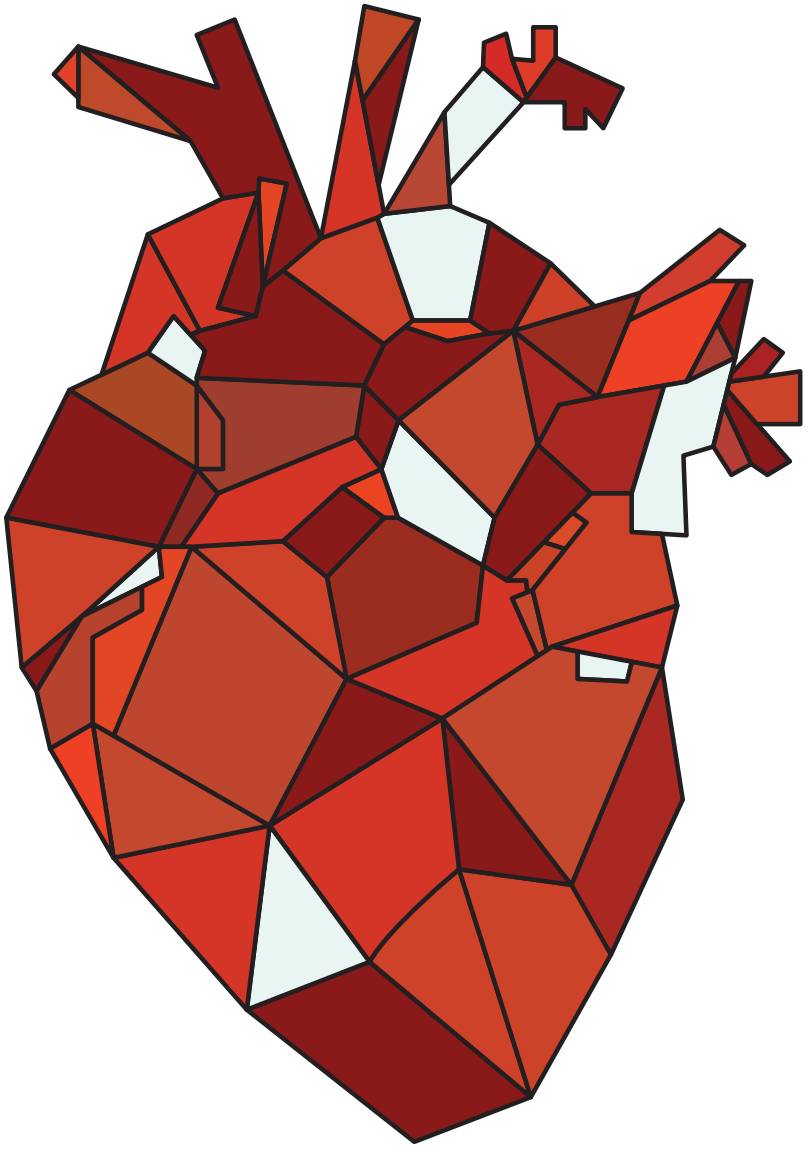
Screening for Cardiovascular Disease:

First results of the ROBINSCA trial



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First results of the ROBINSCA trial

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eerste resultaten van het ROBINSCA onderzoek

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Chapter 1

General introduction

Cardiovascular disease burden

Cardiovascular disease (CVD) is the main cause of death worldwide (1). Within Europe, CVD is responsible for 3.9 million deaths each year, which is 45% of all annual deaths (2). More women die from CVD compared to men; 49% versus 40% of all deaths (2). CVD causes a loss of 64 million disability-adjusted life years (DALYs), accounting for 23% of all DALYs lost across Europe in 2015 (2, 3). The burden of CVD results in high total costs for the European Union economy of approximately €210 billion a year, in terms of direct health care costs, productivity losses and care of patients with CVD (2).

In the Netherlands, CVD is the second most common cause of death after cancer in both women and men until the age of 85 years: then CVD becomes leading cause of death (4). In 2017, CVD mortality accounted for 25% of all-cause mortality in the Netherlands (Table 1). The proportion of CVD-related deaths was comparable in both men and women; 25% and 26% respectively. However, also in the Netherlands the absolute number of women who died from CVD is higher compared to men; 20,039 women and 18,080 men. The main explanation for this difference is the higher proportion of women in higher age groups where the risk of CVD is higher. This is also reflected in the mean age at CVD-related death which is 78 years for men and 84 years for women (4) (Table 1).

Of all different types of CVD, coronary heart disease (CHD) is the main cause of CVD burden in Europe. In the European Union, 632,000 people died from CHD and 3.1 million people were admitted to the hospital in 2015 (2). In the Netherlands, 72,336 people were admitted to the hospital due to CHD in 2017, which was 27% of all CVD-related hospital admissions. Of those who were admitted to the hospital with CHD-related causes, 49,375 were men and 22,961 were women. Considerably more men died from CHD than women: 4,983 men (28% of CVD-related deaths) versus 3,350 women (17% of CVD-related deaths) (4).

Table 1. Causes of death in the Netherlands in 2017.

Causes of death	**Men**		**Women**		**Total**	
	N (%)*	Mean age at death	N (%)*	Mean age at death	N (%)*	Mean age at death
Cardiovascular diseases	18,080 (25)	78	20,039 (26)	84	38,119 (25)	81
Cancer	24,532 (34)	73	20,353 (26)	73	44,885 (30)	73
Respiratory diseases	6,305 (9)	80	6,647 (9)	82	12,952 (9)	81
Psychological and behavioral disorders	4,387 (6)	82	8,194 (11)	87	12,581 (8)	85
Nervous system disorders	3,723 (5)	77	4,753 (6)	82	8,476 (6)	80
External causes of injury and poisoning	4,159 (6)	65	3,810 (5)	79	7,969 (5)	71
Other causes	11,475 (16)	73	13,757 (18)	81	25,232 (17)	78
All causes	72,661 (100)	75	77,553 (100)	80	150,214 (100)	78

Adapted from the Dutch Heart Foundation (4).

* Due to rounding differences, the percentages do not add up to 100.

In recent years, cardiovascular mortality has decreased in most of the high-income countries of Western Europe (3, 4). However, the burden of CVD remains serious as the absolute number of CVD cases has increased (2). This is a consequence of several causes, including an increase in life expectancy, a growth in total population size and in the number of elderly people (5, 6). Only a slight decrease in the age-standardized CVD prevalence is observed when controlling for changes in population size and composition (2). Another alarming element in the high CVD burden is the continuous increase in the prevalence of cardiovascular risk factors (7). Therefore, improvement of risk factor management is urgently needed.

Risk factors

Atherosclerosis is the predominant process in the development of CVD. The onset of this process starts early in life and progresses during life. Fatty streaks, which are the first visible manifestation of atherosclerosis, are present in almost all Western children. These streaks are often the initial lesion of atherosclerosis as they can progress asymptomatically into atherosclerotic plaques (8). During this progression, calcium deposits are formed in coronary arteries (9). Plaques often remain clinically unapparent for decades. However, this stage is a serious health threat in many cases. The atherosclerotic plaque eventually can obstruct the blood flow and can become detached causing an obstruction elsewhere in the body (10). Unfortunately, the first clinical manifestation of the disease occurs when an artery is already largely or completely blocked. This can result in serious event as myocardial infarction, stroke or even sudden cardiac death. Although the pathogenesis of atherosclerosis has not been fully clarified yet, it is known that the process is associated with CVD risk factors (10).

The main CVD risk factors are smoking, age, male sex and a family history of CVD. Moreover, unhealthy lifestyles, including limited physical activity and unhealthy diet, can cause obesity, diabetes mellitus, hypercholesterolemia and hypertension. Unfortunately, the prevalence of unhealthy lifestyles is high. A survey from the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV in primary care was carried out in 71 centers from 14 European countries in 2014 and 2015. Of the 6700 reviewed asymptomatic patients who were prescribed treatment, 16.6% were smokers, 39.9% were overweight (body mass index (BMI)≥25 and <30 kg/m^2), 43.5% obese (BMI ≥30 kg/m^2) and 63.9% centrally obese (waist circumference of ≥88 cm for women, ≥102 cm for men) (7). These risk factors and conditions are not only directly related to development of atherosclerosis and CVD, but also to morbidity and mortality from other causes such as cancer and respiratory diseases (11, 12). Improvement of the modifiable risk factors can prevent development of CVD. Despite a reduction in the percentage of current smokers, the prevalence of obesity and diabetes mellitus has increased substantially (13, 14). As a result, development of atherosclerosis is not inhibited and cardiovascular risk is high in the general population.

Prevention

Prevention of diseases can target different stages of the disease development process. First, primary prevention aims to hinder the development of disease before health effects can occur. Primary prevention measures include vaccinations, altering risk behavior, and health education in the general population. Then, secondary prevention is early detection of a preclinical disease phase so that early treatment can prevent or delay the onset of disease symptoms. Population-based screening programs can identify the asymptomatic individuals with preclinical disease. Last, tertiary prevention focuses on the stage in which the disease has manifested. The aim is to halt disease progression and improve survival and quality of life. As many other diseases, prevention of CVD can also be targeted at the above described prevention levels.

The main goal of CVD prevention is to improve the modifiable risk factors by adopting a healthy lifestyle and/or starting preventive drug treatment (15, 16). In general, lifestyle interventions apply to every individual. Lifestyle advice includes:

- Smoking cessation; CVD risk begins to reduce within six months after abstinence and approaches the risk of non-smokers after ten to fifteen years (17).
- Healthy balanced diet; CVD risk can be reduced by a Mediterranean diet consisting of daily consumption of vegetables, fruits, whole grains and healthy (unsaturated) fats, weekly intake of fish, poultry, beans and eggs, moderate consumption of dairy products and alcohol, and limited intake of red meat and salt (18).
- Regular physical activity; physical activity not only reduces CVD mortality but also all-cause mortality. It improves body weight, hypertension, cholesterol, diabetes mellitus and mental health (19).

Besides lifestyle change recommendations, initiation of drug treatment may be considered for preventing CVD events. Drug treatment is aimed at lowering lipids and blood pressure. Lipid-lowering drugs include statins which reduce CVD morbidity and mortality by decreasing low-density lipoprotein cholesterol (LDL-C) (20, 21). Statins are the first choice in patients with hypercholesterolemia as they are able to halt progression of coronary atherosclerosis when dosed to reduce LDL-C by at least 50% (22). Statin use can achieve a relative reduction in CVD mortality of 31% according to pooled results from 19 randomized-controlled trials (RCT) (23). Combination treatment may be required when treatment goals cannot be reached with one single drug. Additionally, reduction of blood pressure using antihypertensive drugs is effective as well in decreasing CVD risk. All major blood pressure lowering drugs are effective in reducing CHD-related events with about 25% when systolic blood pressure is lowered by 10 mmHg (24).

Primary CVD prevention, offered by national governments, focuses mainly on improving the lifestyle-related risk factors. Educational programs and smoking cessation interventions are promoted and available for the general population. Currently, the Dutch guideline for Cardiovascular Risk Management (CVRM) of the Dutch College of General Practitioners (NHG) advises a combination of opportunistic and systematic screening to detect at-risk individuals who might benefit from preventive drug treatment (25, 26). Opportunistic screening

has no predefined strategy and takes place when the opportunity arises. Systematic screening involves actively inviting a specific subgroup of the general population for screening. However, as systematic screening is time-consuming for general practitioners (GP), not every at-risk individual will be identified using this strategy.

As described above, cardiovascular mortality has decreased in recent years. This may be explained by improved prevention in terms of risk factor control and better treatment. Changes in risk factors can rapidly cause substantial declines in mortality (27, 28). A CHD model (IMPACT) estimated that approximately half of the CHD mortality decrease is attributable to risk factor reduction and also approximately half to improved treatment (29). Despite the mortality decline, increases in the prevalence of obesity and diabetes mellitus maintain the high ongoing CVD burden. Prevention of CVD remains a high priority to reduce morbidity and mortality, and to reduce the burden on quality of life, health care systems and economy (30).

Currently, one of the problems in CVD prevention is that a large proportion of the population is missed for preventive measures. A substantial number of individuals who might benefit from prevention remains unidentified. Primary prevention is proven to be effective in reducing morbidity and mortality of CVD, however, effects of these prevention strategies are often limited. The preventive measures are not targeted directly to at-risk subgroups and moreover, not all at-risk subjects feel addressed by the general preventive measures. Furthermore, adjusting lifestyle and adhering to preventive treatment is known to be challenging (31). The EUROASPIRE IV survey showed that CVD prevention guidelines to reduce unhealthy lifestyles in high-risk individuals are poorly followed (7). Prevention often needs to be initiated when there are no symptoms yet. This makes it difficult to comprehend that prevention is actually important.

