.6 [2.0 - 3.3]	2.5 [2.0 - 3.3]	2.5 [2.0-3.3]	2.5 [2.0-3.2]
HDL cholesterol, mmol/l	1.2 [1.0 - 1.4]	1.2 [1-1.5]	1.2 [1.0-1.5]	1.2 [1.0 - 1.5]	1.2 [1.0 - 1.5]	1.2 [1.0-1.5]	1.2 [1.0-1.5]
eGFR†, ml/min/1,73 m2	77 [64 -89]	78 [66-91]	81 [69-91]	79 [66-98]	81 [69-92]	79 [67-91]	82 [70-93]
CRP, mg/l	2.4 [1.1 – 5.0]	1.8 [0.8-4.0]	1.6 [0.8-3.3]	1.8 [0.8 - 3.9]	1.6 [0.8 - 3.3]	1.7 [0.8-3.5]	1.5 [0.8-3.2]
Antihypertensive drugs, (%)	3,963 (75)	540 (75)	2,003 (75)	783 (77)	1,760 (74)	1,881 (76)	644 (72)
Lipid-lowering medication (%)	3,517 (67)	500 (69)	2,002 (75)	753 (74)	1,749 (74)	1,821 (74)	665 (74)

Data are presented as n (%) for categorical variables and as means ± standard deviation or median (interquartile range) for continuous variables. AAA, aortic abdominal aneurysm; BP, blood pressure; CAD, coronary artery disease; CeVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; METh/wk, metabolic equivalent of task hours per week; PA, physical activity; PAD, peripheral artery disease. * For 27 participants, no MET value was available for the sports activity they reported. These participants were excluded from this analysis. † eGFR was estimated using the CKD-EPI formula.

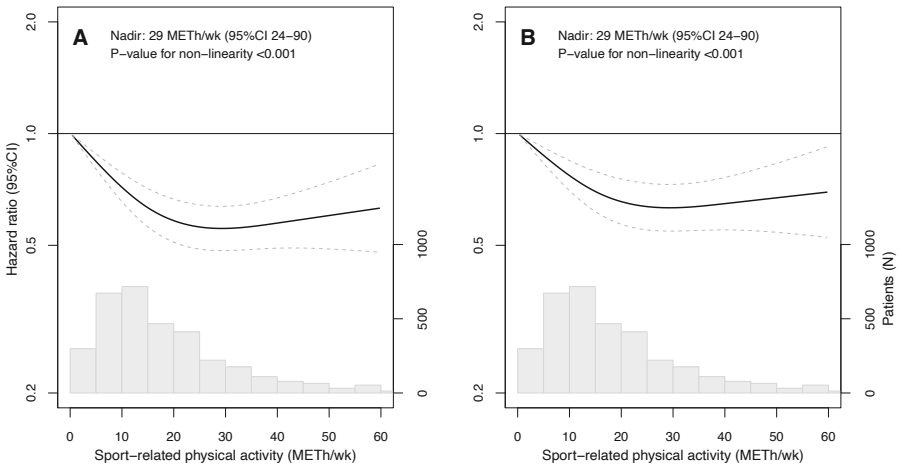
Baseline characteristics were similar for resistance and endurance exercise (Table 1). Participants who engaged in vigorous intensity exercise were younger (58 *vs* 60 years) and more frequently male (78% *vs* 74%) compared to those who engaged in light-moderate intensity (Table 1). Moreover, T2D and MetS were less prevalent among vigorous exercisers (7% *vs* 14%, and 39% *vs* 46%, respectively).

Exercise volume

Compared to no exercise, any exercise volume (>0 METh/wk) was related with risk reductions for all-cause mortality and recurrent events. Reverse J-shaped relations were observed for both outcomes, with nadir exercise volume at 29 METh/wk (95%CI 24-90) which related with HR 0.56 (95%CI 0.48-0.64) for all-cause mortality and HR 0.63 (95%CI 0.55-0.73) for recurrent vascular events (Figure 2). The relation with recurrent vascular events was driven by reductions in cardiovascular mortality and non-fatal stroke risk, while no relation with non-fatal myocardial infarction was found (Figure S2). Compared to no exercise, exercise volumes >0 and ≤7.5 METh/wk were related with HR 0.67 (95%CI 0.50-0.72) for all-cause mortality and HR 0.76 (95%CI 0.63-0.91) for recurrent events; and >7.5 METh/wk with HR 0.68 (95%CI 0.61-0.76) and HR 0.73 (95%CI 0.64-0.82), respectively (Table 2).

Together, BMI, insulin resistance, SBP, systemic inflammation and LDL-C mediated 29% (95%CI 21-42) of the relation between exercise volume and all-cause mortality and 32% (95%CI 22-48) for recurrent cardiovascular events. Systemic inflammation and insulin resistance were the most important mediators for both endpoints. Inflammation accounted for 16% (95%CI 12-24) of the relation with all-cause mortality and 17% (95%CI 11-26) with recurrent vascular events and insulin resistance accounted for 5% (95%CI 2-9) and 8% (95%CI 5-14), respectively.

FIGURE 2 Continuous relation between exercise volume and all-cause mortality and recurrent vascular events



This figure shows the best fitting restricted cubic splines (with 3 knots at the 10th, 50th and 90th percentile) for the continuous association between sports-related physical activity level and risk of all-cause mortality (A) and recurrent vascular events (B). The nadir and corresponding 95%CI for sports-related physical activity are provided in the plots. All splines are adjusted for age, sex, smoking status, number of pack years, alcohol consumption and education. The histograms in the plots show the number of participants at a specific physical activity level. Non-exercisers (N = 5,266) are not included in the histogram. METh/wk: Metabolic equivalent of task hours per week

Exercise type

Compared with non-exercisers, resistance exercise had a lower risk of all-cause mortality, HR 0.66 (95%CI 0.57-0.77) and recurrent vascular events, HR 0.76 (95%CI 0.65-0.89). Combined endurance-resistance activities were similarly related to lower risk for all-cause mortality (HR 0.66, 95%CI 0.58-0.74) and recurrent vascular events (HR 0.75, 95%CI 0.66-0.85, Table 3). These relations were driven by reduced risk of cardiovascular mortality and non-fatal stroke (Table S2).

The five mediators accounted for 21% (95%CI 14.2-33.9) of the relation between resistance training and all-cause mortality and 27% (95%CI 13.9-61.0) of the relation with recurrent vascular events (Table 3). Systemic inflammation was the most important mediator, with PMEs 11% (95%CI 7-20) and 14% (95%CI 9-34), respectively. Insulin resistance mediated 5% (95%CI 2-9) of the relation with all-cause mortality and 9% (95%CI 4-21) of the relation with recurrent vascular events.

TABLE 2 Relation between exercise volume, type and intensity with risk of all-cause mortality and recurrent vascular events

		Exercise volume HR (95%CI)		**Exercise type** HR (95%CI)		**Exercise intensity** HR (95%CI)*	
Model	**No exercise**	>0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance-endurance	Light to moderate	Vigorous
All-cause mortality							
Events (n)	1,725	134	397	187	344	386	133
Follow-up (persyr)	52,855	7,298	24,252	9,587	21,963	22,853	8,426
Crude	*Reference*	0.52 (0.43-0.63)	0.52 (0.47-0.58)	0.61 (0.53-0.71)	0.49 (0.44-0.55)	0.54 (0.48-0.6)	0.49 (0.41-0.58)
Model 1	*Reference*	0.56 (0.47-0.68)	0.58 (0.52-0.65)	0.59 (0.51-0.69)	0.59 (0.52-0.66)	0.58 (0.52-0.65)	0.58 (0.49-0.69)
Model 2	*Reference*	0.60 (0.50-0.72)	0.67 (0.60-0.75)	0.66 (0.57-0.77)	0.66 (0.58-0.74)	0.65 (0.58-0.73)	0.65 (0.55-0.78)
Model 3	*Reference*	0.62 (0.51-0.74)	0.68 (0.61-0.77)	0.69 (0.59-0.80)	0.67 (0.59-0.75)	0.66 (0.59-0.74)	0.69 (0.58-0.83)
Recurrent vascular events							
Events (n)	1,329	128	371	166	333	363	126
Follow-up (persyr)	48,756	6,740	22,791	9,033	20,499	21,339	7,938
Crude	*Reference*	0.66 (0.55-0.79)	0.61 (0.54-0.68)	0.68 (0.58-0.80)	0.60 (0.54-0.68)	0.63 (0.56-0.71)	0.58 (0.49-0.7)
Model 1	*Reference*	0.70 (0.58-0.84)	0.64 (0.57-0.72)	0.67 (0.57-0.79)	0.66 (0.58-0.74)	0.66 (0.59-0.74)	0.64 (0.53-0.77)
Model 2	*Reference*	0.76 (0.63-0.91)	0.74 (0.65-0.83)	0.76 (0.65-0.89)	0.75 (0.66-0.85)	0.75 (0.66-0.84)	0.74 (0.61-0.89)
Model 3	*Reference*	0.78 (0.64-0.94)	0.76 (0.67-0.85)	0.79 (0.67-0.93)	0.77 (0.68-0.87)	0.76 (0.68-0.86)	0.78 (0.65-0.94)

Hazard ratios for guideline-compliant exercise volume, different exercise types, and exercise intensities, compared to people that do not exercise. Model 1 adjusted for age and sex. Model 2 for model 1 and smoking status, pack years, alcohol consumption, education level. Model 3 for model 2 and systolic blood pressure, LDL-cholesterol, type 2 diabetes and body mass index. *For 27 participants no MET value was available for the sports activity they reported. These participants were excluded from this analysis. Abbreviations – HR: hazard ratio, 95%CI: 95% confidence interval

For combined endurance-resistance exercise, the total PMEs were 27% (20-42) and 38% (24-61) for all-cause mortality and recurrent vascular events. Insulin resistance and inflammation were the most important mediators. Compared to resistance exercise, LDL-C was a more important mediator, accounting for PME 4% (95%CI 2-7) and PME 5% (2-11), respectively.

Exercise intensity

Compared to non-exercisers, light-moderate exercise related to lower risk of all-cause mortality, HR 0.65 (95%CI 0.58-0.73), and recurrent vascular events, HR 0.75 (95%CI 0.66-0.84). These relations were similar for vigorous exercise, HR 0.65 (95%CI 0.55-0.78) and HR 0.74 (95%CI 0.61-0.89), respectively (Table 2).

The five mediators accounted for 24% (95%CI 18-34) of the relation between light-moderate exercise and all-cause mortality and 33% (95%CI 26-51) with recurrent vascular (Table 3). For vigorous exercise, total PMEs of 31% (95%CI 20-54) for all-cause mortality and 36% for recurrent events were observed (Table 5). For both intensities, systemic inflammation was the most important mediator, but the PME for insulin resistance was higher for vigorous exercise than light-moderate exercise: 8% (95%CI 4-16) vs 3% (95%CI 1-6) for all-cause mortality.

TABLE 3 Mediation analysis of the effects of exercise volume, type and intensity

		Exercise volume		**Exercise type**		**Exercise intensity***	
		PME (95%CI)		PME (95%CI)		PME (95%CI)	
	No exercise	>0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance-endurance	Light to moderate	Vigorous
All-cause mortality							
Total effect, HR (95%CI)	*Reference*	0.59 (0.52-0.66)	0.68 (0.61-0.76)	0.64 (0.54-0.72)	0.64 (0.58-0.72)	0.63 (0.57-0.69)	0.65 (0.55-0.80)
Direct effect, HR (95%CI)	*Reference*	0.64 (0.56-0.69)	0.76 (0.68-0.85)	0.70 (0.61-0.79)	0.72 (0.65-0.82)	0.70 (0.64-0.78)	0.75 (0.62-0.90)
Indirect effect, HR (95%CI)	*Reference*	0.92 (0.91-0.96)	0.89 (0.87-0.92)	0.91 (0.86-0.93)	0.88 (0.86-0.91)	0.89 (0.86-0.92)	0.88 (0.83-0.92)
Total PME (%)		14.8 (8.2-16.9)	28.5 (20.7-42)	21.4 (14.2-33.9)	27.4 (20.4-42.1)	24.0 (17.7-33.9)	31.1 (20.4-54.1)
Mediated through:							
Body mass index (%)		-0.4 (-1.8-0.9)	0.7 (-1.6-3.3)	1.0 (-1.5-4.4)	-0.2 (-2.4-2.1)	0.7 (-1.0-2.3)	-0.5 (-4.6-4.1)
Insulin resistance (%)		2.7 (1.1-5.5)	5.0 (2.1-8.8)	5.2 (2.1-8.7)	4.2 (1.9-7.1)	3.3 (1.0-5.5)	8.2 (3.8-16.3)
Systolic blood pressure (%)		1.8 (-0.9-3.7)	3.1 (1.3-3.8-5.8)	2.3 (0.3-4.5)	3.1 (1.2-5.9)	3.0 (1.3-5.8)	1.9 (-0.6-5.1)
Inflammation (%)		8.7 (2.1-10.1)	16.4 (11.4-24.7)	11.4 (6.8-20.0)	16.5 (12.3-24.2)	14.5 (10.4-19.6)	16.7 (10.7-28.0)
LDL-cholesterol (%)		2.1 (0.7-3.7)	3.3 (1.2-6)	1.5 (-0.9-4.8)	3.8 (2.0-7.4)	2.5 (1.0-5.2)	4.8 (1.7-10.7)
Recurrent vascular events							
Total effect, HR (95%CI)	*Reference*	0.72 (0.65-0.86)	0.73 (0.64-0.82)	0.72 (0.62-0.85)	0.72 (0.63-0.79)	0.72 (0.65-0.80)	0.71 (0.59-0.86)
Direct effect, HR (95%CI)	*Reference*	0.78 (0.69-0.92)	0.80 (0.72-0.90)	0.79 (0.70-0.93)	0.82 (0.71-0.91)	0.80 (0.73-0.90)	0.81 (0.65-0.95)
Indirect effect, HR (95%CI)	*Reference*	0.92 (0.91-0.96)	0.90 (0.88-0.92)	0.91 (0.88-0.94)	0.88 (0.85-0.91)	0.90 (0.87-0.92)	0.88 (0.85-0.92)
Total PME		24.2 (10.9-48.7)	32.0 (21.1-50.9)	27.0 (19.3-61.0)	37.9 (23.9-60.8)	33.0 (25.6-51.3)	36.3 (19.6-68.2)

TABLE 3 (Continued)

		Exercise volume		Exercise type		Exercise intensity*	
		PME (95%CI)		PME (95%CI)		PME (95%CI)	
	No exercise	>0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance-endurance	Light to moderate	Vigorous
Mediated through:							
Body mass index (%)		-0.2 (-3.5-1.6)	-0.5 (-2.9-1.2)	-0.1 (-2.6-2.9)	-0.4 (-3.0-1.9)	0.1 (-2.1-1.3)	-1.5 (-7.1-2.2)
Insulin resistance (%)		6.7 (3.4-13.7)	8.0 (4.8-13.5)	8.8 (4.4-20.9)	8.3 (4.6-13.7)	7.2 (3.7-11.7)	12.2 (5.1-25.1)
Systolic blood pressure (%)		2.5 (-1.3-9.9)	3.6 (1.4-8.0)	3.2 (0.3-7.7)	4.5 (1.5-9.9)	4.2 (1.8-8.6)	2.7 (-0.4-6.9)
Inflammation (%)		12.1 (1.8-28.1)	17.1 (10.6-26.1)	13.7 (8.6-34.2)	20.2 (13.4-32.6)	18.2 (12.8-28.6)	18.0 (9.4-36.7)
LDL-cholesterol (%)		3.2 (1.8-6)	3.7 (1.6-8.0)	1.4 (-1.3-6.1)	5.3 (2.4-11.3)	3.4 (1.4-8.5)	4.9 (1.4-12.4)

Mediation analysis of the associations between exercise volume, type and intensity and all-cause mortality and recurrent vascular events. Total effect represents the full size of the association between the exposure and the health outcomes. The direct effect is the effect of the exposure that is effectuated through other paths than the included mediators. The indirect effect represents the effect size that is brought about through exercise-related changes in the included mediators. The PME indicates the proportion of the overall effect that is mediated through the included mediators. All models are adjusted for age, sex, smoking status, pack years, alcohol consumption and education level. *For 27 participants no MET value was available for the sports activity they reported. These participants were excluded from this analysis. Abbreviations – 95%CI: 95% confidence interval, HR: hazard ratio, LDL: Low-density lipoprotein, METh/wk: Metabolic equivalent of task hours per week, PME: Proportion mediated effect

Subgroup and sensitivity analyses

Subgroup analyses

The effects of exercise volume, type and intensity were similar for men and women (all p-values for interaction >0.40, Table S3). The total PME through the included mediators was lower in females (e.g. 23% for vigorous exercise and all-cause mortality vs 31% in the full analysis). Specifically, the PME for systemic inflammation was smaller in females, while a larger PME was found for insulin resistance (Table S3).

In patients with low-grade inflammation (N = 3,557), the protective effect of exercise volume, type and intensity with all-cause mortality and recurrent events was smaller compared with the main analysis (p for interaction <0.01, Table S3). A smaller PME through inflammation was observed, *e.g.* a total PME of 7% (95%CI -2;12%) in the association between exercise volume and all-cause mortality vs. a PME of 29% (95%CI 21-42) in the main analysis.

In patients with MetS (n= 4,547), the total PME was lower, *e.g.* the total PME for exercise volume and recurrent vascular events was 19% (95%CI 5-34) compared to 32% (95%CI 21-51) in the main analysis mainly due to a lower PME through insulin resistance (Table S3). Across subgroups with differing BMI, the associations of exercise volume, type and intensity with all-cause mortality and recurrent cardiovascular events were stronger in people with BMI <25 kg/m^2 or ≥30 kg/m^2 (all p-values for interaction <0.02, Tables S3e-g). BMI remained an unimportant mediator in these subgroups. In patients without T2D, the HOMA-IR formula was used instead of the triglyceride-glucose ratio and findings were similar to the primary analysis (Table S3h). In a sensitivity analysis, using traditional Cox regression to estimate the relationship between exercise volume, type and intensity across these subgroups, HRs were comparable to the main analyses (Table S4a/b).

Sensitivity analyses

When the mediators were assessed individually to assess independence of the causal paths, a similar PME was found compared to the main analysis (Table S1). In analyses excluding patients that experienced an event in the first 1, 3, and 5 years after inclusion, the exercise volume, type and intensity relations were similar in direction to the main analysis, but the HRs were slightly closer to 1 (Figure S5a-c).

DISCUSSION

This study shows that the majority of patients with established CVD report that they do not regularly perform physical exercise. Moreover, we show that exercise is strongly related with reduced risk of recurrent cardiovascular events and all-cause mortality in patients with established CVD, even at a low volume. The associations are reverse J-shaped, with a nadir at 29 METh/wk. METh/wk captures both exercise quantity and intensity, and therefore, more METh/wk can be achieved through either a longer time doing mild intensity exercise or a short time spent on vigorous intensity exercise. The present study found similar relations for different exercise types (muscle-strengthening *vs* endurance) and intensities (light-moderate *vs* vigorous). Over a third of the relations was mediated through changes in BMI, insulin resistance, SBP, systemic inflammation and LDL-C. Systemic inflammation was the most important mediator and accounted for over 15% of the total effect.

Few long-term studies on exercise have been performed in patients with established CVD, but the available studies report similar risk reductions.[2,3,29,30] One previous study in coronary artery disease patients also found a reverse J-shaped association with mortality risk that plateaued around 20 METh/wk.[29]

In general population studies, muscle-strengthening activities have been associated with reductions in risk of mortality and cardiovascular events compared with no exercise, albeit not as strongly as the associations found in the present study.[31] Endurance and resistance training have previously been directly compared in clinical trials, in populations at high CVD risk.[9,32,33] Some found that endurance exercise was more effective in lowering BMI and subcutaneous fat mass than resistance training, but overall resistance exercise and endurance exercise were similarly beneficial for CVD risk factors.[9,32,33] We add to this existing literature that, in patients with established CVD, there is no great difference in the associations of different exercise types and intensities. Moreover, to our knowledge, we are the first to quantify the contribution of different mediating factors of physical exercise benefits in patients with CVD.

Multiple studies have investigated the physiological effects of exercise, but the relative contributions of these mediators in the association with clinical endpoints remains unknown. For the first time, our study identifies systemic inflammation and insulin resistance as the main mediators for cardiovascular risk reduction with exercise.

Exercise results in the release of anti-inflammatory myokines, and adipokines.[34,35] Myokine release is stronger in vigorous and endurance exercise, which could explain why inflammation was a more important mediator in these associations. In our study, the beneficial effects of exercise on mortality and recurrent event risk through reduced inflammation was attenuated in patients with low-grade inflammation, possibly because the underlying cause for the low-grade inflammation negates the effects of exercise.

Exercise-induced release of adipokines, like IL-6 and adiponectin, accelerates lipolysis, inhibits gluconeogenesis and, increases insulin sensitivity.[34,36,37] Moreover, exercise stimulates GLUT-4 expression, which results in increased glucose uptake during exercise and improved glycogen storage in rest.[38]

Although the mediators included in this analysis explain about a quarter to a third of the associations with exercise, the lion's share remains unexplained. Previous research has indicated that the benefits of physical exercise exceed the effect that could be expected based resulting changes in traditional cardiovascular risk factors alone.[39] A potential alternative mediator is cardiorespiratory fitness, which is a strong independent predictor of CVD and all-cause mortality.[40] Additionally, regular exercise induces angioneogenesis and vasodilatation and reduces endothelial dysfunction, ultimately leading to better oxygen delivery.[20,39,41] Theoretically, part of the relation between exercise and health outcomes could also be effectuated through placebo effect. For some patients with established CVD, exercise constitutes an active intervention targeted at reducing health risks and as such it is subject to placebo effect.[42] Placebo effect has been shown to significantly and beneficially affect functional and quality of life measures and may reduce (cardiovascular) event risk.[42,43] Furthermore, in patients with a history of CVD, it has been hypothesized that exercise increases atherosclerotic plaque stability and improves vascular function and coronary circulation, thus limiting ischemic damage from a next vascular event.[44–46] This is a potential explanation for our findings that higher exercise intensity primarily reduces the mortality rate and has little effects on non-fatal myocardial infarction.

Our study shows that clinically relevant reductions in all-cause mortality and cardiovascular event risk can be achieved through compliance with international exercise guidelines for CVD management. Generally, the observed benefits were similar across exercise types and intensities. We recommend that health care professionals focus on motivating their patients to perform any type of exercise that is in line with

their capabilities and personal preferences. We identified some subgroups in which the relations of exercise and clinical outcomes were weaker (e.g. patients with MetS or low-grade inflammation), possibly because underlying conditions negate exercise effects mediated through inflammation and insulin sensitivity. However, in these subgroups a protective association of exercise volume, type and intensity was still found, and therefore it remains important to motivate these patients to exercise.

Strengths and limitations

Strengths of the current study include its large sample size, prospective data collection, endpoints adjudication based on medical records and low rate of loss to follow-up. Study limitations include the need for categorization of exposure and mediator variables, and unavailability of data on other potential mediators. Exercise type was not directly assessed in the baseline questionnaire, but approximated based on national guidelines, possibly resulting in misclassification. Moreover, exercise was self-reported, and this should be taken into account when interpreting the results of this study. Although the EPIC physical activity questionnaire was validated against 3-day activity diaries, it was not validated for measuring absolute values of exercise volume. It is however possible to use the results to rank people based on their physical activity. Furthermore, the effect estimates found in this study were similar to those found in studies based on accelerometer-measured exercise levels.[2] The analyses on exercise type were not subject to this limitation, as detailed information on exercise type was available and this was classified based on standards specifically designed for the Dutch population.[25]

Residual confounding is an important limitation in lifestyle-related research and may arise from difficult-to-measure confounders like social-economic status, frailty or diet. The majority of the study population was treated with blood pressure- and lipid-lowering therapy, which may partly explain the small PMEs through systolic blood pressure and LDL-cholesterol. Evidence suggests that in patients using lipid-lowering therapies, the LDL-cholesterol lowering effects of exercise are smaller,[13] while add-on blood pressure-lowering effects are still observed for patients using blood pressure-lowering drugs.[12] Blood pressure- and lipid-lowering pharmacological therapies are standard of care in patients with established CVD, but caution is warranted in applying the current study's findings to populations without blood pressure and LDL-cholesterol medication. Mediation analysis with structural equation models assumes independence of the included causal pathway, which is difficult to assess. However, in a sensitivity

analysis assessing mediators independently, the PME was similar compared to the main analysis. Finally, exercise and mediator levels were measured at the same time. This cross-sectional assessment means that it is impossible to establish the direction of the causal effect. However, the included mediators were selected because previous intervention studies showed that exercise influenced them (and not the other way around).

CONCLUSION

Physical exercise is associated with a reduced risk of all-cause mortality and recurrent vascular events in patients with established CVD. When counselling CVD patients on lifestyle optimization, they should be advised to perform physical exercise in a manner that fits with their person abilities and preferences. Any level of exercise is associated with clinically relevant reduction in mortality and CVD risk reductions and health benefits are similar across different exercise types and intensities. Up to a third of the effect of exercise is mediated through improvement in traditional cardiovascular risk factors, of which systemic inflammation and insulin resistance are the most important. This study reiterates the importance of physical exercise in patients with established CVD.

REFERENCES

1. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. British Journal of Sports Medicine 2020; 54: 1451–1462.
2. Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality : systematic review and harmonised meta-analysis. British Medical Journal 2019; 366: 14570.
3. Geidl W, Schlesinger S, Mino E, et al. Dose-response relationship between physical activity and mortality in adults with noncommunicable diseases: A systematic review and meta-analysis of prospective observational studies. International Journal of Behavioral Nutrition and Physical Activity; 17. Epub ahead of print 2020. DOI: 10.1186/s12966-020-01007-5.
4. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019; 140: e596–e646.
5. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021; 1–111.
6. Ciolac EG, Rodrigues-da-Silva JM. Resistance Training as a Tool for Preventing and Treating Musculoskeletal Disorders. Sports Medicine 2016; 46: 1239–1248.
7. Giovannucci EL, Rezende LFM, Lee DH. Muscle-strengthening activities and risk of cardiovascular disease, type 2 diabetes, cancer and mortality: A review of prospective cohort studies. Journal of Internal Medicine 2021; 290: 789–805.
8. Ashton RE, Tew GA, Aning JJ, et al. Effects of short-term, medium-term and long-term resistance exercise training on cardiometabolic health outcomes in adults: systematic review with meta-analysis. British journal of sports medicine 2020; 54: 341–348.
9. Yarizadeh H, Eftekhar R, Anjom-Shoae J, et al. The Effect of Aerobic and Resistance Training and Combined Exercise Modalities on Subcutaneous Abdominal Fat: A Systematic Review and Meta-analysis of Randomized Clinical Trials. Advances in Nutrition 2021; 12: 179–196.
10. Lin X, Zhang X, Guo J, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials. Journal of the American Heart Association 2015; 4: 1–28.
11. Thompson PD, Franklin BA, Balady GJ, et al. Exercise and Acute Cardiovascular Events. Circulation 2007; 115: 2358–2368.
12. Naci H, Salcher-Konrad M, Dias S, et al. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure. Br J Sports Med 2019; 53: 859–869.
13. Albarrati AM, Alghamdi MSM, Nazer RI, et al. Effectiveness of low to moderate physical exercise training on the level of low-density lipoproteins: A systematic review. Biomed Res Int; 2018. Epub ahead of print 2018. DOI: 10.1155/2018/5982980.
14. Fiuza-Luces C, Santos-Lozano A, Joyner M, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. Nature Reviews Cardiology 2018; 15: 731–743.

15. Ahmed HM, Blaha MJ, Nasir K, et al. Effects of Physical Activity on Cardiovascular Disease. The American Journal of Cardiology 2012; 109: 288–295.
16. Zheng G, Qiu P, Xia R, et al. Effect of aerobic exercise on inflammatory markers in healthy middle-aged and older adults: A systematic review and meta-analysis of randomized controlled trials. Frontiers in Aging Neuroscience; 11. Epub ahead of print 2019. DOI: 10.3389/fnagi.2019.00098.
17. Cerqueira É, Marinho DA, Neiva HP, et al. Inflammatory Effects of High and Moderate Intensity Exercise—A Systematic Review. Frontiers in Physiology 2020; 10: 1–14.
18. Nystoriak MA, Bhatnagar A. Cardiovascular Effects and Benefits of Exercise. Frontiers in Cardiovascular Medicine 2018; 5: 1–11.
19. Sampath Kumar A, Maiya AG, Shastry BA, et al. Exercise and insulin resistance in type 2 diabetes mellitus: A systematic review and meta-analysis. Annals of Physical and Rehabilitation Medicine 2019; 62: 98–103.
20. Pinckard K, Baskin KK, Stanford KI. Effects of Exercise to Improve Cardiovascular Health. Frontiers in Cardiovascular Medicine 2019; 6: 1–12.
21. Simons PCG, Algra A, van de Laak MF, et al. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol 1999; 15: 773–81.
22. Pols MA, Peeters PH, Ocké MC, et al. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol 1997; 26 Suppl 1: S181-9.
23. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc; 32. Epub ahead of print 2000. DOI: 10.1097/00005768-200009001-00009.
24. Caspersen CJ, Powell KE, Christenson GM. Physical Activity, Exercise, and Physical Fitness: Definitions and Distinctions for Health-Related Research. Public Health Reports 1985; 100: 126–131.
25. Wendel-Vos S, van den Berg M, M D, et al. Beweegrichtlijnen en Wekelijks Sporter. RIVM-Briefrapport 2019-0237. 2019.
26. VanderWeele TJ. Marginal Structural Models for the Estimation of Direct and Indirect Effects. Epidemiology 2009; 20: 18–26.
27. Hong G. Ratio of Mediator Probability Weighting for Estimating Natural Direct and Indirect Effects. Proceedings of the American Statistical Association, Biometrics Section 2010; 2401–2415.
28. Lange T, Vansteelandt S, Bekaert M. A Simple Unified Approach for Estimating Natural Direct and Indirect Effects. American Journal of Epidemiology 2012; 176: 190–195.
29. Stewart RAH, Held C, Hadziosmanovic N, et al. Physical Activity and Mortality in Patients With Stable Coronary Heart Disease. Journal of the American College of Cardiology 2017; 70: 1689–1700.
30. Barbiellini Amidei C, Trevisan C, Dotto M, et al. Association of physical activity trajectories with major cardiovascular diseases in elderly people. Heart 2022; 108: 360–366.

31. Momma H, Kawakami R, Honda T, et al. Muscle-strengthening activities are associated with lower risk and mortality in major non-communicable diseases: a systematic review and meta-analysis of cohort studies. British Journal of Sports Medicine 2022; bjsports-2021-105061.

32. Schroeder EC, Franke WD, Sharp RL, et al. Comparative effectiveness of aerobic, resistance, and combined training on cardiovascular disease risk factors: A randomized controlled trial. PLOS ONE 2019; 14: e0210292.

33. Bateman LA, Slentz CA, Willis LH, et al. Comparison of Aerobic Versus Resistance Exercise Training Effects on Metabolic Syndrome (from the Studies of a Targeted Risk Reduction Intervention Through Defined Exercise - STRRIDE-AT/RT). The American Journal of Cardiology 2011; 108: 838–844.

34. Ertek S, Cicero A. State of the art paper Impact of physical activity on inflammation: effects on cardiovascular disease risk and other inflammatory conditions. Archives of Medical Science 2012; 5: 794–804.

35. Leal LG, Lopes MA, Batista ML. Physical exercise-induced myokines and muscle-adipose tissue crosstalk: A review of current knowledge and the implications for health and metabolic diseases. Frontiers in Physiology 2018; 9: 1–17.

36. Stanford KI, Goodyear LJ. Exercise regulation of adipose tissue. Adipocyte 2016; 5: 153–162.

37. Fisman EZ, Tenenbaum A. Adiponectin: A manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? Cardiovascular Diabetology 2014; 13: 1–10.

38. Richter EA, Hargreaves M. Exercise, GLUT4, and Skeletal Muscle Glucose Uptake. Physiological Reviews 2013; 93: 993–1017.

39. Green DJ, Smith KJ. Effects of Exercise on Vascular Function, Structure, and Health in Humans. Cold Spring Harbor Perspectives in Medicine 2018; 8: a029819.

40. Kaminsky LA, Arena R, Ellingsen Ø, et al. Cardiorespiratory fitness and cardiovascular disease - The past, present, and future. Progress in Cardiovascular Diseases 2019; 62: 86–93.

41. Thyfault JP, Bergouignan A. Exercise and metabolic health: beyond skeletal muscle. Diabetologia 2020; 63: 1464–1474.

42. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol 2008; 59: 565–90.

43. Gallone G, Baldetti L, Angelini F, et al. The Placebo Effect on Symptoms, Quality of Life, and Functional Outcomes in Patients With Angina Pectoris: A Meta-analysis of Randomized Placebo-Controlled Trials. Canadian Journal of Cardiology 2022; 38: 113–122.

44. Winzer EB, Woitek F, Linke A. Physical Activity in the Prevention and Treatment of Coronary Artery Disease. Journal of the American Heart Association 2018; 7: 1–15.

45. Hambrecht R, Wolf A, Gielen S, et al. Effect of Exercise on Coronary Endothelial Function in Patients with Coronary Artery Disease. New England Journal of Medicine 2000; 342: 454–460.

46. Borges JP, da Silva Verdoorn K. Cardiac Ischemia/Reperfusion Injury: The Beneficial Effects of Exercise. In: Advances in Experimental Medicine and Biology. 2017, pp. 155–179.

SUPPLEMENTAL MATERIAL

Supplemental appendix 1 Supplemental methods

Statistical analyses

Cox proportional hazard models were used to assess the association between exercise and all- cause mortality and recurrent vascular events. The proportional hazard assumption was visually checked using Schoenfeld residuals and log-minus-log plots. The functional form of covariates in the model was assessed using Martingale residuals.

For sports-related physical activity as a continuous variable, a restricted cubic spline was used when the linearity assumption did not hold. The number of knots used in the spline was selected based on Akaike's Information Criterion, with a value decreased by at least 2 points deemed sufficient to select a model with additional knots over a more parsimonious model.

Nadir levels of sports-related physical activity, *i.e.* the level of sports-related physical activity that is associated with the lowest hazard ratio, were obtained from the cubic splines. 95% confidence intervals for these nadirs were estimated using bootstrapping methods. In 1,000 random samples, drawn with replacement, a new restricted cubic spline was fitted adjusted for age, sex, smoking status, number of pack years, alcohol consumption and education and the nadir for physical activity level was extracted. From these 1,000 nadirs, the 95% confidence interval was extracted by placing them in an ascending order and taking the value for the 2.5th and 97.5th percentile.

Mediation analysis based on a counterfactual framework was performed using the marginal structural model approach proposed by VanderWeele (2009), Hong (2010) and Lange (2012)[1–3]. This model was first applied to each potential mediator individually, to ensure that the causal paths were independent of other mediators. For the main analyses, multiple mediators were combined into a single model to estimate the total mediated effect.

1. Multinomial logistic regression models were used to condition the mediator on the exposure and confounders in the exposure-mediator relation.
2. A new dataset was created by replicating the original data with addition of a new variable: *exposure1**. In the first replication, *exposure1** took the value for

the exposure that was observed. In the second replication, *exposure1** took the counterfactual value from the observed exposure. This procedure was repeated 4 more times, until a dataset with 5 auxiliary variables was obtained.

3. The multinomial logistic regression models from step (1) were used to estimate the probability of the observed mediator value given *exposure** for each observation in the pseudo-population. This procedure was repeated to obtain such a probability for each mediator included in the analysis. To assess the effects of all mediators simultaneously, the calculated weights for each individual mediator were multiplied.
4. Ratio of mediator probability weighting on the combined probability was used to ensure balance of the covariates in the pseudo-population. Through this weighting procedure adjustment for confounding in the exposure-mediator and the mediator-outcome relation was achieved. Weighted Cox proportional hazard models including only the direct and indirect effects and confounders in the exposure-outcome relation were used to estimate each effect.
5. Direct and indirect effects are additive on the log(hazard) scale. To calculate the proportion mediated effect (PME), the indirect effect of through each mediator was divided by the total effect on the log(hazard) scale.
6. Bootstrapping was used to obtain 95% confidence intervals for the direct effects, indirect effects and PMEs. The entire procedure was repeated in 1,000 bootstrap samples and the 2.5th and 97.5th percentiles of the distributions for each estimand were set as the lower and upper bounds of the confidence intervals.

Operationalization of mediators

Based on published reviews on the physiological effects of exercise[4,5] and availability in the UCC-SMART cohort, the following variables were selected as potential mediators in the association from physical activity to cardiovascular events and all-cause mortality: body mass index, systolic blood pressure, systemic inflammation, insulin resistance and cardiorespiratory fitness. All mediators were classified into quintiles to ensure stability of the models used in the mediation analysis.

Mediator	Operationalization of the mediator
Body mass index	Sex-specific quintiles of body mass index as calculated as weight / height^2 at inclusion in the cohort. Quintile cut-offs (kg/m^2) Men: 24.0, 25.7, 27.4, 29.7 Women: 22.6, 25.0, 27.3, 30.5
Systolic blood pressure	Sex-specific quintiles of the mean of the second and third of a total of three blood pressure measurements at inclusion in the cohort. Quintile cut-offs (mmHg) Men: 122, 132, 141, 154 Women: 120, 131, 141, 156
LDL-cholesterol	Sex-specific quintiles of LDL-cholesterol measurements at inclusion in the cohort. LDL-cholesterol was estimated using the Friedewald formula. Quintile cut-offs (mmol/l) Men: 1.9, 2.4, 2.9, 3.6 Women: 2.0, 2.5, 3.1, 3.9
Systemic inflammation	Sex-specific quintiles of plasma C reactive protein levels at inclusion in the SMART cohort. All patients with plasma C reactive protein levels > 10 mg/L were excluded from the analysis, as these values were thought to be indicative of an ongoing inflammatory process. Quintile cut-offs (mg/L) Men: 0.8, 1.5, 2.6, 5.0 Women: 0.9, 1.7, 3.1, 6.3
Insulin resistance	Sex-specific quintiles of baseline triglyceride-glucose index. Triglyceride (Tg) and fasting glucose (FBG) concentrations were measured at baseline. Formula: *ln [Tg (mg/dL)* × *FBG (mg/dL)/2]* [6] Quintile cut-offs Men: 7.5, 7.8, 8.1, 8.5 Women: 7.5, 7.8, 8.1, 8.4

TABLE S1 Proportion mediated effect through single mediators

	Proportion mediated effect (95%CI) , %					
Mediator	0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + aerobic	Light-moderate	Vigorous
All-cause mortality						
Body mass index	-0.1 (-1.3; 1.3)	0.8 (-1.3; 3.3)	1.1 (-1.3; 3.9)	-0.1 (-2.7; 2.4)	0.7 (-1.1; 2.7)	-0.2 (-3.7; 3.1)
Insulin resistance	2.0 (-1.2; 6.3)	5.2 (2.3; 8.9)	2.9 (-1.0; 8.2)	2.1 (-2.4; 7.6)	2.0 (-0.8; 5.5)	3.4 (-3.0; 13.7)
Systolic BP	2.0 (-1.2; 6.0)	4.0 (1.5; 8.2)	2.6 (-0.7; 7.9)	2.5 (-2.1; 7.3)	2.4 (-0.6; 5.5)	2 (-2.6; 12.8)
Inflammation	3.3 (-1.1; 9.8)	5.4 (1.7; 1.8)	3.5 (-0.5; 15.2)	3.5 (-1.8; 21.7)	3.1 (-0.5; 18.5)	4.2 (-2.3; 21.1)
LDL-cholesterol	3.1 (-1.1; 9.7)	4.4 (1.5; 21.2)	2.8 (-0.7; 14.5)	3.6 (-1.6; 20.8)	2.9 (-0.4; 18.2)	4.2 (-2.1; 20.4)
Recurrent vascular events						
Body mass index	-0.7 (-4.4; 0.7)	-0.4 (-2.7; 1.5)	-0.1 (-2.6; 2.3)	-0.4 (-2.9; 1.8)	-0.1 (-2.1; 1.9)	-1.1 (-6.0; 2.1)
Insulin resistance	3.9 (-3.3; 17.4)	3.0 (-2.1; 13.3)	3.2 (-2.0; 16.7)	3.0 (-2.4; 12.9)	2.9 (-1.7; 11.6)	3.5 (-4.8; 23.7)
Systolic BP	4.0 (-2.3; 16.6)	3.3 (-1.9; 12.7)	3.3 (-1.7; 15.4)	3.2 (-2.1; 12.1)	3.5 (-1.5; 11.0)	2.4 (-4.1; 22.0)
Inflammation	6.2 (-1.2; 19.6)	5.4 (-1.7; 24.0)	5.6 (-1.5; 21.6)	5.2 (-1.9; 24.3)	5.2 (-1.3; 24.7)	6.3 (-3.8; 29.1)
LDL-cholesterol	6.2 (-1.1; 18.2)	4.5 (-1.5; 23.3)	3.8 (-1.6; 20.7)	4.7 (-1.7; 23.1)	4.4 (-1.1; 24.1)	5.4 (-3.5; 27.6)

Proportion of total effect mediated through a single mediator. PME was derived using structural equation models with a single mediator included. All models are adjusted for age, sex, smoking status, number of pack years, alcohol consumption and education level. 95% confidence levels were obtained using the percentile method in 1,000 bootstrap samples. Abbreviations: 95%CI: 95% confidence interval, BP: blood pressure, LDL: low-density lipoprotein, METh/wk: Metabolic equivalent of task hours per week

TABLE S2 Relations of exercise volume, type and intensity with risk of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke

		Exercise volume		Exercise type		Exercise intensity	
	No exercise	0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + aerobic	Light to moderate	Vigorous
Cardiovascular mortality							
Crude	*Reference*	0.48 (0.36-0.63)	0.48 (0.41-0.56)	0.59 (0.47-0.74)	0.44 (0.37-0.53)	0.49 (0.41-0.57)	0.46 (0.35-0.60)
Model 1	*Reference*	0.53 (0.40-0.69)	0.54 (0.46-0.63)	0.57 (0.46-0.71)	0.53 (0.45-0.64)	0.53 (0.45-0.63)	0.55 (0.42-0.71)
Model 2	*Reference*	0.56 (0.43-0.74)	0.62 (0.53-0.74)	0.64 (0.52-0.81)	0.60 (0.51-0.72)	0.60 (0.51-0.71)	0.63 (0.48-0.82)
Model 3	*Reference*	0.59 (0.45-0.79)	0.65 (0.55-0.77)	0.69 (0.55-0.86)	0.63 (0.52-0.75)	0.62 (0.53-0.74)	0.69 (0.53-0.90)
Non-fatal myocardial infarction							
Crude	*Reference*	0.94 (0.79-1.11)	0.92 (0.83-1.02)	0.90 (0.78-1.04)	0.94 (0.85-1.05)	0.94 (0.84-1.04)	0.91 (0.77-1.06)
Model 1	*Reference*	0.99 (0.84-1.18)	0.91 (0.82-1.00)	0.91 (0.78-1.05)	0.94 (0.84-1.04)	0.94 (0.84-1.04)	0.90 (0.77-1.05)
Model 2	*Reference*	1.03 (0.87-1.22)	0.97 (0.87-1.07)	0.95 (0.82-1.10)	1.00 (0.89-1.12)	0.99 (0.89-1.10)	0.96 (0.82-1.13)
Model 3	*Reference*	1.06 (0.89-1.25)	1.00 (0.90-1.11)	0.97 (0.84-1.13)	1.04 (0.93-1.16)	1.01 (0.91-1.13)	1.02 (0.87-1.20)
Non-fatal stroke							
Crude	*Reference*	0.90 (0.65-1.25)	0.60 (0.48-0.75)	0.83 (0.61-1.11)	0.63 (0.50-0.79)	0.67 (0.54-0.84)	0.67 (0.48-0.95)
Model 1	*Reference*	0.94 (0.68-1.30)	0.64 (0.51-0.80)	0.82 (0.61-1.10)	0.68 (0.54-0.86)	0.70 (0.56-0.88)	0.74 (0.52-1.03)
Model 2	*Reference*	1.00 (0.72-1.38)	0.71 (0.56-0.90)	0.90 (0.67-1.22)	0.75 (0.59-0.96)	0.77 (0.62-0.97)	0.82 (0.58-1.16)
Model 3	*Reference*	1.00 (0.72-1.39)	0.71 (0.56-0.90)	0.91 (0.68-1.23)	0.75 (0.59-0.96)	0.78 (0.62-0.98)	0.83 (0.59-1.17)

Hazard ratios for different types and intensities of sport-related physical activity, compared to people that do not partake in any sport-related physical activity. Model 1 adjusted for age and sex. Model 2, the main model, adjusted for model 1 and smoking status, pack years, alcohol consumption, education level. Model 3 for model 2 and systolic blood pressure, LDL-cholesterol, type 2 diabetes and body mass index. The final model adjusted for model 2 and total number of MET hours of sports-related physical activity per week. Abbreviations –95%CI: 95% confidence interval, HR: hazard ratio

TABLE S3 Mediation analysis – Subgroup analyses

Mediation analysis of the associations between exercise volume, type and intensity and all-cause mortality and recurrent vascular events across subgroups. Total effect represents the full size of the association between the exposure and the health outcomes. The direct effect is the effect of the exposure that is effectuated through other paths than the included mediators. The indirect effect represents the effect size that is brought about through exercise-related changes in the included mediators. The PME indicates the proportion of the overall effect that is mediated through the included mediators. All models are adjusted for age, sex, smoking status, pack years, alcohol consumption and education level. 95%CI: 95% confidence interval, HR: hazard ratio, LDL: Low-density lipoprotein, METh/wk: Metabolic equivalent of task hours per week, PME: Proportion mediated effect

TABLE S3a Mediation analysis in males (N = 6,376)

		Exercise volume		**Exercise type**		**Exercise intensity**	
		0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
All-cause mortality							
Total effect, *HR (95%CI)*	*Reference*	0.70 (0.60;0.85)	0.65 (0.58;0.70)	0.62 (0.57;0.70)	0.64 (0.57;0.71)	0.63 (0.57; 0.73)	0.63 (0.50; 0.79)
Direct effect, *HR (95%CI)*	*Reference*	0.76 (0.63;0.90)	0.75 (0.64;0.79)	0.70 (0.65;0.81)	0.73 (0.66;0.82)	0.72 (0.63; 0.83)	0.73 (0.57; 0.89)
Total PME, *%*		24.3 (10.4;42.5)	31.4 (18.3;37.8)	24.1 (15.9;39.1)	29.0 (19.4;41)	26.7 (18; 42.2)	31.3 (17.9; 54.4)
PME through:							
Body mass index, *%*		-1.3 (-9.5-4.8)	1.4 (-0.6-2.5)	1.2 (0.1-5.2)	0.9 (-0.7-2.4)	1.5 (0.1-3.9)	-0.2 (-3.7-3.8)
Insulin resistance, *%*		9.0 (4.0-30.8)	5.0 (2.1-7.4)	5.0 (2.0-10.1)	4.3 (1.5-7.6)	3.8 (1.8-7.6)	7.0 (2.6-14.2)
Systolic BP, *%*		2.0 (-12.0-7.7)	3.4 (1.6-5.1)	3.4 (1.2-7.9)	3.2 (1.7-4.3)	3.4 (1.7-5.3)	2.5 (0.1-3.5)
Inflammation, *%*		13.4 (5.1-34.6)	17.1 (8.9-18.1)	12.7 (8.3-17.3)	16.0 (10.9-21.9)	14.8 (12.1-22.4)	16.2 (10.5-25.5)
LDL-cholesterol, *%*		1.2 (-4.2-6.6)	4.4 (2.2-6.2)	1.9 (-1.3-4.7)	4.6 (2.2-6.5)	3.2 (0.7-6.4)	5.8 (0.3-9.3)

TABLE S3a (Continued)

		Exercise volume		Exercise type		Exercise intensity	
		0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
Recurrent vascular events							
Total effect, *HR (95%CI)*	*Reference*	0.73 (0.65-0.87)	0.69 (0.64-0.73)	0.70 (0.62-0.79)	0.70 (0.61-0.77)	0.70 (0.62-0.76)	0.70 (0.63-0.77)
Direct effect, *HR (95%CI)*	*Reference*	0.79 (0.68-0.91)	0.78 (0.70-0.84)	0.77 (0.66-0.90)	0.79 (0.67-0.85)	0.78 (0.69-0.84)	0.80 (0.72-0.87)
Total PME, *%*		25.5 (9.4-38.8)	33.7 (18.8-46.1)	28.9 (13.2-55.9)	33.2 (19.1-40.2)	31.5 (23.7-39.8)	36.4 (22.7-48.7)
PME through:							
Body mass index, *%*		0.4 (-2.4-3.7)	0.2 (-1.5-1.7)	0.2 (-0.5-3.2)	0.4 (-1.2-3.3)	0.8 (-0.8-3.0)	-0.8 (-5.2-2.2)
Insulin resistance, *%*		5.4 (2.1-6.0)	7.9 (2.0-13.3)	8.4 (4.1-22.9)	6.3 (3.5-10.4)	6.2 (3.5-10.6)	10.5 (5.0-16.0)
Systolic BP, *%*		4.4 (-3.1-8.3)	3.9 (1.4-5.8)	4.5 (0.6-10.9)	4.1 (0.7-6.3)	4.3 (3.0-8.0)	3.6 (1.1-6.0)
Inflammation, *%*		12.5 (3.6-19.2)	18.0 (10.1-22.4)	14.9 (6.6-22.0)	17.7 (10.4-22.2)	17 (12.1-21.7)	18.2 (11.7-25.8)
LDL-cholesterol, *%*		2.8 (-0.2-18)	3.7 (2.4-5.5)	0.9 (-3.2-3.5)	4.8 (1.4-6.3)	3.2 (1.7-6.3)	4.9 (-3.5-7.3)

TABLE S3b Mediation analysis in females (N = 2,284)

		Exercise volume		Exercise type		Exercise intensity	
		0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
All-cause mortality							
Total effect, *HR (95%CI)*	*Reference*	0.70 (0.60-0.85)	0.60 (0.48-0.67)	0.69 (0.60-0.79)	0.63 (0.53-0.69)	0.62 (0.46-0.71)	0.72 (0.59-0.90)
Direct effect, *HR (95%CI)*	*Reference*	0.76 (0.63-0.90)	0.63 (0.5-0.71)	0.73 (0.61-0.85)	0.68 (0.57-0.77)	0.66 (0.47-0.74)	0.78 (0.63-1.03)
Total PME, *%*		24.3 (10.4-42.5)	11.7 (4-16.8)	14.2 (3.4-30.3)	16.4 (8.7-32.6)	14.3 (3.4-18)	22.6 (12.3-143.8)
PME through:							
Body mass index, *%*		-1.3 (-9.5-4.8)	-1.6 (-7.7-1.2)	2.2 (-2.7-6.3)	-4.4 (-6.2-1.6)	-1.5 (-7.4--0.6)	-3.3 (-24.9-10.2)
Insulin resistance, *%*		9.0 (4.0-30.8)	3.6 (-0.4-4.1)	6.5 (2.1-11.1)	4.0 (0.7-6.3)	3.1 (-0.5-4.7)	12.2 (6.9-39.1)
Systolic BP, *%*		2.0 (-12-7.7)	0.5 (-0.6-3.5)	0.5 (-3.7-8.0)	1.7 (-1.7-9.6)	1.2 (-3.2-4.4)	0.1 (-1.1-10.2)
Inflammation, *%*		13.4 (5.1-34.6)	9.5 (3.2-15.2)	4.8 (-1.1-19.7)	14 (7.7-25.8)	11.3 (-0.4-15.8)	12.7 (-1.7-113)
LDL-cholesterol, *%*		1.2 (-4.2-6.6)	-0.3 (-1.7-1.8)	0.2 (-3.6-1)	1.0 (-3.3-2.2)	0.3 (-2.2-2.2)	0.9 (-1.8-6.9)
Recurrent vascular events							
Total effect, *HR (95%CI)*	*Reference*	0.79 (0.65-0.88)	0.77 (0.66-0.94)	0.84 (0.67-0.97)	0.83 (0.65-1)	0.81 (0.72-1.07)	0.75 (0.53-0.96)
Direct effect, *HR (95%CI)*	*Reference*	0.87 (0.69-0.94)	0.83 (0.69-1)	0.88 (0.72-1.01)	0.92 (0.7-1.09)	0.87 (0.77-1.12)	0.81 (0.58-1.03)
Total PME, *%*		41.4 (10.3-63.9)	27.1 (7.9-114)	29.7 (7-218.5)	58.2 (-368.6-67.4)	35 (-28.9-59.3)	28.9 (-273.8-31)
PME through:							
Body mass index, *%*		-0.9 (-10.9-4.5)	-5.3 (-17.9--0.3)	7.2 (-4.6-19.2)	-10.4 (-30.3-69.4)	-4.4 (-31.1-11.5)	-6.9 (-8.2-114.4)
Insulin resistance, *%*		15.5 (3-31.6)	10 (2.4-42.2)	12.5 (1.7-124.6)	16.4 (-107.5-26.7)	8.7 (-6.4-14.3)	18 (-165.3-20.1)
Systolic BP, *%*		3.6 (-8.5-8.3)	0.4 (-5.1-8.6)	-0.4 (-53.8-4)	6.4 (-46.8-20.3)	2.5 (-6.5-20.5)	0.6 (-7.8-3.8)
Inflammation, *%*		20.4 (3.8-39.1)	19.4 (7-68.7)	8.5 (-8-122.9)	40.3 (-256.1-89.1)	26.4 (-27.4-59.1)	13.3 (-111.1-17.9)
LDL-cholesterol, *%*		2.7 (-7.8-6.6)	2.7 (-0.9-13.8)	1.8 (-3.4-28.9)	5.6 (-40.7-8.3)	1.8 (-4.8-20.4)	3.8 (-105.7-6.9)

TABLE S3c Mediation analysis in subgroup of participants with low grade inflammation (CRP 2- 10 mg/l, N = 3,557)

