Preventive Medicine 132 (2020) 105984

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

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

Daphne M. Stol[a,b,*], Ilse F. Badenbroek[b,a], Monika Hollander[a], Mark M.J. Nielen[b], Roderik A. Kraaijenhagen[c], François G. Schellevis[b,d], Niek J. de Wit[a]

[a] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Netherlands Institute for Health Services Research (NIVEL), Utrecht, the Netherlands
[c] Netherlands Institute for Prevention and E-health Development (NIPED), Amsterdam, the Netherlands
[d] Department of General Practice and Elderly Care Medicine, Amsterdam Public Health Research Institute, Amsterdam University Medical Centers (location VUmc), Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Primary health care
Prevention
Risk assessment
Cardiovascular diseases
Diabetes mellitus
General practitioners
Randomized controlled trial

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 −3.08 cm, 95% CI −3.73: −2.43). No differences were observed for changes in BMI and smoking. Systolic blood pressure (mean −2.26 mmHg, 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.

1. 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 (World Health Organization, 2018). 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 (Yusuf et al., 2004; Piepoli et al., 2016). Lifestyle interventions have been demonstrated to improve these risk factors and to subsequently reduce CMD risk in high-risk patients (Keyserling et al., 2014; Eriksson et al., 2009; Aadahl et al., 2009; Toft et al., 2008). 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 status (Dyakova et al., 2016) and this has prompted the initiation of systematic risk assessment approaches to identify those at

Abbreviations: CMD, cardiometabolic disease; RCT, randomized controlled trial; BMI, body mass index; CVD, cardiovascular disease; DM2, diabetes type 2; EHR, electronic health record; GP, general practitioner; HDL, high-density-lipoproteins; LDL, low-density-lipoprotein

* Corresponding author at: University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, the Netherlands.
E-mail addresses: d.m.stol@umcutrecht.nl (D.M. Stol), I.F.Badenbroek@umcutrecht.nl (I.F. Badenbroek), M.Hollander-2@umcutrecht.nl (M. Hollander), M.Nielen@nivel.nl (M.M.J. Nielen), R.A.Kraaijenhagen@niped.nl (R.A. Kraaijenhagen), F.Schellevis@nivel.nl (F.G. Schellevis), N.J.deWit@umcutrecht.nl (N.J. de Wit).

https://doi.org/10.1016/j.ypmed.2020.105984
Received 17 July 2019; Received in revised form 7 January 2020; Accepted 12 January 2020
Available online 16 January 2020

increased CMD risk.

Targeted prevention of high-risk individuals is recommended by the 2016 guidelines of the European Society of Cardiology (Piepoli et al., 2016). In 2011 the guideline "the prevention consultation for CMD" was developed by the Dutch College of General Practitioners (Dekker et al., 2011), 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 countries (Robson et al., 2016; Hooper et al., 2016; De Waard, 2018), structural implementation of stepwise CMD prevention programs in primary care has not yet taken place due to ongoing controversy about its (cost)-effectiveness (Hollander et al., 2014).

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 (Karmali et al., 2017). On the other hand, however, screening of the general population has not yet been demonstrated to reduce all-cause or CVD related mortality (Dyakova et al., 2016; Si et al., 2014; Krogsbøll, 2012; Jørgensen et al., 2014). 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.

2. Methods

2.1. 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 (Badenbroek et al., 2014).

2.2. 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 (Flowchart 1).

2.2.1. 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 (Alssema et al., 2012; Rauh et al., 2018). The risk score incorporated components from the widely accepted FINDRISC questionnaire and the SCORE risk function and is externally validated (Rauh et al., 2018; Conroy et al., 2003; Lindström and Tuomilehto, 2003). 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.