The availability of effective and affordable risk-reducing medication offers opportunities for a screening program for the early detection and treatment of an increased risk of CVD. Since CHD is often asymptomatic for a long time until serious events occur, secondary prevention may be a good strategy (15, 32). This calls for research into whether screening contributes to lowering CVD morbidity and mortality. Currently, it is still unclear whether early identification of individuals at high risk of CVD followed by early treatment is actually effective, although positive effects are reported (33). It should be investigated which risk assessment method is most appropriate as screening tool assessing the risk of CVD in asymptomatic individuals. Moreover, advantages and disadvantages must be balanced and effectiveness needs to be demonstrated by analyzing potential morbidity and mortality reductions caused by early treatment of modifiable risk factors with lifestyle changes and/or preventive drug treatment.

Screening for cardiovascular diseases

As stated before, screening aims to stop or delay subclinical disease progression to prevent or postpone serious events (Figure 1). The early development of atherosclerosis provides a chance to detect and treat progression in an early phase, leading to gains in healthy life years and survival. Population-based screening might be an appropriate strategy to identify individuals at high risk

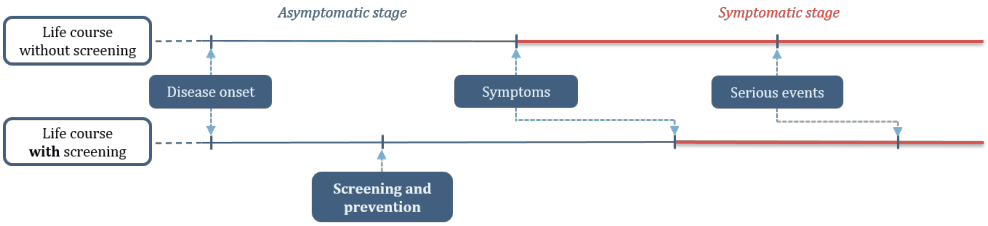


Figure 1. Effect of screening by detecting subclinical disease to prevent or delay disease progression.

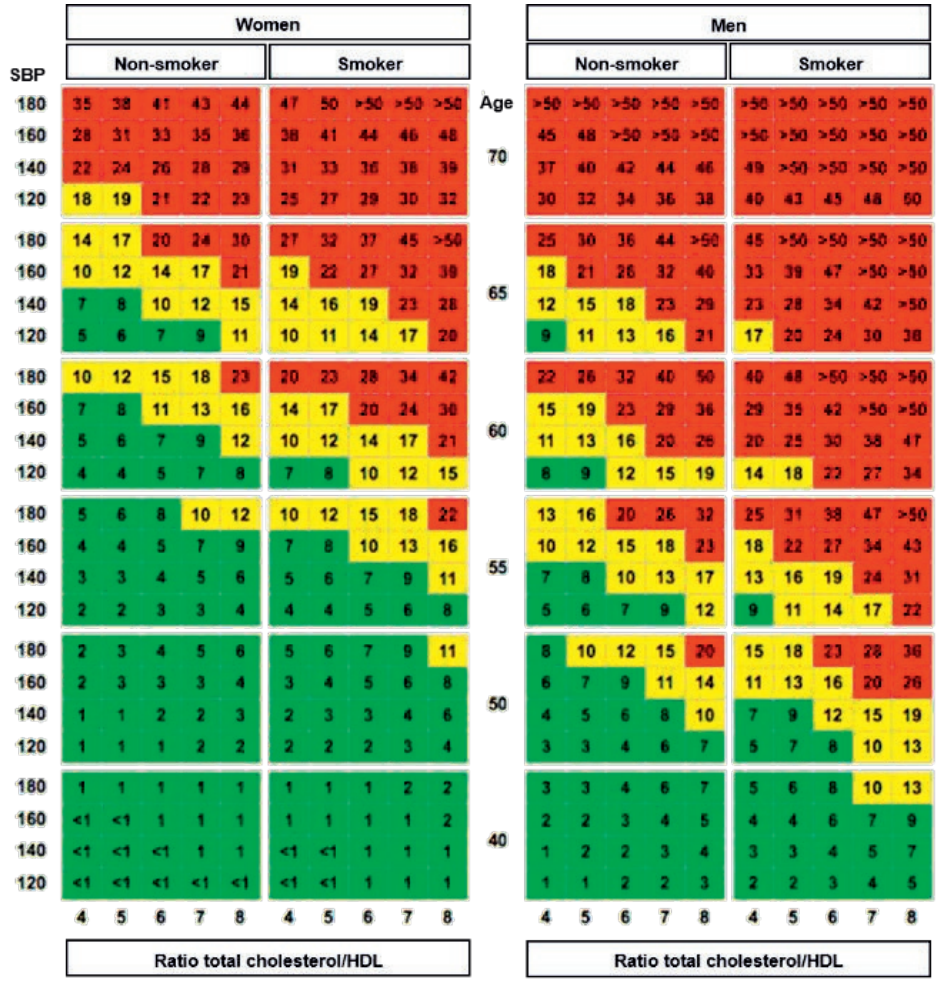
for developing CVD who can benefit from starting preventive treatment. The availability of a detection tool is essential to perform a reliable risk assessment (34). There are a few risk assessment tools that may be suitable as a screening tool.

Traditional risk assessment

Traditionally, identification of individuals at high risk for developing CVD is based on assessment of the main risk factors. Several risk prediction models use these risk factors to calculate the absolute risk of (non-)fatal CVD, for example in the Systematic Coronary Risk Evaluation (SCORE) and the Framingham Heart Score (15, 35, 36). The SCORE model includes age, sex, smoking status, diabetes mellitus status, systolic blood pressure, and total and high-density lipoprotein cholesterol. The absolute risk scores are categorized into three risk categories: low, intermediate and high risk (Figure 2). Based on the calculated risk, GPs can distinguish who requires lifestyle interventions and/or preventive drug treatment. The 2011 edition of the Dutch CVRM-guideline advises SCORE calculation for identification of individuals who are expected to be at high 10-years risk for developing fatal and/or non-fatal CVD (25) (Figure 2a). In 2019, an update of the guideline became available. This edition differs from the previous on several subjects. The most important adjustment is the SCORE table itself. Cardiovascular mortality risk and cardiovascular morbidity risk are displayed separately. The mortality risk is leading in determining the risk category. The morbidity risk is represented by a range instead of one risk percentage, as the morbidity risk estimate is more uncertain than the mortality risk estimate. This risk of morbidity can be used to discuss the CVD risk with the patient (26) (Figure 2b). Since the research in this thesis was conducted before 2019, the previous edition of the CVRM-guideline is integrated in this thesis.

Risk profiling is advised in specific subgroups, for example individuals with diagnosed CVD, diabetes mellitus, kidney disease, a family history of CVD, or one or more risk factors. Advantages of the SCORE model are its ease of use, objectiveness, and it provides a common language for healthcare professionals. However, the SCORE model is limited for different ethnic groups and age ranges (15). Moreover, it has limited accuracy to predict the correct risk status. Especially the classification of intermediate risk is uncertain, as there are intermediate-risk individuals who are actually at higher risk and require a higher level of prevention. On the other hand, the intermediate risk category also includes lower risk individuals who might not need preventive drug treatment. The SCORE model cannot sufficiently distinguish between these two groups of individuals (37).

A.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Ratio total cholesterol/HDL

B.

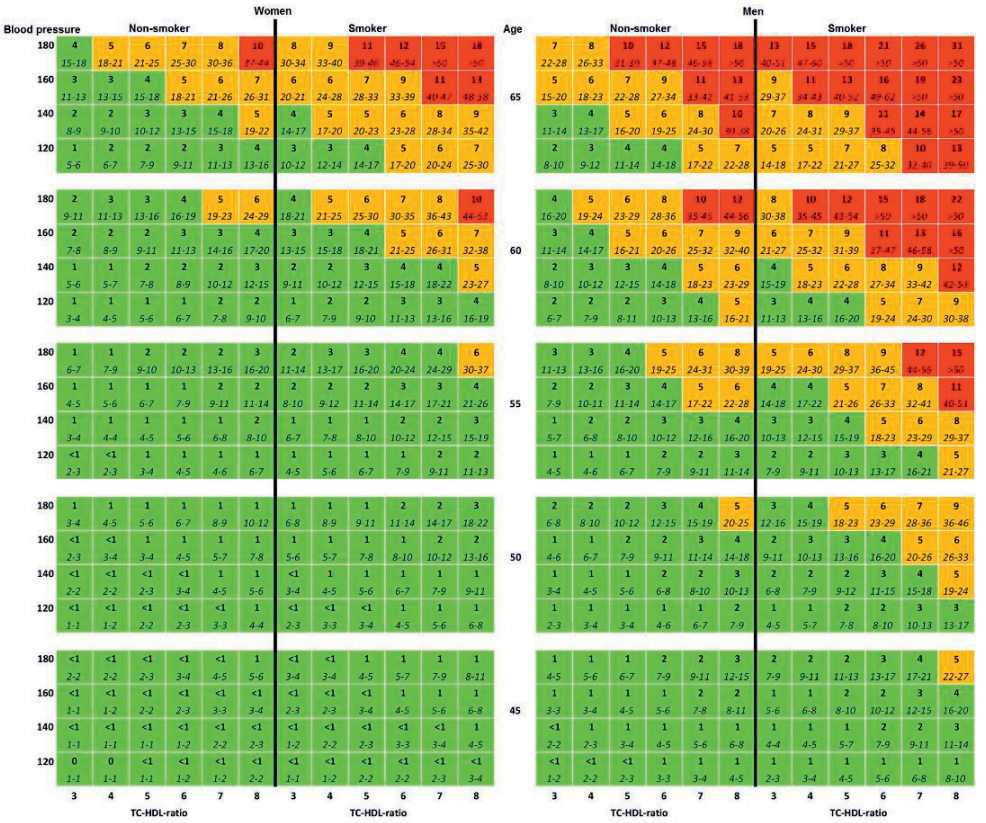

Figure 2. *A.* Risk table for estimating 10-years risk for developing fatal and/or non-fatal cardiovascular diseases based on the Systematic Coronary Risk Evaluation model in the Netherlands (Dutch guideline for Cardiovascular Risk Management of the Dutch College of General Practitioners, edition 2011 (25)). *B.* Risk table for estimating 10-years risk for developing fatal (in **bold**) and non-fatal (in *italic*) cardiovascular diseases based on the Systematic Coronary Risk Evaluation model in the Netherlands (Dutch guideline for Cardiovascular Risk Management of the Dutch College of General Practitioners, edition 2019 (26)).

Coronary artery calcium quantification

Coronary artery calcium (CAC) is argued to be a more accurate risk predictor than traditional risk models (38-41). CAC is strongly associated with major cardiovascular events in asymptomatic individuals, in all races, age groups, and both sexes (42). Previous research has shown that individuals without traditional risk factors but elevated CAC have a substantially higher event rate than those who have multiple risk factors but no CAC (43). The development of coronary artery calcifications is a pathogenic process that is stimulated by several developmental, inflammatory, and metabolic factors (44). The amount of CAC can be quantified using low-dose computed tomography (CT) scanning of the coronary arteries and is expressed as the CAC score (Agatston) (Figure 3) (45). Developments in CT scanning techniques facilitate non-invasive detection of CAC. The absolute CAC score provides an independent risk estimate and is often stratified in three risk groups according to cutoffs of 100 and 400 (46). A decision about a subsequent appropriate preventive treatment strategy can rely on the risk prediction. An

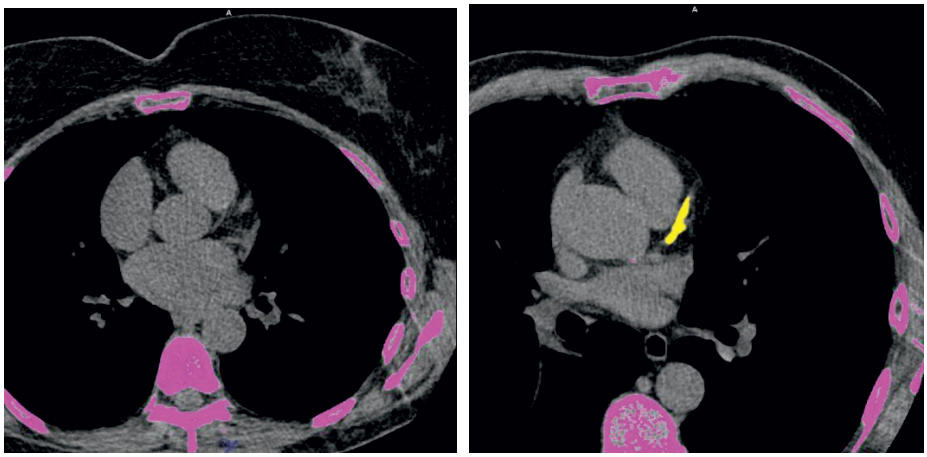

Figure 3. Computed tomography images of the chest for quantification of coronary artery calcification (CAC). Left: CAC score of 0, right: calcifications are highlighted in yellow; CAC score of ≥1000.

earlier study showed that CAC scoring reclassified more than 50% of intermediate-risk elderly individuals as having either low or high risk of CHD events (47). The reclassification rate of the CAC score varied between 22 and 26% in three major population-based cohort studies: the Multi-Ethnic Study of Atherosclerosis, the Heinz Nixdorf Recall study, and the Rotterdam study (48). These studies showed the added value of adding CAC scoring to risk assessment. Another study identified CAC ≥ 100 as a valuable cutoff for considering preventive treatment, as 10-year event rates were consistently above 7.5% in persons with CAC ≥ 100 (42). Furthermore, absence of CAC is associated with low event rates and confers a 15-year warranty period against mortality (42, 49). Based on the observational cohort studies, current CVD prevention guidelines now include statements regarding the application of CAC scoring. The European Society of Cardiology recommends systematic assessment of SCORE in increased risk individuals and additional CAC scoring in individuals with moderate SCORE in their guideline on cardiovascular disease prevention in clinical practice (15). The new 2019 guideline on primary prevention of CVD of the American College of Cardiology/American Heart Association recommends CAC scoring to guide decisions about preventive interventions in select adults, but not as a screening test for all (50, 51). In their 2019 guidelines for the Diagnosis and Management of Chronic Coronary Syndromes, the European Society of Cardiology reported that CAC score may be considered as a risk modifier in the assessment of CVD risk, since it has a net reclassification improvement of 66% over traditional risk factors (52).

