

The background is a collage of organic, hand-cut paper shapes in various shades of teal, light green, and pale yellow. Scattered across these shapes are numerous small, irregular circles and ovals in colors including pink, orange, and light green, creating a textured, artistic effect.

Cost-effectiveness of selective cardiometabolic disease prevention

in primary care

Daphne Stol

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Daphne Marije Stol

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Cost-effectiveness of selective cardiometabolic disease prevention in primary care

(Kosten)-effectiviteit van selectieve preventie van cardiometabole ziekten in de eerste lijn (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,
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door

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geboren op 29 september 1985
te Rijswijk ZH

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1

General Introduction

The aim of health care is not to save money but to save people from preventable suffering and death. Any potential savings on health care costs would be icing on the cake.

Luc Bonneux 1998 BMJ; 316:26-29

Case

Julie van Houten, General practitioner (GP) in an urban practice with an ageing population of 1600 patients, recently learned about selective cardiometabolic disease (CMD) prevention for patients aged 45-70 years without CMD or CMD risk factors in primary care and wonders if she should invite all her patients for a CMD health check?

Immediately a series of questions come up: What is the evidence for the (cost)-effectiveness of selective CMD prevention? Whom should be invited and how should I invite them? Is my practice adequately prepared and can I offer adequate follow-up? What is the best way to implement such a program? Are costs for selective CMD prevention standardly reimbursed?

These legitimate questions are likely to arise if programmed CMD prevention is introduced in primary care. The INTEGRATE study presented in this thesis reports on the effectiveness and cost-effectiveness of selective cardiometabolic disease prevention in primary care and aims to provide answers to several of these questions.

The burden of cardiometabolic diseases

Cardiometabolic diseases (CMD), including cardiovascular disease (CVD), diabetes type 2 (DM2) and chronic kidney disease, is the leading cause of mortality worldwide, accounting for approximately 30% of deaths in high-income countries.¹ In addition, CMD significantly decreases the quality of life due to disease related morbidity. In the Netherlands, approximately 1,6 million individuals have CVD, 1,2 million have DM2 and 40,000 patients suffer from end-stage chronic kidney disease, representing 17% of the total Dutch population.^{2,3} Furthermore, CMD is a key driver of escalating health care costs, accounting for one-sixth of the total healthcare budget in the Netherlands annually.⁴

CVD, DM2 and chronic kidney disease are interrelated, and the presence of one of them immediately increases the risk of developing another disease in this spectrum. This is mainly caused by the fact that they share common modifiable risk factors such as hypertension, hypercholesterolemia, smoking, overweight, physical inactivity and an unhealthy diet.⁵

As a result of more effective treatment, CVD related mortality considerably declined in high-income countries, with an estimated 70% reduction between 1980-2009 in the Nether-

lands.⁶ About half of this decline is attributable to changes in the main cardiometabolic risk factors, such as hypertension, hypercholesterolemia, obesity and smoking.⁷

Despite decreasing mortality rates, the prevalence of CMD is still rising due to ageing and an unhealthy lifestyle. About one quarter of the Dutch population smokes, almost half is overweight or obese and only one in six individuals consumes the recommended daily volume of fruits and vegetables. Furthermore, less than half of the Dutch adults manages the recommended level of physical activity (30 minutes moderate to vigorous exercise on five or more days per week).

Early detection and treatment of CMD and CMD risk factors is likely to reduce the burden of CMD and its related costs. Approximately 80% of these diseases could be prevented by changing the shared risk factors by lifestyle changes or drug treatment.^{5,8}

CMD prevention strategies can be implemented at various levels in society and/or healthcare settings (box 1). One of the approaches to reduce the burden of CMD is to improve CMD risk assessment in primary care by early identification and subsequent treatment of patients at high-risk, who are likely to benefit most from subsequent preventive interventions.

Box 1 Different preventive strategies

Prevention strategies can be classified into four different categories⁹: universal, selective, indicated and care-related prevention, depending on the targeted population. Another type of prevention is opportunistic screening, also known as individual case finding.

Universal prevention strategies address the entire population without taking individual risk factors into account. Examples of universal CMD prevention are the smoking ban in public areas, legislation about the reduction of salt, and to promote physical activity by facilitating a bicycle friendly environment.

Selective prevention strategies identify one or more subgroups of the general population that are deemed to be at increased risk for a certain disease. Examples of selective CMD prevention are identifying and subsequent treatment of – so far asymptomatic- individuals at high risk for CMD, for example all individuals in a certain age range or all individuals with a BMI >25.

Indicated prevention strategies are designed to prevent the onset of a certain disease by targeting individuals who have risk factors or early signs of disease. An example of indicated CMD prevention is the treatment of hypertension.

Care-related prevention strategies aim to delay the severity of complications or the progression of disease in individuals with an already diagnosed disease. Examples of care-related CMD prevention are chronic disease management programs for cardiovascular risk management or diabetes.

Opportunistic screening (individual case finding): In this approach of opportunistic screening a health care professional invites potential high-risk patients for CMD risk assessment during a regular health care consultation. An example of opportunistic CMD screening is inviting a 50-years old obese patient for CMD risk assessment during a consultation for knee pain or a 60-years old smoking patient during a consultation for chronic cough.

CMD prevention in Dutch primary care - a brief history

Before the second millennium, CMD prevention mainly consisted of indicated and care-related prevention, was focussed on single risk factors and was embedded in curative (primary) care. The first (preventive) clinical practice guideline for hypertension and hypercholesterolemia was published by the Dutch College of General Practitioners (NHG) in 1991.^{10,11} Around the millennium CMD prevention shifted towards a multifactorial approach in which an individual's integral CVD risk profile was assessed based on multiple risk factors.¹² This paradigm shift was induced by new insights about the multifactorial aetiology of CMD, the multiplicative effect of CMD risk factors and the fact that health care professionals were dealing with individuals and not with isolated risk factors. Around that period, many risk estimation algorithms were developed, such as the Framingham risk score, ASSIGN, the SCORE risk function, QRISK and PROCAM.¹³ The SCORE risk function, developed by Conroy and colleagues in 2003, is one of these multifactorial risk models and predicts an individual's 10-years CVD mortality risk. This risk function is based on five traditional risk factors: sex, age, smoking status, blood pressure and total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDL).¹⁴

In 2006, this multifactorial risk assessment approach was integrated into the first Dutch multidisciplinary "cardiovascular risk management" guideline (CVRM). This guideline was updated in 2011 with the incorporation of an adapted version of the SCORE risk function, specified for the Dutch-population (SCORE-NL) estimating an individual's 10-years CVD morbidity and mortality risk.¹⁵

In that same period, self-tests for CMD risk factors, such as cholesterol tests, became readily available. Although the general public was interested, the main criticism of these health checks was that they were applied in isolation and not embedded in routine care. Later, initiatives for more 'programmed' formats of early detection of CMD emerged, stressing a crucial role for the connection between preventive and curative care. In 2007, Nivel (the Netherlands Institute for Health Services Research) identified 15 promising prevention initiatives across the Netherlands, mainly directed at individuals at high-risk for CMD.¹⁶ Gradually, CMD prevention was given a more important role in the so far mainly curative focussed CMD care.

By 2011, the NHG and other health care organisations decided to link preventive and curative care in a structural way in order to create more continuous and integrated CMD care. This was driven by the idea that CMD prevention would be more efficient if embedded in curative healthcare.¹⁷ Primary care was considered the most efficient setting for prevention and health promotion, because it is easily accessible, GPs have a longstanding relation with their patients, are familiar with their medical history and social context and the majority of people visit their GP at least once a year. This resulted in the NHG guideline 'the prevention consultation', which provided a framework for programmed selective CMD prevention in primary care. Through structural implementation in general practice the NHG aimed to reach

health gains by early detection and treatment of individuals at increased risk for CMD. In addition, it could result in societal gains such as prolonged societal participation, reduced work absenteeism and a reduction of CMD related healthcare costs.

The NHG guideline “the prevention consultation”

The prevention consultation, further referred to as the selective CMD prevention program, is directed at all patients aged 45-70 years old without known CMD or CMD risk factors, antihypertensive, lipid lowering or antidiabetic drugs (see box 2 for corresponding ICPC and ATC codes).¹⁷

Box 2 CMD and prescriptions

ICPC-codes of CMD:
 K74: Angina pectoris
 K75: Acute myocardial infarction
 K76: Other chronic ischemic heart disease
 K77: Heart failure
 K86: Uncomplicated hypertension
 K87: Hypertension with secondary organ damage
 K89: Transient cerebral ischemia
 K90: Stroke/cerebrovascular accident
 K91: Atherosclerosis
 K92: Peripheral vascular diseases
 T90: Diabetes mellitus
 T93: Lipid metabolism disorder

ATC clusters:
 A10: antidiabetic drugs
 C02-03, C07-C09: antihypertensive drugs
 C10: lipid lowering drugs

Abbreviations: CMD=cardiometabolic diseases, ICPC= International Classification of Primary Care, ATC=Anatomical Therapeutic Chemical Classification System

The selective CMD prevention program takes a stepwise approach. The first step is self-assessment of CMD risk through a 7-item risk score, consisting of questions regarding sex, age, smoking status, BMI, waist circumference and a family history of premature CVD (age <65 years) and DM2 (see appendix 1 of this thesis).¹⁸ The risk score used is developed on the basis of three large Dutch cohort studies, incorporates components of the widely accepted FINDRISK score and the SCORE risk function and was recently externally validated.^{18,19}

On the basis of the risk score, individuals are categorized as having low, intermediate or high risk. The algorithm behind the risk score uses a threshold for a high risk of $\geq 23\%$ for men and $\geq 19\%$ for women to develop CMD in the next seven years (see figure 2 and 3 of chapter 3

(page 52) for an example of the risk result and the interface of the risk estimation). Individuals with a score below threshold are categorized in low risk (no risk factors present) or intermediate risk (one or several risk factors present). These individuals receive tailored lifestyle advice. In case of high risk, individuals are directed to their GP for additional risk profiling according to the SCORE risk function (step 2) - including blood pressure measurement and laboratory tests on fasting glucose, total cholesterol, HDL and LDL levels - and appropriate follow-up treatment (step 3). Treatment is based on recommendations in guidelines issued by the Dutch College of GPs and consists of lifestyle interventions and/or pharmacological treatment. Pilot studies evaluating the implementation of preliminary versions of this program showed participation rates between 33 and 75% and detected a new CMD diagnosis in 20% of high-risk participants who attended the practice.^{20–22}

The five A's

The effectiveness of prevention is not only determined by acquired health gains and acceptable costs, but also by other factors. The five A's of access to health care (affordability, availability, accessibility, accommodation, and acceptability (box 3))²³ together determine the effectiveness of preventive services.

Box 3 Five A's of access to care

Affordability is the interaction between the patient's willingness to pay and the provider's charges

Availability is determined by the extent to which the provider has the requisite resources, such as staff and facilities, to meet the needs of the patient

Accessibility is defined as the geographic accessibility

Accommodation measures the extent to which the preferences of the client are met with regard to the organization of the provider's practice

Acceptability reflects the extent to which the client agrees on the more immutable characteristics of for example a health care provider or health care service, and vice versa.

The five A's commonly result from interaction between patient and health care provider and/or practice and they are also useful to determine facilitators or barriers on an individual and practice level.

On individual patient level, for instance, the willingness of individuals to participate in preventive programs is generally affected by all five A's. Affordability for instance can play a crucial role. If preventive services are not reimbursed by the health insurance company, participation depends on an individual's willingness and ability to pay. A personal contribution can

be expected in case of commercial providers. However, also in present-day primary care certain lifestyle interventions are not routinely reimbursed. Accessibility, availability and accomodation are not a problem in the Netherlands, where primary care is well established and easy accessible allover the country. Finally acceptability to participate in disease specific prevention programs is vital, but might be socially and culturally determined.

The invitation for self-assessment of CMD risk through a risk score at home – as recommended in the Dutch guideline – will provide the individual with knowledge about CMD risk.¹⁷ Being confronted with an increased risk may motivate risk reducing behaviour, such as adopting a healthier lifestyle or visit the GP for additional risk profiling. This probably depends on the individual's perception of the relevance of the CMD risk and their willingness to change behaviour.

On practice level, characteristics of the organisation (affordability, availability, accessibility and accommodation of services) can influence the effectiveness of preventive programs. A well-organized practice with adequate resources, such as sufficient staff and facilities for lifestyle interventions might contribute to its effect. In addition, easy access to reimbursed lifestyle intervention programs will probably increase acceptance (acceptability) of and compliance with the program by patients as well as doctors.²⁴

The focus of this thesis is on risk perception (individual level) and organisational practice characteristics (practice level). In the twinned thesis of Ilse Badenbroek²⁵, which focuses on (non)-participation and implementation of the CMD prevention program, other individual and practice characteristics will be evaluated.

Challenges for implementation of selective CMD prevention

Presently Dutch GP's use up-to-date guidelines on CMD prevention and treatment and many practices offer chronic disease management programs for CMD patients in which improvement of lifestyle plays a crucial role. Whereas the effectiveness of curative care and care-related prevention for CMD is undisputed, that of selective CMD prevention is still controversial. Structural implementation of the prevention consultation has not yet taken place, and only 30% of GPs implemented selective CMD prevention in daily practice.²⁶ Several reasons are suggested for this low compliance.

On the one hand some fundamental discussions are still ongoing, for instance around the responsibility for lifestyle management and behavioural change. Should individuals primarily be kept responsible for their own lifestyle and subsequent risk management or is this the responsibility of general practitioners or public health services? In addition, practical challenges appear such as dealing with the additional workload and the lack of adequate funding of preventive activities.²⁴ Implementation of selective CMD prevention is considered time-consuming, including the selection and invitation of eligible patients. The risk assessment takes on average two consultations

of 10-20 minutes for history taking, examinations and discussing results and treatment options. Without adequate reimbursement, most GPs consider this not the worth its (time) investment.²⁷

However the biggest challenge is the persisting debate about the (cost)-effectiveness of selective CMD prevention in primary care, one of the key evaluation criteria according to Wilson and Jungner.²⁸ Although it was demonstrated that population screening does not reduce 'hard' endpoints such as CMD related morbidity and mortality^{29,30}, previous studies did demonstrate that lifestyle interventions directed at high-risk individuals (selective prevention) do have favourable effects on risk factors such as blood pressure and cholesterol levels and on individual CVD risk profile.^{31,32} Adequate evaluation of the (cost)-effectiveness of selective CMD prevention programs requires a scientifically sound study design and assessment over a long period of time using relevant endpoints such as morbidity and mortality.

Aim of this thesis

The principle aim of this thesis is to assess the effectiveness, and cost-effectiveness of selective CMD prevention in primary care. In the INTEGRATE study we compared a stepwise CMD risk assessment followed by individualized treatment with care as usual in 37 Dutch general practices. Primary outcomes were the number of newly detected patients with CMD, the changes in risk factors for CMD after one-year follow-up and its short-term and long-term cost-effectiveness. Secondary outcomes were risk perceptions among participants and the organization of participating practices in relation to the effectiveness of the program. In this thesis we present the results of the INTEGRATE study and provide definite recommendations on how to proceed with selective CMD prevention in primary care.

Outline of this thesis

Chapter 2 describes the design of the INTEGRATE study, a randomized controlled trial which investigates the effectiveness and cost-effectiveness of CMD risk assessment and treatment integrated in primary care. Chapter 3 describes the risk perception among participants of the Dutch CMD prevention program. CMD risk perception was compared between two groups of which one group received a personalized CMD risk estimate and the other group did not receive this estimate.

Chapter 4 focuses on the effectiveness of selective CMD prevention and compares the intervention and control group after one-year follow-up. Chapter 5 describes the program uptake and the CMD detection rate in all participants after its implementation. The short- and long-term cost-effectiveness are described in chapter 6 in which the results of chapter 4

are related to projected long-term CMD morbidity and mortality. Chapter 7 describes the current organization of selective CMD prevention in primary care and in chapter 8 we describe practice-related factors associated with the effects of the program. This thesis closes with a general discussion and summary of the main findings and provides recommendations on structural embedding of selective CMD prevention in primary care.

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2.1

Design of the INTEGRATE study: effectiveness and cost-effectiveness
of a cardiometabolic risk assessment and treatment program integrated
in primary care

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Abstract

Background: The increasing prevalence of cardiometabolic diseases (CMD) in combination with an ageing population is a major public health problem. Early detection and management of individuals at risk for CMD is required to prevent future health problems with associated costs. General practice is the optimal health care setting to accomplish this goal. Prevention programs for identification and treatment of patients with an increased risk for CMD in primary care have been proven feasible. However, the effectiveness and cost-effectiveness have yet to be demonstrated. The 'Personalized Prevention Approach for CardioMetabolic Risk' (PPA CMR) is such a prevention program. The objective of the INTEGRATE study is to investigate the effectiveness and cost-effectiveness of PPA CMR, as well as to establish determinants for participation and compliance.

Methods: The INTEGRATE study is designed as a stepped-wedge randomized controlled trial with a waiting list control group. In approximately 40 general practices, all enlisted patients without CMD aged 45–70 years, are invited to participate in PPA CMR. After an online risk estimation, patients with a score above risk threshold are invited to the GP for additional measurements, detailed risk profiling and tailored treatment of risk factors through medication and/or lifestyle counseling. At baseline and after twelve months of follow-up lifestyle, health and work status of all participants are established with online questionnaires. Additionally after twelve months, we will determine health care utilization, costs of PPA CMR and compliance. Primary endpoints are the number of newly detected patients with CMD and changes in individual risk factors between the intervention and waiting list control group. Medical data will be extracted from the GPs' electronic medical records. In order to assess factors related to participation, we will send questionnaires to non-participants and assess characteristics of participating practices. For all participants, additional demographic characteristics will be available through Statistics Netherlands.

Discussion: The INTEGRATE study will provide insight into the effectiveness and cost-effectiveness of PPA CMR as well as determinants for participation and compliance, which represents essential information to guide further large-scale implementation of primary prevention programs for CMD.

Trial registration number: NTR4277, The Netherlands National Trial Register, 26-11-2013.

Introduction

The increasing prevalence of cardiometabolic diseases (CMD), including cardiovascular disease, diabetes mellitus and chronic kidney disease, in combination with an ageing population is a major public health problem. CMD mainly results from a long lasting exposure to an unhealthy lifestyle. The most important lifestyle related causes of morbidity and mortality are smoking, obesity and physical inactivity.¹ The increasing number of people with an unhealthy lifestyle is expected to lead to a rising prevalence of CMD in the coming decades.²⁻⁴ Therefore, early detection and adequate management of individuals at risk for CMD is urgent in order to prevent future health problems and further increase in health care costs.

Screening for CMD could be more efficient when structurally embedded in primary health care.^{5,6} General practitioners (GPs) can play an important role in preventing CMD.⁷ General practice is the optimal setting for identifying and treating patients at risk.⁸ GPs provide integrated health care, are aware of the psychosocial context and have a longstanding relationship with their patients.

Several prevention programs for CMD in primary care have been developed. These programs aim to identify patients at risk for CMD and to offer lifestyle advice and treatment when indicated.⁹⁻¹³ The core elements of these programs are evidence-based and the feasibility has been positively evaluated.^{9-12,14-18} Different parties have initiated implementation by offering their program to subgroups within the general population. However, the effectiveness and cost-effectiveness of prevention programs for CMD need to be established first to justify broad implementation in primary care.¹⁹ An effective prevention program also requires structured health care, willingness to participate and compliance of patients at risk. So far, little is known about the characteristics of practices, participants and non-participants in prevention programs in primary care.²⁰⁻²² Knowledge about determinants for non-participation will support the development of tailored strategies to reach specific subgroups. In the INTEGRATE study we aim to assess the effectiveness of a CMD prevention program coupled to an individualized lifestyle intervention. This entire program will be further referred to as “Personalized Prevention Approach for CardioMetabolic Risk” (PPA CMR).

Therefore, the objective of the INTEGRATE study is to investigate the effectiveness and cost-effectiveness of PPA CMR, as well as to assess determinants for successful participation in PPA CMR.

In this paper we will describe the design of the study and we will discuss the choices that have been made for the intervention and with regard to outcome measures.

Methods

Study design

The INTEGRATE study is a clustered stepped-wedge randomized controlled trial with a waiting list control group. A flowchart of the study and a timeline is shown in figure 1 and 2, respectively. All participants are offered the intervention (PPA CMR) during the study period. The intervention is implemented over four time periods, in randomly ordered subgroups. The intervention group starts with PPA CMR at onset of the study, the control group starts with PPA CMR one year later. The one year waiting list period is necessary to measure natural changes in lifestyle and to estimate the number of patients with newly detected CMD without exposure to PPA CMR.

Figure 1 Flowchart of the study design

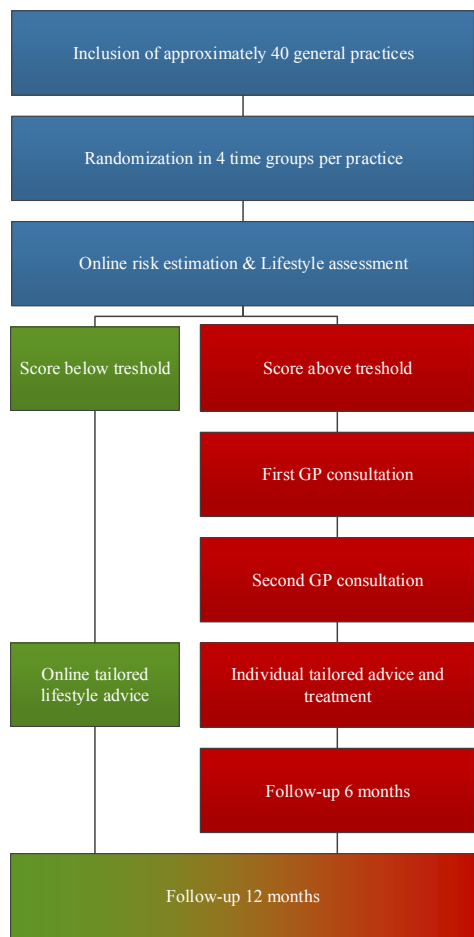


Figure 2 Timeline per practice and overview of measures

Time (months) →	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Intervention group 1	A ₁			B			C								
Intervention group 2		A ₁			B			C							
Waiting list control group 1	D						A ₂			B			C		
Waiting list control group 2		D						A ₂			B			C	

Measurements	Measuring point						Method of data collection		Outcome measure
	A ₁	A ₂	B	C	D		Q	EMR	
Online risk estimation and lifestyle profile	•	•	o	•	•		•		P
Complete lifestyle profile (with additional measures)	o	o		o			•	•	P
Newly detected CMD	o	•		•				•	P
Willingness to change	•	•	o	•	•		•		S
Health status	•	•	o	•	•		•		P
Work status and absence from work	•	•	o	•	•		•		P
Non-healthcare costs of PPA CMR			o	o			•		P
Health care utilization			•	o			•	•	P
Received preventive care			•	o			•	o	P
Compliance with treatment				o	o		•	o	P
Willingness to pay					o		•		S

• = All patients, o = Patients with an increased risk for CMD. Q = questionnaire, P = primary outcome measure, S = secondary outcome measure

Study population

The study will be conducted in approximately 40 general practices in the Netherlands, a representative sample of all Dutch general practices with regard to the distribution in rural/urban and solo/group practices. Inclusion and exclusion criteria for practices and patients are shown in table 1.

Table 1 Inclusion and exclusion criteria for practices and participants

	Inclusion	Exclusion
General practices	• Use of common Electronic Medical Record (EMR) system, in which electronic data extraction is possible.	• Recently performed screening for patients at risk for cardio-metabolic disease
Patients	• Age between 45 and 70 years	<ul style="list-style-type: none"> • Receiving antihypertensive or lipid-lowering treatment. • One of the following ICD-10-codes: K74: Angina pectoris, K75: Acute myocardial infarction, K76: Other chronic ischaemic heart disease, K77: Heart failure, K86: Uncomplicated hypertension, K87: Hypertension with secondary organ damage, K89: Transient cerebral ischemia, K90: Stroke/cerebrovascular accident, K91: Atherosclerosis, K92: Peripheral vascular diseases, T90: Diabetes mellitus, T93: Lipid metabolism disorder

Inclusion criterion for practices

• The use of an Electronic Medical Record (EMR) system, from which electronic data extraction is possible, covering approximately 90% of all Dutch general practices.

Exclusion criterion for practices

- Previously performed systematic CMD screening of the entire or a non-random sample of the practice population.

All eligible patients of the included practices (approximately 28.500 patients) receive an invitation letter from their GP to participate in the INTEGRATE study.

Inclusion criterion for patients

- Age between 45 and 70 years, which is according to the guideline of the Dutch College of GPs.¹³

Exclusion criteria for patients

- Previous diagnosis of CMD according to EMR (see table 1 for list of International Classification of Primary Care (ICPC-1)-coded diagnoses.²³
- Receiving antihypertensive and/or lipid-lowering treatment.

Randomization

Eligible patients are randomized within each general practice into four time groups: two intervention groups and two waiting list control groups. We will use the statistical software program Stata version 12 for the randomization. Every four months a new group starts with the intervention, starting with the two intervention groups. After twelve months the two waiting list control groups will sequentially start with PPA CMR.

Intervention

The intervention program “Personalized Prevention Approach for Cardiometabolic risk” (PPA CMR) is the combination of a screening tool for CMD as used in the professional guideline ‘Preventive Consultation’ (PC) of the Dutch College of General Practice¹³ and a tailored lifestyle intervention. PC is a Dutch prevention program for CMD and has been developed for integration in primary care (in Dutch: ‘PreventieConsult Cardiometabool risico’). In a pilot study in 2009 the PC has been tested with regard to its feasibility and was positively evaluated.^{8,15,17,24}

1. The intervention program of the INTEGRATE study consists of several steps:
Invitation of patients to assess their CMD risk
2. First step of screening: the online risk estimation and lifestyle assessment
3. Second step of screening: completing the CMD risk profile with additional measurements
4. Treatment of patients with an increased risk for CMD with tailored lifestyle advice and/or medication.

Invitation of patients

All eligible patients receive an invitation from their GP to participate in PPA CMR by completing an online risk estimation and optionally an online lifestyle assessment. To enhance participation rates, the accompanying information letter will summarize the details of the study in different languages. In case of non-response, a reminder letter is sent after two weeks. Enclosed with the reminder letter is a paper version of the risk estimation.

The risk estimation and lifestyle assessment

The risk estimation is based on the widely accepted FINDRISK score and is specified for predicting CMD in the Dutch population.^{25,26} This seven item-questionnaire can be completed by self-report and assesses cardiometabolic risk factors including age, gender, body mass index, waist circumference, current family history of cardiovascular disease and/or diabetes.^{13,26} The lifestyle assessment consists of questions involving smoking, physical activity, dietary patterns and willingness to change lifestyle.^{9,12}

The threshold in the risk estimation that will be used is an absolute risk for developing CMD in the next seven years of $\geq 23\%$ for men and $\geq 19\%$ for women.²⁶ Patients with scores below the threshold are at low risk and receive online tailored lifestyle advice based on the reported risk factors and the information provided in the lifestyle assessment. All patients with scores above the threshold are advised to complete their final risk profile with additional measurements, by making an appointment at their general practice.

Completing the CMD risk profile

At the general practice, the risk profile is completed by additional measurements: serum cholesterol level, fasting glucose level and blood pressure. During a second visit the final risk profile is calculated based on the SCORE risk estimation.²⁷

Treatment of patients with an increased risk for CMD

Patients will receive treatment according to their risk profile, based on recommendations on lifestyle advice and drug treatment from guidelines issued by the Dutch College of GPs (including guidelines on cardiovascular risk management, obesity management and diabetes mellitus). Participating practices offer lifestyle interventions in their own conventional manner, with the facilities available to them. Possible facilities for lifestyle interventions include the aid of a lifestyle coach to support active lifestyle change, offering structured programs for smoking cessation services, weight management or exercise programs and collaboration with other local initiatives in health programs.

Control group

Patients allocated to the waiting list control group receive an invitation from their GP - at the same moment the first intervention group is invited- to participate in a health study by completing an online questionnaire including the questions of the risk estimation and lifestyle assessment. However, these patients neither receive a risk score, nor a specific lifestyle advice. These patients will start with a one year waiting period, to be used as control comparison. After a year they are invited to participate in PPA CMR, starting with completing the risk estimation and lifestyle assessment online. Hence, the waiting list control group is offered the identical route as the intervention group. Patients in the waiting list control group receive normal standardized care during the waiting period, including lifestyle advice or diagnostics and treatment for CMD when indicated.

Response-enhancing strategies

During this study we will develop and evaluate different response-enhancing strategies in subgroups of the waiting list group. The response enhancing strategies are adjusted according to the results of non-response analyses performed early in the study (see next paragraph, endpoint 5). Possible strategies include reminders by telephone, translated questionnaires for non-Dutch speaking patients, information gatherings at the general practice and verbal reminders by the GP.

Another strategy is using a toolbox to complete the final risk profile at home. It offers the option to bypass one or both of the GP consultations. The toolbox contains a blood pressure device and a laboratory test form. Patients are asked to measure their blood pressure, visit the laboratory and to complete the results online. In case of a high blood pressure and/or elevated serum cholesterol or glucose levels, patients are advised to consult their GP. Patients without elevated biomedical risk factors receive an online tailored lifestyle advice and will therefore bypass both GP consultations. Like the other response-enhancing strategies, the toolbox option will be implemented during the intervention period of the waiting list control group.

Endpoints and measurements

The endpoints of the INTEGRATE study are shown in table 2. An overview of all measurements is shown in figure 2. For our secondary endpoints we will use the information provided for our primary endpoints.

Table 2 Primary and secondary endpoints

Primary endpoints	Secondary endpoints
1. The number of newly detected patients with a CMD in one year follow-up	1. Difference in primary outcome 5 after implementation of different response-enhancing strategies
2. Change in individual risk factors (smoking, physical inactivity, obesity, unhealthy diet, blood pressure and cholesterol levels) for CMD between baseline and one year follow-up.	2. Change in willingness to change lifestyle between baseline and one year follow-up
3. The expected number of newly detected patients with CMD and mortality after 5, 10, 20 years and lifetime	3. Change in health status between baseline and one year follow up
4. Costs-effectiveness of PPA CMR	
5. Non-participation and compliance in different stages of PPA CMR.	

Newly detected patients with CMD at baseline and one year follow-up

The number of newly detected patients with pre-existing CMD will be established after the second consultation and after one year follow-up, based on ICPC-1-coded diagnoses (table 1) in the EMRs.

1. Change in individual risk factors for CMD between baseline and one year follow-up

For patients with an increased risk for CMD, risk and lifestyle profiles will be established at the start of PPA CMR and after twelve months of follow-up. Risk profiles consist of the completed risk profile including the additional measurements done by the GP or with the self-management toolbox. The questions of the online risk estimation and lifestyle assessment are repeated after six months as well (figure 2). For patients with a low risk for CMD we will establish risk and lifestyle profiles at the start of PPA CMR and after twelve months of follow-up. These risk profiles do not contain the additional measurements.

