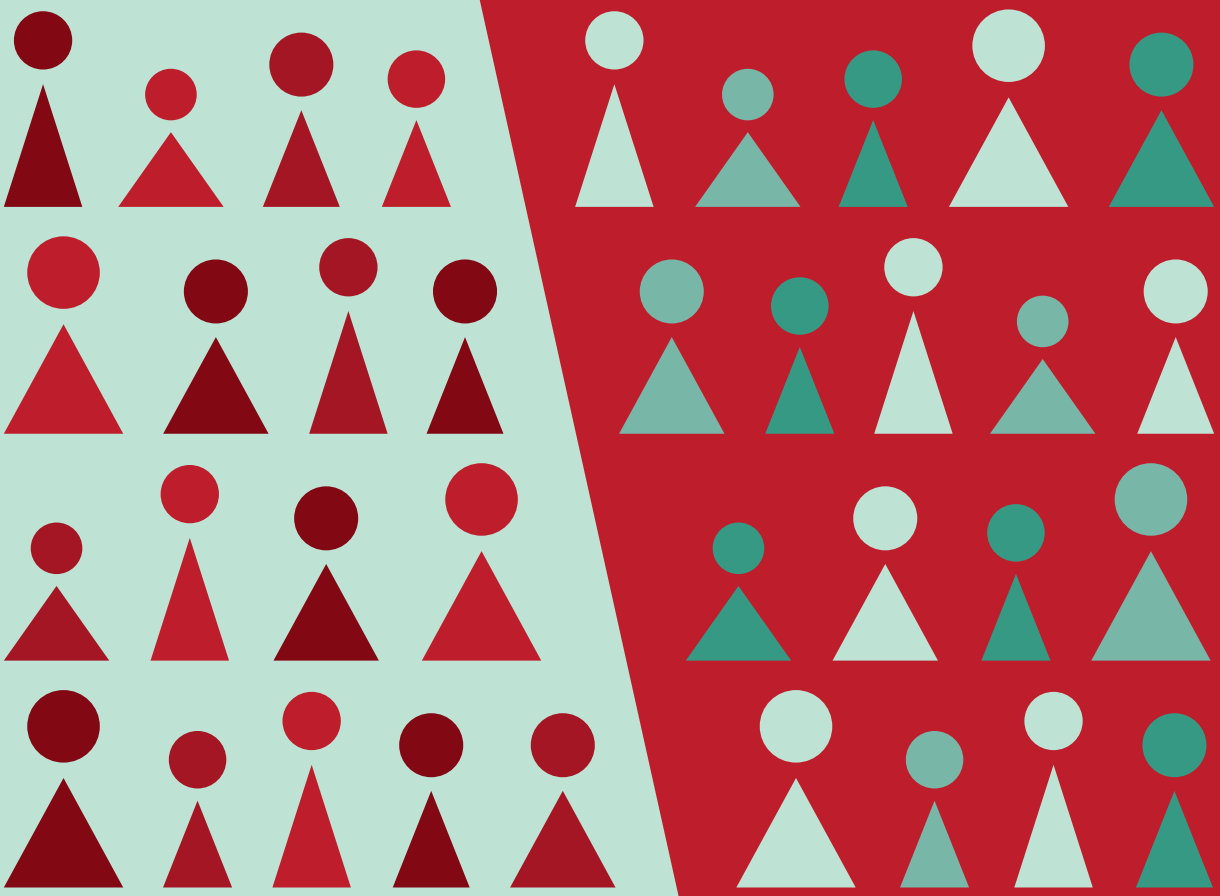
Evaluation of a **stepwise prevention program** for **cardiometabolic diseases** in primary care



Ilse F. Badenbroek

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Evaluation of a stepwise prevention program for cardiometabolic diseases in primary care

Evaluatie van een stapsgewijs preventieprogramma voor cardiometabole ziekten in de eerste lijn

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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door

Ilse Francis Badenbroek
geboren op 29 december 1986
te Helmond

Promotoren: Prof. dr. N.J. de Wit
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Copromotoren: Dr. M.M.J. Nielen
Dr. M. Hollander

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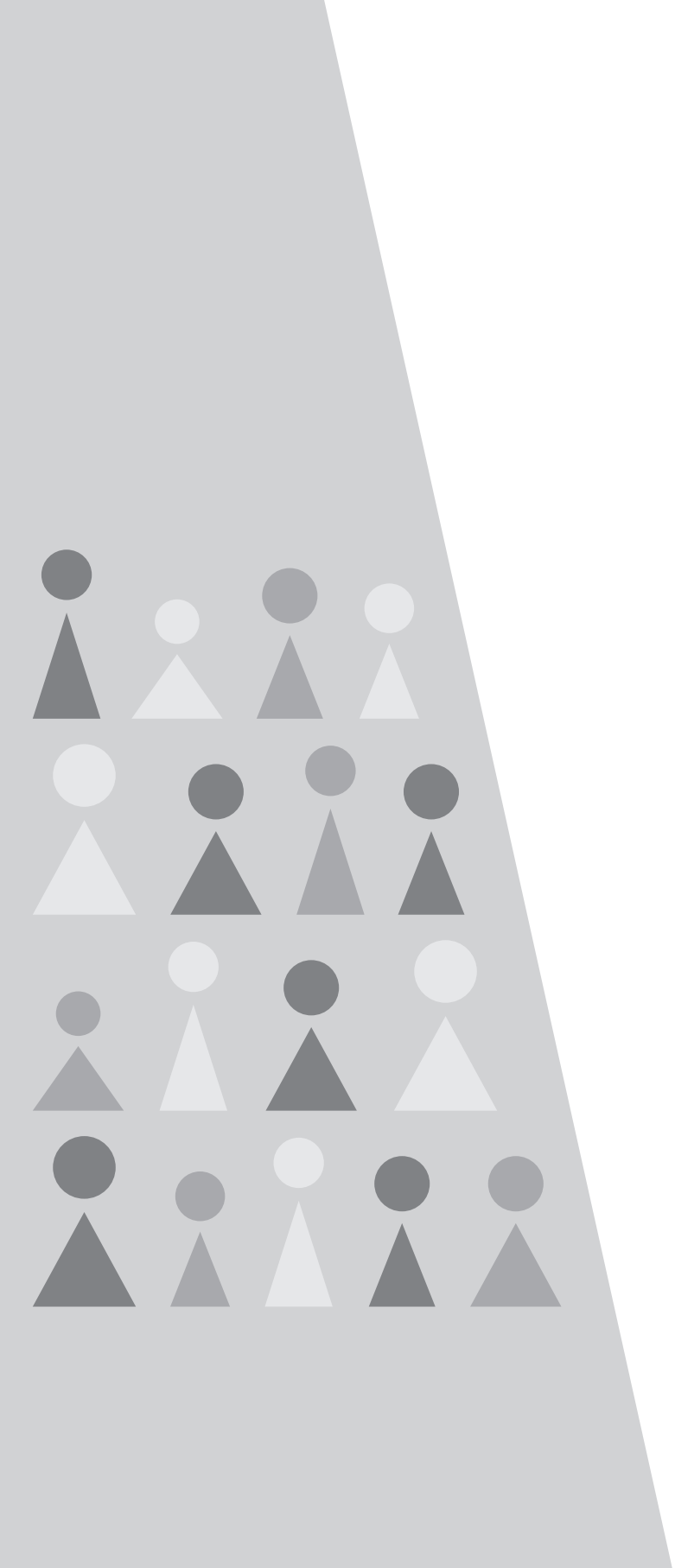


1

General introduction

"The doctor of the future will give no medicine, but will interest his patient in the care of the human frame, in diet and in the cause and prevention of disease."
Thomas Edison, 1903

Prevention programs in healthcare

Despite the passing of more than a century, Edison's idealistic vision of prevention driven medicine is still a distant prospect. However, although curative medicine is still the key focus areas of healthcare (in practice), prevention has been setting foot in various healthcare sectors. This is reflected in the many preventative components that have acquired a position in numerous clinical practice guidelines. Over the last couple of decades prevention programs have been increasingly implemented, including vaccination for influenza and screening programs for cervical, breast and colorectal cancer. Nevertheless, the effectiveness of prevention programs is a frequent subject for discussion, especially when a new program is considered for nationwide implementation. Before elaborate implementation can take place, successfulness of a program should be determined in the broadest sense, considering all components associated including uptake, effectiveness and adoption of the program. Potentially the greatest benefits of prevention can be achieved when aiming to prevent (exactly) those diseases that carry the highest disease burden. If this is done in an early stage, many premature deaths could be prevented and many healthy years could be gained. This would definitely be a step in the right direction in pursuit of the perspective of medicine and lifestyle that Edison foresaw for future generations.

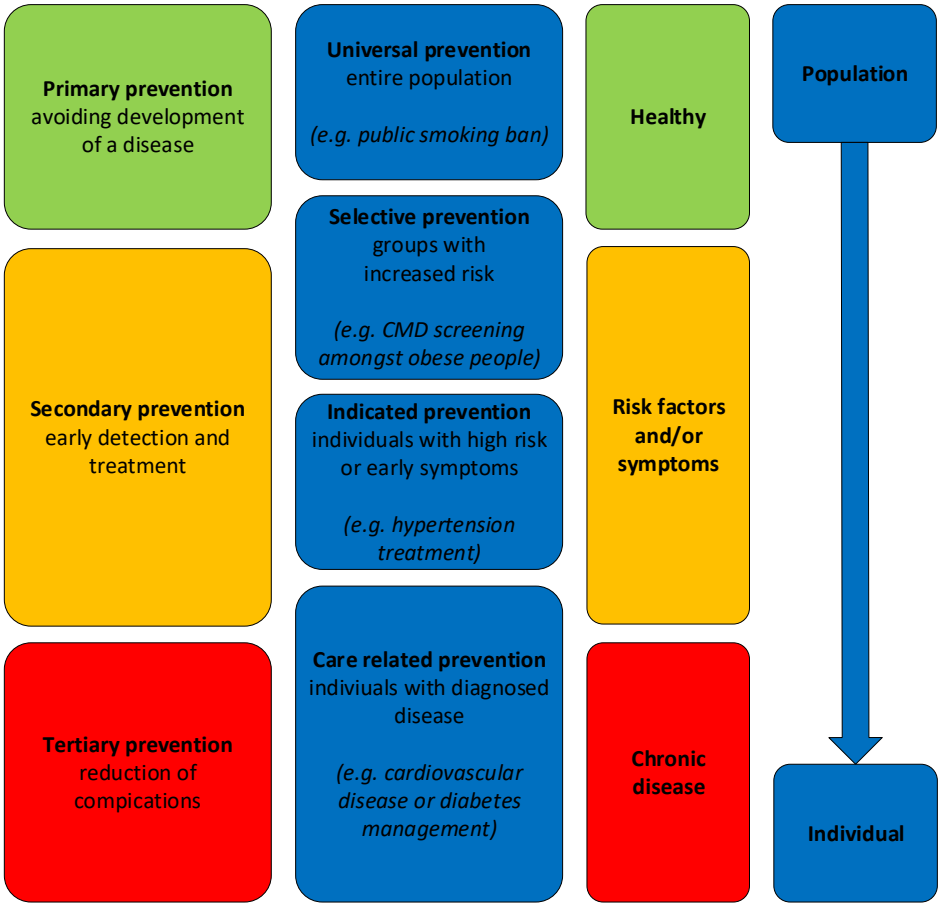
Prevention programs for cardiometabolic diseases

Cardiometabolic diseases (CMD), including cardiovascular disease (CVD), diabetes type 2 (DM2) and chronic kidney disease, are the number one cause of death globally, causing more than 50% of all deaths across the WHO European Region [1]. In the Netherlands alone, over 1.6 million persons suffer from CVD, almost 1.2 million persons are diagnosed with diabetes and approximately 1.7 million persons have chronic kidney damage [2]. Up to 80% of CMD is associated with behavioural risk factors, including smoking, inadequate physical activity, and an unhealthy diet [1]. This means that a vast majority of all morbidity and mortality caused by CMD is preventable by adopting a healthy lifestyle. Given the high disease burden and the preventable nature of CMD, it is not a surprise that early prevention of CMD has been given the outmost attention in the past decades.

Prevention of CMD can be carried out in different forms and with different strategies (figure 1). Universal prevention actions are addressed to the entire population, for instance a smoking ban in public places and a 'fat tax'. Another form of prevention is selective prevention, aimed at a specific subgroup with an increased risk to develop CMD, based on individual risk factors. Individuals at high risk for CMD would benefit most from lifestyle counselling and treatment of risk factors. In order to identify those high-risk persons, a stepwise screening

strategy can be used. Only those with risk factors would qualify for additional measures, so valuable time and costs can be saved compared to strategies aimed at the population as a whole [3]. This strategy strives for a more effective and cost-effective prevention program, which is a prerequisite for broader implementation for these programs.

Figure 1. Types of prevention [4]



CMD prevention in primary care

There has been an ongoing debate about the best setting for prevention of CMD, a community-based or health care setting. In 2008 general practitioners (GPs) suggested that general practice is the designated place to detect individuals with an increased risk for CMD [5]. All Dutch residents are registered in a general practice, primary care is easily accessible and in the

Netherlands 78% of the population visits the GP yearly [6]. Furthermore, a GP is familiar with patients' context, has a trusted relationship with the patients and has access to relevant medical data.

In order to anticipate the increasing disease burden of CMD within an aging population, an increasing prevalence of obesity, and a growing demand for general health checks, the Dutch College of General Practitioners developed the guideline 'Prevention consultation' in 2011 (box 1) [7]. This guideline provides a tool to map the risk for CMD in patients who are 45 years or older, who are not diagnosed with or being treated for hypertension, hypercholesterolemia or an earlier CMD. The guideline can be used when individual patients visit the GP with questions about their risk, but it also contains suggestions for a more active approach: i.e. through programmatic, practice wide implementation of selective CMD prevention in general practice.

So far, nationwide implementation of the programmatic CMD prevention described in the guideline could not yet be recommended, as scientific evidence for effectiveness of the program has not been established, and financial reimbursement for implementation have not been structurally [7]. A realistic evaluation of the selective CMD prevention program looking at effectiveness, cost benefit and acceptance is needed to bring the ongoing debate on broad implementation to an end.

Box 1 The NHG guideline 'Prevention consultation'

The guideline describes a stepwise CMD prevention program (Appendix 1). The first stage of the program is completing a self-assessed risk score, a seven-item questionnaire including questions regarding gender, age, smoking status, body mass index (BMI), waist circumference and a family history of premature CVD (age <65 years) and DM2 (Appendix 2). The risk score was developed with pooled data from three Dutch cohort studies and predicts the combined seven-year risk for CMD, categorizing individuals as having a low, intermediate or an increased risk. The threshold value used to define inceased risk is ≥23% for men and ≥19% for women. In case of a score below threshold, individuals without any risk factor are categorized as low risk and individuals with one or more risk factors are categorized as having an intermediate risk. The risk score is able to accurately predict the absolute disease risk for CMD and has been externally validated [24,25].

At the end of the first stage of the prevention program, individuals with a low or intermediate risk receive tailored life style advice. Individuals with an increased risk are referred to their GP for stage 2 of the program, additional risk profiling, including blood pressure measurement and laboratory tests for fasting glucose, HDL cholesterol and total cholesterol. The GP decides if treatment and follow-up is indicated, based on recommendations in other guidelines issued by the Dutch College of GPs. Tailored lifestyle advice forms an integral part in stage 2 of the prevention program.

Evaluation of a CMD prevention program

When evaluating a selective CMD prevention program all relevant aspects should be addressed, and optimized where possible. Effectiveness and the cost-effectiveness of the program are important elements, but other key elements are frequently overlooked, including participation and barriers and facilitators for implementation.

Participation

Participation is an essential factor for a prevention program, for the cost-effectiveness of a program often depends on a minimum percentage of participation by the target group. A minimum uptake has not been set for the `Prevention Consultation´, but the NHS health check, a cardiovascular prevention program broadly implemented in the UK, was modelled for cost-effectiveness at a participation rate of 75% [8]. Unfortunately in current literature response rates in CMD prevention programs in general show great variation, varying between extremes as 1.2% [9] and 84% [10]. These differences in response rates might be induced by using different invitation methods. The suggested way to invite patients in the guideline 'Prevention Consultation' is by sending an invitation letter, followed by a reminder. During pilot studies of preliminary versions of the 'Prevention Consultation' relatively high response rates were described when reminders by telephone and a pre-scheduled appointment were used [9,11,12]. If the use of optimized invitation strategies could enhance response, this might lead to a more successful prevention program.

It is also known that participation in prevention programs is not equally distributed across different demographic groups within the population [13,14]. Socially vulnerable groups such as individuals with a low socio economic status are less likely to respond to an invitation for a prevention program. This is an unfortunate combination, for risk factors for CMD are overrepresented in this particular group. Prevention programs would therefore cause more healthcare being delivered to groups bearing the least disease burden, an known effect referred to as 'the inverse care law' [15]. Up to now it is still unclear if this effect also extents to the Dutch CMD prevention program 'Prevention Consultation'. There is however evidence that with a culturally adapted invitation strategy for the 'Prevention Consultation' participation rates comparable to the general population can be reached amongst socially vulnerable groups [16]. This underlines the importance of also evaluating tailored response enhancing strategies for selective CMD prevention programs.

Factors determining successful implementation

Previous studies have stressed the importance of the involvement of the GP in prevention programs, for a personal connection and tailored advice might increase the effectiveness of the program [17–19]. Nevertheless, other studies have showed us that GPs and practice nurses struggle with tailoring life style advice and motivational conversation techniques during everyday

practice [20,21]. Therefore it would be informative to further explore the effectiveness of lifestyle advice given in general practice.

There are big differences in how general practices have organized their procedures concerning lifestyle and prevention. In some practices the GPs and practice nurses have no knowledge of referral options for lifestyle advice and programs, other practices have a rich array of preventive services at their disposal, either in their own practice or health centre, or in the immediate vicinity. It would be a logical assumption that practices with more available preventive services could deliver a more effective CMD prevention program. But unfortunately, up to now little is known about the association of practice organisation and preventive services with the effectiveness of a prevention program for CMD.

The RE-AIM model

A well accepted structural method to evaluate a prevention program is captured in the Reach Efficacy Adoption Implementation Maintenance model (RE-AIM) (box 2). This model is developed in 1999 by Glasgow et al. [22] and is designed as a framework for consistent reporting of research results by incorporating different aspects of evaluation. The RE-AIM method evaluates health programs on 5 different dimensions or elements. The first two letters of the acronym RE-AIM stand for Reach and Effectiveness, two key elements of a program that are measured on the individual level. If an intervention or program does not reach the intended population and shows no effect in health gain outcomes, further implementation would be useless. The last three letters stand for Adoption, Implementation and Maintenance, all important elements from a more contextual perspective. Contextual factors are essential to consider during the implementation process [23], as they determine a successful translation from research settings to the final real life implementation in clinical practice. The focus and weights of the different elements of RE-AIM process depend on the characteristics of the program and the setting of the research [22]. When the reach and effectiveness have not yet been determined, as is the case for the 'Prevention Consultation', this should be the main focus of evaluation.

Box 2. The Reach Efficacy Adoption Implementation Maintenance model (RE-AIM) [22]

Reach	Proportion of the target population that participated in the intervention
Effectiveness	Success rate (outcomes) if implemented as in guidelines
Adoption	Proportion of settings, practices, and plans that will adopt this intervention
Implementation	Extent to which the intervention is implemented as intended in the real world
Maintenance	Extent to which a program is sustained over time

The INTEGRATE study

In the INTEGRATE study we evaluated the 'Prevention Consultation', a selective prevention program for CMD in primary care. We implemented the prevention program in 37 different general practices in the Netherlands, using a pragmatic approach. In total almost 31,000 patients were invited to fill in the risk score. A summary of the study design and the different study groups can be found in Appendix 3. For our analyses we had access to data from the risk score, the GP consultations and research questionnaires. In addition, data of the INTEGRATE study was linked to data from Statistics Netherlands. With the data we collected from the different study groups, we were able to perform an evaluation of all different aspects associated with the successfulness of the 'Prevention Consultation'.

Aim of this thesis

The objective of this thesis is to contribute to the scientific knowledge about the evaluation of programmatic CMD prevention in general practice. More specifically, this thesis aims to analyse the implementation and reach of selective CMD prevention program in primary care, by assessing the contribution of patient and practice related factors to the effectiveness of the program, following the RE-AIM model. For this analysis we use the results of the INTEGRATE study. First, an overview of characteristics and motives of non-responders at the different stages of the prevention program will be made and this knowledge will be used for the development of strategies to enhance the response to both stages of the program. Secondly, we will determine the effectiveness of the selective CMD prevention program and assess the effects of practice organizational factors and lifestyle advice given in general practice.
The long-term outcomes and the cost effectiveness of the selective CMD prevention program will be addressed in the corresponding thesis of Stol.

Outline of the thesis

Chapter 2 is a description of the design of the INTEGRATE study, a randomized controlled trial developed to evaluate the effectiveness and implementational issues of a selective CMD prevention program in primary care. **Chapter 3** contains an overview of the characteristics of the non-responders at stage 1 of the CMD prevention program, the reported reasons for non-response at stage 1 as well as suggestions for response enhancing strategies. **Chapter 4** focuses on the profiles of the non-responders at both stages of the CMD prevention program, reporting extensively on the characteristics of the non-responders and the motives for non-response at stage 2 of the program.

Chapter 5 contains an overview and evaluation of all response enhancing strategies that were implemented in the general practices during the last phase of the study. The feasibility and the effect on the response at the different stages of the prevention program are determined. **Chapter 6** discusses the effectiveness of a selective CMD prevention program, comparing the

intervention and control group after one-year follow-up. **Chapter 7** describes the results of an analysis to determine if organizational factors and preventive services provided by general practices are associated with effectiveness of a CMD prevention program. **Chapter 8** discusses the effectiveness of lifestyle advise by given GPs and practice nurses. **Chapter 9** describes the general discussion and concludes with a summary of the main findings.