Large-scale RCTs to investigate the effectiveness of the use of either traditional risk factors or CAC scoring as screening tools are lacking. Information about the balance between advantages and disadvantages is needed to determine the net (cost-)effectiveness of screening in reducing CVD-related morbidity and mortality. Prospective RCTs are also necessary to potentially demonstrate the added value of CAC scoring in subgroups from the risk population (53, 54). Such RCTs will provide high-level evidence to make guidelines and policy regarding (CAC) screening.

The ROBINSCA trial

The largest population-based RCT on screening for a high risk of cardiovascular diseases was initiated in 2014: the Risk Or Benefit IN Screening for CArdiovascular diseases (ROBINSCA) trial. The primary objectives of this trial are:

1. To establish whether screening for CVD by 'classic' risk factor assessment in asymptomatic men and women followed by early treatment according to prevailing guidelines will reduce CHD mortality and morbidity with at least 15% compared with no screening after 5-years of follow up.
2. To establish whether screening for CAC using CT in asymptomatic men and women followed by early treatment according to prevailing guidelines will reduce CHD mortality and morbidity with at least 15% compared with screening with the 'classic' risk factor assessment after 5-years of follow-up (55).

Women, aged 55-74 years, and men, aged 45-74 years, from the national population registry in the Netherlands were invited to participate in the ROBINSCA trial (Figure 4). They received an information brochure, a waist circumference measurement tape, a baseline risk questionnaire and a form to obtain written informed consent. Asymptomatic respondents free of diagnosed CVD but with a potentially increased CVD risk were eligible for participation. Eligible respondents who gave informed consent were randomized (1:1:1) to either the control arm, intervention arm A (screening according to the SCORE model, CVRM-guideline edition 2011), or intervention arm B (screening by means of determining the CAC score using CT (56)). Five year follow-up is required to investigate the effect of screening on CHD events compared to no screening.

Figure 4. Study regions of the ROBINSCA trial (figure from Vonder et al. (56)). Erasmus Medical Center (Rotterdam) is the coordinating center which investigates the primary and secondary outcomes. University Medical Center Groningen is the computed tomography imaging analysis center.

The primary outcome of the ROBINSCA trial is to investigate whether screening for CHD reduces CHD-related events in subjects at increased risk. Secondary outcomes include extended analyses of the primary outcome, sensitivity of the screening tests, reclassification of individuals in risk categories and corresponding change in treatments, contamination between study arms, impact of screening and the cost-effectiveness of screening. These outcomes will provide information that is required to investigate the balance between advantages and disadvantages of cardiovascular screening. Table 2 provides an overview of potential benefits and harms that need to be quantified.

After 5-years of follow-up, primary outcomes will be investigated. Data will be collected through linkages with the causes of death registry and the national hospital discharge registry at Statistics Netherlands. Currently, the follow-up period is still ongoing. Several secondary outcomes are investigated using results of the screening test and additional participant questionnaires. The rationale of and the research conducted in the ROBINSCA trial is described in this thesis.

Table 2. Potential benefits and harms from cardiovascular screening in the ROBINSCA trial.

Benefits	**Harms**
Reduction in CHD-related mortality	False-positive test results
Reduction in CHD-related morbidity	Overtreatment
Reduction in CHD-related hospital admissions	Disruption of quality of life by fear and uncertainty
Increase in (early) treatment options	Radiation exposure
Reduction of overall overtreatment	Detection of other serious abnormalities
Creating a teachable moment for a healthy lifestyle	False reassurance
Increase risk perception	

Research questions

This thesis aimed to evaluate several secondary outcomes of the ROBINSCA trial. The following research questions were formulated:

1. How to conduct a population-based randomized-controlled screening trial to obtain evidence on the effectiveness of screening for cardiovascular risk in an asymptomatic high-risk population?
2. What is the contamination rate in the study arms of the ROBINSCA trial?
3. What are the differences in cardiovascular risk distributions and the number of preventive treatment indications between screening using traditional risk factor assessment or coronary artery calcium scoring in asymptomatic participants of the ROBINSCA trial?
4. What is the coronary artery calcium prevalence and what are predictors in an asymptomatic potential high-risk target population for coronary artery calcium screening?
5. What is the impact of receiving a cardiovascular disease risk screening result on preventive behavior and compliance to subsequent preventive treatment in asymptomatic participants of the ROBINSCA trial?

Aims and outline of this thesis

The research topics are divided in four parts. **Part 1** focuses on background and power of the ROBINSCA trial. **Chapter 2** discusses the rationale, study design and recruitment process of the trial in detail. In **Chapter 3**, the contamination rate is determined, defined as off-study screening, to assure statistical power to estimate the potential screening effectiveness. **Part 2** focuses on cardiovascular disease screening results. More specifically, **Chapter 4** addresses the CVD risk distributions as assessed by both screening tools and estimates the potential reduction in preventive overtreatment based on the expected shift in CVD risk distribution. In **Chapter 5**, the CAC prevalence in the asymptomatic high-risk population is investigated to evaluate the characteristics and predictors in this potential target population for screening. **Part 3** addresses cardiovascular health behavior. **Chapter 6** describes the impact of receiving a cardiovascular disease screening result on preventive behavior in participants. Lastly, **part 4** (**Chapter 7**) discusses these findings to formulate conclusions. Future perspectives and challenges will be considered.

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Part I

The ROBINSCA trial

Chapter 2

Risk or Benefit in Screening for CArdiovascular Disease (ROBINSCA): the rationale and study design of a population-based randomized-controlled screening trial for cardiovascular disease

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Abstract

Objectives: This article aims to describe the rationale, study design, and the recruitment process of the Dutch Risk or Benefit in Screening for Cardiovascular Disease (ROBINSCA) trial, worldwide the first population-based randomized-controlled Computed-Tomography (CT) screening trial for cardiovascular disease, powered to detect a benefit of 15% reduced Coronary Heart Disease (CHD) morbidity and mortality.

Methods: Addresses of men (aged 45-74 years) and women (aged 55-74 years) were obtained (n=394,058) from the national population registry. All received a mailing with an information brochure, a questionnaire and waist measurement tape and an informed consent form. Asymptomatic people with an expected high-risk for developing CHD were included in this study: 1) a waist circumference of ≥ 102 cm (men) or ≥ 88 cm (women), 2) Body Mass Index of ≥ 30 kg/m^2, 3) current smoker and/or 4) a family history of CHD. Eligible respondents were Randomized (1:1:1) to one of the study arms: intervention arm A (screening traditional risk factors), intervention arm B (screening by Coronary Artery Calcium scoring only) or the control arm (usual care). Screened participants with a high risk for developing CHD were referred to the general practitioner for cardiovascular risk management. Linkages with national registries will be performed to measure (CHD-related) morbidity and mortality.

Results: A total of 87,866 (22.3%) people responded to the questionnaire, of which 43,447 (49.4%) were Randomized to intervention arm A (n=14,478 (33.3%)), intervention arm B (n=14,450 (33.3%)), or the control arm (n=14,519 (33.4%)). Of those who were considered to be ineligible, one had prior diagnosis of CHD (n=14,156), a medication for hypercholesterolemia and hypertension (n=13,670), no completed informed consent (n=4,490), previous cardiovascular surgery (n=4,146), and/or a CAC score within the last 12 months (n=393).

Conclusion: Evidence for net-effectiveness of population-based screening for cardiovascular risk in an asymptomatic population will possibly enable large-scale implementation with large health gains.

Introduction

Coronary Heart Disease (CHD) remains a major cause of morbidity and mortality worldwide (1). As stated by the European Heart Network (EHN), about 20% (1.7 million deaths) of all-cause mortality can be attributed to CHD in 2015. A further 17 million men and 13 million women suffered from CHD in 2015 and more than 35 million (14% in males; 11% in females) disability-adjusted life years (DALY) were lost due to CHD (2, 3). The total annual costs of CHD are considerable and estimated at €59 billion annually. About 32% (€18.9 billion) is due to health care costs, 33% (€19.8 billion) due to production losses and 35% (€20 billion) due to the informal care of people with CHD (3).

Despite all medical advances last decades, one major concern is that CHD is often asymptomatic until the presentation of a serious event as myocardial infarction (MI) leading to persisting disability and/or premature death. The underlying process of (sub-clinical) atherosclerosis has one of the longest (stable) unrecognized courses, and therefore mainly untreated. Modifying cardiovascular disease (CVD)-related risk factors can prevent the vast majority of the CVD events (4). However, the combination of a high prevalence of unhealthy lifestyles as well as the suboptimal use of prevention measures and the ageing population remains a concern (3, 5). The rationale of screening is to halt or delay progression of the (subclinical) disease and thereby gain healthy life-years by offering treatment options at an earlier, yet undetected, and hopefully more efficacious stage. Although cost-effective preventive treatment options are available for cardiovascular diseases, there is no hard evidence from RCTs about whether the earlier detection of a high risk for developing CHD in the asymptomatic high-risk population indeed leads to earlier, more effective, less intensive treatment and therefore to health benefits in terms of reduced morbidity and mortality.

The identification of asymptomatic people at risk of CVD relied almost exclusively on traditional risk factors to subsequently stratify individuals into low, intermediate, and high-risk to guide treatment decisions: age, gender, smoking habits, family history of CVD, Body Mass Index (BMI), lipids, and blood pressure (6, 7). However, the observation that the majority of coronary events occur in the intermediate risk group whose members are not considered candidates for intensive treatment as their high-risk counterparts calls for improvement in the risk stratification (8, 9). Computed Tomography (CT) enables the non-invasive detection and quantification of calcifications of coronary arteries (10). This Coronary Artery Calcium (CAC) score is argued to be useful by presenting an individualized cumulative lifetime risk exposure of (un)known risk factors, independently of traditional risk factors, but strongly related to both non-lethal major adverse cardiovascular events (such as myocardial infarction and stroke) and all-cause mortality, as shown by the Multi-Ethnic Study on Atherosclerosis (MESA) (11, 12), Framingham Heart Study (13) and Heinz Nixdorf Recall Study (14-16). Based on the total amount of coronary artery calcium (Agatston score) (17), CAC scoring seems to provide the opportunity for personalized risk assessment to identify those who might benefit most from preventive treatment. The net classification index after CAC scoring compared with traditional risk scoring implies the superiority of CAC scoring above risk factor based testing (8).

The European Guidelines on cardiovascular disease prevention in clinical practice only recommend systematic screening in those likely to be at high risk due to the presence of a family history of premature CVD, familial hypercholesterolemia, major CVD-related risk factors and/or co-morbidities (Class I recommendation; level of Evidence C) (18). The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology state that asymptomatic individuals at intermediate Framingham risk may be reasonable candidates for coronary calcification screening "when a risk-based decision to prescribe statins is uncertain after a patient-physician risk discussion", whereas the American College of Preventive Medicine does not recommend routine screening in asymptomatic individuals using CT (7, 18-20). The IIb recommendation ("may be considered") is mainly caused by the fact that data from large-scale RCTs, indicating that CAC screening for CHD will reduce CHD-related mortality and morbidity, are lacking. The EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) trial is the only small RCT among 2,137 (preferentially selected and higher educated) volunteers, comparing a group that did undergo CAC scanning before risk counselling or a control group that only had risk factor counselling (21). Randomization to CAC scanning was associated with superior CAD factor control on FRS, blood pressure, lipids, and medication after four years of follow-up. Unfortunately, the study was too small to have sufficient statistical power on hard events outcomes as CHD mortality and morbidity (22).