		Exercise volume		Exercise type		Exercise intensity	
		0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
All-cause mortality							
Total effect, *HR (95%CI)*	*Reference*	0.61 (0.43-0.78)	0.67 (0.58-0.80)	0.63 (0.51-0.77)	0.66 (0.53-0.78)	0.65 (0.56-0.77)	0.63 (0.48-0.79)
Direct effect, *HR (95%CI)*	*Reference*	0.64 (0.46-0.80)	0.71 (0.61-0.84)	0.66 (0.53-0.81)	0.70 (0.56-0.81)	0.69 (0.59-0.81)	0.67 (0.50-0.84)
Total PME, *%*		7.5 (-1.5-25.3)	14.3 (7.4-28.4)	10.7 (2.1-27.5)	13 (3.2-26.4)	12 (5.4-21.5)	13.1 (3.9-28.3)
PME through:							
Body mass index, *%*		-0.6 (-6.6-5.4)	-0.9 (-4.2-2.6)	1.9 (-1.0-6.9)	-2.4 (-7.5-1.7)	-0.1 (-4.7-3.4)	-1.4 (-6.7-4.1)
Insulin resistance, *%*		2.5 (-0.8-7.9)	5.0 (1.9-10.6)	4.3 (0.6-15.6)	3.6 (0.1-8.5)	2.7 (0.2-6.0)	5.5 (1.0-14.9)
Systolic BP, *%*		2.6 (-1.3-7.8)	2.6 (-0.3-7.0)	2.9 (0.4-8.1)	2.8 (0.2-7.2)	3.0 (0.4-6.3)	2.8 (-1.9-7.9)
Inflammation, *%*		1.7 (-1.1-7.7)	5.9 (1.9-12.0)	1.8 (-1.6-8.2)	6.2 (0.6-13.1)	5.0 (1.5-11.2)	3.2 (-0.8-9.9)
LDL-cholesterol, *%*		1.3 (-2.3-5.5)	1.7 (-1.1-5.3)	-0.2 (-3.8-3.1)	2.8 (0.0-6.7)	1.4 (-1.9-4.5)	3.0 (-0.6-8)
Recurrent vascular events							
Total effect, *HR (95%CI)*	*Reference*	0.67 (0.48-0.87)	0.71 (0.62-0.88)	0.67 (0.50-0.80)	0.72 (0.59-0.85)	0.70 (0.59-0.82)	0.68 (0.50-0.86)
Direct effect, *HR (95%CI)*	*Reference*	0.69 (0.51-0.88)	0.75 (0.65-0.91)	0.69 (0.51-0.83)	0.76 (0.61-0.90)	0.73 (0.62-0.84)	0.71 (0.52-0.89)
Total PME, *%*		6.6 (-7.1-24)	13.6 (3-36.8)	7.6 (-2-18.4)	14.9 (2.8-45.3)	12.6 (3.6-24.7)	12.4 (1-30.5)
PME through:							
Body mass index, *%*		-1.8 (-8.6-3.1)	-1.8 (-7-1)	-0.3 (-5.1-3.9)	-2.7 (-8.8-1.2)	-1.4 (-7.1-2.1)	-0.5 (-6.2-3.8)
Insulin resistance, *%*		3.3 (-1.9-10.7)	4.7 (0.0-13.2)	4.3 (-0.2-11.8)	4.2 (-2.6-13.8)	3.4 (-0.5-9.6)	5.1 (-1.0-18.2)
Systolic BP, *%*		1.5 (-4.1-9.4)	2.4 (-0.6-7.5)	1.8 (-1.6-6.9)	2.5 (-1.3-11.2)	2.8 (-0.3-7.9)	0.6 (-4.7-8.3)
Inflammation, *%*		1.1 (-3.2-7.8)	6.4 (2.0-17.5)	1.6 (-4.4-8.1)	7.3 (2.7-16.8)	5.9 (1.2-13.5)	4.1 (-1.5-15.7)
LDL-cholesterol, *%*		2.5 (-1.2-10.3)	1.9 (-2.0-7.8)	0.1 (-3.3-4.1)	3.5 (0.0-10.4)	1.9 (-0.8-6.3)	3.1 (-1.0-9.3)

TABLE S3d Mediation analysis in subgroup of participants with metabolic syndrome (N = 4,547)

		Exercise volume		Exercise type		Exercise intensity	
		0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
All-cause mortality							
Total effect, *HR (95%CI)*	*Reference*	0.59 (0.45-0.72)	0.67 (0.57-0.78)	0.70 (0.58-0.89)	0.62 (0.52-0.74)	0.65 (0.56-0.74)	0.65 (0.47-0.80)
Direct effect, *HR (95%CI)*	*Reference*	0.64 (0.50-0.77)	0.73 (0.62-0.85)	0.74 (0.61-0.94)	0.69 (0.58-0.82)	0.71 (0.62-0.81)	0.72 (0.52-0.91)
Total PME, *%*		15.4 (5.3-30.6)	21.9 (11.2-38.8)	15.4 (3-45.3)	21.6 (14.1-34.2)	19.9 (11.9-33.3)	22.9 (11.4-61.2)
PME through:							
Body mass index, *%*		0.6 (-3.1-4.3)	2.3 (0.0-7.9)	2.2 (-1.1-8.9)	1.4 (-1.1-4.7)	1.8 (-1.5-4.9)	1.8 (-4.7-8.5)
Insulin resistance, *%*		2.1 (-0.7-4.8)	3.2 (0.1-6.9)	5.0 (-0.3-16.7)	2.3 (0.2-5.2)	2.2 (-0.5-6.7)	5.0 (-1.6-14.2)
Systolic BP, *%*		1.7 (-0.5-4.7)	1.4 (-0.4-3.5)	0.8 (-2.6-9.7)	1.7 (0.0-4.4)	2.1 (0.5-5.0)	-0.2 (-4.5-2.5)
Inflammation, *%*		8.9 (2.0-18.4)	13.5 (7.4-22.3)	8.0 (-1.5-28.4)	13.7 (8.5-23.2)	12.3 (6.4-20.5)	13.7 (4.7-39.1)
LDL-cholesterol, *%*		2.1 (-1.4-7.1)	1.5 (-1.3-4)	-0.6 (-6.2-3.7)	2.5 (0.3-6.4)	1.4 (-1.0-3.9)	2.6 (-0.6-8.6)
Recurrent vascular events							
Total effect, *HR (95%CI)*	*Reference*	0.70 (0.55-0.92)	0.72 (0.61-0.85)	0.74 (0.62-0.89)	0.71 (0.61-0.81)	0.72 (0.62-0.85)	0.70 (0.54-0.87)
Direct effect, *HR (95%CI)*	*Reference*	0.76 (0.60-0.99)	0.78 (0.67-0.92)	0.78 (0.64-0.94)	0.78 (0.68-0.90)	0.78 (0.67-0.93)	0.76 (0.56-0.95)
Total PME, *%*		20.8 (6.6-88.3)	24.1 (13.5-49.1)	16 (0.1-58.5)	28.2 (17.5-52.2)	25 (12.9-52.4)	22.3 (6.4-64.8)
PME through:							
Body mass index, *%*		0.6 (-6.0-12.3)	1.6 (-2.1-6.0)	2.9 (-4.5-13.8)	0.7 (-3.0-4.0)	1.6 (-1.9-6.7)	0.7 (-5.4-9.0)
Insulin resistance, *%*		2.7 (-1.7-12.3)	4.1 (0.4-12.2)	5.8 (0.7-29.7)	2.9 (-0.3-7.6)	3.5 (0.1-10.4)	4.4 (-1.6-16.4)
Systolic BP, *%*		3.0 (-1.5-12.7)	1.6 (-1.2-5.3)	1.4 (-2.2-9.1)	2.9 (0.1-8.1)	2.9 (-0.1-6.6)	-0.4 (-5.8-3.5)
Inflammation, *%*		11.4 (2.8-39.2)	13.7 (7.1-29.4)	8.0 (-2.0-23.5)	16.2 (10.2-31.3)	14.1 (7.4-32.0)	14.0 (4.5-39.3)
LDL-cholesterol, *%*		3.1 (-3.6-17.1)	3.1 (-1.0-9.7)	-2.1 (-14.5-3.6)	5.4 (2.0-12.7)	2.9 (-0.6-7.9)	3.5 (-2.4-11.3)

TABLE S3e Mediation analysis in subgroup of participants with BMI < 25 kg/m2 (N = 2,895)

		Exercise volume		Exercise type		Exercise intensity	
		0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
All-cause mortality							
Total effect, *HR (95%CI)*	*Reference*	0.67 (0.50-0.83)	0.60 (0.51-0.74)	0.60 (0.46-0.75)	0.65 (0.53-0.78)	0.60 (0.50-0.71)	0.70 (0.51-0.86)
Direct effect, *HR (95%CI)*	*Reference*	0.73 (0.54-0.91)	0.71 (0.61-0.86)	0.68 (0.54-0.82)	0.75 (0.59-0.89)	0.69 (0.56-0.82)	0.83 (0.59-1.02)
Total PME, *%*		24.3 (5.5-54.3)	32.0 (21.7-52.4)	24.9 (10.7-44)	34.8 (20.2-60.2)	27.2 (14.9-47.1)	47.1 (20.7-113.7)
PME through:							
Body mass index, *%*		0.3 (-8.3-14.2)	5.7 (0.9-11.0)	5.3 (-1.3-12.3)	4.9 (0.3-12.0)	3.8 (0.3-9.2)	10.1 (1.2-29.8)
Insulin resistance, *%*		7.9 (1.9-19.3)	6.0 (0.9-11.3)	7.2 (1.9-15.5)	7.3 (2.1-15.1)	6.3 (1.7-12.3)	10.4 (2.7-34.1)
Systolic BP, *%*		3.1 (-2.5-10.9)	4.4 (0.6-9.8)	2.0 (-2.6-8.3)	5.5 (1.6-13.1)	3.1 (-0.1-8.2)	6.8 (0.5-19.6)
Inflammation, *%*		10.8 (2.0-24.0.)	12.6 (7.1-22.2)	8.4 (2.4-16.8)	13.5 (5.7-27.2)	11.4 (4.3-20.0)	13.0 (3.1-34.6)
LDL-cholesterol, *%*		2.2 (-4.3-10.3)	3.3 (0.3-8.1)	1.9 (-1.6-7.5)	3.6 (0.6-9.2)	2.6 (0.3-7.8)	6.8 (1.9-17.6)
Recurrent vascular events							
Total effect, *HR (95%CI)*	*Reference*	0.59 (0.36-0.78)	0.65 (0.55-0.81)	0.68 (0.50-0.84)	0.67 (0.53-0.82)	0.68 (0.54-0.80)	0.57 (0.39-0.81)
Direct effect, *HR (95%CI)*	*Reference*	0.64 (0.41-0.87)	0.78 (0.66-0.96)	0.77 (0.58-0.93)	0.80 (0.64-0.97)	0.79 (0.64-0.95)	0.67 (0.45-0.95)
Total PME, *%*		17.2 (1.7-48.2)	41.9 (25.3-84.3)	33.0 (12.5-62.0)	42.7 (26.2-85.9)	40.9 (22.9-73.4)	29.5 (10.9-75.1)
PME through:							
Body mass index, *%*		-0.6 (-7.4-5.3)	4.9 (0.6-13.1)	4.4 (-2.4-12.0)	4.2 (-0.4-10.2)	3.8 (-1.1-9.6)	3.9 (-1.1-12.6)
Insulin resistance, *%*		7.1 (1.7-22.3)	11.9 (5.9-21.9)	14.1 (4.3-27.2)	11.6 (4.5-27.7)	12.4 (6.1-21.3)	9.5 (2.4-30.5)
Systolic BP, *%*		3 (-3.7-13.3)	6.7 (2.1-15.1)	3.8 (-2.9-12.5)	8.6 (3.3-19.7)	7.3 (2.6-15.1)	5.4 (-0.3-15.3)
Inflammation, *%*		7.9 (0.5-22.4)	15.1 (7.3-31.1)	10.0 (1.8-26.5)	14.8 (6.3-27.4)	15.2 (4.5-26.5)	7.2 (1.3-22.4)
LDL-cholesterol, *%*		-0.2 (-5.5-6.0)	3.3 (0.0-10.4)	0.6 (-6.7-9.0)	3.6 (0.2-9.8)	2.2 (-0.9-8.1)	3.5 (0.0-13.9)

TABLE S3f Mediation analysis in subgroup of participants with BMI between 25 and 30 kg/m2 (N = 4,095)

		Exercise volume		Exercise type		Exercise intensity	
		0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
All-cause mortality							
Total effect, *HR (95%CI)*	*Reference*	0.57 (0.48-0.69)	0.71 (0.68-0.77)	0.67 (0.58-0.78)	0.69 (0.63-0.75)	0.66 (0.61-0.81)	0.72 (0.63-0.85)
Direct effect, *HR (95%CI)*	*Reference*	0.60 (0.51-0.74)	0.80 (0.79-0.89)	0.73 (0.64-0.86)	0.77 (0.72-0.81)	0.73 (0.69-0.88)	0.82 (0.70-0.95)
Total PME, *%*		10.8 (-2.7-23.5)	35 (20.5-61.8)	22.3 (8.1-71.4)	30 (16.7-60.6)	23.7 (14-38.1)	39.5 (20.7-136.1)
PME through:							
Body mass index, *%*		-1.1 (-5.1-1.7)	-0.4 (-3.5-2.3)	-1.2 (-6.5-2.6)	-0.3 (-2.8-3.1)	-1.2 (-3.7-1.3)	0.6 (-3.7-7.0)
Insulin resistance, *%*		2.2 (-0.7-8.1)	7.5 (1.8-16.1)	6.1 (1.2-27.1)	5.3 (-0.1-11.9)	3.5 (0.2-8.6)	12 (3.5-46.7)
Systolic BP, *%*		1.0 (-3.1-5.0)	2.1 (-0.9-7.6)	2.0 (-0.9-7.4)	1.4 (-1.7-7.5)	2.5 (0.0-6.0)	-0.1 (-6.7-8.8)
Inflammation, *%*		4.4 (-3.4-14.3)	22.5 (13.6-38.5)	13 (2.8-40.9)	19.5 (11.1-37.6)	16 (9.0-26.6)	21.9 (10.6-59.9)
LDL-cholesterol, *%*		4.3 (-0.7-9.2)	3.3 (-0.2-9.1)	2.5 (-2.7-11.4)	4.1 (0.2-11.7)	2.9 (0.0-7.4)	5.0 (-1-27.6)
Recurrent vascular events							
Total effect, *HR (95%CI)*	*Reference*	0.81 (0.72-0.98)	0.78 (0.71-0.90)	0.79 (0.68-0.86)	0.79 (0.68-0.90)	0.76 (0.72-0.82)	0.89 (0.78-1.01)
Direct effect, *HR (95%CI)*	*Reference*	0.85 (0.75-1.02)	0.85 (0.79-0.99)	0.85 (0.73-0.93)	0.86 (0.72-0.97)	0.81 (0.78-0.87)	0.98 (0.86-1.08)
Total PME, *%*		22.4 (-94.6-146.8)	36.1 (16.4-125.8)	32.1 (9.0-182.6)	34.1 (12.9-108.7)	25.5 (12.5-65.4)	84.8 (-270-1409)
PME through:							
Body mass index, *%*		0.4 (-13.6-12.1)	0.0 (-7.0-5.1)	-0.2 (-13.9-7.5)	0.2 (-5.7-5.3)	0.1 (-5.4-4.4)	-0.7 (-62.0-25.7)
Insulin resistance, *%*		4.9 (-22.3-42.4)	9.2 (2.3-24.6)	10.5 (-0.6-54.8)	7.0 (-0.5-24.2)	4.7 (-0.4-13.4)	33.5 (-146-295)
Systolic BP, *%*		2.2 (-17.4-31.1)	0.8 (-4.3-8.2)	2.0 (-2.7-13.7)	0.5 (-9.4-10.6)	0.9 (-3.5-7.0)	-0.7 (-20-97.6)
Inflammation, *%*		6.4 (-26.7-58.7)	22.8 (10.3-83.7)	14.6 (4.0-66.4)	21.8 (10.4-92.2)	16.4 (7.1-43.5)	41.0 (-106-728)
LDL-cholesterol, *%*		8.5 (-16.4-46.4)	3.3 (-1.0-11.8)	5.2 (-2.2-36.2)	4.5 (-0.1-18.8)	3.5 (-1.5-9.8)	11.8 (-45.2-96.3)

TABLE S3g Mediation analysis in subgroup of participants with BMI ≥ 30 kg/m2 (N = 1,670)

		Exercise volume		Exercise type		Exercise intensity	
		0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
All-cause mortality							
Total effect, *HR (95%CI)*	*Reference*	0.48 (0.28-0.71)	0.56 (0.43-0.77)	0.63 (0.38-0.89)	0.48 (0.31-0.68)	0.58 (0.45-0.70)	0.42 (0.17-0.71)
Direct effect, *HR (95%CI)*	*Reference*	0.55 (0.32-0.87)	0.63 (0.47-0.87)	0.67 (0.44-0.92)	0.56 (0.36-0.78)	0.65 (0.49-0.79)	0.50 (0.20-0.85)
Total PME, *%*		16.6 (-1.2-60.2)	19.7 (9.0-51.2)	14.8 (-0.7-44.4)	21.3 (8.6-45.2)	19.1 (6.3-37.3)	19.3 (6.7-52.1)
PME through:							
Body mass index, *%*		-1.3 (-9.6-4.1)	1.4 (-2.4-10.5)	-3.7 (-18.9-4.0)	3.4 (-0.8-10.0)	-0.1 (-4.2-4.9)	3.2 (-4.8-11.4)
Insulin resistance, *%*		5.7 (-0.5-18.7)	5.7 (0.9-14.3)	8.4 (1.0-27.2)	4.4 (0.6-11.8)	5.6 (0.4-14.3)	5.8 (-0.3-21.1)
Systolic BP, *%*		1.8 (-3.2-8.6)	1 (-3.7-5.4)	2.8 (-3.5-15.9)	0.6 (-4.1-5.6)	1.1 (-3.3-7.3)	0.1 (-5.2-4.6)
Inflammation, *%*		7.1 (-1.2-34.1)	10.8 (3.8-31.7)	5.1 (-9.5-24.5)	11.6 (4.6-24.2)	11.7 (4.1-24.3)	6.5 (-2.3-19.3)
LDL-cholesterol, *%*		3.2 (-1.2-13.0)	0.7 (-3.1-6.1)	2.1 (-5.6-10.9)	1.3 (-2.2-5.9)	0.8 (-4.0-5.0)	3.7 (-0.6-14.3)
Recurrent vascular events							
Total effect, *HR (95%CI)*	*Reference*	0.68 (0.44-0.99)	0.61 (0.44-0.84)	0.58 (0.34-0.79)	0.63 (0.47-0.90)	0.67 (0.50-0.91)	0.44 (0.22-0.75)
Direct effect, *HR (95%CI)*	*Reference*	0.76 (0.47-1.15)	0.67 (0.47-0.92)	0.60 (0.35-0.83)	0.73 (0.54-1.03)	0.73 (0.56-1.01)	0.48 (0.25-0.81)
Total PME, *%*		27.6 (-12.7-229)	19.6 (6.8-67.1)	7.9 (-7.5-30.1)	29.4 (15.2-120.9)	23.0 (9.1-108.7)	11.6 (-1.9-36.0)
PME through:							
Body mass index, *%*		-2.8 (-26.4-9.7)	0.3 (-7.2-5.5)	-2.1 (-9.6-4.5)	2.2 (-4.2-12.8)	-1.5 (-9.3-6.8)	0.6 (-5.1-6.3)
Insulin resistance, *%*		8.8 (-6.6-68.0)	6.9 (0.6-26.7)	5.6 (-2.5-20.0)	7.6 (1.5-41.1)	8.1 (2.0-36.6)	4.2 (-1.8-14.4)
Systolic BP, *%*		3 (-18.1-48.2)	-0.8 (-8.1-5.0)	1.5 (-5.2-8.6)	-1.9 (-12.2-4.2)	0.7 (-8.3-11.8)	-2.8 (-13.0-2.2)
Inflammation, *%*		12.4 (-38-87.0)	10.5 (3.3-37.3)	2.7 (-7.6-13.4)	15.8 (6.6-75.3)	12.8 (4.1-56.4)	6.5 (-0.5-17.5)
LDL-cholesterol, *%*		6.2 (-3.4-126)	2.7 (-4.2-13.9)	0.2 (-5.8-8.0)	5.6 (-1.5-35.6)	2.9 (-3.3-17.2)	3.1 (-1.7-12.1)

TABLE S3h Mediation analysis in subgroup of participants without T2D at baseline (N = 7,185), using the HOMA-IR formula instead of triglyceride-glucose ratio.

		Exercise volume		Exercise type		Exercise intensity	
		0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
All-cause mortality							
Total effect, *HR (95%CI)*	*Reference*	0.67 (0.47-0.94)	0.69 (0.57-0.8)	0.71 (0.55-0.87)	0.69 (0.56-0.84)	0.66 (0.56-0.8)	0.74 (0.58-0.92)
Direct effect, *HR (95%CI)*	*Reference*	0.71 (0.49-0.98)	0.76 (0.62-0.88)	0.75 (0.58-0.94)	0.75 (0.61-0.88)	0.72 (0.6-0.86)	0.8 (0.62-0.98)
Total PME, %		12.9 (0.7-70.5)	25 (14.4-46)	18.1 (4.3-56.5)	22 (9.3-35.7)	18.6 (9.4-39.9)	26.5 (4.4-86.7)
PME through:							
Body mass index, %							
Insulin resistance, %		1 (-5.2-8.4)	2.8 (-0.4-8.1)	3 (-1.8-10.9)	1.7 (-3-7.1)	2.2 (-0.8-7.1)	2.3 (-11.6-15.4)
Systolic BP, %		0.4 (-5.3-4.9)	5.2 (0.9-11.9)	1.6 (-3.7-10.5)	3.5 (-0.4-7.3)	2 (-0.5-6)	7.9 (-4-39.8)
Inflammation, %		1 (-7.6-10.4)	3 (-0.6-8.2)	4.7 (0-11.8)	0.6 (-4.9-5.7)	1.6 (-1.9-7.3)	1.4 (-4.4-11.5)
LDL-cholesterol, %		8.4 (0-55.3)	13.6 (6.1-27)	8.4 (1-32.2)	15.5 (8.5-26.9)	12.6 (6.3-29.1)	14.1 (5.8-41.1)
Recurrent vascular events							
Total effect, *HR (95%CI)*	*Reference*	0.84 (0.59-1.1)	0.75 (0.62-0.89)	0.86 (0.68-1.04)	0.74 (0.59-0.89)	0.78 (0.65-0.89)	0.76 (0.52-0.93)
Direct effect, *HR (95%CI)*	*Reference*	0.89 (0.62-1.14)	0.8 (0.64-0.95)	0.9 (0.72-1.07)	0.8 (0.63-0.95)	0.83 (0.7-0.96)	0.82 (0.57-1.04)
Total PME, %		35.8 (-102.9-474)	20.5 (5.6-58.4)	29.3 (-136.3-324.7)	24.1 (7.5-56.6)	24.5 (8.7-68)	26.8 (8.1-202.6)
PME through:							
Body mass index, %							
Insulin resistance, %		6.7 (-62.9-76.1)	-1.2 (-7-4.7)	1.9 (-15.7-61.4)	0.7 (-5.2-6.9)	1.2 (-3.8-10.3)	1.7 (-16.4-12.1)
Systolic BP, %		7.1 (-34.4-131.8)	5 (0.2-17.5)	9.7 (-51.7-76.6)	4.9 (-1.4-15.9)	3.6 (-0.4-12.2)	10.6 (1.5-67.7)
Inflammation, %		2.5 (-18-188.9)	2.6 (-2.5-13.8)	4.2 (-76.8-55.2)	2.1 (-3.1-9.4)	2.7 (-4.9-12.3)	2.2 (-2-17.7)
LDL-cholesterol, %		17 (-33.9-152.4)	15.3 (7.6-41.6)	16.2 (-78.3-147.4)	16.2 (7.4-42.3)	17.2 (7.5-39.3)	12.4 (3.7-89.9)

TABLE S4a Hazard ratios for volume, type and intensity with all-cause mortality across subgroups, estimated using Cox regression

		Exercise volume, HR (95%CI)		**Exercise type,** HR (95%CI)		**Exercise intensity,** HR (95%CI)	
Model	**No exercise**	0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
Sex							
Female	*Reference*	0.72 (0.54-0.97)	0.62 (0.47-0.81)	0.69 (0.52-0.92)	0.64 (0.49-0.84)	0.62 (0.49-0.80)	0.71 (0.49-1.01)
Male	*Reference*	0.59 (0.47-0.73)	0.68 (0.60-0.77)	0.65 (0.55-0.78)	0.66 (0.58-0.75)	0.66 (0.58-0.75)	0.64 (0.52-0.79)
CRP							
< 2 mg/l	*Reference*	0.65 (0.48-0.89)	0.80 (0.67-0.95)	0.73 (0.57-0.94)	0.78 (0.65-0.94)	0.75 (0.63-0.90)	0.77 (0.58-1.02)
2 – 10 mg/l	*Reference*	0.65 (0.51-0.82)	0.66 (0.56-0.78)	0.65 (0.52-0.80)	0.66 (0.56-0.78)	0.66 (0.56-0.77)	0.62 (0.48-0.81)
> 10 mg/l	*Reference*	0.58 (0.35-0.96)	0.60 (0.43-0.85)	0.71 (0.45-1.12)	0.54 (0.38-0.77)	0.54 (0.38-0.77)	0.71 (0.44-1.16)
Metabolic syndrome							
No	*Reference*	0.68 (0.52-0.88)	0.67 (0.57-0.79)	0.61 (0.48-0.77)	0.70 (0.60-0.83)	0.65 (0.55-0.77)	0.69 (0.54-0.88)
Yes	*Reference*	0.61 (0.48-0.78)	0.70 (0.59-0.81)	0.73 (0.59-0.89)	0.64 (0.54-0.75)	0.67 (0.57-0.78)	0.66 (0.51-0.85)
Body mass index							
< 25 kg/m2	*Reference*	0.72 (0.55-0.95)	0.64 (0.54-0.77)	0.63 (0.49-0.81)	0.68 (0.56-0.82)	0.64 (0.53-0.76)	0.70 (0.53-0.94)
25 – 30 kg/m2	*Reference*	0.61 (0.47-0.80)	0.73 (0.62-0.86)	0.70 (0.56-0.88)	0.70 (0.59-0.83)	0.69 (0.58-0.81)	0.71 (0.55-0.90)
> 30 kg/m2	*Reference*	0.53 (0.33-0.86)	0.58 (0.42-0.79)	0.67 (0.46-0.97)	0.49 (0.34-0.70)	0.62 (0.47-0.84)	0.40 (0.22-0.73)
Diabetes							
No	*Reference*	0.69 (0.57-0.84)	0.70 (0.62-0.79)	0.66 (0.56-0.78)	0.72 (0.63-0.82)	0.69 (0.61-0.78)	0.68 (0.56-0.83)
Yes	*Reference*	0.47 (0.30-0.73)	0.68 (0.52-0.87)	0.83 (0.60-1.17)	0.52 (0.39-0.69)	0.59 (0.46-0.76)	0.72 (0.45-1.15)

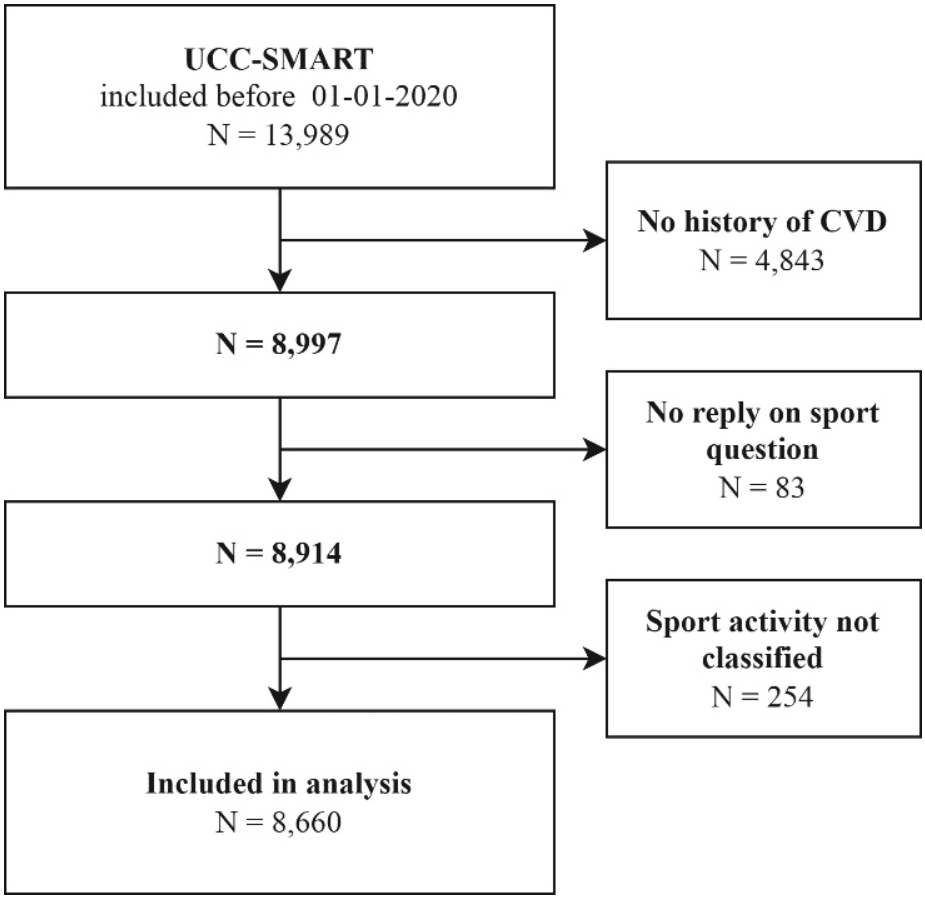
This table presents the results of a sensitivity analysis in which the robustness of the total effects estimated using mediation analysis across subgroups was assessed. All models were adjusted for age, sex, education, smoking, pack years and alcohol consumption. CRP: C reactive protein, 95%CI: 95% confidence interval.

TABLE S4b Hazard ratios for volume, type and intensity with recurrent cardiovascular events across subgroups, estimated using Cox regression

		Exercise volume, HR (95%CI)		**Exercise type,** HR (95%CI)		**Exercise intensity,** HR (95%CI)	
Model	**No exercise**	0-7.5 METh/wk	>7.5 METh/wk	Resistance	Resistance + Aerobic	Light to moderate	Vigorous
Sex							
Female	*Reference*	0.87 (0.63-1.21)	0.84 (0.64-1.12)	0.86 (0.62-1.18)	0.85 (0.64-1.13)	0.85 (0.65-1.10)	0.78 (0.52-1.18)
Male	*Reference*	0.75 (0.60-0.94)	0.72 (0.63-0.82)	0.73 (0.60-0.88)	0.73 (0.63-0.83)	0.73 (0.63-0.83)	0.72 (0.58-0.89)
CRP							
< 2 mg/l	*Reference*	0.95 (0.72-1.26)	0.83 (0.69-0.99)	0.90 (0.70-1.16)	0.84 (0.69-1.01)	0.84 (0.70-1.01)	0.87 (0.66-1.15)
2 – 10 mg/l	*Reference*	0.74 (0.57-0.96)	0.74 (0.62-0.88)	0.72 (0.57-0.91)	0.75 (0.62-0.90)	0.73 (0.61-0.87)	0.73 (0.55-0.95)
> 10 mg/l	*Reference*	0.62 (0.33-1.14)	0.71 (0.49-1.03)	0.61 (0.34-1.07)	0.72 (0.50-1.05)	0.73 (0.51-1.06)	0.59 (0.32-1.09)
Metabolic syndrome							
No	*Reference*	0.86 (0.66-1.13)	0.76 (0.64-0.90)	0.75 (0.58-0.96)	0.80 (0.67-0.96)	0.77 (0.65-0.92)	0.77 (0.59-1.00)
Yes	*Reference*	0.75 (0.58-0.96)	0.76 (0.64-0.89)	0.79 (0.64-0.99)	0.73 (0.62-0.87)	0.75 (0.64-0.88)	0.76 (0.58-0.99)
Body mass index							
< 25 kg/m2	*Reference*	0.72 (0.52-0.98)	0.70 (0.57-0.86)	0.71 (0.53-0.94)	0.70 (0.57-0.87)	0.70 (0.57-0.86)	0.62 (0.44-0.88)
25 – 30 kg/m2	*Reference*	0.89 (0.69-1.14)	0.80 (0.68-0.94)	0.84 (0.67-1.06)	0.81 (0.68-0.96)	0.79 (0.67-0.94)	0.89 (0.70-1.12)
> 30 kg/m2	*Reference*	0.71 (0.44-1.16)	0.64 (0.47-0.89)	0.66 (0.44-1.00)	0.66 (0.47-0.93)	0.74 (0.54-0.99)	0.49 (0.27-0.90)
Diabetes							
No	*Reference*	0.88 (0.72-1.07)	0.76 (0.67-0.87)	0.77 (0.64-0.92)	0.80 (0.70-0.92)	0.80 (0.70-0.91)	0.73 (0.60-0.90)
Yes	*Reference*	0.48 (0.28-0.81)	0.75 (0.57-0.99)	0.84 (0.57-1.23)	0.60 (0.44-0.82)	0.60 (0.45-0.80)	1.05 (0.66-1.65)

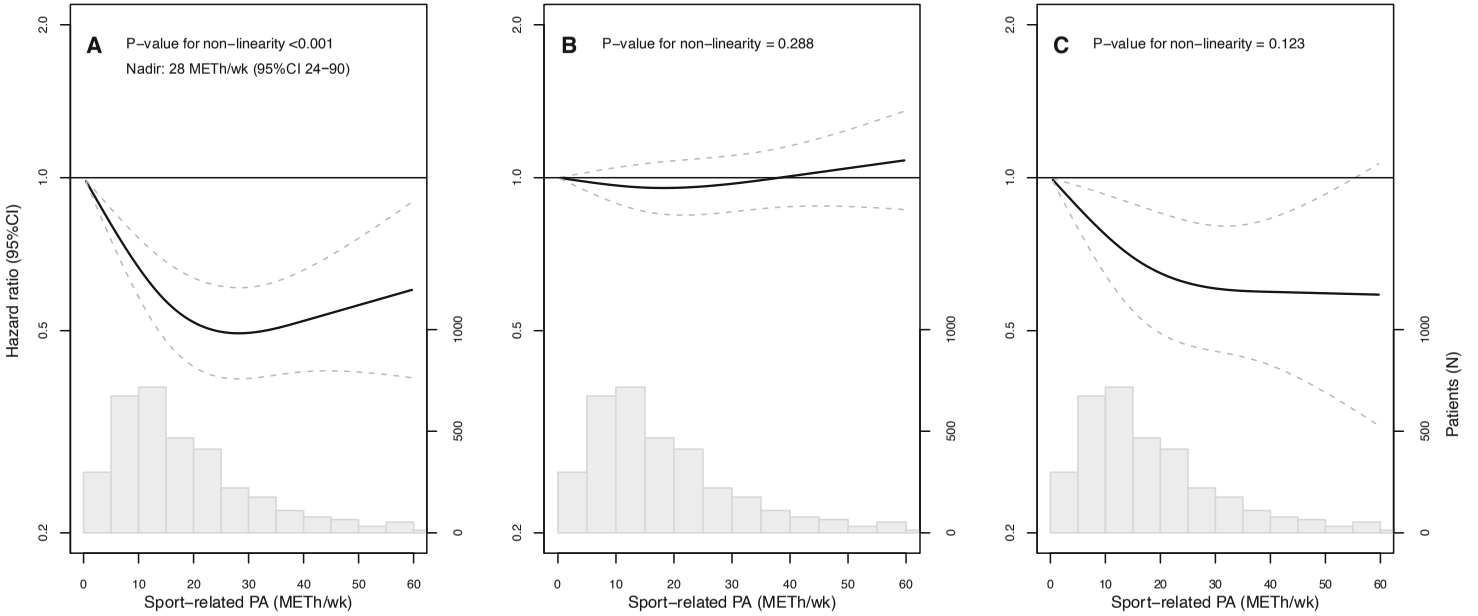
This table presents the results of a sensitivity analysis in which the robustness of the total effects estimated using mediation analysis across subgroups was assessed. All models were adjusted for age, sex, education, smoking, pack years and alcohol consumption. CRP: C reactive protein, 95%CI: 95% confidence interval.

FIGURE S1 Flowchart of patient selection



Flowchart representing the selection of patients from the UCC-SMART cohort for inclusion in the analyses. History of CVD comprised coronary artery disease, cerebrovascular disease, peripheral arterial disease and abdominal aortic aneurysm. UCC-SMART: Utrecht Cardiovascular Cohort – Secondary Manifestations of ARTerial disease, CVD: cardiovascular disease.

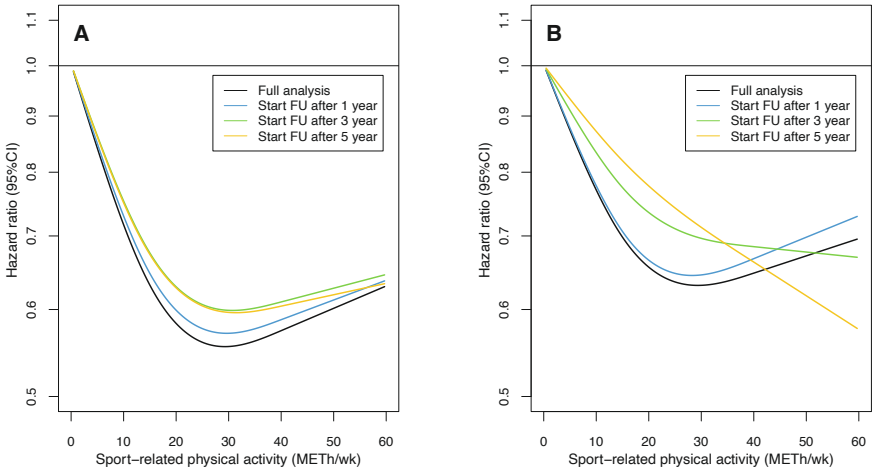
FIGURE S2 Continuous association of sport-related physical activity with MACE components



This figure shows the best fitting restricted cubic splines for the continuous association between sports-related physical activity level and (**A**) risk of cardiovascular mortality, (**B**) non-fatal myocardial infarction and **(C)** non-fatal stroke. The nadir and corresponding bootstrap 95%CI for sports-related physical activity are provided in the plots. The histograms in the plots show the number of participants at a specific physical activity level. Non-exercisers (N = 5,266) are not included in the histograms. Abbreviations - 95%CI: 95% confidence interval, METh/wk: Metabolic equivalent of task hours per week, PA: physical activity

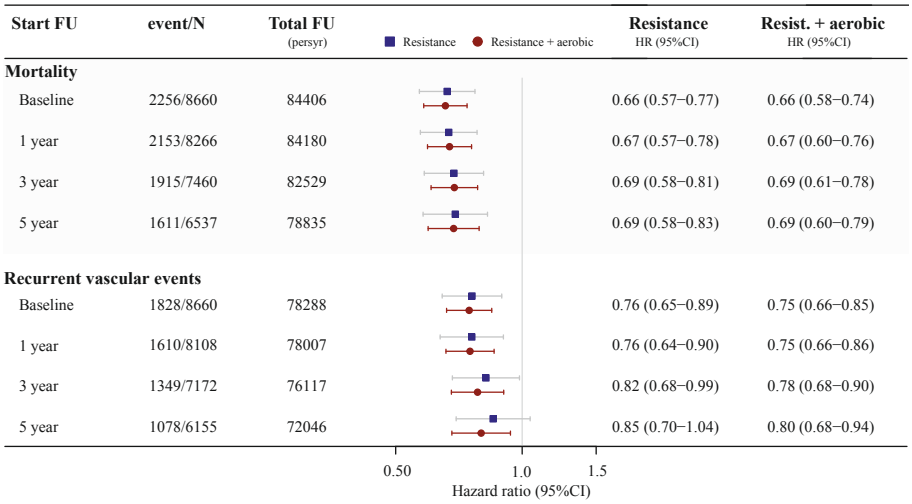
FIGURE S3 Sensitivity analysis: Reverse causation

FIGURE S3a Reverse causation in the continuous association between exercise volume and all-cause mortality and recurrent vascular events



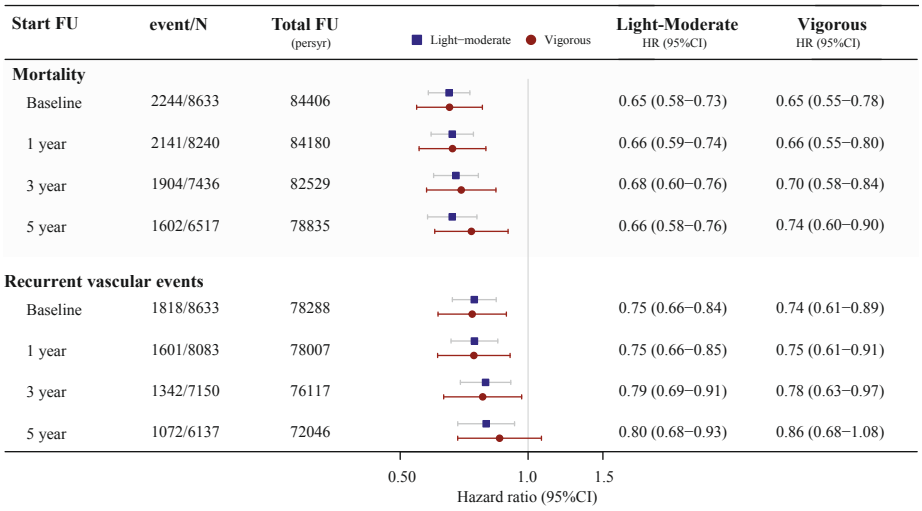
This figure shows the best fitting restricted cubic spline for the continuous association between sports- related physical activity level and risk of all-cause mortality (**A**) and recurrent vascular events (**B**). To assess the impact of reverse causation, splines were fit in the full dataset and in subsets with follow-up starting 1, 3 and 5 year after inclusion in the cohort. All splines are adjusted for age, sex, smoking status, number of pack years, alcohol consumption and education. 95%CI: 95% confidence interval, FU: follow-up, METh/wk: Metabolic equivalent of task hours per week.

FIGURE S3b Reverse causation in the association between exercise type and all-cause mortality and recurrent vascular events



Associations between physic activity type and physical activity intensity in the full dataset and in datasets excluding patients with an event in the first 1, 3 or 5 years of follow-up. Abbreviations: 95%CI: 95% confidence interval, FU: follow-up, HR: hazard ratio

FIGURE S3c Reverse causation in the association between exercise intensity and all-cause mortality and recurrent vascular events



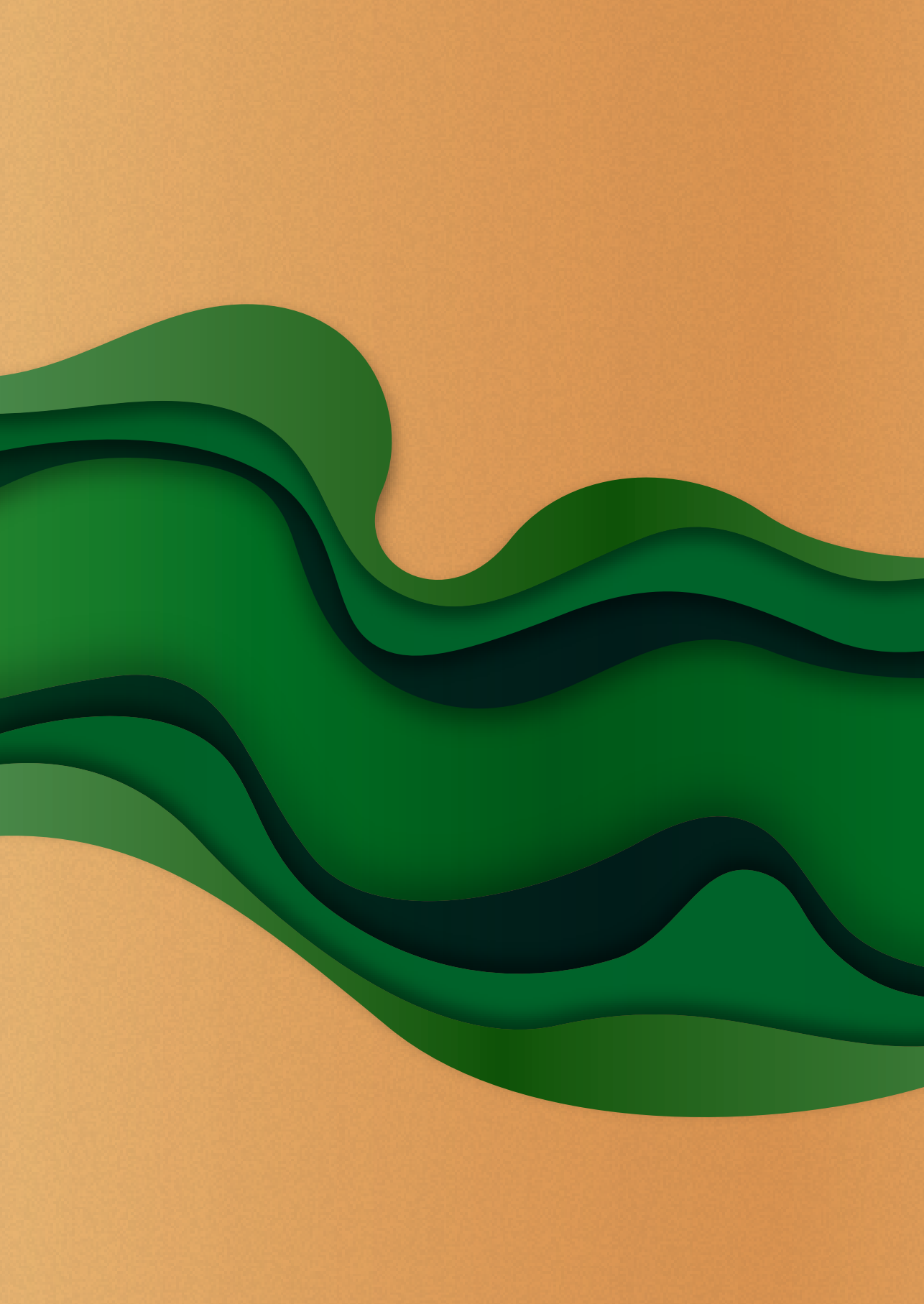
Associations between physic activity type and physical activity intensity in the full dataset and in datasets excluding patients with an event in the first 1, 3 or 5 years of follow-up. Abbreviations: 95%CI: 95% confidence interval, FU: follow-up, HR: hazard ratio

SUPPLEMENTAL REFERENCES

1. VanderWeele TJ. Marginal Structural Models for the Estimation of Direct and Indirect Effects.
2. Epidemiology 2009;20:18–26. doi:10.1097/EDE.0b013e31818f69ce
3. Hong G. Ratio of Mediator Probability Weighting for Estimating Natural Direct and Indirect Effects. Proc Am Stat Assoc Biometrics Sect 2010;:2401–15.
4. Lange T, Vansteelandt S, Bekaert M. A Simple Unified Approach for Estimating Natural Direct and Indirect Effects. Am J Epidemiol 2012;176:190–5. doi:10.1093/aje/kwr525
5. Nystoriak MA, Bhatnagar A. Cardiovascular Effects and Benefits of Exercise. Front Cardiovasc Med 2018;5:1–11. doi:10.3389/fcvm.2018.00135
6. Ahmed HM, Blaha MJ, Nasir K, et al. Effects of Physical Activity on Cardiovascular Disease. Am J Cardiol 2012;109:288–95. doi:10.1016/j.amjcard.2011.08.042
7. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, et al. The Product of Triglycerides and Glucose, a Simple Measure of Insulin Sensitivity. Comparison with the Euglycemic-Hyperinsulinemic Clamp. J Clin Endocrinol Metab 2010;95:3347–51. doi:10.1210/jc.2010-0288

PART III

LONG-TERM BENEFITS FROM A HEALTHY LIFESTYLE IN SECONDARY CVD PREVENTION



CHAPTER 9

LONG-TERM LIFESTYLE CHANGE AND RISK OF MORTALITY AND TYPE 2 DIABETES IN PATIENTS WITH CARDIOVASCULAR DISEASE

Nadia E. Bonekamp
Frank L.J. Visseren
Maarten J. Cramer
Jannick A.N. Dorresteijn
Manon G. van der Meer
Ynte M. Ruigrok
Thomas T. van Sloten
Martin Teraa
Johanna M. Geleijnse
Charlotte Koopal

on behalf of the UCC-SMART study group

European Journal of Preventive Cardiology, 2024, Jan 25;31(2):205-213

ABSTRACT

Aims

To quantify the relationship between self-reported long-term lifestyle changes (smoking, waist circumference, physical activity, and alcohol consumption) and clinical outcomes in patients with established cardiovascular disease (CVD).

Methods

Data was used from 2,011 participants (78% male, age 57 ±9 years) from the UCC-SMART cohort who returned for a reassessment visit (SMART2) after approximately 10 years. Self-reported lifestyle change was classified as persistently healthy, improved, worsened or persistently unhealthy. Cox proportional hazard models were used to quantify the relationship between lifestyle change and risk of (cardiovascular) mortality and incident type 2 diabetes (T2D).

Results

Fifty-seven percent of participants was persistently healthy, 17% improved their lifestyle, 8% worsened, and 17% was persistently unhealthy. During a median follow-up time of 6.1 [IQR 3.6-9.6] years after the SMART2 visit, 285 deaths occurred and 99 new T2D diagnoses were made. Compared to a persistently unhealthy lifestyle, individuals who maintained a healthy lifestyle had a lower risk of all-cause mortality (HR 0.48, 95%CI 0.36-0.63), cardiovascular mortality (HR 0.57, 95%CI 0.38-0.87), and incident T2D(HR 0.46, 95%CI 0.28-0.73). Similarly, those who improved their lifestyle had a lower risk of all-cause mortality (HR 0.52, 95%CI 0.37-0.74), cardiovascular mortality (HR 0.46, 95%CI 0.26-0.81), and incident T2D (HR 0.50, 95%CI 0.27-0.92).

Conclusion

These findings suggest that maintaining or adopting a healthy lifestyle can significantly lower mortality and incident T2D risk in CVD patients. This study emphasizes the importance of ongoing lifestyle optimization in CVD patients, highlighting the potential for positive change regardless of previous lifestyle habits.

LAY SUMMARY

In this study, we investigated whether lifestyle changes were related with improved health outcomes in individuals with cardiovascular disease (CVD). We assessed self-reported lifestyle behaviours (smoking, waist circumference, alcohol consumption and physical activity), at inclusion in the cohort and again approximately 10 years later. The results emphasize the importance of making healthy lifestyle choices, even for individuals already diagnosed with CVD and suggest that it is never too late to improve one's lifestyle.

Key Findings:

- CVD patients who maintained or improved to a healthy lifestyle had an almost 50% lower risks of death from any cause, cardiovascular-related death, and developing type 2 diabetes compared to CVD patients who maintained an unhealthy lifestyle.
- Not smoking and compliance with physical activity recommendations were associated with the lowest risk for all-cause and cardiovascular mortality in patients with established CVD

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality, posing a significant worldwide health burden.[1,2] Patients with established CVD are not only at a high risk of recurrent cardiovascular events but also at a high risk of other diseases, including type 2 diabetes (T2D), due to common risk factors, such as unhealthy lifestyle habits.[3,4]

Healthy lifestyle factors including regular physical activity, healthy body composition, non-smoking and limited alcohol intake, have been associated with improvement of traditional cardiovascular risk factors like systolic blood pressure and low-density lipoprotein (LDL) cholesterol levels.[5–9] A healthy lifestyle also exerts beneficial effects on insulin sensitivity, cardiorespiratory fitness and inflammation.[10–12] Furthermore, a healthy lifestyle is strongly related with reductions in risk of cardiovascular events, mortality and incident T2D in apparently healthy individuals.[13] Therefore, optimizing lifestyle habits is a cornerstone in CVD and T2D prevention and a first-line recommendation in the clinical management of established CVD.[14–21]

While extensive research has explored the relationship between lifestyle factors and health outcomes in healthy populations, it is important to investigate their applicability and impact specifically within the context of CVD populations. The few available studies in CVD populations indicate potentially large benefits from lifestyle improvement, which may even exceed those observed in apparently healthy populations.[22] Lifestyle improvement in patients with CVD has been associated with attenuation of cardiovascular risk factors such as systemic inflammation and kidney function.[23,24] However, the relationship between overall lifestyle change and risk of (cardiovascular) mortality and incident T2D has not been studied in patients with established CVD.

Predominantly, evidence on lifestyle-related health gains emerges from observational studies that primarily address individual lifestyle components. However, these components interconnect and jointly affect health, necessitating research that investigates multiple lifestyle components simultaneously. [25] Moreover, most epidemiological studies assess lifestyle behaviours only at baseline and using such single measurements does not provide insights about the effects of changing lifestyle habits on long-term health outcomes.

The aim of the current study was to investigate the association between long-term changes in self-reported lifestyle behaviours (smoking, waist circumference, physical activity and alcohol consumption) and risk of all-cause mortality, cardiovascular mortality and incident T2D in patients with established CVD. Through these analyses we aimed to enhance the knowledge about the potential benefits of changing lifestyle behaviour in this high-risk population.

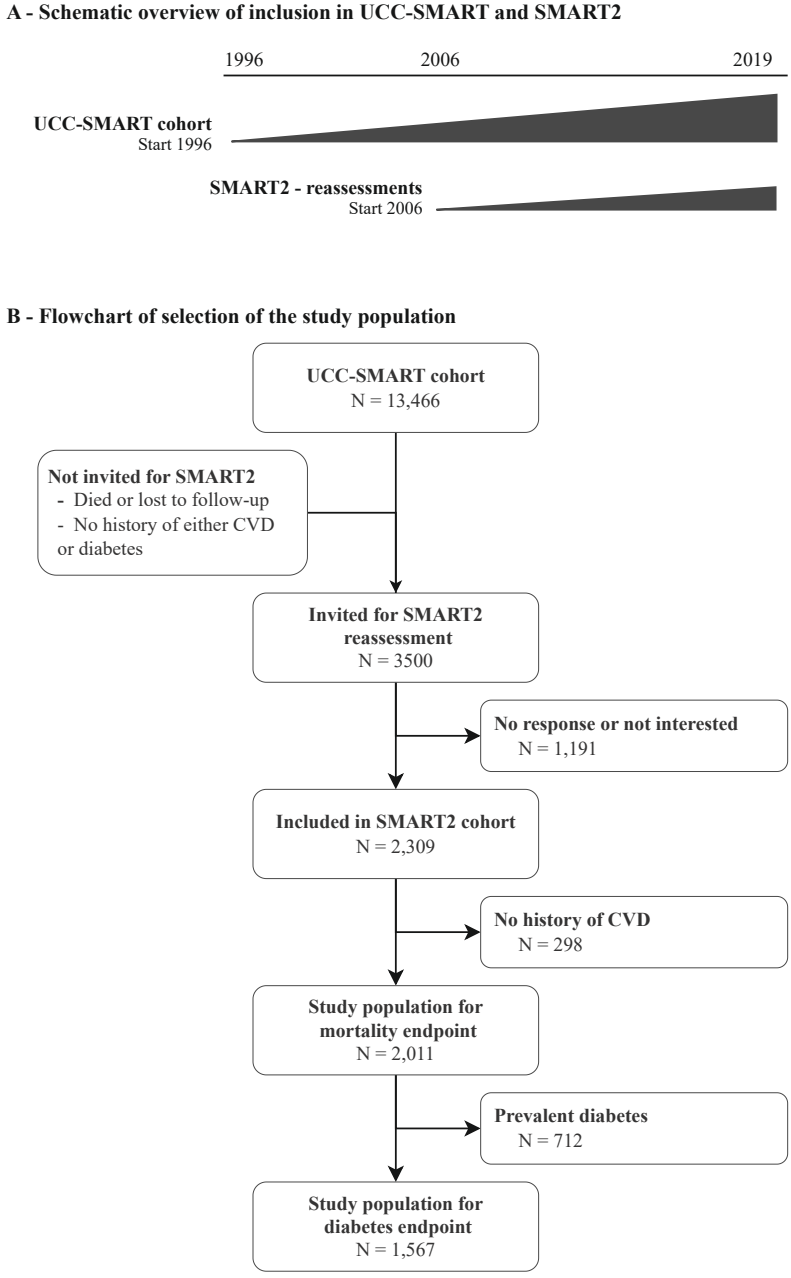
METHODS

Study population

The Utrecht Cardiovascular Cohort – Second Manifestations of ARTerial disease (UCC-SMART) study is an ongoing single-center prospective cohort study in the Netherlands. From 1996 onwards patients referred to our center for cardiovascular risk management were asked to participate in the cohort. The study was approved by the local Medical Ethics Committee and all participants gave written informed consent. Details on the study design have been published previously.[26] From 2006 onwards, a random sample of UCC-SMART participants with either established CVD or T2D and at least four years follow-up after the baseline visit, has been invited for a reassessment visit (*i.e.* the SMART2 visit, Figure 1).