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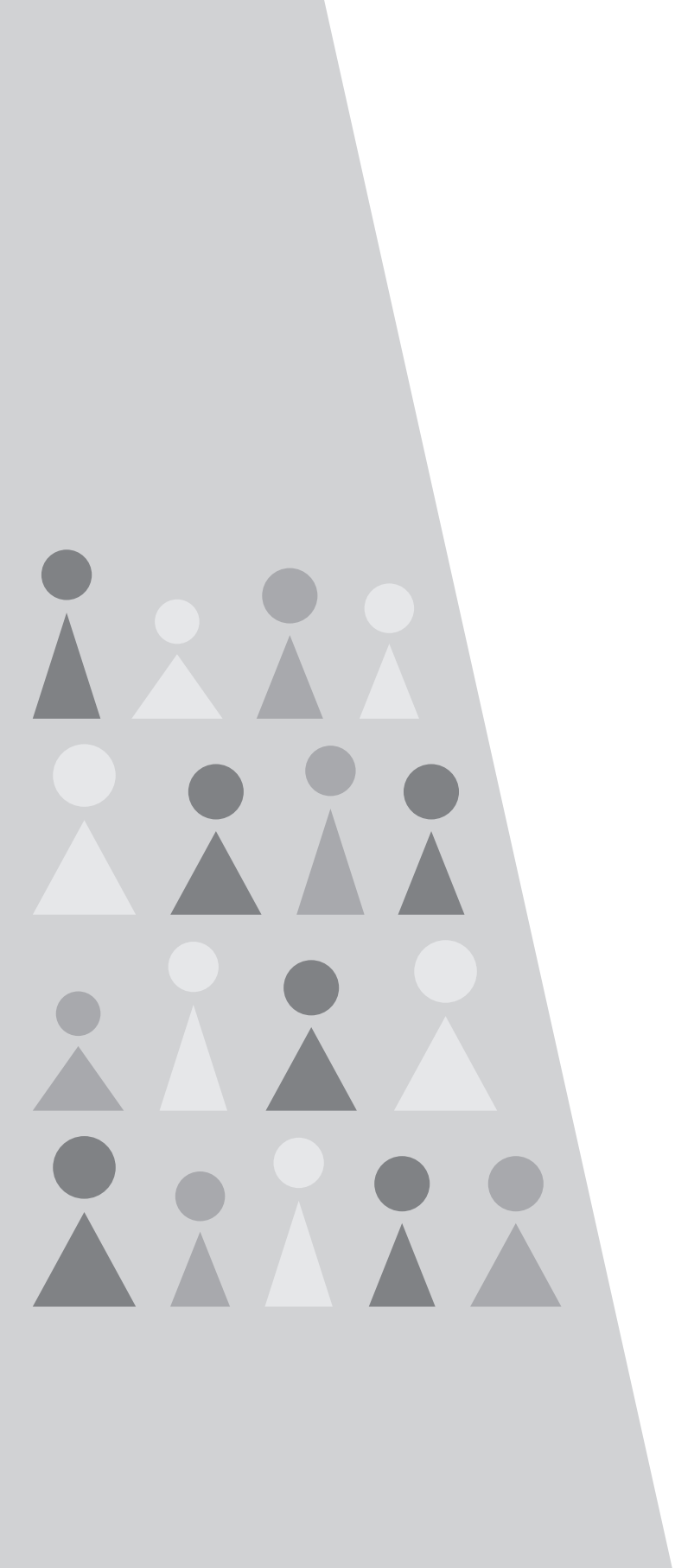

2

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

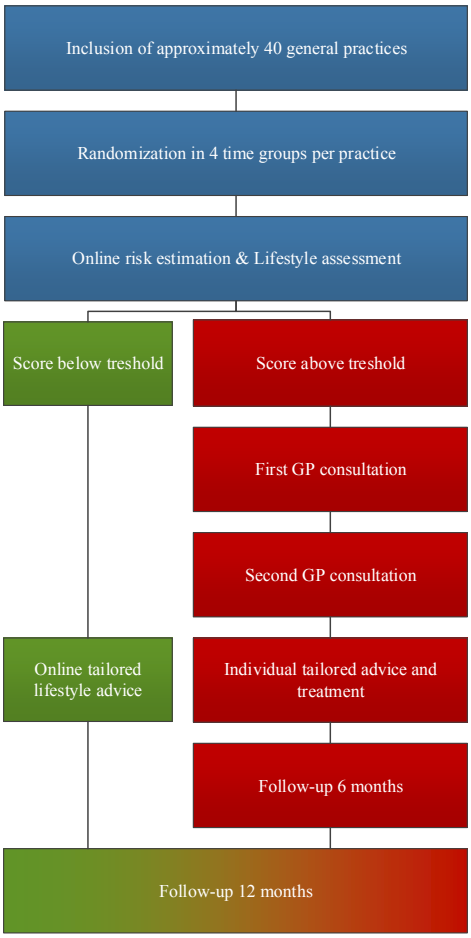

Figure 2 Timeline per practice and overview of measures

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		P/ S
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	• Receiving antihypertensive or lipid-lowering treatment. • One of the following ICPC-I-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 Practice [13] 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 advise 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 ≥ 23% for men and ≥ 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 cession 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 advise and results of previous studies [14] 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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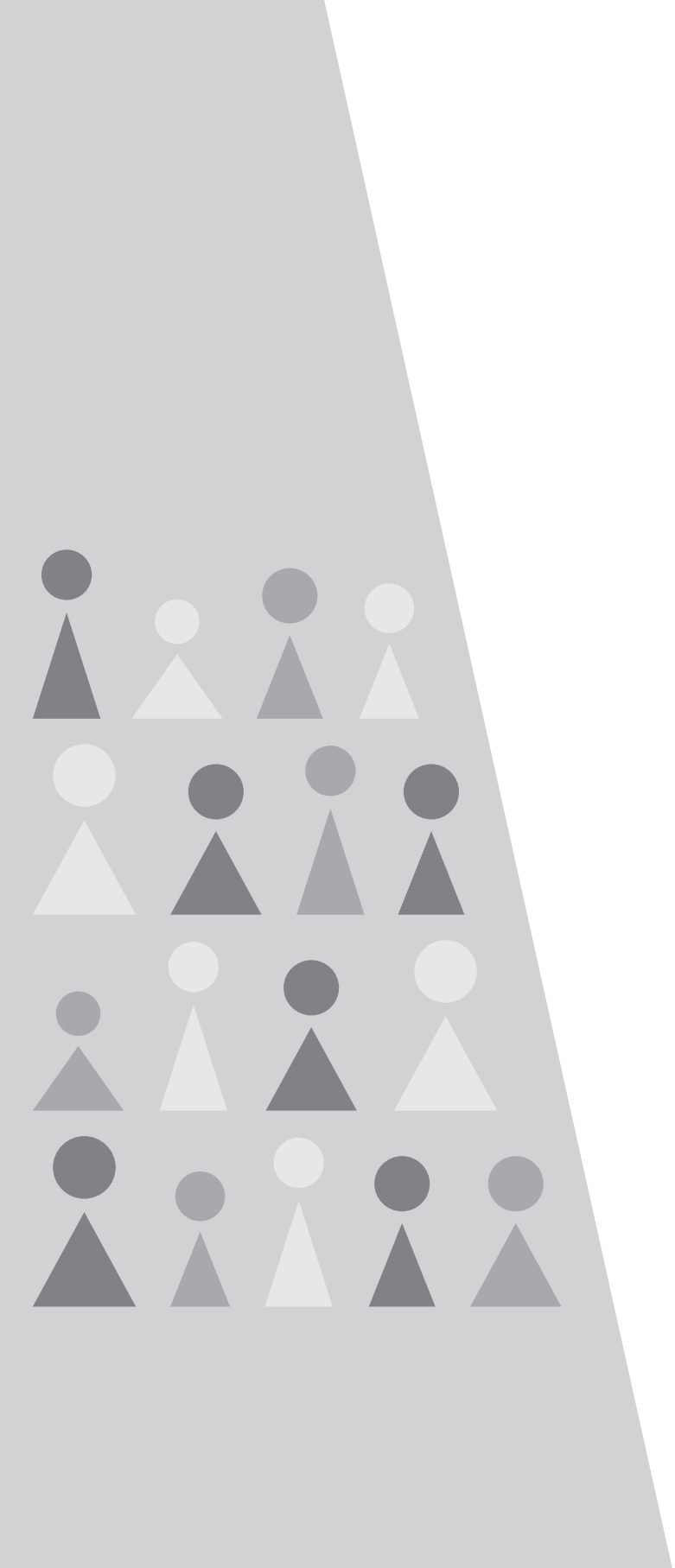

2

2.2

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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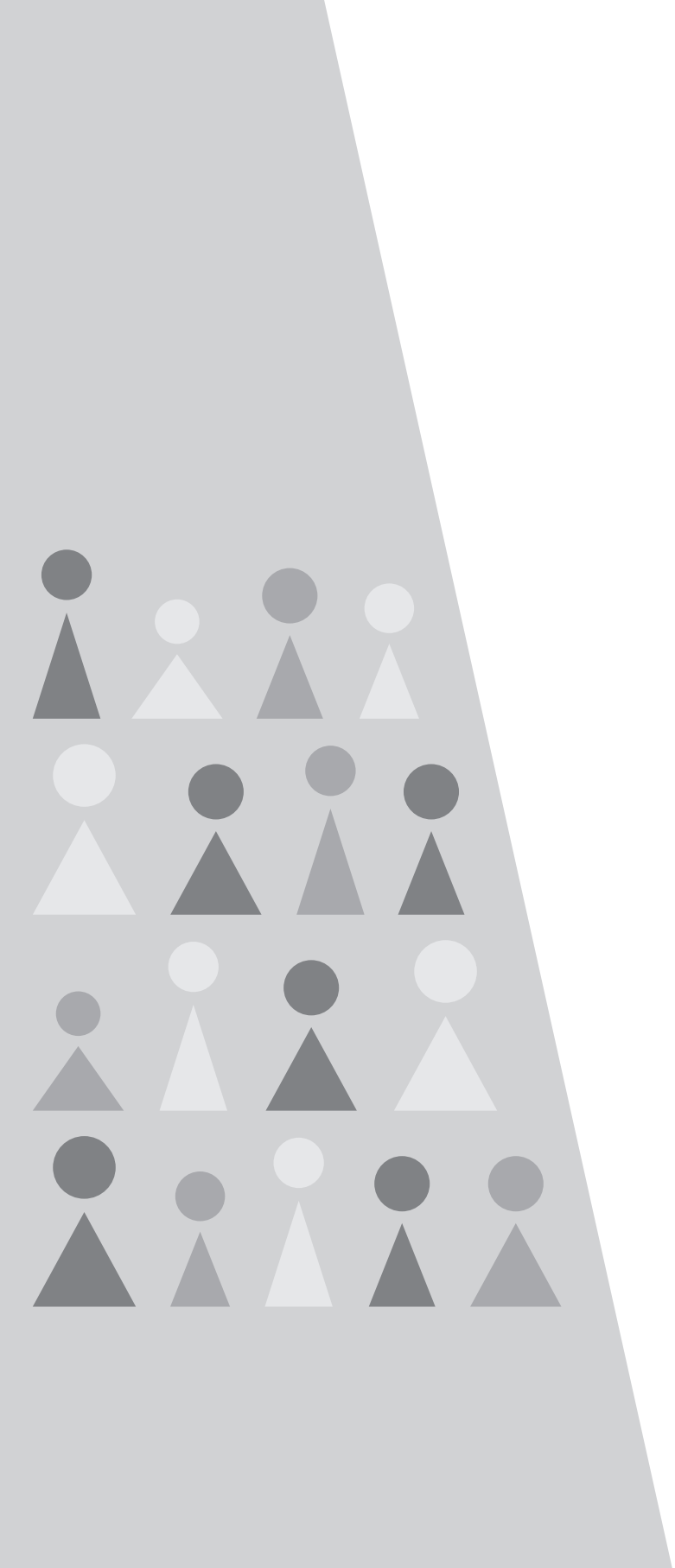

3

Mapping non-response in a prevention program for cardiometabolic diseases in primary care: how to improve participation?

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Abstract

Non-response in prevention programs for cardiometabolic diseases (CMD) in primary care is often overlooked. The aim for this study was to define factors that influence the primary response to a selective CMD prevention program and to determine response-enhancing strategies that influence the willingness to participate. We conducted a non-response analysis within a randomized controlled trial evaluating a selective CMD prevention program, the study was conducted from 2013 to 2018 in Netherlands. A random sample of 5,616 patients from 15 general practices were invited to complete a risk score (RS) as initial step of the program. Non-responders received an additional questionnaire. The response on the risk score was 51% (n=2,872). From the 3,558 non-response questionnaires sent, 786 (22%) were returned. In a multivariable multilevel regression analysis smoking was independently associated with non-response. Of all reported reasons for non-response 'forgot/no time' accounted for 45%. In total, 73% of the non-responders indicated to reconsider participation when approached differently. A personal approach by the patients' own GP, using advertisements and informative campaigns are potentially the best methods to enhance the response. Although a relatively high proportion did not respond to the invitation for the risk score, the majority of them indicated to be willing to participate if a different invitation strategy would be used. With more time and energy, response rates for CMD prevention programs could possibly increase substantially. A next logical step in this process is to test potential response enhancing strategies in research setting.

Introduction

Cardiometabolic diseases (CMD) including cardiovascular disease, diabetes mellitus and chronic kidney disease account for a large part of the disease burden and health care costs. The prevalence of CMD is bound to increase in the next decades due to an aging population with an unhealthy lifestyle [1]. Most of the risk for CMD is attributable to modifiable risk factors such as smoking, unhealthy diet, obesity and physical inactivity: for example, 90% of the risk for an acute myocardial infarction is determined by these risk factors [2]. This calls for preventive actions aimed at stimulating people to adopt a healthier lifestyle. Worldwide many different prevention and screening programs for CMD have been developed to suit this purpose [3,4].

In order for these prevention programs to be successful and cost-effective, high participation rates are crucial [4–6]. Health effects on population level increase with rising participation and compliance rates: with 100% participation and full compliance to CMD prevention programs 93% of all cardiovascular deaths could be prevented [4]. However, participation rates in studies persistently show large variations in participation, ranging from 3% to 75% [7,8], but 100% participation and compliance seems unrealistic [6,9]. The NHS health checks that were introduced in the UK in 2009 were modeled at a participation rate of 75%, but even this rate has not been reached in most regions [10].

Low participation rates are a major problem in the implementation of CMD screening and prevention programs in general. If factors that lead to non-participation in preventive strategies could be determined, it might reveal opportunities to address a large group that up to now has been out of reach. Several studies focused on the characteristics of non-responders in screening and prevention programs for CMD. Most of these studies found non-responders to be more often of younger age and to be a smoker [11–19]. Unfortunately, these studies did not provide a consistent profile of non-responders, nor did they lead to evidence based recommendations to increase participation rates.

Within the context of the large-scale INTEGRATE study, which focuses on the (cost-) effectiveness of a stepwise CMD prevention program in primary care [20], we studied determinants of response to the first step of the prevention program, the self-reported risk score (RS). This response rate determines the domain of the follow-up steps and is vital for the overall success of the program. Therefore, we compared responders with non-responders, aiming to identify factors that influence response to the initial CMD risk score. Such factors can serve as a starting point for response-enhancing strategies that could improve participation rates.

Methods

INTEGRATE study

This cross-sectional study was performed within the framework of a trial, the INTEGRATE study. The INTEGRATE study is a stepped-wedge randomized controlled trial that was conducted in 2013 to 2018 in the Netherlands [20]. The aim of the INTEGRATE study is to assess the effectiveness and cost-effectiveness of a stepwise CMD prevention program coupled to an individualized lifestyle intervention. The detailed study design of the INTEGRATE study is described elsewhere[20].

Study population

To ensure practicability we used a random sample of 15 of the 37 participating practices in the INTEGRATE study for the non-response analysis, with a total of 5,616 eligible patients for the prevention program.

Steps of the INTEGRATE study

In the INTEGRATE study 37 general practices approached all patients between 45 and 70 years old without known CMD, hypertension or hypercholesterolemia. Eligible patients were randomized into an intervention and a waiting list control group. The patients in the waiting list control group received the intervention after one year as well. As the first step of the prevention program, patients received a personal letter from their GP with an invitation to assess their CMD risk through an online risk score (RS). After two weeks a reminder letter was sent to those who did not respond to the first invitation. The reminder invitation also contained a paper version of the RS and a returning envelope. Non-response questionnaires were sent to patients who did not respond online to the call for participation within four weeks after the first invitation. Non responders were identified based on a pseudonymized participation log that was kept by the study team. After filling in the RS, patients with an increased risk were advised to make an appointment with the GP for the second step of the prevention program to complete their CMD risk profile with additional measurements. Patients with a low risk for cardiometabolic diseases received online tailored lifestyle advice. The third and last step of the prevention program was treatment for patients with an increased risk for CMD with tailored lifestyle advice and/or medication.

Responders were defined as patients who completed the online or paper version of the RS within 3 months after receiving the invitation. The online or paper RS consisted of a seven item-questionnaire including age, gender, body mass index (BMI), waist circumference, family history of cardiovascular disease (CVD) and/or diabetes mellitus type II.

Characteristics of non-responders

The content of the non-response questionnaire was based on the literature [6,7,21,22] and previously developed questionnaires about participation in prevention programs [7,23].

The non-response questionnaire contained demographic characteristics (age, gender) and items on risk factors for CMD (smoking status, BMI, family history of type II diabetes mellitus and CVD, physical activity and alcohol consumption). Patients self-reported on weight and length, BMI was calculated afterwards. The risk factors obtained via the questionnaire were equal to the items in the RS. In addition the survey included questions about reasons for non-response, attitudes towards response-enhancing strategies and statements about CMD and screening.

Smoking status was defined as currently smoking (yes/no). BMI was calculated as weight/(height ^{2}) and a cut-off value of 25 kg/m^2 was used to define overweight, a cut-off value of 30 kg/m^2 was used to define obesity. Waist circumference was as defined as increased for females when measured 80 cm or over and for males 94 cm or over. A family history of CVD was defined as having first degree relatives with a cardiovascular event before the age of 65. Family history of DM was defined as having first degree relatives with diabetes mellitus type 2. The question about reasons for non-response had pre-set answer options, including an "other" option with a blanc field and non-responders could choose more than one answer. Answers on all statements about CMD and screening were formulated on a 5-point Likert scale, ranging from "totally agree" to "totally disagree". For the data analysis "totally agree" and "agree" were combined in "agree", "disagree" and "totally disagree" in "disagree". The answers on the questions about attitudes towards response-enhancing strategies were formulated on a 3-point Likert scale, with "yes", "maybe" and "no" as possible answers.

Statistical analysis

Descriptive analyses of all measurements were performed. To examine which factors are independently related to non-response, a multivariable multilevel logistic regression analysis was performed, using all variables to correct for possible confounding. In case of collinearity, the variable with the highest regression coefficient during the univariate analysis was added to the model. Adjusted odds ratios and 95% confidence intervals were reported. Stata version 14 was used for all statistical analyses.

Ethical consideration

The INTEGRATE study, including this non-response analysis, was considered by the UMC Utrecht Institutional Review Board and exempted from full assessment under the Medical Research involving human subjects Act [20,24].

Results

Response

Of the 5,616 patients that were approached 2,058 (37%) completed the RS within the first month. One month after the initial invitation non-response questionnaires were sent to 3,558 patients who had not completed the risk score by then. In addition 814 patients completed the risk score between 1 and 3 months' time, adding up to a total response of N=2,872 (51%). A number of 768 non-response questionnaires were returned, a response rate of 22% (ranging from 13% to 33% between practices). We excluded 430 patients who had completed the RS after receiving the non-response questionnaire. Additional reasons for exclusion were patients with ages under 45 or over 70 (n=9), patients reported to have a cardiometabolic disease (n=10), patients who moved (n=2) or deceased (n=1). In total data from 316 non-responders were analyzed (see Figure 1).

Characteristics of non-responders and responders

Characteristics of the non-responders and responders are listed in table 1. Older patients seemed less likely to participate compared to younger patients, although this trend was not significant in the multivariate analysis. Non-responders were significantly more often smoker than responders (20 vs 15%, OR 0.67). The responders and non-responders did not differ according to gender and BMI. The waist circumference was too high in more than 72% of all subjects but no differences were seen between non-responders and responders. Because of the large amount of missing data on physical activity and alcohol consumption we were not able to add this variable to the analysis.

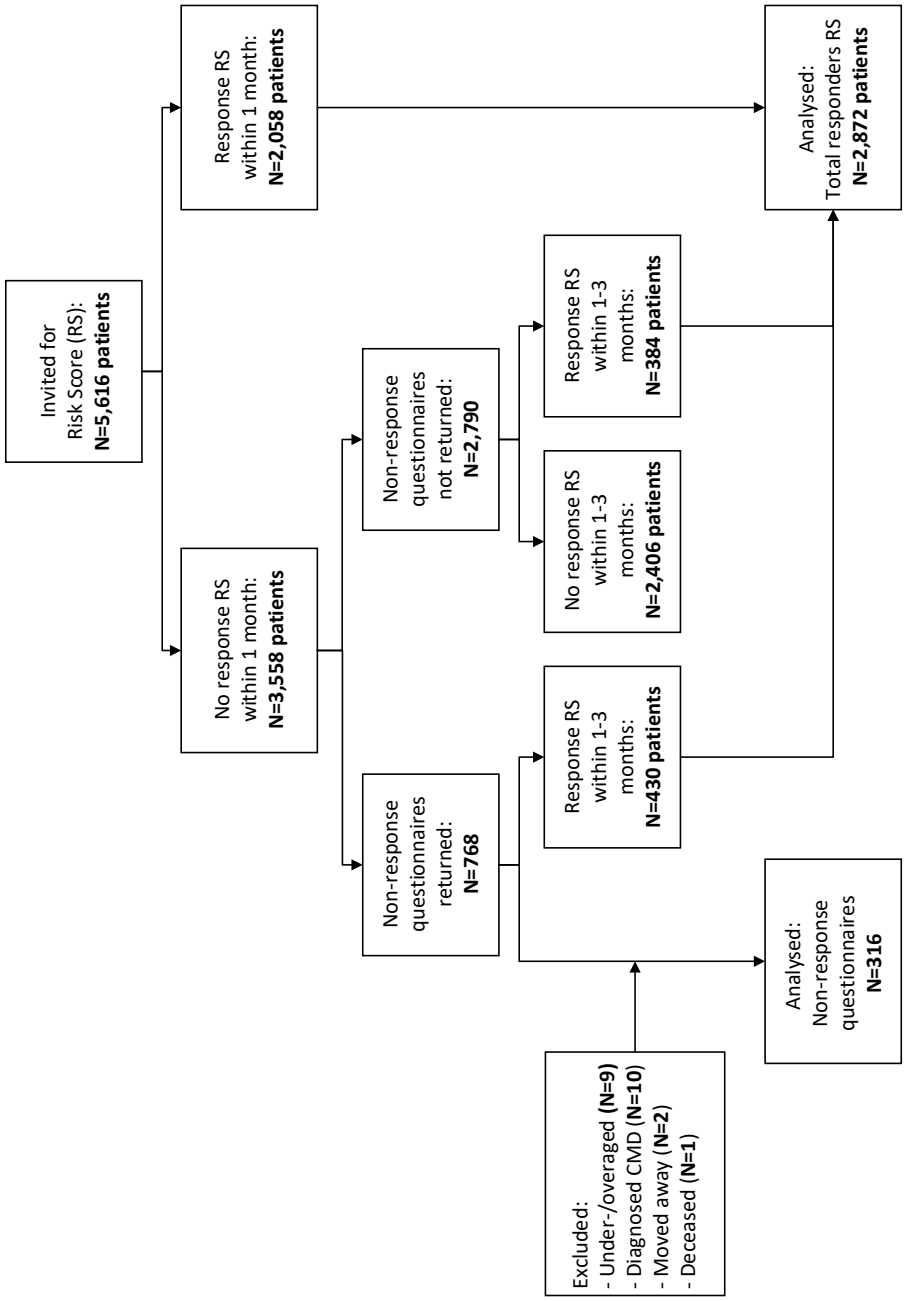

Figure 1 Flowchart of non-responders and responders risk score

Table 1 Characteristics of non-responders and responders

	Categories	N[a]	Non-responders (n=316)	Responders (n=2,872)	Multivariate		
					OR	95% CI	p-value
Age	**45-49 years**	57	18%	23%			
	50-54 years	72	23%	24%	0.92	0.62-1.36	0.68
	55-59 years	61	19%	22%	0.96	0.64-1.44	0.85
	60-64 years	62	20%	16%	0.76	0.50-1.16	0.20
	65+ years	64	20%	16%	0.67	0.44-1.01	0.06
Gender	**Male**	154	49%	46%			
	Female	162	51%	54%	1.02	0.75-1.38	0.94
Body mass index	**<25 kg/m²**	129	48%	53%			
	25-30 kg/m²	111	41%	38%	0.97	0.72-1.29	0.81
	>30 kg/m²	28	11%	9%	0.86	0.54-1.38	0.54
Waist circumference	***Males[b]:***						
	< 94 cm	31	33%	25%			
	≥ 94 cm	64	68%	75%			
	Females[b]:						
	< 80 cm	14	14%	11%			
	≥ 80 cm	83	86%	89%			
	Increased				0.68	0.46-1.02	0.06
Family history of DM	**Yes**	49	18%	17%	0.99	0.71-1.40	0.97
Family history of CVD	**Yes**	82	30%	30%	1.05	0.79-1.40	0.74
Smoking	**Yes**	56	20%	15%	0.67	0.49-0.91	<0.01

DM, diabetes mellitus type 2, CVD, cardiovascular disease

[a] number of complete values for non-responders (complete data for responders)

[b] males and females combined for multivariate analysis

Reasons for non-response

The 316 patients reported 344 reasons for not responding (table 2). The most reported reasons were 'I forgot it' (29%) and 'I had no time' (17%). In 21% of the reported reasons the patient stated having no need for a test, the patients felt healthy enough or didn't want to know their risk. Of all reasons for non-response 14% was due to having been checked by a doctor recently. Study-specific causes including technical problems and privacy concerns accounted for 15% of the reasons for non-response.

Table 2 Reasons for non-response

Reasons non-response (n=344)	n	%
Forgot/no time	**159**	**46%**
I forgot	100	29%
I had no time	59	17%
I have no need for a test	**72**	**21%**
I feel healthy	21	6%
I don't want to know my risk	7	2%
I don't want to participate	23	7%
I already know what the results will be	21	6%
Study-specific reasons	**51**	**15%**
I have no access to internet	22	7%
I had technical problems with the website	11	3%
I have privacy concerns	12	3%
I didn't receive an invitation	6	2%
Already checked by a doctor	**48**	**14%**
I'm regularly checked by a doctor	30	9%
I'm recently checked by a doctor	18	5%
Other	**14**	**4%**

Statements

A large majority of the non-responders felt healthy (83%) and only 16% of the patients expected their own risk for CMD to be elevated (table 3). Non-responders' own estimation of being at increased risk ranged from 1% for chronic kidney diseases to 11% for CVD (data not shown). Almost three-quarters (73%) of the patients felt that they are able to keep themselves healthy, nevertheless a comparable part of the patients (75%) stated being willing to adjust their current lifestyle if that would be necessary for health reasons. Only one-third (34%) of the patients agreed with the statement that a GP should give advice about lifestyle.

Table 3 Statements of non-responders

Statements:	Agree	No opinion	Disagree
I expect to have an elevated risk for cardiometabolic diseases	16%	33%	51%
I'm afraid for the results of the risk estimation	8%	22%	76%
I'm willing to adjust my lifestyle for my health	75%	15%	10%
I feel healthy	83%	8%	9%
I think the general practitioners should give advice about lifestyle	34%	29%	37%
I can take care of own health	73%	16%	11%
My family and friends find it important that I fill in the risk estimation	19%	57%	24%
I'm afraid others, like health insurance companies, find out the results of the risk estimation	24%	25%	51%

Attitude toward response-enhancing strategies

More than half of the non-responders would have performed or considered performing the risk score if the GP would ask him/her personally (table 4). Almost half of the non-responders (45%) thought that making the risk score more visible by using advertisements in media could have convinced them to respond. An almost equal number (46%) thought that explaining more about CMD in the invitation letter could have positively influenced participation. Considerably less people were convinced about the positive effect of a meeting at the general practice (27%) or a reminder by telephone (22%). Thirty-three non-responders (37% of those who answered this question) would have considered filling in the risk score if it was available in their native language. However, only 4 of those 33 patients were migrants.

Table 4 Attitude of non-responders toward response-enhancing strategies

Would you have considered completing the risk estimation in the following situations?	Yes	Maybe	No
If the general practitioners asked me to fill in the risk estimation personally	27%	31%	42%
If the risk estimation was more recognizable by use of advertisement	18%	27%	54%
If more explanation was given in the invitation letter	12%	34%	54%
If a meeting was originated at the general practice with help to complete it	8%	18%	74%
If I would be reminded by telephone	8%	14%	78%
If the risk estimation was available in my native language [a]	25%	12%	63%

[a] 89 non-responders filled in this question

Willingness to participate

Of all non-responders 73% seemed willing to participate, for they answered 'yes' or 'maybe' with one or more of the response-enhancing strategies. This group consisted mainly of patients who reported 'forgot/no time' and 'study-specific reasons' as reason for non-response. When comparing the answers on the statements of this specific group with all non-responders, they reported significantly more often that they feel healthy, that they are willing to adjust their lifestyle if necessary and that they can take care of their own health.