There is an urgent need for large-scale population-based RCTs. Although this type of study requires a large amount of resources and time, it is the only way to provide evidence on the balance between potential benefits (reduction in CHD-related morbidity and mortality, reduction in overuse of statins and aspirin) and harms (radiation risk, overdiagnosis, overtreatment, and impact on quality of life) of CHD screening. The aim of this article is to describe the rationale, study design, and the recruitment process of the Dutch ROBINSCA (Risk or Benefit IN Screening for Cardiovascular disease) trial, a population-based randomized controlled screening trial for cardiovascular diseases, incorporating CAC scoring in one of the intervention arms.

Methods

ROBINSCA study objectives

The ROBINSCA trial is a 3-arms trial, designed 1) to investigate whether population-based screening for a high risk for developing cardiovascular heart diseases by SCORE followed by risk reducing treatment can reduce coronary artery disease-related morbidity and mortality with at least 15% compared to no screening amongst asymptomatic men and women after five years of follow-up and 2) to investigate whether population-based screening for a high risk for developing cardiovascular heart diseases by CAC scoring followed by risk reducing treatment can reduce coronary artery disease-related morbidity and mortality with at least 15% compared to screening by SCORE amongst asymptomatic men and women after five years of follow-up.

Recruitment procedure

To start the study, addresses of all men (aged 45-74 years) and women (aged 55-74 years) who lived in one of the three selected regions in The Netherlands were obtained (n=394,058) after a positive advice for a linkage with the national population registry (Figure 1). All selected people received a mailing with an information brochure, a questionnaire and waist measurement tape to examine eligibility and an informed consent form. The risk questionnaire was based on validated questionnaires to assess the CVD risk (23-25). The questionnaire contains items on age, gender, social-economic status (5- point scale), ethnicity, height, weight, waist circumference, CAC screening in the preceding year (yes/no), presence of chronic diseases and CVD (list: yes/no), surgery for CVD (list: yes/no), prescription of medication for hypertension/ hypercholesterolemia and/or diabetics (yes/no), list of prescribed medication, familial history of CVD (MI or sudden death) in first of second degree relatives before the age of 65 years (6-point scale), and current smoking behavior (smoking last week (yes/no), smoking duration (in years), smoking intensity (cigarettes/day)).

Inhabitants received the information packet in Apeldoorn region in July 2014, in The Hague in October 2014 and in Groningen in June 2016.

Selection of participants

A respondent was considered to be eligible when one or more of the inclusion criteria were fulfilled, while none of the exclusion criteria were met. The inclusion criteria for ROBINSCA are a waist circumference of ≥ 102 cm (men) or ≥ 88 cm (women) (26), Body Mass Index of ≥ 30 kg/m^2, current smoker and/or a family history of MI or sudden death.

Those who had already been diagnosed with cardiovascular disease (MI, heart attack, Cerebral Vascular Accident/Transient Ischemic Accident, heart failure, angina pectoris, aneurysm, stenosis of the carotid artery/femoral artery and atherosclerosis), who have had previous cardiovascular surgery (Coronary Artery Bypass Grafting, Percutaneous Coronary Intervention, or heart transplantation), who were on prescribed cholesterol lowering and blood pressure-lowering drugs, who had a CAC scoring by CT scanning in the previous year and/or no complete informed consent form were excluded for participating in this study. Eligible respondents were Randomized (1:1:1) to intervention arm A, intervention arm B or the control arm (Figure 1).

Screening

Intervention arm A: Participants were invited to one of the local screening sites to measure their risk for developing cardiovascular diseases. A blood sample was taken to determine non-fasted cholesterol levels (Total Cholesterol level, High-Density Lipid-protein (HDL) Cholesterol level; mmol/l). Mean rested blood pressure (mmHg) was measured by two automatic consecutively measurements using an electronic blood pressure device (Microlife WatchBP Office, model TWIN200 AFS).

The 10 years risk for fatal and non-fatal CVD was calculated using the SCORE risk table, as used by the Dutch College of General Practitioners (27). Variables included in the model are

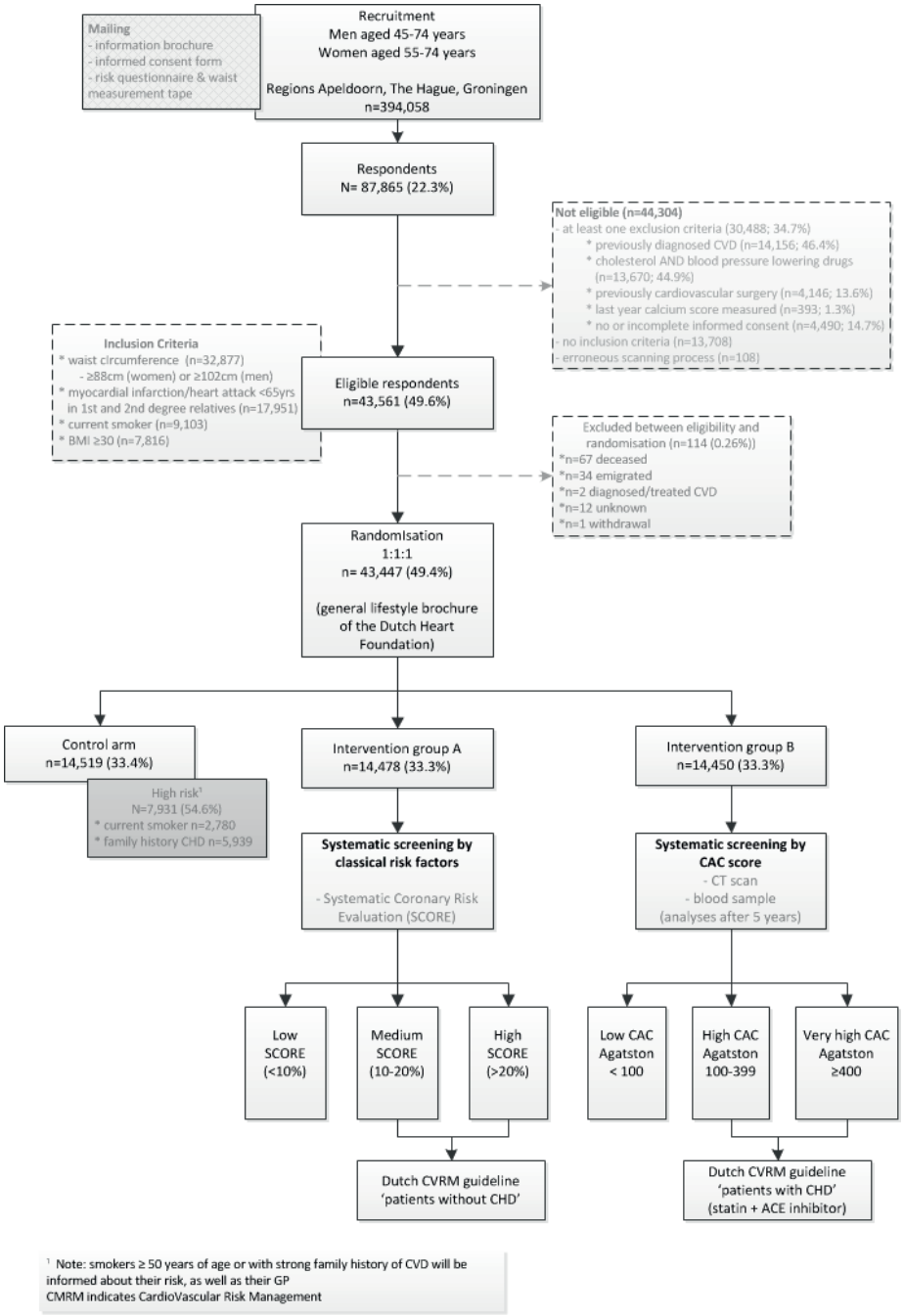

Figure 1. Flowchart of the recruitment, randomization and screening process in the ROBINSCA trial.
Note: Smokers ≥ 50 years of age or with strong family history of CVD will be informed about their risk, as well as their GP.
Abbreviations: BMI = Body Mass Index, CAC = Coronary Artery Calcium, CHD = Coronary Heart Disease, CT = Computed Tomography, CVD = Cardiovascular Disease, CVRM = Cardiovascular Risk Management, SCORE = Systematic Coronary Risk Evaluation

age, gender, smoking status, systolic blood pressure and Total Cholesterol/HDL-Cholesterol ratio). For those participants with established diabetes mellitus, the actual age was increased with 15 years. Since data about diagnosed rheumatoid arthritis was considered to be invalid, there was no recalculation possible in these participants. A SCORE <10% indicates a low 10 years risk for developing CVD, whereas a SCORE of 10-20% were classified as a moderate risk and a SCORE of 20% or more as high risk.

Intervention arm B: All participants Randomized in intervention arm B received an invitation for a CT scan to measure the CAC Score. The scanning protocol has been published previously (28). In brief, the CAC Score was measured using dual-source CT (DSCT) without the use of a contrast agent. According to participants' weight and size (small/slender or large) the radiation dose exposure was adjusted automatically. The DSCT calcium scoring examination followed a scout view and was performed with prospective ECG-triggering. All scans were performed by experienced technicians, who were blinded to the clinical data of the participants. Quantification of coronary calcifications was performed with using dedicated CAC scoring software and the CAC scores were determined according to Agatston method (17) by multiplying each area of interest with a factor indicating peak density within the individual area. The effective dose of CAC screening (accounting for the sensitivity of exposed tissues) is 0.7-2 mSv, depending on the technology used. CAC scores were then divided into 29).

Incidental findings in the chest or abdomen with expected clinical relevance (aortic aneurysm of ≥ 50 mm, calcified pleural plaques and/or pleural fluid (≥ 2 cm thickness), large liver cyst(s) (≥ 10 cm), identifiable abdominal mass) were reported at the general practitioner-after verifying that the participant gave their written informed consent (divided in serious incidental findings versus non-serious incidental findings). Incidental findings with no or limited clinical relevance (valve calcification (aortic valve, mitral valve, e.g.), valve calcification (aortic valve, mitral valve, e.g.), pericardial abnormalities (thickening, calcification, e.g.), hiatus hernia, small to medium size liver cyst(s)) were only reported at the screening site.

Control arm: Study participants who were Randomized in the control arm received usual care (no screening). However, those aged above 55 years who currently smoked and those with a family history of CHD were prompted that they can ask for a risk scoring measurement by their GP, confirm the national guidelines for general practitioners (27). The GP was also informed about this message given to the participant.

Referral and preventive treatment

For participants of intervention group A, a SCORE of 10% and above indicated advice for referral to the GP for preventive treatment according to the Dutch guideline cardiovascular risk management for "patients without cardiovascular disease" from the Dutch College of General Practitioners (27).

Participants in intervention group B with an Agatston score above 100 were referred to the GP for further cardiovascular risk management. It was recognised that the lack of knowledge will

possibly impact the clinical management of the CAC score. Information about the trial, the screening result and the recommended treatment was provided to all general practitioners. The advice for treatment was established in accordance with the current literature and in consultation of the research team and local cardiologists and GPs. The aim of the treatment study protocol was to keep it as close as possible to the current practice in primary care. Therefore, the recommended treatment comprises the prescription of ACE-inhibitors and statins. This is in line with the Dutch guideline cardiovascular risk management for "patients with CHD" from the Dutch College of General Practitioners (27).

End points

The primary outcome is to investigate whether screening for CHD in subjects at increased risk reduces CHD-events. A CHD event is defined as the first occurrence, within the follow-up period after randomization, of non-fatal or fatal coronary heart disease. These data will be collected through linkages with Causes of Death registry and National Hospital Discharge Registry at Statistics Netherlands. The underlying and contributory causes of death of participants who died will be retrieved through linkage with the Causes of Death Registry coded according to the International Classification of Deaths. In a subset of individuals, charts from the GPs and hospitals will be collected and reviewed by an independent committee to assess the validity of the official statistics, as has been done in our other RCTs (30, 31).

Secondary outcomes

Secondary outcomes measures include extensions of the primary outcome measures, sensitivity of the screening test(s), the reclassification of individuals in risk categories and corresponding change in treatments, the effects of CHD screening and cost-effectiveness.