2. Expected newly detected patients with CMD and mortality after 5, 10, 20 years and lifetime

We will use the RIVM-Chronic Disease Model (RIVM-CDM) ^{28,29} to extrapolate the number of possible prevented CMD due to PPA CMR with a time horizon of 5, 10 and 20 years. The calculations are based on changes in risk profile during one year of treatment.

3. Costs-effectiveness of PPA CMR

For patients with an increased risk for CMD, we will establish health status, work status and absence from work at the start of PPA CMR and after six and twelve months of follow-up. Health status is measured by the validated Dutch version of the SF-36 ³⁰ and the EQ-5D. ^{31,32} Work status and absence from work is measured by using parts of the

Productivity Cost Questionnaire (iPCQ).³³ Healthcare and non-healthcare costs are measured after six and twelve months of follow-up. Healthcare costs include the costs of implementing PPA CMR and any lifestyle intervention or treatment that emanates from the use of PPA CMR. Other healthcare costs are the costs of health care utilization during the one year follow-up. These costs are based on standard prices for health care use.³⁴ Non-healthcare costs include expenses made by participants during the study, e.g. own expenses for lifestyle interventions. Data on health care use, needed for the economic evaluation, will be extracted from EMR's of GPs.

For patients with a low risk of CMD we will establish health status, work status and absence from work at the start of PPA CMR and after twelve months of follow-up. After completion of PPA CMR, the willingness to pay for (parts of) this program is evaluated in all participants.

5. *Non-participation and compliance in different stages of PPA CMR*

Participation rates in the different phases of PPA CMR are measured by establishing the number of participants and the number of eligible patients in each stage (after the first invitation, after completion of the online risk estimation, after completing the risk profile and during the treatment phase). Data about the numbers of participants in each phase can be derived from the website for online respondents. The number of practice visits and compliance with treatment is established at six and twelve months with data from EMRs and self-reported compliance. We will collect information on determinants of response and non-response through the use of three different sources. First, we will send questionnaires to a random sample of patients who did not respond to the invitation of their GP for participating in PPA CMR (non-response group 1). This non-response questionnaire contains items on health risk behavior, assumptions about CMD and screening, reasons for not participating and attitudes towards response-enhancing strategies (table 3). In addition, we will send a comparable online non-response questionnaire to patients who scored above the threshold on the online risk estimation, but did not consult their GP (non-response group 2). Second, we will extract anonymized data from EMRs, including information on health care utilization of both participants and non-participants. Finally, all data will be linked with data from Statistics Netherlands to obtain information about socio-economic status (SES) and ethnic background.

Information on determinants of non-participation and successful completion of PPA CMR is used to study the differences in characteristics of responders and non-responders. We will also study differences in characteristics of participating practices (e.g. urban/rural locations, solo/group practices, organization of lifestyle interventions) to find practice-related factors that are associated with participation and compliance rates. The analyses of determinants for participation shall be performed in the first groups starting with the

intervention. Depending on the findings, response-enhancing strategies are developed and implemented in the waiting list control groups that subsequently enter the study. Data collection for subgroups receiving a response enhancing intervention is done in the same way as described above.

Table 3 Overview of measurements among non-responders

Non-response questionnaire	T=0	T=12
Risk estimation (paper)	*	
Online risk estimation and lifestyle profile	o	o
Attitude towards screening and treatment of CMD	•	
Reasons for non-participation	•	
Attitude towards response-enhancing strategies	•	
Newly detected CMD (EMR)		•
Health care utilization (EMR)		•

* = Non-responders group 1 (no response to invitation PPA CMR, no online risk estimation)

o = Non-responders group 2 (score above threshold on risk estimation, but not no GP consultation)

• = All non-responders (group 1 + 2)

Waiting list control group

From the waiting list control group we establish risk profiles, lifestyle assessment, health status, work status and absence from work at baseline and again at the start of PPA CMR one year later. At the start of PPA CMR newly detected patients with CMD will be established, based on ICPC-1-coded diagnoses in the EMRs. Patients who develop a new CMD - documented through an ICPC-1-coded diagnoses in the EMR - will not be eligible for participation in PPA CMR, but will receive questionnaires for follow-up. When the waiting list control group starts with the intervention phase, the patients follow the identical route as the intervention group (figure 2).

Analyses and statistical methods

We will analyze the data from this study according to the intention-to-treat principle. Analyses will be performed with all data available. Since the availability of data will depend on the response rate, a fully complete dataset cannot be expected. Multiple imputation techniques are used for handling missing data.

Sample size calculation

Calculation of the sample size is based on the reduction of smokers in the intervention group after one year follow-up, one of the primary outcome measures. The smoking prevalence in the Netherlands is 25%.³⁵ We expect a reduction in smoking prevalence from 25% to 20% after

one year treatment and a stable number of smokers in the waiting list control group. In order to achieve this reduction, 721 patients are needed in the intervention group. This calculation is based on an alpha of 0.05 (two-sided), a power of beta = 0.80 and a ratio intervention group versus control group of 1:4). The 1:4 ratio represents a fair comparison between the intervention and the large control group. Based on the pilot implementation study of the PC, we expect approximately 21 patients per practice in the intervention group after twelve months follow-up.^{14,15} A low response rate has been taken into account with this estimate. This would result in the inclusion of $721/21 = 34$ general practices. However, in this study patients are clustered within general practices and an oversampling of 15% is needed to correct for this clustering in multi-level analyses. Therefore, we need approximately 40 general practices. The number of participants and practices will result in sufficient power to establish statistically significant differences between other subgroups.

Effectiveness of PPA CMR

We will use multivariable multilevel regression analyses to study the effects of PPA CMR on change in individual risk factors and lifestyle and on the incidence of CMD after one year follow-up. Therefore, we compare the intervention group with the waiting list control group. In addition we will evaluate the influence of different response enhancing strategies on the effectiveness of PPA CMR. We will use linear or logistic regression for continuous or dichotomous data, respectively. Multilevel analysis is needed to correct for clustering of patients within practices.

Cost-effectiveness of PPA CMR

We will perform an economic evaluation to relate net incremental costs and effects of PPA CMR compared to the waiting list control group. Estimated costs are based on the healthcare and non-healthcare costs. After one year of follow-up, cost-effectiveness of PPA CMR will be established. To evaluate cost-effectiveness in the long term, modeling is required. We will use the RIVM-Chronic Disease Model (RIVM-CDM) to perform this long-term economic evaluation. The RIVM-CDM is a Markov-type, dynamic population-based model^{28,29} and is able to relate changes in prevalence of risk factors to changes in future incidence of CMD. The model also contains data on costs of cardiovascular events and associated losses in quality of life. This model has extensively been used for the evaluation of cost-effectiveness of prevention programs targeted at lifestyle improvement.^{34,36-38}

The cost-effectiveness will be calculated per level of change in individual risk factors. Incremental cost-effectiveness ratios (ICER) are derived from calculating the net costs of PPA CMR compared to the waiting list control group, divided by its effect. In addition, we will calculate the incremental cost-utility ratios (ICUR). Therefore, the incremental costs of PPA CMR compared to the waiting list control group will be divided by the effects in quality adjusted

life years (QALY's) gained. Utility values as incorporated in the RIVM-CDM will be used for future cardiovascular events. Probabilistic sensitivity analyses are performed for all calculations.

Determinants of participation and compliance

The number of participants during the different phases of PPA CMR will be presented with frequency tables. Differences between participants and non-participants regarding age, gender, SES, ethnic background, and cardiometabolic risk are determined using univariable analysis (*t*-test, chi-square test). We will use descriptive statistics and multivariable regression analyses to determine the profile of participants and non-participants in PPA CMR.

Privacy and informed consent

To ensure privacy of the patients, the participating practices will send the invitation letters to the patients. Additional information in the invitation letter will inform the participants about the study purposes. At the start of the online risk estimation and lifestyle assessment, all patients are asked to complete a digital informed consent form.

We will obtain data on health care utilization of all patients through data extraction from the EMR of the GPs. Based on the Dutch law for data protection, obtaining informed consent for this part of the data collection is not necessary. All obtained data will be processed anonymous, not traceable to individual patients. The study was considered by the UMC Utrecht Institutional Review Board and exempted from full assessment under the Medical Research involving human subjects Act.

Discussion

This manuscript describes the design of the INTEGRATE study, a study aiming to establish the effectiveness and cost-effectiveness of a Personal Prevention Approach for cardiometabolic risk (PPA CMR) in primary care. An additional aim is to provide more insight into the profile of participants and non-participants and the effectiveness of the various components of the program. Our final goal is to contribute to the reduction of cardiometabolic morbidity and mortality in an aging population.

Choices in study design

In the design of this study we made a number of choices that need to be addressed

Design

We have chosen a stepped-wedge randomized controlled trial design. Patients will either be allocated to the intervention group or the waiting list control group that starts the intervention

after one year. The waiting list control group is necessary to measure ‘natural’ changes in lifestyle among eligible persons and to estimate the number of newly detected CMD without exposure to PPA CMR. At the end of the study PPA CMR is completely implemented in all participating practices and all eligible patients have received the intervention. Implementation of PPA CMR is done in time periods to distribute the workload for the GPs and their staff.

Randomization

Participants are not informed about the existence of a waiting list control group and none of the participants will know to which group they are assigned. Nevertheless, the nature of this intervention makes total blinding of the participants impossible. To minimize bias and maximize the validity of the results, both groups will receive the same standardized care, according to the evidence based practice guidelines issued by the Dutch College of GPs. For practical reasons, selection and randomization of all eligible patients will be done at baseline. Randomization is performed at individual level and is done to equally distribute correlating factors of patients registered within the same practice. Because randomization takes place before consenting to participate, selective response can be induced (see ‘possible methodological threats’). Randomization within practices can cause ‘contamination’, lifestyle changes of patients may affect the lifestyle of their spouse and others in their environment. When spouses are assigned to different groups this can influence the results, causing an underestimation of the effectiveness of PPA CMR.

Integration in routine primary care

Since PPA CMR is based on a Dutch GP guideline and can be considered ‘standard care’, we have chosen to implement PPA CMR into routine primary care. This way we can evaluate the effects of an existing screening program for patients at risk for CMD combined with tailored treatment for risk factors in the most natural way.

Practice characteristics

Lifestyle interventions may differ between general practices. For example, some practices have a lifestyle coach or collaborate with local providers of lifestyle interventions whereas in other practices GPs only give lifestyle advice. Changes in lifestyle are hard to accomplish, especially maintaining a healthy lifestyle asks a lot of perseverance from patients. Intensive support by a lifestyle coach or providing local lifestyle interventions may provide the necessary continuity to achieve a more sustainable reduction in cardiometabolic risk. We will carefully document practice characteristics to evaluate which factors influence compliance with and enhance effectiveness of the program.

Modeling

One year of follow up will not be sufficient to fully assess all the costs and benefits of PPA CMR. Improvements in risk profile will only translate in a reduction in cardiometabolic events in the longer term. Modeling is therefore necessary to extrapolate study findings to the longer term. The RIVM-CDM, developed at the National Institute for Public Health and the Environment, has been widely accepted for evaluation of cost-effectiveness, also in other prevention programs.^{34,36-38} A disadvantage of modeling is the potentially large effect of small uncertainties of input data on the output of the model. For instance, if the effect of PPA CMR on patients' risk profiles would decrease after one year, this could result in an overestimation of the long-term effects of the program. Probabilistic sensitivity analysis will be performed to assess the level of uncertainty of model outputs.

Non-response analyses

The results of the non-response analyses of the INTEGRATE study will provide more information about the characteristics and motives of non-participants in PPA CMR. This knowledge is relevant and essential for the development and evaluation of participation enhancing strategies. The INTEGRATE study has a unique design where the results of the non-response analyses, performed at an early time point during the study, can be used as input for developing interventions to increase the participation rate later in the study. Effective participation enhancing strategies are useful when optimizing implementation of future prevention programs in primary care.

In comparable studies, including the pilot implementation of PC^{14,15} the response rates were low, ranging from 3% to 75%.^{14,15,18} Since this has been taken into account in the sample size calculation, sufficient power is expected even with low response rates. To enhance participation rates, we plan to use several strategies, based on advice and results of previous studies¹⁴ and on non-response analyses during the study. The accompanying information letter will emphasize safety in handling privacy sensitive data, especially digital data. Furthermore, the information letter will contain a short recap of the purpose of the letter and the advice to ask a family member for help with translation if considered necessary. The letter will present the recap in different languages. Reminder letters with a paper version of the risk estimation will be sent to all non-responders after two weeks. Furthermore, we evaluate a subgroup that is offered the possibility to bypass one of the GP consultations by ordering a toolbox. The toolbox is a tool that stimulates self-management; patients are able to take more responsibility for their own health. Furthermore, obtaining the additional measurements through a toolbox is easier to incorporate into one's busy life and this might enhance participation rates. A higher participation rate increases the cost-effectiveness of the entire program.

Possible methodological threats

Several measures minimize possible bias in this study. To prevent selection bias, we aim at a representative sample for all GP practices in the Netherlands. Participating practices will be balanced in urban and rural locations and will have variable sizes, containing both solo and group practices. Selective participation can be an issue, since prevention programs sometimes tend to attract the patients referred to as the ‘worried-well’.^{14,18,39} However, the pilot implementation of the prevention program PC showed no presence of this effect.^{14,15} The non-response analysis performed during study is sensitive to selection bias in case of low response rates and selective responders.

During this study participants are asked to report their own expenses and health care utilization, including consultations. Data collection by self-report can induce recall bias, but in combination with EMR data, we assume the outcome measures to be more reliable.

Implementation challenges

Due to health care policy there is a possibility that changes in the health care environment will occur over time. For example, changes in established compensations for participation in prevention programs by health care insurers can influence the compliance and participation rates. However, these changes will occur in both the intervention groups and the waiting list control groups equally, so we expect this will not influence our study results.

Conclusion

Prevention programs for CMD are an actual topic in health care. Under pressure of politics and society, implementation of these programs has already been initiated. Nevertheless, primary prevention of CMD by early risk factor modification has not yet been proven effective and cost-effective at population level. Before implementation on a large scale can be carried out, scientific support must be presented. If the INTEGRATE study shows PPA CMR to be effective and cost-effective, this will provide the evidence base that is needed for setting up prevention programs for CMD at national level. With determination of the profile of non-responders in prevention programs in primary care, the results of the INTEGRATE study will also assist in the development and implementation of similar prevention programs.

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2.2

Erratum to: Design of the INTEGRATE study: effectiveness and cost-effectiveness of a cardiometabolic risk assessment and treatment program integrated in primary care

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Introduction

The INTEGRATE study investigates the effectiveness and cost-effectiveness of a “Personalized Prevention Approach for Cardiometabolic risk” (PPA CMR). This is a combination of an online risk estimation as used in the Dutch guideline ‘the Prevention consultation’ (Dutch PC-guideline)¹ and a tailored lifestyle intervention. The different steps of PPA CMR are described in our protocol.²

Interim analysis

First results INTEGRATE

The first interim analysis in October 2014 in 11 practices showed expected response rates of 40 % on the first step. However, the results of the online risk estimation (step 2) were different than expected. Only 27 % of the participants had a score above threshold and was eligible for the third step. This is far less than the 60 % that we had expected, based on results of the pilot study in 2009.³ As a consequence, only half of the expected participants proceeds to step 3 of the intervention (additional measurements).

Risk estimation

The explanation for the difference between the findings is a slight change in the algorithm of the risk score used for the 2011 Dutch PC-guideline as compared to the algorithm used in the 2009 pilot study. According to information provided by the guideline team of Dutch College of GPs, responsible for the guideline, the risk score calculation was reassessed before publication in the Dutch PC-guideline.

The assumptions made for the sample size calculation for the INTEGRATE study are based on the results of the risk score calculation in the pilot study.

The guideline authors and the INTEGRATE research team conclude that there is a chance that the risk score calculation as used in the INTEGRATE study could lead to a number of misclassified participants at moderate risk for cardiometabolic diseases (CMD) who score under the threshold. To study this, we have decided to adapt the study protocol.

Amendment in protocol

In addition to our published protocol we will perform additional measurements in a selection of participants with scores below threshold in April and June 2016. We will invite this group for the same intervention as the participants with a score above threshold.

Criteria for inviting people for additional measurements will be participants with one of the following risk factors for CMD:

- a family history of cardiovascular disease
- BMI >27
- smokers aged 50 and older

The results will show the number of newly detected CMD and CMD risk factors in a subgroup of participants with scores below threshold. Sensitivity analyses will show in what range the risk estimation is most (cost-) effective. Based on these results we will be able to give advice whether to reassess the threshold of the risk score in the Dutch PC guideline.

Consequences

The aim of the study remains unchanged: “the effectiveness and cost-effectiveness of a cardio-metabolic risk assessment and treatment program integrated in primary care”.

The sample size calculation is no longer applicable. The intervention group will be smaller than expected in the original protocol. This has consequences for the power of the study. The study might not have sufficient power to detect a difference in the number of smokers. However, the study will have sufficient power to detect differences in the other CMD risk factors such as BMI and blood pressure.

The cost-effectiveness analysis will be performed according to plan.

Additional measurements will be performed in the last two groups of study participants in April and June 2016 (eligible participants n=10.000) with risk scores below threshold and aforementioned risk factors for CMD.

Ethics and funding bodies

The described amendment in our protocol was approved by the UMC Utrecht Institutional Review Board and exempted from full assessment under the Medical Research involving human subjects Act.

We have received additional funding by ZonMw (The Netherlands organization for Health Research and development), Lekker Lang Leven (a collaboration of the Dutch Diabetes

Research Foundation, the Dutch Heart Foundation and the Dutch Kidney foundation) and Innovatiefonds Zorgverzekeraars (Healthcare Insurance Innovation Fund) to compensate for the 6 month delay and the costs for the additional measurements. The Dutch College of GPs who developed the Dutch PC-guideline fully supports the amendment made in our protocol.

Conclusion

The amendment in the protocol is in our opinion the best solution to guarantee the validity of the INTEGRATE study. The aim of our study remains unchanged. However, the amendment will enable us to establish the optimal and most cost-effective threshold for the online risk estimation. Furthermore it gives us the opportunity to advice the Dutch College of GP's how to improve the Dutch PC-guideline.

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Mismatch between self-perceived and calculated cardiometabolic disease risk among participants in a prevention program for cardiometabolic disease: a cross-sectional study

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Abstract

Background: The rising prevalence of cardiometabolic diseases (CMD) calls for effective prevention programs. Self-assessment of CMD risk, for example through an online risk score (ORS), might induce risk reducing behavior. However, the concept of disease risk is often difficult for people to understand. Therefore, the study objective was to assess the impact of communicating an individualized CMD risk score through an ORS on perceived risk and to identify risk factors and demographic characteristics associated with risk perception among high-risk participants of a prevention program for CMD.

Methods: A cross-sectional analysis of baseline data from a randomized controlled trial conducted in a primary care setting. 7,547 individuals aged 45-70 years without recorded CMD, hypertension or hypercholesterolemia participated. The main outcome measures were: 1) differences in cognitive and affective risk perception between the intervention group - who used an ORS and received an individualized CMD risk score- and the control group who answered questions about CMD risk, but did not receive an individualized CMD risk score; 2) risk factors and demographic characteristics associated with risk perception.

Results: No differences were found in cognitive and affective risk perception between the intervention and control group and risk perception was on average low, even among high-risk participants. A positive family history for diabetes type 2 (β 0.56, CI95% 0.39-0.73) and cardiovascular disease (β 0.28, CI95% 0.13-0.43), BMI \geq 25 (β 0.27, CI95% 0.12-0.43), high waist circumference (β 0.25, CI95% 0.02-0.48) and physical inactivity (β 0.30, CI95% 0.16-0.45) were positively associated with cognitive CMD risk perception in high-risk participants. No other risk factors or demographic characteristics were associated with risk perception.

Conclusion: Communicating an individualized CMD risk score did not affect risk perception. A mismatch was found between calculated risk and self-perceived risk in high-risk participants. Family history and BMI seem to affect the level of CMD risk perception more than risk factors such as sex, age and smoking. A dialogue about personal CMD risk between patients and health care professionals might optimize the effect of the provided risk information.

Trial registration: Dutch trial Register number NTR4277, registered 26th Nov 2013

Introduction

The rising prevalence of cardiometabolic diseases (CMD), defined as cardiovascular disease (CVD), diabetes type 2 (DM2) and chronic kidney disease (CKD), calls for effective preventive programs. CVD, DM2 and CKD share risk factors such as dyslipidemia, hypertension, smoking and overweight. Therefore, they are suitable for a combined disease prevention strategy.¹ Self-assessment of CMD risk, for example through an online risk score (ORS) at home, may help to identify individuals at high-risk^{1,2} and might motivate people for risk reducing behavior.³ For these reasons, an ORS has been incorporated as first step in the Dutch primary care CMD prevention program.²

Theoretically, ORSs are easy applicable, user friendly, and have the potential to reach many people at risk compared to individual case finding. However, for the effective implementation of an ORS based prevention strategy, it is conditional that individuals understand their risk and perceive it as being of personal relevance.^{4,5} Only then, individuals may engage in risk reducing behavior, such as adopting a healthier lifestyle or visiting a health care professional for advice or treatment.⁶ However, it is widely known that for lay people, the concept of 'personal disease risk' and the accompanying risk levels and cutoff points are difficult to understand.⁷ While health care professionals are familiar with applying mean group results from clinical research to individual cases, for a patient only the individualized risk of disease counts.

Risk perception is a complex concept including not only a cognitive aspect (i.e. the perceived susceptibility to get a disease) but also an affective component (i.e. feelings about the risk, such as worry).⁸ Furthermore, risk perception is influenced by contextual factors such as preexistent beliefs and medical knowledge about risk factors and risk reducing strategies.⁹⁻¹¹ Besides the traditional cognitive aspect, it is also recommended to measure feelings-of-risk that represents the more affective part of risk perception.^{8,12,13}

People who overestimate their CMD risk might have disproportional worries and - as a consequence - unnecessarily consult a health care professional. However - more important - high-risk individuals with low perceptions of their risk might not engage in the necessary lifestyle changes or not consult a health care professional. Qualitative studies have shown a wide variation in the way people use and understand information from ORS.^{3,10,11}

Little is known to what extent the use of an ORS - applied in a primary care setting - actually influences users' risk perception. In addition, more insight into determinants associated with risk perception in high-risk individuals is needed to optimize future CMD risk communication and management.

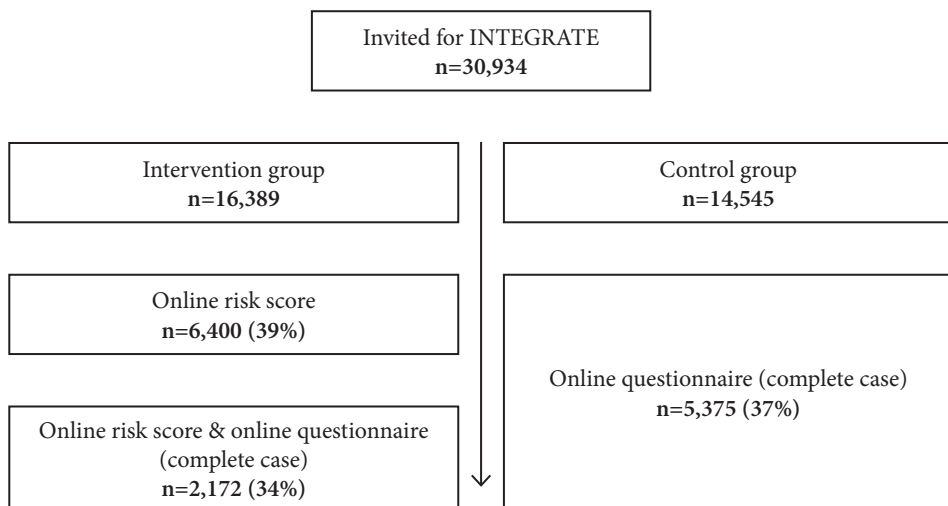
Therefore, the study objective was to assess the impact of communicating individualized CMD risk scores - by using an ORS - on people's risk perception and to identify CMD risk factors and demographic characteristics associated with the level of risk perception within high-risk participants of a Dutch prevention program for CMD.

Methods

Study design

We performed a cross sectional analysis among 7,547 participants from the INTEGRATE study, a stepped-wedge randomized controlled trial on the (cost)-effectiveness of a Dutch CMD prevention program in primary care. In 2014 and 2015, 37 participating general practices invited all listed patients aged 45-70 years without an established CMD, hypertension or hypercholesterolemia to participate in a stepwise prevention program for CMD. The ORS was used as a first step in the prevention program to identify high-risk individuals. Details about the design of the INTEGRATE study have been published elsewhere.¹⁴ For the current study, we used baseline data from participants of the intervention and the control group (figure 1).

Figure 1 Flowchart of participants



The online risk score and online questionnaires were filled out at baseline

Participants and measurements

Intervention group

For the intervention group, we used data of participants who completed the ORS as part of the CMD prevention program. The ORS addressed age, sex, smoking status, body mass index (BMI) (height and weight), waist circumference and family history of DM2 and CVD.

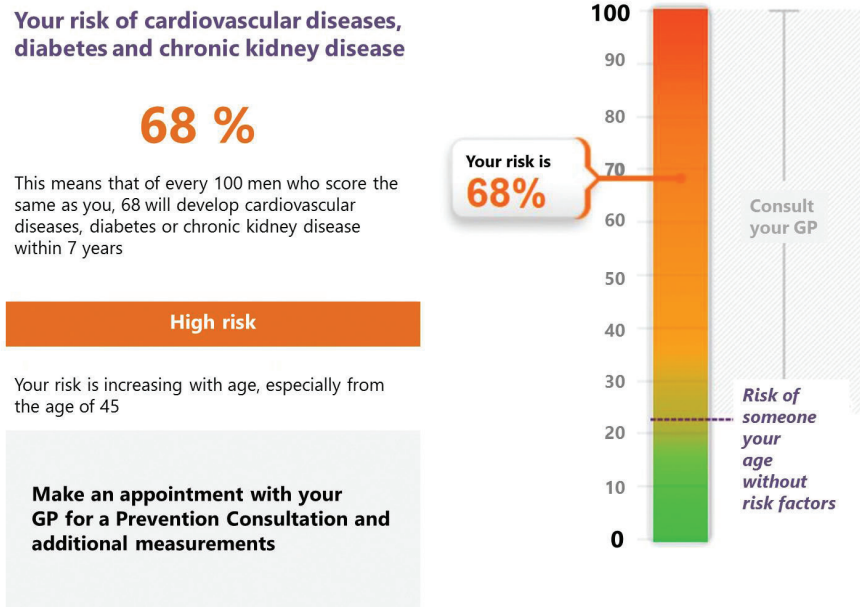
Participants immediately received their individualized CMD risk score online (figure 2 and figure 3). The ORS was developed to identify high-risk individuals who qualify for further risk examination, including blood pressure measurement and laboratory tests on cholesterol and glucose levels, and was recently externally validated.^{1,15} The threshold for high CMD risk in the ORS was an absolute risk for developing a CMD in the next seven years of $\geq 23\%$ for men and $\geq 19\%$ for women.¹ In case of a high-risk for CMD, participants were advised to visit their general practitioner (GP) for further risk profiling. In all other cases they received tailored lifestyle advice and a link to a detailed lifestyle assessment.

After completing the ORS, the participants of the intervention group were automatically invited via email to fill out an additional online questionnaire (OQ). The OQ consisted of questions involving demographic characteristics (age, sex, marital status (single; relationship, but not living together; married/living together) and educational level (low: primary and lower secondary education, middle: upper secondary and intermediate vocational education, high: higher vocational education (applied sciences) and university). In addition, the OQ included questions about CMD risk factors: sex, age, smoking (yes/no), BMI ($<$ or ≥ 25 kg/m²), waist circumference (≤ 80 or > 80 cm for women and ≤ 94 or > 94 cm for men), family history of DM2 and CVD (negative/positive), physical activity (active/inactive) and alcohol consumption (\leq or > 14 units per week for women and \leq or > 21 units per week for men). The cutoff level for physical activity was based on the Dutch recommendation for physical activity which entails 30 minutes moderate to vigorous exercise per day in 5 days per week.¹⁶ Finally, the OQ comprised questions about risk perception.

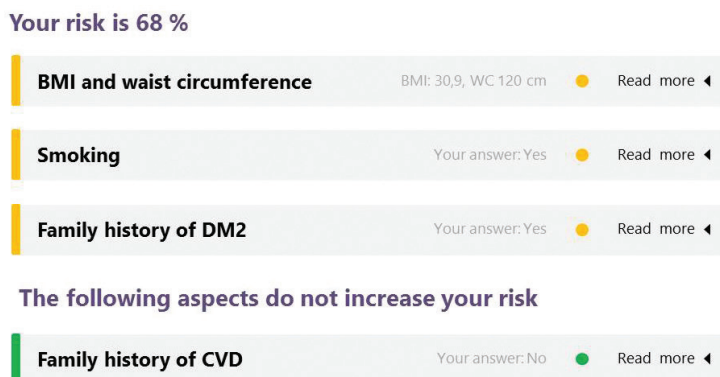
Individuals' risk perception of CVD, DM2 and CKD was measured, assessing both cognitive and affective risk perception. Because there is no agreement in the literature on how perceived risk should be optimally assessed, we chose two measures which are known to correlate best with behavioral change^{12,13} Cognitive risk perception was assessed by asking: '*how do you estimate your risk for developing 1) cardiovascular disease? or 2) diabetes? or 3) chronic kidney disease?*' Answers were given on a 7-point Likert-scale (1=extremely low, 7= extremely high). Affective risk perception was assessed on a 7-point Likert-scale (1=not worried at all, 7= extremely worried) by asking: '*Are you worried about your risk to develop CVD, DM2 and CKD respectively?*'

Control group

Participants of the control group only filled out the OQ, including the same variables as used in the ORS, so that we were able to calculate their CMD risk, but they neither received an individualized CMD risk score nor a tailored lifestyle advice. One year later these participants were invited for the intervention.

Figure 2 Example of risk score for a 62-years old male with a high-risk for CMD

Individuals' risk is presented as a percentage, a natural frequency (e.g. 68 out of 100 will develop CMD in the next 7 years), a bar chart (including comparison to a peer without risk factors) and a verbal label (e.g. a 'high risk')

Figure 3 Example of (non)-contributing risk factors for a 62-years old male with a high-risk for CMD

A list of individuals' risk factors that contribute to the personalized risk is displayed. On request – by clicking the button- additional information on CMD risk and risk factors is provided.