Discussion

Summary of results

In this non-response study we aimed at determining factors that influence response in a risk score for CMD, to be used as input for developing response-enhancing strategies. In multivariable multilevel regression analyses we found non-responders more often to be a smoker. Almost half of all reported reasons for not responding were either 'forgotten it' or 'having

no time'. Almost three quarter of the non-responders seemed willing to participate. Most non-responders felt healthy and expected their risk for CMD to be low, but also stated that they would be motivated to adjust their lifestyle to maintain healthy. A personal request from patients' own GP is potentially the best method to enhance the response. Using advertisements and informative campaigns through media and more extensive information in the initial invitation are other methods that non-responders suggested.

Interpretation of results

Characteristics of non-responders in CMD prevention programs have shown variation in current literature. Lower response amongst younger age [11,14,17–19,25] and smokers [11–15] was reported in most earlier studies in primary care. A possible explanation of the higher age trend among non-responders in our results is compatible with the often reported 'worried well' phenomenon, where responders to prevention programs tent be healthier but have higher levels of worry than non-responders [26]. This could explain why the relatively healthy -younger- patients tend to seek more medical advice. Another possible explanation for the contrast in age of the non-responders in our study and the current literature is that a relatively older selection amongst the non-responders returned our non-response questionnaire.

Willingness to participate and willingness to adjust lifestyle was high amongst non-responders, which is in line with several earlier studies [21,22,27]. Non-responders who are willing to participate have a favorable profile, they are willing to adjust their lifestyle and perceive control over staying healthy, which are both determinants for successful participation [22,28,29]. Most non-responders feel healthy and this may be one of the main reasons why it is so challenging to reach out to this group and getting them involved. The role of the GP in inviting these patients is yet to be specified further, for non-responders seem to value a personal approach. This is consistent with qualitative research that has been done amongst non-responders of the NHS health checks, where recommendations were made to emphasize personal relevance of participating [30,31]. In the Netherlands a more personal approach through the GP has been proven successful and is implemented in the method of inviting women for cervical cancer screening since decades [32].

The non-responders in our study indicated that they desired to be informed better about CMD and risk factors. Other studies suggested more response in prevention programs could be achieved by increasing public awareness through media and giving more consideration to risk communication [27,30,31,33]. This study adds that this line of thinking is also confirmed by the concerning target group, the non-responders, which to our knowledge has not been reported before.

The non-responders in our study surprisingly indicated that reminders by telephone would not persuade them, for this contrasts positive experiences with telephone reminders in the past [8,22].

Strengths and limitations

In this study we succeeded to gain relevant information from a substantial number of indivi-

duals that are usually hard to reach. Another strength of this non-response analysis is the integration in a large intervention study. This allows us to use the results as direct input for further exploration and testing response enhancing strategies in the same population. This is a unique design that creates great potential.

The most important limitation is the low response (22%) to the non-response questionnaire. However, considering this is response amongst non-responders, higher response rates may not be realistic. It is possible that there was a selective response of non-responders with a more positive attitude towards participation. This could mean that our conclusions concerning achievable response rates are somewhat overestimated. It is unclear if and to what extent this factor has biased the results of this study. Nonetheless, our results are comparable to Wall et al. [27] who were able to get a response of 93% to their non-response questionnaire. Another limitation is that we didn't measure willingness to participate directly but as derivative from other statements. The substitute measurements may not entirely reflect true willingness to participate and therefore could have biased our results.

Conclusions

High participation rates are crucial for successful prevention programs. So far, non-response in prevention programs in primary care has not been given sufficient attention. Our non-response analysis shows a clear message of potential for participation in prevention programs for CMD. Willingness to participate amongst non-responders is high and there are strategies we can use to reach them. Response enhancing strategies have been successful for other prevention programs in the past [34,35]. Persuasion of at least half the non-responders with the right methods seems a realistic goal. This means that with more time and energy we should be able to substantially boost response rates. A next logical step in this process is to test potential response enhancing strategies in research setting.

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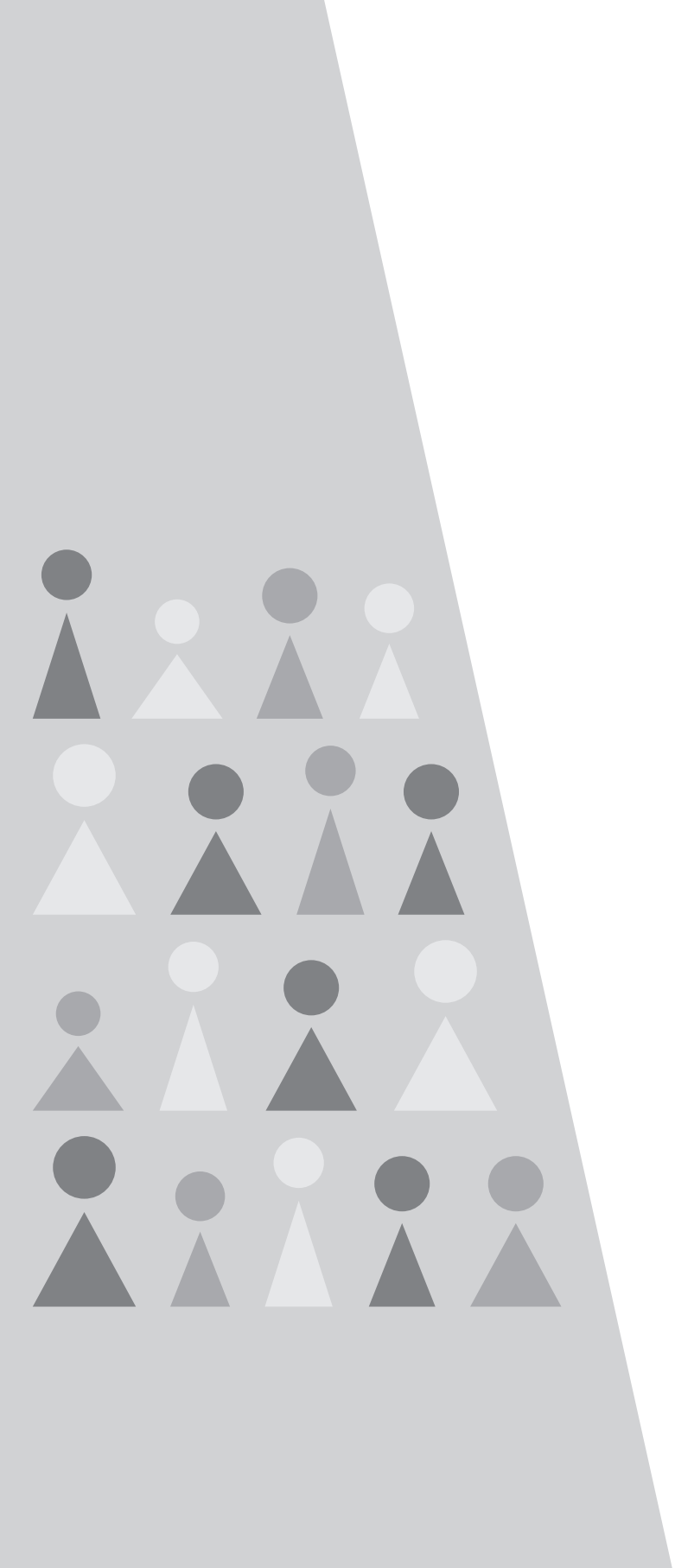

4

Characteristics and motives of non-responders in a stepwise cardiometabolic disease prevention program in primary care

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Abstract

Background: A high response rate is an important condition for effective prevention programs. We aimed at gaining insight into the characteristics and motives of non-responders in different stages of a stepwise prevention program for cardiometabolic diseases (CMD) in primary care.

Methods: We performed a non-response analysis within a randomized controlled trial assessing the effectiveness of a stepwise CMD prevention program in the Netherlands. Patients between 45 and 70 years without known CMD were invited for stage 1 of the program, completing a CMD risk score. Patients with an increased risk were advised to visit their general practice for additional measurements, stage 2 of the program. We analyzed determinants of non-response using data from the risk score, electronic medical records, questionnaires and Statistics Netherlands.

Results: Non-response in stage 1 was associated with a younger age, male sex, a migration background, a low prosperity score, self-employment, being single and having lower consultations rates in general practice. Non-response in stage 2 was associated with a low prosperity score, being employed, having no chronic illness, smoking, a normal waist circumference, a negative family history for cardiovascular disease or diabetes and having a lower consultation rate. More than half of the non-responders in stage 2 reported not visiting the GP because they didn't expect to have any CMD despite their increased risk.

Conclusions: To achieve a larger and more equal uptake of prevention programs for CMD we should use methods adapted to characteristics of non-responders, such as targeted invitation methods and improved risk communication.

Introduction

Globally, cardiometabolic diseases (CMD), including cardiovascular disease (CVD), chronic kidney failure and diabetes mellitus type 2, are highly prevalent and the most common cause of mortality [1]. The incidence of in CMD will increase in future in developed countries as a result of the aging population and an unhealthy lifestyle. To put a halt to rising costs and disease burden caused by CMD, there is an urgent need for effective prevention programs. Primary care is considered to be the most suitable setting for selective CMD prevention because GPs are easily accessible and are familiar with patients' medical background and social context. Therefore they can personalize treatment and offer ongoing counseling on a healthy lifestyle. A stepwise strategy in prevention programs seems to be the most effective way to screen for CMD in primary care, aimed at identifying and treating high risk patients [2,3].

Adequate participation and an optimal response rate is conditional for the (cost) effectiveness of prevention programs, programs often depend on a minimum percentage of participation by the target group [4]. Unfortunately response rates in CMD prevention programs show great variation, varying between extremes as 1.2% [5] and 84% [6]. Also, the right people need to be reached throughout the different steps of the program, to ensure that the program actually reaches the indicated population, i.e. patients with an increased risk for CMD. A younger age, smoking and a low socioeconomic status (SES) are commonly reported as being associated with non-response in CMD prevention, but in the literature there is wide heterogeneity in the characteristics of non-responders [7]. Therefore it is still unclear what the best strategy is to address and motivate sufficient high risk patients to participate in a stepwise prevention program for CMD.

More knowledge about the characteristics and motives of non-responders and responders during the different steps of the program would help to better target individuals at CMD risk thereby improving response rates and increasing effectiveness of prevention programs. We reported the characteristics of non-responders among the participants of the INTEGRATE study[8], a randomized controlled trial assessing the effectiveness of a stepwise CMD prevention program in the Netherlands [9].

Methods

INTEGRATE study

The INTEGRATE study is a stepped-wedge randomized controlled trial conducted from 2014 to 2017. A total of 37 GP practices participated in the study. All patients between ages 45 and 70 without known CMD, hypertension or hypercholesterolemia were approached to participate in a prevention program for CMD. Patients were invited through a letter, signed by their own

GP, inviting them to calculate their risk for CMD by filling in an online risk score. Two weeks after the first invitation patients received a reminder letter that also included a paper version of the risk score. Patients with an increased risk received the advice to make an appointment at the general practice for a consultation including additional measurements. The GP or practice nurse would then provide the patient with personalized lifestyle advise and start medication when considered necessary. All patients who completed the risk score received an additional questionnaire, regardless of whether they consulted the GP. The detailed study design of the INTEGRATE study is described elsewhere [8].

Study population and outcome

For the non-response analysis data of all invited patients from 36 of the 37 practices participating in the INTEGRATE study were available. One practice had to be excluded due to incomplete data from electronic health records (EHR).

We defined responders in stage 1 of the prevention program as patients who completed the risk score, either the online or the paper version. Non-responders in stage 1 did not participate in any part of the program. Responders for stage 2 of the program were defined as patients with an increased risk at the risk score who followed the advice of visiting the general practice for a consultation. All responders in stage 2 either had a case report form filled out by the GP or practice nurse, reported GP consultations in the questionnaire or had a recorded consultation in the GP's EHR. We searched the EHRs for consultations with a relevant code according to the International Classification of Primary Care (ICPCs) combined with a relevant measurement (e.g. blood pressure or blood test) within 6 months after the first invitation. Non-responders in stage 2 were the patients with an increased risk who did not visit the general practice.

Characteristics and motives of non-responders

We collected data on the characteristics of non-responders and responders from different sources, including the GP's EHR, the items of the risk score, the additional research questionnaire and by linking our data to data from Statistics Netherlands.

Data from the GP's EHR were available for all patients who were invited for the first stage of the prevention program. We used information about patients' gender, age, ICPC-coded medical diagnoses and primary health care use. Primary health care use was defined as the number of contacts with the general practice in the last 12 months. Chronic illness was defined as a recorded ICPC code for at least one of 109 possible diseases in which there is generally no prospect of full recovery [10].

Data from the risk score were available for all patients who participated and filled out the risk score. The risk score contained items on age, gender, body mass index (BMI), waist circumference, family history of cardiovascular disease and/or diabetes mellitus type II. A family history of CVD was defined as having first degree relatives with a cardiovascular event

before the age of 65. Family history of DM was defined as having first degree relatives with diabetes mellitus type 2. The additional research questionnaire contained items on reasons for not participating in stage 2 of the program.

We linked our data to data registers of Statistics Netherlands, which contains details about household composition, prosperity, educational level and migration background of all responders and non-responders. Prosperity was defined by Statistics Netherlands based on income and assets per household and was categorized as low (lower tertile of the Dutch households), high (upper tertile of the Dutch households) or middle (middle tertile). Data on education level (highest completed education) was available for 40% of our study population and included recorded data as well as data imputed by Statistics Netherlands. Having a migration background was defined as not born in the Netherlands or having at least one parent who was not born in the Netherlands, with the country of birth being either western of non-western.

A question about the reason for non-response in stage 2 was added to the standard additional questionnaires during the last year when the study was conducted. Non-responders were presented with the question when they had an increased risk and had indicated that they did not visit the general practice for additional measurements. The reasons for non-response indicated by non-responders who consulted the practice at a later stadium were excluded.

Statistical analysis

Descriptive analyses were used for all characteristics of the study population. We used univariate multilevel logistic regression analysis to compare the characteristics of non-responders and responders, reporting crude odd ratios and 95% confidence intervals. A multivariable multilevel logistic regression analysis was also performed, reporting adjusted odds ratios and 95% confidence intervals. Multilevel techniques were used to adjust for clustering of patients within practices. Stata version 15 was used for all statistical analyses.

Ethical consideration

The INTEGRATE study, with inclusion of this non-response analysis, was considered by the UMC Utrecht Institutional Review Board and exempted from full assessment under the Medical Research involving human subjects Act.[8]

Results

In the 36 participating general practices a total of 29,758 patients received an invitation letter for participation in the prevention program. Of these, 12,289 patients (41%) calculated their risk with the online or paper version of the risk score (responders stage 1). An increased risk was found in

5,057 (41%) of the patients of whom 1,648 patients (33%) visited the practice for a consultation and additional measurements (responders stage 2). This resulted in 17,469 non-responders in stage 1 of the program and 3409 non-responders in stage 2. Table 1 shows the response rates in stages 1 and 2 in different patient subgroups, ranging between 26% and 56% resp. 23% and 40%.

Table 1 Response rates of stage 1 and stage 2 of the CMD prevention program by population characteristics

	Response rate stage 1 (n=29,758)	**Response rate stage 2 (n=12,289)**
	(%)	(%)
Overall	**41%**	**33%**
Age		
45-49	37%	25%
50-54	42%	23%
55-59	48%	28%
60-64	52%	33%
65+	56%	36%
Sex		
Female	44%	35%
Male	39%	30%
Ethnicity		
Dutch	43%	34%
Western migrant	38%	35%
Non-western migrant	26%	34%
Educational level *		
Low	32%	30%
Middle	39%	33%
High	45%	33%
Work relationship		
Employee	41%	31%
Self-employed	39%	28%
Not employed (receiving benefits)	43%	37%
No income	42%	34%
Household composition		
Single	34%	34%
Married and/or living together, no children	49%	36%
Married and/or living together, with children	40%	29%
Other multi-person household	37%	25%
Prosperity score		
Low	29%	30%
Middle	38%	35%
High	47%	35%

	Response rate stage 1 (n=29,758)	Response rate stage 2 (n=12,289)
	(%)	(%)
Chronic illness		
no	40%	30%
yes	44%	36%
Mental health problems		
no	42%	34%
yes	39%	34%
CMD risk factors:		
Smoking status		
no		35%
yes		24%
Body mass index		
<25		32%
25-30		34%
>30		33%
Waist circumference		
Normal		28%
Increased		33%
Family history CVD		
no		31%
yes		36%
Family history DM		
no		31%
yes		40%

* data about educational level was available for 40% of the patients

The results of the multilevel analysis are shown in table 2 and table 3. Due to the high number of missing values, educational level was not included in the analysis. A younger age (age 45-49 vs. 65-70 year OR 0.52), male sex (female vs. male OR 1.23), migration background (Dutch vs. non-western migrant OR 1.55), a low prosperity score (low vs. high score OR 0.55), self-employment (employee vs. self-employed OR 1.12), being single (single vs. married/with a partner with no children OR 0.68) and having a lower health care use of primary care (OR 0.99) were all associated with non-response in stage 1 of the CMD prevention program in the multivariate regression model. Another set of individual characteristics showed to be of importance in association with non-response in stage 2 of the program; being employed (employed vs. receiving benefits OR 0.83), a low prosperity score (low vs. high score OR 1.35), smoking (not smoking vs. smoking OR 1.39), an normal waist circumference (OR 0.80), a negative family history for CVD (negative vs. positive OR 0.81) or diabetes type 2 (negative vs. positive OR 1.54), having no chronic illness (no illness vs. illness OR 0.86) and a lower health care use of primary care (OR 0.98) were associated with a higher response in stage 2.

Table 2 Characteristics associated with non-response in stage 1 of the CMD prevention program

	Non-responders stage 1 (n=17,469)	Responders stage 1 (n=12,289)	Univariate		Multivariate	
	n (%)	n (%)	OR	95%CI	OR	95%CI
Age						
45-49	4530 (30)	2702 (22)	1.00		1.00	
50-54	4205 (28)	3017 (25)	**0.86**	[0.80;0.92]	**0.86**	[0.80;0.93]
55-59	2778 (19)	2542 (21)	**0.69**	[0.64;0.74]	**0.72**	[0.66;0.78]
60-64	1911 (13)	2055 (17)	**0.59**	[0.55;0.64]	**0.61**	[0.56;0.68]
65+	1574 (11)	1973 (16)	**0.51**	[0.47;0.55]	**0.52**	[0.47;0.59]
Sex						
Female	8497 (49)	6570 (54)	1.00		1.00	
Male	8972 (51)	5719 (46)	**1.21**	[1.15;1.27]	**1.23**	[1.16;1.30]
Ethnicity						
Dutch	12297 (82)	9316 (87)	1.00		1.00	
Western migrant	1491 (10)	921 (9)	**1.21**	[1.11;1.32]	**1.13**	[1.03;1.24]
Non-western migrant	1237 (8)	424 (4)	**1.98**	[1.76;2.22]	**1.55**	[1.37;1.75]
Work relationship						
Employee	8237 (55)	5821 (55)	1.00		1.00	
Self-employed	2147 (14)	1388 (13)	1.11	[1.03;1.20]	**1.12**	[1.03;1.21]
Not employed (receiving benefits)	3694 (25)	2831 (27)	**0.93**	[0.88;0,99]	1.06	[0.98;1.15]
No income	845 (6)	605 (6)	1.01	[0.91-1.13]	**1.14**	[1.02;1.29]
Household composition						
Single	2661 (15)	1385 (11)	1.00		1.00	
Married and/or living together, no children	4445 (26)	4322 (35)	**0.54**	[0.50;0.59]	**0.68**	[0.63;0.75]
Married and/or living together, with children	6388 (37)	4260 (35)	**0.78**	[0.72;0.84]	**0.76**	[0.70;0.83]
Other multiperson household	3975 (23)	2322 (19)	1.03	[0.94;1.14]	1.00	[0.89;1.12]
Prosperity score						
Low	2867 (19)	1183 (11)	1.00		1.00	
Middle	4729 (32)	2951 (28)	**0.66**	[0.61;0.71]	**0.72**	[0.670.79]
High	7327 (49)	6511 (61)	**0.47**	[0.44;0.51]	**0.55**	[0.50;0.60]
Health care use primary care						
Average consultations per year	*3.4*	*3.6*	**0.99**	[0.99-1.00]	**0.99**	[0.98;0.99]
Chronic illness						
no	8171 (52)	5529 (49)	1.00		1.00	
yes	7580 (48)	5873 (52)	**0.88**	[0.84;0.93]	0.96	[0.91;1.01]
Mental health problems						
no	13980 (89)	10254 (90)	1.00		1.00	
yes	1771 (11)	1148 (10)	**1.13**	[1.05;1.23]	1.09	[1.00;1.20]

Table 3 Characteristics associated with non-response in stage 2 of the CMD prevention program

	Non-responders 2 (n=3,409)	Responders 2 (n=1,648)	Univariate		Multivariate	
	n (%)	n (%)	OR	95%CI	OR	95%CI
Age						
45-49	59 (2)	20 (1)	1.00		1.00	
50-54	255 (8)	77 (5)	1.12	[0.63;1.99]	1.02	[0.54;1.95]
55-59	608 (18)	241 (14)	0.86	[0.51;1.47]	0.91	[0.49;1.68]
60-64	1230 (36)	594 (36)	0.70	[0.42;1.19]	0.73	[0.39;1.37]
65+	1257 (37)	716 (44)	0.60	[0.36;1.01]	0.72	[0.38;1.38]
Sex						
Female	1622 (48)	881 (54)	1.00		1.00	
Male	1787 (52)	767 (47)	1.25	[1.10;1.41]	1.05	[0.91;1.20]
Ethnicity						
Dutch	2583 (89)	1321 (89)	1.00		1.00	
Western migrant	231 (8)	122 (8)	0.97	[0.77;1.22]	0.94	[0.74;1.19]
Non-western migrant	79 (3)	41 (3)	0.98	[0.67;1.45]	0.96	[0.64;1.44]
Work relationship						
Employee	1068 (37)	477 (32)	1.00		1.00	
Self-employed	290 (10)	111 (8)	1.13	[0.89;1.46]	1.12	[0.88;1.45]
Not employed (receiving benefits)	1356 (47)	808 (55)	**0.75**	[0.65;0.87]	**0.83**	[0.69;0.99]
No income	173 (6)	88 (6)	0.88	[0.67;1.17]	0.97	[0.72;1.31]
Household composition						
Single	468 (14)	238 (14)	1.00		1.00	
Married and/or living together, no children	1694 (50)	950 (58)	0.93	[0.78;1.11]	1.03	[0.85;1.24]
Married and/or living together, with children	601 (18)	242 (15)	**1.26**	[1.02;1.58]	1.15	[0.90;1.46]
Other multiperson household	646 (19)	218 (13)	1.58	[1.23;2.05]	1.15	[0.80;1.67]
Prosperity score						
Low	399 (14)	167 (11)	1.00		1.00	
Middle	810 (28)	433 (29)	**0.78**	[0.63;0.97]	**0.74**	[0.59;0.92]
High	1678 (58)	884 (60)	**0.80**	[0.65;0.98]	**0.74**	[0.59;0.92]
Health care use primary care						
Average consultations per year	*3.6*	*4.3*	**0.97**	[0.96-0.99]	**0.98**	[0.96;0.99]
Chronic illness						
no	1351 (43)	582 (37)	1.00			
yes	1767 (57)	1004 (63)	**0.77**	[0.68;0.87]	**0.86**	[0.75;0.99]
Mental health problems						
no	2775 (89)	1410 (89)	1.00			
yes	343 (11)	176 (11)	1.00	[0.82;1.21]	1.12	[0.90;1.40]

	Non-responders 2 (n=3,409)	Responders 2 (n=1,648)	Univariate		Multivariate	
	n (%)	n (%)	OR	95%CI	OR	95%CI
CM risk factors:						
Smoking status						
no	2569 (75)	1385 (84)	1.00			
yes	840 (25)	263 (16)	**1.73**	[1.48;2.02]	**1.39**	[1.15;1.68]
Body mass index						
<25	1574 (46)	731 (44)	1.00			
25-30	1390 (41)	703 (43)	0.92	[0.81;1.04]	0.89	[0.77;1.04]
>30	443 (13)	214 (13)	0.96	[0.80;1.16]	0.95	[0.76;1.20]
Waist circumference						
Normal	480 (14)	184 (11)	1.00			
Increased	2929 (86)	1464 (89)	**0.76**	[0.64;0.92]	**0.80**	[0.64;0.99]
Family history CVD						
no	2243 (66)	997 (61)	1.00			
yes	1165 (34)	651 (40)	**0.80**	[0.70;0.90]	**0.81**	[0.71;0.93]
Family history DM						
no	2757 (81)	1216 (74)	1.00			
yes	651 (19)	432 (26)	**0.66**	[0.58;0.76]	**0.65**	[0.55;0.76]

A sample of 238 non-responders in stage 2 reported 267 reasons for non-response, shown in table 4. This sample of non-responders was representative for the total group of non-responders 2 regarding age, sex, migration background, prosperity score, health care use of primary care and CMD risk factors (data not shown). More than half of the reported reasons stated that no visit to the practice was made because the patient didn't expect to have any CMD despite their increased risk. In more than a quarter of the cases the patient forgot to make an appointment, had no time or did not understand the advice. Already being checked by a doctor regularly contributed to 17% of the reasons for non-response in stage 2 of the CMD prevention program.