The effects of the interventions may have an effect on stroke as well. In an extended analysis, the rate of strokes in each arm will be incorporated in additional analyses as secondary outcome measure. Since fatal coronary heart disease is a large proportion of all deaths, differences in all-cause mortality between arms will be analysed too. The sensitivity of the screen test will be evaluated using the 5-year follow-up data and equals the proportion of subjects who developed CHD and who were correctly identified as intermediate or high-risk participants by the conventional risk assessment (group 2) or by CAC score (group 3). The area under the receiver-operating-characteristic curve, reclassification ratio, integrated sensitivity and specificity will be used as criterions for the performance of the tests (32). In the intervention arms, the change in risk estimates and distribution will be compared to the control arm. At the end of the follow-up period, questionnaires will be sent to the participants to ask for treatments received, compliance, lifestyle, risk perception, and impact of earlier diagnosis. The percentage of overtreatment and/or unnecessary treatments can be deducted.

The favourable and unfavourable effects of CVD screening (Health- Related Quality of Life and health-related behaviour) are assessed in a random subsample of 5000 participants from randomization until 12 months after screening.

Power analysis

The expected annual average event rate was estimated at 1.38%, based on data (year: 2008) for gender and age obtained from Statistics Netherlands. Based on previous population screening trials, the compliance rate in intervention group B was set on 90%, while the contamination rate of CT screening in intervention group A was set on 15%. This might be overestimated, since coronary calcium scoring is not part of the national guidelines for general practitioners. To reach a power of 80% to detect a 15% reduction in CHD under above mentioned conditions, a sample size of 13,028 was needed (Table 1).

Some assumptions were made. The reduction in CHD that can be showed should be at least 15% between intervention group B (CAC score) and intervention group A (SCORE). This implies that comparisons of intervention group A versus controls and intervention group B versus controls should also be possible. Reasons for a 15% reduction threshold derived from an estimated reclassification of about 35%, and the
estimated higher risk categories due to screening by CAC scanning (8). Thereby, a population screening programme with a morbidity and mortality reduction less than 15% seems to become never cost-effective.

Ethical Approval

The study was approved by the Minister of Health, after a positive advice of the Dutch Health Council, because of the Dutch Population Screening Act. All participating centres gave their approval for conducting the study in the centres. Furthermore, the Minister of the Interior and Kingdom Relations gave permission to obtain all addresses from the Dutch population registry of men (aged 45-74 years) and women (aged 55-74 years) living in one of the three regions.

Table 1. Power calculations under different conditions.

CHD-event rate comparison arm (%)	CHD-event reduction (%)	Screen compliance group 3 (%)	Contamination of CAC-screening group 2 (%)	N needed per arm
1.17	15	95	5	10,682
1.17	**15**	**95**	**10**	**11,929**
1.17	15	95	15	13,414
1.17	**15**	**90**	**5**	**12,026**
1.17	15	90	10	13,524
1.38	15	95	5	9,079
1.38	15	90	10	11,496
1.38	**15**	**90**	**15**	**13,028**
1.17	20	90	20	9,554
1.38	20	80	20	11,184
CHD-event rate control arm (%)	CHD-event reduction (%)	Screen compliance group 2 (%)	Contamination of classic-screening group 1 (%)	N needed per arm
1.38	**15**	**95**	**20**	**12,922**

Abbreviations: CAC = Coronary Artery Calcium, CHD = Coronary Heart Disease

Results

Recruitment and randomization

A total of 394,058 addresses of men and women living in Apeldoorn, The Hague or Groningen were obtained from the Dutch Population Registry of which 87,866 (22.3%) people responded to the questionnaire. Of the respondents, almost half (n=43,562; 49.6%) were considered to be eligible for participating in the ROBINSCA trial (Figure 1). In the region Apeldoorn and Groningen, 52.1% and 51.0% of the respondents were considered to be eligible respectively, whereas this was 44.4% of the respondents in the (most urban) region The Hague. Of those who were considered to be ineligible, most of them had prior diagnosis of CHD (n=14,156) and/or a prior prescription of both cholesterol as well as blood pressure lowering drugs (n=13,670). No informed consent or an incomplete informed consent form (n=14.7%), previous cardiovascular surgery (n=4,146), and/or a CAC score within the last 12 months (n=393) were reason for exclusion. A total of 114 eligibles were excluded just before randomization due to death, emigration, diagnosed/treated CHD or withdraw/unavailability. All other eligibles (n=43,447) were Randomized (1:1:1) to intervention arm A (n=14,478 (33.3%)), intervention arm B (n=14,450 (33.3%)), or the control arm (n=14,519 (33.4%)) (Figure 1). Baseline characteristics (gender, age, educational level, region, BMI, waist circumference, family history of myocardial infarction, smoking status, and diabetes mellitus) of study participants were comparable ($p>0.05$) between the three study arms (Table 2), concluding an adequate randomization.

Discussion

Systematic population-based screening in an asymptomatic population is not yet recommended in (inter)national guidelines, although screening for several types of cancer has become a population screening strategy, despite the much lower incidence. The European Guidelines on cardiovascular disease prevention in clinical practice only recommend systematic screening in those likely to be at high risk due to the presence of a family history of premature CVD, familial hypercholesterolemia, major CVD-related risk factors and/or comorbidities (18). The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology stated that asymptomatic individuals at intermediate Framingham risk may be reasonable candidates for coronary calcification screening "when a risk-based decision to prescribe statins is uncertain after a patient-physician risk discussion", whereas the American College of Preventive Medicine does not recommend routine screening in asymptomatic individuals using CT (7, 18-20). The IIb recommendation ("may be considered") is mainly caused by the fact that data from large-scale RCTs, indicating that CAC screening for CHD will reduce CHD-related mortality and morbidity, are lacking.

Long-term RCTs that evaluate hard end-points as morbidity and mortality are needed to overcome well-known biases of screening (lead-time and length time bias and overdiagnosis) in case of using survival rates as reflection of programmes' effectiveness. Evidence for net-effectiveness of population-based screening for cardiovascular risk in an asymptomatic population will enable large-scale implementation with possibly exceptionally large health gains.

Table 2. Baseline characteristics of study participants.

	Control arm n/N (%)	Intervention arm A n/N (%)	Intervention arm B n/N (%)	p-value
Gender				0.866
Male	7044/14519 (51.5)	7456/14478 (51.5)	7480/14450 (51.8)	
Female	7475/14519 (48.5)	7022/14478 (48.5)	6970/14450 (48.2)	
Age (median (IQR))	61 (11)	61 (11)	61 (11)	0.696
Educational level				0.492
Low	2899/14469 (20.0)	2980/14436 (20.6)	3007/14399 (20.9)	
Medium	6476/14469 (44.8)	6419/14436 (44.5)	6307/14399 (43.8)	
Higher	5094/14469 (35.2)	5037/14436 (34.9)	5022/14399 (34.9)	
Region				0.447
Apeldoorn	5858/14519 (40.3)	5855/14478 (40.4)	5887/14450 (40.7)	
The Hague	3594/14519 (24.8)	3662/14478 (25.3)	3526/14450 (24.4)	
Groningen	5067/14519 (34.9)	4961/14478 (34.3)	5037/14450 (34.9)	
Body Mass Index (median (IQR))	26.3 (5)	26.3 (5)	26.3 (5)	0.702
Waist Circumference (median (IQR))	101.5 (14.4)	101.5 (14.5)	101.5 (14.5)	0.700
Family history of CHD				0.269
No	7340/13302 (55.2)	7190/13223 (54.4)	7304/13213 (55.3)	
Yes	5962/13302 (44.8)	6033/13223 (45.6)	5909/13213 (44.7)	
Smoking status				0.218
Former smoker	11420/14519 (78.7)	11503/14478 (79.5)	11454/14450 (79.3)	
Current smoker	3099/14519 (21.3)	2975/14478 (20.5)	2996/14450 (20.7)	
Diabetes Mellitus				0.382
No	14055/14519 (96.8)	14009/14478 (96.8)	13949/14450 (96.5)	
Yes	464/14519 (3.2)	469/ 14478 (3.2)	501/14450 (3.5)	

Abbreviations: CHD = Coronary Heart Disease, IQR = Interquartile Range

This article presented the rationale, study design, and the results of the recruitment process of the Dutch large-scale population-based randomized-controlled screening trial for cardiovascular diseases: the ROBINSCA trial.

Advantages of population-based recruitment over volunteer-based recruitment is that it is assumed that potential differences in background variables (morbidity and mortality, general health e.g.) are comparable between the study population and the target population (high-risk for developing CHD). But, self-selection might always be present. Thereby, it is well-known that less deprived are more likely to have higher risk, but they are less likely to attend screening or take part in trials, although the potentially high gain from screening (33). Future comparison of background characteristics between the study population (data from the questionnaire) and the general population (data from Statistics Netherlands) is warranted to estimate the representativeness of the study population.

Another advantage of the population-based recruitment strategy is that those who were approached with the question to participate in the screening trial were unaware of the in- and exclusion criteria, what limit potential response bias that should increase the risk of study participation.

Data of the ROBINSCA trial will provide more insight on the balance between the harms and benefits of screening for cardiovascular diseases.

Recently, researchers of the Multi-Ethnic Study on Atherosclerosis found that the (absence of) an elevated CAC score is also associated with and increased risk for (the absence of) non-cardiovascular disease (cancer, chronic kidney disease, chronic obstructive pulmonary disease and hip fractures), what suggest a more widespread use in risk prevention of multiple diseases (34). Now-a-days, CAC scoring on low-dose CT for lung cancer screening participants is also recommended in current guidelines (10).

The obstruction of the coronary arteries is seldom not accompanied with an increased calcium score. In that perspective is a CAC of zero indicative for a low risk for CHD in the near future. The absence of CAC seems to be an overall marker for a process of healthy ageing due to the lower risk for not only developing cardiovascular diseases, but also other diseases as cancer and chronic lung diseases (10). It is needed to determine whether (current) over-treatment based on traditional risk factors could be diminished in the asymptomatic population with absent CAC.

The ROBINSCA trial only performed a single screening round. The question is whether multiple CT scans might provide better individualized risk prediction. However, Radford and colleagues found that the progression in CAC score provides no additional prognostic information (35). Nevertheless, more research is needed to further understand the impact of CAC progression on future CHD risk.

Conclusion

Evidence for net-effectiveness of population-based screening for cardiovascular risk in an asymptomatic population will possibly enable large-scale implementation with large health gains. If a population screening programme for cardiovascular risk turns out to be successful, CAC screening is estimated to prevent 100,000 CHD-related death and 500.000 CHD-related hospital admissions in Europe yearly, while considering the assumption of a 15% reduced morbidity and mortality.

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Chapter 3

Contamination rate in the Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial

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Submitted

Abstract

Objectives: The population-based Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial investigates whether screening for a high risk for developing cardiovascular disease (CVD) will reduce coronary heart disease by at least 15% compared to no screening. This sub-study investigated the contamination rate, defined as off-study screening.

Methods: Asymptomatic Dutch individuals, men aged 45-74 years and women aged 55-74 years, were randomized (1:1:1) to: 1) control arm (usual care), 2) intervention arm A (CVD screening by traditional risk assessment) or 3) intervention arm B (CVD screening by coronary artery calcium (CAC) quantification). An online questionnaire about medical examinations by general practitioners performed after screening was sent to a random sample (n=700) of ROBINSCA-participants.

Results: The overall response was 71%. A total of 37.6% was female and the mean age (± standard deviation) was 63.5±7 years. Within intervention arm A, one out of 213 respondents reported an off-study CAC-score measurement (contamination rate: 0.5%). No screening interventions were reported by the 59 respondents from the control arm. In 35.6% of the respondents of intervention arm B potential contamination was reported.

Conclusion: Contamination can diminish statistical power and the potential screening effect in randomized-controlled screening trials. Contamination in intervention arm B could not be determined since the reported off-study examinations may be part of preventive treatment monitoring as well. Almost no contamination was seen in intervention arm A and in the control arm. Future results of the ROBINSCA trial are awaited to demonstrate a potential effect of screening for CVD.

Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD), is number one cause of death worldwide (1-3). To prevent fatal and non-fatal CVD events, current risk assessment involves measuring the main risk factors such as high blood pressure, high cholesterol levels, and smoking for risk calculation in various prediction models (4, 5). However, these models vary widely concerning predictors and outcomes and they lack precise accuracy, since the majority of coronary events occur in individuals at intermediate risk (6-8). There is increasing evidence that the amount of coronary artery calcification (CAC) is strongly related with higher CHD morbidity and mortality independent of main risk factors (9).