Abbreviations: BMI=body mass index, WC= waist circumference, CVD=cardiovascular disease, DM2= Diabetes Mellitus type 2

Analysis

To establish the impact of using the ORS on CMD risk perception we performed a complete case analysis among all participants who had completed the questions about risk perception in the OQ. To create an overall score for CMD risk perception, we calculated composite scores for cognitive and affective risk perception by taking the average of the responses to the risk perception questions regarding CVD, DM2 and CKD. Descriptive statistics were used to present demographics of the intervention and control group (percentages or means). Two-tailed t-tests were used for continuous and Likert-scale outcomes¹⁷ and chi-square test for dichotomous or categorical outcomes to detect differences between the intervention group and control group. Spearman's correlation was used to correlate calculated risk categories and risk perception scores. Statistically significant differences were defined as a p-value <0.05.

To establish risk factors and demographic characteristics associated with risk perception in case of high-risk, we used data of high-risk participants in the intervention group. All participants in this group had received an individualized risk score and were advised to take "action" (visit the general practice) accordingly.

We built two multivariable linear¹⁷ regression models to establish determinants associated with (cognitive and affective) CMD risk perception. CMD risk perception scores (both cognitive and affective) were used as dependent variables. As independent variables we used sex, age, education level, smoking status, BMI, waist circumference, activity level, alcohol intake and family history for DM2 and CVD. We chose to dichotomize all risk factor variables, because thresholds for a high waist circumference and/or high alcohol intake are different among men and women. Using a continuous scale would have required separate regression models for men and women, resulting in the loss of power. All statistical analyses were performed using STATA version 14.0.

Results

At the time the analysis was conducted 6,400 participants of the intervention group completed the ORS - of which 2,172 (34%) completed the ORS and the OQ - in the control group 5,375 participants completed the OQ, leaving a study population of 7,547 participants. Table 1 shows demographics and risk profiles of the participants. Participants of the intervention group were slightly younger, more often highly educated and less often had a positive family history of DM2 compared to participants in the control group.

In addition, more participants of the intervention group showed a healthy lifestyle profile regarding risk factors such as smoking, BMI and physical activity compared to the control group (table 1). CMD risk based on the online risk score did not significantly differ between groups (40.3% vs. 42.8% had a high-risk).

Table 1 Baseline characteristics, risk factors and CMD risk

	Intervention group N=2,172	Control group N= 5,375	P-value
Demographics			
Sex (%)			0.65
Male	45.0	45.6	
Age at randomization (years; mean (SD))	56.1 (SD 7.1)	56.5 (SD 6.9)	< 0.01
Marital status (%)			0.98
Single	14.6	14.6	
Relationship, but not living together	3.3	3.4	
Married/living together	82.1	82.1	
Education level ¹ (%)			< 0.01
Low	12.9	17.6	
Middle	43.3	44.1	
High	43.8	38.3	
CMD risk factors			
Positive CVD family history (%)	31.4	33.4	0.09
Positive DM2 family history (%)	19.7	23.1	< 0.01
Current smoker (%)	10.4	14.7	< 0.01
BMI ≥ 25 (%)	42.0	45.6	< 0.01
High waist circumference ² (%)	80.4	81.0	0.51
Physical Inactivity ³ (%)	48.6	51.7	0.02
High alcohol intake ⁴ (%)	14.7	16.1	0.14
CMD risk			
CMD ⁵ risk based on risk score (%)			0.10
Low	7.0	6.2	
Intermediate	52.7	51.1	
High	40.3	42.8	

Total of percentages may not equal 100% due to rounding

¹ Education level: low = primary & lower secondary education, middle= upper secondary & intermediate vocational education, high= higher vocational education (applied sciences) & university

² >80 cm for women and >94cm for men

³ < 5 days a week of 30 minutes moderate to vigorous exercise per day

⁴ >14 units/week for women and >21 units/week for men

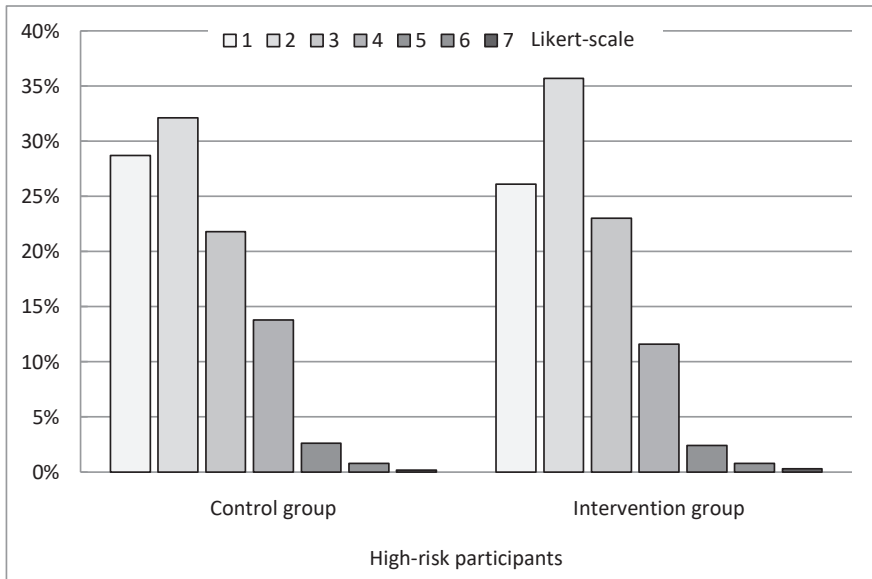
⁵ High absolute risk for men $\geq 23\%$, for women $\geq 19\%$

Abbreviations: CVD=cardiovascular disease, DM2= Diabetes Mellitus type 2, BMI=body mass index

Impact of receiving an individualized CMD risk score through an ORS on risk perception

Receiving an individualized CMD risk score did not influence cognitive or affective risk perception. Among high-risk participants, mean cognitive CMD risk perception scores were 2.3 (SD 1.2) in both intervention and control group. For affective risk perception, corresponding scores were 2.0 (SD 1.1) in both groups. Figure 4 shows the frequency distribution on the 7-point Likert-scale for cognitive CMD risk perception in high-risk participants.

Figure 4 Frequency distribution for cognitive CMD risk perception in high-risk participants



In low- and intermediate-risk participants, the scores for cognitive risk perception did not differ either between intervention and control group. In case of low-risk mean cognitive perception scores were 1.6 (SD 0.8) vs. 1.7 (SD 0.9) ($p=0.31$) and affective perception scores were 1.6 (SD 0.9) vs. 1.5 (SD 0.8) ($p=0.07$) respectively.

Intermediate-risk participants had mean cognitive risk perception scores of 2.2 (SD 1.1) and mean affective risk perception scores of 2.0 (SD 1.1) in both groups.

In both the intervention and control group, very weak correlations were found between risk categories and cognitive (ρ 0.11, $p<0.01$ and ρ 0.09, $p<0.01$, respectively) and affective (ρ 0.07, $p<0.01$ and ρ 0.08, $p<0.01$, respectively) risk perception scores.

Determinants associated with risk perception

Table 2 shows risk factors and demographics associated with cognitive and affective CMD risk perception in high-risk individuals within the intervention group (n=876), who all received a personal risk estimate. A positive family history for DM2 (β 0.56, CI95% 0.39-0.73) and CVD (β 0.28, CI95% 0.13-0.43), a BMI \geq 25 (β 0.27, CI95% 0.12-0.43), a high waist circumference (β 0.25, CI95% 0.02-0.48) and inactivity (β 0.30, CI95% 0.16-0.45) were positively associated with cognitive CMD risk perception.

A positive family history for DM2 (β 0.42, CI95% 0.24-0.59), BMI \geq 25 (β 0.22, CI95% 0.06-0.38), and inactivity (β 0.24, CI95% 0.10-0.39) were positively associated with affective risk perception.

Table 2 Multivariable linear regression of demographics and CMD risk factors associated with CMD risk perception among high-risk† participants within the intervention group (n=876)

	Cognitive risk perception			Affective risk perception		
	beta	95% CI	P-value	beta	95% CI	P-value
Positive DM2 family history	0.56	(0.39-0.73)	<0.01*	0.42	(0.24-0.59)	<0.01*
Positive CVD family history	0.28	(0.13-0.43)	<0.01*	0.15	(-0.00-0.30)	0.06
BMI ≥25	0.27	(0.12-0.43)	<0.01*	0.22	(0.06-0.38)	<0.01*
Inactivity ¹	0.30	(0.16-0.45)	<0.01*	0.24	(0.10-0.39)	<0.01*
High waist circumference ²	0.25	(0.02-0.48)	0.03*	0.21	(-0.02-0.44)	0.08
Age	-0.01	(-0.03-0.00)	0.08	-0.01	(-0.03-0.00)	0.10
Smoking	0.17	(-0.04-0.38)	0.12	-0.02	(-0.24-0.19)	0.82
High alcohol intake ³	-0.08	(-0.26-0.10)	0.40	-0.05	(-0.23-0.14)	0.61
Sex (0=female, 1=male)	0.03	(-0.12-0.18)	0.72	0.04	(-0.11-0.19)	0.63
Education level ⁴						
middle	0.00	(-0.19-0.19)	0.97	0.00	(-0.19-0.19)	0.99
high	0.01	(-0.19-0.21)	0.92	-0.07	(-0.27-0.13)	0.46

† High absolute risk for men ≥ 23%, for women ≥19%

¹ < 5 days a week of 30 minutes moderate to vigorous exercise per day² >80 cm for women and >94cm for men³ >14 units/week for women and >21 units/week for men⁴ Education level: low = primary & lower secondary education, middle= upper secondary & intermediate vocational education, high= higher vocational education (applied sciences) & university

* significant

Abbreviations: CMD= cardiometabolic diseases DM2= Diabetes Mellitus type 2, CVD=cardiovascular disease, BMI=body mass index

Discussion

Summary of results

Communicating individualized CMD risk scores by using an ORS had no significant impact on personal risk perception of participants. Risk perception scores in high-risk participants were relatively low in both the intervention and control group, even though the intervention participants had received the result of the ORS. In high-risk participants, a positive family history for DM2 or CVD, BMI ≥ 25 and physical inactivity were associated with a higher risk perception.

Interpretation of results

Our finding that receiving an ORS generated individualized CMD risk score did not affect individuals' risk perception is notable. The underlying assumption of using an ORS, for example as first step in the Dutch CMD prevention program to identify high-risk individuals, is that the ORS helps people to become aware of their risk and initiate preventive actions accordingly. However, even after completing a risk score and receiving personalized CMD risk estimates, most people with a high CMD risk still had low perceptions of risk. Our results confirm the results of Harle and colleagues who found no improvement in risk perception after providing personalized risk estimates through an ORS for DM2.¹⁸ However the results are in contrast to a recent systematic review¹⁹ which showed that providing patients with CVD risk estimates - primarily oral, written or visual interventions - for primary prevention overall did seem to change risk perception and increased the accuracy of perceived risk. However, the authors indicated that the included studies were heterogeneous (e.g. design and setting) and of low-medium quality. In addition, the included studies rarely assessed web-based interventions.

Several factors have been described which may impede adequate understanding and acceptance of risk. People seem to associate the readily visible risk factors such as BMI and a positive family history for DM or CVD with CMD risk²⁰⁻²³ which is supported by our findings. Possible explanations for why these factors influence risk perception are closeness to an affected relative or the experience of his/her illness and the genetic predisposition which makes a positive family history of personal relevance.²⁴⁻²⁶ However, risk factors such as age, sex and smoking outweigh the aforementioned risk factors by far in relation to their impact on CMD risk. This discrepancy between perceived risk and calculated risk has also been described in previous studies.^{20,27,28} Our participants seemed to value CMD risk factors differently than the established epidemiological models.

Apart from existing beliefs about the influence of particular risk factors, other psychological processes can also play a role in processing risk information. For example, motivated skepticism has been reported in the context of receiving breast cancer risk estimates. If the presented risk estimate is different than expected, people tend to question it.²⁹ In addition, unrealistic

optimism about health prospects or defensive coping strategies might also cause rejection of unexpected (high) risk levels.³⁰

Finally, problems with understanding the communicated risk by an ORS should be taken into account. It is known that people have difficulties with understanding numerical risk.^{9,10,12,31–33} Despite the fact that the personalized ORS incorporated important aspects of risk communication - several numerical risk presentations, a visual display of CMD risk, comparative risk information, positive framing and a clear explanation about CMD risk and risk factors – it apparently does not change risk perception.

Practical implications

A mismatch between calculated risk and risk perception after using an ORS may have major consequences for the effectiveness of CMD prevention programs. Why would patients visit their GP in case of high-risk if they maintain perceptions of low-risk? Interpreting our results, the question rises if an ORS alone is enough to adequately inform people about their risk. Previous qualitative studies have indicated that people prefer to use an ORS together with a health care professional to make sense of the result.^{5,34} To optimize informed decision making, a health care professional could help patients to interpret the result of the ORS, while taking into account their perceptions, preferences and expectations regarding risk management. In addition, the 'risk-age' or 'lifetime-risk calculator' could be used to illustrate CMD risk and to show the effects of changing risk factors or lifestyle.³⁵ Furthermore, raising public awareness about the asymptomatic nature of CMD risk factors and preclinical CMD, the multifactorial etiology of CMD and the multiplicative effect of risk factors could help to improve risk perceptions.

Strengths and limitations

Strengths of this study are the use of a large sample size, its implementation in routine primary care - instead of an evaluation in an experimental setting- and the pragmatic randomized design of the INTEGRATE study, which allowed us to investigate the effect of receiving an online individualized CMD risk score on people's perceived risk. A second important strength is the fact that we have investigated a web-based intervention.

A number of cautions must also be kept in mind. First, we performed a cross-sectional analysis on baseline data. Only prospective research can determine whether the associations found exert a causal influence on risk perception.

Second, we used only few questions to assess risk perception. However, the risk perception measures were carefully chosen based on previous evidence that these measures predict behavior change best. In addition, it was demonstrated that combining individual risk items into multi-item scales did little to nothing to improve predictions.¹² Moreover, we explicitly wanted to minimize the administrative burden for our participants, especially for those with

lower educational levels. Although the questions to measure risk perception were carefully selected and have frequently been used in previous studies^{8,12,13,18,20}, these measures were not validated. Potential ramifications are thus an under- or overestimation of the results. However, even if such a measurement error has occurred this would have affected both the intervention and control group, and would not have changed the difference between the two groups. We did not assess people's absolute risk perception (i.e. a numerical estimate) because there are known difficulties with such an approach³⁶ and it can be argued that it captures people's recall of exact numbers rather than how people think or feel about their risk.^{12,13}

Third, only 34% of the intervention group completed the additional OQ with questions about risk perception. This step was voluntary and may have induced selection bias. The non-responders on the OQ were younger (mean 55.0 vs. 56.1 years; $p < 0.01$) and were more frequently smokers (15.8% vs. 10.4%; $p < 0.01$) compared to the participants. However, a recent study solely among smokers showed that also among this group 62% of the high-risk participants underestimated their CVD risk.³⁷ Although the OQ was automatically sent after completing the ORS, few participants indicated to have made an appointment with the general practice. Due to the very short time frame, only a handful could have received additional measurements in the meantime. This was supported by the finding that risk perception scores between those who indicated to have made an appointment and those who did not were equal.

Fourth, participants of the intervention group were slightly higher educated than the control group. As a result, we might have expected a more accurate risk perception in the intervention group. However, the results did not show such an effect.

Finally, the control group seemed to be less healthy than the intervention group concerning certain behavioral risk factors. However, it is important to state that these differences were too small to translate in differences in absolute CMD risk between the groups according to the calculated risk score.

Therefore, we assume that these two groups still were fairly comparable. Overall, we believe that these limitations did not vitiate the main conclusions of this paper.

Conclusion

Communicating individualized CMD risk scores by using an ORS - as part of a CMD prevention program - does not affect individuals' CMD risk perception. In addition, our results demonstrate a considerable mismatch between calculated CMD risk and individual risk perception. The majority of participants who were informed about a high CMD risk still perceived their risk as being low. A positive family history for DM2 and CVD and a BMI ≥ 25 seemed to determine individuals' risk perception more than sex, age and smoking. From our results we conclude that people value CMD risk factors differently than epidemiological models

do. A dialogue about personal CMD risk and risk perception between patients and health care professionals seems necessary to optimize the effect of the provided risk information.

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Effectiveness of a stepwise cardiometabolic disease prevention program:
results of a randomized controlled trial in primary care

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Abstract

Effective preventive strategies for cardiometabolic disease (CMD) are needed. We aim to establish the effectiveness of a stepwise CMD risk assessment followed by individualized treatment if indicated compared to care as usual. We conducted a RCT between 2014 and 2017. Individuals (45-70 years) without CMD or CMD risk factors were invited for stepwise CMD risk assessment through a risk score (step1), additional risk assessment at the practice in case of high-risk (step2) and individualized follow-up treatment if indicated (step3). We compared newly detected CMD and newly prescribed drugs during one-year follow-up, and change in CMD risk profile between baseline and one-year follow-up among participants who completed step2 to matched controls. A CMD was diagnosed almost three times more often (OR 2.90, 95%CI 2.25:3.72) in the intervention compared to the control group, in parallel with newly prescribed antihypertensive and lipid lowering drugs (OR 2.85, 95%CI 1.96:4.15 and 3.23, 95%CI 2.03:5.14 respectively). Waist circumference significantly decreased between the intervention compared to the control group (mean -3.08cm, 95%CI -3.73:-2.43). No differences were observed for changes in BMI and smoking. Systolic blood pressure (mean -2.26mmHg, 95%CI -4.01:-0.51) and cholesterol ratio (mean -0.11, 95%CI -0.19: -0.02) significantly decreased within intervention participants between baseline and one-year follow-up. In conclusion, implementation of the CMD prevention program resulted in the detection of two- to threefold more patients with CMD. A significant drop in systolic blood pressure and cholesterol levels was found after one year of treatment. Modelling of these results should confirm the effect on long term endpoints.

Trial registration: Dutch trial Register number NTR4277

Introduction

Cardiometabolic disease (CMD), such as cardiovascular disease (CVD), diabetes type 2 (DM2) and chronic kidney disease, is the leading cause of premature death and disability worldwide and is a key driver of escalating health care costs.¹ An estimated 80% of CMD is attributed to modifiable risk factors, including hypercholesterolemia, high blood pressure, smoking, obesity, physical inactivity, unhealthy diet and excessive alcohol intake.^{2,3} Lifestyle interventions have been demonstrated to improve these risk factors and to subsequently reduce CMD risk in high-risk patients.⁴⁻⁷ Therefore, the primary target for reducing the burden of CMD is the identification and treatment of these risk factors in high-risk patients, preventing CMD becoming clinically manifest. A large proportion of the high-risk population is still unaware of its risk status⁸ and this has prompted the initiation of systematic risk assessment approaches to identify those at increased CMD risk.

Targeted prevention of high-risk individuals is recommended by the 2016 guidelines of the European Society of Cardiology.³ In 2011 the guideline “the prevention consultation for CMD” was developed by the Dutch College of General Practitioners⁹, which entails a stepwise CMD risk assessment followed by individualized lifestyle intervention and treatment if indicated. Although systematic CMD risk assessment is already performed in several countries¹⁰⁻¹², structural implementation of stepwise CMD prevention programs in primary care has not yet taken place due to ongoing controversy about its (cost)-effectiveness.¹³

A recent Cochrane review suggests that individual CVD risk assessment may increase the prescription of lipid-lowering and antihypertensive medication and may slightly improve the risk profile of high-risk individuals.¹⁴ On the other hand, however, screening of the general population has not yet been demonstrated to reduce all-cause or CVD related mortality.^{8,15-17} Therefore, we designed the INTEGRATE study aiming to establish the effectiveness of a stepwise CMD prevention program in a randomized clinical trial in primary care.

Methods

Design

The INTEGRATE study (Dutch trial Register number NTR4277) is a stepped-wedge randomized controlled trial (RCT), comparing stepwise CMD risk assessment followed by individualized treatment with care as usual. The intervention was offered to the control group after one year. The study was conducted in 37 general practices in the Netherlands from April 2014 to April 2017. Details about the study design, setting, participant enrolment, and intervention components are described elsewhere.¹⁸

Participants

All patients aged 45-70 years listed in the participating practices without CMD, a CMD risk factor, or antihypertensive, lipid lowering or antidiabetic treatment according to their electronic health record (EHR), were eligible for participation. General practitioners (GPs) invited these patients to participate through a personal letter (figure 1).

Intervention

Patients allocated to the intervention group were invited for the stepwise CMD prevention program. The first step consisted of the completion of a risk score (online or on paper) to estimate their individual CMD risk. The risk score included seven questions about sex, age, smoking status, BMI (height and weight), waist circumference and a family history of premature CVD (age <65 years) and/or DM2 and resulted in the absolute risk to develop a CMD in the next seven years.^{19,20} The risk score incorporated components from the widely accepted FINDRISC questionnaire and the SCORE risk function and is externally validated.²⁰⁻²² The algorithm behind the risk score maintains a threshold for an increased risk of $\geq 23\%$ for men and $\geq 19\%$ for women. Participants at increased risk were advised to visit the practice (second step) for additional risk profiling, which included blood pressure measurement and laboratory tests on total cholesterol, cholesterol ratio (total cholesterol/ high-density-lipoprotein (HDL), low-density-lipoprotein (LDL) and fasting glucose levels). In the third step, that of individualized treatment, patients received lifestyle advice and - if indicated - tailored treatment following recommendations in the Dutch College of GPs guidelines. Due to the pragmatic nature of the program, performance on each step was dependent on the voluntary participation of the individuals.

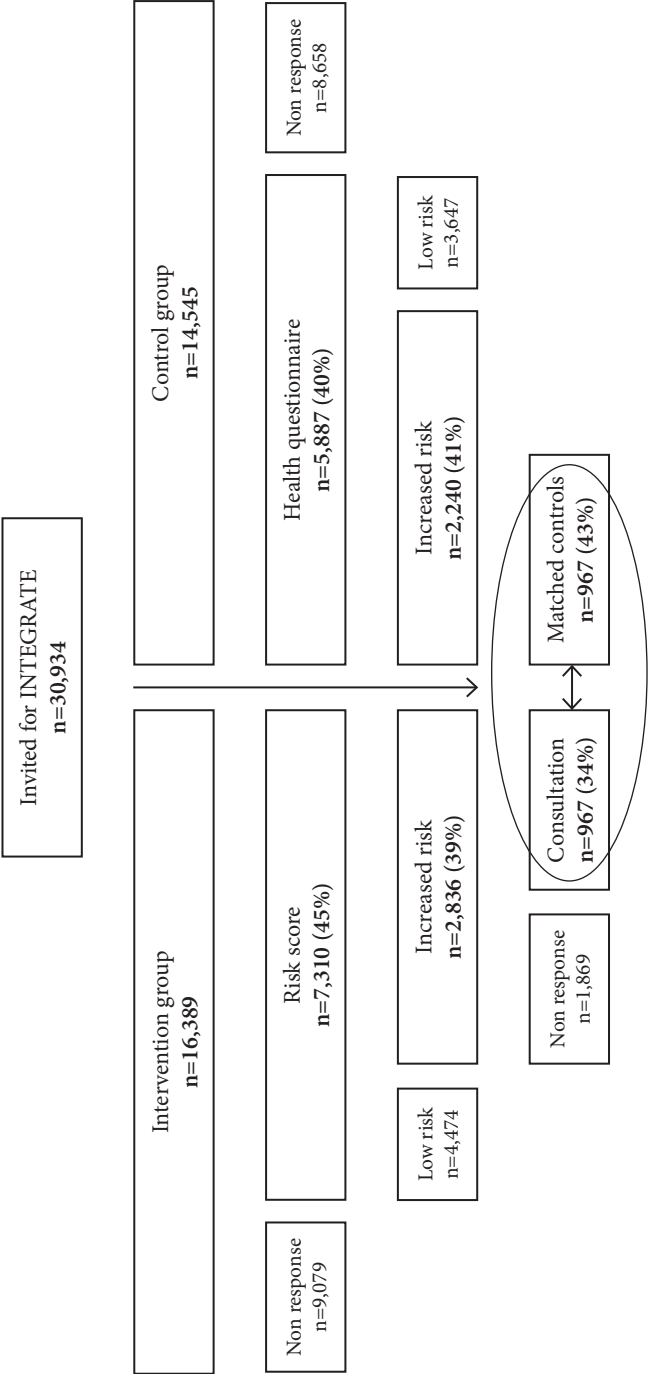
Controls

Participants allocated to the control group were invited to complete a health questionnaire including questions about demographic characteristics, CMD risk factors and lifestyle. These participants did not complete the risk score, and did not receive a personal CMD risk estimate, nor tailored lifestyle advice or treatment. During follow-up, they received care as usual until they were invited for the CMD prevention program one year later.

Outcome variables

We used two primary outcomes: (1) the number of patients with newly detected CMD or with newly started drug treatment (box 1) during one year follow-up and (2) the mean change in individual CMD risk factors and the mean change in absolute 10-year CVD mortality risk (SCORE-EU) between baseline and one-year follow-up.

Figure 1 Flowchart of participants



Box 1 CMD and prescriptions**ICPC-codes of CMD:**

K74: Angina pectoris
 K75: Acute myocardial infarction
 K76: Other chronic ischemic heart disease
 K77: Heart failure
 K86: Uncomplicated hypertension
 K87: Hypertension with secondary organ damage
 K89: Transient cerebral ischemia
 K90: Stroke/cerebrovascular accident
 K91: Atherosclerosis
 K92: Peripheral vascular diseases
 T90: Diabetes mellitus
 T93: Lipid metabolism disorder

ATC clusters:

A10: antidiabetic drugs
 C02-03, C07-C09: antihypertensive drugs
 C10: lipid lowering drugs

Abbreviations: CMD=cardiometabolic disease, ICPC=International Classification of Primary Care, ATC=Anatomical Therapeutic Chemical Classification System

Measurements

Participants in the intervention group filled out the risk score and additional online questionnaires at baseline and one-year follow-up including topics on demographic characteristics and additional CMD risk factors. Participants in the control group filled out the health questionnaire and additional questionnaires on demographics and risk factors at baseline and after one year. Measurements have been described in detail elsewhere.¹⁸

Data collection

We collected data on the following CMD risk factors at baseline and after one-year follow-up: sex, age, smoking status, BMI, waist circumference, a family history of premature CVD and/or DM2, physical activity and diet. These data were derived from the risk score, the health questionnaire and additional questionnaires. From the EHR of the GP we collected data on newly detected CMD and newly prescribed drugs (see box 1.) during one year follow-up.

For the intervention group, additional EHR data on systolic and diastolic blood pressure, total cholesterol, cholesterol ratio (total cholesterol/HDL), LDL and fasting glucose levels were collected at baseline (at the first visit to the GP) and after one year follow-up.

Sample size

We based the power of the study on the change in the main (behavioural) risk factor for CMD, which is smoking. In order to be able to detect a 5% reduction in smoking prevalence, 721 patients

were needed in the intervention group from approximately 40 practices, including 15% over-sampling to correct for clustering in multi-level analyses. This calculation was based on a type 1 error of 0.05 (two-sided) and 1-power of 0.20.

Randomization

Within each practice, patients were randomly allocated on individual level by a computer (Stata version 12.0) to the intervention or the control group. Patients in the intervention group started in two cohorts with two months intercept (and not four months as described previously¹⁸) to ensure a feasible implementation in the practices. Participants in the control group had no knowledge of an ongoing intervention.

Ethics

The study was considered by the UMC Utrecht Institutional Review Board and exempted from full medical ethical assessment according to Dutch legislation. All included participants gave written informed consent.

Analyses

For the analyses, we defined the intervention group as participants who completed the two-step risk assessment, as confirmed in case report forms, EHR or by self-report. Control group risk scores were calculated based on the health questionnaire. Participants of the intervention group were individually matched to participants in the control group with an increased risk based on sex, age (in 5-years categories), smoking status and BMI (<25 or ≥ 25) (flowchart 1).

We used descriptive statistics (percentages and means) to describe baseline characteristics of the intervention and control group. Differences between the groups were examined by t-tests for continuous outcomes and chi-square tests for dichotomous outcomes.

Since the availability of follow-up data was dependent on the response rate of participants, we anticipated on incomplete follow-up and missing data.¹⁸ To minimize the loss of information we used multiple imputation techniques and imputed baseline and outcome variables on CMD risk factors in case of missing data, assuming data were missing at random. For the variables derived solely from the follow-up questionnaires (such as on physical activity and diet) more than 50% of data was missing, due to low (on average 46%) response rates. These variables were not imputed and analyzed, because non-response analysis demonstrated that these missing data were not at random.

Multivariable multilevel regression analysis was used to assess the effect of the intervention on the change in individual risk factors after one-year follow-up between the intervention and control group. We built three models with each risk factor (smoking, BMI and waist circumference) as a dependent variable. We also used multivariable multilevel regression analysis (with eight different models) to investigate differences in incidence of CMD and pre-

scriptions during one-year follow-up. As dependent variables we included newly diagnosed hypertension, hypercholesterolemia, diabetes, the total sum of newly diagnosed CMD and newly prescribed antihypertensive, lipid lowering or antidiabetic treatment and the total sum of newly prescribed medication (box 1). All analyses were controlled for treatment allocation and cluster effects, using a random intercept in each model. We corrected for baseline values in the models analysing CMD risk factor change.

For the intervention group, eight multivariable multilevel models were built to analyze changes in systolic and diastolic blood pressure, total cholesterol, cholesterol ratio, LDL, fasting glucose levels and absolute 10-years risk of fatal CVD (SCORE-EU) between baseline and one-year follow-up. In these models we entered the individual CMD risk factor or SCORE-EU percentage as dependent variables. All analyses were controlled for baseline CMD risk factors, except for the SCORE-EU analysis, since the SCORE-EU outcome is a composite score of CMD risk factors. Measurements were clustered on different levels (within participants and within practices), therefore we fitted a two-level model with patients at level 1 and practices at level 2.

The outcomes were considered statistically significant if p-values were ≤ 0.05 . All statistical analyses were performed using STATA 15.0.

Results

Participation

In total, 30,934 patients were invited to participate in the INTEGRATE study, 16,389 were allocated to the intervention group and 14,545 to the control group. Of the participants in the intervention group 7,313 (45%) filled out the CMD risk score and in the control group 5,887 (40%) of the participants filled out the health questionnaire. Within the intervention group 2,836 (39% of all respondents on the risk score) had an increased risk, of which 967 (34%) visited their GP for additional risk profiling. Within the control group 2,240 (41% of the respondents on the health questionnaire) individuals had an increased risk and from this group 967 participants were individually matched to a participant in the intervention group, resulting in an intervention and matched reference group of 1,934 participants (flowchart 1).