For the current study, data was used from 2,011 participants of the SMART2 reassessment visit with established CVD at inclusion in the UCC-SMART cohort. Established CVD was defined as coronary artery disease (CAD), cerebrovascular disease (CeVD), peripheral arterial disease (PAD) or abdominal aortic aneurysm (AAA), in accordance with previously published definitions.[26,27] Information on cardiovascular history was based on assessments by the treating physician and self-reported medical history. For the T2D endpoint, the study population was limited to patients with CVD without prevalent diabetes (type 1 or 2) at the SMART2 visit as these were not at risk of developing diabetes (N = 1,567, Figure 1). Participants in the current study were included in the UCC-SMART study between 1996 and 2012 and the SMART2 visits took place between 2006 and 2019.

FIGURE 1 Flowchart of selection of the study population



Schematic representation of inclusion in the UCC-SMART study and SMART2 sub study. UCC-SMART: Utrecht Cardiovascular Cohort-Secondary Manifestations of Arterial disease, CVD: cardiovascular disease

Assessment of lifestyle behaviours and other covariates

At inclusion in the UCC-SMART study and at the SMART2 visit, participants completed health questionnaires, anthropometric measurements and laboratory testing. The health questionnaire included questions on medical history, family history, medication use and lifestyle behaviour. Data on smoking and alcohol consumption was self-reported. Smoking status was classified as either current, former or never. Alcohol consumption was collected categorically (no alcohol, <1, 1-10, 11-20, 21-30 or >30 units/week). Leisure-time physical activity was quantified using a modified version of a validated ranking physical activity questionnaire with an additional question on sport activities.[28] Metabolic equivalent of task (MET) values were obtained from the Compendium of Physical activity[29] and used to calculate a total physical activity level per week (in METh/wk) by multiplying the MET value with hours spent on physical activity per week. Waist circumference was measured twice, halfway between the lowest rib and the iliac crest while patients were wearing light clothing and the two measurements were averaged.

Definition of healthy lifestyle and lifestyle change

To assess lifestyle change, self-reported lifestyle behaviours at the SMART2 visit were compared with those reported at the inclusion visit. The lifestyle components included in this analysis were smoking status, body composition (measured as waist circumference), leisure-time physical activity and alcohol consumption. Data on dietary habits, psychological stress and sleep were not available.

Healthy lifestyle targets were obtained from current guidelines for CVD management (Table 1). One point was awarded for each target that participants achieved; when a patient did not reach the target no points were given. A score of 3 or 4 (*i.e.* 3 or 4 healthy behaviours) was defined as a healthy lifestyle. A lower score (0, 1, or 2 healthy behaviours) was deemed to be indicative of an unhealthy lifestyle. Overall lifestyle was assessed at both visits and used to classify an individual's lifestyle trajectory. Lifestyle trajectories were classified as:

1. *Persistently healthy*: Healthy lifestyle at both visits.
2. *Improved*: Unhealthy at baseline but healthy at the SMART2 visit.
3. *Worsened:* Healthy at baseline but unhealthy at the SMART2 visit.
4. *Persistently unhealthy*: Unhealthy lifestyle at both visits.

Overall lifestyle trajectory served as the main determinant in this study and the persistently unhealthy trajectory was used as reference category. Secondary analyses with changes in the four individual lifestyle components as determinants were performed.

TABLE 1 Lifestyle goals for patients with established CVD

Lifestyle component	Healthy behaviour	Unhealthy behaviour
Smoking	Never or former smoker	Current smoker
Body composition *(measured as waist circumference)*	Female: < 88 cm Male: <102 cm	Female: ≥ 88 cm Male: ≥ 102 cm
Leisure-time physical activity	≥ 15 METh/week	< 15 METh/week
Alcohol consumption	No alcohol or ≤ 10 units/week	> 10 units/week

Lifestyle target levels were obtained from international guidelines for prevention and management of cardiovascular disease.[14,15]

Outcome ascertainment

The endpoints in this study were all-cause mortality, cardiovascular death and incident T2D. All-cause mortality comprised all deaths during follow-up. Cardiovascular death was defined as sudden death and death from myocardial infarction, stroke, congestive heart failure, rupture of abdominal aortic aneurysm, or from secondary causes after a cardiovascular event or intervention, e.g. sepsis after bypass surgery. T2D was defined as a new and physician-confirmed diabetes diagnosis in patients aged 35-40 years with BMI >33 kg/m2 or in patients aged >40 years with BMI >27 kg/m2.

All participants were asked to complete an annual follow-up questionnaire on vital status and occurrence of cardiovascular events. When an event was reported, the relevant medical information was obtained from the treating physician. The final categorization of the type of event was made independently by three physicians from the UCC-SMART endpoint committee.27

Data analyses

Patients' characteristics at baseline and at the SMART2 visit were described; categorical variables as absolute number (percentage) and continuous variables as mean and standard deviation or median and interquartile range (IQR), as appropriate. To assess comparability, SMART2 participants' characteristics were compared to those of UCC-SMART participants who were not included in SMART2.

The relationships between lifestyle trajectories and (cardiovascular) death and incident T2D were quantified using the Kaplan Meier method and Cox proportional hazard models. Time-to-event was defined as time after an individual's final visit (*i.e.* the SMART2 visit) until the outcome of interest or until censoring, whichever came first. Time between the initial visit and SMART2 visit was not taken into account in the survival analyses. Person time was calculated separately for each outcome as the sum of time-to-event for all study participants.

Stepwise adjustments were made for confounders. The first model adjusted for age and sex. The second, main model additionally adjusted for education level. Education level was included as a measure of social economic position, which is an important confounder in the relationship between lifestyle behaviours and health outcomes. No adjustments were made for cardiovascular risk factors such as hypertension, lipid levels and insulin resistance, because these were hypothesized to be mediators in the relationships of interest. The proportional hazard assumption was assessed using visual inspection of Schoenfeld residuals.

All analyses were repeated for trajectories of the individual lifestyle components. These models were adjusted for change in the other lifestyle components. The relationship between absolute change in physical activity and waist circumference and the endpoints was assessed using Cox models with restricted cubic splines (3 knots). These models were adjusted for age, sex, education, change in the other three lifestyle components and baseline level of the lifestyle component of interest.

Missing data were imputed with single imputation using predictive mean matching. The main sources of missingness were education level (N = 381, 19%), waist circumference (N = 255, 13%) and LDL-cholesterol (N = 33, 2%). For all other covariates, missingness did not exceed 1%. Physical activity measurements taken before January 2002 (N = 662) were replaced with imputed values, as a new questionnaire was used from this date onwards. Information from the repeated measurements was incorporated in the imputation.

All statistical analyses were performed using R statistical software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant.

Sensitivity analyses

Sensitivity analyses were performed to assess the impact of potential sources of bias. Reverse causation in the relation between lifestyle trajectory and (cardiovascular) death were assessed by running the Cox models after exclusion of 1, 3 and 5 years of follow-up after the SMART2 visit and by adjusting for occurrence of cardiovascular events between the two study visits. The impact of time between the study visits, was assessed by introducing an interaction term in the models and assessing the relation between lifestyle trajectory and mortality in subgroups with an interval of less or more than 10 years between the two assessments. A sensitivity using body mass index (BMI) instead of waist circumference as measure of body composition was performed with a BMI < 25 kg/m^2 considered as healthy. A *'minimally required change'* analysis was performed where a change in the continuous lifestyle components (physical activity and waist circumference) was defined as at least 5% increase or decrease from the baseline visit. The definition of change in smoking and alcohol consumption remained the same in this analysis. Finally, an sensitivity analysis was performed where all four lifestyle behaviours needed to classify as healthy to constitute an overall healthy lifestyle.

To explore the potential impact of healthy survivor bias on the study results, expected smoking behaviour, waist circumference, physical activity and alcohol consumption at the second visit were imputed using multiple imputation for all participants that did not partake in SMART2. The date for the imputed SMART2 visit was set at 4 years after the inclusion visit (*i.e.* the minimum follow-up before patients would be eligible for participation in SMART2) and survival analyses with Cox proportional hazard models were repeated in these imputed datasets comprising 7,191 patients with established CVD and 5,328 participants with CVD but without diabetes and pooled according to Rubin's rules.

RESULTS

Lifestyle trajectories

A total of 2,011 patients with established CVD underwent two consecutive vascular screening visits. The majority of participants were men (N = 1,567, 78%) and mean age at inclusion was 57 ± 9 years. The median time between the first and second visit was 10.0 [IQR 6.5-10.8] years. Patient characteristics at the first and second assessment are shown in Table S1.

The majority of patients had a healthy lifestyle (*i.e.* 3 or 4 healthy behaviours) at the baseline visit (N = 1,327, 66%) and 169 participants (8% of the total population) worsened over time. The remaining 34% of participants (N=684) had an unhealthy lifestyle at baseline, and of these 336 (17%) had improved to a healthy lifestyle at the SMART2 visit (Table 2). PAD and metabolic syndrome were relatively prevalent among patients with an unhealthy lifestyle at baseline. These patients also had higher C-reactive protein (CRP) and LDL-cholesterol levels (Table 2).

Table 3 shows the change in individual lifestyle components and overall lifestyle between the first and second visit. Almost half of all smokers at baseline had ceased smoking at the second visit and very few participants had initiated smoking. On average, waist circumference increased between the two visits (women: 86 ±11cm to 91 ±13 cm, men: 97 ±10 cm to 101 ±11 cm). Physical activity levels and alcohol consumption remained stable over time.

Lifestyle changes and risk of cardiovascular mortality, all-cause mortality, and incident T2D

Median follow-up time after SMART2 was 6.1 [IQR 3.6-9.6] years and ranged from 0 to 14 years. During this time, 285 deaths occurred of which 150 were due to cardiovascular causes (Figure 2, Figure S1). Compared with a persistently unhealthy lifestyle, patients with a persistently healthy lifestyle were at the lowest risk of all-cause mortality, cardiovascular mortality and incident T2D (Figure 2). Improving lifestyle from an unhealthy to a healthy lifestyle was related to approximately 50% relative risk reductions for all-cause mortality, cardiovascular mortality and incident T2D. Patients with a worsened lifestyle, had a lower risk of all-cause and cardiovascular mortality, but not of incident T2D.

TABLE 2 Baseline characteristics stratified for lifestyle trajectories

Characteristic	Persistently Healthy	Worsened	Improved	Persistently unhealthy
N	1,158 (58)	169 (8)	336 (17)	348 (17)
Female sex	255 (22)	50 (30)	71 (21)	68 (20)
Age, *year*	58 ±9	57 ±9	56 ±9	55 ±8
Education				
Low	397 (34)	70 (41)	126 (38)	136 (39)
Middle	652 (56)	85 (50)	182 (54)	185 (53)
High	109 (9)	14 (8)	28 (8)	27 (8)
Coronary artery disease	814 (70)	112 (66)	181 (54)	184 (53)
Cerebrovascular disease	278 (24)	41 (24)	92 (27)	97 (28)
Peripheral arterial disease	128 (11)	32 (19)	76 (23)	94 (27)
Abdominal aortic aneurysm	52 (5)	8 (5)	22 (7)	26 (8)
Diabetes	142 (12)	28 (17)	40 (12)	47 (14)
Metabolic syndrome	439 (38)	85 (50)	217 (65)	235 (68)
Smoking				
Never	357 (31)	24 (14)	23 (7)	18 (5)
Former	669 (58)	109 (65)	116 (35)	97 (28)
Current	132 (11)	36 (21)	197 (59)	233 (67)
Alcohol intake, *units/wk*				
0	187 (16)	20 (14)	47 (11)	23 (7)
< 1	130 (11)	13 (7)	22 (8)	23 (7)
1 - 10	654 (56)	84 (25)	85 (50)	58 (17)
> 10	187 (16)	52 (54)	182 (31)	244 (70)
BMI, *kg/m²*	26 ±3.1	26.8 ±3.2	27.6 ±4.2	28.5 ±4.1
Waist circumference, *cm*	F: 83 ±10 M: 94 ±8	F: 86 ±8 M: 99 ±8	F: 91 ±13 M: 100 ±10	F: 94 ±12 M: 103 ±11
Systolic BP, *mmHg*	139 ±20	140 ±22	139 ±20	140 ±19
Diastolic BP, *mmHg*	82 ±11	81 ±12	81 ±11	83 ±10
Total cholesterol, *mmol/l*	4.6 [4.0-5.5]	4.9 [4.1-5.6]	5.1 [4.4-5.9]	5.2 [4.4-5.9]
LDL-cholesterol, *mmol/l*	2.6 [2.1-3.4]	2.8 [2.3-3.4]	3.1 [2.5-3.8]	3.1 [2.4-3.8]
HDL-cholesterol, *mmol/l*	1.2 [1.0-1.5]	1.2 [1.0-1.4]	1.1 [0.9-1.4]	1.1 [0.9-1.4]
eGFR, *ml/min*	78 ±15	77 ±17	80 ±16	82 ±15
CRP, *mg/l*	1.4 [0.7-3.0]	2.1 [1.0-4.7]	2.4 [1.2-4.8]	2.6 [1.3-5.2]
Physical activity, *METh/wk*	43 [25-69]	35 [19-55]	12 [5-34]	18 [7-41]

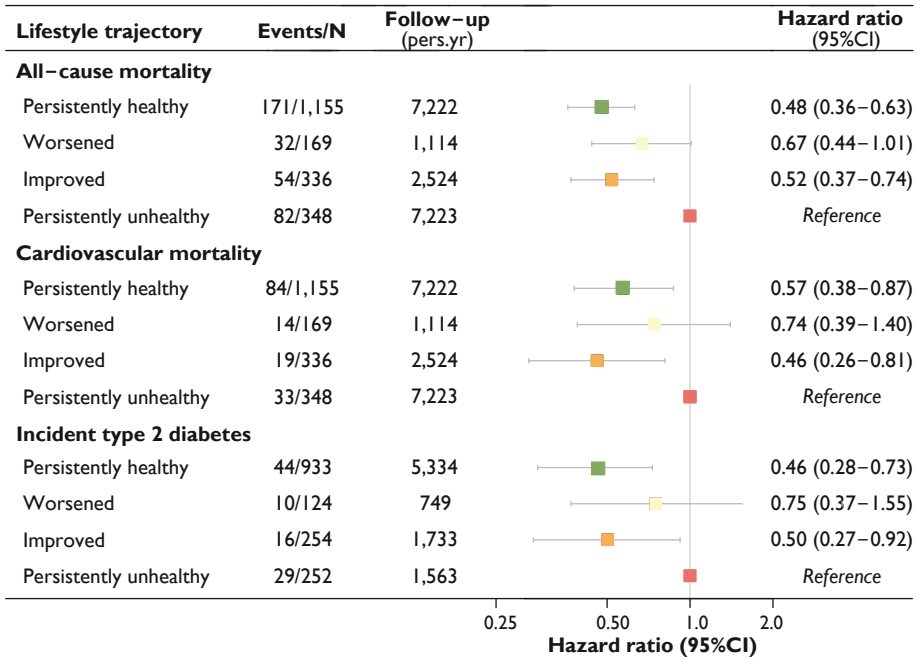
Abbreviations: CAD: coronary artery disease, CeVD: cerebrovascular disease, PAD: peripheral arterial disease, AAA: abdominal aortic aneurysm, BMI: body mass index, BP: blood pressure, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, eGFR: estimated glomerular filtration rate, CRP: C reactive protein

TABLE 3 Change in lifestyle components between baseline and SMART2 visits.

	Persistently healthy	Worsened	Improved	Persistently unhealthy
Smoking	1,358 (68)	55 (3)	301 (15)	297 (15)
Waist circumference	1,054 (52)	385 (19)	88 (4)	484 (24)
Physical activity	1,374 (68)	154 (8)	375 (18)	108 (5)
Alcohol consumption	1,231 (61)	115 (6)	239 (12)	426 (21)
Overall lifestyle score	**599 (29)**	**728 (36)**	**559 (28)**	**125 (6)**

Number of patients that were persistently healthy, improved, worsened or were persistently unhealthy per lifestyle component and overall lifestyle

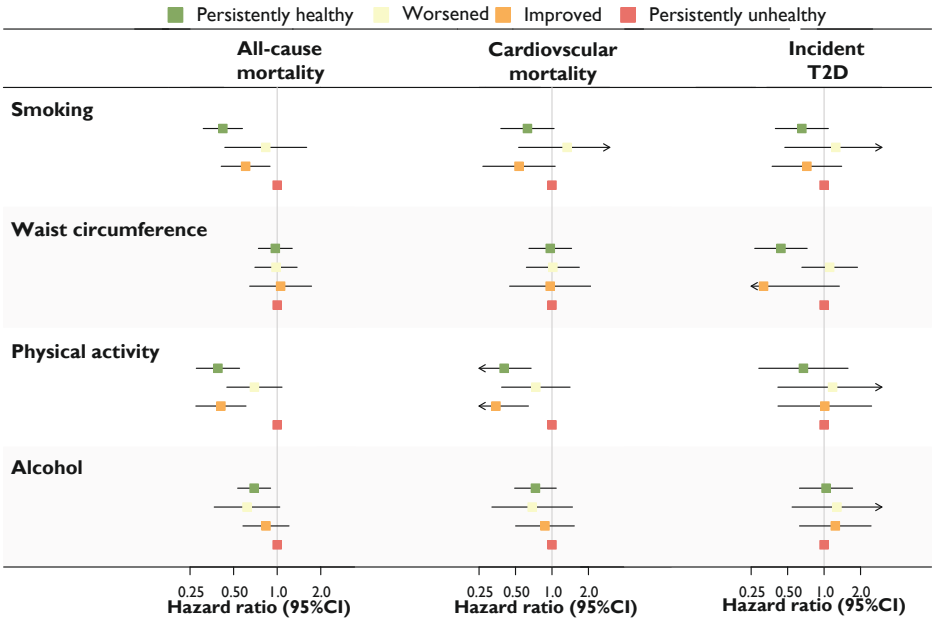
FIGURE 2 Risk of all-cause mortality, cardiovascular mortality and incident T2D for different lifestyle trajectory



Hazard ratio for all-cause mortality and cardiovascular mortality compared to a persistently unhealthy lifestyle. Hazard ratios were adjusted for age, sex and education level. Follow-up time in person years after the SMART2 study visit. Abbreviations: HR – hazard ratios, 95%CI: 95% confidence interval

Of the four lifestyle components, smoking (non-smoking or smoking cessation) and physical activity (persistently healthy or improved levels) were most strongly associated with risk reductions for all-cause mortality and cardiovascular mortality (Figure 3). Changes in waist circumference were not related with all-cause mortality and cardiovascular mortality risk. For incident T2D, the strongest association was found for a persistently healthy and improved waist circumference (Figure 3). No statistically significant relationship with the three other lifestyle components was observed. These findings were supported by an analysis using change in physical activity level and waist circumference as continuous variables (Figure S2).

FIGURE 3 Risk of all-cause mortality, cardiovascular mortality and incident T2D in relation to changes in individual lifestyle component



Hazard ratio for changes in the four individual lifestyles compared to a persistently unhealthy behaviour. Hazard ratios were adjusted for age, sex and education level. Follow-up time in person years after the SMART2 study visit. HR – hazard ratios, 95%CI: 95% confidence interval

Sensitivity analyses

Characteristics and lifestyle behaviour at baseline were comparable between participant that did and did not partake in the SMART2 visit, although SMART2 participants were younger (mean age 57 vs 61 years) and had lower education levels compared to non-

participants. When an overall healthy lifestyle was defined as presence of 4 out 4 healthy behaviours instead of 3 out of 4, the results for a persistently healthy lifestyle were somewhat attenuated compared with the main analysis (Figure S3). Analyses in datasets with imputed values for lifestyle change in non-SMART2-participants, yielded similar results for a persistently healthy lifestyle compared with the main analysis, but resulted in a stronger beneficial relation for a reduced lifestyle trajectory (Figure S4). In this sensitivity analysis, no protective relationship was observed for an improved lifestyle (Figure S4).

In a sensitivity analysis requiring a minimal 5% change from baseline, the size and direction of the effect estimates were similar to the main analysis (Figure S5). In analyses exploring potential reverse causation by excluding the first 1, 3 and 5 years of follow-up, the associations between lifestyle trajectory and all-cause and cardiovascular mortality, were similar in size and direction compared with the main analysis (Figure S6). However, for incident T2D, the association was attenuated or even reversed (Figure S6). Additional adjustment for occurrence of cardiovascular events between the first and second assessment as a source of reverse causation, yielded near identical effect estimates to the main analysis, as well as additional adjustment for time between inclusion and the SMART2 visit. Using BMI as a measure of body composition yielded the same results as when waist circumference was used.

DISCUSSION

In a cohort of patients with established CVD and repeated lifestyle assessments, maintaining a persistently healthy lifestyle or transitioning from an unhealthy to a healthy lifestyle over time was linked to a nearly 50% decrease in all-cause mortality, cardiovascular mortality, and incident T2D, compared to those with a persistently unhealthy lifestyle. The findings suggest that even after CVD manifestation, maintaining or adopting a healthy lifestyle can reduce residual cardiovascular risk.

These study findings align with previous research. Similar reductions in risk of coronary calcification, cardiovascular events and (cardiovascular) mortality were observed in primary CVD prevention cohorts evaluating multiple lifestyle behaviors.[13,21,30–32] An analysis of the UK Biobank demonstrated that maintaining an unhealthy lifestyle over time correlated with almost twice the risk of ischemic heart disease, while

lifestyle improvements were protective. regardless of baseline lifestyle behaviours.[13] In the current study, these relationships with CVD outcomes appear to hold true in a secondary CVD prevention population, despite differences in baseline risk, concomitant medications and morbidity. This conclusion continues upon a previous European-wide survey that showed that CVD patients with poor compliance with lifestyle recommendations, had higher CVD risk factor levels.[33,34] Furthermore, increasing physical activity levels has been associated with 50% relative risk reductions in coronary artery patients.[35] To our knowledge, the relationship between combined lifestyle changes and incident T2D has never been assessed in an established CVD population, but findings in the present study are in line with previous observations that a healthy lifestyle has the potential to significantly improve cardiometabolic risk factors.[33]

Patients with initially healthy lifestyles that declined over time still showed survival benefits compared to persistently unhealthy patients. Similar patterns were noted in earlier studies evaluating lifestyle changes over time. In the UK Biobank, people with declining lifestyle habits had similar cardiovascular event rates compared to those that were able to maintain a healthy lifestyle.[13] This suggests that benefits of a healthy lifestyle endure over time. This hypothesis is reinforced by findings from multiple imputed analyses in the current study, which indicated a protective relationship with all outcomes for a worsened lifestyle trajectory, potentially explained by the after-effects of the initial healthy lifestyle. However, this does not mean that patients with a healthy lifestyle should not be motivated to maintain that lifestyle, because the largest protective relationships are found for people with a persistent healthy lifestyle. Patients with declining lifestyle habits should be counselled that to resume their healthy lifestyle habits, especially sufficient physical activity and not smoking.

Most CVD patients in this study reported being compliant with guideline-recommended lifestyle behaviours and was able to maintain their healthy lifestyle over a period of approximately 10 years. This high adherence rate is consistent with, or even exceeds, adherence rates reported in previous research about compliance with guideline recommendations in secondary prevention of CVD[33,36–38]

This study is among the first to jointly assess the relation of changes in multiple lifestyle components with clinical outcomes, because previous studies primarily focussed on change in individual components.[35,38,40,41] This approach allows for direct comparison

between components and aids prioritization of specific lifestyle changes. Not smoking and high physical activity showed the strongest links to all-cause and cardiovascular mortality, while a healthy waist circumference was more closely tied to lower incident T2D risk.

Strengths and limitations

Strengths of the current study include the large cohort size, the repeated assessment of lifestyle behaviours and the long follow-up duration. Study limitations need to be considered. Data on alcohol consumption was collected categorically and could therefore not be analysed continuously. In the current analysis, lifestyle was limited to smoking, waist circumference, physical activity and alcohol consumption, and did not include other lifestyle factors such as diet, sleep and stress, potentially resulting in an underestimation of the relationship between lifestyle changes and clinical outcomes. To assess overall lifestyle, a healthy lifestyle was defined as having a score of three out of four for healthy behaviours. However, this approach led to a counterintuitive finding wherein 132 participants categorized as having a 'healthy' lifestyle were identified as current smokers. Relatively few outcomes occurred in the worsened and improved groups due to the smaller size of these groups, which resulted in wide confidence intervals. Although, lifestyle was assessed at two separate time points, there was no information available on changes between the two measurements. Further limitations include that lifestyle behaviours were self-reported meaning that they are subject to misclassification and social desirability bias. However, as lifestyle behaviours were compared within-individual, the impact of these potential biases will likely be small. Residual confounding may bias the results, for example from social economic position, which was only evaluated based on education in the UCC-SMART study. Evaluating lifestyle changes over time inherently introduces healthy survivor bias, because only patients that survive until the second assessment can be included. Sensitivity analyses showed that the size and direction of the observed relations was not modified by the interval between the first and second visit, which implies that the effects of healthy survivor bias are small. For the T2D endpoint, associations with lifestyle change attenuated or even reversed when the first 1,3, or 5 years of follow-up were excluded. This may be due to limited power for these analyses or reverse causation could have biased these findings. Therefore, some caution should be taking in extending the association with T2D to a longer follow-up time.

This study illustrates that in CVD patients, a persistently healthy and improved lifestyle were associated with lower risk of (cardiovascular) mortality and incident T2D compared to persistently unhealthy patients. The largest benefit was observed for patients that were able to maintain a healthy lifestyle over time. However, the study also reveals encouraging findings for individuals with an unhealthy lifestyle that change to a healthy lifestyle, indicating that it is never too late to improve their prognosis after CVD has manifested. A non-smoking status and healthy level of physical activity were the main drivers of lifestyle-related mortality risk reductions; while a low waist circumference was most important to prevent T2D. Conversely, patients with an unhealthy lifestyle over time faced a relatively high risk of cardiovascular mortality and incident T2D, underscoring the importance of addressing lifestyle habits in CVD management.

In conclusion, this study assessed the relationship between self-reported changes in lifestyle behaviour and (cardiovascular) mortality and T2D. The findings emphasize the pressing need for ongoing attention for maintaining or adopting a healthy lifestyle within the clinical management of CVD patients. By incorporating lifestyle interventions into their treatment plans, healthcare providers can potentially mitigate the risk of cardiovascular mortality and T2D for their patients. Ultimately, these findings underscore the profound impact that lifestyle choices can have on the outcomes and overall well-being of CVD patients.

REFERENCES

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982–3021.
2. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet [Internet]. 2017 Sep 16;390(10100):1211–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28919117
3. Zhang Y, Pan XF, Chen J, Xia L, Cao A, Zhang Y, et al. Combined lifestyle factors and risk of incident type 2 diabetes and prognosis among individuals with type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. Vol. 63, Diabetologia. Springer; 2020. p. 21–33.
4. Duan MJ, Dekker LH, Carrero JJ, Navis G. Lifestyle patterns and incident type 2 diabetes in the Dutch lifelines cohort study. Prev Med Rep. 2022 Dec 1;30.
5. Ge L, Sadeghirad B, Ball GDC, Da Costa BR, Hitchcock CL, Svendrovski A, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: Systematic review and network meta-analysis of randomised trials. The BMJ. 2020;369.
6. Cheng W, Zhang Z, Cheng W, Yang C, Diao L, Liu W. Associations of leisure-time physical activity with cardiovascular mortality: A systematic review and meta-analysis of 44 prospective cohort studies. Eur J Prev Cardiol. 2018;25(17):1864–72.
7. Wang ZJ, Zhou YJ, Galper BZ, Gao F, Yeh RW, Mauri L. Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: A systematic review and meta-analysis. Vol. 101, Heart. 2015. 1631–1638 p.
8. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: Meta-analysis of Individual participant data from prospective cohort studies of the CHANCES consortium. The BMJ. 2015;350:1–12.
9. Ding C, O'Neill D, Bell S, Stamatakis E, Britton A. Association of alcohol consumption with morbidity and mortality in patients with cardiovascular disease: original data and meta-analysis of 48,423 men and women. BMC Med. 2021 Dec 27;19(1):167.
10. Kelly GS. Insulin resistance: lifestyle and nutritional interventions. Altern Med Rev. 2000 Apr;5(2):109–32.
11. Fan LM, Collins A, Geng L, Li JM. Impact of unhealthy lifestyle on cardiorespiratory fitness and heart rate recovery of medical science students. BMC Public Health. 2020 Jun 26;20(1):1012.
12. Kantor ED, Lampe JW, Kratz M, White E. Lifestyle Factors and Inflammation: Associations by Body Mass Index. PLoS One. 2013 Jul 2;8(7):e67833.
13. Gao Y, Chen Y, Hu M, Song J, Zhang Z, Sun H, et al. Lifestyle trajectories and ischaemic heart diseases: a prospective cohort study in UK Biobank. Eur J Prev Cardiol. 2023 Mar 27;

14. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation [Internet]. 2019 Sep 10;140(11):e596–646. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000678

15. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J [Internet]. 2021 Aug 30;(00):1–111. Available from: https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab484/6358713

16. Masana L, Ros E, Sudano I, Angoulvant D, Ibarretxe Gerediaga D, Murga Eizagaechevarria N, et al. Is there a role for lifestyle changes in cardiovascular prevention? What, when and how? Atheroscler Suppl. 2017 Apr;26:2–15.

17. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD. Community prevalence of ideal cardiovascular health, by the american heart association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol. 2011 Apr 19;57(16):1690–6.

18. Åkesson A, Larsson SC, Discacciati A, Wolk A. Low-Risk Diet and Lifestyle Habits in the Primary Prevention of Myocardial Infarction in Men A Population-Based Prospective Cohort Study. 2014.

19. Chomistek AK, Chiuve SE, Eliassen AH, Mukamal KJ, Willett WC, Rimm EB. Healthy Lifestyle in the Primordial Prevention of Cardiovascular Disease Among Young Women. 2015.

20. Khera A V., Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. New England Journal of Medicine. 2016 Dec 15;375(24):2349–58.

21. Zhang YB, Pan XF, Chen J, Cao A, Xia L, Zhang Y, et al. Combined lifestyle factors, all-cause mortality and cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies. J Epidemiol Community Health (1978). 2021 Jan;75(1):92–9.

22. Xu C, Cao Z. Cardiometabolic diseases, total mortality, and benefits of adherence to a healthy lifestyle: a 13-year prospective UK Biobank study. J Transl Med. 2022 Dec 1;20(1).

23. van 't Klooster CC, van der Graaf Y, Ridker PM, Westerink J, Hjortnaes J, Sluijs I, et al. The relation between healthy lifestyle changes and decrease in systemic inflammation in patients with stable cardiovascular disease. Atherosclerosis. 2020;301(January):37–43.

24. Østergaard HB, Demirhan I, Westerink J, Verhaar MC, Asselbergs FW, de Borst GJ, et al. Lifestyle changes and kidney function: A 10-year follow-up study in patients with manifest cardiovascular disease. Eur J Clin Invest. 2022 Sep 1;52(9).

25. Prochaska JJ, Spring B, Nigg CR. Multiple health behavior change research: an introduction and overview. Prev Med (Baltim). 2008 Mar;46(3):181–8.

26. Castelijns MC, Helmink MAG, Hageman SHJ, Asselbergs FW, de Borst GJ, Bots ML, et al. Cohort profile: the Utrecht Cardiovascular Cohort-Second Manifestations of Arterial Disease (UCC-SMART) Study-an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands. BMJ Open. 2023 Feb 20;13(2):e066952.

27. Simons PCG, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol [Internet]. 1999 Oct;15(9):773–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10608355

28. Pols MA, Peeters PH, Ocké MC, Slimani N, Bueno-de-Mesquita HB, Collette HJ. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol [Internet]. 1997 Feb 1;26 Suppl 1(90001):S181-9. Available from: https://academic.oup.com/ije/article-lookup/doi/10.1093/ije/26.suppl_1.S181

29. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32(9 SUPPL.).

30. Han H, Cao Y, Feng C, Zheng Y, Dhana K, Zhu S, et al. Association of a Healthy Lifestyle With All-Cause and Cause-Specific Mortality Among Individuals With Type 2 Diabetes: A Prospective Study in UK Biobank. Diabetes Care. 2022 Feb 1;45(2):319–29.

31. Liu G, Li Y, Hu Y, Zong G, Li S, Rimm EB, et al. Influence of Lifestyle on Incident Cardiovascular Disease and Mortality in Patients With Diabetes Mellitus. J Am Coll Cardiol. 2018 Jun 26;71(25):2867–76.

32. Limpens MAM, Asllanaj E, Dommershuijsen LJ, Boersma E, Ikram MA, Kavousi M, et al. Healthy lifestyle in older adults and life expectancy with and without heart failure. Eur J Epidemiol. 2022 Feb;37(2):205–14.

33. Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol. 2019 May 1;26(8):824–35.

34. De Bacquer D, Astin F, Kotseva K, Pogosova N, De Smedt D, De Backer G, et al. Poor adherence to lifestyle recommendations in patients with coronary heart disease: Results from the EUROASPIRE surveys. Eur J Prev Cardiol. 2022 Jan 1;29(2):383–95.

35. Gonzalez-Jaramillo N, Wilhelm M, Arango-Rivas AM, Gonzalez-Jaramillo V, Mesa-Vieira C, Minder B, et al. Systematic Review of Physical Activity Trajectories and Mortality in Patients With Coronary Artery Disease. J Am Coll Cardiol [Internet]. 2022 May;79(17):1690–700. Available from: https://linkinghub.elsevier.com/retrieve/pii/S073510972200554X

36. Solomon MD, Leong TK, Levin E, Rana JS, Jaffe MG, Sidney S, et al. Cumulative adherence to secondary prevention guidelines and mortality after acute myocardial infarction. J Am Heart Assoc. 2020;9(6).

37. Shore S, Jones PG, Maddox TM, Bradley SM, Stolker JM, Arnold S V, et al. Longitudinal persistence with secondary prevention therapies relative to patient risk after myocardial infarction. Heart. 2015 May 15;101(10):800–7.

38. Pedersen E, Garcia BH, Halvorsen KH, Eggen AE, Schirmer H, Waaseth M. Adherence to prescription guidelines and achievement of treatment goals among persons with coronary heart disease in Tromsø 7. BMC Cardiovasc Disord. 2021 Dec 1;21(1).

39. Hardcastle SJ, Hancox J, Hattar A, Maxwell-Smith C, Thøgersen-Ntoumani C, Hagger MS. Motivating the unmotivated: how can health behavior be changed in those unwilling to change? Front Psychol [Internet]. 2015 Jun 16;6(June):1–4. Available from: http://journal.frontiersin.org/Article/10.3389/fpsyg.2015.00835/abstract

40. Wu AD, Lindson N, Hartmann-Boyce J, Wahedi A, Hajizadeh A, Theodoulou A, et al. Smoking cessation for secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2022 Aug 8;2022(8).

41. Ibsen DB, Søgaard K, Sørensen LH, Olsen A, Tjønneland A, Overvad K, et al. Modifiable Lifestyle Recommendations and Mortality in Denmark: A Cohort Study. Am J Prev Med. 2021 Jun 1;60(6):792–801.

SUPPLEMENTAL MATERIAL

TABLE S1 Patient characteristics at baseline and at the SMART2 visit

Characteristic	Responders	Non-responders	SMD
	N = 2,011	N = 6,583	
Female sex	444 (22)	1,815 (28)	0.13
Age, *year*	57 ±9	61 ±10	0.38
Education*			0.20
Low	729 (36)	1,456 (32)	
Middle	740 (37)	1,581 (34)	
High	542 (27)	1,576 (34)	
Coronary artery disease	1,291 (64)	4,001 (61)	0.07
Cerebrovascular disease	508 (25)	2,036 (31)	0.13
Peripheral arterial disease	330 (16)	1,175 (18)	0.04
Abdominal aortic aneurysm	108 (5)	609 (9)	0.15
Diabetes	257 (13)	1,228 (19)	0.16
Metabolic syndrome	976 (49)	3,144 (54)	0.11
Smoking			0.05
Never	422 (21)	1,491 (23)	
Former	991 (49)	3,057 (47)	
Current	598 (30)	2,013 (31)	
Alcohol intake, units/wk			0.18
0	275 (13.8)	1251 (19.2)	
< 1	186 (9.3)	683 (10.5)	
1 – 10	871 (43.7)	2818 (43.2)	
> 10	659 (33.1)	1773 (27.2)	
BMI, *kg/m²*	27 ±4	27 ±4	0.05
Waist circumference, *cm*	F: 87 ±11 M: 97 ±10	F: 89 ±13 M: 99 ±11	0.67
Systolic blood pressure, *mmHg*	139 ±20	139 ±21	0.01
Diastolic blood pressure, *mmHg*	82 ±11	81 ±11	0.09
Total cholesterol, *mmol/l*	4.8 [4.1-5.7]	4.6 [3.9-5.5]	0.14
LDL-cholesterol, *mmol/l*	2.8 [2.2-3.6]	2.6 [2.0-3.4]	0.15
HDL-cholesterol, *mmol/l*	1.2 [1.0-1.4]	1.2 [1.0-1.4]	0.02
eGFR, *ml/min*†	79 ±16	77 ±19	0.13
CRP, *mg/l*	1.7 [0.8-3.8]	2.2 [1.0-4.9]	0.19
Physical activity, *METh/wk*	34 [15-61]	36 [17-63]	0.09

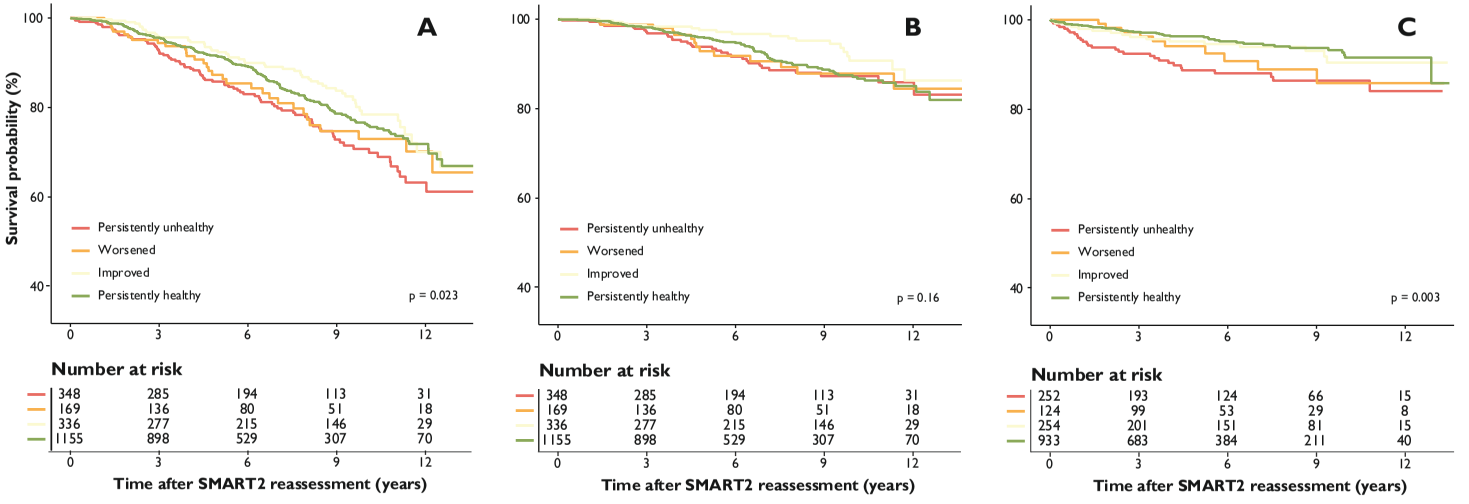
Data are reported as number (percentage), mean ±standard deviation, median [interquartile range]. Abbreviations: BMI: body mass index, LDL: low-density lipoprotein, HDL: high-density lipoprotein, eGFR: estimated glomerular filtration rate, CRP: C reactive protein *Missing for 1,970 non-responders, not imputed †Estimated using the CKD-EPI creatine formula.

TABLE S2 Baseline characteristics of SMART2 responders and non-responders with established cardiovascular disease

Characteristic	Baseline visit	SMART2 visit
	N = 2,011	N = 2,011
Female sex	444 (22)	Unchanged
Age, *year*	57 ±9	66 ±9
Education		
Low	729 (36)	Unchanged
Middle	1,104 (55)	Unchanged
High	178 (9)	Unchanged
Coronary artery disease	1,291 (64)	1,371 (68)
Cerebrovascular disease	508 (25)	555 (28)
Peripheral arterial disease	330 (16)	389 (19)
Abdominal aortic aneurysm	108 (5)	147 (7)
Diabetes	257 (13)	444 (22)
Metabolic syndrome*	976 (49)	1,098 (55)
Smoking		
Never	422 (21)	368 (18)
Former	991 (49)	1,291 (64)
Current	598 (30)	352 (18)
Alcohol consumption, *units/wk*		
0	277 (13)	303 (15)
< 1	188 (9)	318 (16)
1 - 10	881 (44)	849 (42)
> 10	665 (33)	541 (27)
BMI, *kg/m²*	26.8 ±3.6	27.4 ±4.0
Waist circumference, *cm*	F: 86 ±11 M: 97 ±10	F: 92 ±13 M: 101 ±11
Systolic blood pressure, *mmHg*	139 ±20	140 ±17
Diastolic blood pressure, *mmHg*	82 ±11	79 ±10
Total cholesterol, *mmol/l*	4.8 [4.1-5.7]	4.4 [3.8-5.0]
LDL-cholesterol, *mmol/l*	2.8 [2.2-3.6]	2.4 [2.0-3.0]
HDL-cholesterol, *mmol/l*	1.2 [1.0-1.4]	1.2 [1.0-1.5]
eGFR†, *ml/min*	79 ±16	74 ±17
CRP, *mg/l*	1.7 [0.8-3.8]	1.5 [0.8-3.4]
Physical activity, *METh/wk*	34 [15-61]	44 [24-70]

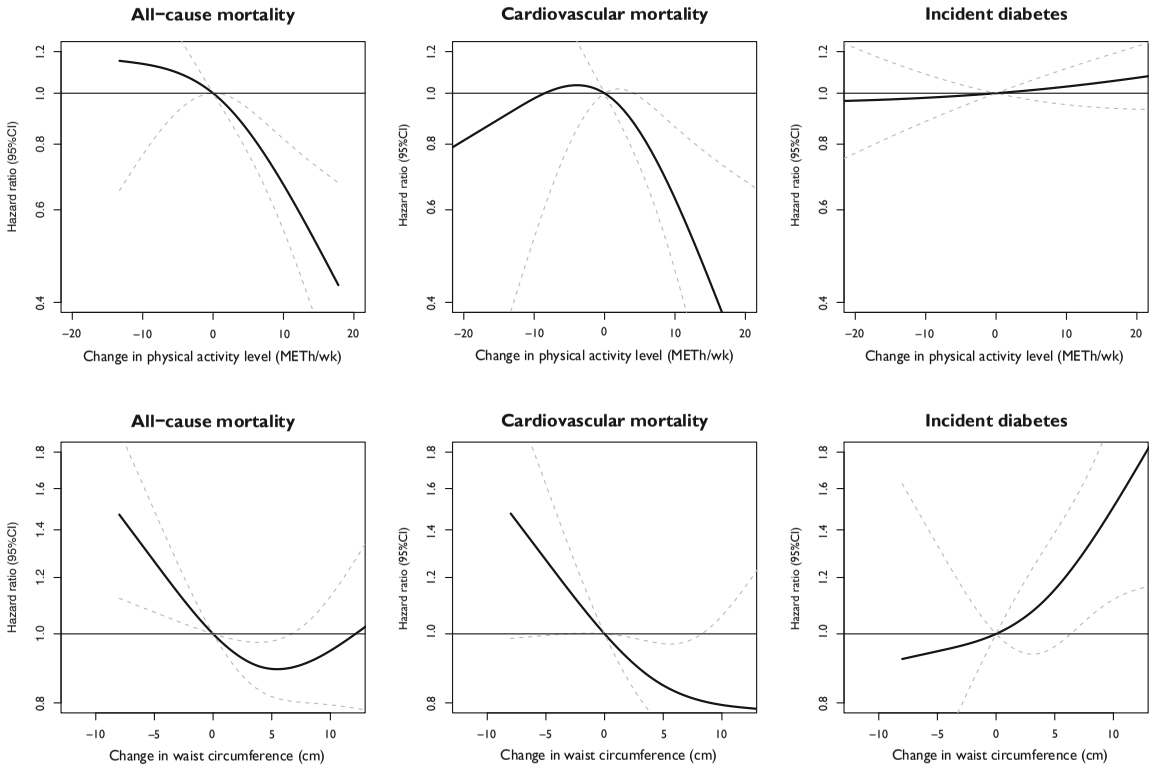
Data presented as number (percentage), mean ±standard deviation or median [interquartile range]. Abbreviations: BMI: body mass index, LDL: low density lipoprotein, HDL: high density lipoprotein, eGFR: estimated glomerular filtration rate. * Defined based on ATP III criteria. †eGFR was estimated using the CKD-EPI formula

FIGURE S1 Kaplan Meier curves stratified for lifestyle trajectory



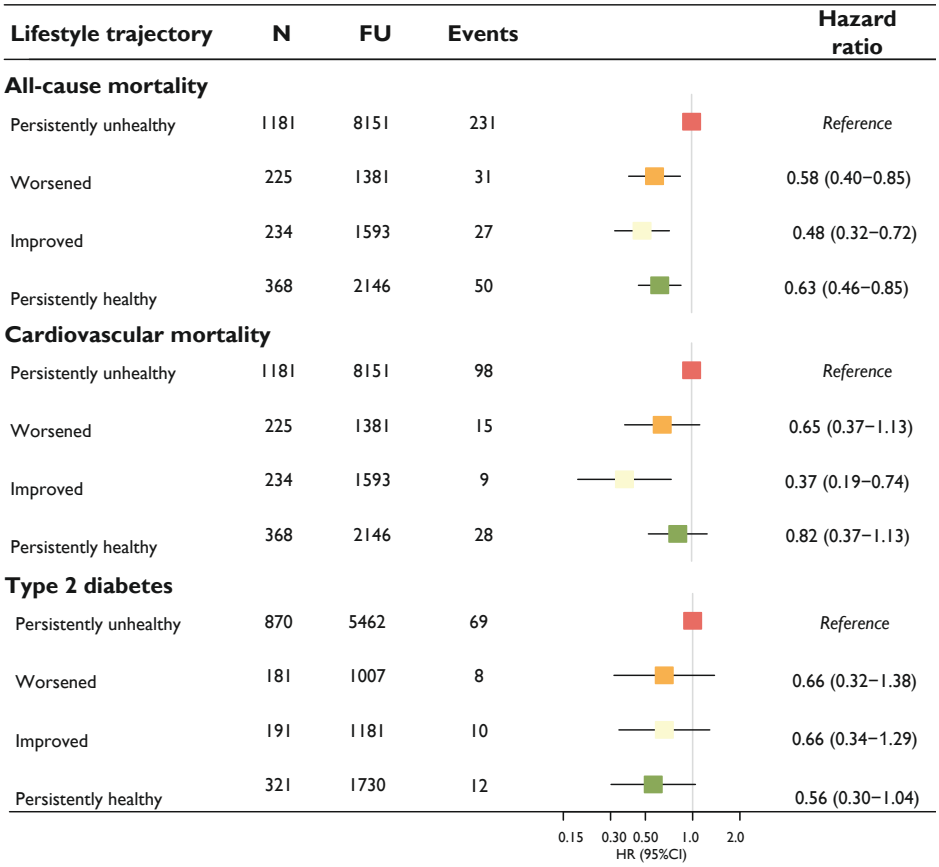
Survival probability for all-cause mortality (A), cardiovascular mortality (B) and incident diabetes (C) after SMART2 visit, stratified for lifestyle trajectory

FIGURE S2 Relationship between continuous change in physical activity level and waist circumference and (cardiovascular) mortality and incident diabetes



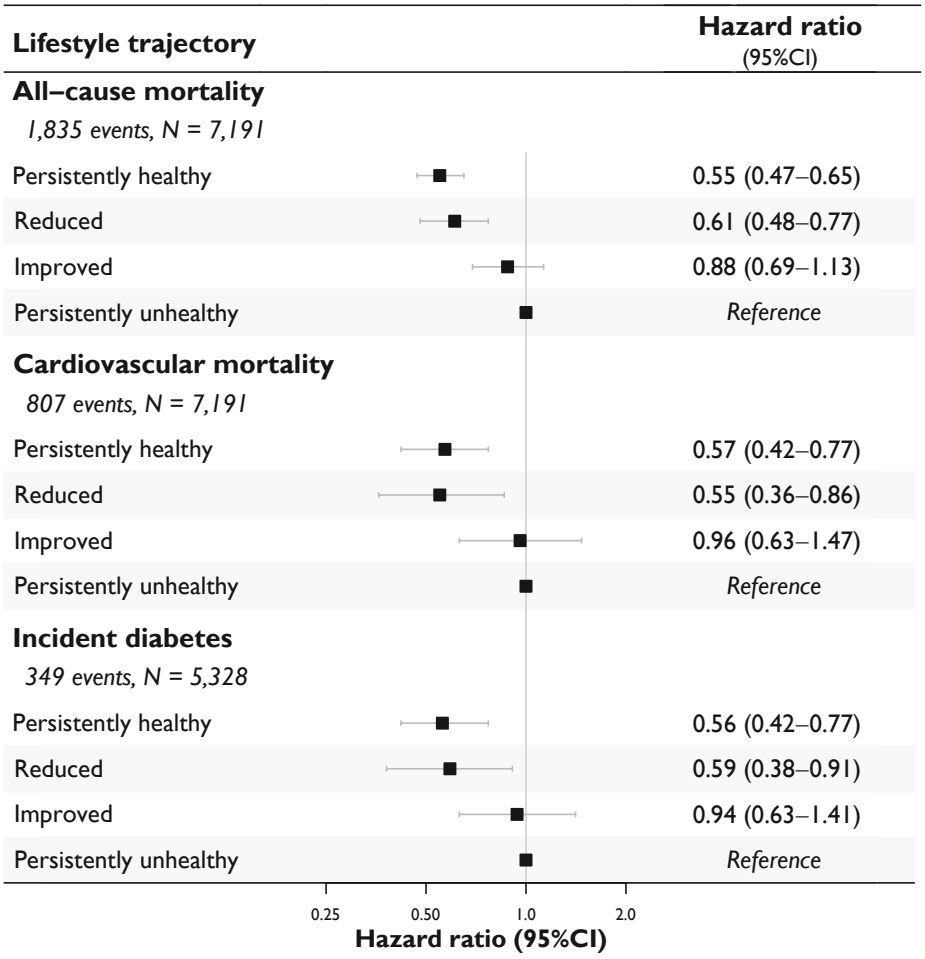
Restricted cubic splines representing the relationship between the continuous change in physical activity level and waist circumference between the two visits. These analyses were adjusted for age, sex, education level, baseline value for physical activity/waist circumference and changes in the three other lifestyle behaviours (smoking, alcohol consumption and waist circumference/physical activity). HR – hazard ratios, 95%CI: 95% confidence interval

FIGURE S3 Associations with healthy lifestyle defined as four out of four healthy behaviours.



Sensitivity analysis with a healthy lifestyle defined as compliance with all four lifestyle components. Hazard ratio for all-cause mortality and cardiovascular mortality compared to a persistently unhealthy lifestyle. Hazard ratios were adjusted for age, sex and education level. Follow-up time in person years after the SMART2 study visit. Abbreviations: HR – hazard ratios, 95%CI: 95% confidence interval

FIGURE S4 Relationship between lifestyle change and mortality risk in multiple imputed datasets.