It has previously been suggested that population-based screening for CVD is a promising strategy for identifying potential high-risk individuals and consequently start preventive treatment to reduce CVD morbidity and mortality (5). Screening aims to stop or delay severe disease progression in asymptomatic individuals by starting often less invasive preventive treatment in an early stage aiming for a longer and mainly healthier life (10). However, information is lacking about the effectiveness of systematic screening for CVD and about benefits and harms of the potential screening strategies resulting in an urgent need for randomized-controlled trials (RCTs) (11). The Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial is the first large-scale population-based randomized-controlled screening trial that investigates whether screening for a high risk of developing CVD followed by preventive treatment will reduce CHD morbidity and mortality by at least 15% in asymptomatic men and women compared to no screening (usual care) (12). Screening is carried out either by 1) a traditional risk factor assessment based on the Systematic Coronary Risk Evaluation (SCORE) model (intervention arm A) or 2) detection and quantification of CAC using a multi-detector Computed Tomography (CT)-scan (intervention arm B) (4, 13).

The required sample size to show a reduction in CHD morbidity and mortality of at least 15% in intervention arm B compared to intervention arm A was calculated, while assuming this size also to be sufficient to demonstrate the effect of both screening interventions compared to the control arm. However, statistical power is not only dependent on the sample size. It is also highly dependent on contamination, which occurs when study participants also receive the intervention to which they were not randomized. When a participant is screened using both screening strategies, it is difficult to determine based on which screening result was acted in terms of preventive treatment. Therefore, blending of interventions between study arms might lead to biased results that decrease visible effects of different screening strategies on trial outcomes. The risk of contamination increases when study participants are family, neighbors or have the same general practitioner (GP) (14). Contamination in randomized-controlled screening trials such as the ROBINSCA trial can diminish the estimated potential screening effectiveness and should therefore be monitored (15).

This study aims to determine the contamination rate in the ROBINSCA trial, defined as performing a CVD screening intervention deviating from randomization intention.

Methods

Study objectives

ROBINSCA trial

The design of the ROBINSCA trial was published elsewhere (12). In short, 330,800 men aged 45-74 years and women aged 55-74 years living in the areas Apeldoorn, The Hague and Groningen of the Netherlands based on the national population registry were invited to participate. Individuals received an invitation letter along with an information brochure, informed consent form and baseline questionnaire with measuring tape. They were asked to complete the questionnaire, measure their waist circumference and give written informed consent. Asymptomatic individuals who fulfilled at least one of the following inclusion criteria were considered eligible to participate in the trial: 1) a high waist circumference (≥88 cm for women or ≥102 cm for men), 2) a high Body Mass Index (BMI ≥30 kg/m^2), 3) a family history of CVD (myocardial infarction or sudden death before the age of 65 years in first and second degree relatives), or 4) current smoking. Individuals with a history of diagnosed CHD or previous CHD surgery, use of both cholesterol- and blood pressure lowering medication, a CAC-score measurement in the previous year, or incomplete informed consent were excluded. To demonstrate a reduction in CHD events of at least 15% with a power of 80%, the sample size needed was 13,000 individuals per study arm with (1:1:1) randomization to the control arm, intervention arm A or intervention arm B, assuming 95% compliance of testing and 20% contamination in intervention arm A. All randomized participants received generic life style recommendations of the Dutch Heart Foundation. Participants in the control arm received usual care since no screening was offered. Participants in intervention arm A were screened by calculating the absolute risk of fatal and non-fatal CVD in the next ten years according to the SCORE risk model using age, gender, blood pressure, total cholesterol, high-density lipoprotein cholesterol and smoking status, as adapted from the Dutch guidelines for general practitioners (13). Participants in intervention arm B underwent CT-scanning to quantify the amount of any coronary artery calcifications, expressed in Agatston score (16). Following screening, participants in the intervention arms were stratified into three risk categories (for arm A: SCORE < 10% (low risk), SCORE 10-20% (intermediate risk), SCORE ≥ 20% (high risk); and for arm B: CAC-score < 100 (low risk), CAC-score 100-399 (high risk), CAC-score ≥ 400 (very high risk)) and results were communicated to both participants and GPs. Participants with an increased CVD risk were advised to consult their GP for preventive treatment according to the Cardiovascular Risk Management (CVRM) guideline of the Dutch College of General Practitioners adapted for this trial in consultation with local cardiologists and GPs. Increased risk participants of intervention arm A were seen as "patients without CVD" (lifestyle advice with additional lipid- and/or blood pressure lowering drug treatment when indicated). Participants at increased risk of intervention arm B were treated as "patients with CHD" and therefore were advised to start with ACE-inhibitors (when blood pressure is normal) and statins (13). After a follow-up of at least five years, the occurrence of non-fatal or fatal CHD events will be compared between the three study arms. The ROBINSCA trial was approved by the Minister of Health of the Netherlands after a positive advice of the Dutch Health Council. Participating centers gave their (medical ethical) approval to conduct the study.

Sub-study

To measure the contamination rate, a random sample (n=700) was selected from the ROBINSCA study population. Per intervention arm, 300 screened participants (100 per risk stratification category) were selected as well as 100 participants from the control arm (Figure 1). This sample received a questionnaire about medical examinations by their GP performed after randomization into the control arm and after screening in the intervention arms.

Contamination questionnaire

Contamination in the ROBINSCA trial was defined as performing an off-study CVD screening intervention in randomized participants. The power calculation was based on 20% potential contamination in intervention arm A by means of determining the CAC-score. Individuals from this intervention arm with an increased CVD risk result are advised to consult their GP which increases the risk of the GP performing an off-study screening. Therefore, the assumption is

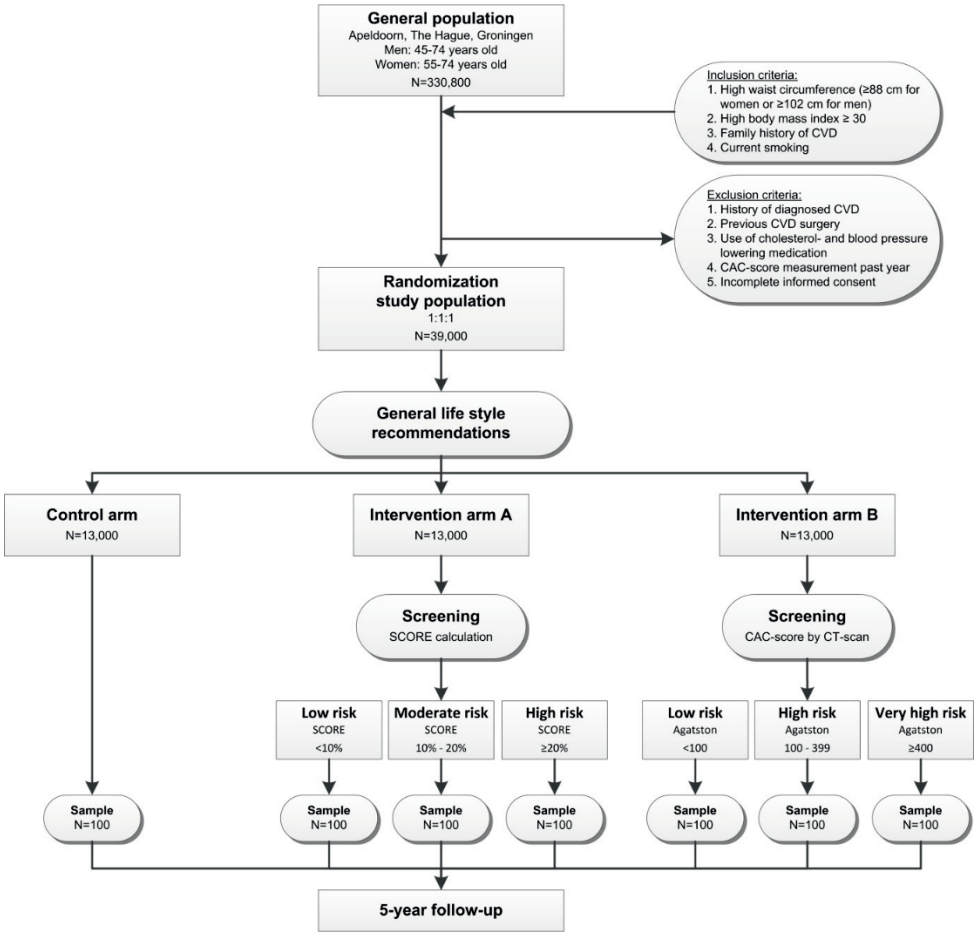

Figure 1. Flowchart of the study design of the ROBINSCA trial and selection of a random sample.
CVD, Cardiovascular Diseases; CAC, Coronary Artery Calcium; SCORE, Systematic Coronary Risk Evaluation; CT, Computed Tomography

that the power calculation automatically covers contamination in the control arm, where the chance that individuals visit their GP is considerably lower. By ensuring an acceptable contamination rate in intervention arm A, the amount of contamination in the control arm is presumably also within the set limit of 20% contamination.

After a median (Interquartile Range (IQR)) follow-up of 16.8 (15.0 - 19.7) months after randomization, participants received an email with the request to fill in an online questionnaire with multiple choice questions and open space to type about 1) whether their GP performed any medical examinations as a consequence of participation in the ROBINSCA trial, 2) the reasons for visiting the GP and 3) performing any medical examinations. Measuring the CAC-score in intervention arm A or in the control arm was regarded as contamination. Additionally, measuring the combination of cholesterol and blood pressure in the control arm was also regarded as contamination since those examinations are part of traditional risk assessment in the SCORE risk model. Performing those measurements in intervention arm B was not considered as contamination. These measurements can be part of monitoring preventive CVD treatment since the recommended ACE-inhibitors cannot be prescribed in participants with a low blood pressure.

Statistical analysis

Descriptive analyses on data from the baseline questionnaire were performed to describe the study population characteristics using means with Standard Deviations (SD), and medians with IQR in respectively normally and non-normally distributed variables. Using the chi-square test, differences in response rates between study arms were analyzed. Frequency analyses were used to calculate contamination rates in the study arms and the chi-square test was used to compare these rates. A P-value of 0.05 was considered to be statistically significant for all analyses. Statistical analyses were carried out using IBM SPSS Statistics Version 24.0 (2016).

Results

Study population characteristics

The random sample of 700 ROBINSCA-participants had a mean age (±SD) of 61.2 ± 7 years and consisted of 278 women (39.7%). The overall response to the contamination questionnaire was 497 (71%). Response rates in the intervention arms were significantly higher, with 71% in intervention arm A (p=0.026) and 75% in intervention arm B (p=0.002), compared to a response rate of 59% in the control arm. Between the intervention arms the response rates were comparable (p=0.270). Table 1 shows the characteristics of the study population. Of the respondents, a total of 37.6% was female, mean age (±SD) was 63.5 ± 7 years and no significant differences were observed in level of education (p=0.418), retirement (p=0.069), smoking behavior (p=0.099) and use of cholesterol or blood pressure medication at baseline (p=0.056) between the study arms. Median follow-up (IQR) since randomization was 16.8 (15.0 – 19.7) months and mean follow-up (±SD) since screening in the intervention arms was shorter with 14.8 ± 3.4 months. Response rates between risk categories in the intervention arms were comparable.

Table 1. Study population characteristics.

	Control arm Usual Care	Intervention arm A SCORE	Intervention arm B CAC-score	Total
Female gender	27/59 (45.8%)	87/213 (40.8%)	73/225 (32.4%)	187/497 (37.6%)
Mean age (SD)	61.0 (7.3)	63.5 (6.8)	64.1 (7.0)	63.5 (7.0)
Education level				
Low	15/59 (25.4%)	67/213 (31.5%)	60/225 (26.7%)	142/497 (28.6%)
Medium	14/59 (23.7%)	51/213 (23.9%)	69/225 (30.7%)	134/497 (27.0%)
High	30/59 (50.8%)	95/213 (44.6%)	96/225 (42.7)	221/497 (44.5%)
Retired	15/59 (25.4%)	73/213 (34.3%)	100/225 (44.4%)	188/497 (37.8%)
Smoking	16/59 (27.1%)	44/213 (20.7%)	35/225 (15.6%)	95/497 (19.1%)
Use of cholesterol or blood pressure medication at baseline	12/59 (20.3%)	47/213 (22.1%)	70/225 (31.1%)	129/497 (26.0%)
Median follow-up since randomization in months (IQR)	15.8 (14.9 - 17.8)	16.8 (14.9 - 23.0)	16.3 (15.0 - 19.6)	16.8 (15.0 - 19.7)
Mean follow-up since screening (SD)	[a]	14.9 (3.6)	14.8 (3.1)	14.8 (3.4)
Risk category	[a]	*Low:* 76/213 (35.7%) *Medium:* 68/213 (31.9%) *High:* 69/213 (32.4%)	*Low:* 76/225 (33.8%) *High:* 76/225 (33.8%) *Very high:* 73/225 (32.4%)	[b]

[a] Not applicable since no screening was offered.