Table 4 Reasons for non-response in stage 2 of the CMD prevention program

Reasons non-response (n=267)	n	%
Forgot/no time/misunderstood	**74**	**28%**
I forgot	21	8%
I had no time	24	9%
I didn't understood that I had to make an appointment	29	11%
I don't expect to have any CMD	**143**	**54%**
I don't expect to have CVD, DM or kidney damage	121	45%
I don't agree with the results of the risk score	11	4%
I feel healthy	11	4%
Other	**50**	**19%**
I'm regularly checked by a doctor	45	17%
I already started working on my lifestyle by myself	2	1%
I depend on others to bring me to the GP	1	0%
I'm afraid to know my risk	1	0%
Due to other health issues	1	0%

Discussion

Summary of results

In this study we aimed at gaining insight into the characteristics and motives of non-responders at different stages of a stepwise CMD prevention program. Non response was in both steps of the CMD prevention program associated with individual demographic, socio-economic and health care consumption data. In a representative sample of non-responders in stage 2, more than half of the reported reasons for non-response were related to the expectation of not having any CMD despite an increased risk.

Strengths and limitations

To our knowledge this is the first study to investigate the characteristics and motives of non-responders at different stages of a stepwise CMD prevention program in the total target population. We managed to collect reliable data about a large amount of non-responders, providing us with important insights and input for strategies to enhance uptake and effectiveness of CMD prevention programs. This analysis was part of a large pragmatic trial, making the response rates representative for a realistic setting. A limitation of this study is that we weren't able to use risk factors such as smoking and BMI in our analysis with the response at the first stage of the prevention program, as the EHRs contained mostly missing data about the CMD risk factors for the non-responders. Also, because of the high amount of missing values we weren't able to use education level in our final models.

Comparison with existing literature

Our results largely confirm earlier reports. Most large studies on CMD prevention programs and CMD risk scores report that a younger age and low SES are associated with non-response [6,7,11–16]. Although the results of studies reporting about associations between response and sex, migration background, social status and health care use are less consistent, male sex [6,12,16,17], having a migration background [12,18], being single [6,12,13,17,19] and not frequently consulting a doctor [13,17,19,20] have also shown to be associated with response in earlier studies. Our findings regarding the characteristics of the responders and non-responders in stage 1 are in line with these insights.

Only few studies report separate non response analysis for different steps of a CMD prevention program, making it harder to put the results about characteristics of non-responders in stage 2 into perspective. Nevertheless, with stepwise CMD prevention programs increasing in popularity it is important to gain more insight into how the different steps of the program are received.

We found a lower prosperity score (SES) to be associated with non-response in stage 2 of the program. This enforces the already smaller contribution of low SES patients to this stage because of the previous selective response in stage 1, making low SES patients extra vulnerable for dropping out during the program. Our study also showed an association between work status and non-response at both stages of the program, self-employed patients were less likely to participate in stage 1 and patients without work were less likely not to complete their risk profile with additional measurements. Dalsgaard et al. [21] also found a positive association between unemployment and response in stage 2 of a stepwise screening program for diabetes type 2. This seems to contradict with the association between low prosperity and non-response, but it may be explained by the fact that unemployed patients have more time for a practice visit.

A characteristic that was associated with non-participation in both stages of the prevention program was health care use of primary care. Earlier studies also showed a positive association between frequent consultations of the general practice and participation in a prevention program for CMD [13,17,19,20]. Patients who have more contact with their GP might feel more inclined to accept an invitation for a CMD risk score and feel less of a threshold to visit the practice. The same reasoning can be made for patients with a chronic illness. This also means that there is a considerable overlap between the patients who eventually end up visiting the GP when being invited and the patients who would be reached with case finding by the GP.

Smoking, a major risk factor for CMD, was associated with non-response in stage 2. Although this finding is not surprising, for smoking is a factor frequently found to be associated with non-response in CMD prevention programs [6,12,13,16,17,19], the effect is undesirable because it leads to relatively more healthier individuals participating in the program.

Furthermore we found that patients with a positive family history of CVD or diabetes were more likely to participate in stage 2 of the prevention program. This is in line with an

earlier report from our group where we showed that family history is a significant factor in CMD risk perception [22] and has an important role in the decision to visit the GP in the context of a prevention program [23].

Earlier we reported an overview of the reasons for non-response in stage 1 [24], almost half of all the reported reasons for non-participation were categorized as 'having a lack of time or haven forgotten it'. For the non-response in stage 2 other motives prevailed, more than half of all the reported reasons for non-response were categorized as 'not expecting to have any CMD'. Risk perception for CMD seems to be low, even when patients had an increased risk. This finding is interchangeable with the conclusion of our earlier article on risk perception in which we showed that patients with a high risk score structurally underestimate their own risk for CMD [22]. This discrepancy between perceived and calculated risk is the main reason for non-response of high risk patients. Possibly a health care professional is needed to communicate the CMD risk, advocating a more personalized approach in this group.

Overall the results of this study describe an image of overrepresentation of socially vulnerable groups amongst the non-responders for CMD prevention programs, including individuals with a low SES and a migration background, as well as individuals with a higher risk for CMD based on their smoking status. This endorses the phenomenon of the inverse care law [25], patients with a low SES suffer the most disease burden and would potentially benefit most from prevention, but are less likely to get involved with prevention programs. Reaching the underserved population with a CMD prevention program might be possible with adapted and targeted invitation methods [7,26,27]. As we reported earlier, almost three-quarter of the non-responders in stage 1 would reconsider participation if invited differently, for instance by means of a personal approach by the GP or with the help of advertisements and informative campaigns [24]. The effectiveness of these response enhancing strategies have yet to be determined.

Conclusion

The results of the non-response analysis at the first stage of our stepwise prevention program for CMD reinforce the inverse care law principle, showing that a collective invitation method leads to underuse of exactly those groups of patients we know to bear the greatest disease burden in our society. After the stage of selecting high risk patients risk perception may play a major role, a large part of the patients with an increased risk for CMD perceive their risk as low and therefore refrain from further action. To achieve a larger and more equally divided uptake of CMD prevention programs targeting our invitation methods and improve manners of risk communication may be future directions.

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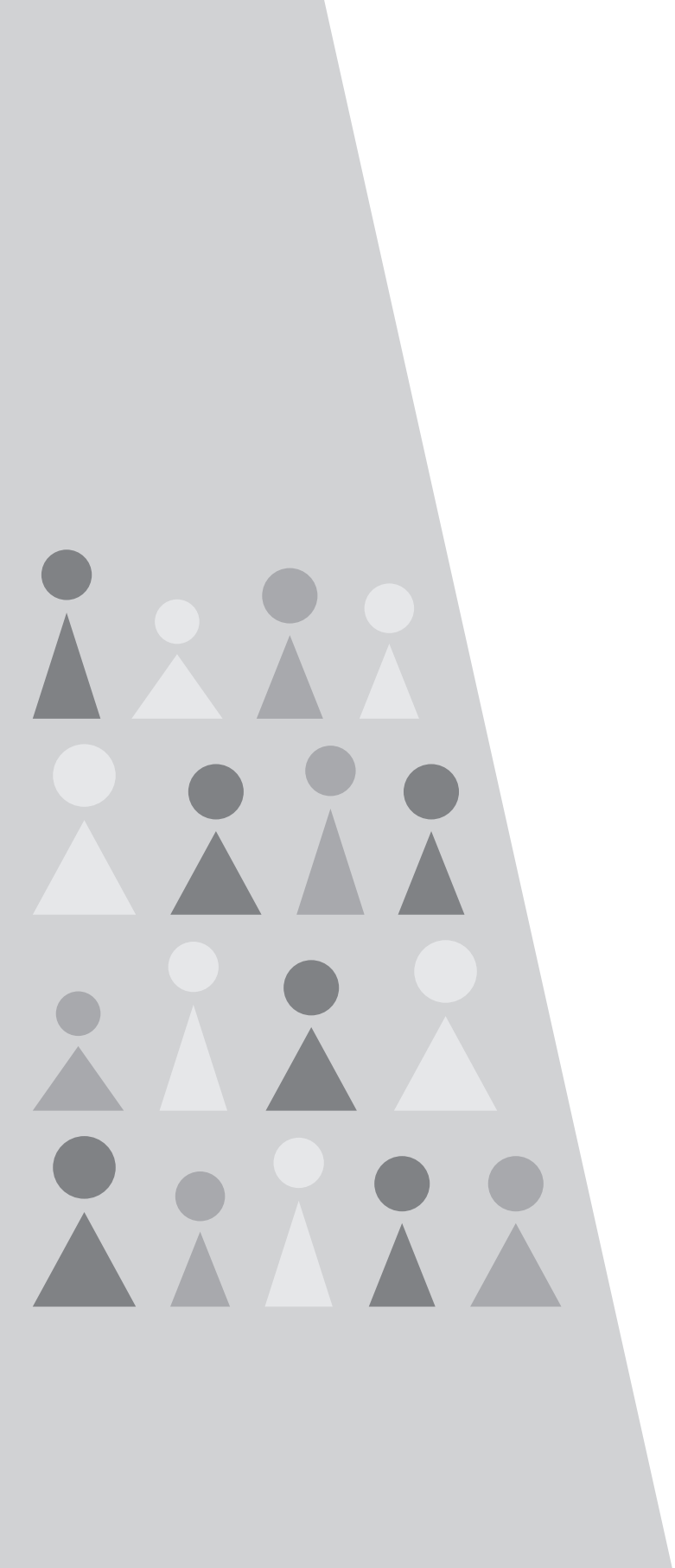

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Feasibility and success rates of response enhancing strategies in a stepwise prevention program for cardiometabolic diseases in primary care

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Abstract

Background: Cardiometabolic diseases (CMD), including cardiovascular disease, diabetes mellitus and chronic kidney disease can be prevented, but evidence for the (cost-)effectiveness of selective CMD prevention programs is lacking. Response rates have an important role in effectiveness, but methods to increase response rates have received insufficient attention. The aim of this study is to determine the feasibility and the success rate of a variety of response enhancing strategies to increase the participation in a selective prevention program for CMD.

Methods: The INTEGRATE study is a Dutch randomized controlled trial to assess the effectiveness and cost-effectiveness of a stepwise program for CMD prevention. During the INTEGRATE study we developed ten different response enhancing strategies targeted at different stages of non-response and different patient populations and evaluated them in 29 general practices.

Results: A face-to-face reminder by the GP increased the response significantly. Digital reminders targeted at patients with an increased risk showed a positive trend in participation. Sending invitations and reminders by e-mail generated similar response rates, but at lower costs and time investment than the standard way of dissemination. Translated materials, information gatherings at the practice, self-management toolkits, reminders by telephone, extended information letters, local media attention and SMS text reminders did not increase the response to our program.

Conclusions: Inviting or reminding patients by e-mail or during GPs consultation may enhance response rates in a selective prevention program for CMD. Different response-enhancing strategies have different target populations and implementation issues, so practice characteristics need to be taken into account when implementing such strategies.

Introduction

Cardiometabolic diseases (CMD), including cardiovascular disease, diabetes mellitus and chronic kidney disease are putting increasing pressure on the healthcare costs. Because of the modifiable nature of many risk factors, 80% of cardiometabolic diseases can be prevented [1]. Selective prevention programs for CMD, targeting an apparently healthy population with a stepwise program in order to select only those at high risk, seems a promising and cost-effective strategy [1,2]. With this approach risk-reducing interventions can be targeted to patients at high risk. However, up to now, no convincing evidence has been provided that selective prevention programs for CMD are (cost)effective [3]. An important aspect in the effectiveness of a prevention program is the response rate [4], as studies have shown a wide variation in participation [2,3,5]. Mapping response rates and identifying methods to improve them has received little attention so far. If we could increase participation in prevention programs, their effectiveness on population level would increase simultaneously.

Several studies have been performed to gain more insight into the characteristics of non-responders in prevention programs for CMD [5–18]. Non-responders are reported to be more often male, smoke more often and being of younger age [5,7–14,16–18]. A lower socio-economic status (SES) and a migrant status is also reported as related to non-response [5,11–13,15,16]. If these groups could be reached with targeted response enhancing strategies, this could lead to an increased participation.

Various studies explored strategies to enhance response rates in preventive and screening programs in general [19,20] and for prevention programs for CMD specifically [21]. Commonly used methods are reminders by letter or telephone, face-to-face reminders by a physician, providing educational material and publicity through different media. With the aforementioned characteristics of non-responders taken into account, more advanced response-enhancing strategies are developed to specifically reach the underperforming groups. Invitations or reminders by e-mail [22] or SMS text messages [23] might be attractive for the younger population. The provision of a toolkit for self-testing already resulted in an enhanced uptake for cervical cancer screening [20]. Patients from lower SES groups and migrants may benefit from culture specific information meetings and translated questionnaires [24].

Successful response enhancing strategies may also be guided by specific preferences of non-responders. During the INTEGRATE study [25] we assessed attitudes towards different response enhancing strategies amongst non-responders. Most non-responders would reconsider participation if they would receive a face-to-face invitation by their own GP, if the awareness of the program could be increased through media exposure or if more informative information would be offered. However, the feasibility and success rates of these strategies have yet to be determined in clinical practice.

The design of the INTEGRATE study [26] allowed to develop and to evaluate response enhancing strategies in the same study population. Here we report on the feasibility and the

success rate of a variety of response enhancing strategies to increase the participation in a selective prevention program for CMD.

Methods

INTEGRATE study

The INTEGRATE study is a stepped-wedge randomized controlled trial that ran from 2014 to 2017. The aim of the INTEGRATE study is to assess the (cost-)effectiveness of a stepwise CMD prevention program. In 37 participating general practices, all listed patients between 45 and 70 years old without CMD, hypertension or hypercholesterolemia were invited to participate in the prevention program. Patients were randomly allocated to an intervention group or a waiting list control group that was invited for the program after one year. To minimize the workload in the GP practices, both the intervention and the waiting list control group were enrolled gradually in different timeslots (intervention group 1 and 2 in April and June 2015 and control group 1 and 2 in April and June 2016). The first step was selecting eligible patients, who were then asked to complete a risk estimation score (RS) consisting of seven risk factors for CMD (age, gender, smoking status, body mass index (BMI), family history of type II diabetes mellitus and cardiovascular disease). Eligible patients received a personal invitation letter from their own GP to complete the RS online. All invitation letters included a short summary of the instruction in English, Turkish and Arab. All patients who did not respond within 2 weeks received a reminder with a paper version of the RS and a return envelope. Patients with a low score on the RS received (online) tailored lifestyle advice. Patients with a high score on the RS (increased risk patients) were advised to visit their GP for additional measurements to complete their risk profile, followed by a tailored lifestyle advice and/or treatment if indicated. Further details of the design of the INTEGRATE study are described elsewhere [26].

Study population

We implemented all the strategies during the follow-up phase of the trial, in which the waiting list control groups were invited for participation in the prevention program. The patients in the waiting list group were randomly assigned to a subgroup within the same practice, the 'strategy group' (exposed to a response enhancing strategy) or to the 'standard method group' (approached as described in the previous section).

Different strategies for increasing response were targeted at either the non-responders who did not respond to the online or paper RS (non-responders stage 1), the non-responders with an increased risk score on the RS who did not contact their GP (non-responders stage 2) or at both types of non-responders (stage 1 + 2).

In 29 of the 37 participating practices in the INTEGRATE study one or more response enhancing strategies was implemented, in 8 practices it was not possible to arrange a strategy within the set timeframe. The different strategies were allocated in consultation with the participating practices, guided by specific practice characteristics such as patient population (number of people of low SES and/or migrant status), the percentage of patients of whom the e-mail address or mobile phone number was known in the practice, the availability of support staff and the individual preferences of the GP or practice nurse.

Response enhancing strategies

Based on the literature and a survey among first phase non-responders we developed ten different response enhancing strategies. The background and implementation of these strategies, their timing, types of non-responders (stage 1, stage 2 or stage 1+2) and the number of practices and patients involved are described in table 1 and figure 1.

Figure 1 Stages of response and timing response enhancing strategies

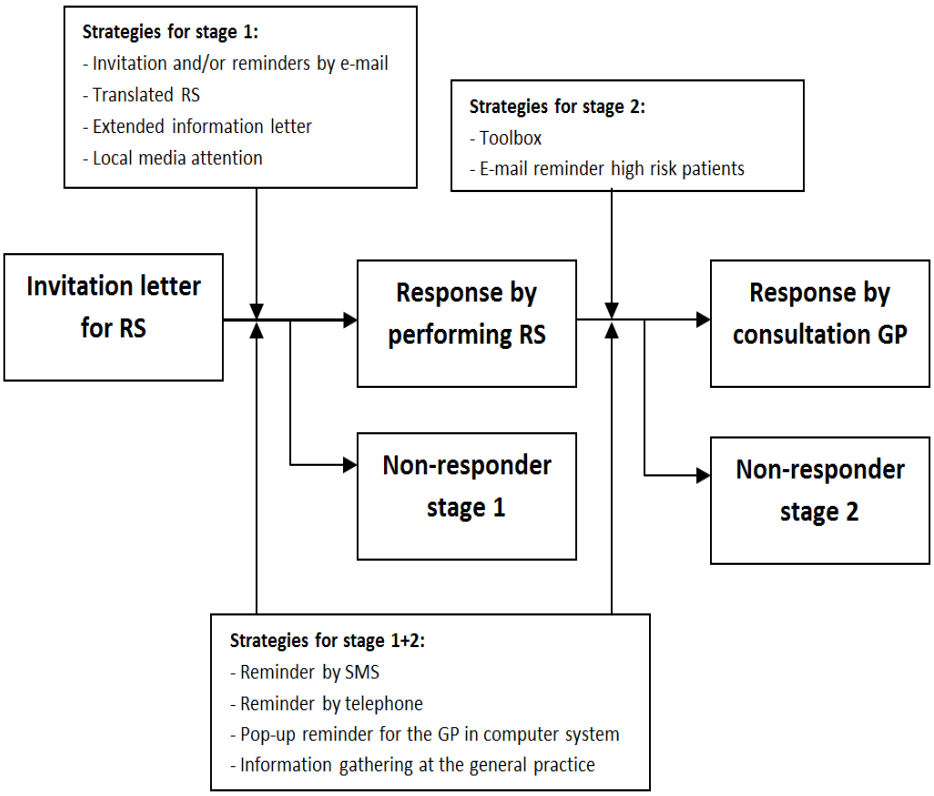

Table 1. Characteristics of response enhancing strategies

	Stage	Strategy group	Standard method group	Practices involved	Procedure
Standard method					Invitation letter for online RS by post, after 2 weeks reminder letter + paper version RS by post. A short recap in English, Turkish and Arab in both letters.
1. Invitation and/or reminders by e-mail	Stage 1	328 patients with known e-mail address	124 patients with known e-mail address	2	Group a (N=124): comparison group (standard method) Group b (N=105): invitation by post and a reminder by e-mail; Group c (N=117): invitation by e-mail and a reminder by post; Group d (N=106): invitation and reminder by e-mail.
2. Translated RS form	Stage 1	4,604 patients	N/A	10	Translated versions of the RS form in English, Turkish and Arab were added to the reminder letter.
3. Extended information letter	Stage 1	337 patients	337 patients	1	Extension of the information letter emphasizing the importance of participating and uncovering CMD and risk factors.
4. Local media attention	Stage 1	381 patients	232 patients	2	Articles about the prevention program and the importance of participating were placed in local newspapers.
5. Reminder by SMS	Stage 1+2	73 patients (73 with known mobile number)	194 patients	2	Four weeks after the paper invitation the GP sent SMS text reminders to patients with a known mobile number, inviting patients to fill in the RS and to make an appointment when this was advised.
6. Reminder by telephone	Stage 1+2	34 patients (random sample)	N/A	1	Practice assistant called the patients after 4 weeks to inform if the RS was filled in and to offer an appointment when the patients this was advised.
7. Pop-up reminder GP in computer system	Stage 1+2	341 patients	340 patients	2	A pop-up message would appear in the computer system of the GP if the patient file was opened. The GP could inform the patient about the RS during a regular consultation.
8. Information gathering at the general practice	Stage 1+2	545 patients	N/A	2	The GP practice organized an information gathering to help patients fill in the RS and/or to offer additional measures at the general practice. Invitation through invitation letter with recap translated in English, Turkish and Arab.
9. Self-management toolkits	Stage 2	174 patients with high score on RS	N/A	6	We offered patients a free toolkit containing a blood pressure device and fingerstick for cholesterol and Hba1c. Patients received online tailored lifestyle advice and were advised to consult their GP if increased blood pressure and/or elevated serum levels were measured.
10. E-mail reminder increased risk patients	Stage 2	112 patients with high score on RS	127 patients with high score on RS	4	We sent patients a reminder by e-mail to contact their GP for an appointment.

Outcome measures

The success rate was based on the response rates of either step of the program. The response to the RS was defined as the percentage of patients who completed the RS (either online or on paper) of the total number of patients who received an invitation to do so. Participation in stage 2 of the prevention program was defined as the number of patients with an increased risk score on the RS who visited the GP according to the case report forms, electronic medical record or self-reported in the study questionnaire.

To determine the feasibility of the response enhancing strategies we estimated the time investment and additional costs per strategy and expressed these in categories (low/average/high) for an average sized practice population for 1 full-time GP (n=2,095 patients). Time investment was low when the time spent was half or less than half the time compared to the standard method. Time investment was high when twice as much time or more was needed. Costs were low when the costs were half or less compared to the costs for the standard method, the costs were high when the costs were twice as high or more.

Statistical analysis

Descriptive analyses of all measurements were performed. Univariate multilevel logistic regression analyses were used to compare the differences in response rates between those exposed to the response enhancing strategies and those exposed to the standard method. Crude odds ratios and 95% confidence intervals were reported. Stata version 15 was used for all statistical analyses.

The response for the RS showed a 3% seasonal variation (June vs. April), most likely due to a lower response during the summer holiday. This difference was seen in the two intervention groups as well as in the waiting list control groups. We therefore adjusted the response rates in the groups invited in June by adding 3% to the response at the RS.

Results

All ten response enhancing strategies turned out to be feasible in the setting of the INTEGRATE study; 29 general practices implemented one or more strategies. Response rates for the RS in the standard method groups was on average 33%, ranging from 16% to 48% between practices. From all patients filling in the RS 38% turned out to be at increased risk, 38% of these patients visited the GP.

We sent a translated version of the RS (strategy 2) to 4604 patients; only 12 (0,3%) completed translated RSs were returned (2 in English, 7 in Turkish and 3 in Arab).

From only 73 of the 188 patients eligible to receive a reminder via SMS (strategy 5), mobile numbers were known. They received a SMS reminder 4 weeks after the invitation letter. Sixteen patients (22%) filled in the RS after receiving the SMS, whereas 11 patients from the standard method group (15%) spontaneously filled in the RS in these 4 weeks. Nine out of the sixteen patients who filled in the RS after is SMS had an increased risk. None of the patient who received an SMS showed up for a GP consultation.

Of the 34 patients who were scheduled for a reminder by telephone (strategy 6), 11 patients (32%) could not be reached by telephone after two attempts within office hours. Among those who could be reached, 13 patients (38%) completed the RS of whom 4 patients had an increased risk and reported to have already made an appointment with the GP. The remainder 10 patients (29%) indicated not to be interested in participating.

The two information gatherings (strategy 8) were scarcely attended: of the 545 invited patients only 3 patients showed up from the first practice and 2 patients at the meeting in the second practice (response rate of 0,9%).

Self-management toolkits (strategy 9) were offered for free to 174 patients at increased risk. 33 toolkits were ordered, 22 patients completed their risk profiles with self-executed measures, resulting in 6 patients at increased risk who were given the advice to visit their GP of whom 1 patient actually visited.

To determine the effectiveness of the other response enhancing strategies (strategy 1, 3,4,7 and 10) we compared the response rates of the RS (stage 1) and participation of stage 2 of the prevention program between the strategy groups and the standard method groups. The results of these analyses are shown in table 2.

We found a significant increase in the participation rate for stage 2 of the prevention program when the GP received a pop-up reminder when opening the patient's electronic medical record (strategy 7) (OR 4.63 [1.15-18.67]

Although invitations and reminders by e-mail (strategy 1) did show a positive trend in improving participation (OR 1.51 [0.92-2.46]), none of the implemented combinations of invitations and/or reminders by e-mail showed a significant increase in response amongst the non-responders at stage 1. However, we observed in practices who implemented strategy 1 that, independently of the invitation method, the response rate for the RS amongst patients with an e-mail address known to the GP practice was statistically significantly higher than amongst patients without a known e-mail address (49% vs. 32%, p=0.000, not shown in table), demonstrating that this variable is strongly associated with response.

Sending an e-mail reminder to increased risk patients (strategy 10) also had a positive, but not statistically significant, effect on the number of patients who consulted their GP (OR 1.46 [0.86-2.48]).

We found no effect of local media attention (strategy 4) on the response rates. Those who received an extended information letter (strategy 3) had a lower response rate to the RS and a

lower participation rate to stage 2 of the program, although this difference was not statistically significant (OR 0.79 [0.58-1.08]).

Table 3 shows an overview of the response enhancing strategies which we implemented during this study, with their target group, an estimation of the costs and time investment required and implementation challenges experienced in the participating practices. The time spent on the standard method was on average 10 hours per practice, with the costs involved estimated at € 750 per average sized practice. The required time for the different strategies ranged from 4 hours to 47 hours, the costs ranged from € 0 to € 2,025. More details about the actual time investment and the calculation of the costs can be found in Appendix 1. E-mail reminders and/or invitations are low in costs and require limited time investment, but do require computer skilled personnel and a substantial part of the patients whose e-mail address is known in the practice. All response enhancing strategies had their specific target population and implementation issues, making different strategies more suitable for different practices depending on practice characteristics and patient population. Therefore, the feasibility of the different strategies strongly depends on the circumstances and characteristics of the practice.