Study population characteristics

The mean age of the participants was 63 years in both groups, and 55% were female (table 1). We observed no difference between intervention and control group with regard to the frequency of CMD risk factors (sex, age, smoking status, BMI, waist circumference and a family history of premature CVD and/or DM2). Participants of the intervention group had a mean systolic blood pressure of 135.6 (SD 18.3) mmHg, a total cholesterol/HDL ratio of 3.9 (SD 1.2),

LDL of 3.7 (SD 0.9) mmol/l and a fasting glucose of 5.4 (SD 0.8) mmol/l. The mean 10 years CVD mortality risk (SCORE-EU) of the participants in the intervention group was 3.3% (SD 2.9).

Table 1 Baseline characteristics

	Intervention group N=967	Control group N= 967	P-value
Demographics			
Gender (%)			0.93
Female	55.4	55.2	
Male	44.6	44.8	
Age (years; mean (SD))	62.8 (5.1)	63.0 (5.0)	0.25
CMD risk factors of risk score			
Positive CVD family history <65 years (%)	40.9	37.3	0.11
Positive DM2 family history (%)	25.9	28.4	0.20
Current smoker (%)	16.6	16.6	1.00
BMI (mean (SD))	25.9 (3.6)	26.0 (4.0)	0.52
Waist circumference (mean (SD))	98.2 (11.8)	99.0 (10.6)	0.12
Additional CMD risk factors (mean (SD))			
Systolic blood pressure (mmHg) (n=799)	135.6 (18.3)	n/a	
Diastolic blood pressure (mmHg) (n=770)	80.0 (9.9)	n/a	
Total/HDL cholesterol ratio (n=766)	3.9 (1.2)	n/a	
Total cholesterol (mmol/l) (n=764)	5.8 (1.0)	n/a	
LDL (mmol/l) (n=736)	3.7 (0.9)	n/a	
Fasting glucose (mmol/l) (n=715)	5.4 (0.8)	n/a	
SCORE-EU† (%) (n=698)	3.3 (2.9)	n/a	

† 10 years CVD mortality risk, the Netherlands is considered a “low-risk” country²¹

Abbreviations: CVD=cardiovascular disease, DM2= Diabetes Mellitus, BMI=body mass index, HDL=High-density-lipoprotein, LDL=Low-density-lipoprotein

Newly detected CMD

During one year follow-up hypertension was diagnosed twice as frequent in the intervention group compared to the control group (OR 2.39; 95% CI 1.72;3.32) (table 2), hypercholesterolemia three times more (OR 3.51; 95% CI 2.40;5.13) and total CMD almost three times more often (OR 2.90; 95% CI 2.25;3.72). Although absolute numbers were small, DM2 was diagnosed seven times more often in the intervention group (OR 7.13; 95% CI 2.12;24.00). A parallel trend was found for new prescriptions for CMD with almost threefold more antihypertensive and lipid lowering drugs prescribed (OR 2.85; 95% CI 1.96;4.15 and OR 3.23; 95% CI 2.03;5.14 respectively) in the intervention group compared to the control group.

Table 2 Newly diagnosed CMD and prescriptions during 12 months follow-up

	Intervention group N=967	Control group N=967	OR	95% CI
Newly diagnosed: n (%)				
Hypertension ¹	127 (13.1)	58 (6.0)	2.39	[1.72;3.32]
Hypercholesterolemia ²	123 (12.7)	41 (4.2)	3.51	[2.40;5.13]
Diabetes mellitus ³	21 (2.2)	3 (0.3)	7.13	[2.12;24.00]
No. of participants with a newly diagnosed CMD†	258 (26.7)	112 (11.6)	2.90	[2.25;3.72]
Newly prescribed: n (%)				
Antihypertensives ⁴	106 (10.9)	40 (4.1)	2.85	[1.96;4.15]
Lipid-lowering drugs ⁵	75 (7.8)	25 (2.6)	3.23	[2.03;5.14]
Antidiabetics ⁶	10 (1.0)	1 (0.1)	10.17	[1.30;79.74]
No. of participants with a new prescription††	161 (16.6)	58 (6.0)	3.13	[2.29;4.30]
Newly diagnosed CMD or newly prescribed: n (%)				
No. of participants with a new recorded CMD or prescription	283 (29.3)	131 (13.6)	2.75	[2.17;3.49]

¹ ICPC codes: K86/K87, ² ICPC code: T93, ³ ICPC code: T90, ⁴ ATC cluster: C02-03, C07-C09, ⁵ ATC cluster: C10, ⁶ ATC cluster: A10

† ICPC-codes: K74: Angina pectoris, K75: Acute myocardial infarction, K76: Other chronic ischaemic heart disease, K77: Heart failure, K86: Uncomplicated hypertension, K87: Hypertension with secondary organ damage, K89: Transient cerebral ischemia, K90: Stroke/cerebrovascular accident, K91: Atherosclerosis, K92: Peripheral vascular diseases, T90: Diabetes mellitus, T93: Lipid metabolism disorder

†† ATC cluster: A10 (antidiabetics), C02-03, C07-C09 (antihypertensives), C10 (lipid lowering drugs).

Abbreviations: CMD=cardiometabolic disease, ICPC=International Classification of Primary Care, ATC=Anatomical Therapeutic Chemical Classification System

Changes in CMD risk factors between groups

After one year, waist circumference significantly decreased with on average 3.08 cm (95% CI -3.73; -2.43) between the intervention and the control group (table 3). No differences were observed for changes in BMI (0.05 kg/m²; 95% CI -0.12;0.22) and smoking status (OR 0.75; 95% CI 0.44;1.28).

Changes in CMD risk factors and SCORE-EU within the intervention group

In the intervention group a significant decrease in systolic blood pressure (-2.26 mmHg; 95% CI -4.01; -0.51) was found between baseline and one year follow up (table 4). Accordingly, the levels of total cholesterol (-0.15 mmol/l; 95% CI -0.23; -0.07), the cholesterol ratio (-0.11; 95% CI -0.19;-0.02) and LDL (-0.16 mmol/l; 95% CI -0.23; -0.08) decreased significantly.

Subgroup analyses showed that patients treated with antihypertensive or lipid lowering drugs had a larger decrease in systolic blood pressure (-15,90 mmHg; 95% -20.34; -11.47) respectively cholesterol levels (e.g. LDL -1.55 mmol/l; 95% CI -1.87;-1.23) compared to those

without pharmacotherapy. Systolic blood pressure also significantly decreased in individuals with a newly diagnosed hypertension who did not receive drug treatment (-6.82 mmHg; 95% CI -13.07;-0.57) (details displayed in table 4). Among those who did not either get a new diagnosis or prescription for CMD no changes in CMD risk factors were found after one year follow up (data not shown). Although the uncorrected mean SCORE-EU of participants in the intervention group did not change after one year (-0.08%; 95% CI -0.21;0.05) after correction for trend related to ageing (annual increase of 0.3%) the corrected mean 10-years CVD mortality risk decreased with -0.39% (95% CI -0.53;-0.25) during one year follow-up.

Table 3 Change in modifiable risk factors between baseline and 12 months follow-up

	Δ intervention group	Δ control group	Multilevel analysis†	
			Beta	95% CI
BMI (kg/m²)	-0.05	-0.11	0.05	[-0.12;0.22]
Waist circumference (cm)	-2.81	0.42	-3.08	[-3.73;-2.43]
			OR	95% CI
Current smoker (%)	-3.25	-2.19	0.75	[0.44;1.28]

† All analyses were corrected for baseline values
Abbreviations: BMI=body mass index



Table 4 Change in CMD risk factors between baseline and 12 months follow-up within the intervention group

	Total group		Recorded diagnosis without prescription in EHR †		Recorded prescription in EHR † ‡	
	Beta	95% CI	Beta	95% CI	Beta	95% CI
<i>Hypertension</i>						
	N=967		N=44		N=106	
Systolic blood pressure (mmHg)	-2.26	[-4.01;-0.51]	-6.82	[-13.07;-0.57]	-15.90	[-20.34;-11.47]
Diastolic blood pressure (mmHg)	-0.59	[-1.48 ;0.31]	-1.60	[-5.60; 2.39]	-6.46	[-8.95;-3.96]
<i>Hypercholesterolemia</i>						
	N=967		N=81		N=75	
Total cholesterol (mmol/l)	-0.15	[-0.23;-0.07]	-0.12	[-0.33; 0.09]	-1.63	[-1.97;-1.30]
Total/HDL cholesterol ratio	-0.11	[-0.19;-0.02]	-0.02	[-0.22; 0.18]	-1.29	[-1.64;-0.94]
LDL (mmol/l)	-0.16	[-0.23;-0.08]	-0.13	[-0.31; 0.06]	-1.55	[-1.87;-1.23]
<i>Diabetes type 2</i>						
	N=967		N=11		N=10	
Fasting glucose (mmol/l)	-0.02	[-0.08; 0.05]	-0.04	[-0.68; 0.59]	-2.59	[-4.54;-0.64]

† Hypertension: ICPC K86/K87; Hypercholesterolemia: ICPC T93; Diabetes type 2: ICPC T90

† ‡ Hypertension: ATC C02-03, C07-C09 with or without ICPC K86/K87; Hypercholesterolemia: ATC C10 with or without ICPC T93; Diabetes type 2: ATC A10 with or without ICPC T90

Abbreviations: CMD=cardiometabolic disease,, HDL=High-density-lipoprotein, LDL=Low-density-lipoprotein, CVD=cardiovascular disease, ICPC=International Classification of Primary Care, ATC=Anatomical Therapeutic Chemical Classification System

Discussion

In this large scale, population-based trial in primary care, implementation of a structured stepwise CMD prevention program resulted in the detection of two- to threefold more patients with CMD in high-risk individuals and a significant decrease in 10-years mortality CVD-risk after one year follow-up. In parallel, about three times more antihypertensive and lipid lowering drugs were prescribed in the intervention group resulting in a significant drop in mean systolic blood pressure (-2.26 mmHg) and cholesterol levels (e.g. -0.16-mmol/l LDL reduction) in the intervention group after one year. Except for a reduction in waist circumference (-3.08 cm), we did not find changes in behavioural risk factors between the intervention and control group after one year.

Strengths and limitations

To our knowledge this is the first large RCT in daily practice evaluating the effectiveness of structural implementation of a stepwise CMD prevention program in primary care. The study practices consisted of both rural and urban practices of variable sizes²³ and we consider the exposed practice population as being representative for the primary care patient population in the Netherlands. The program was implemented in collaboration with the local practice staff, ensuring an efficient and feasible implementation. In our opinion this pragmatic approach and 'real-life setting' make the results generalizable to Dutch primary care.

However, several limitations must be addressed. According to what we had expected, patient selection – due to selective non-response – may have occurred on the two-step risk assessment. A selected group of high-risk participants visited their GP (second step). We found responders to be older (62.7 vs. 61.5 p<0.01), more often female (55.2% vs. 47.2% p<0.01) and less frequently smokers (16.5% vs. 26.6% p<0.01) compared to high-risk participants who did not consult their GP. Although some may label this as selection bias, we consider this a reflection of the 'real life' selection process for participation in CMD prevention programs. We performed a matching procedure to create the most appropriate reference group for comparing this intervention group. In addition, by performing multilevel analysis we controlled for clustering of patients within practices. Moreover, an explicit advantage of stepwise screening methods is that it limits the number of people qualifying for further examinations.²⁴

Secondly, sending a health questionnaire to the control group at baseline may have triggered control-participants to visit their GP for CMD risk assessment. However, even if this so-called Hawthorne effect was induced it would have – above all – reduced the contrast between the analysed groups, resulting in an underestimation of the effect of the intervention.

The third challenge was the high number of missing data, which is probably also associated with the 'real life' setting of the trial. We used multiple imputation techniques to handle small amounts of missing data. However, we faced a large amount of missing data in the voluntary

follow-up questionnaires. Although reminders were sent after two and four weeks, the overall response rate was low (46%). This made us decide to exclude the behavioural risk factors, physical activity and diet, from the final analysis.

Interpretation of results and comparison with existing literature

In 27% of the intervention group we found a newly diagnosed CMD or CMD risk factor that required active monitoring and/or treatment, which is consistent with the 22% found in the 2009 pilot study evaluating the feasibility of the precursory program.²⁵

Our results confirm those of previous studies, which demonstrated that CMD prevention programs including intensive lifestyle interventions directed at high-risk individuals have favourable effects on CVD risk profiles and on individual risk factors such as blood pressure and cholesterol levels.^{4,5,26,27} Additionally subgroup analysis in our study shows that the reduction in blood pressure and cholesterol levels is probably mainly attributable to drug treatment. Although it is hard to confirm that lifestyle changes contributed to this effect, it was remarkable that blood pressure also dropped in a small group (n=44) of newly diagnosed hypertensive patients who did not receive antihypertensive drugs.

In addition we found a significant decrease in waist circumference. Since waist circumference is known for measurement errors²⁸ and BMI did not change in the same direction, drawing firm conclusions about this effect is challenging. A possible explanation described in literature may be an increase in physical activity²⁹, but we did not measure data on physical exercise. No changes were found for the other behavioural risk factors such as smoking and BMI. In general, lifestyle changes are hard to accomplish and often not sustainable over a longer period.³⁰ In addition, attendance and completion rates for lifestyle programs are often modest and considerably variable in general practice.³¹ Earlier we reported that the options for lifestyle interventions within the participating practices were limited and that the awareness of referral options for community-based lifestyle services was low²³, possibly explaining the disappointing changes in lifestyle. This may change in future, as from 2019 on, lifestyle coaching is reimbursed by Dutch health care insurance companies, which may lead to better compliance, higher participation rates and increased effectiveness of lifestyle intervention programs.

Implications for research and practice

Our results show that implementation of a stepwise CMD prevention program is feasible and effective, and can detect high-risk individuals in a simple and non-invasive way. This supports the recommendation of the European Society of Cardiology (2016) for targeted population screening every five year.³ Future research should determine the optimal timeframe for repeated screening.

Although general practitioners have a longstanding relation with their patients and are optimally suited for individual risk assessment, it remains a challenge to reach all patients

eligible for prevention. Also in our study the response rate on the initial invitation was only 45%. Additional non-response analyses may lead to strategies to improve compliance and participation rates.

Furthermore, long term follow-up and modelling of the effects of this program are required to establish its cost-effectiveness in terms of reduced morbidity and mortality, justifying reimbursement and large scale implementation in primary care.

Conclusion

Large scale implementation of a CMD prevention program in primary care proved feasible and effective, resulting in additional detection of patients with CMD (risk factors) and subsequent treatment. Modelling of these results to long term reduction of morbidity and mortality will have to confirm the (cost) effectiveness of the CMD prevention program. Future research should focus on improving participation and achievement of sustained life style changes in order to further optimize the effect of prevention programs.

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Uptake and detection rate of a stepwise cardiometabolic disease
detection program in primary care - a cohort study

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Abstract

Background: Early detection and treatment of cardiometabolic diseases (CMD) in high-risk patients is a promising preventive strategy to anticipate the increasing burden of CMD. The Dutch guideline “the prevention consultation” provides a framework for stepwise CMD risk assessment and detection in primary care. The aim of this study was to assess the outcome of this program in terms of newly diagnosed CMDs.

Methods: A cohort-study among 30,934 patients, aged 45-70 years without known CMD or CMD risk factors, who were invited for the CMD detection program within 37 general practices. Patients filled out a CMD risk score (step1), were referred for additional risk profiling in case of high-risk (step2), and received lifestyle advice and (pharmacological) treatment if indicated (step3). During one-year follow-up newly diagnosed CMD, prescriptions and abnormal diagnostic tests were assessed.

Results: 12,738 patients filled out the risk score of which 865, 6665 and 5208 had a low, intermediate and high CMD risk, respectively. 1,755 high-risk patients consulted the general practitioner, in 346 of whom a new CMD was diagnosed. In an additional 422 patients a new prescription and/or abnormal diagnostic test was found.

Conclusion: Implementation of the CMD detection program resulted in a new CMD diagnosis in one-fifth of high-risk patients who attended the practice for completion of their risk profile. However, the potential yield of the program could be higher given the considerable number of additional risk factors – such as elevated glucose, blood pressure and cholesterol levels- found, requiring active follow-up and presumably treatment in the future.

Introduction

Cardiometabolic diseases (CMD) defined as cardiovascular disease (CVD), diabetes type 2 (DM2) and chronic kidney disease are the leading cause of death and of a reduced quality of life worldwide.^{1,2} CMD are causally related to modifiable lifestyle factors such as smoking, physical inactivity, unhealthy diet and overweight^{3,4} which can be reduced through a healthy lifestyle. About a quarter of the Dutch population smokes and almost half of the people are overweight or obese.⁵ Due to an increasing prevalence of obesity⁵, the related risk factors such as hypertension, dyslipidaemia and an impaired fasting glucose will rise; inevitably leading to increasing rates of CMD.

Early detection and treatment of CMD risk factors could diminish overall CMD risk and a combined approach targeted at case finding of high-risk individuals with subsequent CMD screening might be an efficient preventive strategy.⁶ This is supported by the European Society of Cardiology considering targeted systematic risk assessment for men ≥ 40 and women ≥ 50 without known CMD risk factors.⁴

Although programs for systematic CMD risk assessment⁷⁻⁹ have been implemented in several countries, early detection of CMD in Dutch primary care is still non-programmatic and mainly directed at individual case finding.^{7,10}

In 2011 the Dutch College of General Practitioners (DCGPs) developed a clinical practice guideline to provide a framework for structured stepwise CMD risk assessment and detection in primary care ('the prevention consultation').¹¹ It focuses on all individuals aged 45-70 without known CMD or CMD risk factors. This stepwise program entails the self-assessment of CMD risk through a risk score (first step) and - in case of high-risk - a referral to the practice for further risk profiling (second step) and individualized treatment if indicated (third step). Pilot studies evaluating precursors of this program showed participation rates between 33-75% and found a new CMD in about one-fifth of high-risk patients who attended the practice.¹²⁻¹⁴ As the CMD detection program is not yet widespread implemented, its overall impact is unknown.

Therefore, the aim of the present cohort study was to assess the yield of implementing this stepwise CMD detection program in terms of uptake and detection rate of newly diagnosed CMD in 37 general practices across the Netherlands.

Methods

Design

We performed a cohort study within the framework of the INTEGRATE study among 12,738 patients in the Dutch CMD detection program. The INTEGRATE study is a stepped-wedge randomized controlled trial that was conducted in 37 general practices in the Netherlands.

The design of the study has been described previously.¹⁵ The study was considered by the UMC Utrecht Institutional Review Board and exempted from full ethical assessment.

Participants

Patients, aged 45-70 years without recorded CMD, CMD risk factors or treatment with antihypertensive, lipid lowering or antidiabetic drugs were invited through a personal letter by their GP in a time frame of two years.

The Dutch CMD detection program

The Dutch CMD detection program has a stepwise approach.¹¹ The first step is an online risk score (paper version available), consisting of questions regarding sex, age, smoking status, BMI (increased if ≥ 25 kg/m²), waist circumference (increased if ≥ 80 cm for women and ≥ 94 cm for men) and a family history of premature CVD (age < 65 years) and DM2. The risk score incorporates components of the widely accepted FINDRISK score and the SCORE Risk Charts, and is externally validated.^{6,16-18} On the basis of the risk score, patients are categorized as having low, intermediate or high risk. A high risk is defined as a chance to develop CMD in the next seven years of $\geq 23\%$ for men and $\geq 19\%$ for women.⁶ Patients with a score below threshold are categorized as having a low risk (no risk factors present) or an intermediate risk (one or several risk factors present). These patients receive tailored lifestyle advice online. In case of high risk, patients are referred to their GP for additional risk profiling (step two) - including blood pressure measurement and laboratory tests on fasting glucose, total cholesterol, HDL and LDL levels - and appropriate follow-up treatment (step 3).

Outcome variables

The primary outcome was newly diagnosed ICPC-coded CMD recorded in the electronic health record (EHR) (box 1) in high-risk patients who completed the two-step risk assessment.

Secondary outcomes were 1) new prescriptions of antihypertensive, lipid lowering or antidiabetic drugs without a CMD diagnosis during one year follow-up 2) abnormal diagnostic test results reported during the first GP visit (blood pressure $\geq 140/90$ mmHg, total cholesterol/HDL ratio $\geq 5-8$, total cholesterol level ≥ 8 mmol/l and/ or total cholesterol/HDL ratio ≥ 8 , fasting glucose $\geq 6-7$ mmol/l (pre-diabetes) or fasting glucose levels ≥ 7 mmol/l) without a CMD diagnosis or prescription and 3) newly diagnosed ICPC-coded CMD and new prescriptions in patients with a risk score below threshold.

Box 1 CMD, prescriptions, abnormal diagnostic test results

ICPC-codes of CMD: K74: Angina pectoris K75: Acute myocardial infarction K76: Other chronic ischemic heart disease K77: Heart failure K86: Uncomplicated hypertension K87: Hypertension with secondary organ damage K89: Transient cerebral ischemia K90: Stroke/cerebrovascular accident K91: Atherosclerosis K92: Peripheral vascular diseases T90: Diabetes mellitus T93: Lipid metabolism disorder
ATC clusters of prescriptions: A10: antidiabetic drugs C02-03, C07-C09: antihypertensive drugs C10: lipid lowering drugs
Abnormal diagnostic test results: Blood pressure $\geq 140/90$ mmHg Total cholesterol/HDL ratio $\geq 5-8$ Total cholesterol ≥ 8 mmol/l or total cholesterol/HDL ratio ≥ 8 Fasting glucose $\geq 6-7$ mmol/l (prediabetes) Fasting glucose ≥ 7 mmol/l

Abbreviations: CMD=cardiometabolic diseases, ICPC= International Classification of Primary Care, ATC=Anatomical Therapeutic Chemical Classification System

Measurements

All patients completed the risk score and filled out additional online questionnaires at baseline and one year follow-up including topics on demographic characteristics and CMD risk factors. Measurements have been described in detail elsewhere.¹⁵

Data collection

Baseline data on CMD risk factors (sex, age, smoking status, BMI, waist circumference and a family history of premature CVD and DM2) were derived from the CMD risk score.

For high-risk patients who attended the practice - as confirmed in the EHR, case report forms or self-report - we collected data on newly diagnosed ICPC-coded CMD and prescriptions of antihypertensive, lipid lowering and antidiabetic drugs during one year follow-up (box 1). In addition, we collected data on abnormal diagnostic test results during the first GP visit (box 1). Abnormal diagnostic test results were defined according to thresholds for hypertension and impaired fasting glucose levels and treatment thresholds for hypercholesterolemia in Dutch and/or European guidelines.^{4,19,20}

For low- and intermediate-risk patients we collected data on newly diagnosed ICPC-coded CMD and new prescriptions from the EHR during one year follow-up.

Analysis

Demographic characteristics and CMD risk factors were tabulated for all patients.

The yield of the program was based on the number of high-risk patients 1) who attended general practice and 2) were identified with a new ICPC-coded CMD diagnosis during one year follow-up. We calculated the number needed to screen (NNS) as the inverse of the proportion of high-risk patients with a new CMD diagnosis to all invitees.

In order to estimate the potential additional yield of the program, we examined the number of new prescriptions without a CMD diagnosis during one year follow-up and abnormal diagnostic test results reported during the first GP visit without a CMD diagnosis or prescription recorded in the EHR.

For the low and intermediate risk groups, we tabulated newly diagnosed ICPC-coded CMD and new prescriptions recorded during one year follow-up. Analyses were performed using STATA version 15.

Results

Participants

In total 30,934 eligible patients were approached, of whom 12,738 (41%) consented to participate and completed the risk score as first step of the program. Of those 67% was below the age of 60 years, and 54% were female (5-year age categories displayed in table 1). Of those who completed the risk score 7% (n=865) was categorized as having a low CMD risk, 52% (n=6,665) as having an intermediate risk and 41% (n=5,208) as having a high risk. Detailed description of CMD risk factors per risk category are summarized in table 1.

Of the 5,208 high-risk patients, 1,755 (34%) consulted their GP (figure 1). These patients had a mean systolic blood pressure of 134.4 (SD 17.6) mmHg, a total cholesterol/HDL ratio of 3.9 (SD1.1), LDL of 3.7 (SD0.9) mmol/l and a fasting glucose of 5.4 (SD 0.9) mmol/l. Their mean 10 years CVD mortality risk (SCORE-Risk Charts) was 3.1% (SD 2.6) (table 1).

Table 1 Baseline characteristics

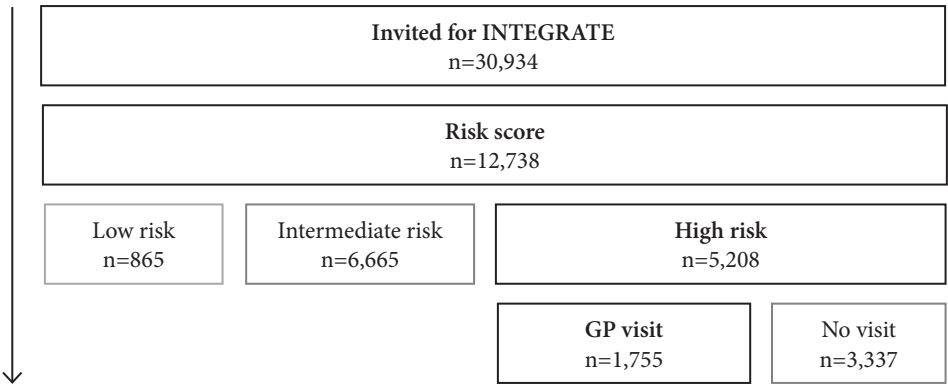
		Risk category			
		Low N=865	Intermediate N=6,665	High N=5,208	Total group N=12,738
Demographics					
Sex (%)					
Female		39.4	58.7	49.4	53.6
Male		60.6	41.3	50.6	46.4
Age (5-years categories) (%)					
45-49 years		35.8	36.3	1.6	22.1
50-54 years		36.8	37.2	6.5	24.6
55-59 years		26.2	23.0	17.1	20.8
60-64 years		1.2	3.5	36.1	16.7
65+ years		-	-	38.8	15.9
CMD risk factors					
Positive CVD family history (%)		0	29.0	36.0	29.9
Positive DM2 family history (%)		0	17.9	21.5	18.1
Current smoker (%)		0	9.3	21.6	13.7
BMI (categories) (%)					
< 25 kg/m2		100	57.7	45.4	55.5
25-30 kg/m2		-	37.2	41.5	36.5
> 30 kg/m2		-	5.1	13.1	8.0
Waist circumference (categories) (%)					
Women	< 80 cm	98.8	9.5	5.7	12.6
	80-88 cm	0.3	32.6	15.4	24.5
	> 88 cm	0.9	57.9	79.0	63.0
Men	< 94 cm	100	20.3	20.2	27.3
	> 94 cm	-	79.8	79.8	72.7
Additional CMD risk factors of high-risk participants who consulted their GP (mean (SD))					
				N=1,755	
Systolic blood pressure in mmHg (n=1477)				134.4 (17.6)	
Diastolic blood pressure in mmHg (n=1461)				79.9 (9.8)	
Total cholesterol in mmol/l (n=1411)				5.8 (1.0)	
Total cholesterol/HDL ratio (n=1407)				3.9 (1.1)	
LDL in mmol/l (n=1334)				3.7 (0.9)	
Fasting glucose in mmol/l (n=1283)				5.4 (0.9)	
SCORE Risk Charts† (%) (n=1285)				3.1 (2.6)	

Total of percentages may not equal 100% due to rounding

† 10 years CVD mortality risk, The Netherlands is considered a “low-risk” country¹⁷

Abbreviations: CMD=cardiometabolic diseases, CVD=cardiovascular disease, DM2= Diabetes Mellitus type 2, BMI=body mass index, GP= general practitioner, HDL=High-density lipoprotein, LDL=Low-density lipoprotein

Figure 1 Flowchart of participants



Detection rate of the program

EHR data were available for 12,393 (97%) patients. Table 2 shows that in about one in five at least one CMD (19.7%) was newly diagnosed. In total, 9.2% was diagnosed with hypertension, 9.6% with hypercholesterolemia and 1.6% with diabetes. In addition, we found new prescriptions for antihypertensive and lipid lowering drugs in absence of an EHR recorded CMD diagnosis in 1.3% and 1.4% of the patients respectively. No antidiabetic prescriptions were found without a DM2 diagnosis. In an additional 21.9% of patients in whom no CMD diagnosis or prescription was recorded, we found abnormal diagnostic test results for CMD; elevated blood pressure ($\geq 140/90$ mmHg) in 18.1%, abnormal cholesterol levels (total cholesterol /HDL ratio ≥ 5 or total cholesterol ≥ 8 mmol/l) in 8.4% and an increased fasting glucose level (≥ 6 mmol/l) in 22.2%. In 43.8% of patients, either a new CMD diagnosis, a new prescription or an abnormal diagnostic test result was found.

Table 2 Detection rate and potential yield of stepwise CMD risk-assessment

	High risk category GP visit	NNS
	N=1755	N=30,934
Newly diagnosed: % (n)		
Hypertension ¹	9.2 (n=161)	
Hypercholesterolemia ²	9.6 (n=169)	
Diabetes mellitus ³	1.6 (n=28)	
Newly prescribed without recorded diagnosis: % (n)		
Antihypertensives ⁴	1.3 (n=23)	
Lipid-lowering drugs ⁵	1.4 (n=25)	
Antidiabetics ⁶	0 (n=0)	
Abnormal diagnostic test without recorded diagnosis or prescription: % (n)		
Blood pressure $\geq 140/90$ mmHg	18.1 (n=318)	
Total cholesterol/HDL ratio $\geq 5-8$	8.0 (n=140)	
Total cholesterol ≥ 8 mmol/l or total cholesterol/HDL ratio ≥ 8	0.4 (n=7)	
Fasting glucose $\geq 6-7$ mmol/l (pre-diabetes)	21.9 (n=385)	
Fasting glucose ≥ 7 mmol/l	0.3 (n=5)	
Newly diagnosed CMD, newly prescribed or abnormal diagnostic test result % (n)		
No. of participants with newly diagnosed CMD†	19.7 (n=346)	89
No. of participants with newly diagnosed CMD or prescription††	21.9 (n=385)	80
No. of participants with new CMD, prescription or abnormal diagnostic test	43.8 (n=768)	40

¹ ICPC codes: K86/K87, ² ICPC code: T93, ³ ICPC code: T90, ⁴ ATC cluster: C02-03, C07-C09, ⁵ ATC cluster: C10, ⁶ ATC cluster: A10

† ICPC codes: K74, K75, K76, K77, K86, K87, K89, K90, K91, K92, T90 and T93

†† ICPC codes + ATC cluster: A10 and C02-03, C07-C10

Abbreviations: CMD=cardiometabolic diseases, GP=general practitioner, NNS=number needed to screen, ICPC= International Classification of Primary Care, ATC=Anatomical Therapeutic Chemical Classification System

Number needed to screen

The calculated NNS among all invitees (n=30,934) to find a newly confirmed CMD diagnosis was 89 (table 2). Although a detailed and thorough cost-effectiveness analysis is required, a first estimation demonstrates that costs per newly diagnosed individual with CMD would be €489. For this estimation, direct medical costs were taken into account: €2 per patient for invitation, €40 per high-risk patient who attended the general practice (two standard consultations and laboratory costs) and an estimated €1000 per practice for implementation (15-20 hours of time investment at €50/hour). Taking a broader definition of new CMD (confirmed diagnosis, prescription or an abnormal diagnostic test result) the number needed to screen would decrease to 40.