[b] Not applicable as a result of different risk measures.

SCORE, Systematic Coronary Risk Estimation; CAC, Coronary Artery Calcium; SD, Standard Deviation; IQR, Interquartile Range

Contamination

The reported medical examinations performed by GPs after randomization into the control group and after screening in the intervention arms are summarized in Table 2. Blood pressure measurements were reported most often, followed by cholesterol measurements. It appeared that these measurements were repeated in some respondents from intervention arm A. Thirteen (5.8%) respondents from intervention arm B reported a repeated CAC-score measurement. The category 'other' in Table 2 consists of referral to second-line care and blood measurements other than cholesterol determination. CAC-score measurements or a combination of cholesterol and blood pressure measurements as part of traditional risk assessment were reported by none of the 59 respondents from the control arm indicating a contamination rate of 0%. Within intervention arm A, one out of 213 respondents indicated an off-study CAC-score measurement resulting in a contamination rate of 0.5%. This respondent reported a wish to reduce the CVD risk and

Table 2. Medical examinations by general practitioner and contamination in the control arm and intervention arms.

	Control arm Usual Care N = 59	Intervention arm A SCORE N = 213	Intervention arm B CAC-score N = 225
Blood pressure measurement	1 (1.7%)	65 (30.5%)	93 (41.3%)
Cholesterol measurement	0	46 (21.6%)	85 (37.8%)
Weight measurement	1 (1.7%)	26 (12.2%)	40 (17.8%)
CAC-score measurement	0	1 (0.5%)	13 (5.8%)
Other	1 (1.7%)	7 (3.3%)	17 (7.6%)
Contamination rate	**0%**	**0.5%**	**35.6%** [a]

[a] Unclear whether this was actual contamination.

SCORE, Systematic Coronary Risk Estimation; CAC, Coronary Artery Calcium

received a CAC-score measurement as a precaution. There was no statistically significant difference between contamination rates of the control arm and intervention arm A (p=0.598). In intervention arm B, 80 out of 225 (35.6%) answers reported a combination of cholesterol and blood pressure. However, it is unclear from the questionnaire whether this is contamination or treatment monitoring. The most common stated reason for these measurements was the wish to reduce the CVD risk followed by need for explanation.

Discussion

Although screening for CVD is becoming a more important strategy to reduce fatal and non-fatal CVD events in potential high-risk individuals, data from RCTs to prove this is lacking (10). The ROBINSCA trial is the first large-scale population-based RCT that investigates the effect of screening for a high risk of CVD in asymptomatic individuals. In this study, the contamination rate in the ROBINSCA trial was measured as contamination might affect the power of a RCT to demonstrate effectiveness of interventions. Risk of contamination in the ROBINSCA trial was substantially present, because participants within the different study arms can be family or neighbors who discuss screening with each other, visit the same GP practice or because of familiarity with the SCORE model as Dutch guideline for CVD risk management or unfamiliarity with CAC-scoring for preventive purposes (13). The latter, on the contrary, can also prevent off-study screening in the control arm and intervention arm A.

First, the contamination rate of 0.5% in intervention arm A was far below the acceptable contamination rate of 20% as predefined in the power calculation. As stated before, CAC-scoring is no standard procedure in general practices, explaining the infrequency of CAC-score measurements performed. Regarding the only off-study CAC-score measurement, it is possible that CAC-scoring was suggested by the GP, but another possibility is that the participant explicitly asked for CAC-scoring after discussing with an individual from intervention arm B. The reported repetitions of cholesterol measurements in intervention arm A can be caused by GPs measuring low-density lipoprotein (LDL) cholesterol, which is not a required measurement for a SCORE assessment. However, according to the CVRM guideline, LDL cholesterol is an important treatment target and therefore checked routinely when cholesterol treatment is prescribed (13). Blood pressure measurements were possibly repeated to observe whether blood pressure was stable over time. Second, almost none of the controls visited their GP and none of them received an off-study intervention. This follows our hypothesis, as controls are not advised to consult their GP. The significantly lower response rate in the control arm compared to the intervention arms can be explained by possible recall bias of participation in the ROBINSCA trial since controls did not receive any intervention since randomization. Another explanation might be a disappointment of being randomized into the control arm and not receiving a CVD risk assessment.

Last, a combination of blood pressure and cholesterol measurements was performed in 35.6% of the individuals from intervention arm B. This is the maximum potential contamination, however, these measurements can also be part of monitoring preventive drug treatment.

Treatment advice for elevated CAC-scores includes ACE-inhibitors which are frequently used for blood pressure lowering treatment. However, anti-hypertensive treatment is not appropriate when systolic blood pressure is below 100 mmHg and therefore blood pressure needs to be monitored. Cholesterol measurements might have been performed to determine LDL cholesterol for treatment target routine, even though GPs were asked to treat individuals in intervention arm B independently from cholesterol levels. The most common stated reason to visit the GP among individuals from intervention arm B receiving blood pressure and cholesterol measurements was the wish to reduce the CVD risk. This might indicate that the GP started preventive treatment including treatment monitoring. In contrast, the second most cited reason was need for explanation which might indicate unfamiliarity of the intervention resulting in a traditional CVD risk assessment according to the SCORE model and thus contamination. Our hypothesis is that a part of the GPs indeed performed a full SCORE assessment as a consequence of unfamiliarity with CAC-scoring and that another part performed the measurements only for treatment monitoring routine after acting on the CAC-score result. We expect this distribution to be within the limit of 20% contamination. However, the exact amount is unknown and will be investigated among a sample of GPs. Thirteen respondents from intervention arm B reported a CAC-score measurement after visiting their GP. However, this is very unlikely as measuring the CAC-score is not part of current guidelines. It is possible that these respondents misinterpreted the question and/or immediately checked the box of CAC-score measurement after seeing the addition of "CT-scan" between brackets. In summary, the contamination rate in the ROBINSCA trial is expected to be below the acceptable predefined rate.

There are no reports on contamination in CVD screening trials available since this is the first CVD screening trial in women and men. The study protocol of a Danish cardiovascular screening (DANCAVAS) trial with CVD screening in only men was published in 2015, but the investigators did not report yet on contamination (17). Similar screening RCTs have been performed in the field of cancer. For example in lung cancer screening, Saghir et al (18) and Baecke et al (19) determined the rate of contamination, defined as an off-study CT-scan or X-ray for lung cancer screening purposes, in the Danish Lung Cancer Screening Trial (DLCST) and the Dutch-Belgian randomized-controlled lung cancer screening trial (NELSON) respectively, where CT screening is compared to no screening. They report limited observed contamination, which is in line with our findings. However, they conclude that the contamination rate might be underestimated because it is possible that some participants who received an off-study intervention do not fulfill the questionnaire as they understand that off-study interventions may affect the outcomes of the trial. This might have happened within our study as well, although the exact purpose of the questionnaire was obviously not mentioned in the general introduction in the invitation.

There are several limitations to this study. First, the accuracy of self-reported questionnaires is questionable due to possible recall bias (20). Second, the selected sample is relatively small with respect to the total ROBINSCA study population. By randomly selecting the sample there is only a small chance that family members or neighbors were invited. This might have resulted in

an underestimation of the rate of contamination. However, we still expect the contamination rate to be under 20% in the ROBINSCA population. Third, the contamination rate could not be determined in intervention arm B and more research is needed to explore whether the CVD risk was assessed using the traditional risk SCORE model. Strength of this study was the method of data collection, as the contamination questionnaire was a straightforward and short online survey ensuring a high and reliable response. In addition, the questionnaire was sent to the ROBINSCA-participants instead of to GPs. It is possible that GPs are more aware of the study design and how contamination can adversely affect the power of a RCT resulting in non-response or desirable answers.

In conclusion, almost no contamination was seen in the ROBINSCA trial. Future results of the ROBINSCA trial are awaited to demonstrate a potential effect of the early detection and treatment of a high risk for developing CHD.

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Part II

Cardiovascular disease screening results

Chapter 4

Screening for cardiovascular disease risk using traditional risk factor assessment or coronary artery calcium scoring: the ROBINSCA trial

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Abstract

Aims: Screening for a high cardiovascular disease (CVD) risk followed by preventive treatment can potentially reduce coronary heart disease (CHD)-related morbidity and mortality. ROBINSCA (Risk Or Benefit IN Screening for CArdiovascular disease) is a population-based randomized controlled screening trial that investigates the effectiveness of CVD screening in asymptomatic participants using the Systematic COronary Risk Evaluation (SCORE) model or Coronary Artery Calcium (CAC) scoring. This study describes the distributions in risk and treatment in the ROBINSCA trial.

Methods and results: Individuals at expected elevated CVD risk were randomized into screening arm A (n=14,478; SCORE, 10-year fatal and non-fatal risk); or screening arm B (n=14,450; CAC scoring). Preventive treatment was largely advised according to current Dutch guidelines. Risk and treatment differences between the screening arms were analysed. 12,185 participants (84.2%) in arm A and 12,950 (89.6%) in arm B were screened. 48.7% were women, and median age was 62 (InterQuartile Range 10) years. SCORE screening identified 45.1% at low risk (SCORE<10%), 26.5% at intermediate risk (SCORE 10-20%), and 28.4% at high risk (SCORE≥20%). According to CAC screening, 76.0% were at low risk (Agatston<100), 15.1% at high risk (Agatston 100-399), and 8.9% at very high risk (Agatston≥400). CAC scoring significantly reduced the number of individuals indicated for preventive treatment compared to SCORE (relative reduction women: 37.2%; men: 28.8%).

Conclusion: We showed that compared to risk stratification based on SCORE, CAC scoring classified significantly fewer men and women at increased risk, and less preventive treatment was indicated.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and it is responsible for 45% of all annual deaths in Europe (1, 2). Although various preventive measures in terms of lifestyle and timely drug treatment are known to reduce CVD burden, their application is suboptimal and unhealthy lifestyles remain frequent. Population-based screening for cardiovascular risk aims to identify individuals at increased risk in order to stop or delay disease progression by preventive treatment. This might be an appropriate strategy to reduce CVD-related events (3-5). However, there is no evidence from randomized controlled trials (RCT) on the effectiveness of screening and a reliable screening modality yet.

One potentially suitable risk assessment tool is the Dutch Systematic Coronary Risk Evaluation (SCORE) risk model, which predicts 10-year risk for developing fatal and non-fatal CVD (4, 6, 7). Although this model is easy to use and is integrated into current guidelines, it has limited accuracy in predicting the correct risk status. The indication for preventive treatment is often uncertain in intermediate-risk individuals, limiting the ability to prevent coronary heart disease (CHD) in this group (4, 8). Another potential screening modality is quantification of coronary artery calcification (CAC), expressed as CAC score, using computed tomography (CT) scanning (9, 10). Evidence shows that CAC scoring is a strong independent predictor of CHD events and improves classification of intermediate-risk individuals, causing a large shift in the distribution of CVD risk (11, 12). Currently, European and American guidelines recommend considering additional CAC scoring to guide preventive therapy decisions in intermediate-risk adults (4, 13).

In CVD screening, the expected difference in CVD risk distribution between the SCORE model and CAC scoring might cause an effective shift towards more correctly classified individuals and more accurate risk reduction. Additionally, a reduction in preventive overtreatment with cardiovascular medication is expected when CAC scoring is used as the screening modality. This will not only be beneficial for participants as it reduces potential side effects, but it will also save costs (14). However, the effect of the shift in risk distribution in the setting of CVD screening in an elevated risk population is unknown.

The Risk Or Benefit IN Screening for CArdiovascular diseases (ROBINSCA) trial is a population-based randomized controlled screening trial to investigate whether screening for a high risk of CVD in asymptomatic individuals followed by early treatment will reduce CHD-related morbidity and mortality compared to no screening (15). The SCORE model and CAC scoring are used as potential screening modalities. The aim of the present study is to present the CVD risk distributions in both screening arms and to investigate the shift in risk distribution and the potential reduction in preventive (over)treatment due to the use of different risk assessment tools.

Methods

Study population

The design, objectives and recruitment of the ROBINSCA trial have been described previously (15). In summary, 394,058 individuals, women aged 55-74 years and men aged 45-74 years from three regions in the Netherlands, were selected from the national population registry, and received an invitation to participate, including an information brochure, a baseline questionnaire, a waist circumference measuring tape and a written informed consent form. Asymptomatic individuals were subsequently selected based on at least one of the following inclusion criteria: 1) a high self-measured waist circumference (≥88 cm for women and ≥102 cm for men); 2) a high body mass index (BMI; ≥30 kg/m^2); 3) a family history of myocardial infarction or sudden death before the age of 65 years in first- or second-degree relatives; and/or 4) current smoking. Exclusion criteria were: 1) previously diagnosed CVD; 2) previous CVD surgery; 3) prescription of a combination of cholesterol- and blood pressure-lowering medication; 4) CAC score measurement in the past year; and/or 5) incomplete informed consent. In total, 43,447 eligible individuals were randomized (1:1:1) to either the control arm where usual care was continued, or to one of the two intervention arms where screening was offered. All participants received generic healthy lifestyle recommendations of the Dutch Heart Foundation (Figure 1). The current study focuses only on the screening arms.