Table 2. Response rates strategy and standard method groups for response enhancing strategies

	Strategy group			Standard method group			Difference in response (OR with 95%CI)	
	Invited (n)	Response RS (%) *	Consultations GP (n (%)) **	Invited (n)	Response RS (%) *	Consultations GP (n (%)) **	Stage 1	Stage 2
1. Postal invitation+ Email reminder (b)	105	45%	N/A	124	48%	N/A	0.89 [0.53-1.50]	N/A
1. Email invitation + Postal reminder (c)	117	50%	N/A	124	48%	N/A	1.12 [0.68-1.86]	N/A
1. Email invitation + Email reminder (d)	106	58%	N/A	124	48%	N/A	1.49 [0.89-2.51]	N/A
3. Extended information letter	337	39%	N/A	337	45%	N/A	0.79 [0.58-1.08]	N/A
4. Local media attention	381	37%	N/A	232	38%	N/A	0.93 [0.67-1.31]	N/A
7. Pop-up reminder GP in computer system	341	37%	16 (36%)	338	33%	3 (10%)	1.22 [0.51-2.93]	4.63 [1.15-18.67]
10. E-mail reminder increased risk patients	124	N/A	57 (46%)	144	N/A	52 (36%)	N/A	1.51 [0.92-2.46]

*Response rates for RS shown are a corrected for a 3% lower response in groups invited in June

** number and percentage of patients with increased risk at RS that consulted GP

Abbreviations: RS= risk score

Table 3. Target population, costs, time investment and implementation issues of different response enhancing strategies.

Response enhancing strategy	Target population	Time *	Costs **	Implementation issues
Standard method	Total	Average	Average	Printing and folding invitation letters is time consuming
1. Invitation and/or reminders by e-mail	Young	Low	Low	E-mail address often unknown, computer skilled personnel necessary
2. Translated RS	Migrant	Average	High	Costly and time consuming when not targeted
3. Extended information letter	Total	Average	Average	Overload of information may provide opposite effect
4. Local media attention	Total	Average	Average	Willingness (local) media channels required
5. Reminder by SMS	Young	Average	Average	Mobile phone numbers sometimes unknown, computer skilled personnel necessary
6. Reminder by telephone	Total	High	Average	Motivated personnel necessary, unavailability of patients during office hours
7. Pop-up reminders GP computer system	Total	High	Average	Manually entering reminders is time consuming, motivated GP necessary, time consuming during consultation hours
8. Information gathering general practice	Low SES or migrant	Average	High	Motivated personnel necessary, targeted population difficult to reach
9. Self-management toolkits	Young	Average	High	Self-management skills patients necessary, preferably with feedback results to GP
10. E-mail reminder increased risk patients	Young	Average	Average	Feedback from online RS to GP necessary, computer skilled personal necessary

* Time investment for standard method for average sized general practice (n=2,095 patients) was 10 hours

Low: 5 hours or less, Average: 6-19 hours, High: 20 hours or more

** Costs investment for standard method for average sized general practice (n=2,095 patients) were €750

Low: €375 or less, Average: €376 to €1499, High: €1500 or more

Abbreviations: RS= risk score

Discussion

Main findings

In this study we evaluated different strategies to increase the participation rates in a selective prevention program for CMD in primary care. Using a pop-up reminder, integrated in the computer system of the GP, increased the participation to our prevention program significantly. We also found a positive trend in the response rate when using e-mail invitations and reminders, a method that requires little time investment and the costs. Translated materials, information gatherings at the practice, self-management toolkits, reminders by telephone, extended information letters, local media attention and SMS text reminders did not increase the response to our program.

Strengths and limitations

This is the first study to implement and evaluate different response enhancing strategies within the context of an RCT evaluating the effectiveness of a CMD prevention program. For most response enhancing strategies we were able to compare the effect of the intervention to a control group from the same practice. The design of the INTEGRATE study made it possible to develop different response enhancing strategies with input from the target population and implement the strategies in the same study population. One of the most important limitations of our study is that due to the many strategies tested, the number of patients in the strategy and standard method groups were small, which influenced the statistical power and therefore the robustness of the results. Nevertheless, the results provide a useful insight in the more and less effective strategies.

Comparison with current literature

The positive effect of face-to-face reminders by the GP is in line with the results of a meta-analysis of Cheong et al. [21], who found reminding physicians to invite patients for cardiovascular screening to be effective. The time investment for entering pop-ups in the computer system, however, is high so this method would be best suited for practices that work with a computer system that has an option to create pop-ups automatically. This method also requires that the GP is motivated to address the cardiovascular risk when a patient consults for different reasons.

To our best knowledge, this is the first study on the effect of reminders and invitations by e-mail on the response rates in prevention programs for CMD. This strategy can be easily implemented, the extra time investment and the costs are low. The different combinations of e-mail invitations and/or reminders for the RS that we implemented did not significantly increase response. Nevertheless, approaching patients by e-mail resulted in comparable response rates as the standard method, but at lower costs and with less time investment. A remarkable observation was that patients whose e-mail address was known in the GP practice,

were more likely to participate regardless the method of approaching. This might be explained by the health care consumption pattern of these patients. Those with a high health care utilization have more frequent contacts with their GP, which makes it more likely that their e-mail address is recorded. In addition, patients who have a better relationship with their GP might feel addressed more urgently when their GP sends them a personal invitation for a RS. In contrast, patients with a tendency to avoid health care have no regular contacts with their GP and may also not be inclined to fill in a RS.

Sending an additional reminder by e-mail to patients with an increased risk showed a positive trend on the response rate at stage 2 of the program. Both this additional reminder and the face-to-face reminders target patients who scored high on the RS, these patients showed to have an increased risk for CMD and also showed to be willing to enter the program by participating in stage 1. Nevertheless, on average only 1 in 3 patients with an increased risk visited their GP. These non-responders are an interesting target group for they could potentially benefit most from a prevention program.

The effectiveness of reminders by telephone was low in this study. This is in line with the non-response analysis we performed earlier, where 78% of the non-responders reported that they would not reconsider participation when approached by telephone [25]. Letter and telephone reminders showed significantly higher response rates in cancer screening programs [19,20] and prevention programs for CMD, some of them in a study population with a low SES [9,27,28]. It is a possibility that reminders by telephone are more effective when they can be targeted more specifically.

The effect of the extended information letter showed a negative effect on the response rate, although this effect was not statistically significant. It is possible that an information 'overload' decreased the motivation to participate. Previous studies showed heterogeneous results for extended educational material and public information campaigns [20,29]. The extended information letter that we used in our study was not personalized, a potentially stimulating factor that might be addressed more with a face-to-face reminder [5,15,30]

Translated materials and information gatherings, strategies specifically targeted at the migrant and/or low SES population, were unsuccessful even though the costs were high. These strategies cannot be recommended for other prevention programs.

Conclusions

Patients identified at increased CMD risk are the optimal target group for response enhancing strategies, this could be achieved with the installation of pop-ups in the GPs' computer systems to facilitate personal reminders. Invitation by e-mail for a prevention program is feasible at relatively low costs and time investment, further research to confirm these findings is

warranted. Finally, enhancing response in prevention programs for CMD is a difficult and complex process. There is no 'one size fits all' response enhancing protocol for all general practices, population and practice characteristics need to be carefully considered to select successful recruitment strategies.

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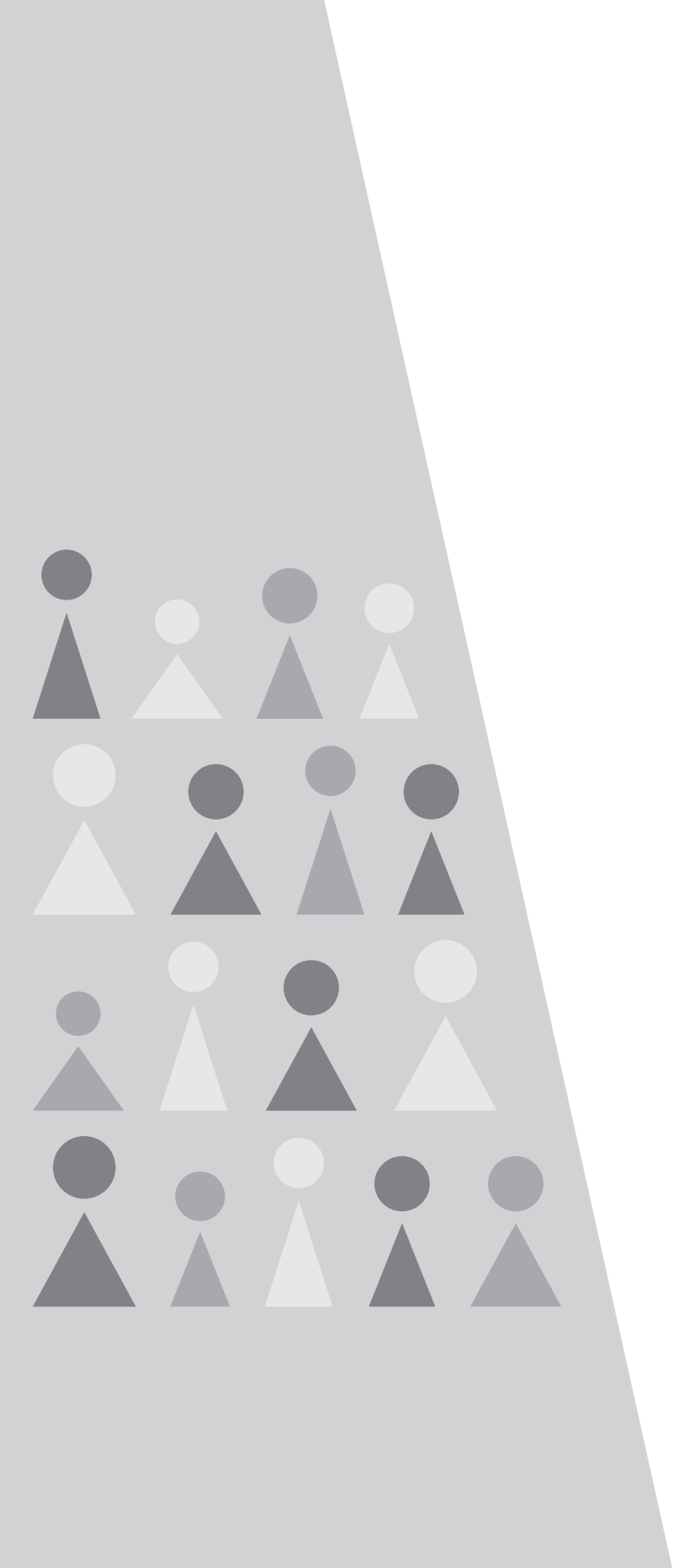
Appendix 1 Detailed overview of different response enhancing strategies

Response enhancing strategy	Time investment				Costs			
	Fixed	Variable	Total per practice *	Category	Fixed	Variable	Total per practice *	Category
Standard method	*Standard time = Writing + formatting + mailing letters +: **4 hours***	*Standard time = Printing + handling letters: **1 min p.p.***	10 hours	Average		*Standard costs: Printing materials and postal costs: **€ 2 p.p.***	€ 750	Average
1. Invitation and/or reminders by e-mail	Formatting e-mails and mailing: 4 hours		4 hours	Low			€ -	Low
2. Translated RS	Standard time	Standard time + Extra printing and handling translations: 1 min p.p.	16 hours	Average	Translation costs: € 500	Costs standard method + extra postal costs: € 1 p.p.	€ 1625	High
3. Extended information letter	Standard time + Formatting extra information letter: 2 hours	Standard time + Printing and handling extra letter: 1 min p.p.	18 hours	Average		Costs standard method + Printing and postal costs extra letter: € 0.50 p.p.	€ 1250	Average
4. Local media attention	Standard time + Formatting article, addressing editors: 3 hours	Standard time	13 hours	Average	Mostly free of charge	Costs standard method	€ 938	Average
5. Reminder by SMS	Standard time + Formatting and sending SMS: 3 hours	Standard time	13 hours	Average		Costs standard method + Costs SMS for bundle: €0.20 p.p.	€ 825	Average
6. Reminder by telephone	Standard time	Standard time + Time for calling: 5 min p.p.	41 hours	High		Costs standard method	€ 750	Average
7. Pop-up reminders GP in computer system	Standard time	Standard time + Entering pop-ups in system: 1 min p.p. + Addressing patients during consultation: 5 min p.p.	16 hours + 31 hours for GP	High		Costs standard method	€ 750	Average
8. Information gathering at the general practice	Standard time + Organization for gathering: 8 hours	Standard time	18 hours	Average		Costs standard method	€ 750	Average
9. Self-management toolkits	Standard time	Standard time + 10 min p.p. ordering a toolkit, time for mailing kits	13 hours**	Average		Costs standard method + € 75 p.p. (costs kit + shipping costs)	€ 2025	High
10. E-mail reminder increased risk patients	Standard time + Formatting emails and mailing: 2 hours	Standard time	12 hours	Average		Costs standard method	€ 750	Average

Abbreviations: p.p.= per patient, min= minute(s), RS= risk score, * Average practice size of 2,095 patient, approximately 375 patients eligible for prevention program, ** If 19% of patients with increased risk on RS order the box (17 patients



6

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 status[8] 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 Practitioners[9], 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[10-12], 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 ≥23% for men and ≥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.

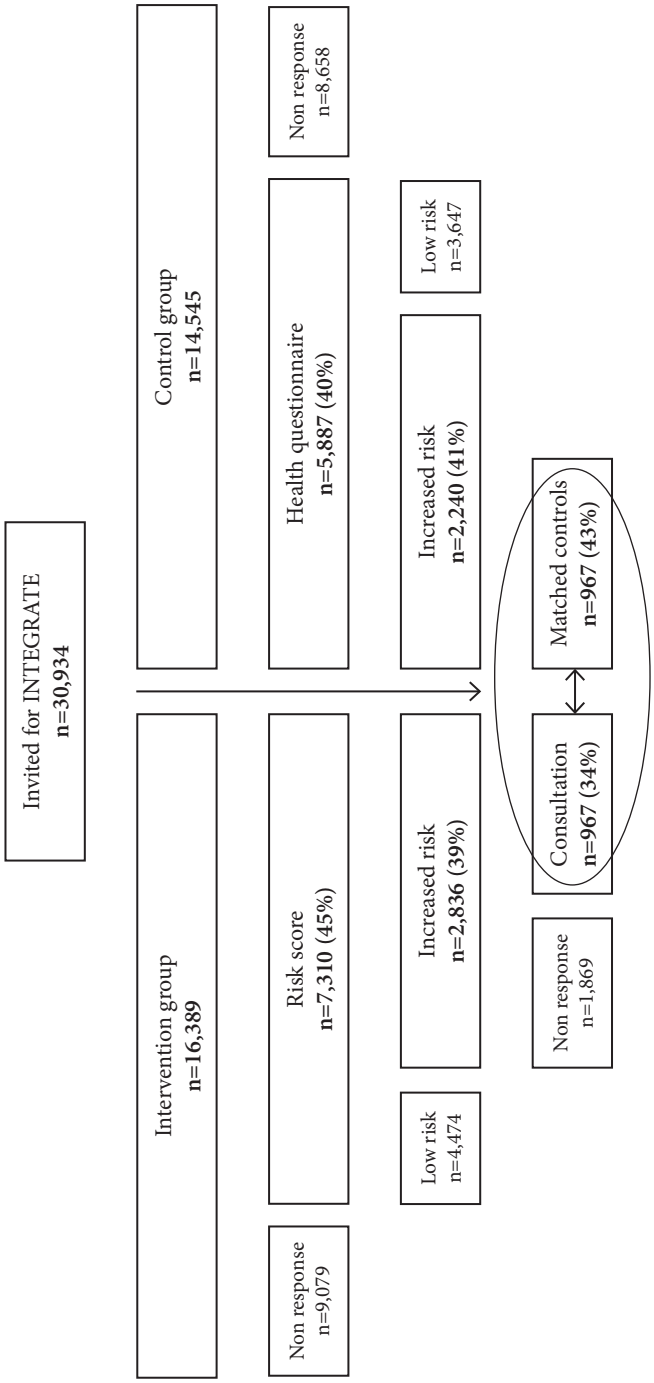

Figure 1 Flowchart of participants

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% 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.

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[18]) 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" country[21]

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/m^2; 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/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]
			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
			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]

† 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 sizes[23] 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 errors [28] 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 [29], 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 low [23], 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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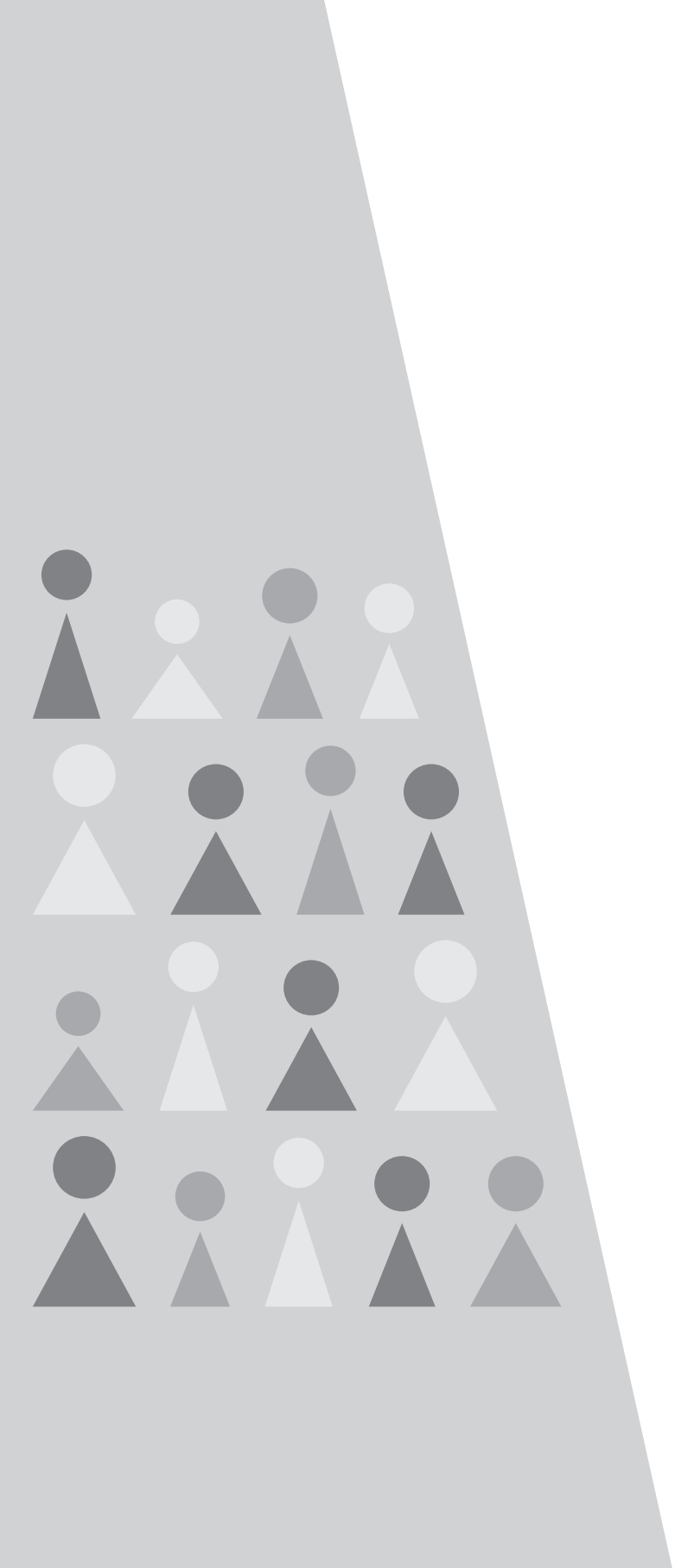

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The association between GP organizational factors and the effectiveness of a prevention program for cardiometabolic diseases: a prospective intervention study

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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 CMD [15] followed by individualized treatment was implemented in 37 participating general practices. Details about the study design are described elsewhere [16], 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 (≥23% for men and ≥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)

	BMI		Smoking		Systolic blood pressure		TC/HDL ratio	
N=967	% ↓ *	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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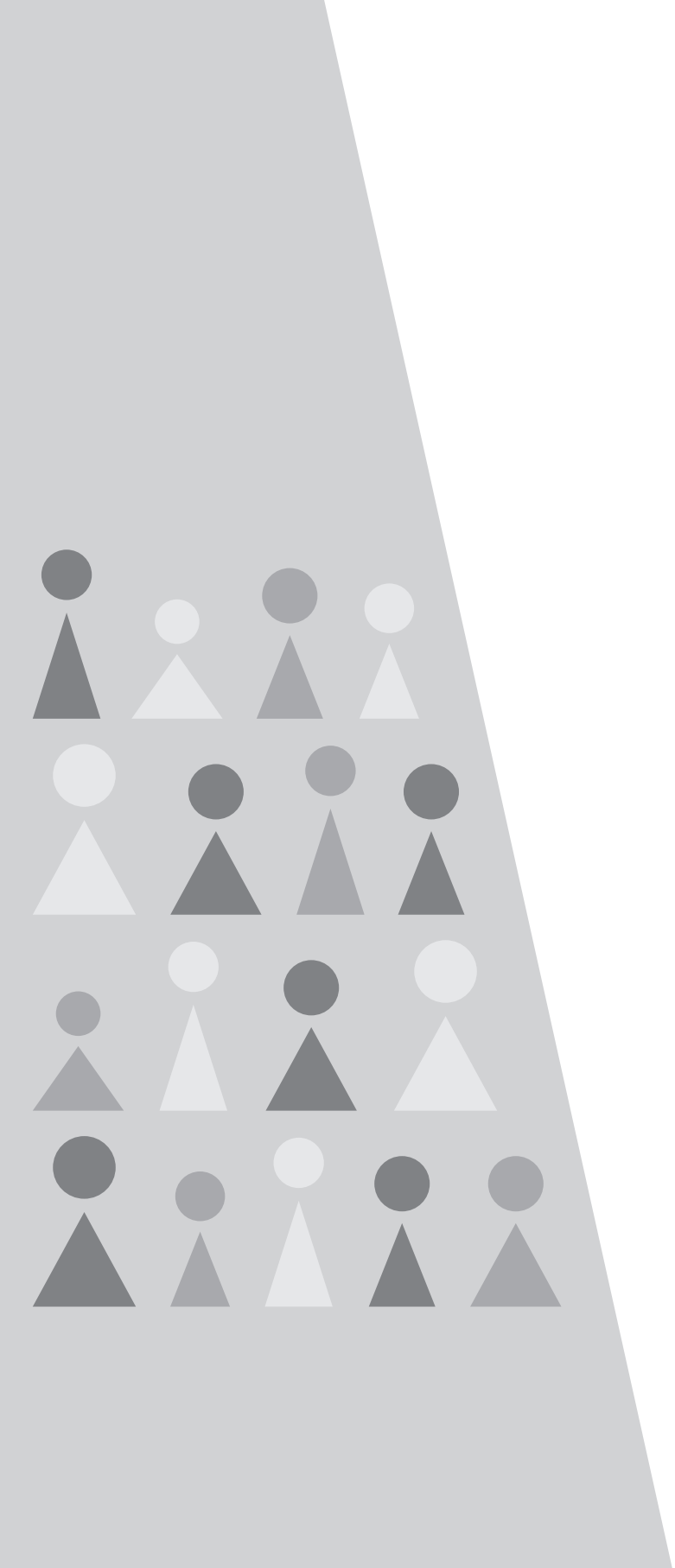

8

Lifestyle advice and willingness to change during a prevention program for cardiometabolic diseases in general practice

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Submitted, short report

Abstract

In this short report we describe the results of a study conducted as part of the INTEGRATE study, a cluster randomized controlled trial assessing the effectiveness of a stepwise cardio-metabolic disease prevention program in general practice. Patients aged 45-70 were invited to complete a risk score, in case of increased risk score followed by measurements at the practice, lifestyle advice and drug treatment when indicated. In this substudy we approached participating patients and GP's about the extent to which lifestyle advice was discussed and about their willingness to change lifestyle. The results show that lifestyle advices regarding obesity were given to only half of the obese patients. Only one third of the patients reported l to have received lifestyle advice about healthy diet and physical exercise. Participants who completed the entire CMD prevention program were not more frequently motivated to change their lifestyle than individuals from the control group.

Introduction

Cardiometabolic diseases (CMD), including cardiovascular disease (CVD), diabetes type 2 (DM2) and chronic kidney disease are the number one cause of death globally [1]. The leading factor in CMD development is an unhealthy lifestyle, including physical inactivity, smoking and an unhealthy diet. Preventive measures are indicated and necessary to reduce the growing disease burden. The use of selective prevention programs, aimed at identifying asymptomatic individuals at high risk for developing CMD and initiate lifestyle changes and treatment when indicated, could be an efficient method for preventing CMD [2].

General practice is probably the best suitable setting for a selective CMD prevention program, since GPs are easily accessible health care providers, usually have a longstanding relation with their patients and are aware of the patients' medical history and personal and social context. For instance, implementation through general practice increased attendance rates of cervical cancer screening and flue vaccination in the Netherlands [3,4]. On the other hand, GPs often do not prioritize prevention and lifestyle is seldom a topic of conversation during consultations [5,6]. Previous studies have also shown that GPs and practice nurses struggle with applying motivational interviewing techniques and giving tailored lifestyle advice during everyday practice [7,8]. Risk communication and lifestyle advice during consultations are indispensable factors to motivate patients to change their lifestyle. Up to now, however, it is unclear how often lifestyle advice is given, and how lifestyle advice is perceived by patients within the context of CMD prevention in general practice. In addition, willingness to change is conditional for lifestyle improvement; without motivation, participation in a lifestyle program would be meaningless. So far little is known about the effects of CMD prevention programs on the motivation of participants to change their lifestyle.

In this study we aimed to assess how often indicated lifestyle advice is given in general practice during a selective CMD prevention program, how it is perceived by patients, and if participants in a selective CMD program are better motivated to change their lifestyle.