2.2.2. Controls

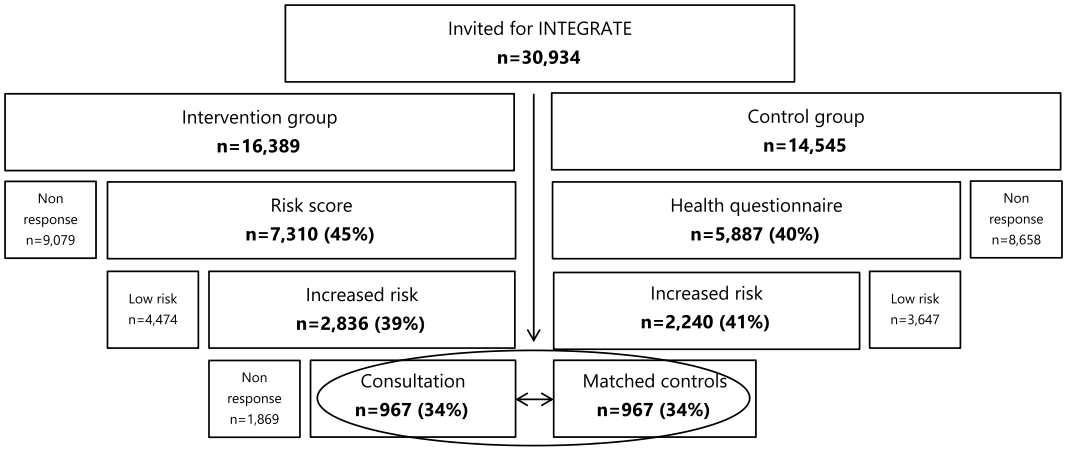
Participants allocated to the control group were invited to complete a health questionnaire including questions about demographic characteristics, CMD risk factors and lifestyle. These participants did not complete the risk score, and did not receive a personal CMD risk estimate, nor tailored lifestyle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

2.3. 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.

2.4. 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



Flowchart 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.

described in detail elsewhere (Badenbroek et al., 2014).

2.5. 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.

2.6. 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% oversampling 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.

2.7. 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 previously (Badenbroek et al., 2014)) to ensure a feasible implementation in the practices. Participants in the control group had no knowledge of an ongoing intervention.

2.8. 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.

2.9. 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-year 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 (Badenbroek et al., 2014). 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) $> 50\%$ 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 prescriptions 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.

3. Results

3.1. 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 7313 (45%) filled out the CMD risk score and in the control group 5887 (40%) of the participants filled out the health questionnaire. Within the intervention group 2836 (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 2240 (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 1934 participants (see Flowchart 1).

3.2. 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).

3.3. 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.

3.4. 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/m^2; 95% CI −0.12: 0.22) and smoking status (OR 0.75; 95% CI 0.44: 1.28).

3.5. 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

Table 1
Baseline characteristics.

	Intervention group	Control group	p-Value
	N = 967	N = 967	
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[a] (%) (n = 698)	3.3 (2.9)	n/a	

Abbreviations: CVD = cardiovascular disease, DM2 = diabetes mellitus, BMI = body mass index, HDL = high-density-lipoprotein, LDL = low-density-lipoprotein.

[a] 10 years CVD mortality risk, the Netherlands is considered a “low-risk” country (Conroy et al., 2003).

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

	Intervention group	Control group	OR	95% CI
	N = 967	N = 967		
Newly diagnosed: n (%)				
Hypertension[a]	127 (13.1)	58 (6.0)	2.39	[1.72; 3.32]
Hypercholesterolemia[b]	123 (12.7)	41 (4.2)	3.51	[2.40; 5.13]
Diabetes mellitus[c]	21 (2.2)	3 (0.3)	7.13	[2.12; 24.00]
No. of participants with a newly diagnosed CMD[g]	258 (26.7)	112 (11.6)	2.90	[2.25; 3.72]
Newly prescribed: n (%)				
Antihypertensives[d]	106 (10.9)	40 (4.1)	2.85	[1.96; 4.15]
Lipid-lowering drugs[e]	75 (7.8)	25 (2.6)	3.23	[2.03; 5.14]
Antidiabetics[f]	10 (1.0)	1 (0.1)	10.17	[1.30; 79.74]
No. of participants with a new prescription[h]	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]