Newly diagnosed CMD in low and intermediate risk categories

A new ICPC-coded CMD diagnosis was found in 1.6% of patients with a low risk and in 4.3% of patients with an intermediate risk (table 3).

Table 3 Newly diagnosed CMD and prescriptions in low and intermediate risk categories

	Risk category	
	Low	Intermediate
	N=836*	N=6,465*
Newly diagnosed: % (n)		
Hypertension ¹	0.7 (n=6)	1.9 (n=125)
Hypercholesterolemia ²	0.5 (n=4)	1.4 (n=90)
Diabetes mellitus ³	0 (n=0)	0.4 (n=24)
Newly prescribed without recorded diagnosis: % (n)		
Antihypertensives ⁴	0.3 (n=3)	1.1 (n=70)
Lipid-lowering drugs ⁵	0 (n=0)	0.2 (n=11)
Antidiabetics ⁶	0 (n=0)	0 (n=0)
Newly diagnosed CMD or newly prescribed % (n)		
No. of participants with newly diagnosed CMD†	1.6 (n=13)	4.3 (n=276)
No. of participants with new recorded CMD or prescription††	1.9 (n=16)	5.4 (n=350)

* no. of participants with available electronic health record data

¹ ICPC codes: K86/K87, ² ICPC code: T93, ³ICPC code: T90, ⁴ ATC cluster: C02-03, C07-C09, ⁵ ATC cluster: C10, ⁶ ATC cluster: A10

† ICPC codes: K74, K75, K76, K77, K86, K87, K89, K90, k91, K92, T90 and T93

†† ICPC codes + ATC cluster: A10 and C02-03, C07-C10

Abbreviations: CMD=cardiometabolic diseases, ICPC= International Classification of Primary Care, ATC=Anatomical Therapeutic Chemical Classification System

Discussion

Summary of results

Implementation of a structured stepwise CMD detection program in general practice results in a participation rate of 41%, and new diagnosis of CMD in 20% of the high-risk-patients (NNS 89). Over 40% of patients required active follow-up, receiving either a new diagnosis, a new prescription or had an abnormal diagnostic test result during their GP visit. In low- and intermediate-risk categories small numbers of new CMD diagnoses were found (2% and 4% respectively).

Strengths and limitations

This is the first large study evaluating the uptake and detection rate of the Dutch CMD detection program in a real-life clinical setting. The roll-out of the “prevention consultation” was coordinated and implemented by the local staff of each practice. This resulted in a pragmatic and feasible implementation in each practice. With this approach we have tackled some earlier identified challenges such as good preparation of involved staff and the integration of the program within everyday practice.²¹

Another strength was that we were able to collect the EHR data of 97% of the patients, instead of the anticipated 90%.¹⁵ The small number of missing data (3%) was equally distributed among patients of different risk categories and therefore we assume these data were missing at random and did not influence our results.

The risk score we used was recently externally validated among 3,544 patients of the Australian Diabetes, Obesity and Lifestyle Study, showing robust discriminative performance across populations, though recalibration was recommended to account for disease incidence per region.^{6,18}

However, some limitations should be considered. Due to the stepwise nature of the program, we anticipated non-response.¹⁵ This was 59% on the initial invitation and 66% on the second step of the risk assessment. In case of non-response, we did send reminders after two weeks as recommended in the guideline. The response and accompanying detection rate of the program may have been larger if we had incorporated more labour-intensive strategies for enhancing the response (e.g. telephone reminders or reminders by email)^{14,22}

Another limitation was that our primary outcome was based on ICDPC-coded diagnoses in the EHR. Under-registration may have differed between professionals and practices. However, even if under-registration did play a role, this would have resulted in an underestimation of the total estimated yield.

Interpretation of results and comparison with existing literature

We found a new CMD diagnosis in 20% of high-risk patients attending general practice. This is comparable with the results of previous Dutch pilot studies.^{12,13} A population-based cohort study estimating the yield of the UK NHS health check identified 18,4% active smokers, 22,7% obese patients (BMI ≥ 30 kg/m²), 30,1% patients with blood pressure levels $\geq 140/90$ mmHg and 66,1% with total cholesterol levels ≥ 5 mmol/l.²³ However, it is hard to compare our results with those from international equivalents, since variable selection criteria for participation in structured CMD risk assessment are used in different countries.^{7,9,24} For example, the NHS health check targets all patients 40-75 without known CMD or CMD risk factors for complete screening and does not use a stepwise approach.²⁵

A remarkable result is that we found abnormal diagnostic test results recorded in an additional 22% of the high-risk patients who attended general practice, without a CMD diagnosis

or prescription recorded in the EHR. In some patients (e.g. with a total cholesterol ≥ 8 mmol/l, a total cholesterol/HDL ratio ≥ 8 or fasting glucose levels ≥ 7 mmol/l), these abnormal diagnostic test results may reflect under-registration of a diagnosis. However single abnormal test results do not always implicate the presence of CMD. For example, in case of high blood pressure they may reflect a “white coat” effect or a transient deviation of the norm due to stress or temporary illnesses. In addition, single abnormal test results do not always require treatment, because treatment indications are frequently based on the overall CMD risk instead of single risk factors.^{4,19} Nevertheless, abnormal diagnostic test results often require active follow-up and one could argue that at least a part of these individuals will develop CMD in the (near) future. For example, it is estimated that one- to two-third of those with prediabetes (fasting glucose between 6-7 mmol/l) will develop diabetes within six years.²⁶ Moreover, impaired fasting glucose levels are associated with an increased risk for CMD.²⁰ Taking this into account, the program has the potential to identify additional patients who are likely to develop CMD in the future.

Implications for research and practice

Stepwise screening methods – such as in the Dutch CMD detection program- are preferred, selecting people at high-risk - who are likely to benefit most from interventions- reducing the number of people that needs to be screened.²⁷ In addition, previous studies have shown that this stepwise program is positively evaluated by general practitioners and patients.^{28,29} To further optimize acceptance, compliance and participation rates of the program, additional analyses of non-response and response-enhancing strategies are warranted.

The cost-effectiveness of CMD detection programs has not yet been established ^{24,30}, however prevention of CMD either by lifestyle changes or medication is considered cost-effective in many scenarios.⁴ Future economic evaluation of this program will add to the evidence on this topic.¹⁵ It is important to establish the cost-effectiveness in order to justify and create wider acceptance for large-scale implementation of stepwise CMD detection programs in primary care.

Conclusion

The Dutch CMD detection program proved adequate in identifying high-risk patients in general practice, and resulted in the detection of a newly diagnosed CMD in one-fifth of patients. The future yield of this program is expected to be higher given the considerable amount of additional risk factors found, such as pre-diabetes and elevated blood pressure and cholesterol levels, requiring active follow-up and presumably treatment in the (near) future.

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Cost-effectiveness of a stepwise cardiometabolic disease prevention
program: results of a randomized controlled trial in primary care

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Abstract

Objectives: To establish the cost-effectiveness of a stepwise cardiometabolic disease (CMD) risk assessment followed by individualized treatment if indicated compared to care as usual. A computer-based simulation model was used to project long-term health benefits and cost-effectiveness, assuming the prevention program was implemented in Dutch primary care.

Design: Stepped-wedge randomized controlled trial

Setting: Primary care

Participants: 1,934 participants aged 45-70 years without recorded CMD or CMD risk factors.

Interventions: The intervention group was invited for stepwise CMD risk assessment through a risk score (step1), additional risk assessment at the practice in case of increased risk (step2) and individualized follow-up treatment if indicated (step3). The control group was not invited for risk assessment, but completed a health questionnaire.

Primary and secondary outcome measures: Short-term (one year follow-up) and long-term (60 years) cost-effectiveness of stepwise CMD risk assessment compared to no assessment. EQ5D-5L outcomes were used to estimate Quality Adjusted Life Years (QALY).

Results: The intervention resulted in significant improvements in cholesterol and blood pressure. After one year, the quality of life slightly decreased in the intervention group and slightly improved in the control group: -0.003 (SD=0.086) vs. +0.012 (SD=0.078) ($p<0.01$). The average costs in the intervention group were 260 Euro higher than in the control group and differences were mainly driven by healthcare costs. Despite the improvements in cholesterol and blood pressure, the intervention was not cost-effective (ICER of 482,000 Euro/QALY after 60 years). Sensitivity and scenario analyses resulted in similar high cost-effectiveness ratios.

Conclusion: Implementation of this primary care based stepwise CMD prevention program is not cost-effective in the short- and long-term. Wide scale implementation of this program in primary care cannot be recommended.

Trial registration: Dutch trial Register number NTR4277

Introduction

The increasing burden of cardiometabolic diseases (CMD), defined as cardiovascular disease (CVD), diabetes type2 (DM2) and chronic kidney disease, is mainly caused by an unhealthy lifestyle and ageing. CMD is the major cause of death worldwide and is associated with a lower quality of life and high health care costs.¹ In the Netherlands, CMD account for about one sixth of total Dutch health care costs.² CMD share common modifiable risk factors such as smoking, obesity, hypertension and hypercholesterolemia³ and could be prevented by changes in lifestyle or pharmacological treatment.⁴

To prevent a further rise in CMD and related health care costs, early detection and adequate management of individuals at risks could be an effective preventive strategy. European guidelines^{4,5} underline the importance of risk assessment and management of individuals without pre-existing CMD and CMD risk factors. In the Netherlands, the Dutch College of General Practitioners developed the “prevention consultation” guideline in 2011, which is a primary care based stepwise CMD prevention program.⁶

The effectiveness of early detection of CMD on long term CMD morbidity and mortality is often questioned and the cost-effectiveness of these programs has not yet been established.^{7–11} There is a lack of studies with robust economic evaluations alongside trials.¹¹ A recent review of Hilligsman and colleagues on the cost-effectiveness of early detection of CMD suggests that screening programs for DM2 and CVD could represent good value for money¹⁰, although the heterogeneity between studies made an unequivocal conclusion difficult.

In 2013, the INTEGRATE study was designed to investigate the effectiveness and cost-effectiveness of a primary care based stepwise CMD prevention program. The effectiveness analysis showed promising results on surrogate outcomes such as blood pressure and cholesterol levels with a significant decrease after one year of treatment.¹² However, given that implementation of structured CMD prevention in primary care is time and resource intensive, establishing long-term cost-effectiveness in terms of morbidity and mortality is required to justify widespread implementation.

Therefore, the aim of the present study was to estimate both short- and long-term cost-effectiveness of the CMD prevention program. In order to investigate this, we used a computer-based simulation model to project long-term health benefits and cost-effectiveness, assuming the prevention program was implemented in Dutch primary care.

Methods

Design

The INTEGRATE study (Dutch trial Register number NTR4277) is a stepped-wedge randomized controlled trial (RCT). In total, 37 Dutch general practices participated from April 2014 to April 2017. Stepwise CMD risk assessment followed by tailored lifestyle and/or pharmacological treatment, if indicated, was compared with care as usual. The control group was invited for the intervention one year later. Details about the study design, randomization, intervention components and measurements are described elsewhere.¹³

Participants

Eligible for participation were all patients listed in the participating practices aged 45-70 years without recorded CMD, hypertension, hypercholesterolemia and without antihypertensive, lipid lowering or antidiabetic drugs according to the patient's electronic health record (EHR) (appendix 1).

Intervention

Intervention participants were invited for a stepwise CMD prevention program. To identify high-risk patients - as first step of the program- participants filled out a risk score (online or on paper) to estimate their individual CMD risk. The risk score consisted of seven simple questions about sex, age, smoking status, BMI (height and weight), waist circumference and a family history of premature CVD (age <65 years) and/or DM2 and calculates the risk to develop a CMD in the next seven years.¹⁴ The risk score was recently externally validated.¹⁵ High-risk was defined as an absolute risk of $\geq 23\%$ for men and $\geq 19\%$ for women. High-risk participants were advised to attend their general practice (second step) for additional risk profiling, including measurement of blood pressure and laboratory tests (e.g. cholesterol levels and fasting glucose). As last step, patients received tailored lifestyle advice and/or pharmacological treatment.

Controls

Control participants were invited to complete a health questionnaire including questions about demographic characteristics, CMD risk factors and lifestyle. During one-year follow-up, they received care as usual until they were invited for the intervention one year later.

Outcome variables

Both the short-term and the long-term analysis used the cost per QALY as outcome parameter. For the short-term cost-effectiveness, EQ5D-5L outcomes were used to calculate Quality Adjusted Life Years. For the long-term cost-effectiveness, a computer-based simulation model was used that included data on utility values associated with age and disease outcomes related to CMD.

Measurements

Participants in the intervention group completed the risk score and additional online questionnaires at baseline and one-year follow-up including among others EQ5D-5L health status, work status and absence from work, health care costs other than those extracted from the EHR (e.g. costs made for lifestyle interventions or treatment emanating from the program) and non-health care costs (participants' expenses during the study, e.g. travel costs and costs for lifestyle interventions following medical advice).

Participants in the control group filled out the health questionnaire at baseline and additional questionnaires after one-year follow-up including the same variables as described for the intervention group. Measurements have been described in detail elsewhere.¹³ the effectiveness and cost-effectiveness have yet to be demonstrated. The 'Personalized Prevention Approach for CardioMetabolic Risk' (PPA CMR

Data collection

As input for this study, we used the data collected for the effectiveness analysis.¹² The intervention group included all participants who completed the two-step risk assessment. These participants were individually matched to participants in the control group to generate the most suitable reference group.

For both the intervention and the control groups, extracted EHR-data were used to establish health care utilization during one-year follow-up. For the intervention group, EHR-data on systolic blood pressure and total cholesterol were collected at baseline (at the first visit to the GP) and after one-year follow-up. Case report forms (CRF) and questionnaires were used to collect data on referrals to lifestyle services outside the GP practice.

Cost data

Cost data were based on EHR, CRF, questionnaire data, and on a fixed price for implementation of the intervention per practice. The implementation costs included costs for the selection of patients, invitations and handling. Table 1 shows the specification of cost types and their sources. Table 2 shows the unit prices for different types of costs used throughout this study. Other types of health care use outside the GP practice, such as lifestyle interventions for smoking cessation, increasing physical activity, weight reduction, lowering alcohol consumption, and improving nutrition were based on CRF and self-report of patients. The patient questionnaires also included data on patient costs. These included costs for travelling, laboratory tests, medication, consultation of other (non-reimbursed) healthcare professionals, subscriptions (e.g. for fitness center) and other non-specified costs related to the intervention. Finally, data on productivity losses, either from absence of work or from being less productive at work, were based on patient completion of the iMTA Productivity Cost Questionnaire (iPCQ)¹⁶ which was included in the questionnaires.

Intervention costs consisted of program implementation costs, lifestyle intervention costs, healthcare costs and patient costs. The short-term CEA included these different components of intervention costs and productivity costs. In the long-term CEA, the total costs in the first year were the intervention costs, and the total costs in later years were the healthcare costs simulated with the RIVM Chronic Disease Model (see section below). All costs were calculated separately for the control and intervention groups, except for the implementation costs in the short-term CEA because the study design did not allow distinction of these costs between intervention and control group.

Table 1 Specification of cost types and their sources

Cost type	Source
Intervention costs	
Implementation costs	Fixed (bottom-up) price per practice
Patient selection	
Invitations	
Handling	
Lifestyle program costs (reimbursed)	
Smoking cessation costs	CRF/Questionnaires (volumes)
Physical activity costs	CRF/Questionnaires (volumes)
Losing weight costs	CRF/Questionnaires (volumes)
Lowering alcohol consumption costs	CRF/Questionnaires (volumes)
Improving nutrition costs	CRF/Questionnaires (volumes)
Healthcare costs (reimbursed)	
GP practice consultations	EHR (number)
Hospitalization	Questionnaires (costs)
Out-of-hours primary care services	Questionnaires (costs)
Outpatient clinic	CRF/Questionnaires (costs)
Emergency care	Questionnaires (costs)
Patient costs (not reimbursed)	
Travel costs	Questionnaires (costs)
Laboratory tests	Questionnaires (costs)
Medication	Questionnaires (costs)
Other (not reimbursed) healthcare professionals	Questionnaires (costs)
Subscriptions (e.g. fitness centre)	Questionnaires (costs)
Other	Questionnaires (costs)
Other costs	
Productivity costs	Questionnaires & iPCQ

CRF= case report forms, filled out by practice nurse or GP

iPCQ: iMTA Productivity Cost Questionnaire; EHR: electronic medical record

Table 2 Unit costs of program components (in 2014 Euro)

	Unit	Cost	Source
Flyer with lifestyle advice		0.50	expert opinion
Online lifestyle advice		0.00	expert opinion
GP/ practice nurse (PN)	Consultation	33.00	Dutch costing guidelines ¹⁷
GP/PN	Home visit	50.00	Dutch costing guidelines
GP/PN	Telephone consultation	17.00	Dutch costing guidelines
Mental health care (private)	Consultation	98.00	Dutch costing guidelines
Mental health care (group)	Consultation	56.84	Sobell, Sobell, & Agrawal (2009) ¹⁸
Psychologist	Consultation	64.00	Dutch costing guidelines
Dietician	Consultation	58.00	Lammers & Kok (2012) ¹⁹
Complementary medicine	Consultation	61.52	average online tariffs (2019)
Out-of-hours primary care services	Consultation	128.97	tariff: 134.21 (2019)
Outpatient clinic	Consultation	91.00	Dutch costing guidelines
Emergency room	Visit	259.00	Dutch costing guidelines
Hospital	Day visit	476.00	Dutch costing guidelines
Physiotherapist	Consultation	33.00	Dutch costing guidelines
Physical activity	Gym visit	5.00	online tariffs: 20 Euro for 4 weeks

The RIVM Chronic Disease Model (CDM)

The CDM is a Markov-type multistate-transition model simulating the evolution of chronic diseases in relation to risk factor levels in the Dutch population. It was developed by the Dutch National Institute for Public Health and the Environment and applied in multiple cost-effectiveness studies.^{20–24} Among other common chronic diseases, it includes congestive heart failure, diabetes mellitus type 2, myocardial infarction and stroke. Blood pressure and cholesterol are two of the model's lifestyle-related risk factors. The model describes demography, risk factor prevalence, disease incidence, mortality, and their development over time in 1-year steps. These developments depend on transitions between risk factor levels, with subsequent influence on disease incidence and mortality. Systolic blood pressure and total cholesterol both stratify into eight classes in the CDM. For a more detailed description, see appendix 2. Relative risks associated with different risk factor levels were derived from literature, whereas incidence, prevalence, transition rates and mortality rates in the model apply to the Dutch population. Disease prevalence is associated with average annual, per patient, costs and with disability weights, reflecting the burden of disease on individual level. Healthcare costs were based on Dutch costs-of-illness studies^{25,26}, and quality-adjusted life years (QALY) were computed using the Global and Dutch burden of disease studies.^{27–30} Healthcare costs include costs in life years gained. The CDM takes a healthcare perspective and therefore cannot simulate productivity

losses. The model allows specifying alternative scenarios, by adjusting the input parameters. In this study, we simulated two scenarios for the study population: the reference scenario without the observed changes in cholesterol and blood pressure, and the intervention scenario with the age- and sex-specific observed effects, and compared the results.

Analysis

We adopted a societal perspective to measure costs and outcomes in the short-term CEA. In the long-term CEA we adopted a healthcare perspective, for reasons described in the previous paragraph. The long-term CEA was modeled with a one-off INTEGRATE intervention in the Dutch population aged 45-70.

The change in systolic blood pressure and total cholesterol specified to age, sex, and control/intervention group in the one-year intervention period was calculated and used as input for the CDM^{20,31} to simulate future healthcare costs and effects on CVD incidence and prevalence, and effects on mortality (appendix 3). The time horizon of the simulations was 60 years, representing the maximum lifetime of a cohort starting at the age of 45, the minimum age of the study population. The discount rate for costs was 4% and for effects 1.5%, following Dutch guidelines for cost-effectiveness analysis.¹⁷ To estimate results for the whole of the Netherlands, we multiplied the results for the INTEGRATE population by a factor of 5000/37, as there are around 5000 GP practices in the Netherlands, of which 37 representative practices were included in the INTEGRATE study.

Sensitivity and scenario analyses

Sensitivity analyses were performed for the effect sizes on blood pressure and cholesterol levels, implementation costs, and lifestyle + healthcare + patient costs, with parameter values of 80% and 120% of the baseline value. The effectiveness study showed a (non-significant) potential effect on smoking cessation: of the intervention group 3.25% quitted smoking, of the control group 2.19%.¹² It is well known that smoking cessation interventions have highly favourable ICERs.³² To explore the potential additional effect of reduced smoking, we performed a scenario analysis wherein more patients would quit smoking.

Results

Short-term CEA

The control and the intervention group both consisted of 967 patients. Quality of life improved slightly in the control group, whereas the intervention group experienced a (small) decrease in quality of life after one year: +0.012 (SD=0.078) vs. -0.003 (SD=0.086), $t=2.708$ $p<0.01$). The lifestyle program costs were highest for losing weight and lowest for lowering alcohol

consumption (Table 3). Healthcare costs formed the larger part of the intervention costs. Table 3 shows the costs in the control and intervention groups. The average total costs in the intervention group were 260 Euro higher than in the control group. The intervention costs used in the long-term CEA (taking a healthcare perspective, see methods section) were the difference in total costs minus the difference in productivity costs: 223 Euro. The implementation costs were 1,200 Euro per GP practice, and could not be specified to control or intervention group due to the study design. Implementation costs are therefore not shown in table 3. The one-year ICER was not formally calculated as the intervention was more costly and less effective compared to the control group (the intervention was “dominated” by the control group).

Table 3 Costs in the control and intervention groups

	Mean costs (€)		Percentage of patients (%)	
	Control ²	Intervention	Control	Intervention
Intervention costs¹				
Healthcare costs (reimbursed)				
Claimed (GP practice) consultations	133.94	244.75	91.7%	87.6%
Lifestyle program costs (reimbursed)		20.61		12.3%
Smoking cessation costs	n.a.	1.71		0.8%
Increasing physical activity costs	n.a.	5.95		5.9%
Losing weight costs	n.a.	10.98		5.0%
Lowering alcohol consumption costs	n.a.	0.19		0.1%
Improving nutrition costs	n.a.	1.77		5.5%
Patient costs related to intervention (not reimbursed)		90.98		57.7%
Travelling	n.a.	1.49		54.1%
Laboratory tests	n.a.	9.73		52.5%
Medication	n.a.	27.27		52.7%
Other (not reimbursed) healthcare professionals	n.a.	13.05		54.3%
Subscriptions (e.g. fitness centre)	n.a.	32.02		53.8%
Other	n.a.	7.43		39.4%
Other costs				
Productivity costs	65.54	102.87	16.1%	19.9%
Total costs	199.48	459.42	93.2%	94.7%

¹ The intervention costs in this table do not include the implementation costs as these could not be specified to either control or intervention group.

² n.a.: not applicable. Patients in the control group were not asked for costs emanating from the program that could only occur in the intervention group.

Long-term CEA

The intervention resulted in significant improvements in cholesterol and blood pressure.¹² These improvements were modelled with the CDM using transition probabilities as reported in appendix 3. QALYs were gained via reduced incidence of CVD as shown in table 4. Table 4 shows the cumulative discounted results after 5, 10, 20 and 60 simulated years. The ICER of 482,000 Euro/QALY after 60 years indicates that the intervention is by no means cost-effective. The simulations of the intervention scenario showed reduced and delayed morbidity and mortality but not enough to balance the intervention costs that form the majority of the total costs. The disease figures show the difference in (discounted) patient years with the disease. Figure 1 shows the difference in mortality between the intervention group and the control group and demonstrates the delay of death caused by the intervention. In the first decades, the intervention resulted in lower total mortality compared to the control group. After about 25 years, total mortality in the intervention group was higher than in the control group. By that time - due to the intervention - less people had died in the intervention group and thus contributed to the larger pool of possible deaths. On average, patients in the intervention group increased their life expectancy with 1/3rd day.

Table 4 Cumulative discounted simulated results for the Netherlands from the healthcare perspective: years with disease, costs, QALYs gained, and ICER

	5 years	10 years	20 years	60 years
AMI prevalence	-9.12	-39.3	-121	-160
CVA prevalence	-2.82	-13.7	-50.1	-72.4
CHF prevalence	-1.13	-5.96	-27.7	-46.3
AMI incidence	-5.52	-11.4	-19.4	-21.2
CVA incidence	-1.95	-4.79	-10.6	-13.2
CHF incidence	-0.742	-2.21	-7.01	-9.77
QALYs gained	4.19	19.4	74.0	135
Intervention costs				
Implementation costs: 1,200 Euro per GP practice (million Euro)	6.00	6.00	6.00	6.00
Lifestyle + healthcare + patient costs in the year of intervention: 223 Euro per patient (million Euro)	58.2	58.2	58.2	58.2
Future healthcare costs (million Euro)	-0.0316	-0.110	0.0548	0.984
Total costs (million Euro)	64.1	64.1	64.2	65.2
ICER (million Euro/QALY)	15.3	3.31	0.868	0.482

AMI: acute myocardial infarction, CVA: stroke, CHF: congestive heart failure, QALY: quality-adjusted life year gained, ICER: incremental cost-effectiveness ratio

Figure 1 Mortality difference over the years between the control and intervention groups

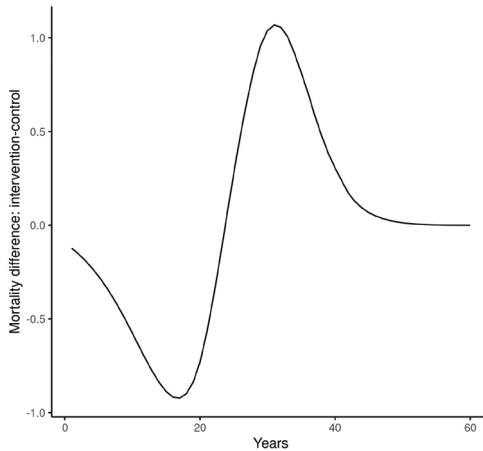
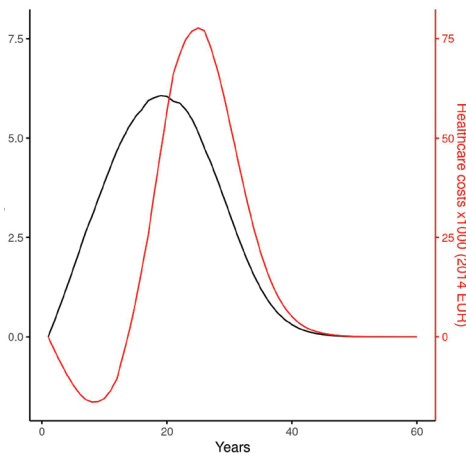


Figure 2 shows the development over time of healthcare costs and QALYs gained in the intervention scenario compared to the reference scenario. QALYs gained were always positive, with a peak after 20 years. In the first 15 years, savings in healthcare costs were anticipated. In the next five years however, these savings were nullified and after 20 years, the cumulative healthcare costs were consistently higher in the intervention scenario than in the reference scenario, because of the inclusion of costs in life years gained.

Figure 2 Discounted results over 60 simulated years from the Chronic Diseases Model. Black line: Annual number of QALYs gained (1.5% discount rate); Red line: annual healthcare costs (2014 Euro, 4% discount rate)



Sensitivity and scenario analyses

With this ICER far above the cost-effectiveness threshold of 20,000 Euro/QALY that is often used in the Netherlands, none of the sensitivity analyses showed any result approaching this threshold (appendix 4). Particularly the variation in implementation costs had negligible effect on the ICER. The scenario analysis on smoking cessation was aimed at exploring a hypothetical maximum health effect of the intervention, i.e. to explore what the yield of the lifestyle improving programs would have been if all smoking patients had successfully participated in a smoking cessation intervention rather than part of all patients following a plethora of other lifestyle improvement programs. This scenario analysis was based on the notion that of all possible changes in lifestyle, smoking cessation is associated with the highest health gains overall. If all smokers in the intervention group (16.55%, N=161)¹² would have quit smoking, the ICER would have been 8,000 Euro per QALY. This includes additional lifetime healthcare costs per quitter of 3,850 Euro and 0.67 QALY gained per quitter (calculated from Over et al. NTR 2014³³). To reach an ICER of 20,000 Euro per QALY, an additional 18 smokers in the intervention group should have quit smoking besides the 31 who already reported to have quit smoking (these effects were not included in the main analysis because they were not significant).

Discussion

Summary of results

Although the INTEGRATE study - a large scale, population-based trial - demonstrated that implementation of a structured stepwise CMD prevention program resulted in a significant decrease in blood pressure and cholesterol levels in high-risk individuals¹², this appeared by no means cost-effective on short- and long-term endpoints. In parallel, the additional sensitivity analyses showed that cost-effectiveness cannot be achieved even with better treatment compliance and lower intervention costs.

Strengths and limitations

To our knowledge, this is the first economic evaluation that considers the cost-effectiveness of early detection of CMD with a stepwise approach. Moreover, this is one of the few large-scale clinical studies that investigated the cost-effectiveness of targeted CMD prevention in primary care alongside a trial to ensure that appropriate outcome and cost data were collected. The second strength is that changes in systolic blood pressure and cholesterol levels were modelled simultaneously, because various CMD risk factors are known to have a multiplicative effect.³⁴ Another strength is that we have chosen the societal perspective for the short-term cost-effectiveness analysis, including health gains and health care costs as well as broader societal costs and consequences of the intervention such as productivity losses.

For the long-term cost-effectiveness analysis, we adopted the health-care perspective, because the CDM cannot simulate costs other than healthcare costs up to now.

In addition, some other limitations should be addressed. Besides blood pressure and cholesterol levels no other risk factors were modelled, possibly leading to an underestimation of the reported results. Particularly, the non-inclusion of the non-significant effect that the intervention had on quitting smoking may have contributed to the high ICER that was found. In addition, the CDM modelled systolic blood pressure and total cholesterol levels via discrete classes. The real distribution of these parameters is continuous and even slight improvements in these risk factors will have a favourable outcome on health. Nevertheless, our data from the clinical study also showed substantial numbers of patients with increased levels of blood pressure and cholesterol in the first year after the intervention (appendix 3). The unfavourable ICERs certainly relate to the fact that the pattern of improvement over patients in the intervention group was not visible in all participating patients. Using discrete levels implies a simplified reflection of the reality, however the classes used correspond to relative risks based on the best literature available. Furthermore, the CDM is based on assumptions about the long-term maintenance and changes in risk factors, which could have resulted in a slight under- or overestimation of the long-term outcomes of the intervention. Despite this unavoidable variability, this could not have compromised our main conclusions as only very small health gains were achieved at relatively high costs.