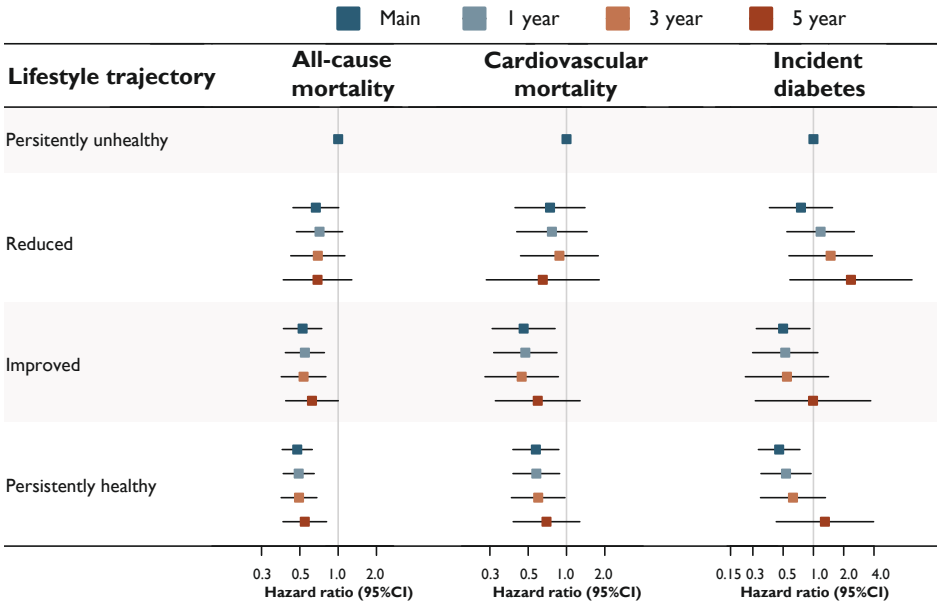
Hazard ratio for all-cause mortality and cardiovascular mortality compared to a persistently unhealthy lifestyle, pooled from 5 multiple imputed datasets. Hazard ratios were adjusted for age, sex and education level. Follow-up time in person years after the SMART2 visit. Events and follow-up time were not imputed, as this information was complete for all participants and were the same in each imputed data set. HR – hazard ratios, 95%CI: 95% confidence interval

FIGURE S5 Minimal change from baseline values

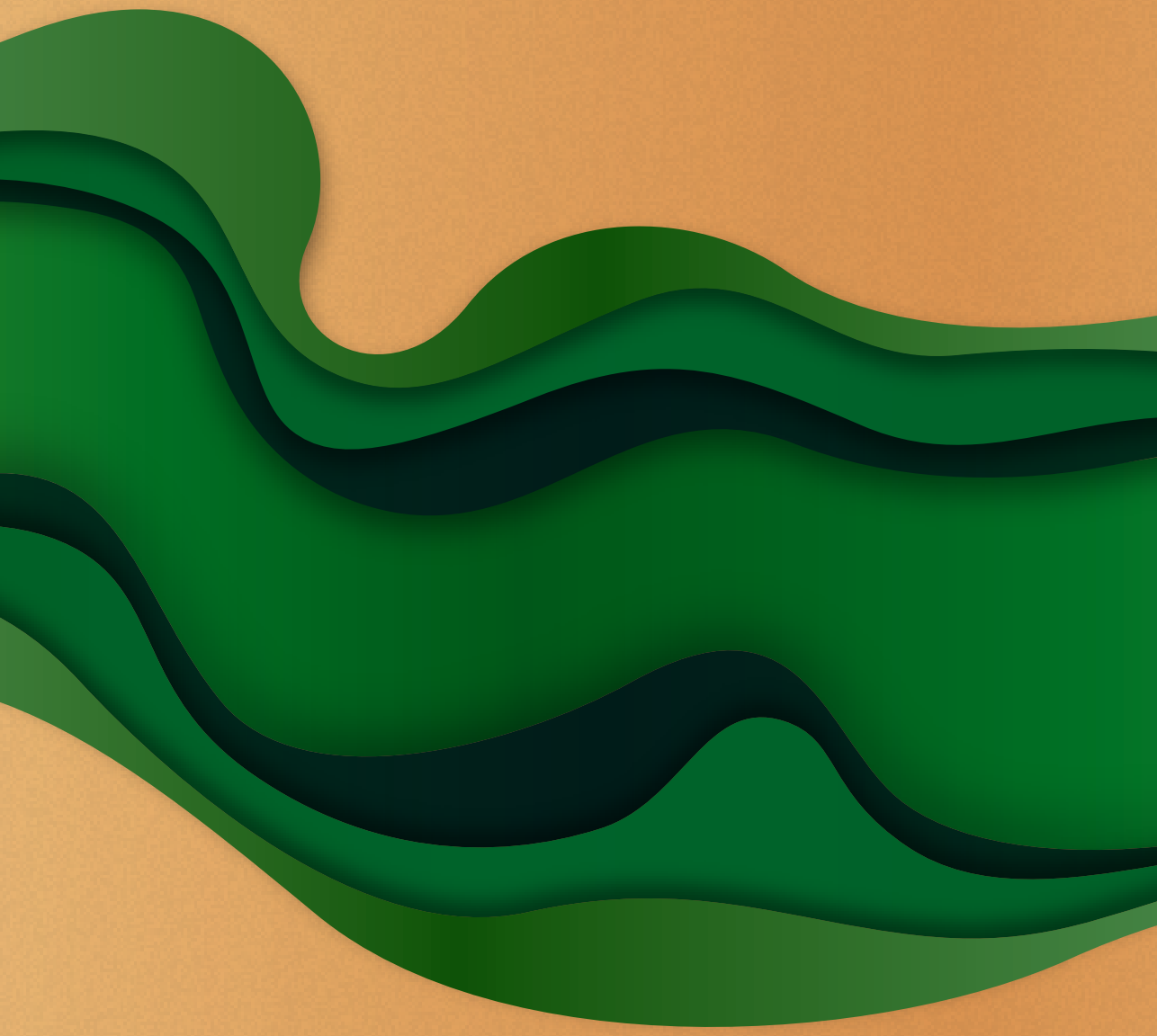
Lifestyle trajectory	N	Events	Follow–up (pers.yr)	Hazard ratio (95%CI)
All–cause mortality				
Persistently healthy	598	98	3,852	0.51 (0.39–0.67)
Reduced	726	105	4,485	0.68 (0.44–1.05)
Improved	559	102	4,044	0.57 (0.40–0.81)
Persistently unhealthy	125	32	891	*Reference*
Cardiovascular mortality				
Persistently healthy	598	48	3,852	0.62 (0.41–0.94)
Reduced	726	50	4,485	0.87 (0.46–1.65)
Improved	559	38	4,044	0.52 (0.29–0.92)
Persistently unhealthy	125	14	891	*Reference*
Incident diabetes				
Persistently healthy	945	45	5,407	0.48 (0.29–0.77)
Reduced	110	9	667	0.81 (0.38–1.72)
Improved	248	17	1,700	0.55 (0.30–1.01)
Persistently unhealthy	255	28	1,572	*Reference*

Legend: Hazard ratio for all-cause mortality and cardiovascular mortality compared to a persistently unhealthy lifestyle. In this sensitivity analysis, physical activity level and waist circumference needed to change ≥5% from the baseline value. The criteria for change in smoking behaviour and alcohol consumption were unaltered in this sensitivity analysis. Abbreviations: HR – hazard ratios, 95%CI: 95% confidence interval

FIGURE S6 Reverse causation



To assess the potential impact of reverse causation, sensitivity analyses with multivariable adjusted Cox models were run after excluding the first 1, 3, and 5 years of follow-up. 95%CI: 95% confidence interval



CHAPTER 10

LIFETIME BENEFIT FROM MEDITERRANEAN DIET AND PHYSICAL ACTIVITY IN PATIENTS WITH CARDIOVASCULAR DISEASE

Nadia E. Bonekamp
Johanna M. Geleijnse
Anne M. May
Jannick A.N. Dorresteijn
Steven H.J. Hageman
Yvonne T. van der Schouw
Frank L.J. Visseren
Charlotte Koopal

on behalf of the UCC-SMART study group

Submitted

ABSTRACT

Background

Lifestyle optimization is a central recommendation in secondary cardiovascular disease (CVD) prevention, but it unclear how much life years free of recurrent CVD can be realized with lifestyle interventions

Objectives

To determine the increase in life-years free of CVD that can be achieved by adopting a Mediterranean diet and/or increasing physical activity levels in patients with established CVD.

Methods

13,331 patients aged 45-79 years with atherosclerotic CVD from the UCC-SMART study and the Alpha Omega Cohort (AOC) were included. Individual 10-year and lifetime risk of recurrent cardiovascular events and CVD-free life expectancy were estimated using the competing-risk adjusted SMART-REACH model. To determine absolute survival benefits from lifestyle interventions, the SMART-REACH model was combined with treatment effects for the Mediterranean diet and increased physical activity.

Results

Median CVD-free life expectancy with current treatment was 74[70-78] year in the UCC-SMART study and 78[75-81] in the AOC study. Adopting a Mediterranean diet was associated with a mean predicted lifetime benefit of 1.9 (95%CI 0.1-3.8) life years free of CVD events, while increased physical activity yielded 3.7 (95%CI 2.2-5.4) additional CVD-free life years. Combining both interventions resulted in a mean predicted lifetime benefit of 5.8 (95%CI 3.4-7.8) CVD-free life years. Lifetime benefits were larger in younger patients and in patients with a high predicted lifetime risk of CVD.

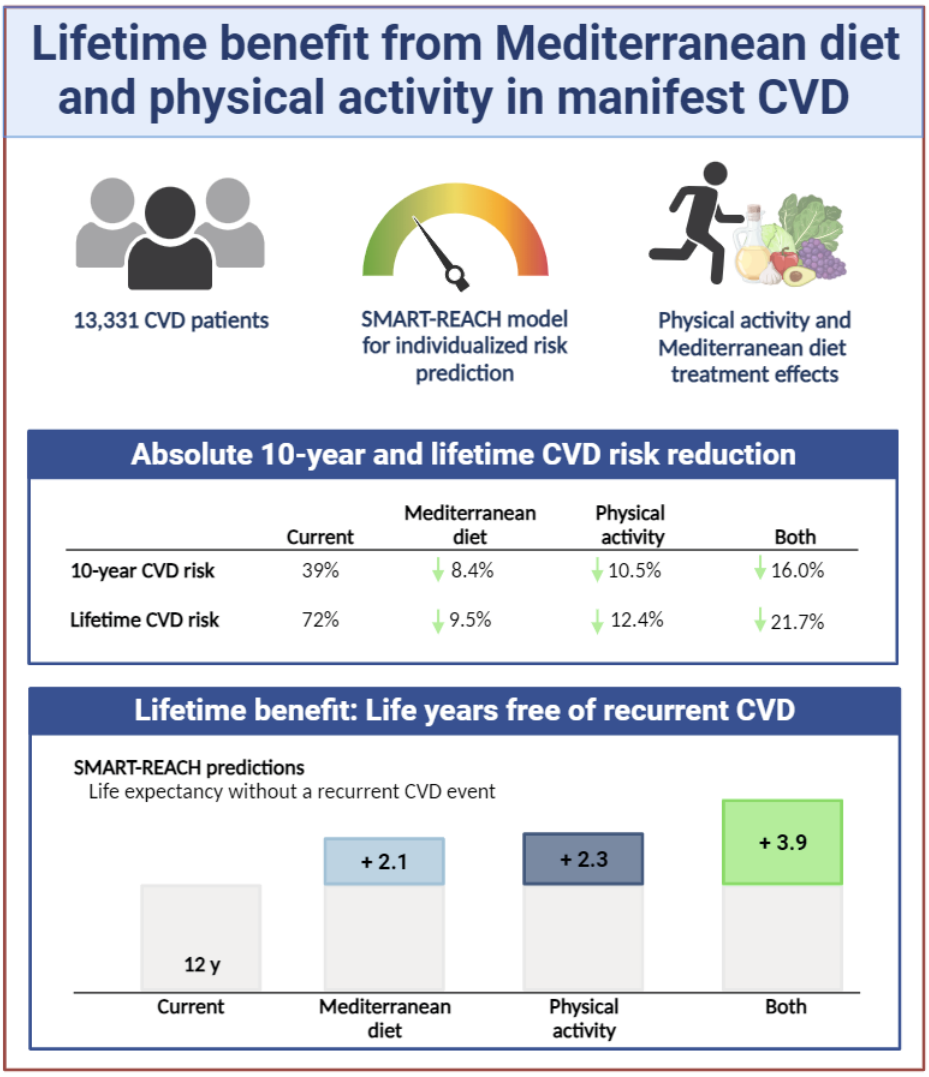
Conclusions

In CVD patients, adopting a Mediterranean diet, guideline-recommended physical activity, and especially both, is predicted to result in significant CVD risk reductions and recurrent CVD-free life years gained.

CONDENSED ABSTRACT

In patients with cardiovascular disease (CVD), adopting a Mediterranean diet and increasing physical activity can significantly extend CVD-free life years. This study, encompassing 13,331 patients, found that a Mediterranean diet added 1.9 CVD-free life years, increased physical activity contributed 3.7 CVD-free years, and combining both interventions resulted in 5.8 additional CVD-free life years. The benefits were more pronounced in younger patients and those with higher CVD risk. These findings underscore the potential for substantial CVD risk reduction and increased CVD-free life years through lifestyle modifications in secondary CVD prevention.

CENTRAL ILLUSTRATION



INTRODUCTION

Promoting a healthy lifestyle is a core recommendation in global guidelines for preventing and managing cardiovascular disease (CVD)1,2 Extensive observational evidence supports the positive impact of healthy dietary and exercise habits on cardiovascular outcomes. A recent meta-analysis indicated that the Mediterranean diet, a dietary pattern rich in legumes, whole grains, and healthy fats, might be the most effective diet for CVD prevention.3 Notably, the CORDIOPREV trial demonstrated a 28% reduction in CVD risk in patients with established CVD assigned to a Mediterranean diet on top of optimal pharmacologic treatment.4 Physical activity appears to yield benefits even surpassing those achieved through dietary changes.5–8

Recognizing the importance of promoting healthy habits in patients with established CVD, European Society of Cardiology (ESC) and American College of Cardiology (ACC) guidelines for prevention of CVD include healthy diet and physical activity as a central preventive measure, alongside non-smoking, lowering systolic blood pressure and low-density lipoprotein (LDL) cholesterol and use of antithrombotic medication.1,2

In clinical practice, motivating patients to adhere to lifestyle interventions often poses a challenge. Potential explanations include insufficient awareness among patients and healthcare providers regarding the impact of a healthy lifestyle, and a lack of intuitive tools to communicate the benefits of healthy lifestyle with patients.9 To enhance motivation for lifestyle change, it is necessary to provide patients with personalized information about the benefits of such a change.

Recently, European Association for Preventive Cardiology consensus statement highlighted the potential of online tools for patient personalized nutritional guidance. However few tools are available that predict the long-term effects of lifestyle change.10–12 Lifetime prediction models, such as the SMART-REACH model, are highly suitable for this purpose, as they offer a personalized estimate of healthy life years gained from an intervention. These tools also provide insights into the effect of treating other cardiovascular risk factors such as smoking, lipid-lowering, blood pressure-lowering or anti-platelet therapy, and can therefore be used to decide upon an optimal and personalized treatment strategy. Currently, only one lifetime prediction model exists to predict life years gained with a healthy diet, but it is not personalized and might overestimate lifestyle effects due to strong correlation between the

included food groups. 13 Moreover, this model was not specifically designed for patients with established CVD, who are at high risk for (cardiovascular) events. Valid and individualized predictions on CVD risk are crucial for guiding personalized medical interventions and preventive measures, ultimately reducing morbidity and mortality associated with CVD.

The aim of the current study was to estimate the individualized 10-year and lifetime benefit from interventions targeted at adopting a Mediterranean-style diet, guideline-recommended physical activity levels, or both, in patients with established CVD using a guideline-recommended and externally validated algorithm.

METHODS

Study population

The Utrecht Cardiovascular Cohort – Secondary Manifestations of ARTerial disease (UCC-SMART) study is an ongoing prospective cohort study. Details on study design have been published previously.[14] Briefly, from 1996 onwards, patients with established cardiovascular disease or high risk thereof were included. For the present analysis, data was used from 8,947 patients aged 45 or older with a history of coronary artery disease (CAD), cerebrovascular disease (CeVD), and/or peripheral arterial disease (PAD, Table S1), who were enrolled between December 1996 and January 2023.

The Alpha Omega Cohort (AOC) is a prospective cohort study comprising 4,837 patients aged 60-80 years with a history of myocardial infarction within 10 years before inclusion in the cohort (between 2002 and 2006). In the initial years, the AOC was a clinical trial where patients were randomized to low-dose *omega*-3 fatty acid supplementation or a placebo. The trial had a neutral effect on cardiovascular events and mortality.[15]

Data collection

In both cohorts, patients completed a questionnaire on demographics, lifestyle and medical history, and physical and laboratory examinations upon inclusion. In both cohorts, dietary intake was assessed using a food frequency questionnaire (FFQ). In the UCC-SMART study, data on dietary habits was retrospectively collected in December 2022. All participants in active follow-up were invited to complete the

FFQ-NL 1.0 and 45% completed the questionnaire (30% of the total UCC-SMART cohort). FFQ-NL 1.0 is a 160-item FFQ designed for the Dutch population that assesses dietary intake over the past 12 months.[16,17] In the AOC, dietary intake was assessed using a 203-item FFQ.[18] For both FFQs, energy and nutrient intake were calculated by linking the responses to the Dutch Food Composition Database.[19] Participants' baseline compliance with the Mediterranean diet was assessed using the 14-point Mediterranean Diet Adherence Screener (MEDAS).[20]

In the UCC-SMART cohort, physical activity was assessed with the EPIC physical activity questionnaire.[21] In AOC, physical activity level was quantified using the Physical Activity Scale for the Elderly (PASE).[22] Metabolic equivalent of task values for the reported physical activities were obtained from the Compendium of Physical activity.[23] For the current analyses, people with a weekly activity level ≥ 7.5 METh/wk was considered to be physically active as this indicated compliance with guideline-recommended physical activity levels.[1,2]

Missing data in both cohorts was imputed using single imputation with predictive mean matching (aregImpute function, Hmisc package). In the UCC-SMART cohort, missingness was highest for education level (n = 3,045, 34%) and CRP (N = 756, 8%). No data on chronic heart failure was available, so all patients were assumed not to have heart failure upon inclusion. In the AOC, missingness was highest for history of cerebrovascular disease (24%) and history of heart failure (23%).

SMART-REACH model for estimating CVD risk

Individual 10-year and lifetime risks of recurrent CVD (comprising myocardial infarction, stroke or cardiovascular death) were predicted using the ESC guideline-recommended SMART-REACH model.[24] The SMART-REACH model is an externally validated and competing-risk adjusted prediction model that includes the following predictors: sex, current smoking, diabetes mellitus, systolic blood pressure, total cholesterol, creatinine, number of cardiovascular disease locations, atrial fibrillation and chronic heart failure (CHF). Internally, the SMART-REACH model consists of two Fine and Gray hazards functions, predicting cardiovascular events and non-CVD mortality respectively. The SMART-REACH model uses age as the time axis (i.e. left truncation). The model allows for modelling of personalized benefits of cardiovascular preventive interventions, both in terms of absolute risk reduction (ARR) as well as number of life years free of

recurrent cardiovascular events and is recommended by prevention guidelines.[1] The SMART-REACH model is available via an online calculator (www.U-Prevent.com).

Individual predictions for lifetime benefit of lifestyle interventions

Patient-level data from the UCC-SMART and AOC studies were used to predict individual 10-year and lifetime risk of cardiovascular events using the SMART-REACH model. Measures of treatment benefit can be estimated by combining causal hazard ratios (HR) from trials and meta-analyses with annual risks of CVD events and non-CVD mortality as estimated in the SMART-REACH model. The HR for Mediterranean diet was based on the CORDIOPREV trial which compared a Mediterranean diet intervention to a low-fat diet in secondary CVD prevention and found a HR 0.72 (95%CI 0.54 – 0.96).[4] In the absence of extensive, long-term intervention studies deemed suitable for lifetime predictions, the effect estimate for physical activity was based on a meta-analysis of observational studies in patients with coronary heart disease. This meta-analysis found a pooled HR 0.63 (0.51-0.78) for increasing physical activity over time.[8] In the primary analyses, no effect of either intervention on the competing endpoint (non-cardiovascular death) was assumed.

The HR for Mediterranean diet was applied to all patients, given a very low compliance score in the two cohort: the median MEDAS score was 3.0 [IQR 3.0-4.0] compared 8 in the low-fat group and 11 in Mediterranean diet group in the CORDIOPREV trial (Figure S1). The HR for physical activity was only applied to patients that had low physical activity levels at inclusion in the cohort (<7.5 METh/wk).[1]

Distributions of predicted CVD risk and benefit from lifestyle interventions

Expected individual benefits from Mediterranean diet, physical activity or a combined intervention are presented as ARR in 10-year risk and lifetime risk, and as lifetime benefit in CVD-free life years gained from the intervention. These results are presented for the entire population and stratified for age groups (45-50, 51-55, 56-60, 61-65, 66-70, 71-75 and 75-80 year at inclusion) and for deciles of predicted 10-year and lifetime risk at inclusion in the UCC-SMART and AOC studies.

To assess the expected benefit of lifestyle interventions in combination with the other STEP1 treatment recommendations, an additional analysis was performed where the SMART-REACH model was used to predict the benefit when achieving all these STEP1 goals, including the lifestyle targets. HRs for the individual STEP1 targets (Table S2)

were only applied when a patient was not already compliant with the respective target at baseline.

Sensitivity analyses

The primary analyses were repeated in a subgroup of patients with a history of CAD at inclusion in the UCC-SMART and AOC study (N = 10,749), HRs for the treatment effect of a Mediterranean diet and physical activity were originally based on studies involving CAD patients.

To account for the inherent uncertainty in the estimates for the treatment effects of the Mediterranean diet and physical activity, a Monte Carlo simulation (MCS) with 1,000 iterations was used to estimate the distribution of 10-year ARR, lifetime ARR and lifetime benefit. HRs were assumed to derive from a log-normal distribution, which was modelled based on the reported HR and the 95%CI. In each MCS iteration, a random sample was drawn from the distribution and the outcomes were calculated as described earlier. All other input variables were maintained at their original values for this analysis.

Furthermore, to address potential favourable or adverse effects of the Mediterranean diet and physical activity interventions on the competing endpoint (non-cardiovascular causes of death), a sensitivity analysis was undertaken. In this analysis, a treatment effect on the competing endpoint was included by varying HRs between 0.5 and 1.5, in 0.01 increment steps. We evaluated 10-year ARR, lifetime ARR, and lifetime benefit across this range of HRs. Results of the main analysis and sensitivity analysis were combined in a web-application. All results presented in this application are based on analyses in the UCC-SMART cohort. The application was developed using the R Shiny package.[25]

RESULTS

Study population

Mean age in the UCC-SMART cohort was 62 ±9 years and 69 ±6 in the AOC (Table 1). Both cohorts predominantly consisted of men, 74% and 78%, respectively. At inclusion in the UCC-SMART study, 66% of patients had CAD, 29% had CeVD and 17% had PAD. All patients in the AOC had CAD (specifically a history of MI), the prevalence

of CeVD was 7% and 12% for PAD. A vast majority of patients reported using lipid-lowering (73% in UCC-SMART, 85% in the AOC), blood pressure-lowering (78% and 98%, respectively), and anti-thrombotic medication (87% and 98%, respectively).

TABLE 1 Patient characteristics in the UCC-SMART study and Alpha Omega cohort

	UCC-SMART study	Alpha Omega Cohort
	N = 8,947	*N = 4,837*
Age, year	62.2 ±8.7	69.0 ±5.6
Male sex, n (%)	6,621 (74)	3,783 (78)
Cardiovascular history*		
CAD, n (%)	5,912 (66)	4,837 (100)
CeVD, n (%)	2,606 (29)	338 (7)
PAD, n (%)	1,549 (17)	587 (12)
Chronic heart failure, n (%)	*NA*	275 (6)
Diabetes, n (%)	1,629 (18)	1,014 (21)
Current smoker, n (%)	2,406 (27)	713 (16)
Alcohol consumer, n (%)	7,398 (82)	3,585 (74)
MEDAS score†	4.0 [3.0-5.0]	3.0 [3.0-4.0]
Physical activity		
Compliant with guidelines, n (%)	2,682 (30)	1,795 (37)
Physical activity volume, METh/wk	36 [17-62]	35±41
Body mass index, kg/m^2	27 ±4.6	28 ±3.8
Systolic BP, mmHg	139 ±21	142 ±22
Total cholesterol, mmol/l	4.5 [3.8-5.4]	4.6 [4.0-5.3]
HDL-cholesterol, mmol/l	1.2 [1.0-1.4]	1.2 [1.1-1.5]
LDL-cholesterol, mmol/l	2.5 [2.0-3.3]	2.5 [2.0-3.1]
Triglycerides, mmol/l	1.4 [1.0-2.0]	1.7 [1.2-2.3]
eGFR, ml/min/1.73m^2‡	78 [66-90]	84 [72-101]
hsCRP, mg/dl	2.0 [1.0-4.3]	1.7 [0.8-3.8]
Lipid-lowering medication, n (%)	6,564 (73)	4,122 (85)
BP-lowering medication, n (%)	7,018 (78)	4,340 (90)
Antithrombotic agents, n (%)	7,745 (87)	4,718 (98)

Data are presented as number (percentage), mean ± standard deviation or median [interquartile range]. Abbreviations: CAD: coronary artery disease, CeVD: cerebrovascular disease, PAD: peripheral arterial disease, MEDAS: Mediterranean Diet Adherence Screener, BP: blood pressure, HDL: high-density lipoprotein, LDL-cholesterol: Low-density lipoprotein, eGFR: estimated glomerular filtration rate, NA: not available. * CVD manifestation groups are non-mutually exclusive. † Dietary intake data available for 2,046 participants in the UCC-SMART cohort and for 4,365 participants in the AOC with plausible reported dietary intake. ‡ Estimated using the CKD-EPI formula

Plausible dietary intake data was available for 2,046 participants (23%) in the UCC-SMART cohort and for 4,365 participants (90%) in the AOC. Compliance with the Mediterranean diet was low in both cohorts. Among patients with available dietary intake data, the median MEDAS scores was 3.0 [IQR 3.0-4.0], out of a maximum score of 14 (Figure S1). 2,682 participants in the UCC-SMART study (30%) and 1,795 (37%) AOC-participants were compliant with guideline-recommended physical activity levels.

10-year and lifetime CVD benefit from lifestyle interventions

In the UCC-SMART study, median predicted 10-year and lifetime risks of recurrent CVD were 37.4 [IQR 22.7-66.4] and 73.1 [IQR 53.9-86.6], respectively (Table 2). The median remaining life years with treatment used at inclusion in the cohort was 10.9 years [IQR 8.0-14.1]. Distributions of 10-year ARR, lifetime ARR and lifetime benefit are shown in Figures S2-S4

The median 10-year ARR from Mediterranean diet initiation was 8.3% [IQR 5.5-10.8] and lifetime ARR was 9.5% [IQR 6.0-10.5] (Table 2). The median lifetime benefit from adopting a Mediterranean diet was 2.1 [IQR 1.6-2.8] CVD-free life years. With a physical activity intervention, 10-year ARR was 10.5% [IQR 0.0-15.5], lifetime ARR 12.4% [0.0-15.4] and lifetime benefit 2.3 CVD-free life years [IQR 0.0-3.6]. The largest benefits were estimated for a combined Mediterranean diet and physical activity intervention: 15.9% [5.9-25.2] 10-year ARR in CVD risk, 21.7% [IQR 7.5-25.7] in lifetime risk and 3.9 [IQR 2.7-5.8] CVD-free life years lifetime benefit.

In AOC, the predicted lifetime risk was lower (60.8%, IQR 47.5-75.4) compared with the UCC-SMART cohort (Table 2). Predicted lifetime benefits from lifestyle interventions were 1.5 [IQR 1.2-1.8] CVD-free life years from a Mediterranean diet and 0 [IQR 0-2.3] CVD free life years for physical activity. Among non-physically active patients, lifetime benefit from a physical activity intervention was 2.2 [IQR 1.7-2.6] CVD-free life years. A combined Mediterranean diet and physical activity intervention resulted in a median gain of 1.7 [IQR 1.3-2.3] CVD-free life years.

TABLE 2 Expected 10-year and lifetime risk and benefit from initiation of Mediterranean diet and physical activity interventions

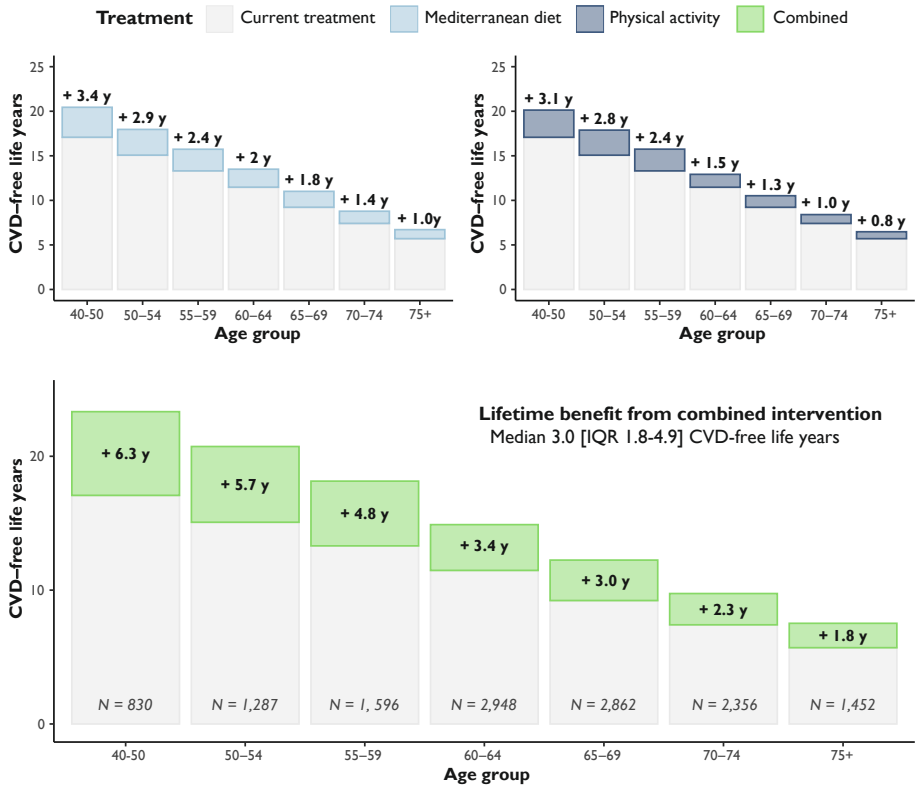
		Lifestyle intervention		
	Current treatment	**MED diet**	**Exercise***	**MED diet + Exercise**
UCC-SMART cohort				
10-year risk				
Estimated 10-year risk, %	37.4 [22.7-66.4]	29.0 [17.1-55.9]	28.8 [15.7-57.1]	22.0 [11.7-46.7]
Absolute risk reduction, %	*Reference*	8.3 [5.5-10.8]	10.5 [0.0-15.5]	15.9 [5.9-25.2]
Lifetime risk				
Estimated lifetime risk, %	73.1 [53.9-86.6]	63.6 [44.4-80.2]	63.0 [41.1-82.6]	52.9 [32.7-74.8]
Absolute risk reduction, %	*Reference*	9.5 [6.0-10.5]	12.4 [0.0-15.4]	21.7 [7.5-25.7]
Lifetime benefit				
Remaining CVD life years	10.9 [8.0-14.1]	13.1 [9.5-16.9]	12.9 [9.7-16.9]	15.1 [11.3-19.5]
Lifetime treatment benefit, *y*	*Reference*	2.1 [1.6-2.8]	2.3 [0.0-3.6]	3.9 [2.7-5.8]
Alpha Omega Cohort				
10-year risk				
Estimated 10-year risk, %	38.8 [20.5-63.6]	30.4 [15.4-53.7]	36.6 [17.6-61.5]	28.5 [13.2-51.5]
Absolute risk reduction, %	*Reference*	8.5 [5.1-10.4]	0.0 [0.0-14.6]	8.9 [5.3-23.4]
Lifetime risk				
Estimated lifetime risk, %	60.8 [47.5-75.4]	51.3 [38.1-67.2]	59.0 [38.0-73.7]	49.5 [29.8-65.4]
Absolute risk reduction, %	*Reference*	9.4 [7.5-10.4]	0.0 [0.0-14.8]	9.6 [7.7-24.3]
Lifetime benefit				
Remaining CVD life years	8.5 [6.7-10.8]	10.1 [7.9-12.5]	8.9 [7.1-11.2]	10.5 [8.3-13.0]
Lifetime treatment benefit, *y*	*Reference*	1.5 [1.2-1.8]	0.0 [0.0-2.3]	1.7 [1.3-2.3]

Expected 10-year and lifetime risk of cardiovascular events and expected CVD-free survival calculated using the original SMART-REACH model and on the SMART-REACH model with additional treatment effects for initiation of a Mediterranean diet and exercise. MED diet: Mediterranean diet, ARR: Absolute risk reduction, CVD: cardiovascular disease, NA: not applicable. * The protective hazard ratio from initiating physical activity was only applied to patients that had low physical activity levels at inclusion in the UCC-SMART and AOC studies. The presented outcomes represent expected treatment effects for the entire population, including those that are physically active.

Distribution of benefit from lifestyle interventions

The largest benefits from the lifestyle interventions were observed in the youngest patients (aged 45-50 years, Figure 1). Mean benefit from a combined Mediterranean diet and physical activity intervention ranged between 3.4 CVD-free life years in patients aged 45-50 years to 1.0 years in CVD patients aged 75 or older. For a Mediterranean diet or physical activity intervention separately, a similar pattern was observed with smaller net benefits. Predicted 10-year ARR increased with age (Figure S5), while lifetime ARR was similar across age groups (Figure S6)

FIGURE 1 CVD-free life years gained from adopting a Mediterranean diet, an active lifestyle or both across age groups.



Predicted life years gained with initiation of a Mediterranean diet, physical activity or both for different ages at initiation of lifestyle change. Combined analysis in the UCC-SMART and AOC studies (N = 13,331). CVD: cardiovascular disease.

In line with the findings across age groups, expected lifetime benefit from lifestyle interventions decreased in higher deciles of 10-year risk (Figure S7). Patients in the

highest lifetime risk decile had the largest lifetime benefit from lifestyle interventions (*e.g.* 5.5 years, 95%CI 5.3-5.6 from a combined Mediterranean diet and physical activity intervention).

Lifestyle interventions in combination with other STEP 1 goals

Figure 2 show the expected lifetime benefit from lifestyle interventions in patients who also achieve the other STEP1 prevention treatment goals as specified in the ESC Prevention of CVD guidelines (*i.e.* non-smoking, LDL-cholesterol and systolic blood pressure below target levels, and use of antithrombotic medications). The total lifetime benefit from achieving all STEP1 risk factor goals, including healthy diet and physical activity, was 7.4 [IQR 5.3-9.7] CVD-free life years. The absolute added benefit from Mediterranean diet and physical activity was slightly smaller when all other STEP1 goals were already achieved. Similar to the main analysis, the largest benefits from healthy diet and physical activity were observed for the youngest age groups, for a combined Mediterranean diet and physical activity intervention (6.1 CVD free life-years).

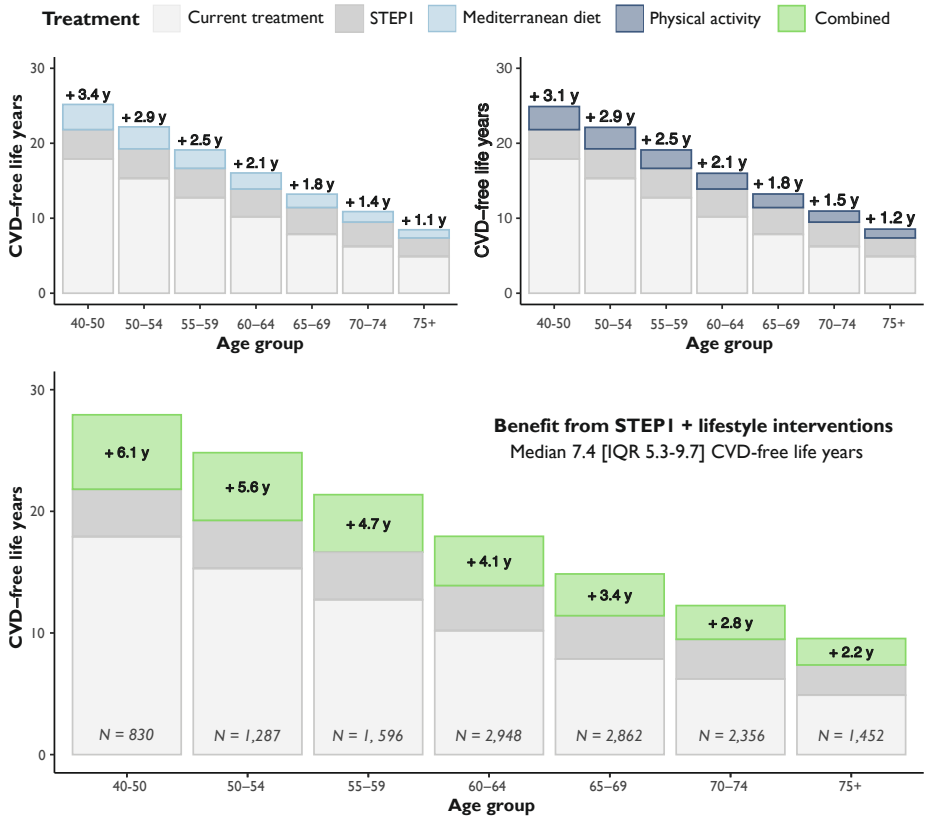
Sensitivity analyses

Figure 3 shows the distributions of mean lifetime benefit from lifestyle interventions after 10,000 Monte Carlo simulations. This analysis shows the distribution in the mean lifetime benefit for Mediterranean diet (median 1.9 CVD-free life years, 95%CI 0.1-3.8), physical activity (3.7, 95%CI 2.2-5.4) and combined intervention (5.8, 95%CI 3.4-7.8). The median lifetime benefit from a Mediterranean diet intervention exceeded one, two, and five years in 82%, 45% and 1% of simulations. These percentages were higher for physical activity (99% above 1 year, 98% above 2 years, and 6% above 5 years) and the combined intervention (100%, 100% and 77%, respectively).

The distributions of predicted 10-year and lifetime CVD risk and ARRs from lifestyle interventions in a subgroup of 10,749 patients with CAD were similar to the main analysis (Table S3). Figure S8 shows the impact of including an effect of lifestyle interventions on the competing endpoint (death of non-cardiovascular causes) into the model. The impact is shown for potential HRs between 0.5 and 1.5. Increasing numbers of CVD-free life years are predicted for a decreasing HR for non-CVD mortality. For example, when an HR 0.80 on non-CVD death is assumed for both the Mediterranean diet and physical activity, the median lifetime benefit from a Mediterranean diet would

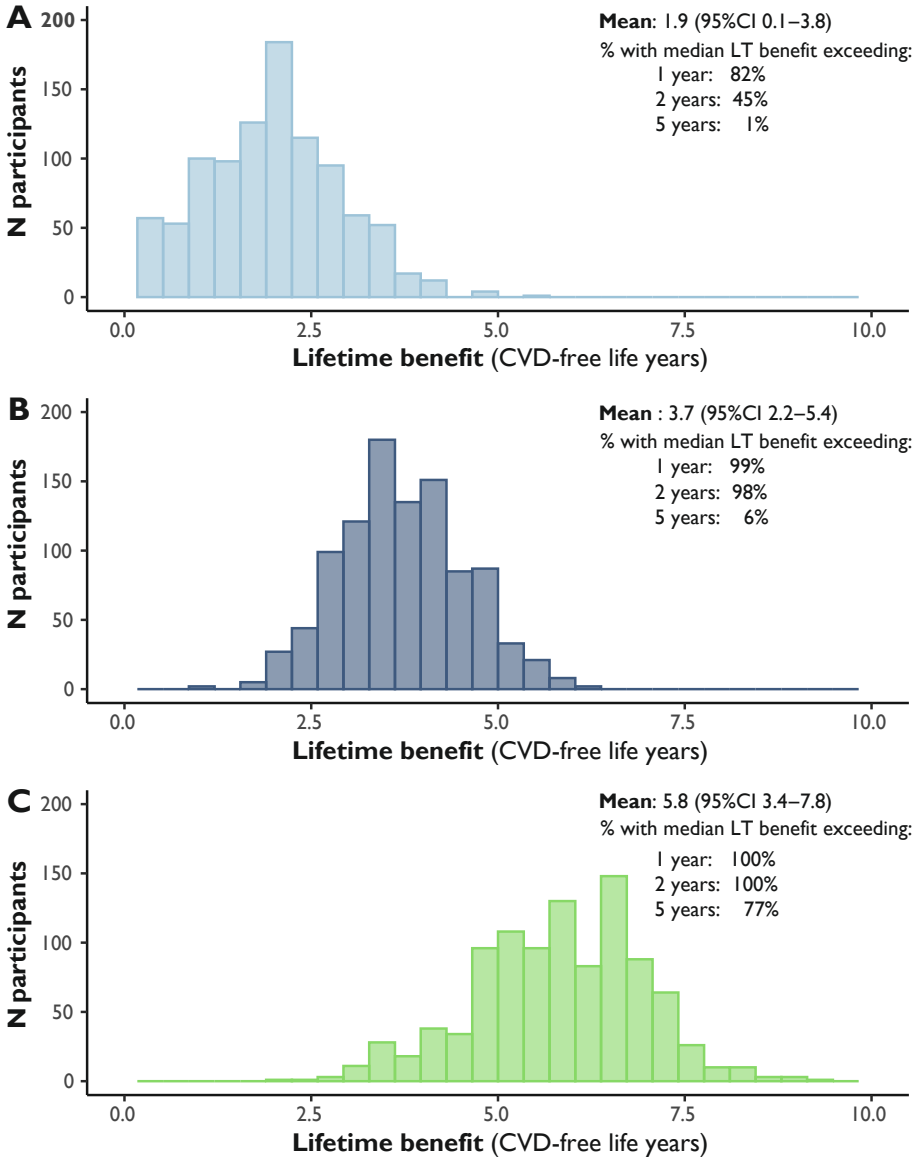
be 2.3 CVD-free life years, 3.3 from physical activity and 6.3 from both. An online tool is available to estimate the mean 10-year ARR, lifetime ARR and lifetime benefit with different input parameters for the treatment effects of Mediterranean diet and physical activity on cardiovascular event risk and on non-cardiovascular mortality risk.

FIGURE 2 Lifetime benefit from combined achievement of all ESC Prevention Guidelines STEP1 goals



Expected life years gained with initiation of a Mediterranean diet, physical activity or both for different ages at initiation of lifestyle change in the hypothetical scenario of all patients reaching all other STEP1 treatment targets as described in the 2021 ESC Prevention of Cardiovascular Disease Guidelines (stop smoking, LDL-cholesterol < 1.8 mmol/l and >50% reduction, systolic blood pressure 130-140 mmHg and use of antithrombotic therapy).

FIGURE 3 Distribution of median lifetime benefit in 10,000 Monte Carlo simulations



Distributions of the median lifetime benefits in 10,000 simulations from Mediterranean diet **(A)**, Physical activity **(B)** or both **(C)**. In each Monte Carlo simulation, a hazard ratio for the effect of a Mediterranean diet and physical activity is drawn from a log-normal for these treatment effects and lifetime benefit from Mediterranean diet, physical activity or both was calculated. CVD = cardiovascular disease, 95%CI = 95% confidence interval

DISCUSSION

This study is the first to quantify the potential lifetime benefits from interventions targeted at a Mediterranean diet and physical activity in secondary CVD prevention. Treatment effect estimates were combined with the validated and competing-risk adjusted SMART-REACH model, and then applied to two large cohorts of patients with different manifestations of established CVD, comprising over 13,000 patients. Our findings reveal the substantial potential of diet and physical activity interventions in lowering both 10-year and lifetime risk of CVD events. On average, almost six years CVD-free life years could be gained from initiating these interventions on top of current treatment, even in patients already reaching all other STEP1 treatment targets as described in the 2021 ESC Prevention of CVD guidelines.

The most significant benefits from a Mediterranean diet and physical activity intervention were predicted for younger patients and patients within the highest lifetime CVD risk. Younger patients have a longer life expectancy and therefore stand to gain more from lifestyle intervention. However, even in patients aged 75 years or older, the mean predicted combined diet and physical activity benefit was still 1.8 CVD-free life years, under the assumption that treatment benefits manifest quickly after the intervention is initiated. Patients with established CVD generally have a very high lifetime risk of recurrent CVD events, which explains why the largest benefits were observed in these patients.

The uncertainty around the effect estimates for physical activity and especially the Mediterranean diet was broad which led to a wide distribution of lifetime benefit from lifestyle interventions. However, beneficial effects were consistently observed in the Monte Carlo simulations, with a mean benefit from a combined diet and physical activity of almost six CVD-free life years (5.8, 95%CI 3.4-7.8). Furthermore, these models assume lifelong adherence to the interventions, which is likely difficult to achieve. Future research, especially long-term cardiovascular outcome trials, are needed to provide a more precise estimate of lifetime treatment benefits. A 2019 Cochrane systematic review previously advocated for additional research on dietary interventions in secondary CVD prevention[26] and for physical activity where there is no long-term RCT in secondary prevention available.

In the main analyses, it is assumed that Mediterranean diet and physical activity had no effect on the competing non-cardiovascular death endpoint, because no valid HR was available for this endpoint in populations with established CVD. Nevertheless, both nutrition and physical activity are generally associated with multiple health benefits and reduced risk of various outcomes.[27–29] Therefore, our main results may underestimate the actual potential benefit from these lifestyle interventions on overall lifetime benefit. In a sensitivity analysis where a range of potential effect estimates for non-CVD mortality were included, we observed that lifetime benefit in CVD-free life years increased even further when a protective effect on non-CVD death was assumed.

One previous model assessed the lifetime benefit from sustained adherence to healthy dietary habits in the general population.[13] In this study, up to 13 additional life years were predicted when an optimal diet was initiated at an age of 20 years. Similar to our study, the authors of this model concluded that lifetime benefit is larger when a healthy diet is initiated at a younger age. For patients aged 60 years, the expected gain in life expectancy was approximately 8 years, which still exceeds the predictions in the present study (approximately 2 years with either a Mediterranean diet or physical activity and 4 years with both). These differences may be explained by differences in study endpoints (overall life expectancy vs. CVD-free life expectancy) or by the fact that the effect estimate in the general-population study was calculated by combining 14 HRs for different dietary components, without adjustment for possible interrelatedness.

The magnitude of lifetime benefit that can be considered relevant, depends on several factors such as patient believes and preferences, risk of side effects, physician preference, costs of the intervention and costs and benefit of alternative interventions. For example, the predicted benefits from the Mediterranean diet and physical activity intervention in the current study are comparable with lifetime benefits from pharmacological interventions, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition.[30] Combining lifestyle interventions with guideline-directed pharmacological interventions, such as the STEP1 recommendations from the ESC Prevention Guidelines, can yield substantial and clinically relevant benefits.

Strengths and limitations

The SMART-REACH model previously showed good performance in external validation.[24] This model uses predictors that are available in routine clinical practice which facilitates implementation in routine patient care. Contrary to many CVD prediction models, SMART-REACH is adjusted for competing risks which improves accuracy of absolute risk predictions by limiting overestimation.[31] Finally, the estimates for treatment benefit in this study are presented as ARR and CVD-free life years. Presenting benefit in terms of additional disease-free survival may aid the discussion on lifestyle choices with CVD patients.

Study limitations need to be considered. The presented benefits from diet and physical activity interventions in this study heavily rely on the validity of the HRs that were obtained from existing literature. The CORDIOPREV trial is one of the few long-term cardiovascular outcome trials in CVD patients and the only one performed in the last decade. However, the CORDIOPREV trial compared a Mediterranean diet to a low-fat diet instead of usual diet. As a result, the HR used in this analysis could be an underestimation or an overestimation of the effect in a stable CVD population that does not currently receive active dietary guidance. For physical activity, no long-term cardiovascular outcome trial is available and instead, the effect estimate for physical activity was based on a meta-analysis of nine prospective cohort studies comprising over 33,000 patients that observationally assessed the relationship of increased physical activity with cardiovascular outcomes.[8] Observational studies are subject to biases such as residual confounding and misclassification of lifestyle behaviours which may have led to an overestimation of the treatment effect for physical activity. Assumptions were made regarding the stability of treatment effects over 30 years, as the effects were based on long-term studies. Furthermore, it is unclear if patients would be able to comply with the intervention for the rest of their life, although the CORDIOPREV reported that only 1 in 8 patients was no longer compliant with the intervention at the end of the 7-year trial.[4] Success of the Mediterranean diet intervention would also depend on the acceptability of such a diet as previous studies have reported that adherence to a Mediterranean diet is lower in non-Mediterranean countries.[32] It was assumed that effects of a Mediterranean diet and physical activity were independent, which may lead to an overestimation of the total treatment effect. However, in the CORDIOPREV trial, the benefits of a Mediterranean diet remained robust after adjustment for physical activity.[4] Furthermore, treatment effects used in this study were extrapolated to CeVD and PAD patients, although they were based

on studies in CAD patients only, because no studies in CeVD or PAD patients have been performed.

CONCLUSION

Treatment with a Mediterranean diet, physical activity or the combination has the potential to substantially increase CVD-free survival among patients with established CVD receiving optimal pharmacological treatment. This study presents a tool to estimate personalized 10-year and lifetime benefits from these interventions given a patient's cardiovascular risk factors. This individualized prediction tool can be used to improve lifestyle counselling in clinical care for patients with established CVD.

REFERENCES

1. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021; 1–111.
2. Virani SS, Newby LK, Arnold S V., et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. Epub ahead of print 20 July 2023. DOI: 10.1161/CIR.0000000000001168.
3. Karam G, Agarwal A, Sadeghirad B, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. BMJ 2023; e072003.
4. Delgado-lista J, Alcala-diaz JF, Torres-peña JD, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet 2022; 399: 1876–85.
5. Ding D, Van Buskirk J, Nguyen B, et al. Physical activity, diet quality and all-cause cardiovascular disease and cancer mortality: A prospective study of 346 627 UK Biobank participants. Br J Sports Med 2022; 1148–1156.
6. Xu F, Cohen SA, Lofgren IE, et al. Relationship between diet quality, physical activity and health-related quality of life in older adults: Findings from 2007-2014 national health and nutrition examination survey. Journal of Nutrition, Health and Aging 2018; 22: 1072–1079.
7. Abbate M, Gallardo-Alfaro L, Bibiloni M del M, et al. Efficacy of dietary intervention or in combination with exercise on primary prevention of cardiovascular disease: A systematic review. Nutrition, Metabolism and Cardiovascular Diseases 2020; 30: 1080–1093.
8. Gonzalez-Jaramillo N, Wilhelm M, Arango-Rivas AM, et al. Systematic Review of Physical Activity Trajectories and Mortality in Patients With Coronary Artery Disease. J Am Coll Cardiol 2022; 79: 1690–1700.
9. Hardcastle SJ, Hancox J, Hattar A, et al. Motivating the unmotivated: how can health behavior be changed in those unwilling to change? Front Psychol 2015; 6: 1–4.
10. Vassiliou VS, Tsampasian V, Abreu A, et al. Promotion of healthy nutrition in primary and secondary cardiovascular disease prevention: a clinical consensus statement from the European Association of Preventive Cardiology. Eur J Prev Cardiol 2023; 30: 696–706.
11. Bush CL, Blumberg JB, El-Sohemy A, et al. Toward the Definition of Personalized Nutrition: A Proposal by The American Nutrition Association. J Am Coll Nutr 2020; 39: 5–15.
12. Sahyoun NR. Nutrition Education for the Healthy Elderly Population: Isn't It Time? J Nutr Educ Behav 2002; 34: S42–S47.
13. Fadnes LT, Økland JM, Haaland ØA, et al. Estimating impact of food choices on life expectancy: A modeling study. PLoS Med 2022; 19: 1–17.
14. Castelijns MC, Helmink MAG, Hageman SHJ, et al. Cohort profile: the Utrecht Cardiovascular Cohort-Second Manifestations of Arterial Disease (UCC-SMART) Study-an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands. BMJ Open 2023; 13: e066952.

15. Kromhout D, Giltay EJ, Geleijnse JM. n–3 Fatty Acids and Cardiovascular Events after Myocardial Infarction. New England Journal of Medicine 2010; 363: 2015–2026.
16. Eussen SJPM, Van Dongen MCJM, Wijckmans NEG, et al. A national FFQ for the Netherlands (the FFQ-NL1.0): Development and compatibility with existing Dutch FFQs. Public Health Nutr 2018; 21: 2221–2229.
17. Sluik D, Geelen A, De Vries JHM, et al. A national FFQ for the Netherlands (the FFQ-NL 1.0): Validation of a comprehensive FFQ for adults. British Journal of Nutrition 2016; 116: 913–923.
18. Feunekes GI, Van Staveren WA, De Vries JH, et al. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. Am J Clin Nutr 1993; 58: 489–496.
19. Dutch Nutrition Center. Dutch Food Composition Table 2006 NEVO-table. The Hague, The Netherlands, 2006.
20. García-Conesa M-T, Philippou E, Pafilas C, et al. Exploring the Validity of the 14-Item Mediterranean Diet Adherence Screener (MEDAS): A Cross-National Study in Seven European Countries around the Mediterranean Region. Nutrients 2020; 12: 2960.
21. Pols MA, Peeters PH, Ocké MC, et al. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol 1997; 26 Suppl 1: S181-9.
22. Schuit AJ, Schouten EG, Westerterp KR, et al. Validity of the physical activity scale for the elderly (PASE): According to energy expenditure assessed by the doubly labeled water method. J Clin Epidemiol 1997; 50: 541–546.
23. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc; 32. Epub ahead of print 2000. DOI: 10.1097/00005768-200009001-00009.
24. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: The SMART-REACH model. J Am Heart Assoc; 7. Epub ahead of print 2018. DOI: 10.1161/JAHA.118.009217.
25. Chang W, Cheng J, Allaire J, et al. shiny: Web Application Framework for R.
26. Rees K, Takeda A, Martin N, et al. Mediterranean-style diet for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews; 2019. Epub ahead of print 13 March 2019. DOI: 10.1002/14651858.CD009825.pub3.
27. Dinu M, Pagliai G, Casini A, et al. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur J Clin Nutr 2018; 72: 30–43.
28. Rezende LFM de, Sá TH de, Markozannes G, et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770000 cancer cases. Br J Sports Med 2018; 52: 826–833.
29. López-Ortiz S, Lista S, Valenzuela PL, et al. Effects of physical activity and exercise interventions on Alzheimer's disease: an umbrella review of existing meta-analyses. J Neurol 2023; 270: 711–725.
30. Kaasenbrood L, Ray KK, Boekholdt SM, et al. Estimated individual lifetime benefit from PCSK9 inhibition in statin-treated patients with coronary artery disease. Heart 2018; 104: 1699–1705.

31. Hageman SHJ, Dorresteijn JAN, Pennells L, et al. The relevance of competing risk adjustment in cardiovascular risk prediction models for clinical practice. Eur J Prev Cardiol. Epub ahead of print 20 June 2023. DOI: 10.1093/eurjpc/zwad202.

32. Mattavelli E, Olmastroni E, Bonofiglio D, et al. Adherence to the Mediterranean Diet: Impact of Geographical Location of the Observations. Nutrients 2022; 14: 2040.