Abbreviations: CMD = cardiometabolic disease, ICPC = International Classification of Primary Care, ATC = Anatomical Therapeutic Chemical Classification System.
[a] ICPC codes: K86/K87.
[b] ICPC code: T93.
[c] ICPC code: T90.
[d] ATC cluster: C02-03, C07-C09.
[e] ATC cluster: C10.
[f] ATC cluster: A10.
[g] 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.
[h] ATC cluster: A10 (antidiabetics), C02-03, C07-C09 (antihypertensives), C10 (lipid lowering drugs).

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

	Δ intervention group	Δ control group	Multilevel analysis[a]	
			Beta	95% CI
BMI (kg/m^2)	−0.05	−0.11	0.05	[−0.12; 0.22]
Waist circumference (cm)	−2.81	0.42	−3.08	[−3.73; −2.43]

	Δ intervention group	Δ control group	Multilevel analysis[a]	
			OR	95% CI
Current smoker (%)	−3.25	−2.19	0.75	[0.44; 1.28]

Abbreviations: BMI = body mass index.
[a] All analyses were corrected for baseline values.

−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.

4. 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.

4.1. 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 sizes (Stol et al., 2018) 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 (Den Engelsen et al., 2014).

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

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[a]		Recorded prescription in EHR[b]	
	Beta	95% CI	Beta	95% CI	Beta	95% CI
Hypertension						
	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]
Hypercholesterolemia						
	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]
Diabetes type 2						
	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]

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.

[a] Hypertension: ICPC K86/K87; hypercholesterolemia: ICPC T93; diabetes type 2: ICPC T90.

[b] 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.

was induced it would have - above all - reduced the contrast between the analyzed 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.

4.2. 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 (Van der Meer et al., 2013).

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 (Keyserling et al., 2014; Eriksson et al., 2009; Engberg et al., 2002; Cochrane et al., 2012). 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 errors (Verweij et al., 2013) 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 activity (Church et al., 2009), 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 (Ebrahim et al., 2011). In addition, attendance and completion rates for lifestyle programs are often modest and considerably variable in general practice (Harris et al., 2012). 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 low (Stol et al., 2018), 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.

4.3. 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 (Piepoli et al., 2016). 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.

5. 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.

Author contribution statement

FS, NdW and MN contributed to the study concept and design. DS, IB and the INTEGRATE team were involved in the acquisition of data. DS, IF, MH and MN carried out the analysis and interpretation of data.

DS, MH, MN and IF participated in drafting the manuscript. FS, NdW and RK performed critical revision of the manuscript for important intellectual content. All authors have seen and approved the final version to be published.

Declaration of competing interest

The author(s) declare(s) that there is no conflict of interest.

Acknowledgments

The authors thank NIPED Institute and the Netherlands Institute for Health Services Research (NIVEL) for the contribution to data management. N.P.A. Zuithoff is acknowledged for his statistical advice.

Funding

This work was supported by ZonMw (The Netherlands Organization for Health Research and Development) under grant number 50-51515-98-192; Lekker Lang Leven (a collaboration of the Dutch Diabetes Research Foundation, the Dutch Heart Foundation and the Dutch Kidney Foundation) under grant number 2012.20.1595; and Innovatiefonds Zorgverzekeraars (Healthcare Insurance Innovation Fund) under grant number 2582. The sponsors played no role in study design, data collection, data analysis, data interpretation, or writing of the report.

References

Aadahl, M., von Huth Smith, L., Pisinger, C., Toft, U.N., Glümer, C., Borch-Johnsen, K., et al., 2009. Five-year change in physical activity is associated with changes in cardiovascular disease risk factors: the Inter99 study. Prev. Med. 48 (4), 326–331 (Apr).