Methods

Design and participants

This study was performed as part of a pragmatic randomized controlled trial conducted from 2014 to 2017 in the Netherlands, the INTEGRATE study (Dutch trial Register number NTR4277). In the INTEGRATE study a stepwise CMD prevention program was implemented in 37 participating general practices. Details about the study design are described elsewhere [9,10]. Enlisted patients aged between 45 and 70 years without known CMD, hypertension or hypercholesterolemia according to their electronic health record were eligible for participation in the CMD prevention program.

Intervention

In the INTEGRATE study all eligible patients were randomly allocated within each practice to the intervention group or the control group. Patients in the control group received care a usual. Patients in the intervention group received a personal letter from their GP inviting them to assess their risk for CMD by completing a risk score, the first step of the CMD prevention program. The risk score contained 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. In case of an increased risk for CMD, patients were advised to visit the practice to complete the second step of the program. At the practice, additional measurements were taken by the GP or practice nurse, including blood pressure, cholesterol and fasting glucose levels. All participants who attended the practice received tailored lifestyle advice and drug treatment when indicated.

In this substudy we assessed the frequency, perception and impact of lifestyle advice as given to participants in the INTEGRATE study.

Data collection

During the INTEGRATE study patients in the control group completed a general health questionnaire, including the risk score items without further explanation. All patients in the intervention group who finished the online risk score received additional questionnaires. The GP or practice nurse who performed the consultation also filled in a case report form with information about the lifestyle advices discussed. For patients with an increased risk who attended the practice we collected data on newly diagnosed ICPC-coded CMD during 1-year follow- up.

Outcome and measurements

The percentage of lifestyle advices discussed during consultation with participants was reported by the health care professionals through a question with pre-categorized answers (yes/no) including lifestyle advice on smoking cessation, physical exercise, (over)weight management advice and advice on healthy diet. Only indicated lifestyle advices were considered, meaning we reported on smoking cessation advice only in case the patient smoked. We reported on advice on physical exercise, (over)weight management and healthy diet in case the patient had a BMI over 25 kg/m^2 or increased waist circumference (≥94cm for men and ≥80cm for women). Lifestyle advices discussed during consultation, as perceived by the patient, was reported as the number of patients with a positive answer to the question “Did your GP or practice nurse give you advice about (e.g. smoking cessation)?”. Willingness to change lifestyle was defined as the number of participants who indicated that they wanted to improve lifestyle regarding to smoking, weight, exercise or diet. These questions were also formulated as yes-no questions, e.g. “Do you want to stop smoking?”.

A diagnosis of hypertension, hypercholesterolemia or diabetes mellitus was defined by recording of the corresponding ICPC code in the electronic medical record during one year follow up (K86:uncomplicated hypertension, K87:hypertension with secondary organ damage, T90:diabetes mellitus, T93:lipid metabolism disorder).

Analyses

For the analyses we defined the intervention group as participants who visited the general practice for additional measurements, as confirmed by case report forms, electronic medical records or by self-report. Risk scores for participants in the control group were calculated with data from the health questionnaire. Participants of the intervention group were individually matched to participants from the control group with an increased risk (according to their risk score) based on sex, age (in 5-year categories), smoking status and BMI (<25 or ≥25).

We used descriptive measures to report on lifestyle advices given and received. Logistic regression analysis was used to determine the effect of participation in the selective CMD prevention program on the willingness to change lifestyle compared to the control group, adjusted for age, sex and clustering within practices. Odds ratios and 95% confidence intervals were reported. All statistical analyses were performed using STATA 15.0.

Results

From the 16,389 patients who were allocated to the intervention group and who were invited for the first step of the prevention program 7,313 (45%) completed the risk score. A number of 2,240 participants had an increased risk and were invited for a consultation at the practice and additional measurements. In total 967 participants (43% of those invited for a consultation) visited the practice for additional risk profiling and were individually matched to participants in the control group. The mean age of the participants was 63 years and 55% was female. A flowchart of the trial and the baseline characteristics can be found elsewhere [10].

A number of 664 case report forms were completed after consultation by the GP or the practice nurse. In total 519 participants from the intervention group who visited the practice (54%) filled out the additional questionnaire. The characteristics of the responders to the additional questionnaire were comparable to the non-responders in terms of age, gender, smoking status, family history, BMI and waist circumference (data not shown). For the analyses of willingness to change we compared the answers of these 519 patients from the intervention group with matched individuals from the control group. For the analyses of lifestyle advices we used data from the 319 patients from the intervention group who both filled out the additional questionnaire and also had a case report form completed by the GP or practice nurse (33% of total number in intervention group).

Advice on smoking cessation was given to 87% of the smokers (table 1). Advices on physical exercise, (over)weight management advice and advice on healthy diet was given in about half of the participants with an increased BMI or waist circumference.

In total 76% of the smokers who received smoking cessation advice during the consultation actually recollected this advice. Almost two third of the participants who received lifestyle advices about (over)weight management reported to recall this advice. Lifestyle advices about physical exercise and healthier diet were remembered less well, only one third of the participants recalled to have discussed those.

Table 1 Lifestyle advice given as reported by the GP and reported by the patient

	Advice given by GP, reported by GP		**Advice given by GP, self-reported**	
	N	**%**	**N**	**%**
Smoker				
Smoking cessation advice	33/38	87%	25/33	76%
BMI over 25 kg/m^2				
Advice on physical exercise	84/153	55%	30/84	36%
(Over)weight management advice	76/153	50%	50/76	66%
Advice on healthy diet	99/153	65%	37/99	37%
Waist circumference increased				
Advice on physical exercise	117/258	45%	39/117	33%
(Over)weight management advice	86/258	33%	52/86	60%
Advice on healthy diet	151/258	59%	52/151	34%

* BMI= body mass index, GP=general practitione

Amongst the different subgroups with lifestyle related risk factors in the intervention group the willingness to change was not different from participants in the control group for the respective lifestyle adjustments (table 2). A subgroup analysis amongst patients who were newly diagnosed with hypertension, hypercholesterolemia or diabetes mellitus showed the same outcomes for willingness to change.

Table 2 Willingness to change lifestyle in intervention and control group

	Intervention group			Control group			
	yes	no	%	yes	no	%	OR [95%CI] *
Total group of patients							
Motivated for smoking cessation	35	24	59%	43	16	73%	0.56 [0.25-1.25]
Motivated for losing weight	289	156	65%	280	189	60%	1.22 [0.93-1.61]
Motivated to exercise more	185	267	41%	179	290	38%	1.11 [0.85-1.45]
Motivated for healthier diet	161	280	37%	146	320	31%	1.26 [0.95-1.67]
Patients with new diagnosis**							
Motivated for smoking cessation	14	6	70%	17	5	77%	0.61 [0.14-2.63]
Motivated for losing weight	70	34	67%	78	35	69%	0.86 [0.47-1.57]
Motivated to exercise more	52	55	49%	43	70	38%	1.54 [0.89-2.68]
Motivated for healthier diet	43	59	42%	48	65	42%	0.96 [0.55-1.68]

* corrected for age, sex and clustering at practice level

** ICPC-codes: K86: uncomplicated hypertension, K87: hypertension with secondary organ damage, T90: diabetes mellitus, T93: lipid metabolism disorder.

Discussion

In this study we showed that lifestyle advice is not yet optimally provided within the framework of a selective CMD prevention program in general practice. Although almost all smokers do receive smoking cessation advice, lifestyle advices regarding body weight are given to only half of the participants. On top of that, patients do not always remember that life style change was discusses during the consultation: in only half of the cases participants recalled to have received lifestyle advice concerning healthy diet and physical exercise. Furthermore, the results of this study show that participants who completed the CMD prevention program including a CMD risk score, additional measurements and a consultation at the practice, are not more frequently motivated to change their lifestyle than individuals from the control group.

This study is amongst the firsts to report on implementation factors of CMD prevention programs supported with quantitative data. Furthermore, this is one of the sparse studies that have focused on the effect of a CMD prevention program on willingness to change lifestyle. Because of the pragmatic design of the study the results are representative for a real life setting and are therefore more realistic than results coming from studies that were performed under strictly controlled conditions.

In this study we measured the lifestyle advices given in the general practices and whether the patients could recall these advices. Although there is a possibility this was also influenced by the quality of the given advices and the skills of the GPs and practice nurses, we were not

able to take this variation into account in this study. Another limitation of this substudy is the amount of patients we could include in the analyses, a larger sample could have increased the validity of the results.

Although screening programs for CMD have a positive effect on individual cholesterol levels and blood pressure [11,12], little to no effect is achieved on lifestyle change in a real life setting [12,13]. This could be explained by many factors related to the participants, the quality of the program, or implementational factors associated with the health care professionals. The results of this study show that participation in the CMD prevention program was not able to increase motivation to change lifestyle. In an earlier study we showed that risk perception amongst patients with an increased risk is inadequate, for they categorically estimate their own risk as being low [14]. Earlier research has showed that lifestyle advice given in general practice is often incomplete and untailored [7,8]. This, added up with our finding that GPs and practice nurses often do not give the lifestyle advice indicated, could argue for more complete and tailored risk communication and lifestyle advice in general practice. But surprisingly, earlier research has showed that risk perception and willingness to change lifestyle are not strongly associated [15], based on trials demonstrating that optimizing risk communication does not increase motivation for lifestyle change [16,17]. Probably this association is more complex. Although information and communication play a part in risk perception it, it is mostly determined by other factors such as emotions, culture and social environment [18]. So if we really want to accomplish change in lifestyle we have to involve these contextual factors in future interventions. Creating a social environment that makes healthy choices easier and more accessible might nudge individuals in the right direction. This means we should strive for a broader approach to prevent CMD Primary care needs to be supported by other key sectors/professionals in fighting this battle.

Conclusion

Participation in a selective CMD prevention program does not increase willingness to change lifestyle. Communication regarding lifestyle advice in general practice could be more optimal and complete. However, since it is known that optimized risk communication alone is not sufficient to increase willingness to change, a broader approach to prevent CMD would be desirable.

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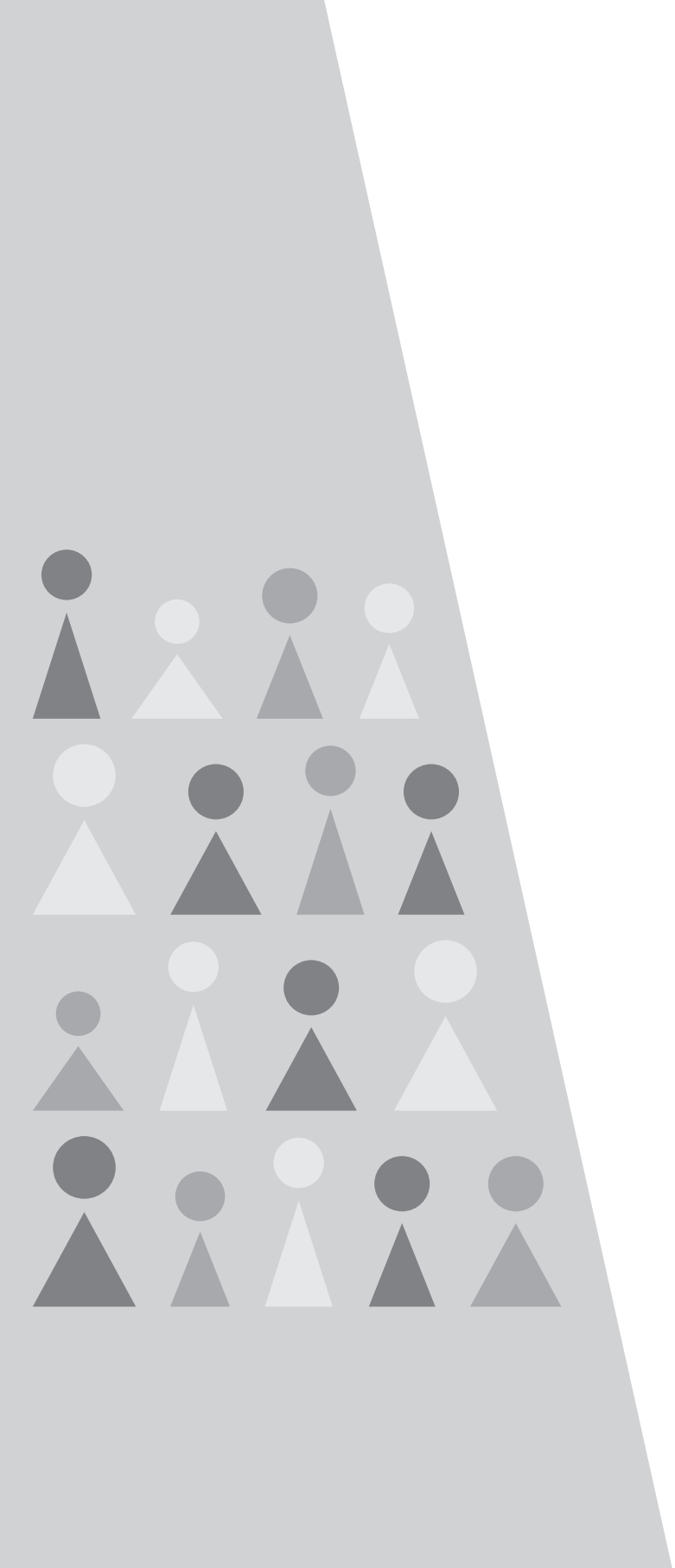

9

General discussion

Main findings

The objective of the INTEGRATE study was to contribute to the scientific knowledge about the programmatic cardiometabolic diseases (CMD) prevention in general practice. The twinned thesis by Stol focuses on the effectiveness and cost-effectiveness of the program. This thesis aimed to evaluate a selective CMD prevention program in primary care (the 'Prevention Consultation') by explicating the different aspects based on the RE-AIM model, focussing on the reach, effectiveness and implementation of the program. Using the results of the INTEGRATE study, we started by composing an overview of characteristics and motives of non-responders at the different stages of the prevention program. This knowledge was then used for the development of strategies to enhance the response to both stages of the program. Furthermore, we determined the effectiveness of the selective CMD prevention program with a special focus on practice organizational factors, lifestyle advices given in general practice and willingness to change lifestyle. In this paragraph the main findings of the chapters are summarized and put into the context of the current literature.

Characteristics and motives of non-responders

Main findings

The willingness to participate in a CMD prevention program amongst non-responders of stage 1 of the program (completing the risk score) was relatively high (chapter 3). The most reported reason for non-response is pragmatic; non-responders either forget it or they can't find the time to complete the risk score. This fits with the finding that the majority of the non-responders is willing to reconsider participation if a different invitation strategy would be used. We used the input from non-responders in the first phase as described in chapter 3 to further develop response enhancing strategies, which we implemented in the next phase of the INTEGRATE study (see chapter 5).

Non-response at both stages of the CMD prevention program, completing the risk score (stage 1) and visiting the GP with a high risk (stage 2), was not equally distributed amongst different demographic and socio economic groups (chapter 4). This inequality causes underrepresentation of socially vulnerable groups amongst the participants of the prevention program, meaning relatively less individuals with a low socio economic status and/or an immigration background are included in the prevention program. In chapter 4 we also described that the most reported reason for non-response at stage 2 of the program (the GP consultation) is expecting to have a low risk for CMD. This indicates that risk perception is inadequate, even though all individuals in this stage were informed about their increased risk and they were all advised to take further actions.

Interpretation

Willingness amongst non-responders and domination of practical reasons for refraining from prevention programs for CMD has been demonstrated in earlier research [1]. This indicates potency for higher response rates when using different invitation strategies. Furthermore, response enhancing strategies have been demonstrated successful for other prevention programs in the past [2,3].

The study described in chapter 4 shows underrepresentation of socially vulnerable groups amongst the participants of the CMD prevention program. This effect is worrisome, especially because is it known that exactly those groups have the highest risk for CMD [4,5]. This might further widen the health gap between low and high socio economic groups, an undesirable side effect of the program. Given this knowledge it would be interesting to explore if different methods of inviting individuals would have a positive influence on the response rates of socially vulnerable groups, particularly because culturally adapted invitation methods applied in specific settings have shown to be successful in the past [6]. We evaluated response enhancing strategies aimed at specific subgroups within the population in chapter 5.

The mismatch in risk perception shown in chapter 4 is in line with the results of our study about risk perception, described in the twinned thesis and it is also consistent with earlier studies regarding risk perception [7,8]. This suggests that current risk communication is insufficient in conveying the level of risk and the severity of the risk from a health professional perspective to the patient.

Response enhancing strategies

Main findings

In the study described in chapter 5 we evaluated different response enhancing strategies, developed on the basis of input from non-responders described in chapter 3 and previous studies. The results of this study show that all implemented strategies are feasible but their effect on the response rates seems to be limited. A role may still be set for inviting patients by email, for this method ensures a large reduction in costs and time investment. Another effective strategy to explore further is letting GPs invite patients face to face during consultation hours, as this enhanced response rates in the sample in which we tested it. Furthermore, the strategies that were specifically designed to increase response in socially vulnerable groups, such as translation of risk score questionnaires and organizing information gatherings at the general practice, proved not to be effective.

Interpretation

Our findings are in line with the results of an earlier meta-analysis by Cheong et al. [9], that also showed a positive effect in the uptake of screening for cardiovascular disease when physicians

received a computer based reminder during contact with eligible patients. This method requires motivation and time investment of the GP, who would have to find the time to address cardiovascular risk when a patient consults for a different reason. We found no positive effect of telephone reminders, a strategy that was demonstrated successful in other studies in the past [6,10–12]. Our result is in line with the non-response analysis we described in chapter 3, where 78% of the non-responders reported that they would not reconsider participation when approached by telephone.

The strategies targeting socially vulnerable groups were time consuming and costly, and in addition the effect of these strategies was disappointing. We would therefore not recommend translation of risk score questionnaires and organizing information gatherings at the general practice in future programs.

Effectiveness the prevention program, impact of practice organization and delivery of lifestyle advice

Main findings

The implementation of the CMD prevention program in general practice is feasible and effective in short term follow-up (chapter 6). Comparing the intervention with the control group after 1 year of follow up shows a statistically significant lower systolic blood pressure and more favorable cholesterol ratio. Although waist circumference significantly decreased in the intervention group, no changes were found for the other behavioral risk factors such as smoking and BMI.

In the study described in chapter 7 we focused on the relationship between short term effectiveness of the CMD prevention program and differences in practice organization and available preventive services between the participating practices. The results of this analysis shows practice organization characteristics and available preventive services are not associated with effectiveness of the CMD prevention program. A possible explanation for this finding is the effectiveness of the protocolized pharmaceutical treatment and only a limited additional contribution of lifestyle programs to the effects on individual risk factors.

Fidelity with lifestyle advice during the program shows to be only modest: GPs and practice nurses give smoking cessation advice adequately, but lifestyle advice on obesity is discussed in half of the cases and about two-third of the patients cannot recall the lifestyle advises given regarding healthy diet and physical exercise (chapter 8). In chapter 8 we also describe that after completing the prevention program, the participants from the intervention group were not more willing to change their lifestyle than the individuals in the control group.

Interpretation

These positive effects of the CMD prevention programs on short term outcomes have been demonstrated in earlier studies with improvements on CVD risk profiles [13–15]. The effect on lifestyle after one year however was limited, as is also supported by earlier research [16–19].

The suboptimal delivery of lifestyle advice in the general practice is in line with earlier research, showing that lifestyle advices given in general practice are a) often not well tailored, b) are limited to one subject instead of multiple factors and c) are often discussed without the aid of motivational interviewing techniques [20,21]. This indicates that there is room for improvement in communicating lifestyle advice in general practice.

Participation in the CMD prevention program had shown to have no effect on willingness to change lifestyle. A low motivation to tackle unhealthy lifestyle habits is therefore likely to be an important factor in the disappointing results in lifestyle change found during the INTEGRATE study. This again underlines how difficult it is to change unhealthy behavior.

Methodologic considerations

The INTEGRATE study was set up as a pragmatic trial in daily primary care practice rather than a clinical trial with preset optimal experimental conditions. As a consequence, there are a number of methodologic issues concerning this design that need to be taken into account when interpreting the results.

Natural response

Within this design we were dependent upon the willingness of individuals to participate. The acceptance of the natural course of response resulted in a selected group of patients completing all the steps of the program. We tried to correct for this selective response as good as possible by matching the group participants to individuals from the control group based on individual risk factors for CMD.

Another consequence of the natural course of implementation was a suboptimal response rate. We strived to make the responses reflect the daily clinical practice as much as possible, thereby creating a realistic image of the potential reach of the CMD prevention program. It was a deliberate choice not to increase participation rates by for instance approaching eligible individuals by telephone, for the implementation of this strategy would have been problematic in a real life setting. As a consequence of this pragmatic approach we may not have reached the highest uptake rates possible, and the effects and range of the prevention program may not have reached its full potential. This makes it harder to compare our response rates to those of other CMD prevention programs implemented under more favourable conditions. It does however make it easier to translate the results of our study to real life conditions.

Generalizability

We included a broad variety of general practices in the INTEGRATE study with a good representation of both urban and rural environment [22]. The participating practices were relatively less often single-handed and more often group practices when compared to the reference practices from Nivel Primary Care Database (2015). On the other hand, the distribution of practice types amongst our participants matches with the current trend of decreasing single-handed practices and the increasing group practices [23]. Furthermore, included practices were better organized regarding chronic disease management compared to reference practices and were motivated for performing CMD prevention [22]. This 'frontrunner' status of participating practices could have led to an overestimation of the effect of the intervention, suggesting that effectiveness and cost-effectiveness of the prevention program may be lower during a broader implementation among less well organized practices.

Control group

Although we tried to create a control group without contamination, several matters could have influenced the care-as-usual given by the control group. First, patients in the control group were informed about the research and filled out a health questionnaire at baseline. Filling out the health questionnaire could have increased awareness of lifestyle and possibly influenced behavior (Hawthorne effect). Secondly, the staff from the participating practices was involved with activities related to the prevention program, this could have also improved the CMD care and preventive activities in the control group. Both these matters would have led to a healthier control group, thereby underestimating the effectiveness of the program.

Evaluation using the RE-AIM model

To reach a general conclusion about the evaluation of the 'Prevention Consultation', we chose to evaluate the results of the INTEGRATE study within the framework of RE-AIM [24].

Reach

The reach of the CMD prevention program was suboptimal with participations rates of 41% resp. 33% to the two different steps of the program. This means that a considerable number of individuals did not respond to the initial invitation to participate, and that a substantial part of the individuals with an increased risk score ignored the advice to visit the GP. Furthermore, the uptake showed an underrepresentation of socially vulnerable groups who suffer a relative high disease burden. Response enhancing strategies were not able to boost these participation rates, even when strategies were tailored for socially vulnerable groups. Also, the cost-effectiveness analyses which are included in the twinned thesis showed that optimizing response rates in

our study would not have resulted in cost-effectiveness of the CMD prevention program, due to relatively high intervention costs. This makes further attempts to optimize the reach of this prevention program futile.

Effectiveness

The selective CMD prevention program was effective in terms of short term outcomes, with a positive effect on systolic blood pressure and cholesterol level. When implementing a CMD prevention program, effective treatment should be available. Use of antihypertensive and cholesterol lowering drugs is known to be effective, lifestyle adjustment also has an important role in treatment of risk factors for CMD. However, the program showed little to no effect on lifestyle change. As discussed in the thesis of Stol the program is not cost effective in terms of long term outcomes.

Adoption

The 'Prevention Consultation' is not yet implemented countrywide in the Netherlands, so adoption so far solely depends on initiatives of individual practices and practices involved in pilot studies. In 2014 approximately 30% of the Dutch GPs had implemented the CMD prevention program in their practice [25]. This study had no specific focus on determining adoption of the prevention program, however we experienced recruitment for practices to participate in our study to be very difficult. The overall attitude toward a CMD prevention program amongst GPs was quite sceptic due to a lack of scientific proof of effectiveness and missing structural financing.

Implementation

Because of the pragmatic nature of the INTEGRATE study, the described results concerning the reach and effectiveness of the program have taken many implementation factors into account and are therefore for a large part already representative for a real life setting. We described that general practices with extensive lifestyle related services at their disposal are not able to deliver a more effective prevention program than practices with less of these opportunities. This means that we have no starting point to optimize lifestyle programs at this point. Furthermore, we have shown that GPs and practice nurses struggle with delivering the indicated lifestyle advice at the appropriate moment, this could be a challenging issue during a broader implementation.

Maintenance

The 'Prevention consultation' advices a 5-year cycle of repeat, which is in line with the European guidelines for cardiovascular disease prevention [26]. Within the context of this study we cannot make any statements about this term.

Conclusion

After evaluation according to the RE-AIM framework, with a focus on reach and effectiveness, we can conclude that broad implementation of the 'Prevention Consultation' in the Netherlands cannot be advised. Further research to determine the optimal methods for adoption, implementation and maintenance of this program is therefore not warranted.

Implications for prevention programs

Although this CMD prevention program has not been found to be effective, there are lessons to be learned for other prevention programs.

Inequalities in uptake of preventive care

Lower uptake of prevention programs by socially vulnerable groups, including people with a low socio-economic status and/or an immigration background, is a well-known phenomenon in prevention programs [27]. Besides possible language barriers and lack of financial and logistic support, there are several explanations for a lower uptake,. One important factor is health literacy, as stated by the WHO: "*People cannot achieve their fullest health potential unless they are able to take control of those things which determine their health*" [28]. Health literacy can be defined as "people's knowledge, motivation and competences to access, understand, appraise and apply health information in order to make judgements and take decisions in everyday life concerning health care, disease prevention and health promotion to maintain or improve quality of life during the life course" [29]. Every 3 to 4 people out of 10 in the Netherlands have inadequate or limited health literacy levels [30]. This should be taken into account during the development and implementation of future prevention programs. Possible measures could be adapting information and procedures to be more simple, transparent and accessible and educating healthcare professionals delivering the program about how to support people with health literacy problems [28,31].