SUPPLEMENTAL MATERIAL

TABLE S1 Definitions of established CVD in the UCC-SMART and Alpha Omega cohorts

CVD manifestation	Definition in UCC-SMART	Definition in Alpha-Omega cohort
Established CVD	Coronary artery disease, cerebrovascular disease and/or peripheral artery disease as defined below upon inclusion in the cohort.	Coronary artery disease, cerebrovascular disease and/or peripheral artery disease as defined below upon inclusion in the cohort.
Coronary artery disease	History of myocardial infarction (STEMI, nSTEMI), coronary syndrome requiring PCI or CABG.	Verified clinical diagnosis of myocardial infarction within 10 years before inclusion in the study.
Cerebrovascular disease	History of transient ischemic attack, cerebral infarction, subarachnoid haemorrhage, carotid artery stenosis or ischemic retinal syndrome.	Self-reported stroke or CVA
Peripheral artery disease	Renal artery stenosis, peripheral arterial disease Fontaine classification II or higher.	Self-reported claudicatio intermittens or treatment for peripheral arterial disease, including angioplasty or bypass surgery, amputation or medication.
Chronic heart failure	Not available	Self-reported heart failure

CVD = cardiovascular disease, UCC-SMART = Utrecht Cardiovascular Cohort-Second Manifestations of Arterial Disease, AOC: Alpha Omega cohort

TABLE S2 Treatment effects used for calculating lifetime benefit from STEP1 cardiovascular prevention interventions

ESC prevention guidelines STEP 1 treatment target	Treatment effect* Hazard ratio	Reference
Smoking Stop smoking	CVD events: 0.60 Non-CVD mortality†: 0.73	1 2
Healthy diet Mediterranean diet	0.72	3
Physical activity At least 150-300 min/wk of moderate intensity or 75-150 min/wk of vigorous activity	0.63	4
LDL-cholesterol ≥ 50% reduction and < 1.8 mmol/l	0.78 per 1.0 mmol/l decrease	5
Systolic blood pressure < 140 mmHg, to 130 mmHg if tolerated	0.80 per 10 mmHg decrease	6
Antithrombotic therapy Use of antithrombotic therapy	*Assumption: SoC is provided* (aspirin or equivalent), no additional treatment effect	

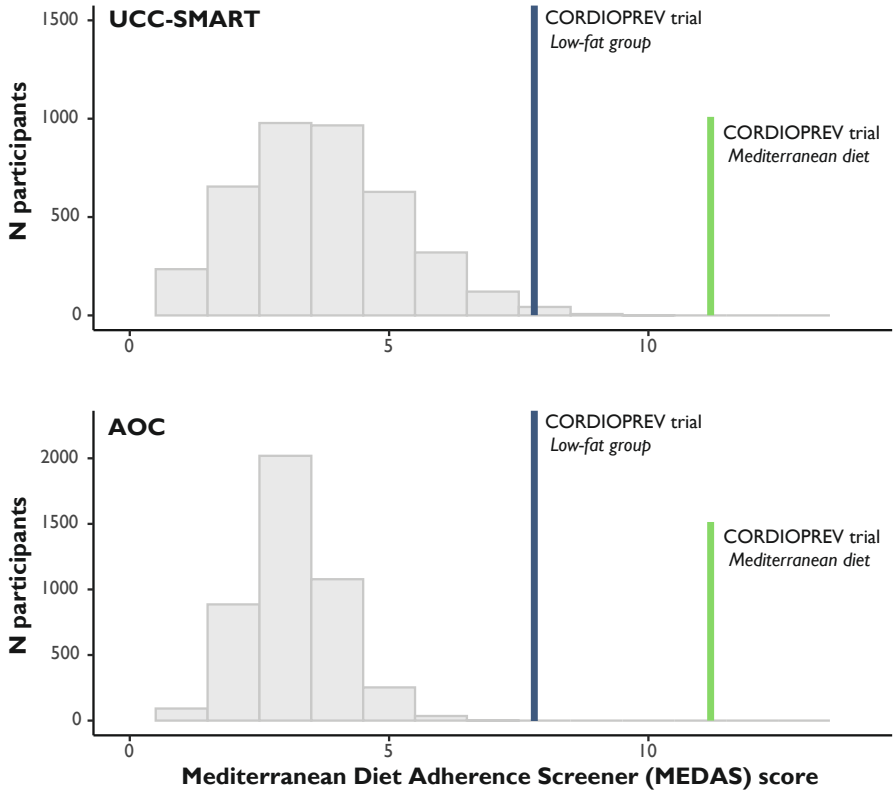
STEP 1 treatment targets for patients with established cardiovascular disease as recommended in the ESC guidelines for prevention of cardiovascular disease.[7] * Treatment effects are applied when a patient is not currently on the therapy/treatment target. † Smoking cessation has been shown to not only reduce risk of cardiovascular events, but also of the competing endpoint in the SMART-REACH model, death of non-cardiovascular events. CVD = cardiovascular disease, SoC = standard of care, ESC = European Society of Cardiology

TABLE S3 Sensitivity analysis in patients with CAD

		Lifestyle intervention		
	Current	**MED diet**	**Exercise**	**MED diet + Exercise**
10-year risk				
Estimated 10-year risk, %	40 ±11	31 ±10	33 ±11	23 ±10
Absolute risk reduction, %	*Reference*	8.4 [7.1-9.5]	0 [0-12.0]	10.0 [8.2-18.4]
Lifetime risk				
Estimated lifetime risk, %	68 ±9.5	58 ±10	61 ±10	51 ±11
Absolute risk reduction, %	*Reference*	9.5 [8.7-10.0]	0 [0-13.9]	10.5 [9.5-23.2]
Lifetime benefit				
CVD-free life expectancy, y	76 [73-80]	78 [75-81]	77 [74-81]	80 [76-82]
Lifetime treatment benefit, y	*Reference*	1.8 [1.4-2.4]	0 [0-2.7]	2.7 [1.7-4.5]

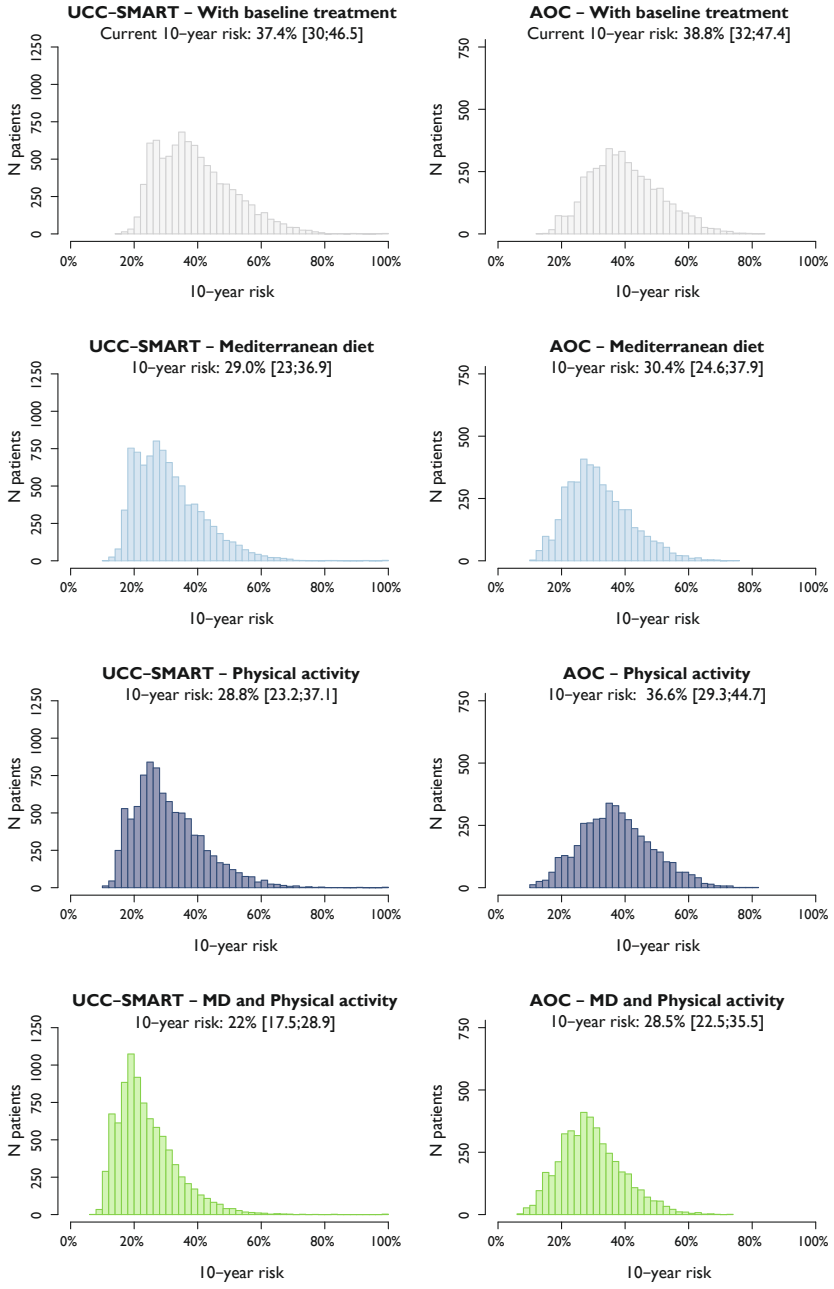
Expected 10-year and lifetime risk of cardiovascular events and expected CVD-free survival calculated using the original SMART-REACH model and on the SMART-REACH model with additional treatment effects for initiation of a Mediterranean diet and exercise. MED diet: Mediterranean diet, ARR: Absolute risk reduction, CVD: cardiovascular disease, NA: not applicable.

FIGURE S1 Distribution of Mediterranean Diet Adherence Screener (MEDAS) scores in the UCC-SMART and AOC studies



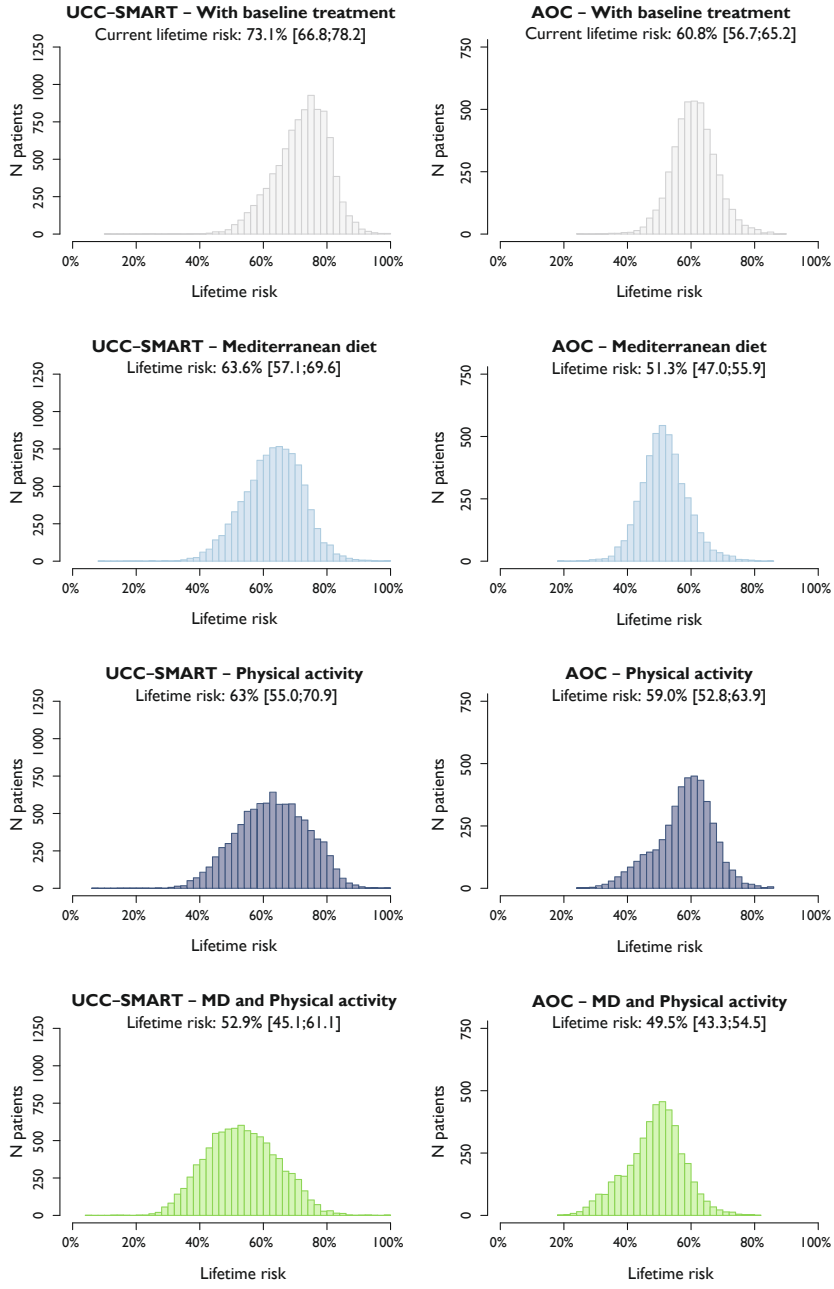
Distribution of the MEDAS scores in the UCC-SMART and Alpha Omega cohorts and comparison to the achieved MEDAS scores at the end of the CORDIOPREV intervention study. The blue bar represents the mean MEDAS score after 7 years in the low-fat arm of the trial and the green bar represents the mean MEDAS score achieved by participants in CORDIOPREV's Mediterranean diet arm. MEDAS scores for the CORDIOPREV trial were obtained from Delgado-Lista et al.[3] UCC-SMART = Utrecht-Cardiovascular Cohort – Secondary Manifestations of Cardiovascular disease, AOC = Alpha-Omega cohort, MedDiet = Mediterranean diet.

FIGURE S2 Distribution of 10-year cardiovascular risk with and without lifestyle interventions



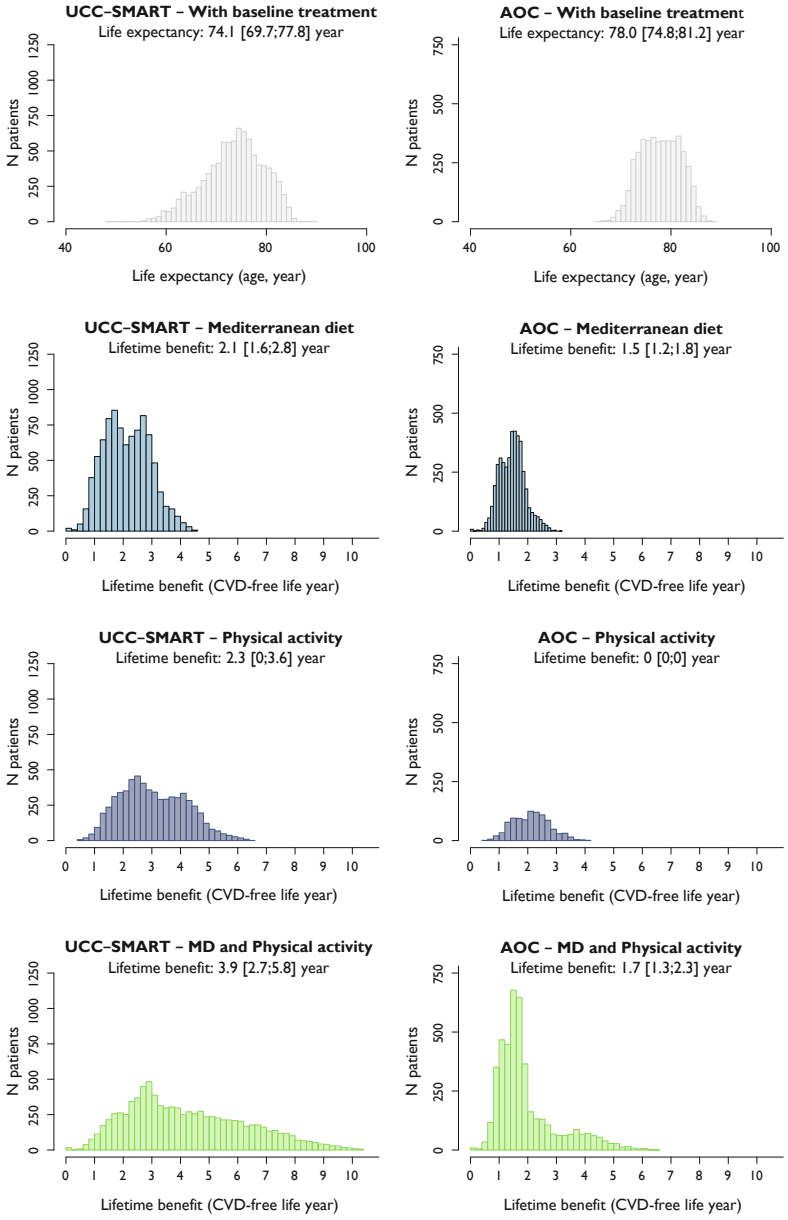
Distribution of 10-year risk with current treatment and with a Mediterranean diet intervention, physical activity intervention or both. UCC-SMART = Utrecht-Cardiovascular Cohort – Secondary Manifestations of Cardiovascular disease, AOC = Alpha-Omega cohort, MedDiet = Mediterranean diet.

FIGURE S3 Distribution of lifetime cardiovascular risk with and without lifestyle interventions



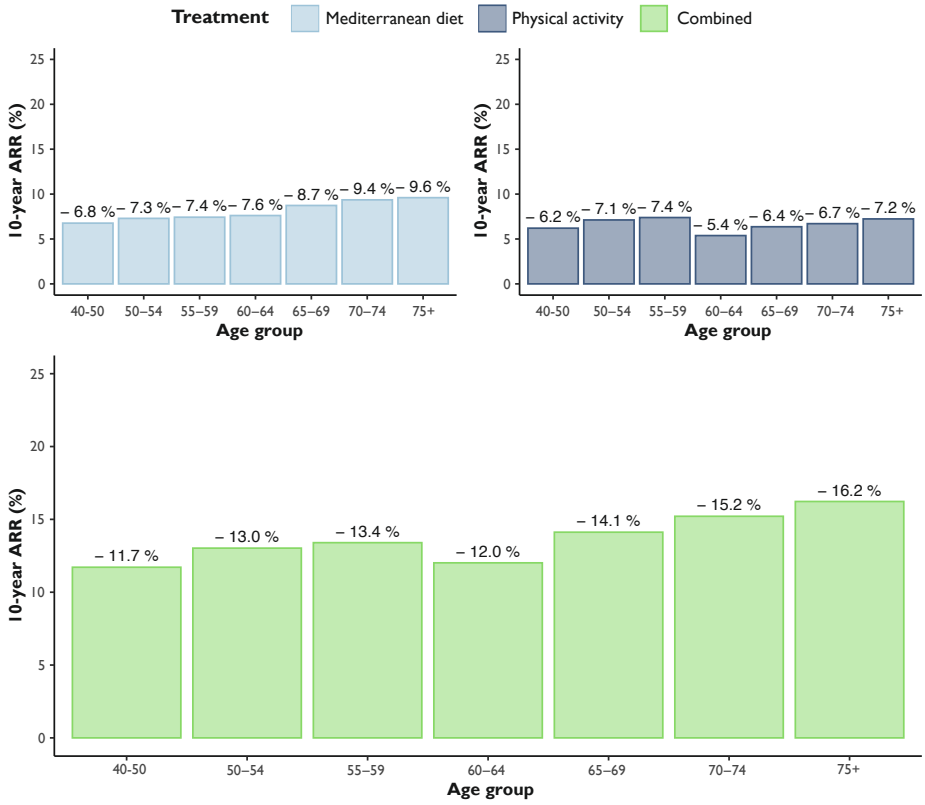
Distribution of lifetime risk with current treatment and with a Mediterranean diet intervention, physical activity intervention or both. UCC-SMART = Utrecht-Cardiovascular Cohort – Secondary Manifestations of Cardiovascular disease, AOC = Alpha-Omega cohort, MedDiet = Mediterranean diet.

FIGURE S4 Distribution of current life expectancy and predicted lifetime benefit from lifestyle interventions



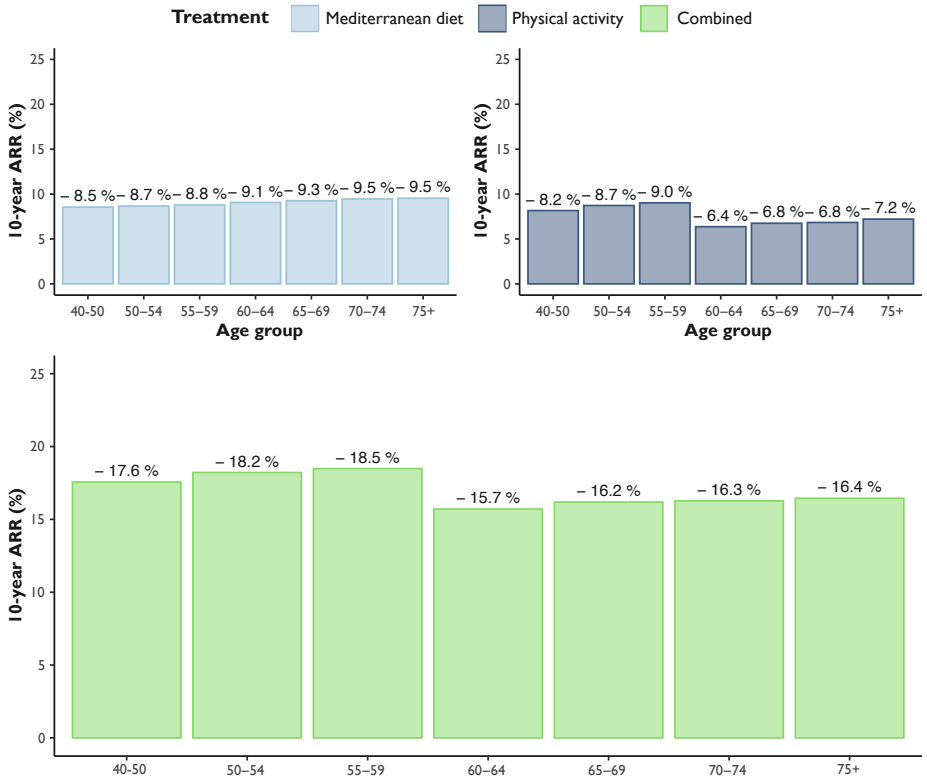
Distribution of life expectancy with current treatment and predicted lifetime benefit in cardiovascular disease-free life years with a Mediterranean diet intervention, physical activity intervention or both. UCC-SMART = Utrecht-Cardiovascular Cohort – Secondary Manifestations of Cardiovascular disease, AOC = Alpha-Omega cohort, MedDiet = Mediterranean diet, CVD = cardiovascular disease

FIGURE S5 10-year absolute cardiovascular risk reduction from Mediterranean diet, physical activity or both across age groups



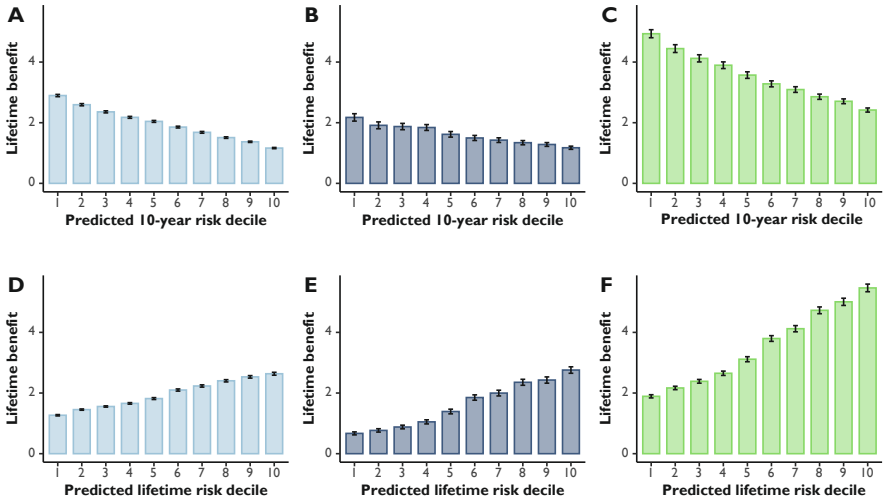
Absolute risk reduction in 10-year risk of cardiovascular event achieved through initiation of a Mediterranean diet, physical activity or both for different ages at initiation of lifestyle. Combined analysis in the UCC-SMART and AOC studies (N = 13,331). CVD: cardiovascular disease. ARR = Absolute risk reduction

FIGURE S6 Lifetime absolute cardiovascular risk reduction from Mediterranean diet, physical activity or both.



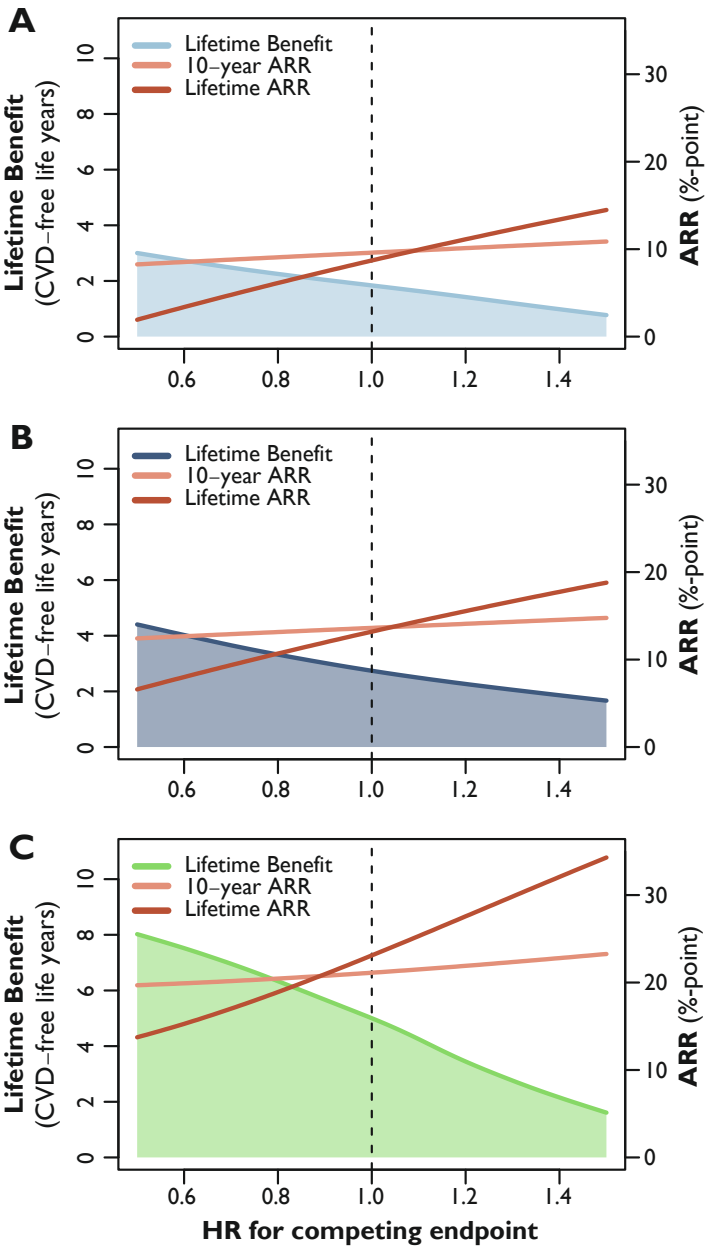
Absolute risk reduction in lifetime risk of cardiovascular event achieved through initiation of a Mediterranean diet, physical activity or both for different ages at initiation of lifestyle. Combined analysis in the UCC-SMART and AOC studies (N = 13,331). CVD: cardiovascular disease. ARR = Absolute risk reduction

FIGURE S7 Lifetime benefit from Mediterranean diet and physical activity across deciles of predicted 10-year and lifetime risk



Distribution of lifetime benefit achieved with Mediterranean diet, physical activity or both across deciles of predicted 10-year CVD risk (A-C) and across deciles of predicted lifetime risk (D-F). Error bars represent the 95% confidence interval for the mean benefit in each group. combined analysis in the UCC-SMART and AOC studies. UCC-SMART = Utrecht-Cardiovascular Cohort – Secondary Manifestations of Cardiovascular disease, AOC = Alpha Omega cohort.

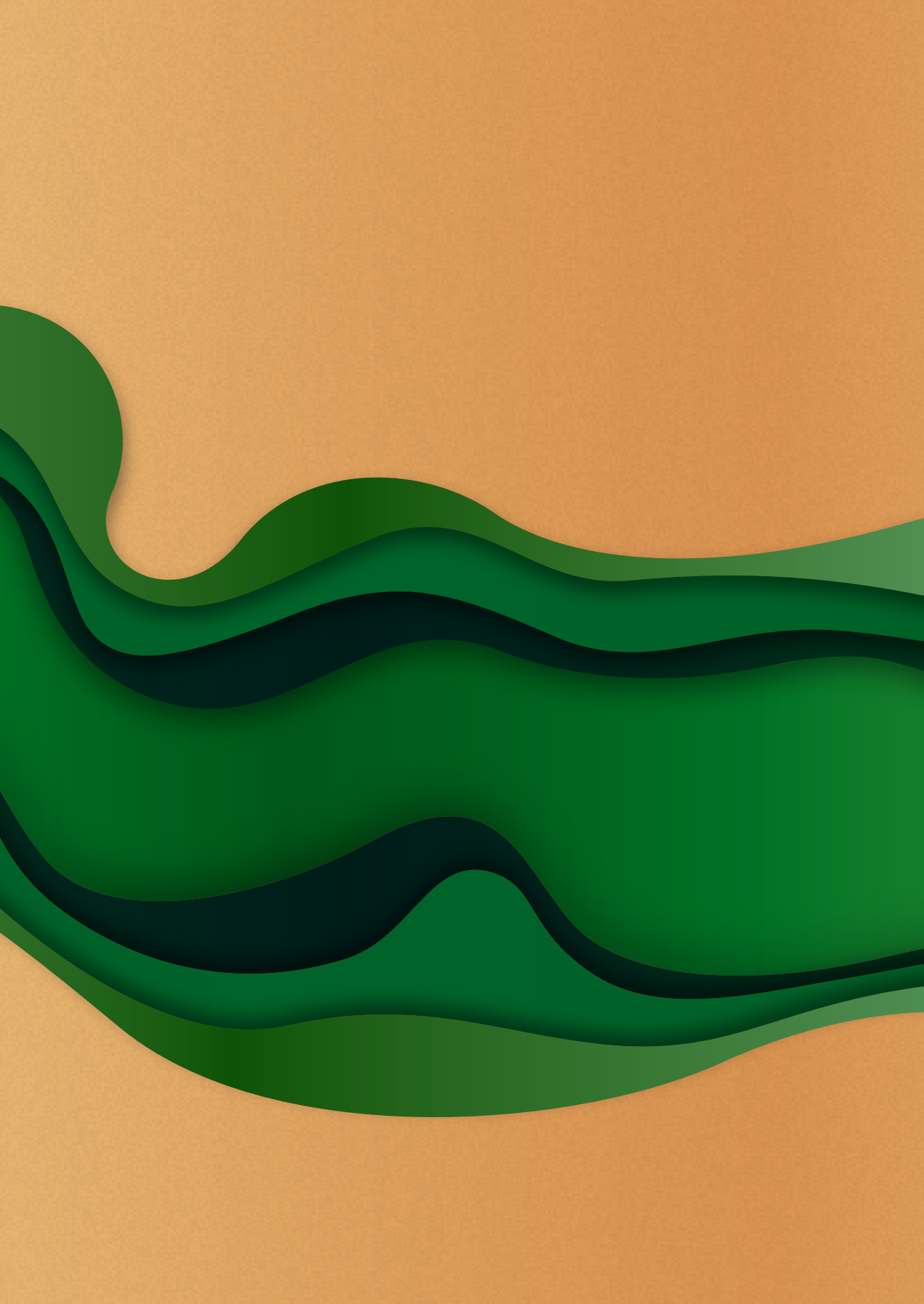
FIGURE S8 Accounting for effect of lifestyle interventions on competing endpoint (non-CVD death)



Mean lifetime benefit and 10-year and lifetime absolute CVD risk reduction achieved with a Mediterranean diet intervention (A), physical activity intervention (B) or both (C) for different effect estimates for the effects of these intervention on the competing endpoint of non-CVD death. CVD = cardiovascular disease, ARR = absolute risk reduction for cardiovascular event

SUPPLEMENTAL REFERENCES

1. Mons U, Müezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: Meta-analysis of Individual participant data from prospective cohort studies of the CHANCES consortium. The BMJ 2015; 350: 1–12.
2. Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: Systematic review and meta-analysis. Arch Intern Med 2012; 172: 837–844.
3. Delgado-lista J, Alcala-diaz JF, Torres-peña JD, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet 2022; 399: 1876–85.
4. Gonzalez-Jaramillo N, Wilhelm M, Arango-Rivas AM, et al. Systematic Review of Physical Activity Trajectories and Mortality in Patients With Coronary Artery Disease. J Am Coll Cardiol 2022; 79: 1690–1700.
5. Cholesterol Treatment Trialists Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. The Lancet 2012; 380: 581–590.
6. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. The Lancet 2016; 387: 957–967.
7. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021; 1–111.



CHAPTER 11

COST-EFFECTIVENESS OF MEDITERRANEAN DIET AND PHYSICAL ACTIVITY IN SECONDARY CVD PREVENTION

Nadia E. Bonekamp
Frank L.J. Visseren
Yvonne T. van der Schouw
Manon G. van der Meer
Martin Teraa
Ynte M. Ruigrok
Johanna M. Geleijnse
Charlotte Koopal

on behalf of the UCC-SMART study group

In revision

ABSTRACT

Aims

The efficacy of a healthy lifestyle in secondary prevention of cardiovascular disease (CVD) is well established and a first-line recommendation in CVD prevention guidelines. The aim of this study was to assess if they are also cost-effective in patients with established CVD.

Methods

A cost-utility analysis (CUA) was performed comparing a combined Mediterranean diet and physical activity intervention to usual care in CVD patients. The CUA had a healthcare perspective and lifetime horizon. Costs and utilities were estimated using a microsimulation on a cohort of 100,000 CVD patients sampled from the UCC-SMART study. Cost-effectiveness was expressed as incremental cost-effectiveness ratio (ICER), incremental net health benefit (INHB) and incremental net monetary benefit (INMB).

Results

Mediterranean diet and physical activity yielded 2.0 incremental quality-adjusted life years (QALYs) and cost reductions of €1,236 per person compared to usual care, resulting in an ICER of €-626/QALY (95%CI -1,929 to 2,673). At a willingness-to-pay of €20,000/QALY, INHB was 2.04 (95%CI 0.99-3.58) QALY and INMB was €40,757 (95%CI 19,819-71,605). The interventions remained cost-effective in a wide range of sensitivity analyses, including worst-case scenarios and scenarios with reimbursement for food and sports costs.

Conclusion

In patients with established CVD, a combined Mediterranean diet and physical activity intervention was cost-saving and highly cost-effective compared to usual care. These findings strongly advocate for the incorporation of lifestyle interventions as integral components of care for all CVD patients.

LAY SUMMARY

Lifestyle optimization, including physical activity and healthy diet, is a central recommendation for preventing recurrent cardiovascular events. In this study, we assessed if improving physical activity habits and adherence to a heart-healthy Mediterranean diet would also be a cost-effective option. The results were remarkable - following the Mediterranean diet and engaging in physical activity was expected an increase of 2.0 quality-adjusted life years (QALYs, equal to a life year in perfect health) and cost savings. This means that lifestyle optimization in secondary CVD prevention improves population health, while reducing overall health care costs. These findings underscore the importance of implementing lifestyle changes in the care for all individuals with CVD. A health lifestyle is not only effective in improving health but also a prudent financial decision.

Key messages

- A combined Mediterranean diet and physical activity intervention is expected to result in two additional QALYs and three addiotional life years free of recurrent cardiovascular events per patient with with established CVD
- Targeting a healthy lifestyle is expected to lead to costs savings compared to usual care, due to the low costs of the intervention and the high efficacy in preventing recurrent cardiovascular events.

Lifestyle optimization in secondary CVD prevention was shown to result in a dominant incremental cost-effectiveness ratio (ICER) of €-626/QALY, which strongly advocates for healthy policy targeted at implementing lifestyle interventions in regular care for CVD patients.

INTRODUCTION

Patients with established cardiovascular disease (CVD) are at a high recurrent CVD risk.[1] Adopting a healthy diet and sufficient physical activity are first-line recommendations for clinical management of these patients, alongside lipid- and blood pressure-lowering and antithrombotic therapy.[1,2] The recent CORDIOPREV trial showed that a Mediterranean diet (rich in olive oil, fish, nuts, fruits, and vegetables) was superior to a low-fat diet in secondary CVD prevention and resulted in 28% CVD event risk reduction,[3] adding to a body of evidence of Mediterranean-style diets' effectiveness in observational cohort studies,[4] and randomized controlled trials (RCTs), in both primary[5] and secondary CVD prevention.[6,7]

In contrast with diet, there are no long-term RCTs on the effect of physical activity interventions on (recurrent) CVD events. However, in observational studies, higher physical activity levels have consistently been linked to a lower risk of cardiovascular events.[8,9] A meta-analysis of nine prospective cohorts assessing change in physical activity over time showed that initiating an active lifestyle was associated with a 45% relative risk reduction compared with a persistently inactive lifestyle.[9] Combining lifestyle interventions in secondary CVD prevention has been shown to attenuate cardiovascular risk factors and recurrent CVD events risk by up to 48%.[10]

In light of increasing healthcare costs,[11] policymakers are faced with the challenge to find cost-effective, or even cost-saving, treatment options to enhance health outcomes and optimize allocation of limited financial resources. Lifestyle interventions offer promising opportunities, due to the low costs of the interventions and the (often costly) medical events prevented.[12–14] However, previous cost-utility analyses (CUA) often did not employ a lifetime perspective or are based on older RCTs which complicates application to current practice and policymaking.

The aim of this study was to assess cost-effectiveness of a combined Mediterranean diet and physical activity intervention compared with usual care in patients with established CVD from a healthcare perspective.

METHODS

Study population

The Utrecht Cardiovascular Cohort – Secondary Manifestations of ARTerial disease (UCC-SMART) study is an ongoing, prospective cohort study. For the current study, data was used from 8,947 patients aged 45 or older with established CAD, cerebrovascular disease (CeVD), and/or peripheral artery disease (PAD) included between December 1996 and February 2023. All participants provided written informed consent. Details on the cohort design have been published previously.[15] To ensure stability of the CUA, an analysis cohort of 100,000 patients with established CVD was created by sampling these 8,947 patients with replacement.

Diet and physical activity interventions

The Mediterranean diet intervention was based on the CORDIOPREV trial,[3] which compared Mediterranean to low-fat diet in patients with CAD. After seven years follow-up, recurrent CVD risk was 28% lower (hazard ratio (HR) 0.72 (95%CI 0.54-0.96)) in the Mediterranean diet group.[3] For this CUA, an a Mediterranean-style diet intervention was modelled according to the CORDIOPREV, which included two face-to-face and four group sessions with a dietitian, and six telephone calls with a healthcare provider yearly. The costs for provision of olive oil were included. It was assumed that none of the UCC-SMART participants already complied with a Mediterranean-style diet.

No long-term RCTs on physical activity interventions are available in patients with established CVD. Therefore, the physical activity treatment effect used in this CUA was based on a 2022 meta-analysis assessing change in physical activity levels that reported a pooled HR of 0.55 (95%CI 0.44-0.70) for CVD events with increased physical activity.[9] The actual physical activity intervention was modelled on an intervention that effectively improved physical activity levels in a Dutch healthcare setting,[16] and consisted of 12 consultations with a general practitioner and five group sessions with a physical therapist. It was assumed patients would meet guideline-recommended physical activity levels after this intervention. International CVD prevention guidelines recommend at least 150 moderate-intensity or 75 minutes of vigorous-intensity physical activity per week, i.e. at least 7.5 Metabolic equivalent of task (MET) hours per week. The HR for increased physical activity was only applied to patients that were previously inactive (i.e. self-reported physical activity level <7.5

METh/wk). Usual care was defined as the treatments that patients received upon inclusion.

Cost-utility analysis

A CUA from a healthcare perspective with a lifetime horizon was performed in accordance with Dutch guidelines (Table 1, Figure 1).[17,18] Details on the CUA design and model inputs are described in the Supplemental Methods and Tables S1-S5.

TABLE 1 Cost-utility analysis characteristics

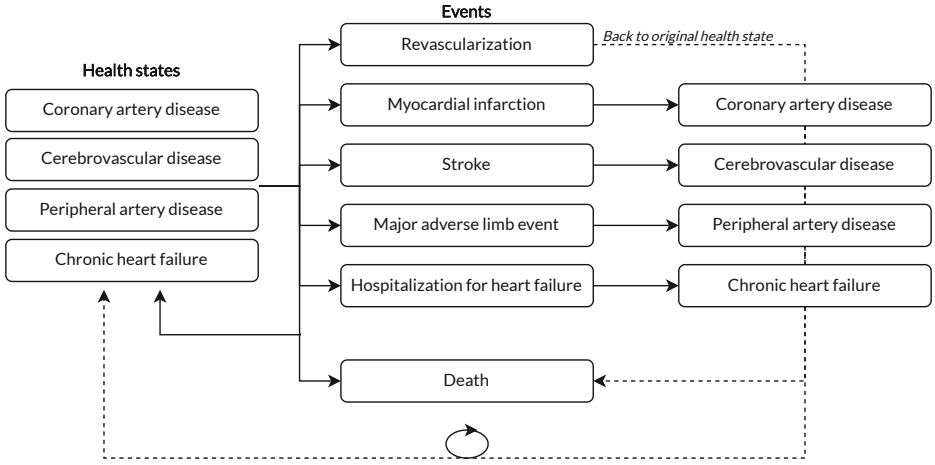
	Model parameters
Type	Cost-utility analysis
Perspective	Healthcare perspective
Population	Patients with established CVD
Time horizon	Lifetime
Intervention	Mediterranean diet and physical activity intervention
Comparator	Care as usual, no intervention on diet or physical activity
Discount rate (/yr)	Costs: 4.0% , Utilities: 1.5%
Outcome	ICER: incremental cost-effectivenes ratio INHB: Incremental net health benefit INMB: incremental net monetary benefit

CVD: cardiovascular disease

In short, costs for the lifestyle intervention, for chronic care for CVD patients, for management of (cardiovascular) events and for care related to dying were included. Indirect patients costs and productivity loss were not included. Costs were converted to Euros and indexed to January 2022. A utility value (*i.e.* indicator for quality of life) was assigned to each chronic health state. Disutilities (*i.e.* utility penalties for factors that lower quality of life) were included for increasing age, female sex and for CVD events (Table S5). Utility values were used to calculate patients' QALYs by multiplying time in a health state with the utility value of that health state. Costs were discounted at an annual rate of 4% and utility was discounted at an annual rate of 1.5%. The main outcome was the incremental cost-effectiveness ratio (ICER). Incremental net health benefit (INHB) and incremental net monetary benefit (INMB) were calculated for WTPs of €20,000/QALY and €50,000/QALY.[19,20] A microsimulation model with 1-year cycles was used to estimate life expectancy, QALYs and costs, both under usual care and with addition of the lifestyle intervention.

The probability of cost-effectiveness at different WTPs was estimated in a probabilistic sensitivity analysis. The microsimulation was repeated 1,000 times in a Monte-Carlo simulation with all input parameters randomly drawn from a suitable distribution for each iteration. Event rates, utilities and disutilities were drawn from a beta distribution, costs from a gamma distribution and HRs from a log-normal distribution.

FIGURE 1 Health states



Schematic representation of the microsimulation model. The model was run with a lifetime perspective and 1-year time intervals. Patients' initial health state was based on their medical history. In each interval patients were at risk for death or a cardiovascular event. In the next interval they would transfer to the associated health state or remain in the previous health state if that was associated with lower utility.

Sensitivity and scenario analyses

Scenario analyses were performed to assess the impact of model assumptions on the outcomes of the CUA. These included a worst-and best-case scenario, univariate sensitivity analyses, and discounting as recommended by the British National Institute for Health and Clinical Excellence (NICE, annual rate 3.5% for both costs and health effects).[21]

The CUA was repeated in subgroups based on age (<50, 50-75, and ≥75 years), and on CVD type (CAD, CeVD or PAD). Scenarios with different degrees of reimbursement for food and sports costs were assessed, including no reimbursement for any of these costs, reimbursement of incremental costs for a Mediterranean compared with

a Western-style diet (€3.82/day), reimbursement of all food costs (€10.89/day) and reimbursement of sports club membership (€47/month, Supplemental Methods, Table S4). To evaluate the impact of non-compliance, sensitivity analyses were conducted with the probability of being compliant with the lifestyle intervention ranging from 0 to 100%. It was assumed that intervention costs would still be incurred.

Previous studies have shown that benefit-based initiation of preventive treatment is cost-effective.[22] In a sensitivity analysis, the expected lifetime benefit from lifestyle interventions was calculated by combining the externally validated, competing-risk adjusted SMART-REACH model[23] with the treatment effects for Mediterranean diet and physical activity. The cost-utility outcomes were calculated for scenarios where a lifetime benefit threshold of 1, 2, 3, 4 and 5 CVD-free life years gained from the combined lifestyle intervention was used before it was assigned to a patient. Finally, cost-effectiveness was estimated for scenarios where treatment effects of Mediterranean diet and physical activity decreased over time. Relative decreases by 1%, 5% and 10% compared to the previous year were assessed.

RESULTS

Baseline characteristics

The mean age of 8,947 CVD patients was 62 ±8.7 years and 74% (N = 6,621) was male (Table 2). Most patients had a history of CAD (N = 5,912, 66%). Seventy-three percent of the population was treated with lipid-lowering therapy and 78% with blood pressure-lowering medications. Dietary intake data was available for 2,227 participants and the median Mediterranean diet score in this group was 3.0 [IQR 2.0-4.0] (Figure S1). Only 2,694 (30%) had physical activity levels that were guideline-compliant. Patient characteristics were similar for the 100,000-patient cohort used in the microsimulation (Table S6).

TABLE 2 Patient characteristics

	UCC-SMART cohort *N = 8947*
Age, year	62 ±8.7
Male sex	6,621 (74)
Coronary artery disease	5,912 (66)
Cerebrovascular disease	2,607 (29)
Peripheral arterial disease	1,550 (17)
Diabetes	1,630 (18)
Smoking	
Never	2,091 (23)
Former	4,422 (49)
Current	2,434 (27)
Exercise	
No exercise	5,454 (61)
≥ 7.5 METh/wk	2,694 (30)
Among exercisers, *METh/wk*	14 [8-24]
Dietary intake*	
Daily energy intake, *kcal/day*	1,906 [1,449-2,386]
MEDAS score (out of max. 14)	3 [2-4] Range: 0 to 10
MEDAS score > 5	222 (11)
Body mass index, *kg/m²*	27 ±4.6
Systolic blood pressure, *mmHg*	139 ±21
Diastolic blood pressure, *mmHg*	81 ±11
Total cholesterol, *mmol/l*	4.5 [3.8-5.4]
HDL-cholesterol, *mmol/l*	1.2 [1.0-1.4]
LDL-cholesterol, *mmol/l*	2.5 [2.0-3.3]
Triglycerides, *mmol/l*	1.4 [1.0-2.0]
eGFR†, *ml/min/1.73m²*	78 [66-90]
Lipid-lowering medication	6,564 (73)
Blood pressure-lowering medication	7,018 (78)
Antiplatelets	7,229 (81)

Baseline characteristics of participants of the UCC-SMART cohort. Data are presented as number (percentage), mean ± standard deviation or median [interquartile range] unless otherwise indicated. UCC-SMART = Utrecht Cardiovascular Cohort-Secondary Manifestations of ARTerial disease, MEDAS: Mediterranean diet adherence screener, HDL = high-density lipoprotein, LDL = low-density lipoprotein, eGFR = estimated glomerular filtration rate. * Data on dietary intake was available for 2,227 participants. † Estimated using CKD-EPI creatinine formula

Effectiveness and cost-effectiveness of lifestyle interventions

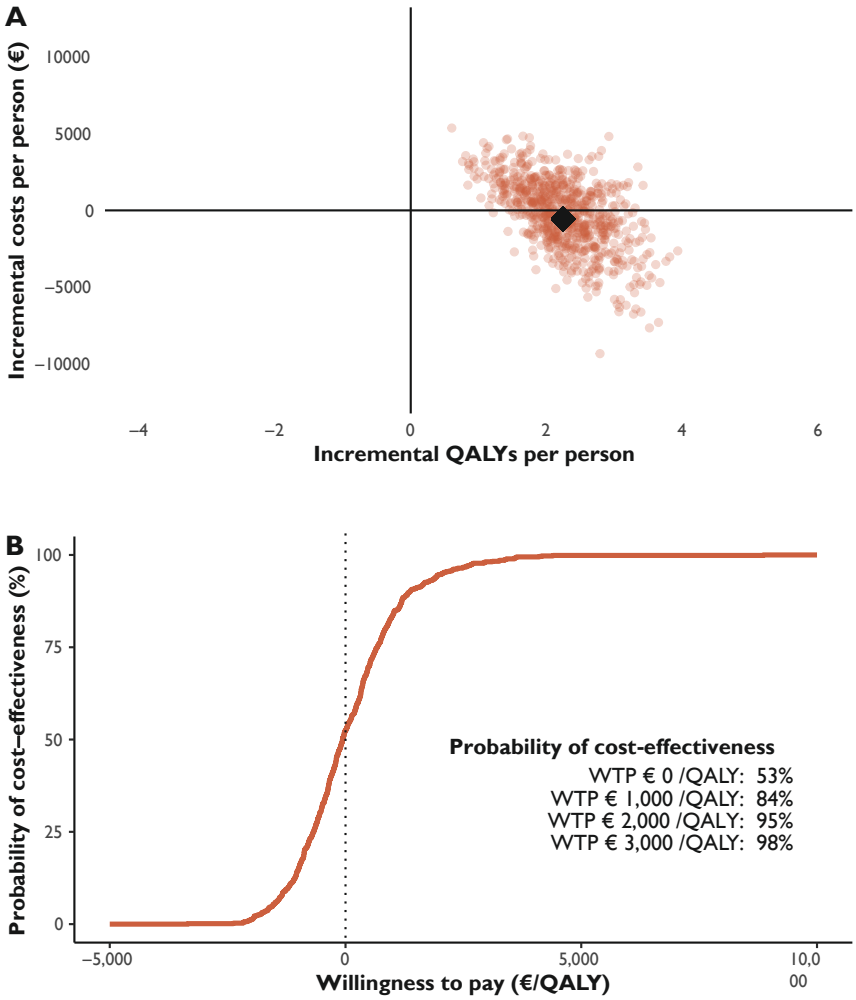
Over a 10-year period, the mean number of CVD events per patient was 0.4 (95%CI 0.3-0.4) under usual care and 0.2 (95%CI 0.1-0.3) with initiation of the Mediterranean diet and physical activity (Table 3, Figure 2). Predicted life expectancy free of a recurrent CVD event was 7.8 (95%CI 7.1-8.5) years with usual care and 11.1 (95%CI 9.4-14) years with the lifestyle interventions (3.3 CVD-free life years increment, 95%CI 1.7-6.1). On average 2.0 (95%CI 1.1-3.4) QALYs were gained with the lifestyle intervention. Costs for usual care were €82,107 (95%CI 68,866-87,761) per person with usual care, and €80,870 (95%CI 69,523-86,023) per person with the lifestyle intervention. On average, the combined Mediterranean and physical activity intervention resulted in €1,236 cost savings.

TABLE 3 Costs, effects and cost-effectiveness of usual care and the combined lifestyle intervention

	Usual care	**Lifestyle intervention**
	Per patient	Per patient
Effectiveness		
Cardiovascular events		
10-year, N	0.4 (0.3, 0.4)	0.2 (0.1, 0.3)
Lifetime, N	2.1 (1.7, 2.1)	1.9 (1.4, 1.9)
Survival time		
CVD-free life years	7.8 (7.1, 8.5)	11.1 (9.4, 14)
Incremental	*Reference*	+ 3.3 (1.7, 6.1)
QALY	10.1 (9.9, 11.4)	12.1 (11.6, 14.3)
Incremental	*Reference*	+ 2.0 (1.1, 3.4)
Costs		
Total costs	€ 82,107 (68,866, 87,761)	€ 80,870 (69,523, 86,023)
Incremental	*Reference*	€ -1,236 (-5,205, 3,651)
Cost-effectiveness		
ICER, *€/QALY*	*Reference*	€ -626 (-1,929, 2,673)
WTP €20,000/QALY		
INHB, *QALY*	*Reference*	2.04 (0.99, 3.58)
INMB, *€*	*Reference*	€ 40,757 (19,819, 71,605)
WTP €50,000/QALY		
INHB, *QALY*	*Reference*	2.00 (1.07, 3.47)
INMB, *€*	*Reference*	€ 100,037 (53,426, 173,712)

95% confidence intervals were estimated from the probabilistic sensitivity analysis, using the percentile method. CVD: cardiovascular disease, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, INHB: incremental net health benefits, INMB: incremental net monetary benefit, WTP: willingness to pay.

FIGURE 2 Probabilistic sensitivity analysis



Results from 1,000 iterations of the probabilistic sensitivity analysis**.** Panel **A** depicts the cost-effectiveness plane where incremental costs in each iteration are plotted against incremental utility. Panel **B** presents the cost-effectiveness acceptability curve and shows the probability of the Mediterranean diet and physical activity intervention being cost-effective depending on willingness to pay for an additional QALY. QALY: Quality-adjusted life year, WTP: willingness to pay.

The lifestyle intervention was cost-effective compared with usual care with an ICER of €-626 (95%CI -1,929; 2,673)/QALY. For a WTP of €20,000/QALY, the INHB was 2.04 (95%CI 0.99-3.58) QALY and the INMB was €40,757 (95%CI 19,819-71,605). For a WTP of €50,000/QALY, INHB was 2.00 (95%CI 1.07-3.47) QALY and INMB was

€100,037 (95%CI 53,426-173,712). Estimated ICERs in the probabilistic sensitivity analysis ranged between €-3,823 and €8,863/QALY. There was an 83% probability of a dominant ICER (*i.e.* gains in QALYs at reduced costs, Figure 3).

Scenario and sensitivity analyses

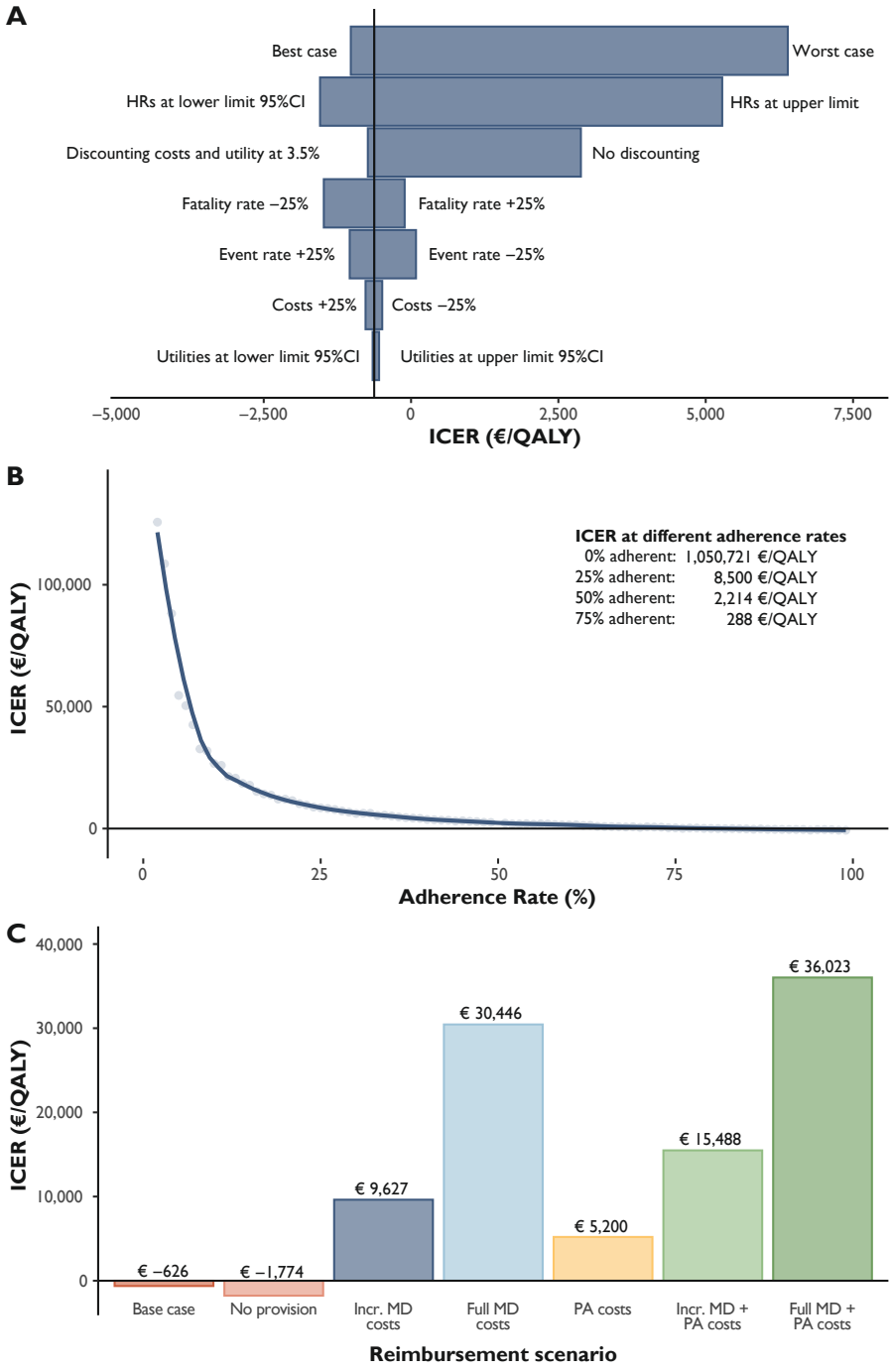
Univariate sensitivity analyses indicated that the analysis was most sensitive for uncertainty in the treatment effects for Mediterranean diet and physical activity (Figure 3A). The ICER was estimated at €5,280/QALY and the INMB at €9,489 when the HR for Mediterranean diet and physical activity were set at the upper, least effective limit of their 95%CI (0.96 and 0.78 respectively). Putting both HRs at the lower limit of their confidence interval (0.54 for Mediterranean diet and 0.51 for physical activity) resulted in an ICER of €-1,544/QALY and an INMB of €70,911. A higher CVD event rate or a lower case-fatality rate resulted in a more favourable ICER. The CUA was relatively insensitive to uncertainty in the input values for costs and utility (Figure 3C, Figure S2, Table S7).