Alssema, M., Newson, R.S., Bakker, S.J.L., Stehouwer, C.D. a, Heymans, M.W., Nijpels, G., et al., 2012. One risk assessment tool for cardiovascular disease, type 2 diabetes, and chronic kidney disease. Diabetes Care 35 (4), 741–748 (Apr).

Badenbroek, I.F., Stol, D.M., Nielen, M.M., Hollander, M., Kraaijenhagen, R. a, De Wit, G. a, et al., 2014. Design of the INTEGRATE study: effectiveness and cost-effectiveness of a cardiometabolic risk assessment and treatment program integrated in primary care. BMC Fam. Pract. 15 (1), 1–10 (Erratum in BMC Fam Pract. 2016;17(1):42).

Church, T.S., Martin, C.K., Thompson, A.M., Earnest, C.P., Mikus, C.R., Blair, S.N., 2009. Changes in weight, waist circumference and compensatory responses with different doses of exercise among sedentary, overweight postmenopausal women. PLoS One 4 (2) (Feb 18).

Cochrane, T., Davey, R., Iqbal, Z., Gidlow, C., Kumar, J., Chambers, R., et al., 2012. NHS health checks through general practice: randomised trial of population cardiovascular risk reduction. BMC Public Health 12 (1), 944 (Jan).

Conroy, R., Pyörälä, K., Fitzgerald, A., Sans, S., Menotti, A., de Backer, G., et al., 2003. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur. Heart J. 24 (11), 987–1003 (Jun).

De Waard, A.-K.M., 2018. Towards Successful Selective Prevention of Cardiometabolic Diseases in Primary Care Challenges Across Europe. Utrecht University [dissertation].

Dekker, J., Alssema, M., Janssen, P., Van der Paardt, M., Festen, C., van Oosterhout, M., et al., 2011. NHG-Standaard het PreventieConsult module cardiometabool NHG-standaard [Guideline for cardiometabolic prevention by Dutch college of GPs]. Huisarts Wet. 54 (3), 138–155.

Den Engelsen, C., Koekkoek, P.S., Godefrooij, M.B., Spigt, M.G., Rutten, G.E., 2014. Screening for increased cardiometabolic risk in primary care: a systematic review. Br. J. Gen. Pract. 64 (627), 616–626.

Dyakova, M., Shantikumar, S., Colquitt, J.L., Drew, C.M., Sime, M., MacIver, J., et al., 2016. Systematic versus opportunistic risk assessment for the primary prevention of cardiovascular disease. Cochrane Database Syst. Rev.(1).

Ebrahim, S., Taylor, F., Ward, K., Beswick, A., Burke, M.D.S.G., 2011. Multiple risk factor interventions for primary prevention o f coronary heart disease (Review). Cochrane Database Syst. Rev.(1).

Engberg, M., Christensen, B., Karlsmose, B., Lous, J., Lauritzen, T., 2002. General health screenings to improve cardiovascular risk profiles: a randomized controlled trial in general practice with 5-year follow-up. J. Fam. Pract. 51 (6), 546–552 (Jun).

Eriksson, M.K., Franks, P.W., Eliasson, M., 2009. A 3-year randomized trial of lifestyle intervention for cardiovascular risk reduction in the primary care setting: the Swedish Björknäs study. PLoS One 4 (4), 11–12.

Harris, M.F., Fanaian, M., Jayasinghe, U.W., Passey, M.E., McKenzie, S.H., Davies, G.P., et al., 2012. A cluster randomised controlled trial of vascular risk factor management in general practice. Med. J. Aust. 197 (7), 387–393.

Hollander, M., Stol, D., Badenbroek, I., Nielen, M., De Wit, N., Schellevis, F., 2014. De impasse van het cardiometabool preventieconsult [Impasse of Dutch cardiometabolic prevention]. Huisarts Wet. 57 (6), 290–291.