Another important factor for lower uptakes of preventive services by socially vulnerable groups is their lower prioritization of prevention. People from socially vulnerable groups have a higher exposure to challenges in other life domains, including repayment of debts, unfavorable housing and working conditions or social isolation. This fits the well-known pyramid of Maslow, describing a ´hierarchy of needs´, where basic physiologic needs are prioritized and people will only strive to fulfil higher needs when the basic needs of survival are fulfilled [32]. Differences in the priority given to daily-life needs are known to play are role in for instance healthy food choices and fall risk prevention [33,34]. So when trying to involve socially vulnerable groups in health prevention programs we should focus on tackling problems in more essential life domains first or trying to combine efforts with a more integrated approach of support.

Invitation strategies for prevention programs

Reaching and involving the complete target population in prevention programs will always be a challenge, even with more consideration for socially vulnerable groups. Earlies studies evaluating preliminary versions of the 'Prevention Consultation' achieved higher uptakes, for instance with the aid of telephonic invitations and pre-scheduled appointments [10–12]. In our study we choose to only test invitation strategies that would be suitable for large scale implementation regarding to time investment and logistic feasibility. Nonetheless, these strategies might be useful for other prevention programs.

An invitation strategy that showed promising results in our study was invitation by e-mail. This method required little time investment and the costs were low. With an incredibly high and still growing amount of Dutch people with access to the internet (98% of all households [35]) and a mobile device with internet access (89% of all adults [35]), spreading invitations and assessments by post seems obsolete. Of course with the right considerations concerning data protection, digitalizing invitations for prevention programs has the potency to benefit cost-effectiveness.
The response enhancing strategies we tested targeting people with limited health literacy or a language barrier were not successful, even though the time investment and costs were high, especially for the translation of the risk scores questionnaire and telephone reminders. For the 'Prevention Consultation' only 4% of the target population nationwide would be individuals with an non-western immigration background [36], of which a considerable part is probably able to read Dutch of would be able to have someone translate it for him or her. The question is if all extra costs of response enhancing strategies outweigh their benefits. There is no clear cut answer for this question, but this will have to be taken into consideration during the implementation of future prevention programs, thereby carefully weighing the composition of the target population and the nature of the program.

Prevention of CMD in future

Based on the findings described in this thesis, we conclude that selective CMD prevention programs should not be implemented in primary care on a largescale. But what are the alternative options to achieve CMD prevention in future? After reading this chapter so far it might look like it's an impossible task to motivate people to adopt a healthy lifestyle. But looking at CMD prevention from an optimistic perspective, following Edison' [a], we see a growing awareness of the importance of prevention and promotion of a heathy lifestyle amongst medical and para-medical professionals, reflected in the large array of preventive services that are offered

[a] *"The doctor of the future will give no medicine, but will interest his patient in the care of the human frame, in diet and in the cause and prevention of disease."* Thomas Edison, 1903

nowadays. Prevention of CMD is and will still be of great importance, even though we concluded that a programmatic approach of selective prevention of CMD in primary care is not (cost)effective. It is however vital to identify alternative methods for achieving this goal.

The role of primary care in preventing CMD

The guideline ´Prevention Consultation´ was originally developed to anticipate the growing disease burden of CMD and as a tool to be used in the consulting room when patients came with questions about their cardiometabolic risk. These issues are still relevant in clinical practice, since patients with risk factors for CMD will still visit their GP. In some cases patients will address this topic by themselves and in other cases the GP will find it relevant to bring it up. This method is defined as opportunistic screening at which screening and risk profiling for CMD occur at hoc in a primary care setting for selected patients only, and not in a programmatic way. Earlier research has shown that this so called ' opportunistic screening' is less costly than applying an active programmatic approach [37]. In this type of screening GPs will continue to play a major role and the appropriateness and importance of the GPs' involvement in opportunistic prevention is endorsed by the results of the INTEGRATE study. In chapter 3 of this thesis we showed that non-responders were most likely to reconsider participation in a CMD prevention program when their GP would invite them face to face. A face to face reminder from the GP during consultation hours was also the only effective response enhancing strategy described in chapter 5. Responders to a CMD prevention program typically have more contact with their general practice then non-responders (chapter 4), which creates opportunities to let them asses their CMD risk at hoc on invitation by the GP.

The individual setting during a GP consultation makes it easier for GPs to tailor CMD risk communication, making it more understandable and relevant to the patient. This is a necessity, for the result of the risk score alone is not enough to convince high risk patients of their own high risk and the need to undertake further action, as we showed in chapter 4 and in the article on risk communication described in the twinned thesis. It seems obvious to rethink the way methods of risk communication and lifestyle advice communication are embedded in the GP training and general practice, for there is still room for improvement in delivering personal risk and lifestyle advises (see chapter 8). But although previous studies have shown that risk perception can be improved by better communication strategies, this might have no effect on willingness to change lifestyle [17,38,39]. So the question is whether all the extra effort in communication is worth it, if it does not pay off in more motived patients ready to take a next step.

This next step is treatment, regardless whether the method of detection was through opportunistic screening or a programmatic approach. After detection of individual risk factors for CMD a GP should be able to offer an effective treatment. As described in chapter 6, the individuals who benefit most from participation in the CMD prevention program are the ones

receiving treatment with antihypertensive drugs or lipid lowering therapy. The cost-effectiveness of this risk factor treatment for the individual has been established for a long time [40,41]. But unfortunately, even if a patient is motivated to address her of his lifestyle, the current lifestyle programs offered to reduce CMD risk in primary care seem to have little effect outside a strictly controlled research setting [16,17]. So in order to effectively induce lifestyle change and thereby reduce CMD risk, we will have to look beyond the scope of the general practice.

Universal prevention of CMD

Universal prevention is aimed at the population as a whole and is therefore the strategy that has the most potency to lay a solid foundation for a healthier lifestyle in the community. In chapter 3 of this thesis we described that non-responders suggested they would consider to assess their CMD risk if they would be approached through media channels. Attempts to increase knowledge and further awareness of the impact of CMD and the importance of a heathy lifestyle are very suitable approaches for mass media campaigns. It could also be a good strategy to address socially vulnerable groups, for this type of prevention reaches the complete cross-section of the population through a variety of channels and might be especially beneficial for people with a low education level [42,43].

With the focus shifting from the individual to the population as a whole, the responsibility of improving lifestyle and health in the population also shifts from curative medicine to public health and policy makers. In addition to individual determinants it has become increasingly clear that factors in the physical, socio-cultural and socio-economic environments at both micro- and macro-level also play a key role in behavior patterns and change of lifestyle [44,45]. This asks for an integrated approach with collaboration of policy makers with different disciplines including regional administrators, public health, the private sector, educational institutions and spatial planning.

Even with optimization of contextual factors it will still be a challenge to bring about behavioral change within fixed patterns. Besides that, regulations regarding choices in terms of lifestyle and leisure time are always at odds with the right to self-determination. One way of getting around both these issues is to focus on the future generations. Protecting children from the health consequences arising from unhealthy habits and therefore giving every child equal opportunities at the start of life is a goal that can generally count on a wide support within communities. In 2018 the Dutch government drafted a Prevention Agreement with a broad coalition of social parties and the business community [46]. In the agreement the goals set for 2040 are aimed especially at the young; a smoke-free generation, children exercising in a healthy environment and no drinking of alcohol under the age of 18. The measures planned to achieve these goals include smoking bans for all public area's as well as schools, playgrounds and sports clubs, promotion of better nutrition, sport and exercise and reducing the amount

of adverts for alcohol seen by under the age of 18. Hopefully these measures will help shape an optimal environment for our next generation to grow up in, leading them to live a life with a healthier lifestyle, without knowing otherwise.

Conclusion

The selective CMD prevention program which was studied in the INTEGRATE program is feasible and effective in terms of short term outcomes, with a positive effect on systolic blood pressure and cholesterol levels. However, large scale implementation of this type of CMD prevention programs in general practice is not cost effective in terms of long term health gains. The reach of the program is limited and, without the availability of effective strategies to increase or equalize uptake, could widen health and social inequalities. The program shows no effect on motivation to change lifestyle. Therefore, this selective CMD prevention program in primary care is not suitable for large-scale implementation. Because prevention of CMD remains an important objective, we underline the importance of ongoing opportunistic screening for CMD risk in primary care and increased commitment for universal prevention. On population level universal prevention, especially aimed at the younger population, remains the optimal strategy to effectively prevent CMD as well as to reduce health inequalities.

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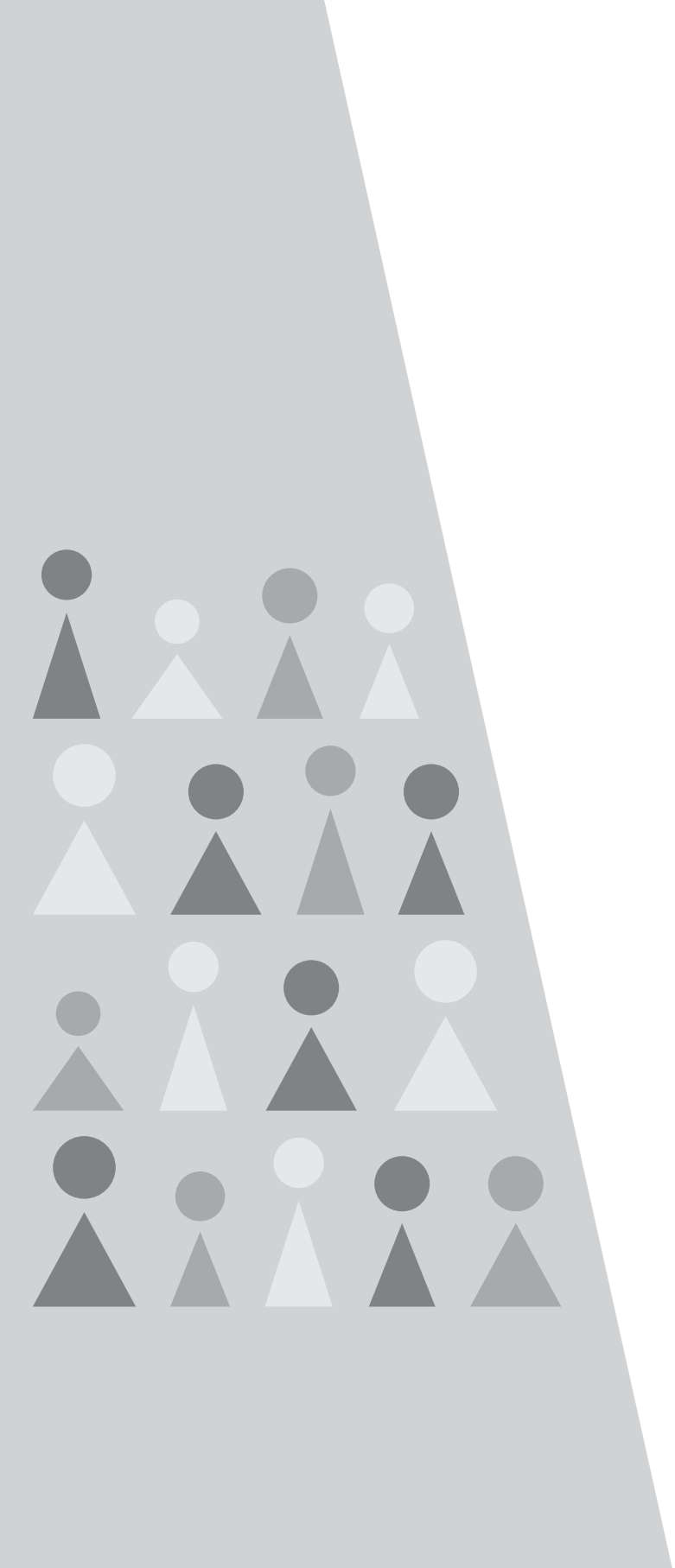


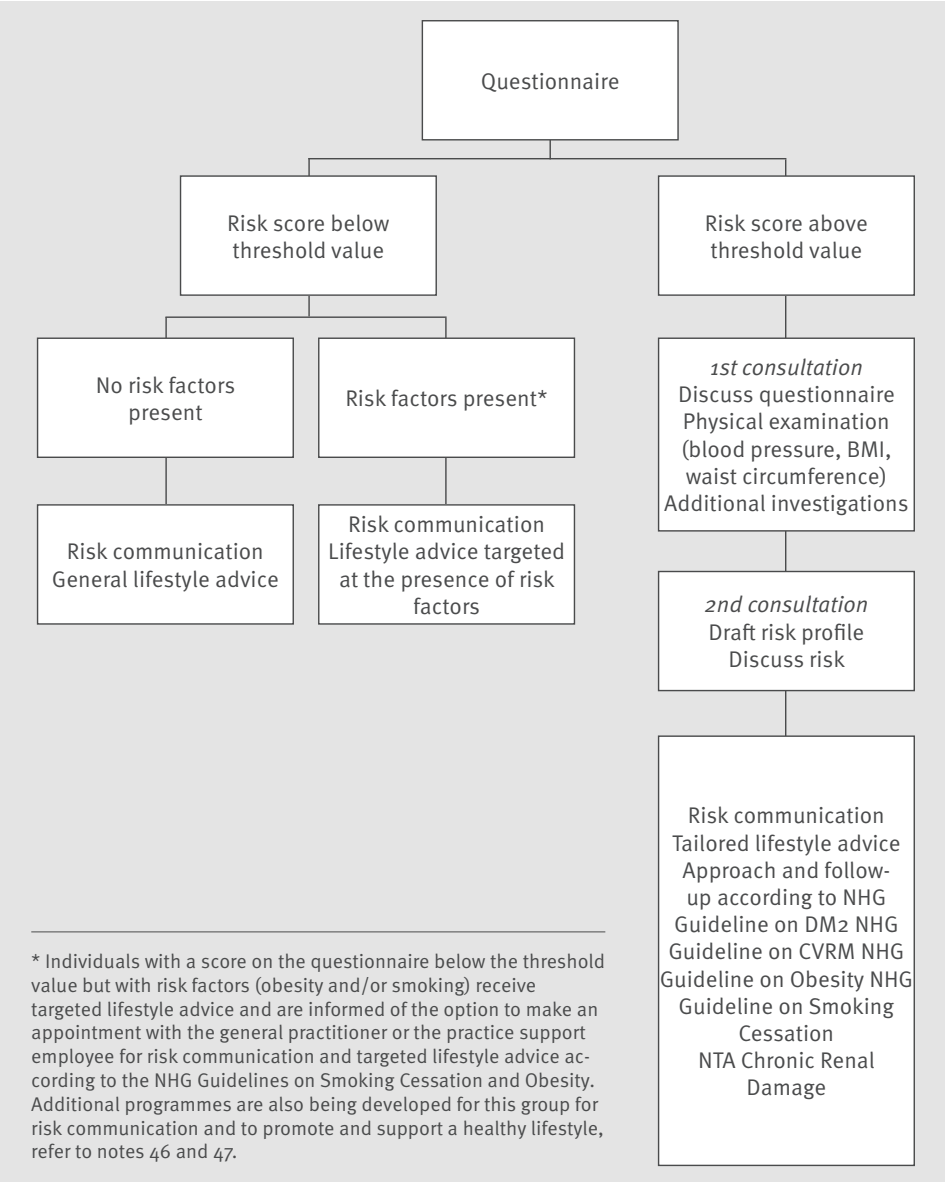
Appendices

1. Flowchart Prevention Consultation

2. Risk score for men and women

3. Study design and response rates INTEGRATE study

Appendix 1 Flowchart Prevention Consultation



* Individuals with a score on the questionnaire below the threshold value but with risk factors (obesity and/or smoking) receive targeted lifestyle advice and are informed of the option to make an appointment with the general practitioner or the practice support employee for risk communication and targeted lifestyle advice according to the NHG Guidelines on Smoking Cessation and Obesity. Additional programmes are also being developed for this group for risk communication and to promote and support a healthy lifestyle, refer to notes 46 and 47.

Appendix 2 Risk score for men and women

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
2. BMI	< 25 kg/m²	0
	25 – 30 kg/m²	4
	> 30 kg/m²	12
3. Waist circumference	< 94 cm	0
	≥ 94 cm	3
4. Smoking	Yes	9
	No	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
2. BMI	< 25 kg/m²	0
	25 – 30 kg/m²	4
	> 30 kg/m²	12
3. Waist circumference	< 80 cm	0
	80 – 88 cm	3
	> 88 cm	9
4. Smoking	Yes	0
	No	1
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	

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.

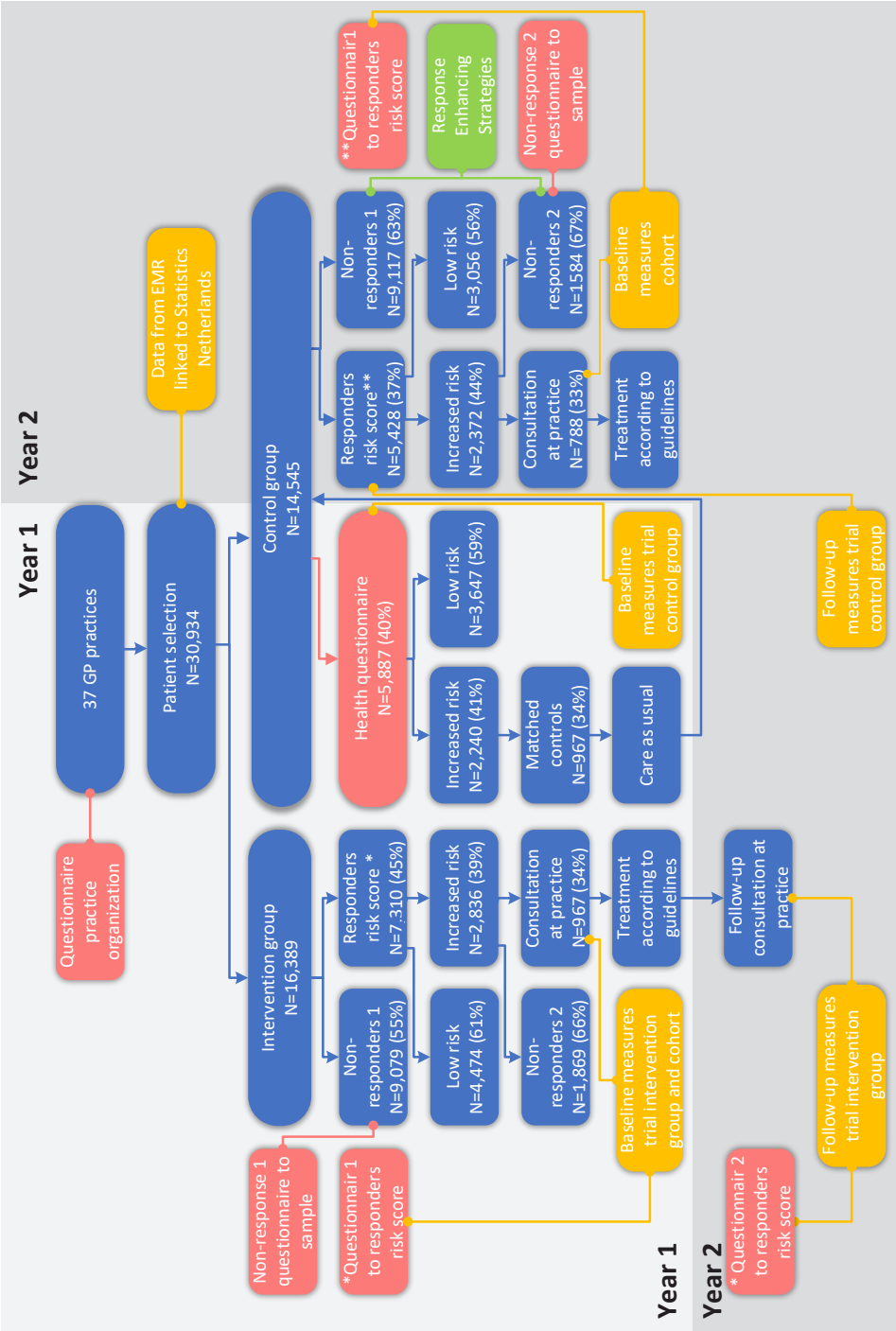
First consultation
- discussion of questionnaire;
- measurement of height, weight, waist circumference, blood pressure;
- referral letter for laboratory.

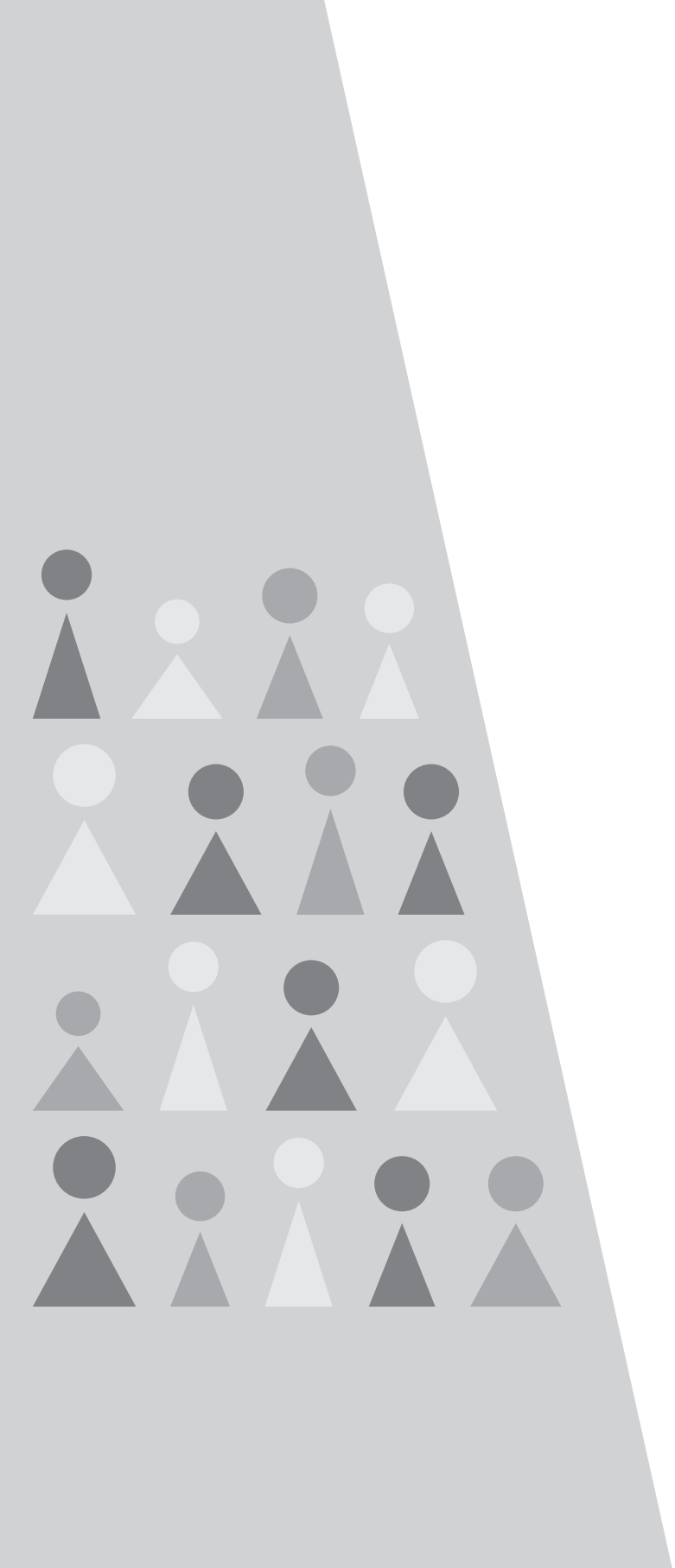
Second consultation
- drawing up risk profile;
- discussion of risk;
- if indicated, start treatment according to the relevant NHG Guideline(s).

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.

Appendix 3 Study design and response rates INTEGRATE study





Summary

Introduction

Over the last decades prevention programs have been increasingly implemented. Before elaborate implementation of a prevention program can take place, success of these programs should be determined in the broadest sense, considering all components associated including uptake, effectiveness and adoption of the program.

In order to anticipate on the increasing disease burden of cardiometabolic diseases (CMD), including cardiovascular disease, diabetes type 2 and chronic kidney disease, the Dutch College of General Practitioners developed the guideline 'Prevention consultation' in 2011. The guideline describes a stepwise CMD prevention program for primary care (Appendix 1). The first stage of the program is completing a self-assessed risk score, a seven-item questionnaire including questions regarding gender, age, smoking status, body mass index (BMI), waist circumference and a family history of premature CVD (age <65 years) and DM2 (Appendix 2). Individuals with an increased risk are referred to their GP for stage 2 of the program which includes additional risk profiling, including blood pressure measurement and laboratory tests for glucose and cholesterol, followed by treatment when indicated. Tailored lifestyle advice forms an integral part in stage 2 of the prevention program.

So far, nationwide implementation of the programmatic CMD prevention described in the guideline could not yet be recommended, as scientific evidence for effectiveness of the program has not been established and financial reimbursement for implementation have not been structurally available. A realistic evaluation of the stepwise CMD prevention program is needed in order to overcome this status quo . The effectiveness and cost-effectiveness of the program are important elements, but other key elements are frequently overlooked, such as participation rate and barriers and facilitators for implementation. The twinned thesis by Stol focuses on the effectiveness and cost-effectiveness of the program. This thesis aimed to evaluate the 'Prevention Consultation' by explicating the different aspects based on the RE-AIM model (Reach, Effectiveness, Adoption, Implementation and Maintenance), with a specific focus on the reach, effectiveness and implementation of the program.