Assuming an adherence rate of 25%, the ICER was €8,500/QALY. The ICER exceeded €20,000/QALY from an adherence rate below 13% and €50,000/QALY when the adherence rate dropped below 7% (Figure 3B). With reimbursement of incremental Mediterranean diet costs, the ICER was estimated at €9,627/QALY and at €30,466/QALY for full reimbursement of all Mediterranean diet costs (Figure 3C). When gym costs were reimbursed, the ICER increased to €5,200/QALY. If both diet and sports costs were fully reimbursed, the ICER would amount to €36,023/QALY.

The lifestyle intervention was most cost-effective in patients aged <50 years (INHB at €20,000 threshold 2.17 QALY) and least cost-effective in patients aged >75 years (INHB 1.97). Compared with CAD and PAD patients, treatment with Mediterranean diet and physical activity was most cost-effective in CeVD patients (INHB 2.07 QALY vs 1.98 and 2.05 QALY respectively, Figure S3/Table S7). The ICER, INHB and INMB were similar across a range of lifetime benefit thresholds for treatment initiation (Figure S4, Table S7).

In a scenario where lifestyle treatment effects reduced by 10% per year since treatment, the combined lifestyle intervention remained cost-effective. The ICER for this scenario was €5,122/QALY and the expected INHB at a €20,000/QALY WTP threshold was 0.44 QALY (Figure S5, Table S7).

FIGURE 3 Scenario and sensitivity analyses



◄——— Scenario and sensitivity analyses. Panel **A** presents the results of a univariate sensitivity analysis. Panel **B** presents the expected ICER for different adherence rates. Panel **C** shows the impact of reimbursing food costs and exercise costs on the ICER. In the base case analysis, the Mediterranean diet intervention includes provision of extra-virgin olive oil. This plot presents the ICER for scenarios where the costs for a Mediterranean diet and physical activity are reimbursed to different degrees: no costs reimbursed, additional costs for Mediterranean diet compared with Western-style diet (€ 3.82/day) reimbursed, full costs for the Mediterranean diet (€ 10.89 /day) reimbursed and membership costs for a sports club (€ 47/month) reimbursed. The final two scenarios show combinations of reimbursement for Mediterranean diet and physical activity costs. ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life year, MD: Mediterranean diet, PA: physical activity.

DISCUSSION

This CUA assessed a combined Mediterranean diet and physical activity intervention in secondary CVD prevention, and showed that it is highly cost-effective. Initiation of this lifestyle intervention increased CVD-free life expectancy by more than three years and yielded two additional QALYs per person while reducing overall healthcare costs. As such, the ICER was dominant at €-626/QALY (95%CI -1,929; 2,673), and even in a wide range of sensitivity analyses, including low adherence rates and higher costs, it remained well below international WTP thresholds.

The combined lifestyle intervention for patients with established CVD remained highly cost-effective in extensive scenario and sensitivity analyses and was robust to assumptions made in the CUA. Potential explanations for the highly cost-effective results include the low costs for the lifestyle intervention on the one hand and the strong protective effect of the Mediterranean diet (28% relative risk reduction) and active lifestyle (36% relative risk reduction) on the other hand. Cost reductions were driven by a reduction in the CVD event rates as a result of the lifestyle intervention. Univariate sensitivity analyses indicated that the CUA results were sensitive to the HRs for the Mediterranean diet and physical activity treatment effect and the available estimates for treatment effects from these interventions have a wide confidence interval. However, even when both hazard ratios were set at the upper limit of their 95%CI (*i.e.* the least effective), the interventions were still cost-effective relative to usual care with a modest ICER of €5,280/QALY.

Our findings are in line with previous cost-effectiveness analyses of lifestyle-related interventions in clinical CVD management.[12–14] An analysis of a Mediterranean

diet intervention based on the Lyon diet heart study reported an ICER of €579 per incremental QALY over a 4-year time horizon.[5] Exercise-based cardiovascular rehabilitation programmes have previously been shown to be cost-effective with outcomes ranging from dominant ICERs to approximately €40,000/QALY.[13,14,24] However, these analyses often had a relatively short time horizon (3-5 year) which may be insufficient to capture the interventions' full impact on health and costs.

In clinical practice, long-term adherence to lifestyle interventions often proofs difficult. Sensitivity analyses indicated that a low adherence rate to the lifestyle intervention negatively affected cost-effectiveness. When the protective effect of Mediterranean diet and physical activity reduces by 10% per year, possibly through reduced adherence, the intervention maintains its cost-effectiveness but to a significantly lesser degree. Several barriers, such as comorbidities, cultural factors and lack of adequate information material, may hinder patients in adopting or maintaining a Mediterranean diet and/or physical activity. High costs of such healthy lifestyle habits also prove an important barrier for adherence.[25–27] On average, a healthy diet is 20-30% more expensive compared to a typical Western-style diet,[25] and membership costs are incurred to maintain regular physical activity. Providing (partial) reimbursement for these costs could improve adherence to lifestyle interventions. Previous analyses on provision of healthy meals and reimbursement of gym membership costs have shown that these interventions are effective in improving healthy behaviour, reducing healthcare utilization and reducing healthcare costs.[28–30] Scenario analyses on different extents of reimbursement for diet and exercise costs in the current study indicate that such reimbursement would still result in a cost-effective intervention, with ICERs ranging between dominant to €36,023 per incremental QALY. These findings provide an important signal to policy makers and healthcare insurers to consider including healthy diet and physical activity costs in insurance coverage.

These findings of this CUA have important implications for healthcare policy. The Dutch Health Institute employs an explicit WTP threshold between 20,000-80,000 €/QALY for new healthcare interventions,[17,18] the British National Institute for Health and Care Excellence WTP threshold is approximately 20,000-30,000 £/QALY[31] and the WTP threshold in the United States is 50,000 $/QALY.[32] By demonstrating an ICER of €-653 /QALY compared to usual care and positive INHB and INMB at thresholds of €20,000 and €50,000 per QALY, this study highlights the high likelihood of cost-effectiveness of treatment targeted at a healthy lifestyle at these WTP thresholds

used by health authorities. This suggests that implementing a lifestyle intervention in secondary CVD prevention could be a viable and attractive treatment strategy for health authorities and policymakers to consider.

Compared to other common treatments, the lifestyle intervention is highly cost-effective. For proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibition therapy ICERs range between €46,000 to 87,000/QALY[33], for intensive blood pressure lowering an ICER of €27,532/QALY has been estimated[34] and for antithrombotic therapy in accordance with a COMPASS regime (low-dose rivaroxaban + aspirin) expected ICERs range between €26,381 and 32,109/QALY.[35] As the burden of CVD and its associated costs continue to rise, the focus on preventive measures becomes increasingly vital. By encouraging lifestyle modifications, healthcare systems can proactively address the root causes of CVD and work towards building a healthier population while simultaneously reducing healthcare costs.

Strengths and limitations

The UCC-SMART study is representative of patients with established CVD in the Netherlands and basing the cohort for the cost-effectiveness analysis on this study ensures a realistic distribution of cardiovascular risk factors and treatment benefits. Extensive sensitivity analyses were performed and showed robustness of this study's results to assumptions made in the CUA modelling process.

This study has several limitations. Extrapolation of continuing treatment effects of Mediterranean diet beyond the observed 7-year RCT timespan is a key limitation. Nonetheless, the cumulative incidence curves in the CORDIOPREV trial diverged after longer follow-up, suggesting treatment effects might even increase over time[3]. Physical activity treatment effects were derived from pooled observational studies, in absence of RCT data. Finally, the current analysis modelled effects of lifestyle intervention on CVD risk alone. In practice, lifestyle modifications will likely also reduce risk of other non-communicable diseases, such as type 2 diabetes and several types of cancer. Incorporating these additional benefits would likely result in increased QALY gains and a more cost-effective result.

In conclusion, in patients with established CVD, a combined intervention with a Mediterranean diet and physical activity was highly cost-effective compared to usual care. The combined lifestyle intervention resulted in QALY gains at a reduced cost.

These findings indicate that lifestyle interventions are not only effective in reducing residual CVD risk , but are also highly cost-effective and should be considered for all CVD patients. This study makes a strong case for renewed focus on a healthy lifestyle in the clinical management of CVD patients, as this is not only likely to benefit individual patients but also to significantly impact healthcare systems and society.

REFERENCES

1 Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;1–111.

2 Virani SS, Newby LK, Arnold S V., et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. Published Online First: 20 July 2023.

3 Delgado-lista J, Alcala-diaz JF, Torres-peña JD, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet. 2022;399:1876–85.

4 Tang C, Wang X, Qin L-Q, et al. Mediterranean Diet and Mortality in People with Cardiovascular Disease: A Meta-Analysis of Prospective Cohort Studies. Nutrients. 2021;13:2623.

5 De Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99:779–85.

6 Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. New England Journal of Medicine. 2018;378:e34.

7 Karam G, Agarwal A, Sadeghirad B, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. BMJ. Published Online First: 2023. doi: 10.1136/bmj-2022-072003

8 Posadzki P, Pieper D, Bajpai R, et al. Exercise/physical activity and health outcomes: an overview of Cochrane systematic reviews. BMC Public Health. 2020;20. doi: 10.1186/s12889-020-09855-3

9 Gonzalez-Jaramillo N, Wilhelm M, Arango-Rivas AM, et al. Systematic Review of Physical Activity Trajectories and Mortality in Patients With Coronary Artery Disease. J Am Coll Cardiol. 2022;79:1690–700.

10 Giannuzzi P, Temporelli PL, Marchioli R, et al. Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network. Arch Intern Med. 2008;168:2194–204.

11 Goryakin Y, Thiébaut SP, Cortaredona S, et al. Assessing the future medical cost burden for the European health systems under alternative exposure-to-risks scenarios. PLoS One. 2020;15:e0238565.

12 Dalziel K, Segal L, De Lorgeril M. A mediterranean diet is cost-effective in patients with previous myocardial infarction. Journal of Nutrition. 2006;136:1879–85.

13 Oldridge N, Taylor RS. Cost-effectiveness of exercise therapy in patients with coronary heart disease, chronic heart failure and associated risk factors: A systematic review of economic evaluations of randomized clinical trials. Eur J Prev Cardiol. 2020;27:1045–55.

14 Shields GE, Wells A, Doherty P, et al. Cost-effectiveness of cardiac rehabilitation: a systematic review. Heart. 2018;104:1403–10.

15 Castelijns MC, Helmink MAG, Hageman SHJ, et al. Cohort profile: the Utrecht Cardiovascular Cohort-Second Manifestations of Arterial Disease (UCC-SMART) Study-an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands. BMJ Open. 2023;13:e066952.

16 Vermunt PWA, Milder IEJ, Wielaard F, et al. A lifestyle intervention to reduce Type 2 diabetes risk in Dutch primary care: 2.5-year results of a randomized controlled trial. Diabetic Medicine. 2012;29:e223–31.

17 Hakkaart-van Roijen L, van der Linden N, Bouwmans C, et al. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Dutch National Health Care Institute. 2016;1–73.

18 Dutch Institute National Health Care (Zorginstituut Nederland). Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidzorg (Protocol for the execution of economic evaluation in healthcare). 29-02-2016. 2016;120.

19 Stinnett AA, Mullahy J. Net Health Benefits. Medical Decision Making. 1998;18:S68–80.

20 Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the Economic Evaluation of Health Care Programmes. (4th ed.). 4th edition. Oxford University Press 2015. https://books.google.co.uk/books?id=IvWACgAAQBAJ (accessed 31 July 2023)

21 NICE. Guide to the methods of technology appraisal. http://www nice org uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal jsp. 2008.

22 Hageman SHJ, Dorresteijn JAN, Bots ML, et al. Residual cardiovascular risk reduction guided by lifetime benefit estimation in patients with symptomatic atherosclerotic disease: effectiveness and cost-effectiveness. Eur J Prev Cardiol. 2022;29:635–44.

23 Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: The SMART-REACH model. J Am Heart Assoc. 2018;7. doi: 10.1161/JAHA.118.009217

24 Edwards K, Jones N, Newton J, et al. The cost-effectiveness of exercise-based cardiac rehabilitation: a systematic review of the characteristics and methodological quality of published literature. Health Econ Rev. 2017;7:37.

25 Springmann M, Clark MA, Rayner M, et al. The global and regional costs of healthy and sustainable dietary patterns: a modelling study. Lancet Planet Health. 2021;5:e797–807.

26 World Health Organization. Global status report on physical activity 2022. Geneva 2022.

27 Kearney M, Kearney J, Dunne A, et al. Sociodemographic determinants of perceived influences on food choice in a nationally representative sample of Irish adults. Public Health Nutr. 2000;3:219–26.

28 Berkowitz SA, Terranova J, Randall L, et al. Association Between Receipt of a Medically Tailored Meal Program and Health Care Use. JAMA Intern Med. 2019;179:786.

29 Hager K, Cudhea FP, Wong JB, et al. Association of National Expansion of Insurance Coverage of Medically Tailored Meals With Estimated Hospitalizations and Health Care Expenditures in the US. JAMA Netw Open. 2022;5:e2236898.

30 Homonoff T, Willage B, Willén A. Rebates as incentives: The effects of a gym membership reimbursement program. J Health Econ. 2020;70:102285.

31 Minacori R, Geale K, Geale K. Is there Evidence of a Difference Between Willingness to Pay and Willingness to Accept Thresholds? A Review of Nice Technology Appraisals. Value in Health. 2016;19:A492–3.

32 Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014;371:796–7.

33 Michaeli DT, Michaeli JC, Boch T, et al. Cost-effectiveness of cholesterol-lowering drugs for secondary cardiovascular prevention in the UK: ezetimibe, evolocumab, and alirocumab. Eur Heart J. 2022;43. doi: 10.1093/eurheartj/ehac544.2367

34 Richman IB, Fairley M, Jørgensen ME, et al. Cost-effectiveness of Intensive Blood Pressure Management. JAMA Cardiol. 2016;1:872.

35 Petersohn S, Pouwels X, Ramaekers B, et al. Rivaroxaban plus aspirin for the prevention of ischaemic events in patients with cardiovascular disease: a cost-effectiveness study. Eur J Prev Cardiol. 2020;27:1354–65.

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Microsimulation

The costs and benefits of an intervention with Mediterranean diet and physical activity compared to usual care were estimated using a microsimulation in a cohort of 100,000 patients with stable CVD was sampled with replacement from the UCC-SMART study. The simulation was run for 1-year time intervals and repeated until the entire population had died (lifetime perspective). This methodology for the microsimulation has been previously described.[1]

For each participant, the expected treatment effect from Mediterranean diet and physical activity was estimated. It was assumed that none of the participants in the UCC-SMART study was naturally compliant with a Mediterranean diet and that the hazard ratio of 0.72 for Mediterranean diet was therefore applicable to all patients. The physical activity treatment effect (HR 0.63) was only applied to patients that were not already meeting guideline-recommended physical activity levels (>7.5 METh/wk). If patients were expected to benefit from both interventions, the treatment effects were multiplied, resulting in an overall HR of 0.45 for the combined lifestyle intervention.

Example: probabilities 70-year-old man

Event	Usual care	LifestyleTx
Revasc.	7.9 %	3.6%
MALE	4.9 %	2.2%
MI	1.9 %	0.8%
Stroke	1.5 %	0.7%
CHF hosp.	2.6 %	1.2%
Fatal MI	0.2 %	0.1%
Fatal stroke	0.3 %	0.1%
Fatal CHF	0.8 %	0.4 %
nCVD death	0 %	0 %
Stable	80.0%	90.9 %

Event and mortality probabilities under usual care were estimated in each time interval based on the population event rates (Table S1), population case fatality rates (Table S2) and age-sex specific adjustment factors (Table S3). The event and mortality probabilities under treatment with Mediterranean diet and physical activity were calculated by

multiplying these probabilities under usual care with a patient's expected treatment effect from the lifestyle interventions. In the first time interval of the microsimulation, all patients started in the stable health state that corresponded to their medical history. In subsequent time intervals, a draw from the set of potential events was made based on the estimated probabilities. The health state at the start of the next time interval corresponded to the event (e.g. CeVD after a non-fatal stroke), unless patients previously were in a health state that was associated with higher costs and disutility. For example, a patient in the heart failure health state, would remain in this health state in the next interval if they experienced a non-fatal myocardial infarction. Death was an absorbing state: after a patient dies, it remains in the death health state. The simulation was repeated until all patients in the cohort died (65 cycles).

After the health state and events in each time interval were determined, the corresponding costs and utility were calculated for each patient and each time interval (Tables S… and …). These were discounted at an annual rate of 1.5% for utilities and 3% for costs. For each patient, the 10-year and lifetime CVD event rate, CVD-free life expectancy, total costs and total utility were calculated.

Assessing cost-effectiveness

The main outcomes measures to assess cost-effectiveness in this study were the incremental cost-effectiveness ratio (ICER), incremental net health benefit (INHB) and incremental net monetary benefit (INHB). INHB and INMB are measures that represent cost-effectiveness in a single metric. For INHB, monetary gains (cost savings) are converted to health gains using the willingness-to-pay value and for INMB, health gains (incremental QALYs) are converted into a monetary value, again using the willingness-to-pay. For both INHB and INMB, a positive value indicates that the intervention is cost-effective at the given willingness-to-pay threshold.

ICER, INHB and INMB were calculated as follows:

$$\textbf{ICER} = \frac{\text{Costs intervention} - \text{Cost usual care}}{\text{Utility intervention} - \text{Utility usual care}}$$

$$\textbf{NHB} = \text{Utility} - \frac{\text{Costs}}{\text{WTP}} \text{ (for both intervention and usual care)}$$

$$\textbf{INHB} = \text{NHB}_{\text{Intervention}} - \text{NHB}_{\text{Usual care}}$$

$$\mathbf{NMB} = \text{Utility} * \text{WTP} - \text{Costs (for both intervention and usual care)}$$

$$\mathbf{INMB} = \text{NMB}_{\text{Intervention}} - \text{NMB}_{\text{Usual care}}$$

The Dutch payer employs different WTP thresholds for health care interventions based on the severity of the underlying disease. These WTP values are € 20,000 /QALY for severities between 0.10 and 0.40, € 50,000 /QALY for severities ranging between 0.41 and 0.70, and € 80,000 /QALY for severities ranging between 0.71 and 0.90. Disease severity is calculated using the proportional shortfall method.

$$\textbf{Proportional shortfall} = \frac{\textbf{Remaining QALY}_{\textbf{No CVD}} - \textbf{Remaining QALY}_{\textbf{CVD}}}{\text{Remaining QALY}_{\text{No CVD}}}$$

Proportional shortfall for chronic CVD in this study population was estimated using an online shortfall calculator designed for the British population.[2] Given the study populations mean age of 62 years and 26% females, the expected average remaining QALYs without CVD would be 17.29. The microsimulation in the current study yielded a mean remaining 10.1 QALY per person with CVD. These findings indicate a burden of disease for chronic CVD of 0.42 based on the proportional shortfall method. Because this value is very close to the 0.40 threshold used by the Dutch Health Institute, INHB and INMB were presented for both the € 20,000 /QALY and € 50,000 /QALY WTP values.

Compliance with Mediterranean diet in the UCC-SMART cohort

Compliance with the Mediterranean diet in the UCC-SMART cohort was assessed by applying the Mediterranean Diet Adherence Screener (MEDAS) score to responses on a 160-item food frequency questionnaire.[3] The MEDAS score is a 14-item screener to continuously assess compliance with a Mediterranean-style diet that was also used in the CORDIOPREV trial. Among 2,046 UCC-SMART participants for whom dietary intake data was available, the median MEDAS score was 3 [IQR 2-4] compared with a mean score of 11.2 in the intervention arm of the CORDIOPREV trial (Figure S1).[4] As such, it was assumed that none of the included patients was already compliant with a Mediterranean diet and that the intervention could be applied to all participants.

TABLE S1 CUA inputs: Cardiovascular and mortality event rates

Event	**N events**	**Follow-up** (py)	**Event rate**†
Myocardial infarction	645	77,478	0.00699092
Revascularization	1,309	67,440	0.02810538
Stroke	514	78,766	0.00618449
Major limb event	647	76,927	0.01721619
Hospitalization for heart failure*	*NA*	*NA*	0.01151301
Death	2,329	81,389	0.00700815

Observed event rates in patients with established CVD in the UCC-SMART cohort.
* Data on hospitalization for CHF was not available in the UCC-SMART cohort. The CHF event rate was obtained from: Vidal-Petiot et al. Lancet 2016.[5] † Event-rate for a 60-year-old woman. Risk of event in the next year. Event and mortality rates are adjusted for age and sex and updated in each cycle of the cost-effectiveness analysis (Table S3). py = person year, NA = not available

TABLE S2 CUA inputs: Cardiovascular event fatality event rates

	Age group (year)						
	0-44	45-55	55-64	65-74	75-84	85-94	≥95
Myocardial infarction							
Men	1.8%	2.3%	4.2%	8.7%	17.8%	37.2%	61.4%
Women	2.6%	2.7%	4.9%	8.9%	17.8%	34.5%	56.1%
Stroke							
Men	6.5%	7.2%	9.3%	13.9%	23.5%	40.9%	57.9%
Women	6.2%	8.3%	11.5%	14.6%	23.7%	40.8%	61.8%
Heart failure							
Men	12.0%	12.8%	15.8%	23.0%	36.1%	52.7%	67.7%
Women	9.9%	11.4%	17.5%	21.7%	30.7%	46.1%	62.2%

Case fatality rates based on publicly available data for 2021 from Statistics Netherlands and Dutch Hospital Data. Obtained from https://www.hartenvaatcijfers.nl/ on June 16th, 2023.

TABLE S3 CUA inputs: Age- and sex-adjustment factors for cardiovascular event and all-cause mortality risk

Age (year)	Event risk		Mortality risk	
	Women	Men	Women	Men
41	0.2	0.2	0.3	0.4
42	0.2	0.3	0.3	0.4
43	0.2	0.3	0.3	0.5
44	0.3	0.3	0.4	0.5
45	0.3	0.3	0.4	0.5
46	0.3	0.4	0.4	0.5
47	0.3	0.4	0.4	0.6
48	0.4	0.4	0.5	0.6
49	0.4	0.5	0.5	0.7
50	0.4	0.5	0.5	0.7
51	0.5	0.6	0.6	0.8
52	0.5	0.6	0.6	0.8
53	0.5	0.7	0.6	0.9
54	0.6	0.7	0.7	0.9
55	0.7	0.8	0.7	1.0
56	0.7	0.9	0.8	1.0
57	0.8	1.0	0.8	1.1
58	0.8	1.0	0.9	1.2
59	0.9	1.1	0.9	1.2
60	1.0	1.2	1.0	1.3
61	1.1	1.3	1.1	1.4
62	1.2	1.5	1.1	1.5
63	1.3	1.6	1.2	1.6
64	1.4	1.7	1.3	1.7
65	1.5	1.9	1.4	1.8
66	1.7	2.1	1.5	1.9
67	1.8	2.3	1.6	2.1
68	2.0	2.5	1.7	2.2
69	2.2	2.7	1.8	2.4
70	2.4	2.9	1.9	2.5
71	2.6	3.2	2.0	2.7
72	2.8	3.5	2.1	2.9
73	3.0	3.8	2.3	3.0

TABLE S3 (Continued)

Age (year)	Event risk		Mortality risk	
	Women	Men	Women	Men
74	3.3	4.1	2.4	3.2
75	3.6	4.5	2.6	3.4
76	3.9	4.9	2.8	3.7
77	4.3	5.3	2.9	3.9
78	4.7	5.8	3.1	4.2
79	5.1	6.3	3.3	4.4
80	5.5	6.9	3.6	4.7
81	6.0	7.5	3.8	5.0
82	6.6	8.1	4.0	5.4
83	7.2	8.9	4.3	5.7
84	7.8	9.7	4.6	6.1
85	8.5	10.5	4.9	6.5
86	9.3	11.5	5.2	6.9
87	10.1	12.5	5.5	7.4
88	11.0	13.6	5.9	7.9
89	12.0	14.8	6.3	8.4
90	13.1	16.1	6.7	8.9
91	14.2	17.6	7.1	9.5
92	15.5	19.2	7.6	10.1
93	16.9	20.9	8.1	10.8
94	18.4	22.7	8.6	11.5
95	20.0	24.8	9.2	12.3
96	21.8	27.0	9.8	13.1
97	23.8	29.4	10.5	13.9
98	25.9	32.0	11.1	14.8
99	28.2	34.9	11.9	15.8
100	30.8	38.0	12.6	16.8

Age and sex-specific adjustment factors for annual risk of recurrent cardiovascular events and all-cause mortality

TABLE S4 CUA inputs: Costs

Item	Cost*	Range	Source	Ref.
Chronic care costs				
Coronary artery disease	€ 2,092	€ 1,569 - € 2,615	Registry	6
Cerebrovascular disease	€ 2,985	€ 2,239 - € 3,731	Registry	6
Peripheral artery disease	€ 3,752	€ 2,814 - € 4,690	Registry	6
Chronic heart failure	€ 2,500	€ 1,875 - € 3,125	Registry	6
Lifestyle intervention costs				
Mediterranean diet intervention				
Face-to-face counselling (2)	€ 83	€ 62 - € 104	CEA manual	7
Group session (4)	€ 11	€ 8 - € 13	CEA manual	7
Telephone call (6)	€ 125	€ 93 - € 156	CEA manual	7
Food provision	€ 140	€ 105 - € 175	RCT	4
Scenario: Incremental MD costs	*€ 1,394*	*NA†*	Observational	8
Scenario: Full MD costs	*€ 3,977*	*NA†*	Observational	8
Physical activity intervention				
Year 1				
Intake with GP (1)	€ 121	€ 106 - € 177	CEA manual	7
Consultation with GP (11)	€ 887	€ 748 - € 1,246	CEA manual	7
Group session (5)	€ 40	€ 30 - € 50	CEA manual	7
Scenario: Sports club membership	*€ 637*	*NA†*	*Registry*	9
Year ≥ 2				
No further intervention	€ 0	€ 0 - € 0	CEA manual	7
Scenario: Sports club membership	*€ 637*	*NA†*	*Registry*	9
Event costs				
Revascularization	€ 21,258	€ 15,943 - € 26,572	RCT	10
Myocardial infarction	€ 6,348	€ 4,761 - € 7,935	CEA manual	7
Stroke	€ 17,342	€ 13,006 - € 21,677	RCT	11
Major adverse limb event	€ 9,170	€ 6,878 - € 11,463	RCT	12
Hospitalization for heart failure	€ 5,614	€ 4,210 - € 7,017	RCT	13
Death (last year of life)	€ 1,557	€ 1,168 - € 1,946	Observational	14

All costs were adjusted to reflect the January 2022 price level using the Dutch price indices as a reference. Numbers between brackets indicate the number of visits, for example *Group session (4)* indicates 4 group sessions per year. CEA = cost-effectiveness analysis, GP = general practitioner, RCT = randomized controlled trial. * Costs for chronic care and the lifestyle interventions are presented as costs/year. Costs for events are incurred as a lump sum in the cycle that the event occurs. † No range provided for costs of the scenario analysis as these were not included in the univariate or probabilistic sensitivity analyses.

TABLE S5 CUA inputs: Utilities

Item	Utility	95%CI	QoL tool	Ref.
Baseline utility, per health state				
Coronary artery disease	0.629	0.603 ; 0.654	EQ-5D	[15]
Cerebrovascular disease	0.523	0.485 ; 0.561	EQ-5D	[15]
Peripheral artery disease	0.642	0.586 ; 0.698	EQ-5D	[15]
Chronic heart failure	0.493	0.455 ; 0.531	EQ-5D	[15]
Disutility				
Patient characteristics				
Age (per year)	-0.0003	-0.001 ; 0.00005	EQ-5D	[15]
Male sex	0.001	-0.0002 ; 0.002	EQ-5D	[15]
Events				
Revascularization	-0.08	-0.100 ; -0.070	EQ-5D	[16]
Myocardial infarction	-0.147	-0.184 ; 0.110	EQ-5D	[17]
Stroke	-0.178	-0.223 ; -0.134	EQ-5D	[17]
Major adverse limb event	-0.12	-0.150 ; -0.090	TTO, SG	[18]
Hospitalization for heart failure	-0.105	-0.116 ; -0.094	EQ-5D	[19]

Utilities for health states and disutility of age, sex and (cardiovascular) events. QoL = Quality of Life, EQ-5D = EuroQOL- 5 dimension, TTO = time trade-off, SG = standard gamble
* 95%CI not available, assumed range -25% and +25% of the reported value.

TABLE S6 Baseline characteristics of the 100,000 patients sampled from the UCC-SMART cohort, stratified for CVD manifestation

	UCC-SMART cohort	CVD MANIFESTATION		
		CAD	CeVD	PAD
	N = 100,000	*N = 65,946*	*N = 29,223*	*N = 17414*
Age, yr	62 ±8.7	63 ±8.5	63 ±9	62 ±9.1
Male sex	73,792 (74)	53,174 (81)	18,837 (65)	11,756 (68)
Coronary artery disease	65,946 (66)	65,946 (100)	6,120 (21)	4,945 (28)
Cerebrovascular disease	29,223 (29)	6,120 (9)	29,223 (100)	2,354 (14)
Peripheral arterial disease	17,414 (17)	4,945 (8)	2,354 (8)	17,414 (100)
Diabetes	18,289 (18)	13,022 (20)	4,988 (17)	3,694 (21)
Smoking	0 (0)	0 (0)	0 (0)	0 (0)
Never	23,595 (24)	16,496 (25)	6,987 (24)	1,709 (10)
Former	49,265 (49)	35,335 (54)	13,869 (48)	7,007 (40)
Current	27,025 (27)	14,096 (21)	8,317 (29)	8,652 (50)
Exercise				
No exercise	61,032 (61)	38,801 (59)	18,620 (64)	12,639 (73)
≥ 7.5 METh/wk	29,760 (30)	20,895 (32)	7,936 (27)	3,581 (21)
Among exercisers, METh/wk	14 [8.0-24]	15 [8.0-25]	14 [7.5-24]	14 [7.8-24]
Dietary intake				
Daily energy intake, *kcal*	1,913 [1,452-2,393]	1,949 [1,488-2,394]	1,822 [1,314-2,357]	1,897 [1,493-2,466]
MEDAS score (max 14)	3 [2-4]	3 [2-4]	4 [3-5]	4 [2-5]
Body mass index, *kg/m2*	27 ±4.6	27 ±4.8	27 ±4.1	26 ±4.2

TABLE S6 (Continued)

	UCC-SMART cohort	CVD MANIFESTATION		
		CAD	CeVD	PAD
Systolic blood pressure, *mmHg*	139 ±21	137 ±20	142 ±22	145 ±21
Diastolic blood pressure, *mmHg*	81 ±11	80 ±11	82 ±12	81 ±11
Total cholesterol, *mmol/l*	4.5 [3.8-5.4]	4.3 [3.7-5.1]	4.7 [4.0-5.7]	5.2 [4.3-6.0]
HDL-cholesterol, *mmol/l*	1.2 [1.0-1.4]	1.1 [1.0-1.4]	1.2 [1.0-1.5]	1.2 [0.9-1.4]
LDL-cholesterol, *mmol/l*	2.5 [2.0-3.3]	2.4 [1.9-3.1]	2.7 [2.1-3.5]	3.1 [2.2-3.9]
Triglycerides, *mmol/l*	1.4 [1.0-2.0]	1.4 [1.0-2.0]	1.3 [0.9-1.9]	1.5 [1.1-2.3]
eGFR, *ml/min/1.73m2*	78 [66-90]	78 [66-89]	77 [63-89]	77 [63-89]
Lipid-lowering medication	73,004 (73)	54,838 (83)	18,324 (63)	9,307 (53)
BP-lowering medication	78,481 (79)	59,636 (90)	18,984 (65)	10,190 (59)
Antiplatelets	80,529 (81)	58,084 (88)	21,963 (75)	10,618 (61)

Baseline characteristics of the 100,000 participants sampled from the UCC-SMART cohort stratified for type of CVD at baseline. Data are presented as number (percentage), mean ± standard deviation or median [interquartile range]. CAD: Coronary artery disease, CeVD: Cerebrovascular disease, PAD: Peripheral artery disease, MEDAS: Mediterranean diet adherence screener, HDL: high-density lipoprotein, LDL: low-density lipoprotein, eGFR: estimated glomerular filtration rate. * Data on dietary intake was available for 2,227 participants. † Estimated using CKD-EPI creatinine formula

TABLE S7 Results of scenario and sensitivity analyses

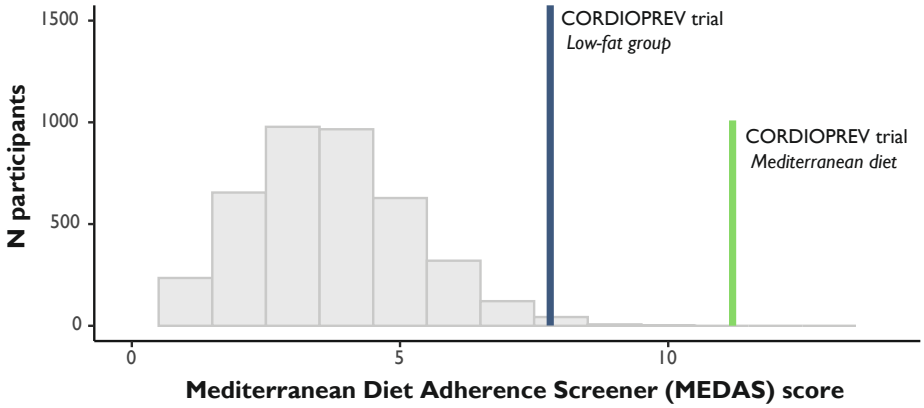
Scenario	Incremental costs (€)	Incremental utility (QALY)	WTP €20,000		WTP €50,000		
			INMB (€)	INHB (QALY)	INMB (€)	INHB (QALY)	ICER (€ / QALY)
Base case	**€ -1,236**	**1.98**	**€ 40,757**	**2.04**	**€ 100,037**	**2.00**	**€ -626**
Univariate sensitivity analyses							
Mortality rate – 25%	€ -2,927	1.98	€ 42,464	2.12	€ 101,769	2.04	€ -1,481
Mortality rate + 25%	€ -212	1.95	€ 39,300	1.97	€ 97,933	1.96	€ -109
Event rate – 25%	€ 166	1.99	€ 39,559	1.98	€ 99,145	1.98	€ 84
Event rate + 25%	€ -2,048	1.97	€ 41,395	2.07	€ 100,415	2.01	€ -1,041
Costs – 25%	€ -979	2.00	€ 41,018	2.05	€ 101,075	2.02	€ -489
Costs + 25%	€ -1,520	1.97	€ 40,876	2.04	€ 99,912	2.00	€ -772
Utility at lower limit 95%CI	€ -1,240	1.90	€ 39,267	1.96	€ 96,309	1.93	€ -652
Utility at upper limit 95%CI	€ -1,113	2.05	€ 42,150	2.11	€ 103,704	2.07	€ -543
No discounting	€ 8,192	2.84	€ 48,661	2.43	€ 133,940	2.68	€ 2,882
Discounting costs and utility at 3%	€ -937	1.28	€ 26,481	1.32	€ 64,796	1.30	€ -734
Treatment effect at lower limit 95%CI	€ -5,083	3.29	€ 70,911	3.55	€ 169,653	3.39	€ -1,544
Treatment effect at upper limit 95%CI	€ 3,404	0.64	€ 9,489	0.47	€ 28,829	0.58	€ 5,280
Subgroup analyses							
Patients aged < 50y	€ 1,638	2.25	€ 43,316	2.17	€ 76,068	1.52	€ 729
Patients aged 50-75y	€ -2,927	1.98	€ 42,464	2.12	€ 102,797	2.06	€ -1,481
Patients aged ≥ 75y	€ -212	1.95	€ 39,300	1.97	€ 93,771	1.88	€ -109
Only CAD patients	€ 166	1.99	€ 39,559	1.98	€ 102,162	2.04	€ 84
Only CeVD patients	€ -2,048	1.97	€ 41,395	2.07	€ 85,676	1.71	€ -1,041
Only PAD patients	€ -979	2.00	€ 41,018	2.05	€ 110,747	2.21	€ -489

TABLE S7 (Continued)

Scenario	Incremental costs (€)	Incremental utility (QALY)	WTP €20,000		WTP €50,000		
			INMB (€)	INHB (QALY)	INMB (€)	INHB (QALY)	ICER (€ / QALY)
Base case	**€ -1,236**	**1.98**	**€ 40,757**	**2.04**	**€ 100,037**	**2.00**	**€ -626**
Decreasing treatment effects over time							
1% decrease per year	€ -776	1.63	€ 33,283	1.66	€ 82,043	1.64	€ - 477
5% decrease per year	€ 1,528	0.97	€ 17,806	0.89	€ 46,807	0.94	€ 1,581
10% decrease per year	€ 2,991	0.59	€ 8,710	0.44	€ 26,262	0.53	€ 5,111
Diet and exercise reimbursement							
No food or sports costs	€ -3,525	1.99	€ 43,274	2.16	€ 102,898	2.06	€ -1,774
Additional MED diet costs	€ 18,978	1.97	€ 20,449	1.02	€ 79,590	1.59	€ 9,627
Full MED diet costs	€ 60,586	1.99	€ -20,787	-1.04	€ 38,912	0.78	€ 30,446
Sports costs	€ 10,267	1.97	€ 29,221	1.46	€ 88,453	1.77	€ 5,200
Additional MED diet and sports costs	€ 30,344	1.96	€ 8,840	0.44	€ 67,616	1.35	€ 15,488
Full MED diet and sports costs	€ 72,302	2.01	€ -32,160	-1.61	€ 28,054	0.56	€ 36,023
Benefit-based treatment							
Threshold 0.5 CVD-free life years	€ -1,186	1.98	€ 40,727	2.04	€ 100,039	2.00	€ -600
Threshold 1.0 CVD-free life years	€ -1,291	1.99	€ 40,997	2.05	€ 100,557	2.01	€ -650
Threshold 1.5 CVD-free life years	€ -1,244	1.97	€ 40,696	2.03	€ 99,875	2.00	€ -631
Threshold 2.0 CVD-free life years	€ -1,231	1.97	€ 40,600	2.03	€ 99,654	1.99	€ -625
Threshold 2.5 CVD-free life years	€ -1,319	1.96	€ 40,489	2.02	€ 99,245	1.98	€ -673

Incremental costs and utility per person in different scenario and sensitivity analyses. QALY: quality adjusted life year, 95%CI: 95% confidence interval, CAD: coronary artery disease, CeVD: cerebrovascular disease, PAD: peripheral arterial disease, MED: Mediterranean, CVD: cardiovascular disease.

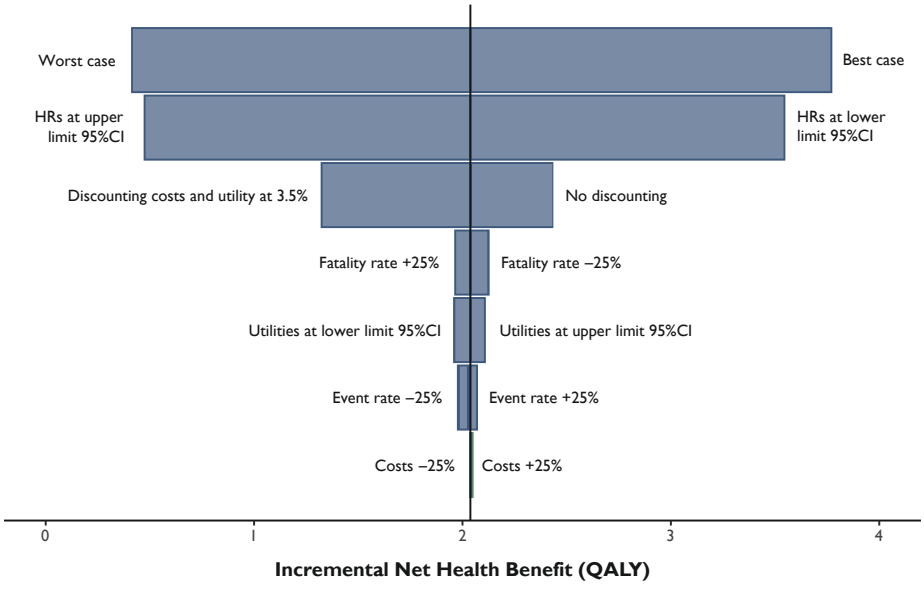
FIGURE S1 Distribution of adherence to the Mediterranean diet in the UCC-SMART study



Distribution of adherence to the Mediterranean diet in the UCC-SMART cohort. Dietary intake data with plausible reported energy intake was available for 2,046 participants. It was assumed that these were representative for the entire study population and that these results indicated that none of the patients in the UCC-SMART cohort was already compliant with a Mediterranean-style diet as achieved in the CORDIOPREV randomized controlled trial.

FIGURE S2 Sensitivity analyses – Net benefit

Univariate sensitivity analyses



Reimbursement for Mediterranean diet and physical activity costs

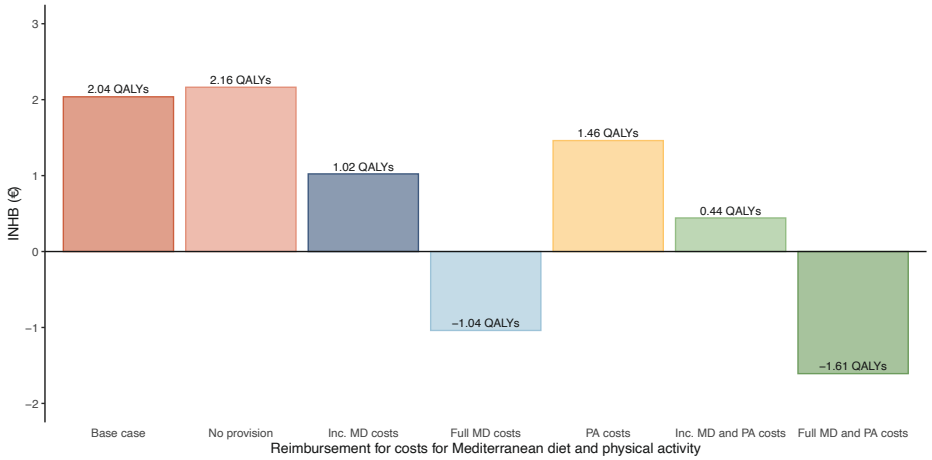
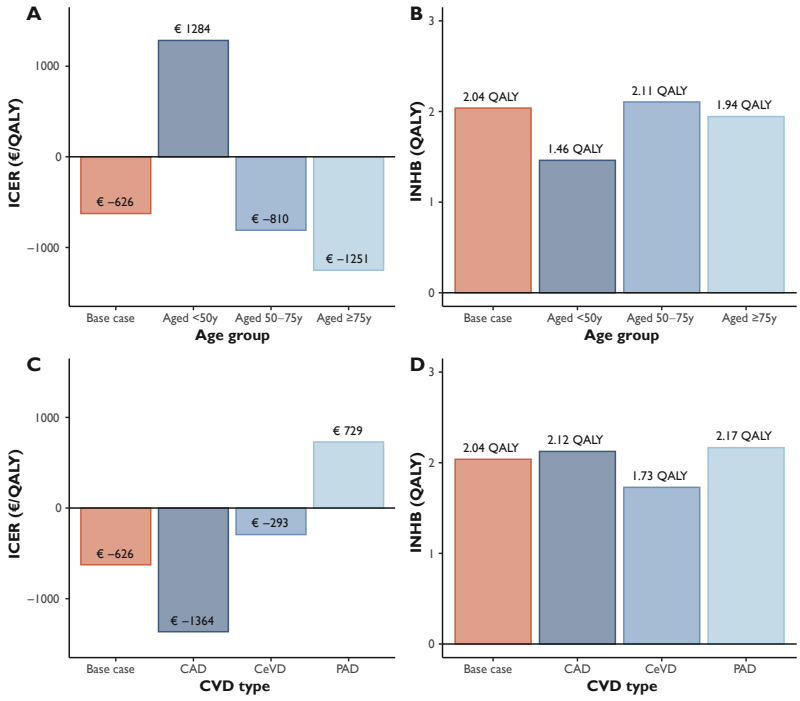
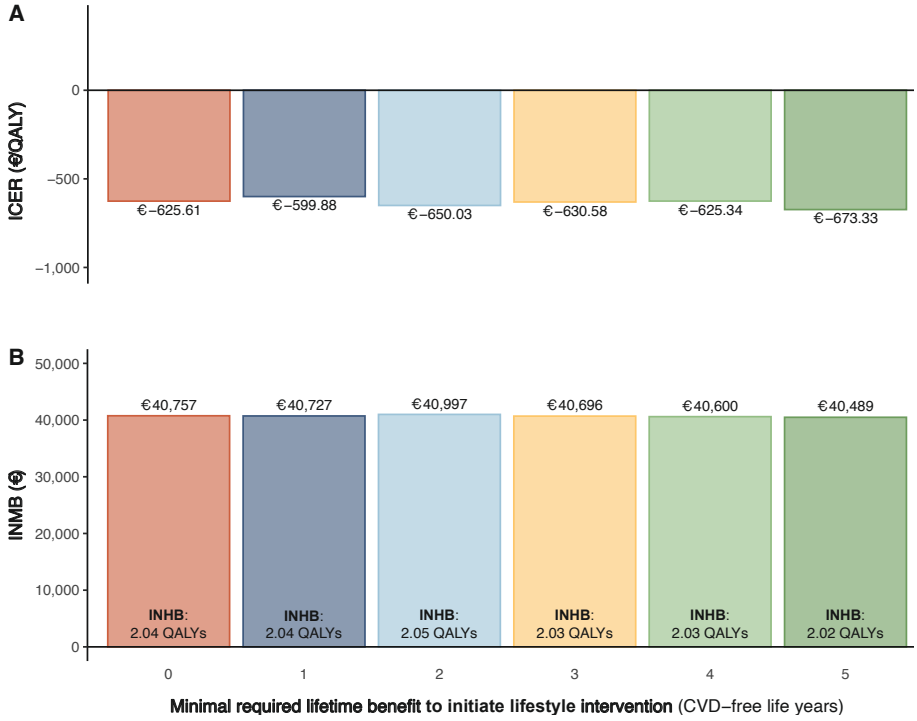


FIGURE S3 Subgroup analyses



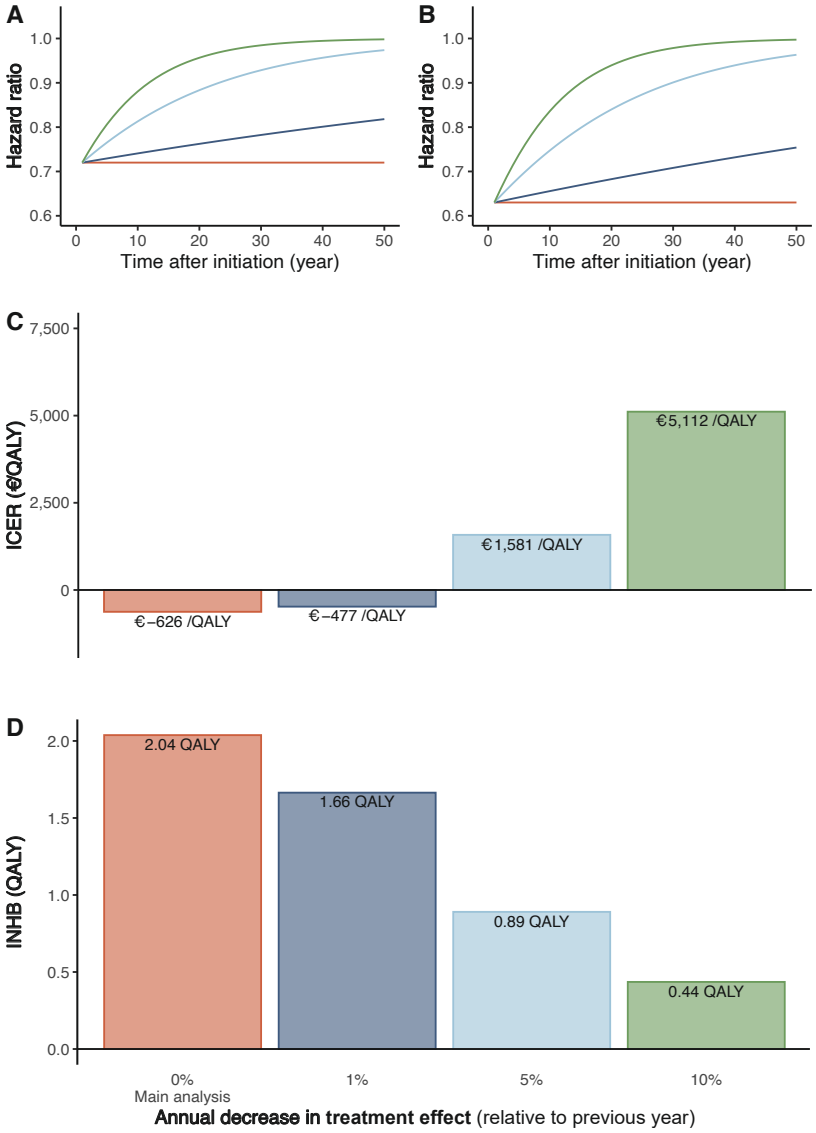
Cost-effectiveness results in subgroup. The ICER and INHB across age subgroups are shown in panels **A** and **B**. The ICER and INHB across subgroups with different CVD manifestations at baseline are shown in panels **C** and **D**. INHB was calculated for a willingness to pay of €20,000/QALY. ICER: Incremental cost-effectiveness ratio, INHB: Incremental Net Health Benefit, QALY: Quality-adjusted life year, MED: Mediterranean diet, PA: physical activity, CVD: cardiovascular disease

FIGURE S4 Lifetime benefit-based initiation of Mediterranean diet and physical activity interventions



In the base case analysis, all patients received both the Mediterranean diet and physical activity intervention. In this sensitivity analysis, these treatments were only given to patients when their expected lifetime benefit from that intervention exceeded a threshold value. Lifetime benefit was calculated by adding the treatment effects for Mediterranean diet and physical activity to the SMART-REACH model. Panel **A** presents ICERs, and panel **B** presents INMB. ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life year, MED: Mediterranean diet, PA: physical activity, CVD: cardiovascular disease

FIGURE S5 Cost-effectiveness of the combined lifestyle intervention for reducing treatment effect with time since treatment initiation



In the base case analysis, treatment effects for Mediterranean diet and physical activity were stable over time. In this sensitivity analysis, the treatment effects decreased as time passed since treatment initiation, with 1%, 5% or 10% compared to the year before. Panels **A** and **B** show the trajectory of the treatment effects for Mediterranean diet and physical activity in the years after treatment initiation. Panels **C** and **D** show the ICER and INHB for these scenarios. ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life year, MED: Mediterranean diet, PA: physical activity, CVD: cardiovascular disease

SUPPLEMENTAL REFERENCES

1. Hageman SHJ, Dorresteijn JAN, Bots ML, Asselbergs FW, Westerink J, van der Meulen MP, et al. Residual cardiovascular risk reduction guided by lifetime benefit estimation in patients with symptomatic atherosclerotic disease: effectiveness and cost-effectiveness. Eur J Prev Cardiol. 2022 Mar 30;29(4):635–44.
2. McNamara S, Schneider PP, Love-Koh J, Doran T, Gutacker N. Quality-Adjusted Life Expectancy Norms for the English Population. Value in Health. 2023 Feb;26(2):163–9.
3. Schröder H, Fitó M, Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, et al. A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. J Nutr [Internet]. 2011 Jun;141(6):1140–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21508208
4. Delgado-lista J, Alcala-diaz JF, Torres-peña JD, Quintana-navarro GM, Fuentes F, Garcia-rios A, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet. 2022;399:1876–85.
5. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. The Lancet. 2016 Oct;388(10056):2142–52.
6. National Institute for Public Health and the Environment. Kosten van ziekten - Cijferboek 2019 (Costs of disease study). 2019.
7. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Dutch National Health Care Institute. 2016;1–73.
8. Lopez CN, Martinez-Gonzalez MA, Sanchez-Villegas A, Alonso A, Pimenta AM, Bes-Rastrollo M. Costs of Mediterranean and western dietary patterns in a Spanish cohort and their relationship with prospective weight change. J Epidemiol Community Health (1978). 2009 Nov 1;63(11):920–7.
9. Statistics Netherlands. CBS Open data Statline. 2023.
10. Osnabrugge RL, Magnuson EA, Serruys PW, Campos CM, Wang K, van Klaveren D, et al. Cost-effectiveness of percutaneous coronary intervention versus bypass surgery from a Dutch perspective. Heart. 2015 Dec 15;101(24):1980–8.
11. van Eeden M, van Heugten C, van Mastrigt GAPG, van Mierlo M, Visser-Meily JMA, Evers SMAA. The burden of stroke in the Netherlands: estimating quality of life and costs for 1 year poststroke. BMJ Open. 2015 Nov 27;5(11):e008220.
12. van den Houten MML, Lauret GJ, Fakhry F, Fokkenrood HJP, van Asselt ADI, Hunink MGM, et al. Cost-effectiveness of supervised exercise therapy compared with endovascular revascularization for intermittent claudication. British Journal of Surgery. 2016 Nov 1;103(12):1616–25.
13. Stevanovic J, Denee L, Koenders JM, Postma MJ. Incidence Description and Costs of Acute Heart Failure in the Netherlands. Value in Health. 2014 Nov;17(7):A328.
14. Polder JJ, Barendregt JJ, van Oers H. Health care costs in the last year of life—The Dutch experience. Soc Sci Med. 2006 Oct;63(7):1720–31.