We carefully assessed health care costs based on extracted EHR data, however the EHR contains no data on the use of hospital care. Because the intervention might have led to some hospital referrals, this could have resulted in a slight underestimation of the intervention related health care costs. On the other hand, we might have overestimated the intervention related patient costs. For example, costs for all new gym subscriptions were considered to be emanating from the intervention. However, we believe that such costs were also made during care as usual.

One final limitation is that the data on patient- and family costs and productivity losses were based on self-report. Self-reported data are vulnerable to recall bias. This bias was assumed equal between the intervention and control group.

Comparison with existing literature and interpretation of results

The advantage of a stepwise screening approach is that only high-risk individuals are targeted – those who are expected to benefit most from preventive treatment – and therefore assumed to be more cost-effective compared to whole population screening.³⁵ This is in line with the 2016 guidelines of the European Society of Cardiology which consider targeted CVD screening in high-risk individuals.⁴

Modelling studies have demonstrated that targeted prevention strategies for CVD or DM2 in high-risk individuals are most likely cost-effective^{22,36–40}, however none of these studies evaluated early detection strategies for CMD (CVD, DM2 and CKD). In addition, most of these

studies did not include a control group, which is a risk for overrating economic value, as usual care is associated with better health care outcomes than no treatment. Furthermore, simulation modelling studies with a positive cost/benefit ratio generally assume lower intervention costs, higher uptake rates, larger treatment effects and sustained compliance than found in clinical trials.¹¹ Nevertheless, economic modelling of clinical trial data remains very important to project results beyond trial duration to estimate its costs and cost-effectiveness, as follow-up in clinical trials in general is too short to observe subsequent disease incidence and mortality.

Despite promising results regarding lifestyle improvement, another large trial investigating the cost-effectiveness of a European prevention program in primary care focusing on CVD only also demonstrated not to be cost-effective.⁴¹ Although many economic evaluations have been performed in the field of CMD, none of these studies assessed a prevention program for the combination of these diseases.¹⁰ Web of Science, NHSEED and the CEA registry to identify relevant articles published between 1 January 2005 and 1 May 2015. Two reviewers independently selected articles, systematically extracted data and critically appraised the study quality using the Extended Consensus on Health Economic Criteria (CHEC). Therefore, it remains difficult to directly compare our results with international equivalents.

The sensitivity and scenario analyses showed that it is very hard to reach cost-effectiveness with the evaluated program. Reducing overall intervention costs with more than 97% (as shown in appendix 4) to around €7 compared to about €223 as shown in the INTEGRATE trial is not a realistic goal. Non-response is a designated pitfall of stepwise screening programs, as lack of compliance in different steps might reduce cost-effectiveness. However, optimizing response rates in our study would not have resulted in a cost-effective program, due to relatively high intervention costs.

The most promising way to optimize cost-effectiveness is to introduce more effective lifestyle interventions, especially focusing on smoking cessation. The results of our trial showed no significant effect on smoking.¹² In absolute numbers, 31 of 161 smokers quit in the intervention group versus 21 out of 161 in the control group. To achieve cost-effectiveness (ICER €20,000 per QALY gained) an additional 18 smokers in the intervention group should have quit, requiring about three times the effect that was achieved with the current program.¹²

In recent years there has been more attention for prevention and treatment of CMD in clinical practice due to renewed guidelines and chronic disease management programs. Ongoing individual case finding might lead to a lower prevalence of undetected high-risk individuals for CMD over time.⁴² number of people with T2DM and costs of three different stepwise screening strategies for T2DM in general practice (GP). Because individual case finding- and structured early detection strategies are fishing in the same waters, this trend may dilute the detection rate of the program and subsequently reduces its cost-effectiveness.

Implications for clinical practice and further research

Stepwise CMD prevention in primary care followed by subsequent treatment appeared not cost-effective. Future research should focus on effective lifestyle interventions and the long-term maintenance of its health benefits, especially focusing on smoking cessation interventions.

It is generally assumed that the higher the risk in patients, the more favourable the cost-effectiveness of preventive procedures. Therefore, alternative strategies to identify high-risk individuals might be promising. Dalsgaard and colleagues found that opportunistic screening for DM2 during a regular GP consultation stimulated higher attendance rates. In addition it was argued that people attending GP practices might have a more unfavourable CMD risk profile and therefore are likely to be at higher-risk.⁴² number of people with T2DM and costs of three different stepwise screening strategies for T2DM in general practice (GP Ideally, this would lead to the identification of more cases at lower costs. However, this hypothesis should be confirmed by future research. Another strategy could be the selection of high-risk individuals based on routine EHR data, improving individual case finding in daily practice.

Alongside targeted and individual case finding approaches, expanding efforts for universal prevention of CMD plays an important role to reduce overall CMD risk in the total population.

Given our results and the fact that CMD prevention programs are already implemented in several countries, it is important that these programs are evaluated to assess whether these are a cost-effective use of resources compared to other interventions to reduce CMD risk.

Conclusion

Implementation of this primary care based stepwise CMD prevention program is not cost-effective in the short- and long-term. Future research should focus on developing more effective lifestyle interventions, with a special focus on smoking cessation, with sustained health effects at reasonable costs. At this moment, the wide scale implementation of the stepwise CMD prevention program in primary care cannot be recommended.

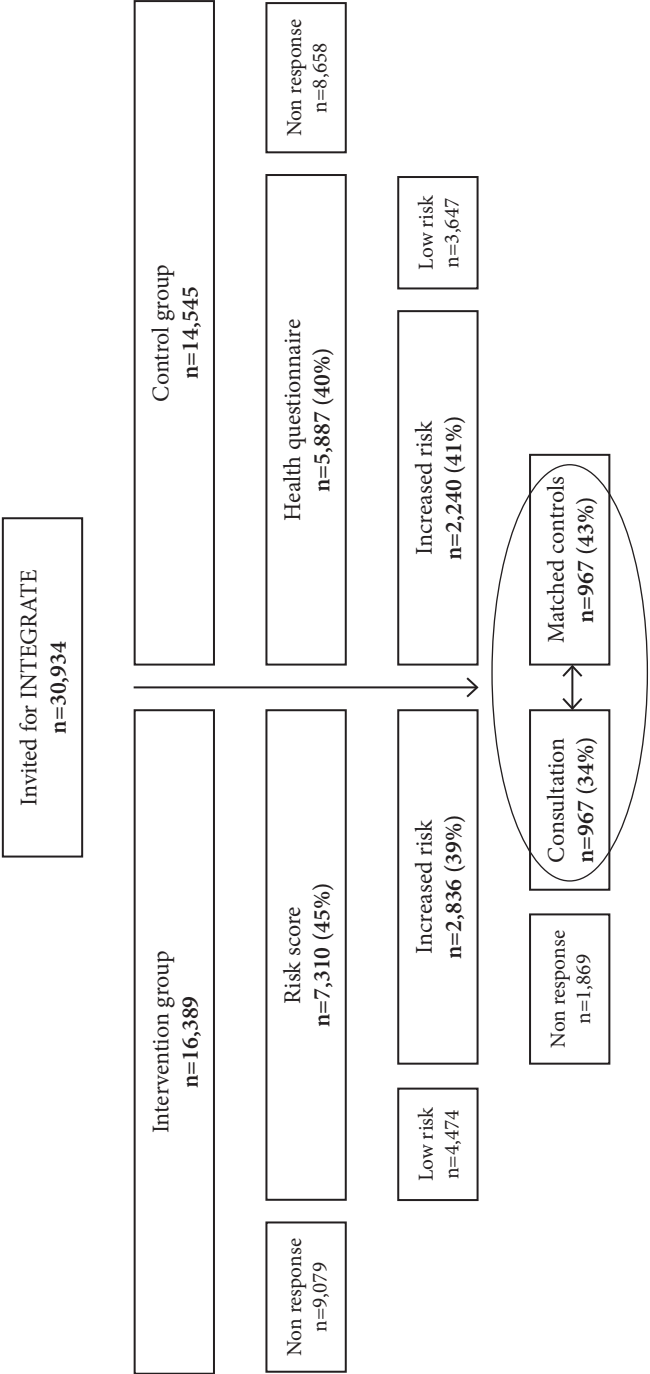
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Appendix 1

Flowchart of participants



Appendix 2

Cholesterol classes in the CDM for men and women

Total cholesterol:	<5	5-6.5	6.5-8	>8
Untreated	Class 1	Class 2	Class 3	Class 4
Treated with statins	Class 5	Class 6	Class 7	Class 8

Blood pressure classes in the CDM for men and women

Systolic blood pressure:	<120	120-140	140-160	>160
Untreated	Class 1	Class 2	Class 3	Class 4
Treated with medication	Class 5	Class 6	Class 7	Class 8



Appendix 3

Cholesterol transitions in the first year after enrolling the INTEGRATE intervention

(N=967 in intervention group)

	class1	class2	class3	class4	class5	class6	class7	class8	total
class1	110	67	2	0	11	2	0	0	193
class2	75	366	70	1	21	5	0	0	538
class3	4	82	98	5	16	10	2	0	217
class4	0	2	7	2	2	3	3	0	19
total	189	517	178	8	51	20	5	0	967

SBP transitions in the first year after enrolling the INTEGRATE intervention

(N=967 in intervention group)

	class1	class2	class3	class4	class5	class6	class7	class8	total
class1	86	69	16	2	2	1	0	0	175
class2	76	219	96	11	4	10	4	2	422
class3	21	96	91	21	3	22	11	2	268
class4	2	13	28	13	0	16	18	12	102
total	185	397	232	47	10	48	33	16	967

Cholesterol transition probabilities

	class1	class2	class3	class4	class5	class6	class7	class8	total
class1	0.570	0.347	0.013	0	0.059	0.011	0	0	1
class2	0.140	0.680	0.130	0.002	0.039	0.009	0	0	1
class3	0.017	0.379	0.452	0.021	0.075	0.046	0.011	0	1
class4	0	0.108	0.370	0.118	0.109	0.152	0.143	0	1

SBP transition probabilities

	class1	class2	class3	class4	class5	class6	class7	class8	total
class1	0.489	0.392	0.091	0.009	0.014	0.003	0	0	1
class2	0.179	0.520	0.228	0.026	0.009	0.024	0.009	0.005	1
class3	0.080	0.360	0.340	0.080	0.013	0.081	0.041	0.007	1
class4	0.019	0.127	0.278	0.125	0.002	0.154	0.176	0.119	1

Appendix 4

Sensitivity analyses

Figure A1 Tornado plot of the difference in Euro/QALY when effect size, implementation costs and lifestyle + healthcare + patient costs were varied with +20% and -20%. Zero corresponds to the default ICER of 482,000 Euro/QALY

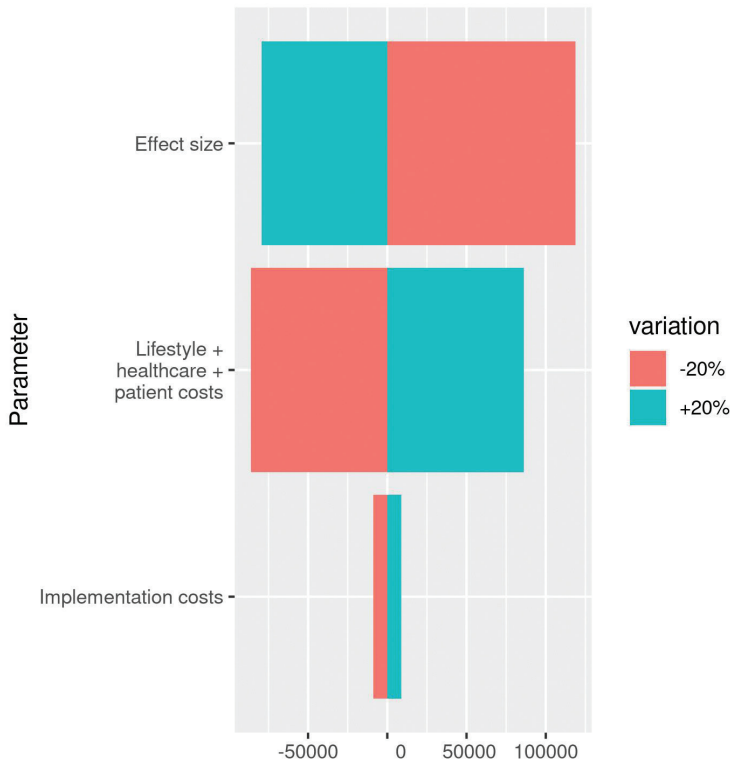


Figure A1 shows that decreasing the lifestyle + healthcare + patient cost with 20% would reduce the ICER with around 86,000 Euro/QALY to 396,000 Euro/QALY. The positive effect of increasing the effect size with 20% would be slightly smaller. Variation of the implementation costs would barely affect the ICER.

Cost-effectiveness could hypothetically be achieved when there would be no implementation costs and lifestyle + healthcare + patient costs would be around 7 Euro instead of 223 Euro (i.e. a reduction of more than 97%).



Implementation of selective prevention for cardiometabolic diseases;
are general practices adequately prepared?

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Abstract

Objective: Current guidelines acknowledge the need for cardiometabolic disease (CMD) prevention and recommend five-yearly screening of a targeted population. In recent years programs for selective CMD-prevention have been developed, but implementation is challenging. The question arises if general practices are adequately prepared. Therefore, the aim of this study is to assess the organizational preparedness of Dutch general practices and the facilitators and barriers for performing CMD-prevention in practices currently implementing selective CMD-prevention.

Design: Observational study

Setting: Dutch primary care

Subjects: General practices

Main outcome measures: Organizational characteristics

Results: General practices implementing selective CMD-prevention are more often organized as a group practice (49% vs. 19%, $p=0.000$) and are better organized regarding chronic disease management compared to reference practices. They are motivated for performing CMD-prevention and can be considered as 'frontrunners' of Dutch general practices with respect to their practice organization. The most important reported barriers are a limited availability of staff (59%) and inadequate funding (41%).

Conclusion: The organizational infrastructure of Dutch general practices is considered adequate for performing most steps of selective CMD-prevention. Implementation of prevention programs including easily accessible lifestyle interventions needs attention. All stakeholders involved share the responsibility to realize structural funding for programmed CMD-prevention. Aforementioned conditions should be taken into account with respect to future implementation of selective CMD-prevention.

Introduction

Cardiometabolic diseases (CMD) including cardiovascular diseases, diabetes mellitus type 2 (DM2) and chronic kidney disease, are the leading cause of death worldwide and account for over a quarter of mortality in the Netherlands.^{1,2} Over the next decades, the prevalence of CMD will increase even further due to a rise in life expectancy combined with a progressing unhealthy lifestyle.³ An estimated 80% of CMD is caused by unhealthy lifestyle and therefore could be prevented.⁴

In recent years several programs for selective CMD prevention have been developed.^{5,6} These programs aim to identify individuals at increased risk for CMD and to subsequently initiate and support lifestyle changes and treatment, if indicated. Given the fact that GPs provide integral health care, have longstanding relationships with their patients and see – at least in the Netherlands – over 75% of their listed patients annually⁷, they have unique opportunities to identify individuals at risk for CMD, to assess their eligibility for lifestyle intervention and to provide long-term follow-up.

The European Society of Cardiology (ESC) also acknowledges the need for adequate cardiovascular disease prevention and recommends five-yearly screening of a targeted population. In addition, the ESC guideline indicates that cardiovascular disease prevention should be delivered in all healthcare settings. In particular, general practitioners (GPs) are proposed as key caregiver to initiate, coordinate and provide long-term follow-up for cardiovascular disease prevention.^{4,8}

Implementing these recommendations in daily practice is a challenge for all stakeholders involved. On the one hand fundamental questions arise, such as whether individuals are responsible for their own lifestyle and subsequent risks and how that relates to the role of health care providers? On the other hand, structural challenges appear such as the consequences for the already increasing workload in general practice and the lack of adequate funding of preventive activities.^{9,10} Several studies have shown that Dutch GPs consider selective CMD prevention worthwhile⁸ and recognize lifestyle interventions as one of their responsibilities.¹¹

Positive associations have been found between various aspects of practice organization and quality of cardiovascular risk management and DM2 care. Structured collaboration, such as cooperation with a practice nurse^{12,13} working in multidisciplinary teams^{14,15}, collaboration in GP-groups^{15,16}, education in cardiovascular risk management for practice nurses¹⁷ and logistic support (e.g. recall system and records on risk factors)^{15,17-19} all improve outcomes of chronic care and prevention programs for CMD. Other factors that might determine successful CMD prevention are the availability of defined care pathways for CMD²⁰ including easily accessible lifestyle interventions^{10,17,21,22} and sufficient financial support.^{10,23} However, so far it is unclear to what extent these aforementioned organizational factors - which are the preamble to successful implementation - are present in Dutch general practices.

Therefore, the aim of this observational study is to assess the organizational preparedness of Dutch general practices and the facilitators and barriers for CMD prevention in general practices currently implementing selective CMD prevention.

Methods

Study design

The study was divided in two parts:

1. an observational study comparing organizational characteristics between practices currently participating in a CMD prevention program (index practices) and a sample of reference practices
2. a descriptive study on the delivery of CMD prevention, including facilitators and barriers for performing CMD prevention in the index practices

Participants

General practices currently implementing selective CMD prevention (index-practices)

This group consists of 37 practices, with in total 117 participating GPs, that consented to participate in the INTEGRATE study. The INTEGRATE study aims to evaluate the (cost)-effectiveness of programmed selective CMD prevention among primary care patients aged 45-70 years. All index practices carry out a CMD prevention program including a tailored lifestyle intervention. Details about the design of the INTEGRATE study and the CMD prevention program have been published elsewhere.²⁴

Representative sample of Dutch general practice (reference practices)

Data on reference practices were derived from two publications of the Netherlands Institute of Health Services Research (NIVEL); the 2015 report of the GP register and the 2015 evaluation of the Dutch GP forecasting report.^{25,26}

NIVEL's GP register covers data of all GP practices in the Netherlands (n=5045 in 2015) with regard to basic organizational aspects and health care delivery, such as personal characteristics of GPs, practice characteristics, cooperation with other health care professionals, participation in chronic care groups and availability of supportive staff. These data are updated annually by Dutch GPs themselves.

The data used for the 2015 evaluation of the Dutch GP forecasting report were derived from different data sources. Among others the NIVEL's GP register (1567 GP practices updated their profile in 2014) and the website of NHG (Dutch College of general practitioners) Practice Accreditation (NPA) were used. An additional questionnaire was sent to a random sample of

1,180 GPs in the Netherlands with questions concerning topics like prevention, accessibility of GP care, cooperation with other health care professionals and coordination of primary care.

Data collection

For both index and reference practices we used data about characteristics of their practice organization (table 1). In the index practices we collected additional information on the delivery of CMD prevention, including facilitators and barriers for performing CMD prevention (table 2).

Index practices

At baseline (before the start of the INTEGRATE study) questionnaires were sent to all index practices containing 47 pre-structured questions on practice characteristics, the participation in chronic disease management programs for DM2, cardiovascular risk management and chronic obstructive pulmonary disease (COPD) and collaboration with other health care professionals within the practice (table 1).

In the questionnaire sent to the index practices we also collected information on aspects of practice organization which have been associated with improved cardiovascular risk management and DM2 care (structured collaboration, training of staff and logistic support), performance of preventive activities, such as attitudes towards preventive activities, access to lifestyle intervention services and barriers for implementing selective CMD prevention (table 2).

The questionnaire was based on the 2015 evaluation of the Dutch GP forecasting report questionnaire and on the questionnaire applied by NIVEL in the 2010 pilot evaluation study of selective CMD prevention.^{26,27} The person in the practice who was most involved with the planned implementation of the CMD prevention program filled out the questionnaire (GP, practice nurse or practice assistant).

Reference practices

Data on practice characteristics, such as practice type and setting were derived from the 2015 report of the GP register.²⁵

The 2015 evaluation of the Dutch GP forecasting report²⁶ was used as data source on quality of care, such as the percentage of practices accredited by the NPA and their participation in a chronic care group. To receive accreditation by the NPA, practices have to meet at least 23 quality standards regarding practice policy, recording, monitoring and improving quality of care, practice organization, patient experiences and professional behaviour. In addition, this evaluation report was used for data on digital and health related services, cooperation with other health care professionals and participation in chronic disease management programs for DM2, cardiovascular risk management and COPD.

Analysis

Practice characteristics of index and reference practices

Descriptive statistics were used to present the practice characteristics of index and reference practices and were presented as percentages. Due to our relatively small number of index practices ($n=37$), a two-tailed binomial test was used for dichotomous outcomes and a chi-square test for categorical outcomes to compare the characteristics of the index practices with the reference practices.

Preventive activities of index practices

Descriptive statistics were used to present the preventive activities of index practices and were presented as percentages. Statistical analyses were performed using STATA version 14.0

Results

Practice characteristics

Characteristics of index practices and the reference practices are presented in table 1. Index practices were more often organized as group practices as compared to the reference practices (49% vs. 19%, $p=0.000$) and were more likely to teach GP trainees (62% vs. 38%, $p=0.004$). The practice location did not differ between index practices and reference practices, with one third located in a rural setting. Index practices more often participated in scientific research (78% vs. 46%, $p=0.000$) and a significantly higher proportion was accredited by the NPA (73% vs. 55%, $p=0.003$). The number of listed patients per full-time GP was comparable. In the Netherlands the average practice size is 2350 patients per full-time GP (data not shown).

Collaboration and participation in chronic disease management

Index practices more frequently employed supportive nursing staff. In nearly all index practices (97%), at least one practice nurse was trained in giving lifestyle advices, compared to 80% of the reference practices ($p=0.006$). The percentage of practices participating in a chronic care group was comparable (89% vs. 81% respectively). All index practices and all reference practices participating in a chronic care group provided a disease management program for DM2 patients. Index practices were more likely to also participate in chronic disease management programs for COPD and cardiovascular risk management (94% vs. 75%, $p=0.008$ and 82% vs. 55%, $p=0.002$, respectively) (table 1).

Table 1 Characteristics of index practices and reference practices

Characteristic	Index practices N=37	Reference practices N= 5045	P-value
Type of practice (%) ¹			
Single-handed practice (1GP)	27	41	0.000*
Practice with 2 GPs	24	40	
Group practice/ Health Care Centre (≥ 2 GPs)	49	19	
Training practice for GP trainees	62	38	0.004
Dispensing practice	11	7	0.327
Practice setting (%) ¹			
Rural†	38	31	0.157*
Rural–urban fringe	16	17	
Urban	46	42	
	N=37	N=1567	
Quality of care (%) ²			
Accreditation by NPA††	73	55	0.031
Participating in chronic care group	89	81	0.293
Previous participation in scientific research	78	46	0.000
Digital and health related services (%) ²			
Consultations out of office hours	35	n/a	
E-consultations available	68	49	0.031
Practice website available	97	n/a	
Health care professionals in general practice (%) ²			
Practice nurse	97	80	0.006
Lifestyle coach	16	n/a	
Dietician	51	46	0.515
Physiotherapist	35	40	0.617
Psychologist	41	34	0.391
Involved in chronic disease management (%) ²†††			
Diabetes mellitus	100	99	1
Chronic obstructive pulmonary disease	94	75	0.008
Cardiovascular risk management	82	55	0.002

1. NIVEL. Cijfers uit de registratie van huisartsen peiling 2015 [2015 report of the GP-register]²⁵

2. NIVEL. De Toekomstvisie Huisartsenzorg 2022, waar staat de huisartsenzorg anno 2014? [The evaluation of the 2015 Dutch GP forecasting report]²⁶

* p-value for categorical variable

† Rural: <1000 addresses per km²; Rural–urban fringe: 1000-1500 addresses per km²; Urban >1500 addresses per km²

†† To receive accreditation by the NPA, practices have to meet at least 23 quality standards regarding practice policy, recording, monitoring and improving quality of care, practice organization, patients experiences and professional behavior.

††† Chronic disease management programs are defined as care programs in which cooperation agreements have been made between GPs and local healthcare providers concerning the programs' content and distribution of responsibilities. In the Netherlands, these programs are funded by health care insurance companies and can be offered if the practice is united in a chronic care group.

Abbreviations: GP: General practitioner; n/a: not available

Preventive activities of index practices

In the majority of the index practices (89%), patients received an individual treatment plan and standard follow-up by the practice nurse or GP in case of an established increased CMD risk. In 86% of the index practices the practice nurse and GP closely collaborated in the follow-up care once an increased CMD risk was detected. Three quarters of the practice nurses received additional education in cardiovascular risk management and/or DM2 care more than twice a year, and 86% of the practice nurses attended a training at least annually. Nearly all practices (97%) offered a smoking cessation program within their practice. Lifestyle support services, such as body weight control/dietary advice and physical exercise programs were offered in 30% and 14% of the index practices respectively. In total, 41% of the index practices indicated not to be up-to-date with the available community-based lifestyle services and 46% had no written overview of these services available, but only 8% indicated this as a barrier for implementation.

In the self-rated questionnaire, index practices scored on average a 7.8 (SD 0.55), on a scale of 0-10, for their overall interest in prevention and preventive activities. An average of 7.6 (SD 0.79) was scored for staff commitment and a 7.5 (SD 0.95) for practice organization regarding CMD prevention.

Limited availability of staff/lack of time (59%) and insufficient financing (41%) were reported as most important structural barriers for the implementation of selective CMD prevention. (table 2)

Table 2 Preventive activities of practices committed to selective CMD prevention

Characteristic	Index practices (N=37)
Activities in case of increased CMD risk (%)	
Individual treatment plan	89
Standard follow-up by practice	89
Structured consultations between practice nurse and GP	51
Occasional consultation between practice nurse and GP according to agreements	35
Verbal information during consultation	100
Written information given	97
Website references given	57
Practice nurse training in cardiovascular risk management or diabetes care (%)	
0 times per year	14
1-2 times per year	11
>2 times per year	75
Lifestyle support service within general practice (%)	
Smoking cessation	97
Weight management/ healthy food sessions	30
Exercise programs	14
Community-based lifestyle services (%)	
Practice is well informed about lifestyle services	59
Written overview of available lifestyle services	54
Access to information about lifestyle services during consultation	62
Written information about lifestyle services on the website	22
Barriers for programmed CMD prevention in general practice (%)	
Insufficient staff/time	59
Financing	41
Patients have no need for prevention	19
Insufficient scientific evidence for the effect of selective CMD prevention	8
Lack of motivation for preventive activities	3
Lack of cooperation between parties involved	5
No clear overview of preventive activities available	8
No hampering factors reported	5
Motivation for prevention (means, SD)	
Interest in prevention of general practice	7.8 (0.55)
Staff commitment to preventive activities	7.6 (0.79)
Organization of cardiovascular prevention	7.5 (0.95)

Abbreviations: CMD: cardiometabolic diseases; GP: general practitioner

Discussion

Summary of results

General practices willing to participate in a selective CMD prevention program are more often organized as group practices and are better organized with respect to chronic disease management as compared to the reference practices. They are motivated for CMD prevention and seem to be ‘frontrunners’ of Dutch general practices considering the degree in which they participate in chronic disease management programmes, the fact that most of them are accredited by the NPA, and their participation in scientific research. Despite their adequate practice organization, almost half of these practices lack an overview of available community-based lifestyle support services.

Interpretation of results

Dutch general practices committed to selective CMD prevention seem to be well organized, motivated for preventive activities and employ skilled practice nurses. These practices seem to have a – more than average – experience with chronic disease management programs for cardiovascular risk management and can therefore be expected to readily implement selective CMD prevention. Altogether, this provides a solid fundament for selective CMD prevention in Dutch primary care. However, being a well-organized practice is not the only condition for success. After identifying patients at increased CMD risk, adequate facilities should be available – and familiar to caregivers – to initiate and support lifestyle changes (e.g. by lifestyle intervention programs).

A close link between general practices and community-based lifestyle services is crucial for effective CMD prevention.⁴ More than half of the index practices fall short in offering adequate lifestyle support services for weight management and/or exercise programs within their practice. This is worrisome since almost half of all index practices also lack an overview of available community-based lifestyle support services. These findings are more or less consistent with the study of Wyers et al.¹⁰ who found that 62% of the respondents (i.e. GPs and health care professionals) were not informed about community-based lifestyle interventions. A qualitative evaluation of the National Health Services (NHS) Health check in the UK revealed the same lack of knowledge among caregivers.²⁸

Nowadays lifestyle intervention programs tend to be local initiatives and due to the ad hoc and often temporary funding their existence is inconsistent by nature.²⁹ The absence of a proper reimbursement system for these services in combination with a lacking local prevention policy are contributing to an unstable and not sustainable prevention program. These circumstances could explain the unfamiliarity among health care professionals with these services.

Practices implementing selective CMD prevention and other health care professionals¹⁰ indicate limited availability of staff/lack of time and inadequate financing as most important

barriers for implementation. In the UK insufficient funding was also described as a limiting factor for implementation of the NHS health check.²¹

Systematic screening of individuals potentially at risk for CMD in primary care is recommended by the ESC and selective CMD prevention, by changing lifestyle and pharmacological treatment if indicated is reported to be cost effective, even in different scenarios.⁴ Dutch health care insurance companies however, still question the cost-effectiveness of large scale implementation of CMD prevention programs in primary care.³⁰ In addition, local governments and health care insurance companies are hesitant to invest in prevention programs because the cost-savings from a successful intervention might not directly flow back to the funding organization: the so called wrong-pocket problem.²⁹ The INTEGRATE study aims to settle this debate by determining the cost-effectiveness of selective CMD prevention.²⁴

Effective CMD prevention calls for long term strategies. Once proven cost-effective it should be indicated who should take the responsibility for the structural financing of CMD prevention programs. This could either be the government (by nominating it as a national screening program) or health care insurance companies.

Therefore, anchoring selective CMD prevention in primary care will require a multi-disciplinary approach with constructive collaboration between healthcare professionals, policy makers and health care insurance companies.

Strengths and limitations

It was possible to compare the characteristics of practices willing to implement selective CMD prevention with a representative sample of reference practices. It was a unique possibility to elucidate to what extent Dutch general practices are ready for programmed CMD prevention in organizational respect.

We compared our data to the results presented in two recently published reports conducted by NIVEL. The NIVEL data are considered to be from a representative sample. The GP register is based on a routine system that is updated annually by the Dutch general practitioners themselves. Although acceptable annual response rates, there is always a chance of selection.

Not all practice characteristics could be compared to the reference practices because data for some characteristics were not available. In addition, the questionnaire was completed by one individual per general practice and could have resulted in a not fully representative reflection of the practice. However, this person was the one who was most engaged with the prevention program. We believe there is only a small chance that these limitations have vitiated our conclusion that the index practices seemed better organized than the reference practices.