Study design of the INTEGRATE study

In chapter 2 we describe the design of the INTEGRATE study, a stepped wedge randomized controlled trial designed to evaluate the 'Prevention Consultation' (Appendix 3). We implemented the prevention program in 37 general practices in the Netherlands and compared the program with care-as-usual. Primary outcomes were the number of newly detected CMD, changes in CMD risk factors after one-year follow-up, cost-effectiveness and determinants of non-participation in different stages of the program. Secondary outcomes included the

effectiveness of response enhancing strategies, practice organisation in relation to effectiveness of the program and willingness of the participants to change lifestyle.

Characteristics and motives of non-responders

The willingness to participate in a CMD prevention program amongst non-responders of stage 1 of the program (completing the risk score) was relatively high (chapter 3). The most reported reason for non-response is pragmatic: non-responders either forget it or they can't find the time to complete the risk score. This fits with the finding that the majority of the non-responders is willing to reconsider participation if a different invitation strategy would be used. We used the input from non-responders in the first phase as described in chapter 3 to further develop response enhancing strategies, which we implemented in the next phase of the INTEGRATE study (see chapter 5).

Non-response at both stages of the CMD prevention program, completing the risk score (stage 1) and visiting the GP with an increased risk (stage 2), is not equally distributed amongst different demographic and socioeconomic groups (chapter 4). This inequality causes underrepresentation of socially vulnerable groups amongst the participants of the prevention program, meaning relatively less individuals with a low socioeconomic status and/or a migrant background are included in the prevention program. In chapter 4 we also describe that the most reported reason for non-response at stage 2 of the program (the GP consultation) is expecting to have a low risk for CMD. This suggests that risk perception is inadequate and that current risk communication is insufficient in conveying the level of risk and the severity of the risk from a health professional perspective to the patient.

Response enhancing strategies

In the study described in chapter 5 we evaluated different response enhancing strategies, developed on the basis of input from non-responders described in chapter 3 and previous studies. The results of this study show that all implemented strategies are feasible but their effect on the response rates seems to be limited. A role may still be set for inviting patients by email, for this method ensures a large reduction in costs and time investment. Another effective strategy to explore further is letting GPs invite patients face to face during consultation hours, as this enhanced response rates significantly in the sample in which we tested it. Furthermore, the strategies that were specifically designed to increase response in socially vulnerable groups, such as translation of risk score questionnaires and organizing information gatherings at the general practice, proved not to be effective.

Effectiveness the prevention program, impact of practice organization and delivery of lifestyle advice

The implementation of the CMD prevention program in general practice is feasible and effective in short term follow-up (chapter 6). A CMD was diagnosed almost three times more often in the intervention compared to the control group. Participants in the intervention group were diagnosed with a CMD more often and had a statistically significantly lower systolic blood pressure and a more favorable cholesterol ratio after 1 year of follow up compared to the control group. Although waist circumference significantly decreased in the intervention group, no changes were found for the other behavioral risk factors such as smoking and BMI.

In the study described in chapter 7 we focused on the relationship between short term effectiveness of the CMD prevention program and differences in practice organization and available preventive services between the participating practices. The results of this analysis show that practice organization characteristics and available preventive services are not associated with effectiveness of the CMD prevention program. A possible explanation for this finding is the effectiveness of the protocolized pharmaceutical treatment and only a limited additional contribution of lifestyle programs to the effects on individual risk factors.

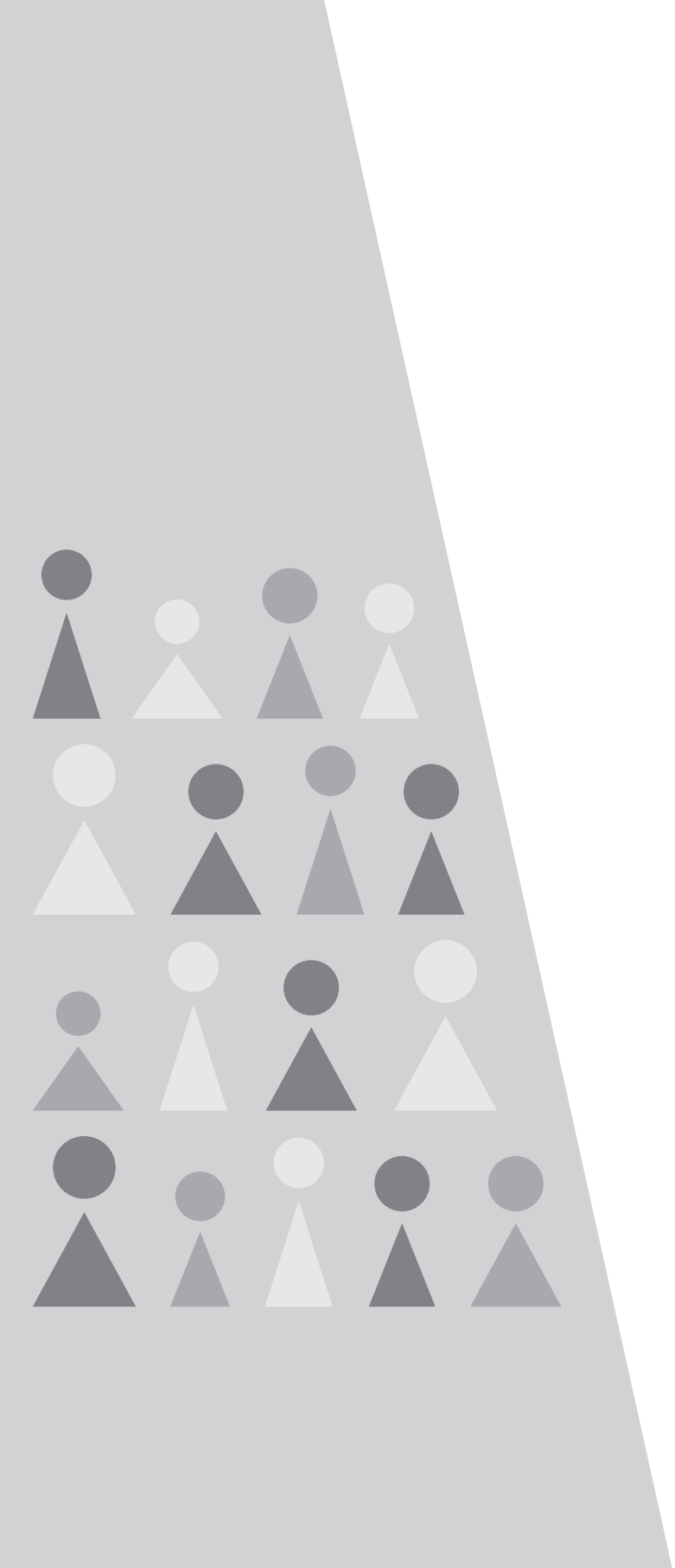
Fidelity with lifestyle advice during the intervention shows to be only modest: GPs and practice nurses adequately provide smoking cessation advice but lifestyle advice on obesity is discussed in half of the cases only and about two-third of the patients cannot recall the lifestyle adviees given regarding healthy diet and physical exercise (chapter 8). In chapter 8 we also describe that after completing the prevention program, the participants from the intervention group were not more willing to change their lifestyle than the individuals in the control group.

Conclusion

The stepwise CMD prevention program which was studied in the INTEGRATE program is feasible and effective in terms of short term outcomes, with a positive effect on the number of newly detected CMD and on systolic blood pressure and cholesterol levels. However, large scale implementation of this type of CMD prevention programs in general practice is not cost effective in terms of long term health gains (twinned thesis Stol). The reach of the program is limited and, without the availability of effective strategies to increase or equalize uptake, could widen health and social inequalities. The program shows no effect on motivation to change lifestyle.

After evaluation according to the RE-AIM framework, with a focus on reach and effectiveness, we can conclude that broad implementation of the 'Prevention Consultation' in the Netherlands cannot be recommended . Further research to determine the optimal methods for adoption, implementation and maintenance of this program is therefore not warranted.

Because prevention of CMD remains an important objective, we underline the importance of ongoing opportunistic screening for CMD risk in primary care and increased commitment for universal prevention. On population level universal prevention, especially aimed at the younger population, remains the optimal strategy to prevent CMD as well as to reduce health inequalities.



Samenvatting

Introductie

In de afgelopen decennia zijn er steeds meer preventieprogramma's geïmplementeerd. Voordat uitgebreide implementatie van een preventieprogramma kan plaatsvinden zou het succes van een programma moeten worden bepaald, in de ruimste zin van het woord. Hierbij moet rekening gehouden worden met alle componenten die daarbij bij van belang zijn, inclusief deelnamebereidheid, effectiviteit en acceptatie van het programma.

Om te anticiperen op de toenemende ziektelast van cardiometabole ziekten (CMZ), zoals hart- en vaatziekten, diabetes mellitus type 2 en chronische nierschade, heeft het Nederlands Huisartsen Genootschap in 2011 de richtlijn 'Het PreventieConsult' ontwikkeld. De richtlijn beschrijft een stapsgewijs preventieprogramma voor CMZ in de huisartsenpraktijk (zie bijlage 1). De eerste fase van het programma is het invullen van de Risicotest, een vragenlijst met zeven items over geslacht, leeftijd, rookstatus, Body Mass Index (BMI), buikomvang en familiegeschiedenis van vroegtijdige hart- en vaatziekten (leeftijd <65) jaar) en diabetes type 2 (zie bijlage 2). Personen met een verhoogd risico worden doorverwezen naar hun huisarts voor fase 2 van het programma, aanvullende risicoprofilering, waaronder een bloeddrukmeting en bloedtesten voor glucose en cholesterol, zo nodig gevolgd door behandeling. Leefstijladvies op maat is een standaard onderdeel in fase 2 van het preventieprogramma.

Tot dusver kon landelijke implementatie van programmatische preventie van CMZ zoals beschreven in de richtlijn nog niet worden aanbevolen, omdat er geen wetenschappelijk bewijs is voor de effectiviteit van het programma en structurele financiële ondersteuning voor implementatie ontbreekt. Een realistische evaluatie van het preventieprogramma is noodzakelijk om deze impasse te doorbreken. Effectiviteit en kosteneffectiviteit van het programma zijn belangrijke elementen, maar andere cruciale elementen worden vaak over het hoofd gezien, waaronder deelnamebereidheid en belemmerende en bevorderende factoren voor implementatie. Het gekoppelde proefschrift van Stol richt zich op de effectiviteit en kosteneffectiviteit van het programma. In dit proefschrift worden de verschillende aspecten van 'Het PreventieConsult' geëvalueerd aan de hand van het RE-AIM model (bereik, effectiviteit, acceptatie, implementatie en onderhoud), met een specifieke focus op het bereik, de effectiviteit en de implementatie van het preventieprogramma.

Studieopzet van de INTEGRATE-studie

In hoofdstuk 2 beschrijven we de opzet van de INTEGRATE-studie, een stepped-wedge gerandomiseerde studie bedoeld om 'Het PreventieConsult' te evalueren (Bijlage 3). We hebben het preventieprogramma geïmplementeerd in 37 huisartsenpraktijken in Nederland en vergeleken met de gebruikelijke zorg. Primaire uitkomsten waren het aantal nieuw

opgespoorde CMZ, de veranderingen in risicofactoren voor CMZ na een jaar follow-up, de kosteneffectiviteit en determinanten van non-respons gedurende de verschillende fasen van het programma. Secundaire uitkomsten waren de effectiviteit van respons-verhogende strategieën, de associatie van de praktijkorganisatie en de effectiviteit van het programma en de bereidheid van deelnemers om hun leefstijl aan te passen.

Kenmerken en motieven van non-responders

De deelnamebereidheid onder non-responders in fase 1 van het preventie programma (voltooiing van de Risicotest) is relatief hoog (hoofdstuk 3). De meest gerapporteerde reden voor non-respons is pragmatisch: non-responders waren het vergeten het of ze hadden geen tijd gehad om de risicoscore in te vullen. Dit past bij de bevinding dat de meerderheid van de non-responders bereid is om deelname te heroverwegen als een andere uitnodigingsstrategie gebruikt zou worden. De input van non-responders in de eerste fase, zoals beschreven in hoofdstuk 3, hebben we gebruikt om respons-verhogende strategieën verder te ontwikkelen. Deze strategieën hebben we in de volgende fase van de INTEGRATE-studie geïmplementeerd (zie hoofdstuk 5).

Non-respons in beide fasen van het preventieprogramma, het voltooien van de Risicotest (fase 1) en het huisartsenconsult in geval van een verhoogd risico (fase 2), was niet gelijk verdeeld over verschillende demografische en sociaaleconomische groepen (hoofdstuk 4). Deze ongelijkheid veroorzaakt een ondervertegenwoordiging van sociaal kwetsbare groepen onder de deelnemers aan het preventieprogramma, wat betekent dat relatief minder individuen met een lage sociaaleconomische status en/of een (im)migratieachtergrond deelnamen. In hoofdstuk 4 hebben we ook beschreven dat de meest gerapporteerde reden voor non-respons in fase 2 van het programma (het huisartsenconsult) samenhangt met de verwachting een laag risico op CMZ te hebben. Dit suggereert dat de risicoperceptie van deelnemers onvoldoende is en dat de huidige methode van risicocommunicatie onvoldoende is om het risiconiveau en de ernst van het risico vanuit het perspectief van de zorgprofessional naar de patiënt over te brengen.

Respons-verhogende strategieën

In de studie beschreven in hoofdstuk 5 hebben we verschillende strategieën om de respons te verbeteren geëvalueerd. De strategieën zijn ontwikkeld op basis van input van non-responders zoals beschreven in hoofdstuk 3 en eerdere studies. De resultaten van deze studie laten zien dat alle geïmplementeerde strategieën uitvoerbaar zijn, maar hun effect op de respons lijkt

beperkt. Mogelijk is er nog een rol weggelegd voor het uitnodigen van patiënten per e-mail, want deze methode zorgt voor een grote reductie in kosten en tijdinvestering. Een andere effectieve strategie om nader te onderzoeken is om huisartsen patiënten tijdens hun spreekuur persoonlijk uit te laten nodigen. Deze methode verbeterde de respons in de steekproef waarin we het uittesten significant. Verder bleken de strategieën die specifiek waren ontworpen om de respons in sociaal kwetsbare groepen te verhogen, zoals het vertalen van vragenlijsten met de Risicotest en het organiseren van informatiebijeenkomsten in de huisartsenpraktijk, niet effectief.

Effectiviteit van het preventieprogramma, impact van praktijkorganisatie en toepassing van leefstijladviezen

De implementatie van het preventieprogramma voor CMZ in de huisartsenpraktijk is haalbaar en effectief op korte termijn (hoofdstuk 6). Bij de deelnemers in de interventiegroep werden meer nieuwe CMZ opgespoord en zij hadden een significant lagere systolische bloeddruk en een gunstigere cholesterolratio ten opzichte van de controlegroep na 1 jaar follow-up. Hoewel de buikomvang significant afnam in de interventiegroep, werden er geen veranderingen gevonden voor de andere gedragsmatige risicofactoren zoals roken en BMI.

In de studie beschreven in hoofdstuk 7 hebben we ons gericht op de associatie tussen de korte-termijneffectiviteit van het preventieprogramma en verschillen in praktijkorganisatie en beschikbare leefstijlprogramma's tussen de deelnemende praktijken. Uit deze analyse blijkt dat de kenmerken van praktijkorganisatie en beschikbare leefstijlprogramma's niet geassocieerd zijn met de effectiviteit van het preventieprogramma voor CMZ. Een mogelijke verklaring voor deze bevinding is de effectiviteit van geprotocolleerde medicamenteuze behandeling en de slechts beperkte aanvullende bijdrage van leefstijlprogramma's aan de effecten op individuele risicofactoren.

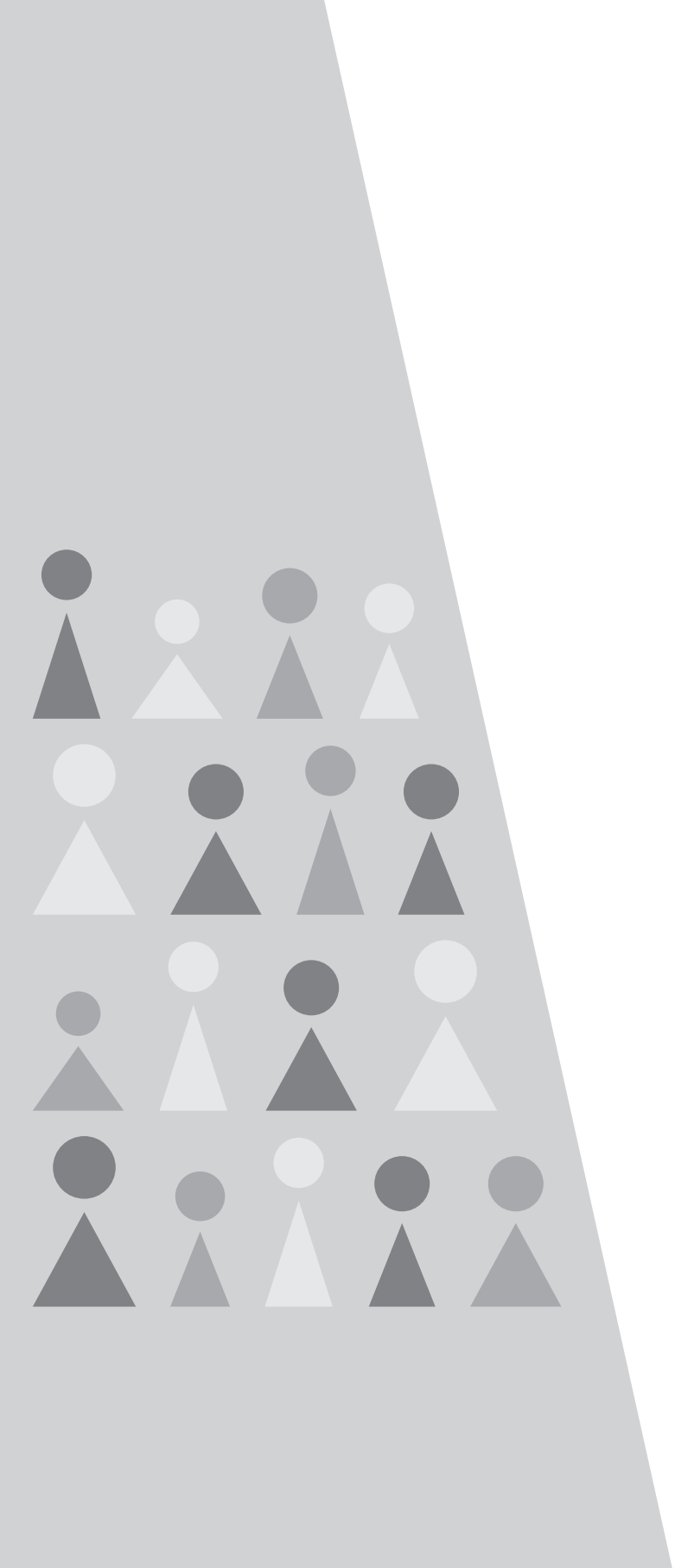
De toepassing van leefstijladviezen tijdens de uitvoering van het programma is niet optimaal: huisartsen en praktijkverpleegkundigen geven adequaat stoppen-met-rokenadviezen, maar leefstijladvies rondom obesitas wordt maar in de helft van de gevallen besproken. Ongeveer tweederde van de patiënten kan zich de leefstijladviezen over een gezond dieet en lichaamsbeweging herinneren (hoofdstuk 8). In hoofdstuk 8 beschrijven we ook dat de deelnemers uit de interventiegroep na het voltooien van het preventieprogramma niet meer gemotiveerd waren om hun leefstijl aan te passen dan de mensen in de controlegroep.

Conclusie

Het stapsgewijze preventieprogramma voor CMZ dat werd bestudeerd in het INTEGRATE-programma is uitvoerbaar en effectief op korte termijn, met een positief effect op nieuw opgespoorde CMZ en op de systolische bloeddruk en het cholesterolgehalte van de deelnemers. Grootschalige implementatie van dit type preventieprogramma's in de huisartsenpraktijk is echter niet kosteneffectief in termen van gezondheidswinst op lange termijn (zie gekoppelde proefschrift Stol). Het bereik van het programma is beperkt en zou, zonder de beschikbaarheid van effectieve strategieën om de deelname te vergroten of beter de verdelen, de gezondheids- en sociale ongelijkheden kunnen vergroten. Het programma heeft geen effect op de motivatie om de leefstijl te veranderen.

Na evaluatie volgens het RE-AIM model, met focus op bereik en effectiviteit, kunnen we concluderen dat brede implementatie van het 'Preventieconsult' in Nederland niet aan te raden is. Nader onderzoek om de optimale methoden voor acceptatie, implementatie en onderhoud van dit programma te bepalen is daarom niet gerechtvaardigd.

Omdat preventie van CMZ een belangrijke doelstelling blijft, onderstrepen we het belang van opportunistische screening op CMZ in de huisartsenpraktijk en meer inzet voor universele preventie. Op populatieniveau blijft universele preventie, vooral gericht op het jongere deel van de bevolking, de optimale strategie om CMZ te voorkomen en ongelijkheid in gezondheid te verminderen.



Dankwoord

Na een traject van ruim 7 jaar met voldoende obstakels en uitdagingen is het proefschrift nu echt af. Ik wil graag iedereen bedanken die direct of indirect is betrokken bij het tot stand komen van dit proefschrift. Een aantal mensen wil ik in het bijzonder bedanken.

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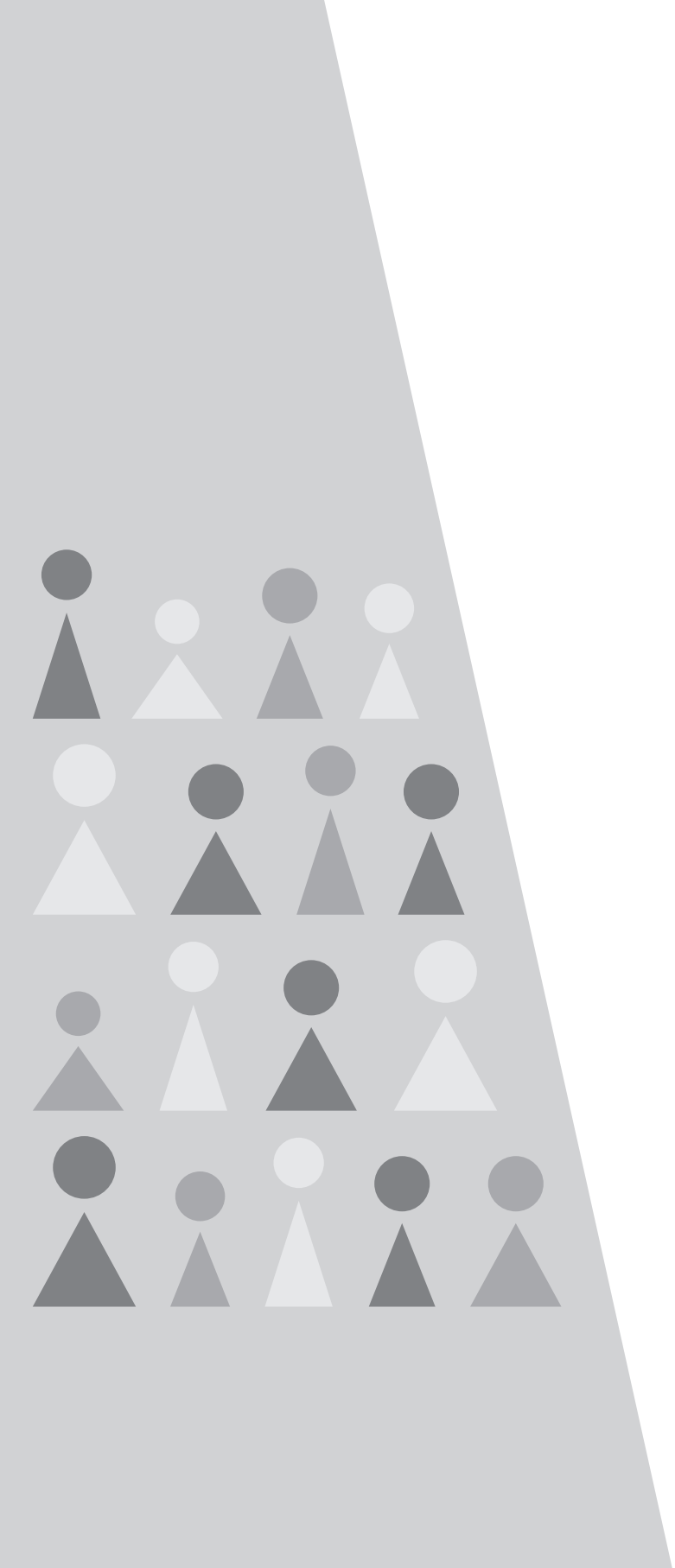

About the author

Ilse Badenbroek was born on December 29th in Helmond, the Netherlands. After graduating from secondary school (Rythovius College in Eersel) in 2005 she started studying Biomedical Science in Hasselt (Belgium). After the first year of studying she switched her study course to Medicine and obtained her bachelor degree in 2008. She then moved to Utrecht to start with the four-year master program SUMMA (Selective Utrecht Medical Master). During SUMMA she gradually developed interest in scientifical research. After receiving her medical degree in 2012 she started working as a resident doctor in a mental healthcare institution (GGZ Centraal in Amersfoort). In 2013 she started a AIOTHO trajectory, combining the clinical work as a general practice trainee with research activities as a PhD student. From 2013 to 2020 she worked for the INTEGRATE project, a collaborative project of Netherlands Institute for Health Services Research (NIVEL) and the Julius Center for Health Science and Primary Care (supervision of prof. dr. F.G. Schellevis and prof. dr. N.J. de Wit). During her trajectory she started her post-graduate Epidemiology master, which she expects to complete in 2020. She is currently enrolled in the final year of her general practice vocational training and expects to complete her general practitioners degree in the beginning of 2021.