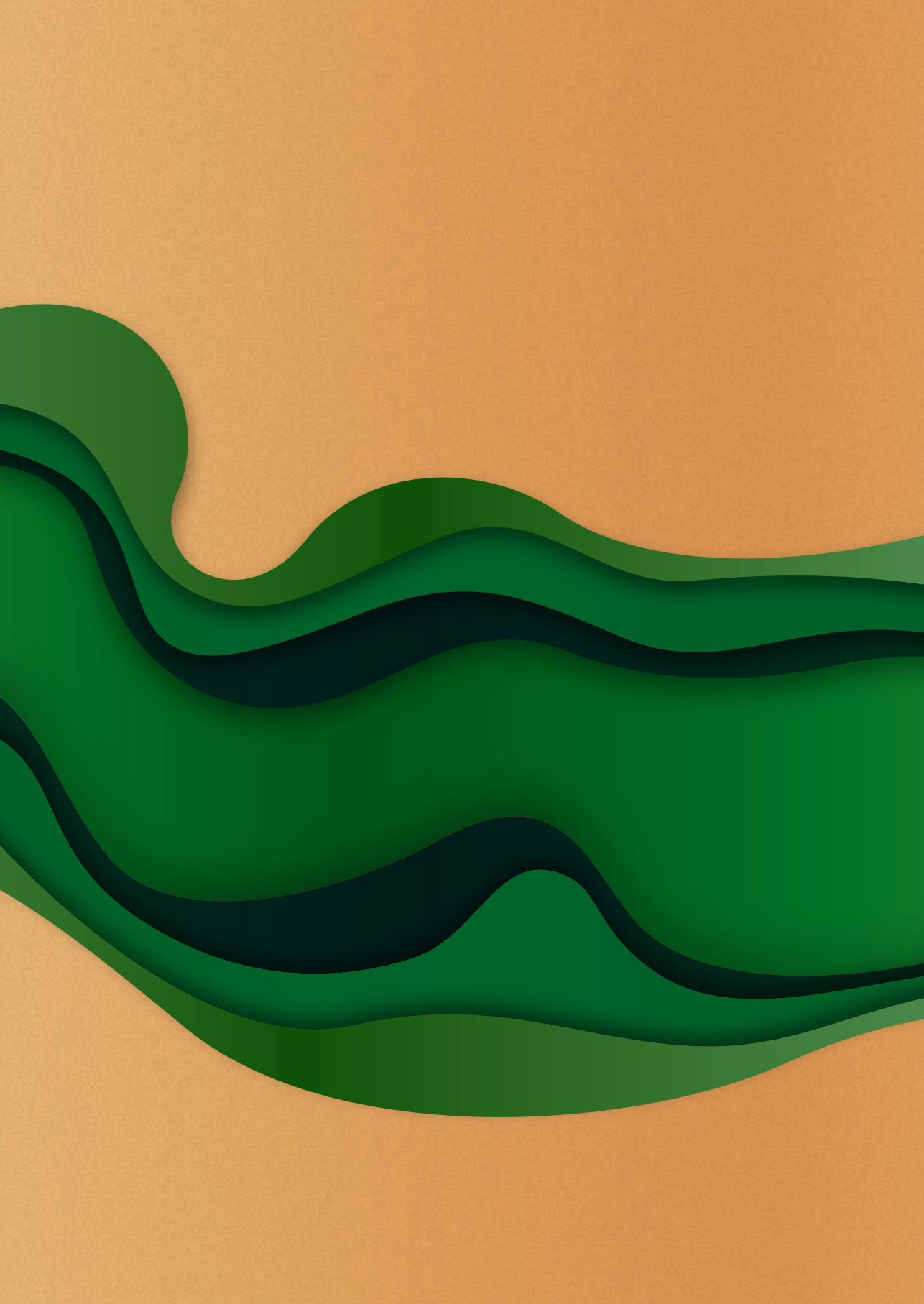
15. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D Scores for the United Kingdom. Medical Decision Making. 2011 Nov 21;31(6):800–4.

16. Cohen DJ, Van Hout B, Serruys PW, Mohr FW, Macaya C, den Heijer P, et al. Quality of Life after PCI with Drug-Eluting Stents or Coronary-Artery Bypass Surgery. New England Journal of Medicine. 2011 Mar 17;364(11):1016–26.

17. Nyman JA, Barleen NA, Dowd BE, Russell DW, Coons SJ, Sullivan PW. Quality-of-Life Weights for the US Population. Med Care. 2007 Jul;45(7):618–28.

18. Davies EW, Matza LS, Worth G, Feeny DH, Kostelec J, Soroka S, et al. Health state utilities associated with major clinical events in the context of secondary hyperparathyroidism and chronic kidney disease requiring dialysis. Health Qual Life Outcomes. 2015 Dec 30;13(1):90.

19. McMurray JJ V, Trueman D, Hancock E, Cowie MR, Briggs A, Taylor M, et al. Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. Heart. 2018 Jun;104(12):1006–13.



CHAPTER 12

GENERAL DISCUSSION

In this thesis, the overarching aims were to evaluate dietary habits and physical activity levels as risk factors for the recurrence of cardiovascular events in patients with established cardiovascular disease (CVD) or type 2 diabetes (T2D) and as potential targets for interventions to mitigate residual cardiovascular risk. To broaden the scope of this thesis's key findings and explore their relevance for clinical management of these high-risk populations, several topics merit further discussion.

LIFESTYLE OPTIMIZATION IN CVD PREVENTION

The Mediterranean diet: just another healthy diet or solution for all?

The Mediterranean diet is one of the most widely advocated dietary patterns to prevent (recurrent) cardiovascular events.[1–3] The Mediterranean diet has repeatedly been shown to reduce cardiovascular event risk both in primary and secondary CVD prevention.[4–7] Its benefits are attributed to an increased intake of polyphenols, mono- and polyunsaturated fatty acids, and fibre. The components are believed to yield several positive outcomes, including weight loss, enhanced insulin sensitivity, a less atherogenic lipid profile, defence against oxidative stress, and a reduction of low-grade systemic inflammation.[8,9] In **Chapter 5** of this thesis, the relative contribution of these potential mediators was assessed and we found that only a small proportion of Mediterranean diet's benefits could be explained by changes in these risk factors but that systemic inflammation levels were indeed an important mediator. Although many other dietary patterns exist and are recommended for CVD prevention, this thesis mainly focused on the Mediterranean diet due to its extensive evaluation in long-term cardiovascular outcome trials such as the Lyon Diet Heart study, the PREDIMED study and the CORDIOPREV trial which consistently demonstrated a protective effect of the Mediterranean diet compared to a reference diet and due to the central place the Mediterranean diet holds in CVD prevention guidelines.[1–6,10]

While the evidence for the Mediterranean diet is compelling, it may be overly simplistic to universally recommend this diet to all CVD patients. The available randomized controlled trials (RCTs) used low-fat, high carbohydrate diets as reference diet. Historically, these low-fat diets were recommended as the optimal dietary approach for preventing cardiovascular disease, based on the diet-heart hypothesis, which posited that dietary saturated fat raises cholesterol levels and contributes to CVD.[11] However, since the beginning of the 21st century the diet-heart hypothesis has been re-evaluated

and largely discarded.[12,13] Instead, recent evidence suggests that substituting saturated fatty acids for unsaturated fatty acids is beneficial and that low-fat, high-carbohydrate diets are associated with increased risk of CVD, especially when carbohydrate content exceeds 60% of total energy intake.[14] Therefore, the choice of control diet in the available Mediterranean diet RCTs could have led to an overestimation of the beneficial effect. In reality, the relative risk reduction achieved through a Mediterranean diet intervention might be closer to the 10-20% reductions that are frequently reported in observational studies (**Chapter 5**),[15,16] instead of the up to 70% reductions as reported in the Lyon Diet Heart study.[4]

Furthermore, it should be considered that the aforementioned Mediterranean diet trials were all conducted in Mediterranean countries[4–6] and it is unclear whether similar protective effects could be realized in populations with culturally different dietary habits. The beneficial effects of a Mediterranean diet appear to be larger in Mediterranean countries[15] and compliance with a Mediterranean-style diet in non-Mediterranean countries is generally poor,[17] as was also described in **Chapters 5** and **10**. A sufficiently high degree of adherence needs to be achieved to result in health benefits (**Chapter 5**,[15]). Possible barriers that prevent adherence to a Mediterranean diet include societal norms, costs, availability of dietary products and individual preferences and tastes. Considering that other dietary patterns exert similar effects on cardiovascular risk factors when compared to the Mediterranean diet (**Chapters 3** and **4**), and supported by existing observational evidence [18], it is reasonable to suggest that alternative dietary patterns might also substantially reduce the risk of recurrent CVD events. These alternative diets could be easier to implement in non-Mediterranean countries and therefore have a larger societal health impact.

Ultimately, there is clear evidence that a Mediterranean diet is a healthy diet with the potential to reduce CVD event risk compared to a typical Western-style diet, however it is unclear how the Mediterranean diet compares to diets that are currently recommended in non-Mediterranean countries. It may therefore be overly simplistic to single out this specific dietary pattern as the optimal diet for CVD prevention. Mediterranean-style diets generally have a significant degree of overlap with other heart-healthy dietary patterns (*e.g.* emphasis on fruits and vegetables, discouragement of red meats). Existing literature and new insights into potential long-term benefit (**Chapter 10**) underscore the importance of integrating dietary considerations into (secondary) CVD prevention and that a Mediterranean diet is a promising option, but

other healthy dietary patterns may also be a viable alternative, especially if these align better with patient preferences or locally available food items.

What constitutes a heart-healthy diet?

What if a patient is unwilling or unable to adopt a Mediterranean-style diet, or if the necessary food items are not available? In such cases, what alternative dietary recommendations can be offered to enhance cardiovascular health? **Chapters 3** and **4** of this thesis were dedicated to network meta-analyses comparing the effects of seven dietary patterns to a minimal dietary intervention in people with CVD or T2D. Although the results indicated that all active dietary interventions had only modest effects on cardiovascular risk factors, all of them outperformed conventional diets although none emerged as a definitive standout. The modest effects of dietary interventions on cardiovascular risk factors could be explained by the high prevalence of use of lipid- and blood pressure medications, which is supported by larger effect sizes observed in apparently healthy populations.[10] The small effect on cardiovascular risk factors does not preclude a protective effect on cardiovascular event rates, possibly because the effects are mediated through alternative pathways (**Chapter 5**). In a network meta-analysis that assessed long-term efficacy of dietary patterns long-term benefits were observed for both primary ánd secondary CVD prevention populations.[10,19] It appears that, although adopting a healthy dietary diet in general is more beneficial then making no dietary changes at all, there may not be a one-size-fits-all optimal diet for lowering cardiovascular risk factors in CVD patients. The only exception might be a dietary patterns with reduced simple carbohydrate content that may exhibit greater efficacy in improving glycemic control for people with T2D (**Chapter 4**,[20]).

In previous trials, the DASH diet has been shown to effectively reduce systolic blood pressure and body weight [21,22] and DASH is recommended as a strategy to achieve blood pressure control in hypertensive patients. In **Chapter 6**, target trial emulation was used to investigate the relationship between compliance with the DASH diet and (cardiovascular) mortality in CVD patients. Surprisingly, this analysis did not find a significant association between DASH compliance and the risk of all-cause or cardiovascular mortality in this population, potentially due to limited contrast in the study groups or underestimation of sodium content. Remarkably, in CVD patients the relationship between DASH compliance and (cardiovascular) mortality was not mediated by blood pressure (**Chapter 5**). Use of concomitant blood pressure and lipid-lowering medications could have attenuated the benefits of dietary patterns that

have previously been shown to be highly effective in populations that do not use such medications.

While the dietary patterns explored in this thesis place specific emphasis on various dietary components, there appear to be some common principles that underlie a heart-healthy diet. All these diets recommend consuming high amounts of vegetables, fruits, and legumes, increasing fiber intake, limiting red (processed) meat consumption, avoiding sugar-sweetened beverages, and limiting salt and alcohol. Some elements, such as olive oil in the Mediterranean diet, low-fat dairy in the DASH diet, or avoiding all animal-based protein in a plant-based diet, are unique to their respective dietary patterns. However, when considering the shared components among these patterns, a clear set of guidelines for a heart-healthy diet becomes evident. Natural compliance with these components has been associated with reduced recurrent CVD risk[23] and in a model where such common recommendations are applied to apparently healthy individuals it is predicted that lifelong adherence to a healthy diet can yield a significant increase in life expectancy.[24] In **Chapter 10**, a similar approach was used to model individualized lifetime benefit of adopting a Mediterranean diet. In the future, this model could be expanded upon to include lifetime treatment effects for alternative heart-healthy dietary patterns or even diet components to aid further personalization of lifestyle optimization in CVD prevention.

Although not directly assessed in this thesis, the role of food processing deserves special mention in the context of CVD prevention. In recent years, there has been increasing attention for ultra-processed foods, which undergo multiple biological, chemical or physical processes before consumption. Most of these food items tend to offer low nutritional value, with minimal protein, vitamins or fibre content, but they are often high in refined sugar, sodium and saturated fatty acids content. Over the past decades, the consumption of ultra-processed foods has seen a significant increase and now constitutes almost 60% of daily energy intake in the United States.[25] Higher consumption of ultra-processed foods has been shown to increase body weight,[26] T2D incidence[27] and CVD event risk.[28,29] The healthful dietary patterns assessed throughout this thesis all tend to emphasize whole foods and avoiding ready-to-eat, store bought items. International guidelines on CVD prevention currently recommend lowering intake of processed foods, specifically processed meats, as a tool to lower sodium and *trans*-fatty acid intake.[1,3,30] Given the available evidence, it may be prudent to include stronger recommendations on avoiding ultra-processed food items in future

guidelines and to encourage patients to prepare their meals from whole foods as much as possible. Such guidance could provide patients with specific and easy-to-understand instructions for improving their dietary habits.

In summary, it appears that there may not be a single, universally optimal diet for promoting cardiovascular health. Nevertheless, there are several dietary components that can contribute to lowering cardiovascular event risk. While the Mediterranean diet stands as a widely recommended dietary approach for CVD prevention and has demonstrated promising results in multiple RCTs, patients unwilling to fully adopt a Mediterranean-style diet can consider a dietary regimen that includes ample fruits, vegetables, legumes, fish, and whole grains, while minimizing red meat consumption and avoiding ultra-processed foods. This approach serves as a promising starting point for optimizing dietary choices in secondary CVD prevention.

Is more physical activity always better?

International guidelines provide consistent recommendations for physical activity to enhance overall and cardiovascular health, advising individuals to engage in at least 150–300 minutes of moderate-intensity aerobic physical activity or 75–150 minutes of vigorous-intensity aerobic physical activity per week.[1–3,30–32] This serves as a minimal recommendation and patients are encouraged to recognize that additional benefits can be achieved with higher physical activity levels. In **Chapters 7** and **8**, a J-shaped association of metabolic equivalent task hours per week (METh/wk) and all-cause mortality and recurrent CVD events is observed which seemed to level off at around 50 METh/wk. Interestingly, this association was primarily driven by reductions in risk of non-fatal stroke and cardiovascular mortality and not by a reduction in non-fatal myocardial infarction risk. In fact, non-fatal myocardial infarction risk increased with higher physical activity risk. Potential explanations for this finding include that vigorous physical activity induces rupture of atherosclerotic plaques or arrhythmia in scarred myocardial tissue.[33,34]

These findings should not be taken as a reason for health care providers to be overly cautious when recommending vigorous physical activity for CVD patients. The associations observed in this thesis indicated that increased physical activity levels was associated with health benefits until relatively high physical activity levels that exceed the average physical activity levels in CVD patients.[35,36] Moreover, in **Chapter 9**, it was shown that only a small proportion of CVD patients increase their physical

activity level over time, while increasing physical activity over time appears to have a similar or even stronger impact on all-cause mortality and CVD mortality as smoking cessation. A meta-analysis involving nine prospective cohorts and over 33,000 CVD patients, indicated that becoming physically active was linked to a 50% lower mortality risk compared to those that stayed physically inactive. In **Chapter 10**, this significant risk reduction was translated to absolute risk reductions and lifetime benefits. For some patients, including those with heart failure, obesity or those with a high burden of cardiovascular risk factors, pre-participation screening may be considered to identify risk factors associated with high intensity physical activity and to create a personalized sports prescription.[37]

Does the type of physical activity matter?

Physical exercise is traditionally classified as either endurance or resistance training and both modalities are recommended for specific purposes.[37,38] Endurance training can be used to increase cardiorespiratory fitness or reduce subcutaneous fat mass,[39,40] while resistance training is effective to improve musculoskeletal functioning and glycemic control.[41,42] In **Chapter 8**, the relationship between resistance exercise and combined endurance-resistance training with risk of all-cause mortality and recurrent CVD event were compared in patients with established CVD and it was observed that both were associated with similar reductions in risk of these outcomes compared to not exercising. Consistent with previous literature, insulin resistance emerged as a stronger potential mediator for resistance training than for combined endurance-resistance training, possibly because resistance training is a strong stimulus for increased expression of GLUT-4 transporters in skeletal muscle, resulting in increased glucose uptake in skeletal muscles during exercise and improved glycogen storage in rest.[43]

Sports cardiology guidelines identify exercise intensity, measured as MET or energy expenditure per minute, as the most important determinant of exercise's cardiovascular benefits.[37,44] However, in **Chapter 8**, it was shown that the associations of light-moderate (MET 3-6) and vigorous exercise (MET >6) with cardiovascular outcomes was similar in strength, as long as a similar exercise volume (intensity * time spent on exercise) was achieved. The clinical implication of this finding is that it may not be necessary to council patients specifically on high-intensity exercise, but that low-intensity exercise may also suffice as long as patients spend sufficient time on that.

In **Chapter 8** we observed that mediating factors differed to some extent between different exercise types and intensities. For instance, resistance training's effects were mediated relatively more by insulin resistance, while LDL-cholesterol and systolic blood pressure emerged as important mediators of resistance-endurance training. This means that some types of physical exercise may be more suited for specific CVD patients given their specific cardiovascular risk profile. Future research could expand on the findings included in this thesis to achieve personalized exercise prescriptions that optimally tackle an individual patient's risk profile, e.g. a prescription of individualized combination of resistance and aerobic training.

Finally, the context in which physical activity is performed should be considered when evaluating a CVD patient's physical activity status. In apparently healthy populations, paradoxical findings on the health effects of leisure-time physical activity and occupational physical activity have been described over the last two decades.[45-47] Leisure-time physical activity is consistently associated with lower risk of a range of health outcomes, but neutral or harmful associations have been found for increasing occupational physical activity levels. In **Chapter 7** of this thesis, we assessed these paradoxical associations in patients with established CVD and similarly found that high occupational physical activity levels were not associated with lower risk of all-cause mortality, recurrent cardiovascular event or incident T2D. It appears that the so called *physical activity paradox* also holds in patients with established CVD. Potential explanations for these contrasting effects of occupational and leisure-time physical activity include that occupational physical activity comprises repetitive movements with little recovery time, as well as increased resting heart rate and static posture associated with physically demanding occupations.[48] However, methodological limitations of physical activity research should also be considered when assessing these associations. Residual confounding, e.g. from social-economic position, smoking behaviour, or shift work, could at least partially explain why higher occupational physical is associated with increased risk of some health outcomes. For clinical practice, it is important that health care providers distinguish leisure-time and occupational physical activity. Based on the available evidence it appears that high occupational activity should not be considered a substitute for leisure-time physical activity and health care providers should encourage their patients to meet leisure-time physical activity targets regardless of the intensity of physical activity required by their job.

IMPLEMENTING HEALTHY LIFESTYLE IN CVD MANAGEMENT

Should we wait for more trial evidence?

Within the hierarchy of clinical evidence and evidence-based medicine, randomized controlled trials (RCTs) hold a prominent position. In cardiovascular medicine, long-term cardiovascular outcome trials that directly assess the impact of a new treatment on the occurrence of cardiovascular events, are generally seen as a requirement for including such a treatment in clinical guidelines for CVD management and reimbursement. However, performing a long-term cardiovascular outcome trial on dietary or physical activity interventions can be a challenging proposition. Such trials are resource-intensive, require several years to yield conclusive results, and may be difficult to design in such a way that they are representative of routine clinical practice, for example because of the inability to blind participants to their treatment assignment. Consequently, there are few RCTs available that assess the long-term effect of dietary interventions in CVD management. For physical activity interventions such a trial has never even been conducted. This raises the question: should we await more cardiovascular outcome trials before firmly establishing the central role of lifestyle interventions in CVD management?

Observational studies on the relationship between lifestyle behaviours and cardiovascular outcomes are abundant and consistently indicate that both healthy diets and physical activity are associated with decreased CVD risk in a secondary prevention population (e.g. **Chapters 2**, **7** and **8)**[31,49]. However, it is important to realize that observational evidence cannot be directly translated to an expected effect of an active intervention to change lifestyle behaviour. Observational data inherently suffers from potential sources of bias, such as residual confounding and reverse causation, which could lead to an overestimation of the association and prevents causal interpretation of study findings. Evidence from shorter-term RCTs that have assessed the effect on cardiovascular risk factors indicates that risk factors can be ameliorated through lifestyle changes (**Chapters 3** and **4**, [50]). However, it is challenging to directly translate change in risk factor levels to cardiovascular event risk, as a large part of the effects of healthy diet and physical activity are not mediated through traditional risk factors (**Chapters 5** and **8**). In summary, the available evidence points toward a beneficial effect of lifestyle optimization, but the evidence is currently insufficient to provide an exact estimate of the impact of these interventions.

While long-term RCTs are the gold standard, a balance needs to be struck between waiting for the highest level of evidence and acting upon the substantial and compelling data that already supports a healthy lifestyle. The current short-term experimental evidence and extensive body of observational evidence should not be ignored and together make a strong case for implementing physical activity interventions, which is supported by the few long-term cardiovascular outcome trials that are out there.[4–6,51] Based on the current evidence, the balance is strongly leaning towards a beneficial effect of lifestyle change in secondary CVD prevention with limited adverse effects and this should therefore be recommended to these patients. However, this does not mean that long-term trials are no longer necessary. Questions remain on the actual size of risk reductions achievable through lifestyle change and previous studies have shown that reliance on observational evidence alone is not sufficient to draw conclusions on effectiveness of interventions, *e.g.* therapy targeted at increasing HDL-cholesterol or oestrogen-replacement therapy.[52,53] In future, trials should be performed to assess the long-term effects of physical activity intervention and to compare a Mediterranean diet to a more valid reference diet, such as current guideline diets. Pragmatically, a combination of evidence-based interventions and ongoing research may provide the most beneficial approach to improve the health of CVD patients.

Do lifestyle interventions measure up to pharmacological advances?

Ultimately, the goal of secondary CVD prevention is to lower the risk of recurrent cardiovascular events as much as possible, regardless of approach used to achieve this reduction.[1] Lifestyle optimization should therefore not be a goal in itself, but regarded as one of several tools available to address recurrent CVD event risk. Changing dietary and physical activity habits is notoriously difficult and it might seem easier to prescribe cardiovascular medications that effectively reduce cardiovascular risk, such as blood pressure- or lipid-lowering drugs. However, most patients with established CVD are at a (very) high risk of recurrent risk, resulting in a significant residual risk even after pharmacological interventions have been employed. Lifestyle interventions are one of the potential approaches to tackle this residual risk. **Chapter 10** demonstrates that lifestyle optimization results in clinically meaningful reductions in 10-year cardiovascular event risk and survival free of recurrent CVD, even when added on top of pharmacological treatment in accordance with the 2021 ESC guideline on CVD prevention's STEP 1 goals (smoking cessation, systolic blood pressure between 130-140 mmHg, LDL-cholesterol <1.8 mmol/l and use of antithrombotic therapy). Furthermore, it is important to consider that the benefits of a healthy lifestyle extend

beyond CVD and that healthy dietary and physical activity habits are also associated with risk of other diseases, including several types of cancer, T2D, kidney failure and neurodegenerative diseases (**Chapter 7**).[7,38,54–56] Given the overlap in risk factors for developing CVD and cancer,[57] patients with established CVD are often also at high cancer risk. Therefore, it may be prudent to recommend lifestyle interventions to all CVD patients, regardless of their residual CVD risk.

Health care costs are also an important aspect to consider when choosing between different therapeutic strategies. As was shown in **Chapter 11**, a combined dietary and physical activity intervention is a highly cost-effective strategy in secondary CVD prevention. Compared to usual care, a combined Mediterranean diet and physical activity intervention was expected to increase life expectancy and quality of life, while health care costs were reduced. Previous cost-effectiveness analyses of dietary interventions and cardiac rehabilitation yielded similar highly cost-effective results compared to usual care.[58–60] The main driver of the cost-effective results are the relatively low costs of lifestyle interventions compared to pharmacological interventions. For instance, the incremental cost-effectiveness ratio (ICER) for SGLT2 inhibitors and GLP1-RA compared to standard CVD care have been estimated at approximately €130,000 per QALY gained[61,62] versus the dominant ICER of -€600/QALY gained reported in **Chapter 11**. Other pharmacological options to treat residual cardiovascular risk, such as proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibition, intensive blood pressure-lowering or combined low-dose rivaroxaban and aspirin, are also much less cost-effective compared to a lifestyle intervention.[63–65] Because CVD is highly prevalent, the budget impact of implementing a lifestyle intervention to lower residual risk for all patients with established CVD is expected to be very large.

The big question: How to improve adherence to lifestyle interventions?

Lifestyle optimization has been a central recommendation for CVD management for decades, but in practice very few patients comply with lifestyle recommendations. In **Chapter 2** and **8**, we observed that Dutch CVD patients comply very poorly with recommendations on healthy diet and physical exercise. This is in line with international reports on healthy lifestyle behaviour in the European Union and the United States of America.[35,66] Furthermore, in **Chapter 9**, it was shown that the majority of CVD with an unhealthy lifestyle was unable to achieve lifestyle optimization as recommended in CVD prevention guidelines after a follow-up of 10 years. Potential causes include

patient motivation, health care providers' lack of time for and knowledge of lifestyle counselling, a obesogenic environment and cultural differences.[67] Increased costs associated with compliance to lifestyle recommendations, such as higher expenses for food items and sport club memberships, can pose an additional barrier for some patients.[68,69] In **Chapter 11**, we explored the cost-effectiveness of lifestyle intervention when these additional costs were partially or fully reimbursed and found that even with full compensation for food and exercise costs, the lifestyle intervention remained cost-effective compared to usual care. This is an important signal to health policy makers and provides a direct target that could help patients in adopting a healthier lifestyle.

Several strategies are being employed to improve dietary and physical activity habits in the general population, such as changing food environments, providing financial stimuli or engaging the employer to create a healthier work environment. Online tools have emerged as valuable assets to improve personalized cardiovascular risk prediction and to select treatment strategies that are most beneficial and best suited to individual patients' risk factors and preferences. These tools can be useful to translate relative treatment effects as reported in clinical trials, into more tangible, absolute measures of treatment benefits such as absolute 10-year risk reduction or increase in life expectancy free from recurrent cardiovascular events.[70] In **Chapter 10**, treatment effects for interventions targeted at a Mediterranean-style diet and increased physical activity were included in the guideline-recommended SMART-REACH model.[1,71] This model demonstrated that lifestyle interventions are expected to result in significant CVD risk reductions for all patients with established CVD, but that these are most pronounced in younger patients and patients at high predicted lifetime CVD risk. When these personalized lifestyle benefit calculations become available in online tools, they can be used to aid the shared decision making process and motivate patients and health care provider alike to incorporate lifestyle changes in the treatment strategy to prevent recurrent cardiovascular events. For the future, it would be very interesting to expand upon the treatment effects incorporated in **Chapter 10** and to incorporate a range of heart-healthy diets and physical activity regimes in the models and assess effectiveness of such interventions for improving lifestyle behaviours in clinical trials. This could be used to further improve adherence to lifestyle interventions, as patients would be able to gain more insight in the trade-off between choosing a lifestyle that aligns with their current preferences and an optimally beneficial lifestyle that requires more drastic behavioural changes.

CHALLENGES IN LIFESTYLE RESEARCH

Observational research: pitfalls and promises

The majority of lifestyle-related research follows an observational study design, which inherently introduces potential sources of bias that could affect study findings.[72] In lifestyle-related research, some of these biases deserve special consideration.

One of the prominent sources of bias is selection bias, which occurs when the study population is not representative of the target population.[72] In the context of lifestyle-related research, participants with a pronounced interest in physical activity or dietary habits might be more inclined to enrol, while those with unhealthy lifestyle behaviours may be less willing to participate. For instance, in **Chapter 2**, the response rate to a food frequency questionnaire was lower among CVD patients with lifestyle-related comorbidities such as obesity or T2D. Selection bias may influence study results, but is especially of concern when translating study findings to clinical practice, as the observed relationships may not hold in people that were underrepresented in study populations.

Lifestyle is a highly complex determinant that not only encompasses dietary and physical activity habits, but also other factors such as smoking behaviour, alcohol consumption, sleep pattern, psychological stress and social context. This multifaceted aspect of lifestyle makes adequate measurement of lifestyle behaviour difficult, which potentially introduces misclassification bias. In this thesis, self-reported questionnaires were used to assess dietary intake, physical activity, smoking behaviour, and alcohol consumption. Such memory-based based questionnaires are susceptible to unintentional and intentional misclassification.[73,74] Unintentional misclassification, typically stemming from memory lapses, is unlikely to significantly affect study results when it does not correlate with patient characteristics or clinical outcomes. In contrast, intentional misclassification, such as social desirability bias, may arise because participants change their replies to align with what they expect will be viewed favourably by others. For example, patients with obesity may be more prone to underreport caloric intake, which could potentially explain the relatively low daily energy intake in patients with a body mass index exceeding 30 kg/m^2 observed in **Chapter 2** of this thesis.

Residual confounding is a source of bias that should be considered in all observational studies, but is especially pertinent in lifestyle-related research. Lifestyle behaviours

are strongly related to each other and to other factors that affect cardiovascular event risk, such as social economic position, age and comorbidities. For instance, the paradoxical finding of beneficial associations of leisure-time physical activity versus the harmful associations for occupational physical activity, which have been described in apparently healthy people[45] as well as in CVD patients (**Chapter 7**), could be subject to residual confounding from factors such as income, smoking habits or negative effects of shift work. While we attempted to address these potential sources of confounding as thoroughly as possible in this thesis, it is essential to exercise caution when extrapolating the results to clinical practice. A further challenge arises because theoretical confounding factors in the relationship between lifestyle behaviours and cardiovascular outcomes are often also potential mediators in these relationships, *e.g.* body mass index.[75] Statistical adjustment for these factors is therefore likely to result in diluted association between exposure and outcome, while not adjusting presents a biased result. Throughout this thesis, we have dealt with this issue by making stepwise adjustments, first including only true confounders and then adding those covariates that theoretically could be both confounder and mediator (*e.g.* **Chapters 2, 6,** and **7**).

Reverse causation is of special concern in observational studies assessing the relationships of physical activity with health outcomes.[72,76] In these studies, the group of non-active participants will likely not only contain people that choose not to be active, but also people who are unable to be physically active due to underlying disease.[75] In **Chapter 9**, we assessed the relationship of adopting a healthy lifestyle after initially having an unhealthy lifestyle and found that better compliance with lifestyle recommendations was associated with approximately 50% lower risk of (cardiovascular) mortality and incident diabetes. The strength of these associations exceeds those observed in previous analyses[31,77] and potential explanations include the presence of reverse causation.

However, despite these pitfalls, observational evidence also holds many promises for future investigation of the (causal) relationship between lifestyle factors and cardiovascular health outcomes. Observational studies are less expensive compared to randomized controlled trials (RCTs) and can therefore be used to cost-efficiently include large sample sizes or to accrue long follow-up times. This can result in precise results and allows for explorative analyses across subgroups. Furthermore, a well-designed prospective cohort is less sensitive to selection and can be used to answer

a multitude of research questions, while a clinical trial is typically adept to answer only one or two.

Target trial emulation, as, used in **Chapter 6**, is an increasingly popular methodology that can be used to approximate causal effects in observational data. By first explicitly designing an optimal clinical trial before modelling this in observational data, target trial emulation brings potential sources of bias to light and allows the researcher to deal with them.[78,79] While bias cannot actually be eradicated in target trial emulation, it provides a clear framework in which the results of an observational study should be interpreted. Compared to traditional RCTs, target trial emulation is much less expensive, does not suffer from ethical questions concerning clinical equipoise and allow researchers to assess potential effects over a long follow-up time, although the limitations of observational data cannot be removed in this methodology.

Experimental research: Are clinical trials the solution?

Traditionally, RCTs hold a high place in the hierarchy of scientific evidence. Randomisation, if performed correctly, ensures that no association between patient characteristics and treatment assignment exists, which eliminates confounding as a source of bias. Using a placebo-control ensures that differences in outcomes can be attributed to the intervention under study. However, RCTs on dietary and physical activity interventions are not always as straightforward as a placebo-controlled intervention on pharmacological interventions.

Firstly, participants in these trials are aware of what they eat and how they move, meaning that in lifestyle-related research, participants cannot be blinded to their treatment assignment. Knowledge of treatment allocation may cause a study participant to change their behaviour in a way that is not in line with the study protocol. For example, participants that are assigned to a control group without active intervention, may be more likely to look for alternative treatments outside of the trial, which could dilute trial results.[80] Patients may also be more likely to drop out of the trial if they are assigned to the control group and expect that they will gain no benefit from participation.[81] In **Chapters 3** and **4**, risk of bias was assessed in over 90 dietary intervention trials and for almost all there was at least some concern regarding bias, mainly arising from lack of blinding.

Secondly, results from lifestyle trials are often not directly applicable to clinical practice. It is often challenging to include a large number of people in dietary or physical activity trials and several trials report a very large number of patients that were contacted concerning trial participation compared to the number of patients ultimately included in the trial. This could result in a study population that is not reflective of the target population, as patients with a keen interest in improving their lifestyle may be more likely to participate. Participants that volunteer for participation may already have a healthier lifestyle and therefore less potential to improve and benefit from the intervention. This self-selection bias would theoretically yield an underestimation of the true effect in the target population.[82]

Finally, long-term RCTs that directly assess the effect of interventions on cardiovascular event rates hold a central place for cardiovascular treatment guidelines. However, few such trials have been performed regarding dietary interventions and none exist for physical activity interventions. [10] As described in **Chapter 3** and **4**, RCTs with a shorter follow-up time are performed more frequently, but these generally only assess the effects of lifestyle interventions on intermediate risk factors. It is difficult to translate these effects to cardiovascular risk reductions, given that only a proportion of lifestyle effects are mediated by traditional CVD risk factors (**Chapters 5, 8**) and that CVD patients receive concomitant medications to treat the risk factors that are also being targeted by lifestyle changes.

FUTURE PERSPECTIVES

Even though unhealthy dietary habits and physical inactivity have been identified as causes of disease by Hippocrates in ancient times, a strategy to prevent people from adopting such habits has not yet been found. Contrarily, over 2000 years later an unhealthy lifestyle has become increasingly common and the incidence of non-communicable, lifestyle-related diseases is still on the rise and there is growing recognition of a wide range of contributing factors.[83,84] This persisting challenge underscores the urgency of evolving lifestyle research in the context of CVD. As we look to the future, new fields of research and new methodologies emerge that could play an important role in combating these health issues.

Personalized lifestyle recommendation is an emerging field that uses data on medical history, laboratory findings and patients preferences to create an individualized recommendation for lifestyle changes.[85–87] There appears to be considerable heterogeneity in the treatment effect of lifestyle interventions and it is worth trying to unravel mechanisms that explain that heterogeneity.[88] Together with increasingly available evidence on interaction between lifestyle habits and genome and machine-learning techniques, the possibility arises of personalized recommendations on body composition, diet, physical activity level and type. Models such as the one described in **Chapter 10**, lend themselves very well to estimate the impact of such targeted lifestyle interventions and communicating the effects of a personalized lifestyle approach to patients.

In the near future, the results of ongoing lifestyle RCTs will be published. The ongoing AUStralian MEDiterranean Diet Heart trial (AUSMED),[89] will shed light on the efficacy of a Mediterranean diet relative to standard-care for reducing recurrent CVD event risk in a non-Mediterranean country. Preliminary reports show that good compliance with the Mediterranean diet can be achieved, but it remains to been seen if CVD risk reductions similar to the Lyon Diet Heart and CORDIOPREV trials can be achieved.[90] The CENTURY trial (NCT00756379) is currently assessing the impact of comprehensive intervention including lifestyle modification on recurrent CVD event risk in patients with established CVD. In this RCT, radiographic testing is used to reinforce the intervention and intensify treatment when necessary.[91] This trial could shed new insights on methods to increase adherence to lifestyle interventions over time. The initial five years follow-up of this trial were completed in 2022 and the first results are expected soon.

CONCLUDING REMARKS

Lifestyle optimization, including a healthy diet and being physically active, is a first-line recommendation for the clinical management of patients with established CVD. However, it is often difficult to integrate lifestyle guidance into clinical practice and compliance with recommended lifestyle remains poor. The findings in this thesis contribute to further awareness of the importance of a healthy lifestyle even when CVD is already clinically manifest and offer new insights into the association between lifestyle behaviors and recurrence of cardiovascular events in these patients. The

evidence in this thesis demonstrates that significant health benefits could likely be realized, in a cost-effective manner, in CVD patients that receive state-of-the-art cardiovascular risk managing medications. Furthermore, individualized treatment effect prediction can be used to communicate personalized benefits from lifestyle change in clinical practice with the aim to improve compliance with long-standing guideline recommendations. As we look toward the future, refinement of lifestyle management could potentially be achieved through the development of personalized lifestyle prescriptions and the initiation of pragmatic clinical trials focused on bolstering adherence to lifestyle recommendations. Lifestyle optimization requires a large effort from patients, health care providers and healthy policy makers, but has the potential to significantly improve the health and well-being of patients with established CVD.

KEY FINDINGS OF THIS THESIS

In this thesis, we demonstrated that:

- Compliance with dietary recommendations is suboptimal in patients with established CVD (**Chapter 2**)
- Theoretical modelling of relative adherence to a healthy dietary pattern, such as a DASH or Mediterranean diet, showed modest but clinically relevant protective relationships with cardiovascular and mortality outcomes in patients with established CVD (**Chapter 5**, **Chapter 6**).
- Interventions aimed at adopting one of various popular dietary patterns yield marginal effects on intermediate cardiovascular risk factors such as body weight, systolic blood pressure and LDL-cholesterol in pharmacologically treated people with established CVD or T2D (**Chapter 3**, **Chapter 4**).
- Attenuation of traditional cardiovascular risk factors, such as blood pressure and LDL-cholesterol, is not the main mechanism of action for effectuating benefits of a healthy lifestyle. Rather, systemic inflammation and insulin resistance emerge as pivotal mediators for reducing cardiovascular risk through lifestyle changes (**Chapter 5**, **Chapter 8**).
- High leisure-time physical activity levels are associated with reduced risk of recurrent cardiovascular events and incident T2D. However, paradoxically, high levels of occupational physical activity tend to elevate risk of these outcomes. (**Chapter 7**).

- Achieving high exercise volumes is key for lowering risk of recurrent cardiovascular events in CVD patients, irrespective of the specific intensity or type of exercise employed to reach these volumes (**Chapter 8**).
- It is never too late to adopt a healthy lifestyle, as changing lifestyle behaviours over time, encompassing smoking cessation, losing weight, increasing physical activity and moderating alcohol consumption, over time is associated with lower risk of cardiovascular events in CVD patients (**Chapter 9**).
- Adopting a Mediterranean diet and increasing physical activity has the potential to substantially increase life expectancy free of recurrent CVD event, especially in younger patients and in patients with a high lifetime risk of cardiovascular events (**Chapter 10**).
- An intervention aimed at improving adherence to a Mediterranean diet and physical activity recommendations are highly cost-effective in CVD (**Chapter 11**).

REFERENCES

1. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J [Internet]. 2021 Sep 7;42(34):3227–337.
2. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J. 2023 Aug 25;
3. Virani SS, Newby LK, Arnold S V., Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation [Internet]. 2023 Jul 20;
4. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779–85.
5. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. New England Journal of Medicine [Internet]. 2018 Jun 21;378(25):e34. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1800389
6. Delgado-lista J, Alcala-diaz JF, Torres-peña JD, Quintana-navarro GM, Fuentes F, Garcia-rios A, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet. 2022;399:1876–85.
7. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur J Clin Nutr. 2018 Jan 10;72(1):30–43.
8. Tosti V, Bertozzi B, Fontana L. Health Benefits of the Mediterranean Diet: Metabolic and Molecular Mechanisms. The Journals of Gerontology: Series A. 2018 Mar 2;73(3):318–26.
9. Schwingshackl L, Morze J, Hoffmann G. Mediterranean diet and health status: Active ingredients and pharmacological mechanisms. Br J Pharmacol. 2020 Mar 25;177(6):1241–57.
10. Karam G, Agarwal A, Sadeghirad B, Jalink M, Hitchcock CL, Ge L, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. BMJ. 2023;
11. KEYS A, MIENOTTI A, KARVONEN MJ, ARAVANIS C, BLACKBURN H, BUZINA R, et al. THE DIET AND 15-YEAR DEATH RATE IN THE SEVEN COUNTRIES STUDY. Am J Epidemiol. 1986 Dec;124(6):903–15.
12. Ramsden CE, Zamora D, Majchrzak-Hong S, Faurot KR, Broste SK, Frantz RP, et al. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). BMJ. 2016 Apr 12;i1246.
13. DuBroff R, de Lorgeril M. Fat or fiction: the diet-heart hypothesis. BMJ Evid Based Med. 2021 Feb;26(1):3–7.

14. Jo U, Park K. Carbohydrate Intake and Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis of Prospective Studies. Nutrients. 2023 Apr 2;15(7):1740.

15. Soltani S, Jayedi A, Shab-Bidar S, Becerra-Tomás N, Salas-Salvadó J. Adherence to the Mediterranean Diet in Relation to All-Cause Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. Advances in Nutrition. 2019 Nov;10(6):1029–39.

16. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur J Clin Nutr. 2018 Jan 10;72(1):30–43.

17. Vilarnau C, Stracker DM, Funtikov A, da Silva R, Estruch R, Bach-Faig A. Worldwide adherence to Mediterranean Diet between 1960 and 2011. Eur J Clin Nutr. 2019 Jul 28;72(S1):83–91.

18. Mente A, Dehghan M, Rangarajan S, O'Donnell M, Hu W, Dagenais G, et al. Diet, cardiovascular disease, and mortality in 80 countries. Eur Heart J. 2023 Jul 21;44(28):2560–79.

19. Ge L, Sadeghirad B, Ball GDC, Da Costa BR, Hitchcock CL, Svendrovski A, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: Systematic review and network meta-analysis of randomised trials. The BMJ. 2020;369.

20. Nicholas AP, Soto-Mota A, Lambert H, Collins AL. Restricting carbohydrates and calories in the treatment of type 2 diabetes: a systematic review of the effectiveness of 'low-carbohydrate' interventions with differing energy levels. J Nutr Sci. 2021 Sep 14;10:e76.

21. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. New England Journal of Medicine [Internet]. 2001 Jan 4;344(1):3–10.

22. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of Weight-Loss Diets with Different Compositions of Fat, Protein, and Carbohydrates. New England Journal of Medicine [Internet]. 2009 Feb 26;360(9):859–73.

23. Sijtsma FPC, Soedamah-Muthu SS, De Goede J, Oude Griep LM, Geleijnse JM, Giltay EJ, et al. Healthy eating and lower mortality risk in a large cohort of cardiac patients who received state-of-the-art drug treatment1-3. American Journal of Clinical Nutrition. 2015 Dec 1;102(6):1527–33.

24. Fadnes LT, Økland JM, Haaland ØA, Johansson KA. Estimating impact of food choices on life expectancy: A modeling study. PLoS Med. 2022;19(2):1–17.

25. Juul F, Vaidean G, Lin Y, Deierlein AL, Parekh N. Ultra-Processed Foods and Incident Cardiovascular Disease in the Framingham Offspring Study. J Am Coll Cardiol. 2021 Mar;77(12):1520–31.

26. Hall KD, Ayuketah A, Brychta R, Cai H, Cassimatis T, Chen KY, et al. Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. Cell Metab. 2019 Jul;30(1):67-77.e3.

27. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Debras C, Druesne-Pecollo N, et al. Ultraprocessed Food Consumption and Risk of Type 2 Diabetes Among Participants of the NutriNet-Santé Prospective Cohort. JAMA Intern Med. 2020 Feb 1;180(2):283.

28. Juul F, Vaidean G, Lin Y, Deierlein AL, Parekh N. Ultra-Processed Foods and Incident Cardiovascular Disease in the Framingham Offspring Study. J Am Coll Cardiol. 2021 Mar;77(12):1520–31.

29. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Méjean C, Andrianasolo RM, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). BMJ. 2019 May 29;l1451.

30. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;74(10):e177–232.

31. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020 Dec;54(24):1451–62.

32. Health Council of the Netherlands. Beweegrichtlijnen 2017. The Hague; 2017.

33. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of Exercise on Coronary Endothelial Function in Patients with Coronary Artery Disease. New England Journal of Medicine [Internet]. 2000 Feb 17;342(7):454–60. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM200002173420702

34. Olver TD, Ferguson BS, Laughlin MH. Molecular Mechanisms for Exercise Training-Induced Changes in Vascular Structure and Function. Prog Mol Biol Transl Sci [Internet]. 2015;135:227–57.

35. De Bacquer D, Astin F, Kotseva K, Pogosova N, De Smedt D, De Backer G, et al. Poor adherence to lifestyle recommendations in patients with coronary heart disease: Results from the EUROASPIRE surveys. Eur J Prev Cardiol. 2022 Jan 1;29(2):383–95.

36. Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol. 2019 May 1;26(8):824–35.

37. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. Eur Heart J. 2021 Jan 1;42(1):17–96.

38. Valenzuela PL, Ruilope LM, Santos-Lozano A, Wilhelm M, Kränkel N, Fiuza-Luces C, et al. Exercise benefits in cardiovascular diseases: from mechanisms to clinical implementation. Eur Heart J. 2023 Jun 1;44(21):1874–89.

39. Yarizadeh H, Eftekhar R, Anjom-Shoae J, Speakman JR, Djafarian K. The Effect of Aerobic and Resistance Training and Combined Exercise Modalities on Subcutaneous Abdominal Fat: A Systematic Review and Meta-analysis of Randomized Clinical Trials. Advances in Nutrition. 2021;12(1):179–96.

40. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2015;4(7):1–28.

41. Ciolac EG, Rodrigues-da-Silva JM. Resistance Training as a Tool for Preventing and Treating Musculoskeletal Disorders. Sports Medicine [Internet]. 2016 Sep 25;46(9):1239–48. Available from: http://link.springer.com/10.1007/s40279-016-0507-z

42. Giovannucci EL, Rezende LFM, Lee DH. Muscle-strengthening activities and risk of cardiovascular disease, type 2 diabetes, cancer and mortality: A review of prospective cohort studies. J Intern Med [Internet]. 2021 Oct 2;290(4):789–805. Available from: https://onlinelibrary.wiley.com/doi/10.1111/joim.13344

43. Richter EA, Hargreaves M. Exercise, GLUT4, and Skeletal Muscle Glucose Uptake. Physiol Rev [Internet]. 2013 Jul;93(3):993–1017. Available from: https://www.physiology.org/doi/10.1152/physrev.00038.2012

44. Tjønna AE, Stølen TO, Bye A, Volden M, Slørdahl SA, Ødegård R, et al. Aerobic interval training reduces cardiovascular risk factors more than a multitreatment approach in overweight adolescents. Clin Sci. 2009 Feb 1;116(4):317–26.

45. Holtermann A, Schnohr P, Nordestgaard BG, Marott JL. The physical activity paradox in cardiovascular disease and all-cause mortality: The contemporary Copenhagen General Population Study with 104 046 adults. Eur Heart J. 2021;42(15):1499–511.

46. Cillekens B, Lang M, van Mechelen W, Verhagen E, Huysmans MA, Holtermann A, et al. How does occupational physical activity influence health? An umbrella review of 23 health outcomes across 158 observational studies. Br J Sports Med [Internet]. 2020 Dec 25;54(24):1474–81. Available from: https://bjsm.bmj.com/lookup/doi/10.1136/bjsports-2020-102587

47. Coenen P, Huysmans MA, Holtermann A, Krause N, Mechelen W Van, Straker LM, et al. Do highly physically active workers die early ? A systematic review with meta-analysis of data from 193 696 participants. Br J Sports Med. 2018;52:1320–6.

48. Holtermann A, Krause N, van der Beek AJ, Straker L. The physical activity paradox: six reasons why occupational physical activity (OPA) does not confer the cardiovascular health benefits that leisure time physical activity does. Br J Sports Med [Internet]. 2018 Feb;52(3):149–50.

49. Mente A, Dehghan M, Rangarajan S, O'Donnell M, Hu W, Dagenais G, et al. Diet, cardiovascular disease, and mortality in 80 countries. Eur Heart J. 2023 Jul 21;44(28):2560–79.

50. Pan B, Ge L, Xun Y qin, Chen Y jing, Gao C yun, Han X, et al. Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. International Journal of Behavioral Nutrition and Physical Activity. 2018 Dec 25;15(1):72.

51. Dibben G, Faulkner J, Oldridge N, Rees K, Thompson DR, Zwisler AD, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database of Systematic Reviews. 2021 Nov 6;2021(11).

52. Rosenson RS. The High-Density Lipoprotein Puzzle: Why Classic Epidemiology, Genetic Epidemiology, and Clinical Trials Conflict? Arterioscler Thromb Vasc Biol [Internet]. 2016 May 19;36(5):777–82.

53. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA [Internet]. 1998 Aug 19;280(7):605–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9718051

54. Posadzki P, Pieper D, Bajpai R, Makaruk H, Könsgen N, Neuhaus AL, et al. Exercise/physical activity and health outcomes: an overview of Cochrane systematic reviews. BMC Public Health. 2020 Dec 1;20(1).

55. Veronese N, Solmi M, Caruso MG, Giannelli G, Osella AR, Evangelou E, et al. Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. Am J Clin Nutr. 2018 Mar;107(3):436–44.

56. Quintela BCSF, Carioca AAF, de Oliveira JGR, Fraser SDS, da Silva Junior GB. Dietary patterns and chronic kidney disease outcomes: A systematic review. Nephrology. 2021 Jul 28;26(7):603–12.

57. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation. 2016;133(11):1104–14.

58. Dalziel K, Segal L, De Lorgeril M. A mediterranean diet is cost-effective in patients with previous myocardial infarction. Journal of Nutrition [Internet]. 2006;136(7):1879–85.

59. Oldridge N, Taylor RS. Cost-effectiveness of exercise therapy in patients with coronary heart disease, chronic heart failure and associated risk factors: A systematic review of economic evaluations of randomized clinical trials. Eur J Prev Cardiol. 2020 Jul 26;27(10):1045–55.

60. Shields GE, Wells A, Doherty P, Heagerty A, Buck D, Davies LM. Cost-effectiveness of cardiac rehabilitation: a systematic review. Heart. 2018 Sep;104(17):1403–10.

61. Cohen LP, Isaza N, Hernandez I, Lewis GD, Ho JE, Fonarow GC, et al. Cost-effectiveness of Sodium-Glucose Cotransporter-2 Inhibitors for the Treatment of Heart Failure With Preserved Ejection Fraction. JAMA Cardiol. 2023 May 1;8(5):419.

62. Hu Y, Zheng SL, Ye XL, Shi JN, Zheng XW, Pan HS, et al. Cost-effectiveness analysis of 4 GLP-1RAs in the treatment of obesity in a US setting. Ann Transl Med. 2022 Feb;10(3):152–152.

63. Michaeli DT, Michaeli JC, Boch T, Michaeli T. Cost-effectiveness of cholesterol-lowering drugs for secondary cardiovascular prevention in the UK: ezetimibe, evolocumab, and alirocumab. Eur Heart J. 2022 Oct 3;43(Supplement_2).

64. Richman IB, Fairley M, Jørgensen ME, Schuler A, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of Intensive Blood Pressure Management. JAMA Cardiol. 2016 Nov 1;1(8):872.

65. Petersohn S, Pouwels X, Ramaekers B, ten Cate-Hoek A, Joore M. Rivaroxaban plus aspirin for the prevention of ischaemic events in patients with cardiovascular disease: a cost-effectiveness study. Eur J Prev Cardiol. 2020 Sep 1;27(13):1354–65.

66. Li Y, Xia PF, Geng TT, Tu ZZ, Zhang YB, Yu HC, et al. Trends in Self-Reported Adherence to Healthy Lifestyle Behaviors Among US Adults, 1999 to March 2020. JAMA Netw Open. 2023 Jul 14;6(7):e2323584.

67. Hardcastle SJ, Hancox J, Hattar A, Maxwell-Smith C, Thøgersen-Ntoumani C, Hagger MS. Motivating the unmotivated: how can health behavior be changed in those unwilling to change? Front Psychol [Internet]. 2015 Jun 16;6(June):1–4. Available from: http://journal.frontiersin.org/Article/10.3389/fpsyg.2015.00835/abstract

68. Springmann M, Clark MA, Rayner M, Scarborough P, Webb P. The global and regional costs of healthy and sustainable dietary patterns: a modelling study. Lancet Planet Health. 2021 Nov;5(11):e797–807.

69. Kearney M, Kearney J, Dunne A, Gibney M. Sociodemographic determinants of perceived influences on food choice in a nationally representative sample of Irish adults. Public Health Nutr. 2000 Jun 2;3(2):219–26.

70. Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. BMJ. 1995 Nov 18;311(7016):1356–9.

71. Kaasenbrood L, Ray KK, Boekholdt SM, Smulders YM, LaRosa JC, Kastelein JJP, et al. Estimated individual lifetime benefit from PCSK9 inhibition in statin-treated patients with coronary artery disease. Heart. 2018 Oct;104(20):1699–705.

72. Parfrey PS, Barrett BJ, editors. Clinical Epidemiology. Vol. 1281. New York, NY: Springer New York; 2015.

73. Archer E, Pavela G, Lavie CJ. The Inadmissibility of What We Eat in America and NHANES Dietary Data in Nutrition and Obesity Research and the Scientific Formulation of National Dietary Guidelines. Mayo Clin Proc. 2015 Jul;90(7):911–26.

74. Kipnis V, Midthune D, Freedman L, Bingham S, Day NE, Riboli E, et al. Bias in dietary-report instruments and its implications for nutritional epidemiology. Public Health Nutr. 2002 Dec 22;5(6a):915–23.

75. Shiroma EJ, Lee IM. Can we proceed with physical activity recommendations if (almost) no clinical trial data exist on mortality? Br J Sports Med. 2018 Jul;52(14):888–9.

76. Rezende LFM, Ferrari G, Lee DH, Aune D, Liao B, Huang W, et al. Lifestyle risk factors and all-cause and cause-specific mortality: assessing the influence of reverse causation in a prospective cohort of 457,021 US adults. Eur J Epidemiol. 2022 Jan 3;37(1):11–23.

77. Gonzalez-Jaramillo N, Wilhelm M, Arango-Rivas AM, Gonzalez-Jaramillo V, Mesa-Vieira C, Minder B, et al. Systematic Review of Physical Activity Trajectories and Mortality in Patients With Coronary Artery Disease. J Am Coll Cardiol [Internet]. 2022 May;79(17):1690–700.

78. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol [Internet]. 2016 Nov;79:70–5.

79. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available: Table 1. Am J Epidemiol [Internet]. 2016 Apr 15;183(8):758–64.

80. Friedberg JP, Lipsitz SR, Natarajan S. Challenges and recommendations for blinding in behavioral interventions illustrated using a case study of a behavioral intervention to lower blood pressure. Patient Educ Couns. 2010 Jan;78(1):5–11.

81. Whitehead WE. Control groups appropriate for behavioral interventions. Gastroenterology. 2004 Jan;126:S159–63.

82. Morris MC. A Potential Design Flaw of Randomized Trials of Vitamin Supplements. JAMA. 2011 Apr 6;305(13):1348.

83. Li Y, Cao G ying, Jing W zhan, Liu J, Liu M. Global trends and regional differences in incidence and mortality of cardiovascular disease, 1990–2019: findings from 2019 global burden of disease study. Eur J Prev Cardiol. 2023 Feb 14;30(3):276–86.

84. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet [Internet]. 2017 Sep 16;390(10100):1211–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28919117

85. Lamb JJ, Stone M, D'Adamo CR, Volkov A, Metti D, Aronica L, et al. Personalized Lifestyle Intervention and Functional Evaluation Health Outcomes SurvEy: Presentation of the LIFEHOUSE Study Using N-of-One Tent–Umbrella–Bucket Design. J Pers Med. 2022 Jan 15;12(1):115.