Conclusion

The organizational infrastructure of Dutch general practices is considered adequate for performing most steps of selective CMD prevention and practices willing to implement CMD prevention meet the majority of criteria which are assumed to be essential for adequate and effective prevention. Worrisome is the lack of knowledge about available community-based lifestyle services and the limited options for lifestyle interventions within the practices. Therefore, implementation of defined prevention programs including easily accessible services for lifestyle support should be the focus of attention. In addition, policy makers, health care insurance companies and healthcare professionals share the responsibility to realize sufficient and structural financing for the entire chain of CMD prevention. Aforementioned conditions should be taken into account with respect to future implementation of selective CMD prevention.

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The association between GP organizational factors and the effectiveness
of a prevention program for cardiometabolic diseases: a prospective
intervention study

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Abstract

Background: Due to the rising disease burden of cardiometabolic diseases (CMD), prevention programs for CMD are increasingly implemented in primary care. Organizational practice characteristics and availability of preventive services may be associated with a more effective program.

Aim: To identify possible organizational success factors from general practices related to an effective primary prevention program for CMD.

Design and setting: A prospective intervention study involving 37 Dutch general practices.

Methods: Patients aged 45-70 years without known CMD, hypertension or hypercholesterolemia were invited for the prevention program. The outcome measures were an improvement (yes/no) in four different CMD risk factors between baseline and one year follow-up on individual level (BMI, smoking, systolic blood pressure and cholesterol ratio). Multivariate logistic regression analysis was used for assessing associations between practice organizational characteristics and outcomes.

Results: Just over half of the participants showed an improvement on one or more risk factors. Marginal differences were found in the four different outcomes between the practices with different organizational characteristics. None of the practice characteristics we tested showed a significant association with an improvement in one of the outcome measures.

Conclusion: In this study general practice organizational and preventive services characteristics showed no impact on the effectiveness of a CMD prevention program. Possible explanations could be the effectiveness of protocolized pharmaceutical treatment and only limited contribution of lifestyle programs on the improvement of CMD risk factors.

Introduction

During the past decades healthcare systems have been confronted with an increasing disease burden of cardiometabolic diseases (CMD), including cardiovascular disease, diabetes mellitus type 2 and chronic kidney disease. CMD are the number one cause of death globally and are accountable for more than half of all deaths across the WHO European Region.¹ Worldwide an estimated amount of 17.9 million persons die of cardiovascular disease each year, diabetes causes another 1.6 million deaths yearly and approximately 1.2 million people die from kidney failure.¹ Lifestyle related risk factors are accountable for 80% of all CMD.² This has caused a shift from a curative to a more preventive approach, with counselling for a healthy life style as indispensable factor. Initiatives worldwide led to the development of different CMD prevention programs^{3,4}, sharing the main goal to identify and treat people at high risk for CMD. Although previous studies have shown positive effects of prevention programs for CMD in terms of risk profile improvement^{5,6}, evidence to support long term effectiveness of these programs is still missing.^{3,4,7}

CMD prevention programs are commonly organized within primary care. The general practitioner (GP) is an easily accessible health care professional and therefore has a unique position within most healthcare systems to deliver a prevention program. The GP is appointed as key-caregiver for CMD prevention in the most recent European Guidelines on cardiovascular disease prevention in clinical practice.² In everyday practice, however, preventive activities are often not prioritized by GPs.^{8,9} Improvements in practice organization might help to overcome this paradox, for instance, a lack of time and focus can be tackled by deployment of practice nurses and lifestyle coaches, supporting the GP with preventive services. This leads to different methods of delivery of preventive programs for CMD between practices, depending on available staff and other organizational practice characteristics.^{9,10} Earlier studies showed that organizational practice characteristics such as practice type, support by non-medical staff and an overview of available lifestyle services are associated with improved quality indicators of standard cardiovascular prevention.¹¹⁻¹⁴ Nevertheless, more than half of the general practices willing to participate in a selective CMD prevention program fall short in offering adequate lifestyle support services and almost half of the practices lack an overview of available community-based lifestyle support services.¹⁰

Practice related factors may be a key in effective deliverance of a CMD prevention program, but up to now little is known about this relationship. In order to address this gap in knowledge, the aim of this study was to identify whether organizational factors are related to the effectiveness of CMD prevention program in primary care.

Methods

Design

This study is part of the INTEGRATE study, a Dutch stepped-wedge randomized controlled trial conducted from 2014 to 2017 (Dutch trial Register number NTR4277). A stepwise prevention program for CMD¹⁵ followed by individualized treatment was implemented in 37 participating general practices. Details about the study design are described elsewhere¹⁶, as well as the outcomes of the effectiveness of the prevention program.⁶ Earlier we reported the organizational characteristics of the 37 participating practices.¹⁰

Participants

All enlisted patients aged 45-70 years without known CMD, hypertension or hypercholesterolemia according to their electronic health record were eligible for participation. Patients received a personal letter from their GP inviting them to complete the first step of the CMD prevention program, the risk score. The risk score consisted of seven items including sex, age, smoking status, body mass index (BMI), waist circumference and a family history of premature cardiovascular disease (age <65 years) and/or diabetes and resulted in the absolute risk to develop a CMD in the next seven years.^{17,18} After filling in the risk score, online or on paper, participants with an increased risk for CMD ($\geq 23\%$ for men and $\geq 19\%$ for women) were advised to visit the practice for the second step of the program. At the practice, additional measurements were done, including blood pressure, cholesterol and fasting glucose levels. During the third step of the program participants received a tailored lifestyle advice and pharmaceutical treatment when indicated. All participants who filled in the online risk score received additional questionnaires.

For the present analysis we used data from all participants who visited the general practice for additional profiling, confirmed in case report forms, electronic medical records or by self-report. We imputed missing baseline and outcome data on CMD risk factors using the multiple imputation techniques, described in more detail in the study describing the effectiveness of the program.⁶

Outcome variables

The primary outcome for this analysis was effectiveness of the CMD prevention program, defined as an improvement in one or more CMD risk factors between baseline and one year follow-up on individual level. Individual CMD risk factors were smoking, systolic blood pressure and total cholesterol/high density cholesterol ratio (TC/HDL ratio), all modifiable variables from the Coronary Risk Evaluation (SCORE).¹⁹ BMI was added as outcome variable for evaluation of lifestyle change, next to smoking status. Outcomes for BMI, systolic blood pressure and TC/HDL ratio were dichotomized on individual level into 'no change or a deterioration (higher

value)' and 'an improvement' (i.e. lower value) between baseline and follow-up. Data was collected from the electronic health record of the GP and through additional questionnaires.

Practice characteristics

Questionnaires containing questions about on the practice organization and the delivery of CMD prevention were sent to all participating practices. The key professional in the implementation of the CMD prevention program filled in the questionnaire. More details about the questionnaires and an overview of the characteristics of the participating practices at baseline is reported elsewhere.¹⁰

To prevent multiple testing a selection of characteristics with the highest potential was made, based on literature.¹²⁻¹⁴ The selected practice organizational characteristics were type of practice (single handed/2 GPs/group practice of health care center), practice setting (urban/urban-rural fringe/rural), quality of care (practice accreditation and participation in chronic care group), health professionals in general practice (lifestyle coach and dietitian), involvement in chronic disease management, lifestyle support service within general practice (weight management/healthy food sessions and exercise programs) and community-based lifestyle services (informed about lifestyle services, written overview available, access to information during consultation).

Analyses

Multivariate logistic regression analysis was used to assess the association between practice organizational characteristics and in improvement in individual risk factors after one-year follow-up. Outcomes were corrected for age and sex in all four different models. We also corrected for clustering within practices. Odds ratios and 95% confidential intervals were used for reporting, all statistical analyses were performed using STATA 15.0.

Results

Baseline organizational characteristics of the participating practices are shown in table 1. A lifestyle coach was present in 16% of the participating practices and weight and diet management/physical exercise programs were offered in 30% and 14% of the practices, respectively. A total of 59% of the practices was well informed about available lifestyle programs in the region.

From the 16389 eligible individuals that were invited for the first step of the program, 7313 (45%) completed the risk score and 2240 (31%) had an increased risk and were invited to contact their GP. A total of 967 participants (43% of those invited) visited the practice for additional profiling. An overview of the characteristics of the individual participants can be found elsewhere.⁶ Just more than half of the participants showed an improvement in BMI

(52%), systolic blood pressure (51%) and TC/HDL ratio (53%) after one year of follow-up, and four percent of the smokers had stopped smoking.

Table 1 Baseline characteristics of participating general practices

Practice characteristics (N=37)	%
Type of practice (%)	
Single-handed practice (1GP)	27
Practice with 2 GPs	24
Group practice/Health Care Centre (>=2 GPs)	49
Practice setting (%)	
Urban	46
Urban - Rural fringe	16
Rural	38
Quality of care (% yes)	
Accreditation by NPA	73
Participation in chronic care group	89
Health professionals in general practice (% yes)	
Lifestyle coach	16
Dietician	51
Involved in chronic disease management (% yes)	
Cardiovascular risk management	82
Lifestyle support service within general practice (% yes)	
Weight management/healthy food sessions	30
Exercise programs	14
Community-based lifestyle services (% yes)	
Practice is well informed about lifestyle services	59
Written overview of available lifestyle services	54
Access to information about lifestyle services during consultation	62

Marginal differences were seen on the four different outcomes between practices with different organizational characteristics (table 2). None of the practice characteristics we analyzed was significantly associated with outcome improvement. No clustering of outcome improvement was observed in any of the practice organizational characteristics, reaffirming that none of the characteristics was associated with an overall improvement in CMD risk profile.

Table 2 Association between practice characteristics and percentage participants with improvement in CMD risk factors (adjusted ORs and 95%CI)

N=967	BMI		Smoking		Systolic blood pressure		TC/HDL ratio	
	% ↓ *	OR [95%CI]	% ↓	OR [95%CI]	% ↓	OR [95%CI]	% ↓	OR [95%CI]
Type of practice								
Single-handed practice (1GP) (reference)	48		9		54		58	
Practice with 2 GPs	50	1.10 [0.65-1.84]	3	0.31 [0.09-1.10]	47	0.78 [0.40-1.49]	48	0.65 [0.32-1.35]
Group practice/Health Care Centre (≥2 GPs)	53	1.23 [0.80-1.91]	4	0.44 [0.18-1.07]	52	0.98 [0.56-1.70]	53	0.80 [0.43-1.46]
Practice setting								
Urban (reference)	53		3		51		52	
Urban-rural fringe	52	0.96 [0.65-1.41]	4	1.42 [0.49-4.08]	58	1.48 [0.86-2.56]	47	0.86 [0.49-1.55]
Rural	50	0.90 [0.64-1.26]	6	2.25 [0.99-5.17]	48	0.92 [0.60-1.40]	59	1.31 [0.86-1.99]
Quality of care								
Accreditation by NPA (no/yes)	50/52	1.09 [0.78-1.53]	5/4	0.69 [0.30-1.59]	54/50	0.88 [0.55-1.42]	48/54	1.18 [0.71-1.96]
Participation in chronic care group (no/yes)	55/51	0.87 [0.60-1.25]	6/4	0.55 [0.24-1.29]	47/52	1.26 [0.74-2.14]	60/51	0.71 [0.41-1.21]
Health professionals in general practice								
Lifestyle coach (no/yes)	52/51	0.96 [0.67-1.37]	4/4	0.81 [0.30-2.24]	49/59	1.59 [1.00-2.52]	53/53	1.08 [0.64-1.82]
Dietician (no/yes)	49/53	1.19 [0.89-1.58]	5/4	0.70 [0.33-1.49]	47/54	1.36 [0.91-2.02]	59/49	0.70 [0.48-1.04]
Involved in chronic disease management								
Cardiovascular risk management (no/yes)	49/53	1.15 [0.80-1.67]	5/4	0.94 [0.38-2.38]	49/52	1.10 [0.68-1.78]	54/53	0.97 [0.60-1.57]
Lifestyle support service within general practice								
Weight management/healthy food sessions (no/yes)	51/54	1.15 [0.84-1.56]	4/4	0.98 [0.44-2.20]	49/55	1.32 [0.87-2.01]	53/52	0.97 [0.60-1.57]
Exercise programs (no/yes)	52/47	0.80 [0.43-1.49]	4/0	1.00 [1.00-1.00]	51/62	1.65 [0.79-3.43]	53/54	1.09 [0.47-2.54]
Community-based lifestyle services								
Practice is well informed about lifestyle services (no/yes)	51/53	1.08 [0.81-1.45]	4/5	1.30 [0.61-2.79]	51/51	1.02 [0.67-1.57]	54/52	1.05 [0.66-1.66]
Written overview of available lifestyle services (no/yes)	51/54	1.13 [0.85-1.49]	4/4	1.13 [0.52-2.44]	52/51	0.94 [0.62-1.42]	51/55	1.30 [0.83-2.02]
Information lifestyle services during consultation (no/yes)	50/53	1.12 [0.84-1.50]	4/4	1.14 [0.53-2.48]	54/49	0.77 [0.52-1.15]	52/54	1.09 [0.79-1.52]

* percentage of participant that showed an improvement in CMD risk factor (e.g. lower BMI).

ORs adjusted for age and sex at individual level and adjusted for clustering at practice level

Abbreviations: OR= odds ratio, BMI= body mass index; TC/HDL ratio= total cholesterol/high density cholesterol ratio

Discussion

Summary of results

In this study we aimed to identify organizational characteristics of primary care practices which were associated with the effectiveness of a prevention program for CMD. Although all four individual CMD risk factors improved for the majority of patients, none of the practice characteristics was significantly associated with this improvement. Based our data, practice organization does not seem to contribute the effectiveness of CMD prevention programs in general practice.

Strengths and limitations

This study was part of a large randomized controlled trial with a pragmatic approach, making the results representative for a 'real-life setting' in primary care. Another strength was the use of actual change in risk factors for CMD on individual level, in contrast to earlier studies using indicators of performance (e.g. percentage of recorded risk factors or percentage of patients with achieved protocolled treatment targets) derived from electronic health records as a measure for the quality of preventive care delivery. The total number of general practices used in our analysis was small compared to earlier studies that assessed practice characteristics.¹¹⁻¹⁴ On the other hand, with both rural and urban practices of variable sizes, our study practices were heterogeneous enough to be representative for Dutch general practice and their patient population.⁶ The available data on individual level was limited to the 976 participants that finished step 2 of the prevention program, divided between the 37 practices. A larger data set would have increased the validity of our results. The final limitation of this study is the generalizability of our results. The extent to which our results can be extrapolated to other countries might be limited, for health care systems might not be comparable and it is unclear how the organizational practice factors of Dutch general practices relate to practices in other countries.

Comparison with existing literature

To our knowledge this is the first study to investigate the relationship between practice organizational characteristics and the effectiveness of a prevention program for CMD. Our study results do not compare well with the outcomes of earlier research because of crucial differences in study aim and design. Earlier research focused mainly on the association between practices characteristics and the quality of standard cardiovascular management for patients with mostly known cardiovascular disease. In these earlier studies practices characteristics were associated with a better performance in some process quality indicators for standard cardiovascular prevention.¹¹⁻¹⁴ Nevertheless, none of these practice characteristics were associated with an improvement in CMD risk factor outcome in newly detected high-risk patients after one year follow-up in our study.

Even though practices vary in organizational factors and availability of preventive services, pharmaceutical treatment protocols for individuals are standardized in the Netherlands. Practices with a lifestyle coach, dietician or lifestyle support services do not have better outcomes than practices without these facilities. This suggests a lack in effectiveness of offering lifestyle programs for this population, either by too little referrals, a low attendance rate or low effectiveness of the lifestyle programs themselves. Lifestyle changes probably only have a limited additional contribution to the effect of antihypertensive and anti-hypercholesterolemia treatment ⁶, which explains the small differences in outcomes found in our study.

Implications for research and/or practice

In the INTEGRATE study, differences in general practice organizational characteristics and availability of preventive services showed no impact on the effectiveness of a CMD prevention program, possibly due to the highly standardized pharmaceutical treatment and the limited contribution of lifestyle programs to CMD risk factor improvement. These exploratory findings should be viewed in the light of sample size limitations and further research to confirm these findings is warranted. Future research should also focus on the development of effective lifestyle programs before valid recommendations about the organization of preventive services for primary prevention of CMD in the general practice can be made.

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9

General discussion

Goal of thesis

This thesis investigated different aspects of effectiveness and cost-effectiveness of a selective CMD prevention program in primary care. This final chapter discusses the main findings, their interpretation and provides recommendations for and considerations about the future of selective CMD prevention in primary care.

Main findings

Based on the results of the INTEGRATE study we conclude that although programmatic selective CMD prevention in primary care may be successful in detecting CMD and CMD risk factors, these programs are not cost-effective in the long run.

We have shown that implementation of the selective CMD prevention program in general practice is feasible and effective: a 2-3 fold increase in CMD diagnoses was found in the intervention group compared to the control group. In one-fifth of the high-risk participants within the intervention group a new CMD diagnosis was established. Among these high-risk participants we have found a significant drop in blood pressure and cholesterol levels and a relative reduction in CMD risk profile according to the SCORE after one-year follow-up (chapter 4). We have also shown that if additional abnormal diagnostic test results were taken into account, the yield of the program was even higher. In that case in over 40% of high-risk participants either a new CMD diagnosis, a new prescription or an abnormal diagnostic test result was found during one-year follow-up (chapter 5). Finally, Dutch primary care seemed adequately organized to facilitate a selective CMD prevention program, although attention should be paid to the limited awareness of existing community-based lifestyle interventions (chapter 7).

Despite these promising results, the main conclusion of the INTEGRATE RCT is that a selective CMD prevention program is not cost-effective when taking short- and long-term outcomes into account. Sensitivity analyses demonstrated that even under more favourable circumstances, programmed CMD prevention in primary care is unlikely to be cost-effective (chapter 6).

Risk perception among the study participants was generally low, even among high-risk participants who recently learned about their increased personal CMD risk. Individuals with a family history for DM2 and CVD and a BMI >25 kg/m² had a higher risk perception. We conclude that risk communication through an online risk score does not lead to adequate risk perception (chapter 3). In the last chapter we demonstrated that practice-related factors were not associated with the outcome of the selective CMD prevention program (chapter 8).

Given the results of this thesis, the question arises if and how to proceed with selective CMD prevention in primary care. We will answer these questions in the next paragraphs.

Methodological considerations

Before we discuss the consequences of these results, it is important to address some methodological issues which may have affected the validity of our results.

Design of the INTEGRATE study

The stepped-wedge randomized design of the INTEGRATE study and its pragmatic implementation enabled us to investigate the effects of the selective CMD prevention program in a real-life setting compared to care as usual. Evaluation was done in the context of daily practice within the existing primary health care facilities. This may have caused some limitations. The involved staff was aware of the ongoing intervention in the practice, which may also have improved the CMD care and preventive activities in the control group. In addition, the control group was invited at baseline in order to collect information about their baseline CMD risk. In this way the control group – although not aware of the ongoing intervention – may have been affected by the invitation to complete a health questionnaire (Hawthorne effect). However, if such an effect occurred it has led to a diminished contrast between both groups and an underestimation of our results.

Generalizability

We were able to include a broad variety of general practices, both located in urban and rural areas of the Netherlands.¹ For this reason we assume that our results are generalizable for Dutch primary care. However, the practices may have differed in the extent to which they, before participating in the study, already practiced opportunistic case finding, which is an ongoing process. As opportunistic screening and programmed detection of individuals at high CMD risk are fishing in the same waters, this might have diluted the detection rate of high-risk individuals.

Use of electronic health record (EHR) data

EHR data is extensively used in national and international contexts to conduct primary care research.³ Dutch EHR data is assumed to be of high quality.⁴ However, there are some challenges with the use of routine primary care data.

EHR data are not recorded in a standardized way and is restricted by the accuracy and strategy of the recording health care professionals. Inter- and intra-individual differences between professionals in recording and – to a lesser extent – underrecording are likely to occur. A systematic review investigating the validity of coded diagnoses in the UK reported that most of the diagnoses in the EHR were well recorded.⁵ However, as diagnoses or symptoms might not always be recorded, it is not clear how many diagnoses are missed when extracting data. Furthermore, it is known that accuracy of recording increases if there is a financial incentive.⁶

This could explain why the classical CVD and DM2 parameters - for which specific care is reimbursed - were overall properly recorded and the recording of diet and physical activity levels fell behind. We believe that the impact of incomplete recording on the outcomes of the INTEGRATE study were limited, mainly because they appeared in both the intervention and control group. Incomplete recording may have resulted in underreporting of CMD symptoms and diagnoses, however this will not have changed our conclusions.

Missing data

Missing data is a commonly faced challenge in research. We conducted a large clinical trial with a pragmatic approach and also encountered a variable number of missing data. As recommended, smaller numbers of missing data were handled with multiple imputation techniques.⁷ Although we have sent multiple reminders, we had to deal with a large number of missing data from the self-reported follow-up questionnaires due to non-response. Given the fact that we used EHR data of 97% of all participants, we could – at least partly- overcome this problem by combining the questionnaire data with data derived from the EHR. However, the number of remaining missing data on diet and physical activity forced us to leave these variables out of the final effectiveness-analysis.

Is programmed CMD prevention in primary care justified according to the Wilson & Jungner criteria?

Nationwide implementation of a CMD prevention program is resource intensive with regard to facilities, manpower and costs, and should therefore be considered carefully. As it aims to reduce CMD morbidity and mortality in high-risk individuals selective CMD prevention can be regarded as screening, and should thus be evaluated according to the Wilson and Jungner screening criteria⁸ (box 1) Roughly these 10 criteria can be subdivided in “disease-based” criteria (1, 4 and 7), “test-related” criteria (3,5,6 and 10) and “treatment” criteria (2,8 and 9).

The Dutch CMD prevention program meets all three “disease-based” screening criteria. As for the “test-related” criteria, it is debatable if selective CMD prevention meets criterion 5 “there should be a suitable test or examination” For the first step of risk-assessment the (online) risk score is used and as second step the universal SCORE risk function to identify high-risk individuals. The SCORE consortium tried to optimize the predictive validity for different European populations (low and high-risk countries).⁹ The risk function is based on predicting population risk and does not specifically predict a personalized individual risk. However, up to now it is the best available test in primary care at relatively low costs. The selective CMD prevention program meets Wilson and Jungner criteria 3 and 6, as there are adequate facilities for diagnosis and treatment of CMD and previous studies have shown that this program is

acceptable for health care professionals and the eligible population.^{10,11} Despite the fact that repeated CMD risk screening (criterion 10) is already recommended¹², the optimal timeframe of repeated screening is not yet known.

Box 1 Wilson & Jungner WHO criteria†

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

† Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO, 1968.

The program does not fulfil all criteria for 'treatment'. Although there is an accepted treatment for patients with clinically established CMD (criterion 2), risk factor treatment goals for individuals at high risk only remain arbitrary. This is shown by the diverse recommendations for risk factor treatment goals in national and international guidelines. For example, the American Heart Association advocates a stricter definition for hypertension than European guidelines.^{12–14} Moreover, the absolute risk reduction in people without clinically manifest disease is small¹⁵ and therefore numbers needed to benefit are high. Although we have found promising results in our study for treatment of blood pressure and cholesterol after one year, this effect did not result in health benefits on the long-term according to the simulated scenarios (chapter 6). Criterion 8 states that there should be an agreed policy on whom to treat as patients. In this program we identified potential high-risk individuals aged 45–70 years old and the Dutch guideline on cardiovascular risk management subsequently indicates treatment possibilities depending on the level of risk.¹⁴⁹ A high-risk approach seems justifiable and is in line with the current paradigm for CMD prevention as these individuals benefit most from the interventions offered.¹⁶

The key conclusion of the INTEGRATE study is that criterion 9, which calls for demonstrated cost-effectiveness of preventive programs, could not be established. Even under more

favourable conditions, it seems hard to reach cost-effectiveness. For this program to become cost-effective, more effective lifestyle interventions at relatively low costs should be developed.

Summarizing, although the selective CMD prevention program does meet some important “disease-related” evaluation criteria according to Wilson and Jungner, the most essential criterion of cost-effectiveness was not met. Considering this, we conclude that the selective CMD prevention program in the present format should not be implemented in primary care.

Other strategies to improve CMD prevention in primary care?

Now that it has been established that the current programmatic approach of CMD prevention is not cost-effective and that large scale implementation is not recommended, the question arises which alternative approaches for selective CMD prevention in primary care are plausible.

The cost-effectiveness analysis showed that costs for programmed CMD prevention can only be legitimised if dramatic success rates of lifestyle interventions can be achieved (e.g. smoking cessation rates should have been at least twice as high); we doubt whether that is a realistic scenario. Another major factor with regard to cost-effectiveness are the relatively high intervention costs. As a result, even if response rates within the current program would have been maximal, it would still not result in selective CMD prevention becoming cost-effective. Given the results from the INTEGRATE study and the limited room for improvements of the program we do not believe that programmatic CMD prevention in primary care will ever become cost-effective. However, we believe that our study results can be used to improve other forms of selective CMD prevention in primary care. For example, recommendations on patient and/or practice level might improve opportunistic screening methods.

Improvements on patient level

One of the striking results of the Integrate study was that risk perception was poor, even among those at substantially increased risk. Therefore, for every CMD prevention approach improving risk perception and risk communication is essential. Patients should feel eligible and personally addressed by the importance of prevention. As many individuals at risk do continue to feel healthy (because of the often asymptomatic nature of CMD risk factors or preclinical CMD) they are probably less motivated to take action. A possible solution for this problem in risk communication is to raise the public awareness about the asymptomatic nature of preclinical CMD.¹⁷ Awareness of risk seems conditional for people to consciously make lifestyle changes. In chapter 3 we have shown that providing an online personal CMD risk estimate without explanation by a healthcare provider did not influence risk perception.

In addition, risk perception scores were generally low among subgroups with different risk levels. A recent trial of Silarova and colleagues adds to this evidence suggesting that is unlikely that simply informing people online about their risk to develop CVD will motivate them for recommended behaviours.¹⁸ Their conclusions are in line with ours that CMD risk communication can possibly be improved if a health care professional assists in interpreting the information provided. This is also supported by a recent study of Denissen and colleagues who found that personally communicating the screening result of either traditional risk assessment or coronary artery calcification scores resulted in 63-94% high-risk individuals consulting their GP¹⁹, compared to the 34% in our study.

Another possible aspect is to take a person's risk-age or lifetime risk into account. Because the SCORE risk function is mainly driven by age, the younger you are, the harder it is to reach the threshold for an increased risk. Despite having a relative high-risk for CMD, younger patients might not feel alarmed by the risk result. Hypothetically, a larger life-time effect can be achieved if CMD prevention aims at a younger population with modifiable risk factors. For this group an additional 'risk-age or lifetime-risk calculator' could be used as an educational tool to illustrate the effect of changing risk factors on long-term CMD risk and to encourage lifestyle changes. Other important aspects on the individual level that might improve effectiveness are willingness to change lifestyle and compliance, which will be addressed in the thesis of Ilse Badenbroek.²

Improvements on practice level

On practice level some crucial elements should be improved in order to make selective CMD prevention more effective. In chapter 7 we have shown that the awareness of available community-based lifestyle services was poor and in chapter 4 we described that the current program achieved no effect on lifestyle. However, raising more awareness among health care professionals about lifestyle interventions does only make sense if more sustainable and effective lifestyle interventions become available. Chapter 6 shows that in order to reach cost-effectiveness it is important to especially focus on effective smoking cessation interventions, as these could result in cost-effective lifetime health gains for those who quit. We have to realize that inadequate reimbursement is indicated as one of the major barriers for implementation of such interventions. The recently introduced reimbursement of lifestyle coaches as well as the integrated combined lifestyle intervention for obese people may improve the success of lifestyle interventions.

How to optimize CMD prevention in the Netherlands

We believe that a strong universal prevention approach is necessary to turn the tide for the increasing burden of CMD. Such a universal strategy aims to reduce CMD risk at population

level through lifestyle and environmental changes and needs to reach a diverse population to have the largest preventive effect. Many of the required interventions (e.g. smoking bans, stimulation of healthy food consumption and a non-sedentary lifestyle) are considered powerful, equitable, rapid and cost-effective prioritizing affordability, availability and acceptability.

Rose defined the prevention paradox: “*a measure that brings large benefits to the community offers little to each participating individual*”.²⁰ He stated that the benefits from a universal approach, in which each individual itself receives only a small benefit, may be unexpectedly large.

However, this implicates that the way towards a healthier population and to reduce overall CMD risk will become mainly a responsibility of politicians and to a lesser extent of curative health care. Although nowadays prevention is considered an important topic in many fields of society, it is still largely depending on dynamics in health care policy. Whereas a few years ago support for prevention among politicians and population was still fragmented²¹, now the time seems ready for a universal prevention approach. The 2018 Dutch prevention charter (Dutch “Preventieakkoord”) is a broadly embraced, integrated initiative with stringent goals and partly binding agreements for reducing lifestyle related risk factors such as smoking, overweight and problematic use of alcohol.²² This charter has broad support from many public, private, voluntary and community branches in society, and has therefore a high chance of achieving the intended goals. One of the main goals in the charter is the “smoke-free generation” in 2040. Through a substantial number of policy recommendations, it aims to reduce the number of current smokers and to prevent new smokers from starting (e.g. by raising taxes, reducing tobacco selling points, and extending smoke-free public spaces).

Another goal of the 2018 prevention charter is to create an overall healthier environment by promoting facilities to increase physical activity (e.g. attractive playgrounds or active commuting to work) and to raise more awareness about healthy food.

It is known that the reduction of overweight and obesity is hard to achieve, because eating is a necessity in life and often coupled to cultural and social events. However, it is important to realize that effective strategies promoting healthy food have the potential to halve the burden of premature CVD.²³ Therefore, collaboration with the food industry is necessary to achieve goals as reducing calories in processed food and/or lessening salt. Reducing the daily intake of salt is one of the most effective food-related ways to contribute to a reduction of CMD. For example, a 3 gram reduction in daily salt intake (to achieve a target of 6 gram daily) would reduce systolic blood pressure by approximately 2 mmHg.²⁴

Furthermore, social pressure, convenience and economic determinants make “healthy behaviour” easier and more acceptable for individuals.²⁰ Therefore, policy makers should, besides focussing on a healthier environment, also nudge healthy choices and make living a healthy lifestyle (financially) more attractive, ensuring the healthy choice is the easy choice.

What role in CMD prevention is left for primary care?

Although programmed CMD prevention cannot be recommended, opportunistic screening i.e. individual case finding or risk-assessment during individual patient consultations, can be continued. As shown in the non-response analysis, the health care utilization of people who participate in programmed CMD prevention is higher.² Therefore, these individuals are likely to be reached through regular consultations as well. The identification of high-risk individuals can be improved by for example implementation of a prediction model - based on data mining of risk factors - in the EHR. Ideally, this tool supports GP's decision making about whom to target for individual case finding or not. This new strategy should be investigated as soon as more effective lifestyle interventions become available.