Hooper, C., Hardie-Boys, N., White, E., et al., 2016. More heart and diabetes checks evaluation—final report. Allen + Clarke, New Zealand. Available at: https://www.health.govt.nz/publication/more-heart-and-diabetes-checks-evaluation, Accessed date: 22 October 2019.

Jørgensen, T., Jacobsen, R.K., Toft, U., Aadahl, M., Glümer, C., Pisinger, C., 2014. Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial. BMJ 348 (June), g3617.

Karmali, K.N., Persell, S.D., Perel, P., Lloyd-Jones, D.M., Berendsen, M.A.H.M., 2017. Risk scoring for the primary prevention of cardiovascular disease (Review). Cochrane Database Syst. Rev. 3.

Keyserling, T.C., Sheridan, S.L., Draeger, L.B., Finkelstein, E.A., Gizlice, Z., Kruger, E., et al., 2014. A comparison of live counseling with a web-based lifestyle and medication intervention to reduce coronary heart disease risk: a randomized clinical trial. JAMA Intern. Med. 174 (7), 1144–1157.

Krogsbøll, L.T., 2012. General health checks in adults for reducing morbidity and mortality from disease : Cochrane systematic review and meta-analysis. BMJ 1–13.

Lindström, J., Tuomilehto, J., 2003. The Diabetes Risk Score: a practical tool to predict type 2 diabetes risk. Diabetes Care 26 (3), 725–731.

Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., Catapano, A.L., et al., 2016. 2016 European guidelines on cardiovascular disease prevention in clinical practice. Eur. Heart J. 37 (29), 2315–2381.

Rauh, S.P., Rutters, F., van der Heijden, A.A.W.A., Luimes, T., Alssema, M., Heymans, M.W., et al., 2018. External validation of a tool predicting 7-year risk of developing cardiovascular disease, type 2 diabetes or chronic kidney disease. J. Gen. Intern. Med. 33 (2), 182–188 (Feb 1).

Robson, J., Dostal, I., Sheikh, A., Eldridge, S., Madurasinghe, V., Griffiths, C., et al., 2016. The NHS Health Check in England: an evaluation of the first 4 years. BMJ Open 6 (1).

Si, S., Moss, J.R., Sullivan, T.R., Newton, S.S., Stocks, N.P., 2014. Effectiveness of general practice-based health checks: a systematic review and meta-analysis. Br. J. Gen. Pract. 64 (618), 47–53.

Stol, D.M., Hollander, M., Nielen, M.M.J., Badenbroek, I.F., Schellevis, F.G., de Wit, N.J., 2018. Implementation of selective prevention for cardiometabolic diseases; are Dutch general practices adequately prepared? Scand. J. Prim. Health Care 36 (1), 20–27 (Jan 2).

Toft, U., Kristoffersen, L., Ladelund, S., Ovesen, L., Lau, C., Borch-Johnsen, K., et al., 2008. The impact of a population-based multi-factorial lifestyle intervention on changes in long-term dietary habits: the Inter99 study. Prev. Med. 47 (4), 378–383 (Oct).

Van der Meer, V., Nielen, M.M., Drenthen, A.J., Van Vliet, M., Assendelft, W.J., Schellevis, F.G., 2013. Cardiometabolic prevention consultation in the Netherlands: screening uptake and detection of cardiometabolic risk factors and diseases — a pilot study. BMC Fam. Pract. 14 (1), 29 (Feb 26).

Verweij, L.M., Terwee, C.B., Proper, K.I., Hulshof, C.T., Van, M.W., 2013. Measurement error of waist circumference: gaps in knowledge. Public Health Nutr. 16 (2), 281–288 (Feb).

World Health Organization, 2018. World health statistics 2018: monitoring health for the SDGs, sustainable development goals. Available at: https://www.who.int/gho/publications/world_health_statistics/2018/en/, Accessed date: 22 October 2019.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., et al., 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364 (9438), 937–952.