86. Dogan A, Li Y, Peter Odo C, Sonawane K, Lin Y, Liu C. A utility-based machine learning-driven personalized lifestyle recommendation for cardiovascular disease prevention. J Biomed Inform. 2023 May;141:104342.

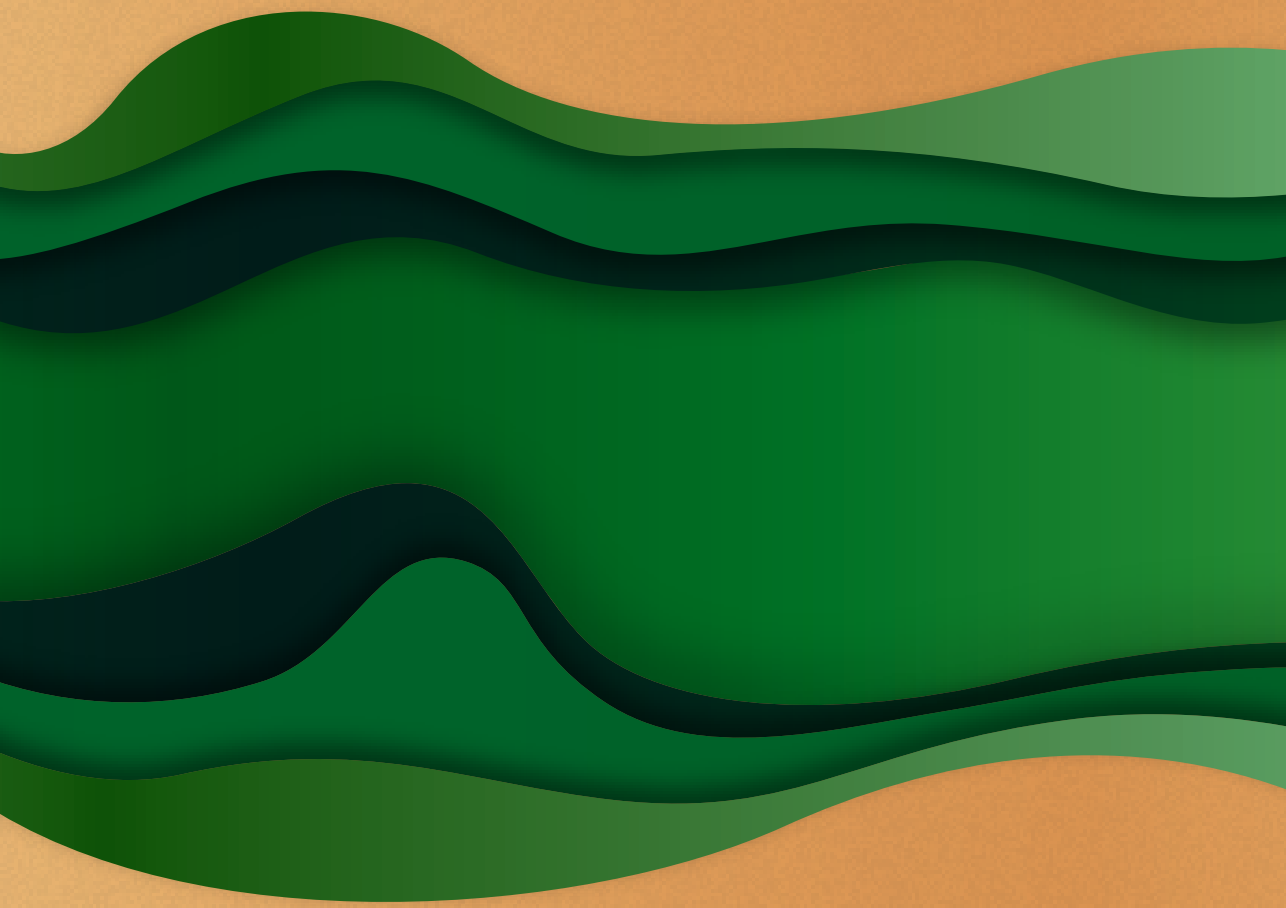
87. Chi CL, Nick Street W, Robinson JG, Crawford MA. Individualized patient-centered lifestyle recommendations: An expert system for communicating patient specific cardiovascular risk information and prioritizing lifestyle options. J Biomed Inform. 2012 Dec;45(6):1164–74.

88. de Vries TI, Dorresteijn JAN, van der Graaf Y, Visseren FLJ, Westerink J. Heterogeneity of Treatment Effects From an Intensive Lifestyle Weight Loss Intervention on Cardiovascular Events in Patients With Type 2 Diabetes: Data From the Look AHEAD Trial. Diabetes Care. 2019 Oct 1;42(10):1988–94.

89. Itsiopoulos C, Kucianski T, Mayr HL, van Gaal WJ, Martinez-Gonzalez MA, Vally H, et al. The AUStralian MEDiterranean Diet Heart Trial (AUSMED Heart Trial): A randomized clinical trial in secondary prevention of coronary heart disease in a multiethnic Australian population: Study protocol. Am Heart J. 2018 Sep;203:4–11.

90. Mayr HL, Tierney AC, Kucianski T, Thomas CJ, Itsiopoulos C. Australian patients with coronary heart disease achieve high adherence to 6-month Mediterranean diet intervention: preliminary results of the AUSMED Heart Trial. Nutrition. 2019 May;61:21–31.

91. Kitkungvan D, Johnson NP, Kirkeeide R, Haynie M, Carter C, Patel MB, et al. Design and rationale of the randomized trial of comprehensive lifestyle modification, optimal pharmacological treatment and utilizing PET imaging for quantifying and managing stable coronary artery disease (the CENTURY study). Am Heart J. 2021 Jul;237:135–46.



APPENDICES

SUMMARY

Cardiovascular disease (CVD), encompassing coronary artery, cerebrovascular and peripheral arterial disease, is the worldwide leading cause of morbidity and mortality contributing to an estimated 18 million deaths each year. Unhealthy lifestyle habits, including smoking, unhealthy diet, physical inactivity and being overweight or obese, are key risk factors for developing atherosclerosis and CVD. Public health measures are focussed on preventing CVD from developing through the promotion of a healthy lifestyle. However, after CVD becomes clinically manifest, *e.g.* when a patients experiences a myocardial infarction, pharmacological interventions instead of healthy lifestyle become the mainstay of clinical CVD management and prevention of recurrent cardiovascular events. Adhering to a healthy lifestyle may be more difficult for CVD patients, due to consequences of the disease or side effects of the pharmacological interventions. Furthermore, the extent to which a healthy lifestyle contributes to reduction of the risk of recurrent cardiovascular events remains largely unclear.

In this thesis, the role of healthy dietary and physical activity habits in the clinical management with stable CVD was explored. **Part I** examined the relationship between different dietary patterns and cardiovascular risk factors and event rates. In **Part II**, the focus lies on different types of physical activity in secondary CVD prevention. Finally, in **Part III**, multiple lifestyle components are investigated together and a personalized assessment of the long-term benefits of a healthy lifestyle for CVD patients is estimated.

In **Chapter 1** of this thesis, an overview of the existing evidence on healthy diet and physical activity for primary and secondary prevention of cardiovascular events is provided. Furthermore, the central objectives and outline of this thesis were outlined. **Part I** of this thesis assessed the role of multiple dietary patterns in the prevention of recurrent cardiovascular events from both an etiological and a therapeutic perspective. To put the potential benefit of changing dietary habits in the right context, it is important to gain an overview of current dietary habits of patients with established CVD. In **Chapter 2** the results of the retrospective collection of dietary intake data through a food frequency questionnaire among 2,656 patients with established CVD from the UCC-SMART cohort are described. CVD patients' compliance with current Dutch dietary guidelines was poor, but compared to the general population they scored better on intake of recommended heart-healthy food items such as legumes and fish.

Furthermore, in this study, a better compliance with the Dutch dietary guidelines was associated with lower stroke risk.

In **Chapters 3** and **4**, the existing evidence on the effect of dietary patterns interventions on cardiovascular risk factor levels in patients with established CVD or type 2 diabetes was systematically collected and pooled using network meta-analysis techniques. **Chapter 3** included 17 randomized controlled trials among CVD populations comparing five distinct dietary patterns and found no significant short- or long-term effects on body weight, systolic blood pressure and LDL-cholesterol levels. There was a considerable risk of bias in the available studies and the heterogeneity between the included studies was significant. In **Chapter 4** a similar analysis was performed in studies comprising individuals with type 2 diabetes. A total of 73 trials were included in this network meta-analysis and an estimate of the relative effects of eight potentially healthy dietary patterns on cardiovascular risk factors and glycemic control was found. In this analysis, all included dietary patterns significantly reduced body weight compared to no dietary intervention. The low carbohydrate and Mediterranean diet were identified as most effective for improving glycemic control. Similar to **Chapter 3**, no statistically significant reductions in blood pressure and lipid levels were observed. Together these two chapters raised the question whether the reductions in cardiovascular event risk that are observed in observational studies and the few available long-term randomized controlled trials could be mediated by other factors than attenuation of traditional cardiovascular risk factors.

Chapter 5 aimed to further elucidate the relative contribution of cardiovascular risk factors to the association between two popular heart healthy diets, the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet, and (cardiovascular) mortality. In this analysis 4,365 patients with a history of myocardial infarction from the Alpha Omega Cohort were included and low compliance with both the DASH and Mediterranean diet was found. A higher dietary compliance score was not associated with risk of cardiovascular or all-cause mortality after a median of 12 years follow-up time. However, explorative analyses in this chapter demonstrated that blood pressure and lipid levels were no mediators between higher dietary compliance scores and the mortality outcomes. Instead, systemic inflammation, measured as high-sensitivity C reactive protein levels, emerged as a central mediator of these dietary patterns. These findings are hypothesis-generating and suggest that the anti-inflammatory potential of dietary patterns should be explored further in future research.

In **Chapter 6**, a target trial emulation was performed to assess the relationship between compliance with the DASH diet and cardiovascular and all-cause mortality risk in patients with established CVD. The study, using data from 4365 post-myocardial infarction patients from the Alpha Omega Cohort, found no significant association between DASH compliance and mortality risk, suggesting that the effects of the DASH diet may have been modified by concomitant use of blood pressure-lowering medications that was highly prevalent in this population.

In **Part II** the focus shifted towards the relationship of different types of physical activity with cardiovascular event risk among CVD patients. **Chapter 7** assessed the differences between physical activity performed in leisure time and at work in relationship to risk of recurrent cardiovascular events, all-cause mortality and incident diabetes. Among 7,058 patients with established CVD from the UCC-SMART cohort, higher leisure-time physical activity levels were strongly associated with reduced risk of these three outcomes. Paradoxically, more physical demanding occupations were not associated with reductions in cardiovascular event, mortality and incident type 2 diabetes risk. Instead, manual or heavy manual occupation showed a trend towards higher recurrent cardiovascular event risk. These findings indicate that physical activity at work should not be regarded as a sufficient alternative for physical activity in leisure-time.

Chapter 8 compared different exercise volumes, types and intensity in relation to all-cause mortality and recurrent cardiovascular event risk. In this analysis, not performing any exercise was associated with significantly worse outcomes but no differences between exercise types, volume and intensity was observed. These findings stress the importance of motivating CVD patients to exercise but suggest that patients should be let free to choose a type of exercise that suits their personal preferences. Furthermore, in **Chapter 8**, a mediation analysis was performed to investigate to which extent exercise effects were mediated by differences in cardiovascular risk factors. In this analysis, body mass index, systolic blood pressure and LDL-cholesterol levels turned out to mediate only a small proportion of the association, similar to the findings in **Chapter 5.** Instead, insulin resistance and systemic inflammation accounted for approximately 5% and 15% of the total associations.

In **Part III,** different lifestyle components and their relationship with clinical endpoints in CVD patients were assessed concurrently. In **Chapter 9**, repeated assessments of smoking, alcohol consumption, physical activity and waist circumference level in the

UCC-SMART cohort were combined to assess patients' individual lifestyle trajectory. In this chapter, improving lifestyle behaviour over time was associated with an almost 50% lower risk of all-cause mortality, cardiovascular mortality and incident type 2 diabetes relative to a maintaining an unhealthy lifestyle. For all-cause mortality and cardiovascular mortality, smoking and physical activity were the main drivers of the lower risk, while for incident diabetes, a persistently healthy or improved waist circumference was most strongly associated with risk reductions. The findings of this study suggest that it is not too late to adopt healthy lifestyle behaviours even after CVD has become clinically manifest.

In **Chapter 10**, treatment effects from the best available evidence on Mediterranean diet and physical activity were added to existing and previously externally validated SMART-REACH model. This model allows for personalized predictions of 10-year and lifetime benefit from adopting a Mediterranean diet, increasing physical activity levels or both. The model was applied to 13,331 CVD patients from the UCC-SMART and Alpha Omega Cohort to estimate the potential of implementing lifestyle interventions in routine clinical care for CVD patients. It was estimated that median gain of 3.7 additional life years free of recurrent CVD events could be realized. Lifetime benefit from lifestyle interventions were largest among younger patients and those at high recurrent CVD risk.

Finally, **in Chapter 11**, cost-effectiveness of implementing a lifestyle intervention based on Mediterranean diet and increased physical activity levels, was assessed. This study yielded a dominant incremental cost-effectiveness ratio of - € 626 per quality-adjusted life year gained. This highly cost-effective finding remained robust in a wide range of scenario analyses, such as reimbursement for food costs and reducing adherence rates. This findings presented in this chapter strongly advocate for incorporating active lifestyle guidance into routine clinical care for patients with established CVD.

NEDERLANDSE SAMENVATTING

Hart- en vaatziekten (HVZ), waaronder coronaire hartziekte, cerebrovasculaire en perifere arteriële ziekte, zijn wereldwijd de belangrijkste oorzaak van morbiditeit en mortaliteit en dragen bij aan naar schatting 18 miljoen sterfgevallen per jaar. Ongezonde levensgewoonten, waaronder roken, een ongezond dieet, lichamelijke inactiviteit en overgewicht of obesitas, zijn belangrijke risicofactoren voor de ontwikkeling van atherosclerose en HVZ. Volksgezondheidsmaatregelen zijn primair gericht op het voorkomen van de ontwikkeling van HVZ en atherosclerose door de bevordering van een gezonde levensstijl. Echter, nadat HVZ klinisch manifest is geworden, bijvoorbeeld wanneer een patiënt een hartinfarct krijgt, worden medicamenteuze interventies de kern van de behandeling van om nieuwe cardiovasculaire events te voorkomen. Het naleven van een gezonde levensstijl krijgt dan vaak minder aandacht en kan moeilijker zijn voor HVZ-patiënten, vanwege de gevolgen van de ziekte of bijwerkingen van farmacologische interventies. Bovendien zijn er nog veel vragen over in hoeverre een gezonde levensstijl bijdraagt aan het verminderen van het risico op terugkerende cardiovasculaire events.

In dit proefschrift werd de rol van gezonde dieet- en bewegingsgewoonten in de klinisch zorg voor patiënten met stabiele HVZ onderzocht. **Deel I** onderzocht de relatie tussen verschillende dieetpatronen en cardiovasculaire risicofactoren en de kans op het krijgen van nieuwe hart- en vaatevents. In **Deel II** lag de focus op verschillende soorten lichamelijke activiteit in secundaire HVZ-preventie. Ten slotte worden in **Deel III** meerdere levensstijlcomponenten samen onderzocht en wordt een gepersonaliseerde inschatting van de lange termijn voordelen van een gezonde levensstijl voor HVZ-patiënten gemaakt.

In **Hoofdstuk 1** van dit proefschrift wordt een overzicht gegeven van het bestaande bewijs over een gezond dieet en lichamelijke activiteit voor de primaire en secundaire preventie van cardiovasculaire gebeurtenissen. Bovendien werden de centrale doelstellingen en de opzet van dit proefschrift geschetst. **Deel I** van dit proefschrift beoordeelde de rol van meerdere dieetpatronen in de preventie van terugkerende cardiovasculaire gebeurtenissen, zowel vanuit een etiologisch als een therapeutisch perspectief. Om het potentiële voordeel van het veranderen van dieetgewoonten in de juiste context te plaatsen, is het belangrijk om een overzicht te krijgen van de huidige dieetgewoonten van patiënten met vastgestelde HVZ. In **Hoofdstuk 2** worden de

resultaten beschreven van de retrospectieve verzameling van voedselinnamegegevens via een voedselfrequentievragenlijst onder 2.656 patiënten met vastgestelde HVZ uit de UCC-SMART-cohort. De naleving van de huidige Nederlandse dieetrichtlijnen door HVZ-patiënten was suboptimaal, maar in vergelijking met de algemene bevolking scoorden ze beter op de inname van aanbevolen hartgezonde voedingsmiddelen zoals peulvruchten en vis. Bovendien bleek uit dit onderzoek dat een betere naleving van de Nederlandse dieetrichtlijnen gepaard ging met een lager risico op een beroerte bij HVZ-patiënten.

In **Hoofdstukken 3** en **4** werd het bestaande bewijs over het effect van dieetpatrooninterventies op cardiovasculaire risicofactoren bij patiënten met HVZ of type 2 diabetes systematisch verzameld en geanalyseerd met behulp van netwerk-meta-analysetechnieken. **Hoofdstuk 3** omvatte 17 gerandomiseerde gecontroleerde onderzoeken onder HVZ-populaties en er werden in totaal vijf verschillende dieetpatronen vergeleken. In deze analyse werden geen significante korte- of langetermijneffecten gevonden op lichaamsgewicht, systolische bloeddruk en LDL-cholesterolniveaus. De beschikbare studies hadden echter een aanzienlijk risico op bias en de heterogeniteit tussen de opgenomen studies was significant. In **Hoofdstuk 4** werd een vergelijkbare analyse uitgevoerd bij studies met mensen met type 2 diabetes. In totaal werden 73 studies opgenomen in deze netwerk-meta-analyse, en een schatting van de relatieve effecten van acht potentieel gezonde dieetpatronen op cardiovasculaire risicofactoren en glycemische controle werd gemaakt. In deze analyse verminderden alle dieetpatronen significant het lichaamsgewicht in vergelijking met geen dieetinterventie. Het koolhydraatbeperkte dieet en het mediterrane dieet bleken het meest effectief voor het verbeteren van de glycemische controle. Net als in **Hoofdstuk 3** werden geen statistisch significante verlagingen waargenomen in bloeddruk- en lipidenniveaus. Samengevoegd riepen deze twee hoofdstukken de vraag op of de verminderingen in het risico op cardiovasculaire gebeurtenissen die worden waargenomen in observationele studies en de paar lange termijn-gerandomiseerde gecontroleerde onderzoeken die gedaan zijn, zouden kunnen worden bemiddeld door andere factoren dan het verminderen van traditionele cardiovasculaire risicofactoren.

Hoofdstuk 5 had als doel om die relatieve bijdrage van cardiovasculaire risicofactoren aan de associatie tussen twee populaire hart-gezonde diëten, het Dietary Approaches to Stop Hypertension (DASH)-dieet en het mediterrane dieet, en (cardiovasculaire) sterfte verder te verduidelijken. In deze analyse werden 4.365 patiënten die een

hartinfarct hadden doorgemaakt uit het Alpha Omega Cohort opgenomen, en er werd een beperkte naleving van zowel het DASH- als het mediterrane dieet gevonden. Een hogere dieetscore was niet geassocieerd met het risico op cardiovasculaire of algemene sterfte na een mediane follow-up van 12 jaar. Echter, verkennende analyses in dit hoofdstuk toonden aan dat bloeddruk- en lipidenniveaus geen bemiddelaars waren tussen hogere nalevingsscores van het dieet en de sterfte-uitkomsten. In plaats daarvan kwam laaggradige systemische inflammatie, gemeten als C-reactieve proteïne, naar voren als een centrale mediator van deze dieetpatronen. Deze bevindingen genereren hypothesen en suggereren dat het ontstekingsremmende potentieel van dieetpatronen verder moet worden onderzocht in toekomstig onderzoek.

In **Hoofdstuk 6** werd een target trial emulation uitgevoerd om de relatie tussen naleving van het DASH-dieet en het risico op (cardiovasculaire) sterfte te beoordelen bij patiënten met vastgestelde HVZ. De studie, gebaseerd op gegevens van 4.365 post-hartinfarctpatiënten uit de Alpha Omega Cohort, vond geen significante associatie tussen DASH-naleving en het risico op sterfte, wat suggereert dat de effecten van het DASH-dieet mogelijk werden beïnvloed door gelijktijdig gebruik van bloeddrukverlagende medicijnen, wat veel voorkwam in deze populatie.

In **Deel II** verschoof de focus naar de relatie tussen verschillende soorten lichamelijke activiteit en het risico op cardiovasculaire gebeurtenissen bij HVZ-patiënten. In **Hoofdstuk 7** werden de verschillen beoordeeld tussen lichamelijke activiteit in de vrije tijd en lichamelijk beweging op het werk in relatie tot het risico op terugkerende cardiovasculaire events, algemene sterfte en het ontstaan van type 2 diabetes. Onder 7.058 HVZ patiënten uit het UCC-SMART-cohort waren hogere niveaus van lichamelijke activiteit in de vrije tijd sterk geassocieerd met een lager risico op deze drie uitkomsten. Paradoxaal genoeg waren meer fysiek veeleisende beroepen niet geassocieerd met verlagingen in het risico op cardiovasculaire events, sterfte en het ontstaan van type 2 diabetes. In plaats daarvan vertoonden fysiek zware beroepen een trend naar een hoger risico op het krijgen van een nieuw cardiovasculaire event. Deze bevindingen geven aan dat lichamelijke activiteit op het werk niet moet worden beschouwd als een afdoende alternatief voor lichamelijke activiteit in de vrije tijd.

Hoofdstuk 8 vergeleek verschillende hoeveelheden, soorten en intensiteit van sportactiviteit in relatie tot algemene sterfte en het risico op cardiovasculaire events bij HVZ-patiënten. In deze analyse bleek het niet uitvoeren van enige gerichte

sportactiviteit geassocieerd te zijn met aanzienlijk slechtere resultaten, maar er werden geen verschillen waargenomen tussen soorten, hoeveelheden en intensiteiten van de lichaamsbeweging. Deze bevindingen benadrukken het belang van het motiveren van HVZ-patiënten om te sporten, maar suggereren dat patiënten de vrijheid moeten hebben om een type lichaamsbeweging te kiezen dat past bij hun persoonlijke voorkeuren. Bovendien werd in **Hoofdstuk 8** een mediatieanalyse uitgevoerd om te onderzoeken in hoeverre de effecten van sport werden bemiddeld door verschillen in cardiovasculaire risicofactoren. In deze analyse bleken body mass index, systolische bloeddruk en LDL-cholesterolniveaus slechts een klein deel van de associatie te bemiddelen, vergelijkbaar met de bevindingen uit **Hoofdstuk 5**. In plaats daarvan droegen insulineresistentie en systemische ontsteking ongeveer 5% en 15% bij aan de totale associaties.

In **Deel III** werden verschillende levensstijlcomponenten en hun relatie met klinische eindpunten bij HVZ-patiënten gelijktijdig beoordeeld. In **Hoofdstuk 9** werden herhaalde metingen van roken, alcoholgebruik, lichamelijke activiteit en tailleomtrek in het UCC-SMART-cohort gecombineerd om individuele levensstijltrajecten van patiënten te beoordelen. In dit hoofdstuk werd gezien dat een verbetering van de levensstijl in de loop van de tijd geassocieerd was met bijna 50% lager risico op algemene sterfte, cardiovasculaire sterfte en het ontwikkelen van type 2 diabetes in vergelijking met een blijvend ongezonde levensstijl. Voor algemene sterfte en cardiovasculaire sterfte waren roken en lichamelijke activiteit de belangrijkste bijdragende factoren voor het lagere risico, terwijl voor het ontwikkelen van diabetes een blijvend gezonde of verbeterde tailleomtrek het sterkst geassocieerd was met risicovermindering. De bevindingen van dit onderzoek suggereren dat het niet te laat is om gezonde levensstijlgewoonten op te pakken, zelfs nadat HVZ klinisch manifest is geworden.

In **Hoofdstuk 10** werden behandeleffecten uit het beste beschikbare bewijs over het mediterrane dieet en lichamelijke activiteit toegevoegd aan het bestaande en eerder extern gevalideerde SMART-REACH-model. Dit model maakt het mogelijk om gepersonaliseerde schattingen te doen over het 10-jarige en levenslange voordeel van het aannemen van een Mediterraan dieet, het verhogen van lichamelijke activiteit niveau of beide. Het model werd toegepast op 13.331 HVZ-patiënten uit de UCC-SMART- en Alpha Omega cohorten om het potentieel van implementatie van levensstijlinterventies in de klinische zorg voor HVZ-patiënten te schatten. De resultaten lieten zien dat een mediane winst van 3,7 extra levensjaren zonder

terugkerende HVZ-events kon worden gerealiseerd in deze patiënten groep. Het levenslange voordeel van levensstijlinterventies was het grootst bij jongere HVZ-patiënten en bij degenen met het hoogste risico op een nieuw HVZ-event.

Ten slotte werd in **Hoofdstuk 11** de kosteneffectiviteit van een levensstijlinterventie op basis van het mediterrane dieet en lichamelijke activiteit beoordeeld. Deze studie resulteerde in een dominante incrementele kosteneffectiviteitsratio van - € 626 per gewonnen quality-adjusted life year. Deze zeer kosteneffectieve bevinding bleef robuust in een breed scala van scenarioanalyses, zoals vergoeding voor voedselkosten en het verminderen van de nalevingspercentages. De bevindingen in dit hoofdstuk pleiten sterk voor het opnemen van actieve levensstijlbegeleiding in de standaardzorg voor patiënten met HVZ.

CONTRIBUTING AUTHORS

Dr. Maarten J.M. Cramer
Department of Cardiology,
University Medical Center Utrecht
Utrecht, the Netherlands

Esther Cruijsen, MSc
Division of Human Nutrition and Health
Wageningen University
Wageningen, The Netherlands

Prof. dr. Gert Jan de Borst
Department of Vascular Surgery
University Medical Center Utrecht
Utrecht, the Netherlands

Iris van Damme, MSc
Division of Human Nutrition and Health
Wageningen University
Wageningen, The Netherlands

Dr. Jannick A.N. Dorresteijn
Department of Vascular Medicine
University Medical Center Utrecht
Utrecht, The Netherlands

Prof. dr. Johanna M. Geleijnse
Division of Human Nutrition and Health
Wageningen University
Wageningen, The Netherlands

Dr Steven H.J. Hageman
Department of Vascular Medicine
University Medical Center Utrecht
Utrecht, The Netherlands.

Prof.dr. Martin Halle
Department of Prevention and Sports Medicine, School of Medicine
University Hospital Klinikum rechts der Isar, Technical University Munich
Munich, Germany

Dr. Charlotte Koopal
Department of Vascular Medicine
University Medical Center Utrecht
Utrecht, The Netherlands.

Prof.dr Anne M. May
Department of Epidemiology,
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht
Utrecht, The Netherlands

Dr. Manon G. van der Meer
Department of Cardiology,
University Medical Center Utrecht
Utrecht, the Netherlands

Prof. dr. Pamela B Morris
Department of Cardiology,
Medical University of South Carolina
Charleston, South Carolina, United States of America

Dr. Ynte M. Ruigrok
UMC Utrecht Brain Center, Department of Neurology and Neurosurgery
University Medical Center Utrecht
Utrecht, the Netherlands

Prof. Yvonne T. van der Schouw
Department of Epidemiology, Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Utrecht, The Netherlands

Dr Thomas T. van Sloten
Department of Vascular Medicine

University Medical Center Utrecht
Utrecht, The Netherlands

Dr. Martin Teraa
Department of Vascular Surgery
University Medical Center Utrecht
Utrecht, the Netherlands

Prof. Frank L.J. Visseren
Department of Vascular Medicine
University Medical Center Utrecht
Utrecht, The Netherlands.

UCC-SMART study group, University Medical Center Utrecht
Prof. dr. F.W. Asselbergs, Department of Cardiology
Dr. M.J. Cramer, Department of Cardiology
Prof. dr. P van der Harst, Department of Cardiology
Dr. M.G. van der Meer (co-PI), Department of Cardiology
Dr. H.M. Nathoe, Department of Cardiology
Prof. dr. G.J. de Borst, Department of Vascular Surgery
Dr. M. Teraa (co-PI), Department of Vascular Surgery
Prof. dr. M.L. Bots, Julius Center for Health Sciences and Primary Care
Dr. M.I. Geerlings, Julius Center for Health Sciences and Primary Care
Dr. M. van Smeden, Julius Center for Health Sciences and Primary Care
Prof. dr. M.H. Emmelot-Vonk, Department of Geriatrics
Prof. dr. P.A. de Jong, Department of Radiology
Prof. dr. T. Leiner, Department of Radiology
Prof. dr. A.T. Lely, Department of Gynaecology and Obstetrics
Dr. N.P. van der Kaaij, Department of Cardiothoracic Surgery
Prof. dr. L.J. Kappelle, Department of Neurology
Dr. Y.M. Ruigrok, Department of Neurology
Prof. dr. M.C. Verhaar, Department of Nephrology
Dr. J.A.N. Dorresteijn (co-PI), Department of Vascular Medicine
Prof. dr. F.L.J. Visseren (chair), Department of Vascular Medicine
Dr. J. Westerink, Department of Vascular Medicine

LIST OF PUBLICATIONS

Publications included in this thesis

Bonekamp NE, van Damme I, Geleijnse JM, Winkels RM, Visseren FLJ, Morris PB, Koopal C. Effect of dietary patterns on cardiovascular risk factors in people with type 2 diabetes. A systematic review and network meta-analysis. *Diabetes Res Clin Pract*. 2023 Jan;195:110207.

Bonekamp NE, Visseren FLJ, Ruigrok Y, Cramer MJM, de Borst GJ, May AM, Koopal C; UCC-SMART Study group; UCC-SMART study group. Leisure-time and occupational physical activity and health outcomes in cardiovascular disease. *Heart*. 2023 Apr 12;109(9):686-694.

Bonekamp NE, May AM, Halle M, Dorresteijn JAN, van der Meer MG, Ruigrok YM, de Borst GJ, Geleijnse JM, Visseren FLJ, Koopal C. Physical exercise volume, type, and intensity and risk of all-cause mortality and cardiovascular events in patients with cardiovascular disease: a mediation analysis. *Eur Heart J Open*. 2023 Jun 13;3(3):oead057.

Bonekamp NE, Cruijsen E, Visseren FL, van der Schouw YT, Geleijnse JM, Koopal C. Compliance with the DASH diet and risk of all-cause and cardiovascular mortality in patients with myocardial infarction. *Clin Nutr*. 2023 Aug;42(8):1418-1426.

Bonekamp NE, Visseren FLJ, Cramer MJ, Dorresteijn JAN, van der Meer MG, Ruigrok YM, van Sloten TT, Teraa M, Geleijnse JM, Koopal C. Long-term lifestyle change and risk of mortality and type 2 diabetes in patients with cardiovascular disease. *Eur J Prev Cardiol*. 2023 Sep 29:zwad316.

Bonekamp NE, Cruijsen E, Geleijnse JM, Winkels RM, Visseren FLJ, Morris PB, Koopal C. Effect of Dietary Patterns on Cardiovascular Risk Factors in Patients with Cardiovascular disease. A Systematic Review and Network Meta-Analysis, *Nutr J*, 2024 Jan. Epub ahead of print

Publications not included in this thesis

El Idrissi A, van Berkel L, **Bonekamp NE**, Dalemans DJ, van der Heyden MA. The toxicology of zinc chloride smoke producing bombs and screens. *Clin Toxicol (Phila)*. 2017 Mar;55(3):167-174.

Bonekamp NE, Caorsi R, Viglizzo GM, Graaf M, Minoia F, Grossi A, Picco P, Ceccherini I, Frenkel J, Gattorno M. High-dose ustekinumab for severe childhood deficiency of interleukin-36 receptor antagonist (DITRA). *Ann Rheum Dis*. 2018 Aug;77(8):1241-1243.

Bonekamp NE, Caorsi R, Frenkel J, Gattorno M. Response to: 'Standard dose of ustekinumab for childhood-onset deficiency of interleukin-36 receptor antagonist' by Cherqaoui *et al*. *Ann Rheum Dis*. 2018 Dec;77(12):e89.

Bonekamp NE, Spiering W, Nathoe HM, Kappelle LJ, de Borst GJ, Visseren FLJ, Westerink J; UCC-SMART Study Group. Applicability of Blood Pressure-Lowering Drug Trials to Real-World Patients With Cardiovascular Disease. *Hypertension*. 2021 Feb;77(2):357-366.

Hoes LLF, Geleijnse JM, **Bonekamp NE**, Dorresteijn JAN, van der Meer MG, van der Schouw YT, Visseren FLJ, Koopal C, on behalf of the UCC-SMART study group, Prevalence and determinants of self-reported low-fat-, low-salt-, and vegetarian diets in patients with cardiovascular disease between 1996 and 2019, *Nutrition, Metabolism and Cardiovascular Diseases*, epub ahead of print

DANKWOORD

Dit is dan echt het einde van mijn promotietijd(perk). Ik vond het geweldig en heb veel geleerd. Onderzoek doe je nooit in je eentje en ik heb heel veel geluk met de mensen die ik de afgelopen jaren om me heen heb gehad. Zonder jullie was deze tijd nooit zo leuk, afwisselend, verbredend en verdiepend geweest. Dank aan iedereen die de afgelopen jaren van dichtbij of op afstand betrokken is geweest bij dit proefschrift. Ik wil graag een aantal van jullie hier in het bijzonder bedanken:

Allereerst mijn promotieteam: mijn promotoren prof. dr. F.L.J Visseren, prof. dr. J.M. Geleijnse en mijn copromotor dr. C. Koopal.

Prof. Dr. F.L.J. Visseren, beste Frank, ik wil je graag bedanken voor de fijne begeleiding de afgelopen jaren. Vol energie stortten we ons samen op een project dat toen ik begon eigenlijk niet veel meer was dan een A4'tje met ideeën. Je gaf me de ruimte om hier zelf invulling aan te geven, maar stuurde me gelukkig altijd op tijd weer bij. Ik heb veel respect voor hoe jij snel tot de kern kan komen en echt de hoofdboodschap van een verhaal kan omkaderen. Ik vond het heel fijn dat je deur open stond voor een laagdrempelige vraag. Ik bewonder en waardeer hoe je met zo'n drukke agenda toch altijd tijd maakt om ons als promovendi persoonlijke begeleiding te geven. Door jou is de Vascu-groep een hechte en fijne plek om te promoveren die ik aan iedereen zou aanraden. Je maakt deze sfeer mogelijk met vascu-lunches, barbecues en Thanksgiving diners die altijd heel gezellig en lekker waren.

Prof. dr. J.M. Geleijnse, beste Marianne, wat een geluk om begeleiding vanuit twee disciplines te krijgen. Jouw expertise op voedingsgebied heeft ontzettend geholpen bij het uitvoeren en afronden van dit proefschrift. Toen ik begon was de voedingswetenschap een nieuw veld voor mij, maar je hebt me hier op een hele prettige manier doorheen geleid. Dankjewel voor de kans om met de voedingsdata uit het Alpha Omega cohort aan de slag te gaan. Bij het bespreken van projecten had je scherpe maar opbouwende kritiek die het niveau van projecten omhoog tilde. Dankjewel voor je positieve begeleiding en je enthousiasme.

Dr. C. Koopal, beste Lotte, direct na die wandeling door Park Oog in Al tijdens de eerste coronagolf hadden we een goede klik. Gedurende mijn hele promotie wist je precies waar mijn sterke punten en mijn valkuilen liggen en daagde je me uit om uit mijn

comfortzone te stappen. Ik vind het heel inspirerend hoe jij je eigen plan trekt en daar vol voor gaat. Ik bewonder hoe je klinische werk combineert met onderzoek en een gezin met twee kleine kinderen. Ik heb de laatste jaren heel fijn met je samengewerkt, zowel toen we 12 uur tijdsverschil hadden als over een kop koffie in de Brink. Dankjewel dat je me zoveel ruimte hebt gegeven om mijn ideeën de vrije loop te laten, maar dat je toch altijd het overzicht hield om me op koers te houden. Heel veel dank voor de fijne en persoonlijke begeleiding de afgelopen jaren!

Prof. dr. O.H. Franco Duran, Prof. dr. ir. E. Kampman, Prof. dr. L.J. Kappelle, Prof. dr. M. Meine, prof. dr. W.M.M. Verschuren, hooggeleerde leden van mijn beoordelingscommissie: ik wil u graag bedanken voor uw bereidheid om dit proefschrift te beoordelen. Ik kijk ernaar uit om in het Academiegebouw over de inhoud van gedachten te wisselen.

Ik wil graag alle coauteurs bedanken voor hun scherpe suggesties en aanvullingen bij de projecten die samen zijn gekomen in dit proefschrift. Een aantal coauteurs kan ik daarbij zeker niet ongenoemd laten:

Prof. dr. Y.T. van der Schouw, beste Yvonne, hartelijk dank voor je begeleiding bij het onderzoeksproject in mijn epidemiologie master. Maandelijks met jou overleggen over de FFQ voor UCC-SMART heeft het mogelijk gemaakt dat we die data nu beschikbaar hebben en dat de eerste projecten daarmee al in dit proefschrift terecht zijn gekomen.

Prof. dr. A.M. May, beste Anne, dank voor je input bij de verschillende projecten over bewegen die we gedaan hebben. Ik vond het heel leuk om Regiodeal-werkpakket overstijgend samen te werken.

Dr. R.M. Winkels, beste Renate, dank voor jouw input bij het uitzetten van de lijn van dit proefschrift. Ik bewonder jouw scherpe suggesties bij projecten, zelfs als je er maar een korte introductie over hebt gehad. Dank ook voor de spiegel in gesprekken over het grotere plaatje en lange termijn plannen.

(Oud-)stafleden van de afdeling Vasculaire Geneeskunde: dr. Jan Westerink, dr. Jannick Dorresteijn, dr. Jan-Steven Burgerhart, dr. Melanie Tan en dr. Thomas van Sloten, dankjulliewel voor jullie behulpzame en inspirerende suggesties tijdens onze wekelijkse researchbesprekingen en voor de gezelligheid tijdens vascu-lunches en op congressen. Er bestaat vast een (statistisch?) significant grote kans dat een van jullie nog eens

tegenkom in de Bilt. Jan, dankjewel dat je mijn eerste stapjes binnen de vasculaire als student wilde begeleiden.

Inge, Corina en Sara, dankjulliewel voor de gezelligheid op het researchbureau. Het was altijd fijn om bij jullie een relativerend oor te vinden.

Margie, wat zou de afdelingen zonder jou worden? Chaos… Dankjewel voor al je logistieke hulp en dat je altijd zo meedenkt in oplossingen.

Veel dank aan alle medewerkers van UCC-SMART: Baukje, Hetty, Lies, Ank, Pauline, Mandy, Rosanne, Rutger en Angela voor de fijne samenwerking als SMART-arts en voor jullie hulp bij het verzamelen van de FFQ data die de basis vormt voor een heel aantal projecten in dit proefschrift (en wellicht meer in de toekomst!). Rosanne en Angela, dank voor jullie onuitputtelijke energie en enthousiasme bij het uitrollen van dit plan.

Dank aan alle deelnemers van het UCC-SMART cohort en het Alpha-Omega cohort. Zonder uw bijdrage was het onderzoek in dit proefschrift niet mogelijk geweest.

Collega's van Regiodeal werkpakket 3, Menrike Menkveld, Tom van Loenhout, Remy Bemelmans, Gerda Pot en Anne van der Wiel, dankjulliewel voor de fijne meetings. Ik heb veel van jullie geleerd over communicatie over wetenschap naar een breder publiek en over het opzetten van brede samenwerkingen.

Mede-onderzoekers uit Wageningen aan de andere kant van de voedselvallei, het was super om vanuit een verschillende achtergrond over een gezamenlijk onderwerp na te denken. Esther, dankjewel voor de mooie link die we hebben kunnen leggen tussen AOC en SMART en voor de projecten die we samen hebben gedaan. Fijn dat je zo vaak toch nog één laatste regel R code voor me wou runnen. Het was heel gezellig samen in Barcelona! Iris, wat fijn dat we in ieder geval één project samen hebben kunnen doen. Ik heb veel respect voor hoe secuur jij te werk gaat! Het was altijd leuk om tijdens een dagje in Wageningen weer bij te praten. Ilse, Tessa, Bo en Eva, we hebben minder nauw samengewerkt maar ik vond het altijd leuk om te horen wat voor projecten jullie aan het doen waren en om samen in Utrecht en Wageningen uit eten te gaan.

Misschien wel het allerbelangrijkste tijdens promoveren: collega's om lief en leed, lach en traan, rejection en acceptance letter mee te kunnen delen. Geweldige Vasculega's,

zonder jullie waren de afgelopen jaren niet half zo leuk geweest! Jullie maken de vasculaire. Dankjulliewel dat jullie er altijd waren voor ochtendkoffies, middagkoffies, taartmomenten (volgens het SOPje), klaagzangen en natuurlijk diverse borrels: vrijdagmiddag, afscheid, inter-vasculair. Geen reden was te gek.

Britt, gezellig om zo lang samen werkbespreking te hebben. Maar... zou je nog één keertje uit kunnen leggen hoe dysbeta nou werkt? Als fantastische hippe HAIO ben je vast druk Deventer en ommestreken te gentrificeren. Soms waren die laatste Amsterdamse trends onnavolgbaar voor ons simpele Utregters. Eline, powervrouw, wijnconnaisseur, hypertensie-guru. Op deze manier wilde ik je onovertroffen spline-script tóch nog acknowledgen! Dankjewel voor alle gezelligheid en leuke borrels. Helena, tussen de weeën door nog aan een rebuttal werken, poeh, dan leg je de lat wel erg onnavolgbaar hoog qua werkethos. We moeten altijd nog een Deens-Nederlands spreekwoordenboek maken! Steven, ik kan me het Van Geuns niet zonder jou als vascu-godfather voorstellen. Als er geborreld moest worden zorgde jij ervoor dat de troepen in het gareel kwamen. Desertie werd afgestraft. Maar op werk kon ik je altijd bereid vinden om te helpen, wanneer iemand ergens vastliep. Ik heb ontzettend veel respect voor wat je allemaal in onderzoeks-land voor elkaar bokst en met de recente beurs zit er vast nog veel moois aan te komen. Maria: ik ben je nog altijd dankbaar dat je aan mij dacht toen jullie uit de Bloemstraat gingen verhuizen. Ik ken weinig mensen die zo hartelijk, zorgzaam en onbaatzuchtig zijn als jij. Je huisdier naar een multiple-imputation package noemen is toch hopelijk geen teken dat je je werk te veel mee naar huis neemt? Pascal, soms denk ik dat je een soort ingebouwde meeluister-Siri hebt. Je kan zelf zo in diepe focus werken, maar er middenin het (niet-altijd)werkgerelateerde rumoer, opeens vliegensvlug een gevatte grap uitgooien. Marga, ik kijk heel erg uit naar je promotie! Voor mij was je soms klaagmuur, dan weer lachspiegel. Ik ga de hapjes en drankjes om de hoek bij Buurten en de Cervezeria missen, maar ook jouw feilloze snack- en menukaartkennis daarbij! Katrien, ik vind het mega knap hoe je alle ballen (kind, huis, opleiding, promotie...) in de lucht houdt en toch tijd houdt voor sport en gezelligheid Lukas: foodvalley-brother-in-arms! Wat was ik blij toen je aangenomen werd en ik een naaste gezonde-leefstijl-collega kreeg. Ik waardeer je onuitputtelijke enthousiasme en optimisme. Met niemand liever zou ik bij Frank in de tuin werkbesprekingen houden. Beloof je niet meer kwijt te raken als er toevallig een hond langs loopt? Milena, jij hebt een onwaarschijnlijk doorzettingsvermogen. Iedere uitdaging op trialgebied weet jij weer helemaal om te buigen. Ik vind het heel leuk om te horen hoe je nu ook aan het klussen bent in jullie eigen huis. Heel veel succes; elk

stapje maakt het weer mooier! Joris: (meer dan?) energieke R-brainiac. Waar sommigen “keep it simple” als motto hanteren, wil ik voor jou “hoe kunnen we deze R-analyse nog complexer maken?” als lijfspreuk voorstellen. Dankjewel voor je energie, spaR-sessies, humor en mede-nerdschap. En… voor een niet-drinker borrel je aardig mee! Paulien, jouw enthousiasme is aanstekelijk. Het was al na twee weken duidelijk dat jij de nieuwe aanjager van Vascu-borrels wordt. Keep me posted! Iris, Stella en Melanie, we hebben maar kort samengewerkt maar ik wens jullie heel veel succes en vooral veel plezier in jullie PhD. Ik weet zeker dat jullie een hele leuke tijd gaan hebben bij de Vascu de komende jaren! Oud- en buurcollega’s: Tamar, Cilie, Bianca, Jesper en Patrick dank voor alle gezelligheid de afgelopen jaren!

Aan al mijn nieuwe collega’s in het Meander, dank voor het warme welkom en de fijne sfeer! Het assistentenweekend was meteen een mooie vuurdoop.

Ik wil mijn paranimfen Iris en Sophie bedanken voor al jullie hulp in de voorbereiding naar de verdediging toe en ben super blij en trots om straks tussen jullie in te staan!

Lieve Iris, je bent de grootste doorzetter die ik ken en als jij ergens je zinnen op zet, krijg je het altijd voor elkaar. Jouw organisatietalent is onovertroffen en kwam heel goed van pas in Barcelona. Zeg nou zelf, wat is er beter dan een sunset cruise met saxofoon op een catamaran. Dankjewel voor je eindeloze adviezen over mijn kleuren en zonder jou zou ik nooit mijn Kibbe body type geweten hebben. We moeten nog even doorzetten voordat we ook mijn Tycho overtuigen dat katten een grote aanwinst zijn. Ik ben heel blij dat je straks naast me staat in het Academiegebouw!

Lieve Sophie, geweldige Fietje, vanaf groep blauw nu samen in het Academiegebouw. We kennen elkaar nu bijna 25 jaar en hebben al zoveel meegemaakt. Samen op school, samen gereisd en samen gewoond. Ik kan me niet voorstellen hoe het zou zijn als ik je niet elke week sprak. Bij jou voel ik me helemaal op mijn gemak op om op de bank in slaap te vallen (zelfs als het een hele goede film is…) of op Shakira over de grond te dansen. Ik ben super trots dat jij op 4 april naast me staat en ik kijk nu al uit naar de komende 25 jaar!

Gelukkig neemt promoveren niet je hele leven over en is er genoeg tijd voor ontspanning met mensen die ver weg staan van R scriptjes, screen failures, rebuttals en data sharing

agreements. Lieve vrienden en familie, dankjulliewel voor al jullie steun en gezelligheid tijdens borrels, etentjes, feestjes en weekendjes weg!

Joey, wat fijn dat ik jou via Tycho ook zo goed heb leren kennen. Soms kan ik je niet helemaal verstaan, maar we begrijpen elkaar! Alleen de cocktails laten we volgende keer staan… Ayla, jouw warmte en zorgzaamheid zijn hartverwarmend; ik vind het heel fijn om met jou over carrièreplanning te praten. Dankjewel voor jullie vriendschap en laten we snel weer een weekendje weg plannen!

Babinski: Mark, Martijn, Suus, Jet wanneer gaan we weer een pubquiz winnen? (fristi telt ook als winst!) Suus en Jet komende verjaardag weer stappen? Tot nu toe levert dat alleen maar succesverhalen op!

Lieve awesome people/zigazig app gang, wat fijn dat we elkaar nog steeds zo vaak zien en dat het altijd weer zo gezellig is, zelfs als het uitgebreid over katten of Taylor Swift gaat… Ik hoop dat we ons etentjes en jaarlijkse sleepover vol houden tot we grijs en bejaard zijn. Odile, zo enthousiast over spelletjes dat je me ondanks mijn initiële weerstand vaak toch weet te overtuigen om mee te doen. Hopelijk kunnen we elkaar straks in de dienst een keertje bellen. Carien, lief oud huisgenootje en ultieme creatieveling. Lego, truien of je eigen siropen, je draait je hand er niet voor om. Je maakt een mean cocktail, waar ik op Nieuwjaarsdag meermaals spijt van heb gehad… Jiawen, ware globetrotter maar nu toch weer aardig dicht in de buurt geland. Zullen we een keertje Belgische biertjes drinken? Arike, jouw kennis over films is ongeëvenaard en ik kijk nu al uit naar jouw eigen whodunnit over onze vriendengroep! Vita, ons profielwerkstuk had zo een hoofdstuk in dit proefschrift kunnen zijn. Ik ben blijkbaar nooit over John Snow heen gekomen, maar jij gelukkig wel. We kunnen nog steeds *hart* met elkaar lachen. Ik heb heel veel zin in jullie bruiloft straks! Eva, huisje-boompje-beestje in Bunnik, bij jou valt het allemaal op zijn plek. Dankjewel voor de bijscholing over échte hitjes. Als ik binnenkort onze woonkamer opnieuw wil verven, bel ik jou voor kleuradvies! Naomi, wat fijn dat we ieder jaar jouw woonkamer weer mogen verbouwen voor onze sleepover! Ook Quirijn, Rolf, Rick en Jeroen, de 'aanhang' die er over de jaren bij is gekomen, dankjulliewel dat jullie ons telkens weer toestaan om jullie huizen een avondje over te nemen, om hard en vals Wannabe mee te zingen, om net iets te veel wijn te drinken of om een poging te doen om de zombie apocalypse af te wenden.

Lieve familie Tromp, Carlo, Inge, Jordy, Irene, Lisette, Mary, Zenzi, Okke, Duux, Yara, Gerald, Harumi en Erina, dankjulliewel voor jullie altijd super hartelijke welkom de afgelopen tien jaren. Ik heb geluk dat ik in zo'n fijne schoonfamilie terecht ben gekomen. Ik kijk er naar uit om nog heel vaak fanatiek 30 seconds met jullie te spelen!

Lieve Anneke, dankjewel voor je steun en al je interesse in ons huis en toekomstplannen. Ik vind het altijd fijn om over een kop thee met jou bij te praten. Thian, ik weet nog dat je aan het oefenen was met je eerste les Latijn en nu heb je bijna je uni diploma te pakken. Je bent een mega gezellige schoonbroer en blijkt ook nog een een onverwacht talent te hebben voor het indraaien van lampen!

Theo, dankjewel voor alle hulp met het verbouwen in ons huis het afgelopen jaar. Zonder jou had ik nog steeds niet geweten hoe ik een moordenaarstang moest gebruiken. Lieve Marga, dankjewel voor je steun en je interesse in alle dingen die ik doe. Ik bewonder jouw energie en hoe je nieuwe uitdaging na uitdaging aangaat. Ik hoop dat je me nog veel reisfoto's uit verre oorden blijft sturen!

Hans, Simkje, Sjoukje, Jan en Tjebbe, ik zie jullie lang niet vaak genoeg. De plek van mijn promotie zal jullie zeker bekend voorkomen. Paul, Harriet, Tina, Bradley en Brian, dank voor alle drukte en gezelligheid! Wat leuk dat jullie ons nieuwe huis nu ook gezien hebben. Syrrita, lief nichtje, jij bokst alles voor elkaar en trekt helemaal je eigen plan. Hou dat vast! Ellis, wat ben jij eindeloos sportief en enthousiast. Kijk uit, want ik kom eraan om je voorbij te gaan in de voetbalpoule!

Lieve oma Riet, ik vind het heel bijzonder dat je aanwezig kunt zijn bij de verdediging van dit proefschrift. Als kind en student vond ik het altijd heerlijk om bij jou en opa te kunnen logeren. Van appeltaart met ananas tot met blote billen van de glijbaan in het zwembad, het was altijd een feestje! Beste Cor, wat fijn dat ik u de afgelopen jaren heb mogen leren kennen. Ik hoop dat ik op uw leeftijd ook nog met zoveel energie kan genieten van uit eten gaan en lekkere weekendjes er tussenuit.

Jorge, grote kleine broer, dankjewel voor alle gezelligheid, al het gekibbel en alle afkortingen waarmee je me aan het lachen maakt. Ik vind het zo leuk om te zien hoe je je ontplooit in Rotterdam en helemaal je eigen leven hebt. Laten we snel weer een keer samen gaan eten!

Lieve papa en mama, dankjulliewel dat jullie altijd 100% achter me staan. Pap, ik snap niet hoe jij binnen een week beter in een onderwerp kan zitten waar ik me al maanden full time mee bezig hou en hoe je me dan precies het boek op kan sturen dat ik nodig heb. Ik vind het heerlijk om een uur met je aan de telefoon te hangen tot we besluiten dat het te veel brommelen wordt. Dankjewel voor al je hulp met het verbouwen in ons huis. Zonder jou hadden we nog steeds in de bruine jaren '70 vibe gewoond. Mam, jij weet al na twee woorden over de telefoon precies hoe het met me gaat. Je steunt me met onuitputtelijke aanmoediging en hoge doses vitamines als ik langskom op Burg42. Dankjewel voor alle zakdoekjes, pepermuntjes, warme kruiken en gesneden fruitbakjes die je me dan weer toestopt. Jouw huis- en tuin-tips zijn altijd welkom, misschien kunnen wij ook binnenkort voor tuinrondleidingen een aanwijsstok invoeren. Ik weet nu al dat je iedereen trots gaat vertellen over de verdediging van dit proefschrift, maar weet dat ik ook heel trots ben op jou en dat je een groot voorbeeld voor me bent.

Tot slot, allerliefste Tycho, ik weet niet waar ik moet beginnen om jou te bedanken. Dit proefschrift staat er mede dankzij jou: van die eerste mail vanuit Sardinië tot het meelezen van manuscripten in de late uurtjes. Je steunt me en gelooft in me ook wanneer ik het zelf even niet meer overzie. Bij jou kan ik mijn ei helemaal kwijt. Ik ben zo blij met ons nieuwe (t)huis en alle nieuwe ideeën die we daar nog op willen loslaten. Ik kijk nu al heel erg uit naar al onze plannen voor de komende jaren. Ik hou van jou!

CURRICULUM VITAE

Nadia Bonekamp was born on July 5, 1995, in Leiderdop, and spent her childhood in Leiden. She obtained her VWO diploma in 2013 from Stedelijk Gymnasium Leiden, concurrently participating in a PreUniversity program at Leiden University. It was during this time that she first encountered research on nutrition for patients with cardiovascular disease through an internship at the Department of Clinical Epidemiology at LUMC.

In 2013, she commenced her Medicine studies in Utrecht. During her bachelor's, she participated in the Honours program and discovered her enthusiasm for research. In the master's phase of the Medicine program, she pursued a master's in Health Economics, Policy, and Law at Erasmus University in Rotterdam. Additionally, she completed a six-month internship at the Market Access department of AstraZeneca. In the final year of her medical education, Nadia conducted a research internship under the guidance of Jan Westerink. In September 2020, she had the opportunity to continue directly into a PhD program in Vascular Medicine, supervised by Frank Visseren, Marianne Geleijnse, and Lotte Koopal, which resulted in this thesis. The PhD program was combined with a Postgraduate master's in Epidemiology, which she completed in August 2022. Since December 2023, Nadia has been working as a medical physician in the Internal Medicine department at Meander Medical Center in Amersfoort.

Since January 2023, Nadia has been living with her boyfriend Tycho in De Bilt, where they use their free time to transform a 1970s house into their dream home. In her leisure time, Nadia enjoys exercising, watching new DIY or cooking videos, and socializing with friends and family over drinks.