Although primary care can still play a supportive role in care-related CMD prevention, we argue that the responsibility for selective CMD prevention is beyond the scope of general practice. This was recently confirmed during the Woudschoten conference²⁵, during which the core values of general practice were redefined. This consensus-based covenant of Dutch GPs stated that programmatic selective prevention is not a core activity of general practitioners.²⁶ In addition, a recent survey among primary care patients showed that patients consider prevention not a primary task of their general practitioner.²⁷

International perspective and future research

For many decades it was believed that CMD health checks would result in health gains on long term CMD morbidity and mortality and in several countries CMD prevention programs are being or have been implemented on a structural basis.^{28,29} Although a 2013 Cochrane review and the Danish Inter99 study concluded that health checks in the general population were not effective in the long run^{30,31}, up to now there was ongoing debate about the effectiveness of programmatic high-risk approaches. One of the reasons was that pragmatic trials in daily practice were missing, that long term 'hard' endpoints were often not taken into account and that evidence for the cost-effectiveness of such initiatives was lacking³². With the INTEGRATE study we provide conclusive evidence that programmatic selective CMD prevention in primary care - although resulting in health gains on short term endpoints - is not cost-effective in reducing long term CMD morbidity and mortality. With increasing health care costs worldwide and limited resources available we recommend not to implement such programs.

In addition, raising public awareness about the asymptomatic nature of CMD risk factors and preclinical CMD could help to improve risk perceptions. Furthermore, it would be interesting to compare clinically-based interventions such as the U-prevent tool³³ - which supports health care providers to communicate risk levels and the effects of preventive treat-

ment – with online interventions for the communication of CMD risk on their effect on health-related behaviour. More insight into the effect of using a heart-age or lifetime risk calculator on risk communication is needed to further improve opportunistic screening in primary care. Ongoing efforts to develop more (cost)-effective lifestyle interventions, especially smoking cessation, should be made. If these interventions become available at reasonable costs, it would be interesting to investigate ways to optimize opportunistic screening in general practice. For example, data-mining for CMD risk factors in the EHR could assist general practitioners to easily identify high risk individuals and subsequently offer those a cost-effective lifestyle treatment.

Conclusion

Although the selective CMD prevention program is considered feasible in detecting high-risk individuals and effective concerning treatment of blood pressure and cholesterol levels after one year, this did not translate in a long-term health effect at reasonable costs. Because CMD prevention is crucial for tackling the rising burden of CMD, we recommend more investments in universal prevention and in ongoing opportunistic screening. The government should play an important role in population-based prevention, focusing on creating a healthier environment to reduce the number of smokers and obese people. Furthermore, an improvement of risk communication and improvement of (cost)-effective lifestyle interventions could contribute to more effective CMD prevention.

In conclusion, this thesis provides definitive proof that programmed selective CMD prevention in primary care is not cost-effective and that its large-scale implementation is not recommended. CMD prevention should be a focus of public health and environmental initiatives and not a priority of curative health care.

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Appendices

1. Risk score

2. Flowchart of Prevention Consultation

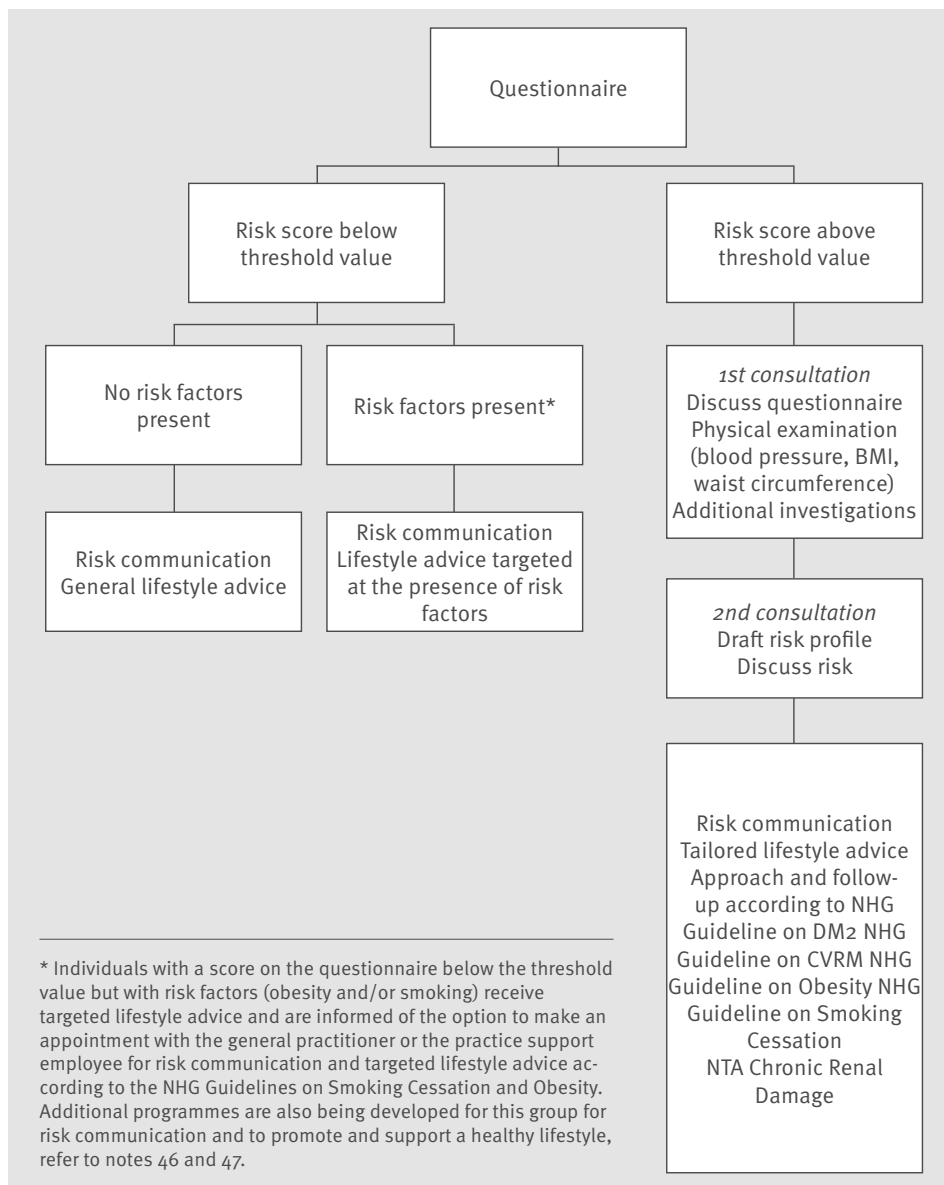
3. Study design and response rates of the INTEGRATE study

Appendix 1 Risk Score¹

Men		number of points
1. Age	30 – 45 years	0
	45 – 50 years	13
	50 – 55 years	17
	55 – 60 years	22
	60 – 65 years	33
	65 – 70 years	37
	70 – 75 years	46
	75 – 85 years	61
	≤ 25 kg/m ²	0
	25 – 30 kg/m ²	4
2. BMI	> 30 kg/m ²	12
	≤ 94 cm	0
3. Waist circumference	≥ 94 cm	3
	Yes	9
4. Smoking	No	0
	Yes	0
5. Father, mother, brother or sister with cardiovascular disease before the age of 65 years	Yes	1
	No	0
6. Father, mother, brother or sister with diabetes type 2	Yes	4
	No	0
Score		
Score ≥ 30 points		
There is a possible increased risk of cardiovascular disease, diabetes type 2 and chronic renal damage. Policy: patients are referred to a consultation with the general practitioner to evaluate and discuss the risk and – if indicated – to start treatment.		
First consultation		
- discussing questionnaire;		
- measuring height, weight, waist circumference, blood pressure;		
- referral letter for laboratory.		
Second consultation		
- setting up a risk profile;		
- discussing the risk;		
- if indicated, start of treatment in accordance with the relevant NHG Guideline(s).		
Score < 30 points		
There is (probably) no absolute increased risk of cardiovascular disease, diabetes type 2 or chronic renal damage.		
Policy: further consultation with the general practitioner is not indicated. If risk factors are present (obesity and/or smoking), targeted lifestyle advice is provided (via the website) and an appointment can be made with the general practitioner for advice and guidance to improve these risk factors.		

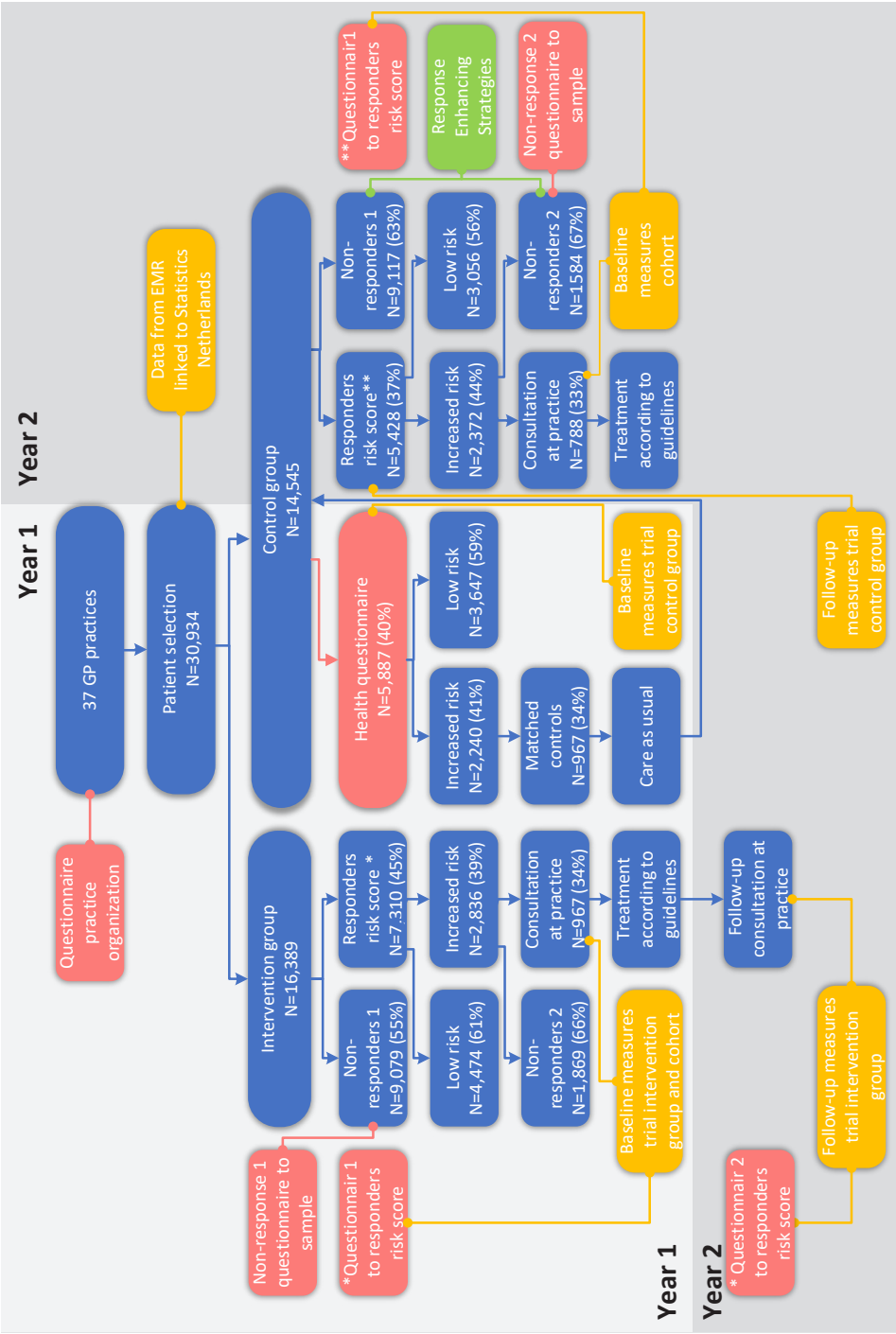
Women		number of points
1. Age	30 – 45 years	0
	45 – 50 years	13
	50 – 55 years	17
	55 – 60 years	22
	60 – 65 years	33
	65 – 70 years	37
	70 – 75 years	46
	75 – 85 years	61
	< 25 kg/m ²	0
	25 – 30 kg/m ²	4
2. BMI	> 30 kg/m ²	12
	< 80 cm	0
	80 – 88 cm	3
3. Waist circumference	> 88 cm	9
	Yes	0
	No	1
4. Smoking	Yes	0
	No	4
5. Father, mother, brother or sister with cardiovascular disease before the age of 65 years	Yes	0
	No	4
6. Father, mother, brother or sister with diabetes type 2	Yes	0
	No	0
Score		
Score ≥ 35 points		
There may be an increased risk of cardiovascular disease, type 2 diabetes or chronic renal damage. Policy: patients are referred to a consultation with the general practitioner to evaluate and discuss the risk and – if indicated – to start treatment.		
First consultation		
- discussion of questionnaire;		
- measurement of height, weight, waist circumference, blood pressure;		
- referral letter for laboratory.		
Second consultation		
- drawing up risk profile;		
- discussion of risk;		
- if indicated, start treatment according to the relevant NHG Guideline(s).		
Score < 35 points		
There is (probably) no absolute increase in the risk of cardiovascular disease, type 2 diabetes or chronic renal damage. Policy: further consultation with the general practitioner is not indicated. If risk factors are present (obesity and/or smoking), targeted lifestyle advice is provided (via the website) and an appointment can be made with the general practitioner for advice and guidance to improve these risk factors.		
This questionnaire is not applicable if:		
- the patient is already receiving treatment for hypertension, dyslipidaemia, type 2 diabetes, cardiovascular disease and/or renal disease;		
- there are symptoms that could indicate cardiovascular disease, diabetes or renal disease; the patient should always contact the general practitioner in that case;		
- age < 30 years.		

¹ Dekker JM, Alsema M, Janssen PGH, Van der Paardt M, Festen CCS, Van Oosterhout MJW et al. Huisarts Wet 2011;54(3):138-55.

Appendix 2 Flowchart of Prevention Consultation¹

¹ Dekker JM, Alsema M, Janssen PGH, Van der Paardt M, Festen CCS, Van Oosterhout MJW et al. Huisarts Wet 2011;54(3):138-55.

Appendix 3 Study design and response rates of the INTEGRATE study





Summary

Introduction

The burden of cardiometabolic diseases (CMD), including cardiovascular disease (CVD), diabetes type 2 (DM2) and chronic kidney disease, calls for cost-effective preventive strategies.

Despite decreasing mortality rates, the prevalence of CMD is still rising due to ageing and an unhealthy lifestyle. Approximately 80% of CMD could be prevented by changing the shared risk factors (hypertension, hypercholesterolemia, smoking, overweight, physical inactivity and an unhealthy diet) by lifestyle and/or drug treatment. Improvement of CMD risk assessment in primary care by early identification of patients at high-risk might be an effective preventive strategy.

The NHG guideline ‘the prevention consultation’ was developed to provide a framework for selective CMD prevention in primary care. This program is directed at all patients aged 45-70 years old without known CMD or CMD risk factors. Patients are invited for self-assessment of CMD risk through a 7-item risk score questionnaire, consisting of questions regarding sex, age, smoking status, BMI, waist circumference and a family history of premature CVD (age <65 years) and DM2 (step1) (see appendix 1). Based on the risk score, people are categorized as having low, intermediate or high risk. In case of high risk, individuals are advised to visit their GP for additional risk profiling (step2) - including blood pressure measurement and laboratory tests on fasting glucose and cholesterol levels - and follow-up treatment if indicated (step 3). Several challenges such as the lack of evidence for its cost-effectiveness and structural reimbursement hampered the large scale implementation of this guideline.

Therefore the aim of this thesis was to assess the effectiveness, and cost-effectiveness of selective CMD prevention in primary care.

Design of the INTEGRATE study

In chapter 2 we described the design of the INTEGRATE study, a stepped wedge randomized controlled trial. The INTEGRATE study compared a stepwise CMD risk assessment followed by individualized treatment with care as usual in 37 Dutch general practices. Primary outcomes were the number of newly detected CMD, the changes in risk factors for CMD after one-year follow-up and its short-term and long-term cost-effectiveness. Secondary outcomes were risk perceptions among participants and the organization of participating practices in relation to the effectiveness of the program.

Risk perception of CMD in primary care

It is known that people often have difficulties in understanding the concept of disease risk. In chapter 3 we investigated whether the invitation for online self-assessment of CMD risk led to adequate risk perception and if demographic characteristics were associated with the level of risk perception. In a cross-sectional study we analysed data of 7,547 patients. The patients of the intervention group completed the online risk assessment and received a personalized CMD risk estimate, the control group answered questions about CMD risk, but did not receive a personalized CMD risk estimate. No differences were found in risk perception between both groups. Risk perception among the study participants was generally low, even among high-risk participants who recently were informed about their increased personal risk. Individuals with a family history for DM2 and CVD and a BMI >25 had a higher risk perception. We concluded that risk communication through an online risk score did not lead to adequate risk perception. We believe that a dialogue between the patient and the GP about personal CMD risk might optimize the effect of the risk information provided.

Effectiveness and cost-effectiveness of a Dutch CMD prevention program in primary care

In chapter 4 we compared newly detected CMD and newly prescribed drugs during one-year follow-up and change in CMD risk profile between baseline and one-year follow-up among participants who completed step 2 of the program with ~~to~~ matched controls. A 2-3 fold increase in CMD diagnoses and prescriptions in the intervention group was found compared to the control group and a relative reduction in CMD risk profile according to the SCORE. Waist circumference decreased significantly more in the intervention group compared to the control group. No differences were observed for changes in BMI and smoking. Systolic blood pressure and cholesterol ratio significantly decreased within intervention participants between baseline and one-year follow-up and not in the control group. These results showed that implementation of a selective CMD prevention program is feasible and effective, and can detect high-risk individuals in a simple and non-invasive way.

In chapter 5 we described in a cohort study the program's uptake and the CMD detection rate in all participants after its implementation. In total 12,738 patients filled out the risk score of which 865, 6,665 and 5,208 had a low, intermediate and high CMD risk, respectively. 1,755 high-risk patients consulted the general practitioner, in 346 (19,7%) of whom a new CMD was diagnosed ('number needed to screen' (NNS) 89). In an additional 422 patients a new prescription and/or abnormal diagnostic test were found (NNS 45). Although the program resulted in a new CMD diagnosis in one-fifth of high-risk patients, the potential yield of the

program could be higher given the considerable number of additional risk factors found, requiring active follow-up and presumably treatment in the future.

Short and long-term cost-effectiveness of the program were assessed in chapter 6, in which the results of chapter 4 were related to projected long-term CMD morbidity and mortality. After one year we found a slight decrease in quality of life in the intervention group compared to a slight improvement in the control group. The average costs in the intervention group were 260 Euro per participant higher than in the control group and were mainly driven by healthcare costs. Despite the improvements in cholesterol and blood pressure, the intervention was not cost-effective (ICER of 482,000 Euro/QALY after 60 years). Sensitivity and scenario analyses resulted in similar high cost-effectiveness ratios. We concluded that implementing this selective CMD prevention program was not cost-effective when taking short- and long-term outcomes into account.

Embedding of CMD risk prevention in Dutch primary care

In an observational study we investigated whether Dutch primary care practices were adequately organized to facilitate a CMD prevention program and we described perceived facilitators and barriers for performing CMD-prevention (chapter 7). The organizational infrastructure of Dutch general practices was adequate for performing most steps of selective CMD-prevention. However, the awareness of easily accessible lifestyle interventions needed attention. In addition, stakeholders involved share the responsibility to realize structural funding for programmed CMD-prevention. In the last chapter (chapter 8) we aimed to identify practice characteristics associated with the outcome of the program. However, we did not find evidence that practice-related factors (as described in chapter 7) were associated to its effect.

Conclusion

Although selective CMD prevention programs in primary care may be successful in detecting CMD and CMD risk factors, these programs are not cost-effective in the long run. Because CMD prevention is crucial for tackling the rising burden of CMD, we recommend universal prevention and ongoing opportunistic screening. The government should play an important role in population-based prevention, focusing on creating a healthier environment to reduce the number of smokers and obese people. Furthermore, an improvement of risk communication and improvement of (cost)-effective lifestyle interventions could contribute to more effective CMD prevention.

In conclusion, this thesis provides definitive proof that programmed selective CMD prevention in primary care is not cost-effective and that its large-scale implementation is not recommended.



Samenvatting

Introductie

Er zijn effectieve preventieve strategieën nodig om de groeiende ziektelast van cardiometabole ziekten (CMZ), zoals hart- en vaatziekten, diabetes mellitus type 2 en chronische nierschade het hoofd te bieden. Ondanks dat de mortaliteit van deze aandoeningen afneemt, stijgt het voorkomen van deze ziekten nog altijd door de vergrijzing en een ongezonde leefstijl. Door de gemeenschappelijke risicofactoren (o.a. hypertensie, hypercholesterolemie, roken, overgewicht, fysieke inactiviteit en een ongezond dieet) te behandelen met leefstijlveranderingen en/of medicatie zou ongeveer 80% van deze aandoeningen voorkomen kunnen worden. Een mogelijk effectieve preventieve strategie is opsporing en behandeling van hoog-risico patiënten door verbetering van de risico inschatting in de eerste lijn.

De NHG -richtlijn het “Preventieconsult” is ontwikkeld om invulling te geven aan stapsgewijze selectieve cardiometabole preventie in de eerste lijn. Deze richtlijn is bedoeld voor alle patiënten tussen de 45-70 jaar die niet bekend zijn met CMZ en/of CMZ risicofactoren. Deze patiënten worden uitgenodigd om thuis een risicotest in te vullen die bestaat uit 7 simpele vragen over geslacht, leeftijd, rookstatus, BMI, buikomvang en familiegeschiedenis van vroegtijdige hart- en vaatziekten en of diabetes type 2 (stap 1). Afhankelijk van de risico-uitslag worden patiënten ingedeeld in een laag, licht verhoogd of verhoogd risico. In het geval van een verhoogd risico wordt deze mensen geadviseerd een afspraak te maken bij de huisarts voor aanvullende risicoprofilering (stap 2) – inclusief bloeddrukmeting en bloedbepalingen van cholesterol en glucose – en ontvangen zij zo nodig behandeling (stap 3).

Tot nu toe werd deze richtlijn nog niet volledig geïmplementeerd in verband met diverse uitdagingen zoals het gebrek aan bewijs voor de (kosten)effectiviteit en structurele vergoeding.

Om die redenen was het doel van dit proefschrift om de effectiviteit en kosteneffectiviteit van dit selectieve preventieprogramma voor CMZ in de eerste lijn te onderzoeken.

Studie opzet van de INTEGRATE studie

In hoofdstuk 2 beschrijven we de studie opzet, een stepped-wedge gerandomiseerde studie. De INTEGRATE studie vergeleek een stapsgewijze risico inschatting gevolgd door gepersonaliseerde behandeling met gebruikelijke zorg in 37 Nederlandse huisartsenpraktijken. De primaire uitkomstmaten waren het aantal nieuw opgespoorde CMZ, de verandering van risicofactoren voor CMZ na een jaar follow-up en de korte- en lange termijn kosteneffectiviteit van het programma. Secundaire uitkomstmaten waren de risicoperceptie van deelnemers, de organisatiegraad van de deelnemende praktijken en de relatie daarvan tot de effectiviteit van het programma.

Risicoperceptie van cardiometabole ziekten

Het concept van ziekterisico is voor mensen vaak lastig te begrijpen. In hoofdstuk 3 hebben we onderzocht of het uitnodigen van patiënten voor het invullen van de online risicotest leidde tot een adequate risicoperceptie en of we demografische kenmerken konden identificeren die samenhangen met risicoperceptie. In een dwarsdoorsnede onderzoek analyseerden we gegevens van 7,547 patiënten. Alle deelnemers vulden vragen in over CMZ risico en risicoperceptie. Het enige verschil tussen de interventie- en controlegroep was dat de deelnemers uit de interventiegroep de risicotest hadden ingevuld en een persoonlijke risico-uitslag ontvingen. De controlegroep vulde alleen de vragenlijst in en ontving geen uitslag. Er werd geen verschil in risicoperceptie gevonden tussen de interventie- en controlegroep. In het algemeen was de risicoperceptie laag, ook onder deelnemers die recent een verhoogd-risico uitslag hadden ontvangen. Een positieve familie- anamnese voor hart-en-vaatziekten en diabetes type 2 en een BMI >25 waren geassocieerd met het hoger inschatten van het risico. Onze conclusie was dat het communiceren van het risico op CMZ via de online risicotest niet leidde tot een adequate risicoperceptie. Onze verwachting is dat een dialoog tussen patiënt en huisarts zal helpen om de gepresenteerde risico informatie beter te begrijpen.

Effectiviteit en kosteneffectiviteit van een stapsgewijs selectief preventieprogramma voor CMZ in de eerste lijn

In hoofdstuk 4 vergeleken we het aantal nieuw opgespoorde CMZ en nieuw voorgeschreven medicatie gedurende een jaar follow-up en de verandering in risicoprofiel tussen baseline en 1 jaar follow-up tussen deelnemers uit de interventiegroep met een compleet opgemaakt risicoprofiel en hun 'gepaarde' controles. Twee tot drie keer zoveel CMZ diagnoses en medicatievoorschriften werden gevonden in de interventiegroep vergeleken met de controlegroep. Er werd ook een relatieve verbetering van het SCORE-risicoprofiel gevonden na een jaar. De buikomvang nam significant meer af in de interventiegroep vergeleken met de controlegroep. Er werden geen verschillen gevonden voor BMI en roken. Het verschil in systolische bloeddruk en de cholesterol ratio van deelnemers uit de interventiegroep tussen baseline en na 1 jaar was significant groter dan in de controlegroep. Deze resultaten laten ons zien dat de implementatie van een selectief CMZ preventie programma in de huisartsenpraktijk haalbaar en effectief is en dat het hoog-risico patiënten kan opsporen op een niet invasieve manier.

In hoofdstuk 5 beschrijven we in een cohortstudie de effecten van deelname aan het programma en de opsporingsgraad van nieuwe CMZ en CMZ risicofactoren na volledige implementatie van het programma onder alle deelnemers. In totaal vulden 12,738 deelnemers de risicotest in, waarvan 865 een laag, 6,665 een licht verhoogd en 5,208 een verhoogd CMZ risico

hadden. Van de hoog-risico patiënten consulteerden 1,755 deelnemers de huisarts, waarbij in 346 (19,7%) een nieuwe CMZ werd gediagnosticeerd ('number needed to screen' (NNS) 89). Bij 422 patiënten werden nieuwe medicatie voorschriften en/of abnormale diagnostische waarden gevonden (NNS 45). Ondanks het feit dat er bij een-vijfde van de hoog-risico patiënten een nieuwe CMZ diagnose werd gevonden, zou de opbrengst nog hoger kunnen zijn als je het grote aantal extra opgespoorde CMZ risicofactoren - die een actief vervolg vereisen - in acht neemt.

De korte- en lange termijn kosteneffectiviteit werd beschreven in hoofdstuk 6, waarbij de resultaten van de effectiviteitsstudie (hoofdstuk 4) werden gerelateerd aan morbiditeit en mortaliteit van CMZ op de lange termijn. Na een jaar vonden we een lichte daling in de kwaliteit van leven voor de interventiegroep en een lichte toename in de controlegroep. De gemiddelde extra kosten per patiënt vanwege de interventie bedroegen €260. Dit waren met name gezondheidszorgkosten. Ondanks de significante verbeteringen in cholesterol en bloeddruk was de interventie niet kosteneffectief (ICER van 482,000 Euro/QALY na 60 jaar). De aanvullende sensitiviteits- en scenario analyses resulteerden tevens in hoge kosteneffectiviteits ratio's. De conclusie was dat het implementeren van dit selectieve preventieprogramma voor CMZ niet kosteneffectief is op korte en lange termijn.

Inbedding van preventie van CMZ in de Nederlandse huisartsenpraktijk

In een observationele studie onderzochten we of de Nederlandse eerste lijn adequaat is toegerust om een preventieprogramma voor CMZ te faciliteren en we beschreven door de praktijk aangewezen bevorderende en belemmerende factoren (hoofdstuk 7). De organisatiegraad van de Nederlandse huisartspraktijk was adequaat om de meeste stappen van selectieve preventie te implementeren. Aandacht was nodig voor het samenstellen van de sociale kaart met betrekking tot toegankelijke leefstijlinterventies. Daarnaast delen alle betrokken partijen de verantwoordelijkheid om structurele financiering voor programmatische preventie van CMZ te realiseren. In het laatste hoofdstuk (hoofdstuk 8) hadden we tot doel om praktijkkenmerken te identificeren die geassocieerd zijn met de uitkomsten van het programma. We vonden echter geen bewijs dat de in hoofdstuk 7 beschreven praktijkkenmerken waren geassocieerd met het gevonden effect van het programma.

Conclusie

Ondanks dat selectieve preventieprogramma's voor CMZ in de eerste lijn succesvol zijn in het opsporen van CMZ en CMZ risicofactoren, zijn deze programma's niet kosteneffectief op de

lange termijn. Omdat preventie van CMZ cruciaal is voor het aanpakken van de toenemende ziektelast van CMZ, raden we daarentegen universele preventie en opportunistische screening aan. De overheid heeft een belangrijke rol in de populatiegerichte preventie en moet zich focussen op het creëren van een gezondere leefomgeving om het aantal mensen die roken of overgewicht hebben te verminderen. Tevens kan het verbeteren van risicocommunicatie en kosteneffectieve leefstijlinterventies bijdragen aan betere effectieve preventie van CMZ.

Concluderend verschaft dit proefschrift definitief bewijs dat de programmatische aanpak van selectieve preventie van CMZ in de eerste lijn niet kosteneffectief is en dat nationale implementatie hiervan niet wordt geadviseerd.



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Daphne Stol was born on September 29th 1985 in Rijswijk ZH, the Netherlands. After graduation from secondary school at the “Christelijk Gymnasium Sorghvliet” in 2003, she started her studies in medicine at the University of Amsterdam. In 2007 she travelled to Stockholm for an internship in research at the Neurology department of the Karolinska Institutet and obtained her medical degree in 2011. She worked as a resident at the internal medicine department of the “Slotervaart” hospital in 2011 and in 2012 as a resident at the cardiology department of the “Sint Lucas Andreas” hospital. In 2013 she started as a so-called “aiotho”, combining clinical work as a GP trainee at the University of Amsterdam with a PhD project under supervision of Prof. Dr. N.J. de Wit and Prof. Dr. F.G. Schellevis, Dr. M. Hollander and Dr. M.M.J. Nielen at the Julius center for Health Sciences and Primary care of the University Medical Center Utrecht. Results of her PhD research are presented in this thesis. She expects to complete her post-graduate Epidemiology master at the end of 2020 and will finish her GP training in the beginning of 2021.