Screening

Screening was performed from 2015 to 2018. In intervention arm A, the 10-year risk for fatal and non-fatal CVD was estimated using the adapted version of the SCORE model as described in the Dutch guideline for Cardiovascular Risk Management (CVRM, edition 2011) by the College of General Practitioners (7). Participants were invited for blood pressure and cholesterol measurement. The algorithm stratifies participants into low (SCORE <10%), intermediate (SCORE 10-20%) or high (SCORE ≥20%) risk according to the guideline (15). In intervention arm B, participants underwent CT scanning using a second-generation dual-source computed tomography system. The CAC imaging protocol has been described elsewhere (16). In short, images were analysed with semiautomatic identification of calcifications. A calcification was defined as an area with a density of ≥130 Hounsfield units and ≥2 adjacent voxels. Individual calcifications per coronary artery could be selected for CAC scoring using dedicated CAC scoring software. We calculated CAC scores according to Agatston (16, 17). CAC scores were stratified into low (Agatston <100), high (Agatston 100-399) and very high (Agatston ≥400) risk, according to cut-offs from literature (18). This terminology was chosen for the screening setting for early detection of preclinical disease. We used this classification in an asymptomatic population as an indication of preventive treatment and to distinguish between SCORE and CAC score.

Study protocol for preventive treatment

Participants were notified about their risk status, as were their general practitioners (GPs). Participants with a SCORE of ≥10% were advised to consult the GP. GPs are asked to initiate preventive treatment according to the Dutch CVRM guideline for 'patients without CVD' (7).

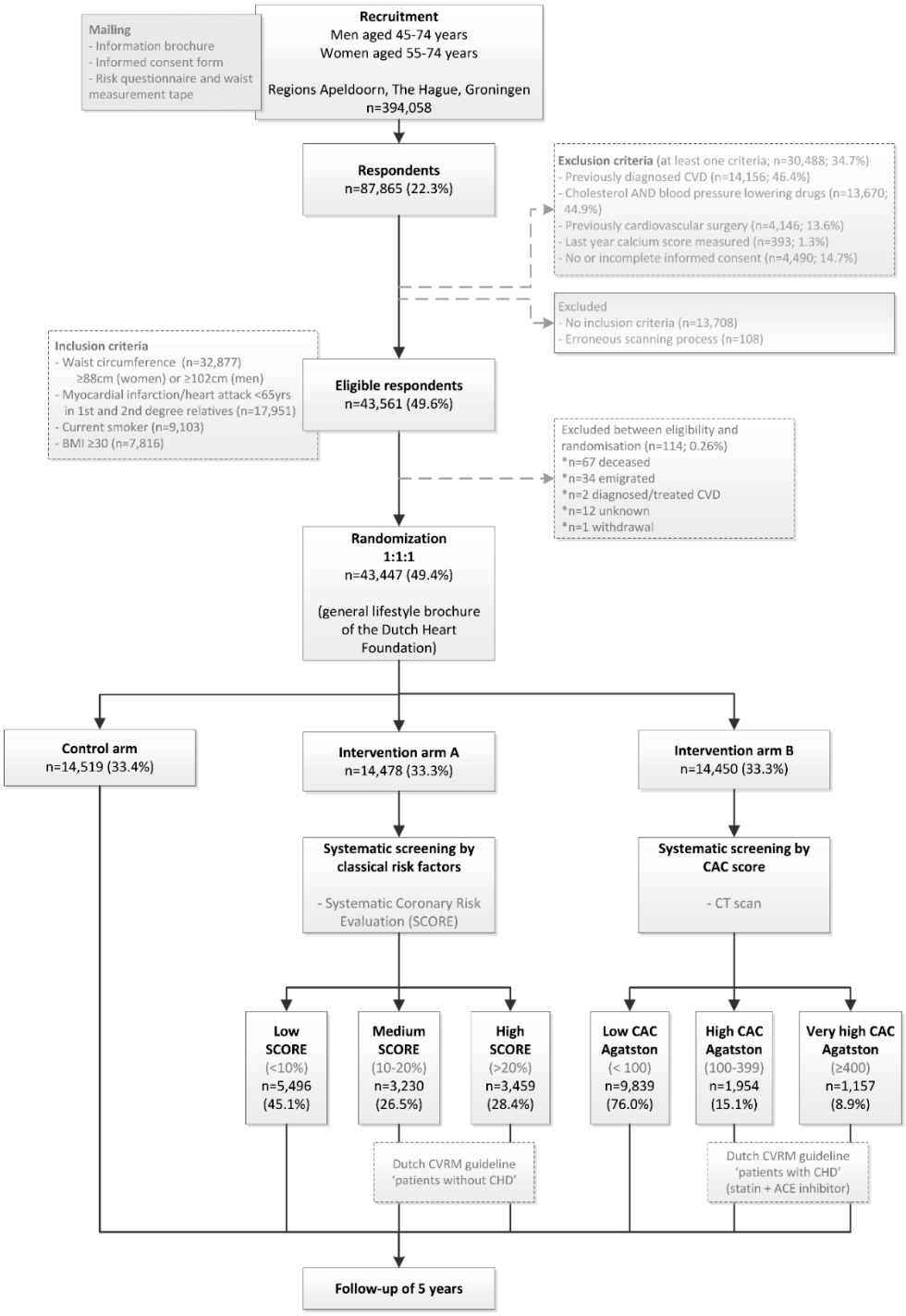

Figure 1. Flowchart of the recruitment, inclusion and randomization process in the ROBINSCA trial.

This guideline recommends lifestyle measures for all high-risk individuals (≥20%), and intermediate-risk individuals (≥10%) who have ≥1 risk-increasing factors. For these individuals, preventive drug treatment is recommended additionally when systolic blood pressure is >140 mmHg and/or LDL-cholesterol >2.5 mmol/L. The treatment advice for a high CAC score was designed in consultation with local cardiologists, GPs and the research team. The study advice recommended prescription of ACE-inhibitors and statins, independent from cholesterol and blood pressure levels (except when blood pressure is too low), for participants with a CAC score ≥100, as adapted from the CVRM guideline for 'patients with CVD' (7).

Statistical analysis

Study population characteristics are expressed as percentages or medians (interquartile range; IQR) as appropriate for men and women separately. The Pearson's chi-squared test and the Mann-Whitney U-test were used to analyse differences in distributions and medians respectively between intervention arm A and B. The distributions of CVD risk in both intervention arms were analysed using the Pearson's chi-squared test and medians were analysed using the Kruskal-Wallis test. The difference in preventive treatment indications between the intervention arms was analysed to check for potential reduction in overtreatment when using CAC scoring and was tested for statistically significant difference using the Pearson's chi-squared test. The differences are presented as absolute and relative differences. A P value of < 0.005 was considered statistically significant after application of the Bonferroni correction. All analyses were performed using IBM SPSS Statistics version 25.0.

Results

Baseline characteristics

In total, 14,478 and 14,450 participants were randomized into intervention arm A and intervention arm B, respectively. Screening attendance rate was high for both intervention arms; 12,185 (84.2%) participants underwent a SCORE assessment and 12,950 (89.6%) participants underwent CT scanning for CAC quantification ($p<0.001$). Table A in the Supplementary data provides information on differences between screened and non-screened individuals. Baseline characteristics of the screened women and men of both intervention arms were comparable (Table 1). Median age of the women (12,232 out of 25,135; 48.7%) was 64.0 years (IQR 8) and of the men (12,903 out of 25,135; 51.3%) 59.0 years (IQR 13) ($p<0.001$). More men were current smokers (25.3 vs. 13.7%, $p<0.001$) and men had a higher BMI compared to women (26.9 vs. 25.5 kg/m^2; $p<0.001$). Reported family history of CHD was comparable for men and women ($p=0.428$). Slightly more women reported baseline use of antihypertensive treatment (21.9 vs. 17.1%; $p<0.001$).

SCORE and CAC score assessment

Based on the Dutch SCORE model, 3,234 out of 6,009 (53.8%) women were classified as low-risk, 1,479 (24.6%) as intermediate and 1,296 (21.6%) as high-risk. A significantly different CVD risk distribution was observed using CAC scoring: more low-risk women were identified. A zero CAC score was measured in 48.0% of the women (2,984/6,223). Further, 35.3% (2,196) had a

Table 1. Baseline characteristics of the study population split for women (a) and men (b).

	Intervention arm A **SCORE** *n/N (%)*	Intervention arm B **CAC score** *n/N (%)*	P value
a) Women	*N=6,009*	*N=6,223*	
Median age (IQR)	64.0 (8)	64.0 (8)	0.786
Educational level†			0.278
Low	2,692/5,987 (45.0)	2,699/6,200 (43.5)	
Medium	1,454/5,987 (24.3)	1,552/6,200 (25.0)	
High	1,841/5,987 (30.7)	1,949/6,200 (31.4)	
Current smoker	827/6,009 (13.8)	850/6,223 (13.7)	0.868
Median BMI (IQR)	25.5 (5.1)	25.5 (5.0)	0.826
Median waist circumference* (IQR)	97.0 (13.5)	96.5 (13.5)	0.277
Family history of CHD#	2,451/5,437 (45.1)	2,518/5,614 (44.9)	0.810
Diabetes Mellitus	152/6,009 (2.5)	178/6,223 (2.9)	0.259
Hypertension in past year	948/5,864 (16.2)	1,005/6,080 (16.5)	0.592
Hypercholesterolemia in past year	938/5,802 (16.2)	974/5,994 (16.2)	0.903
Baseline medical treatment			
Antihypertensive	1,306/5,989 (21.8)	1,370/6,203 (22.1)	0.709
Lipid-lowering	449/5,987 (7.5)	490/6,189 (7.9)	0.388
b) Men	*N=6,176*	*N=6,727*	
Median age (IQR)	59.0 (13)	59.0 (13)	0.095
Educational level†			0.976
Low	1,900/6,165 (30.8)	2,057/6,705 (30.7)	
Medium	1,840/6,165 (29.8)	2,012/6,705 (30.0)	
High	2,425/6,165 (39.3)	2,636/6,705 (39.3)	
Current smoker	1,525/6,176 (24.7)	1,736/6,727 (25.8)	0.146
Median BMI (IQR)	26.9 (4.3)	26.9 (4.4)	0.758
Median waist circumference* (IQR)	104.5 (12.0)	104.5 (12.0)	0.647
Family history of CHD#	2,637/5,718 (46.1)	2,812/6,262 (44.9)	0.183
Diabetes Mellitus	200/6,176 (3.2)	258/6,727 (3.8)	0.067
Hypertension in past year	964/6,020 (16.0)	1,119/6,561 (17.1)	0.116
Hypercholesterolemia in past year	917/5,997 (15.3)	1,001/6,541 (15.3)	0.985
Baseline medical treatment			
Antihypertensive	1,017/6,157 (16.5)	1,187/6,710 (17.7)	0.078
Lipid-lowering	493/6,152 (8.0)	585/6,709 (8.7)	0.149

A P value of < 0.005 was considered statistically significant after application of the Bonferroni correction.

† Educational levels: low; primary, lower secondary general or lower vocational education, medium; intermediate vocational or higher secondary education, high; higher vocational education or university.

* Waist circumference in centimetres.

Family history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives.

CAC: coronary artery calcium; CHD: coronary heart disease; IQR; interquartile range: SCORE: systematic coronary risk evaluation

low CAC score (Agatston 1-99), 12.1% (754) had a high CAC score (Agatston 100-399) and 4.6% (289) had a very high CAC score (Agatston ≥400) (Table 2). Men were stratified into higher risk categories compared to women within both intervention arms. There were 2,262 out of 6,176 (36.6%) men assessed as being at low risk based on the SCORE model, whereas 1,751 (28.4%) and 2,163 (35.0%) were classified as intermediate and high-risk individuals respectively. Among the 6,727 men, 31.2% (2,098) had a zero CAC score. Furthermore, 2,561 (38.1%) men with a low CAC score were identified, followed by 1,200 (17.8%) and 868 (12.9%) with a high and very high CAC score respectively (Table 3).

Table 2. Distributions of cardiovascular risks by baseline characteristics in intervention arm A (Dutch SCORE calculation) and intervention arm B (CAC quantification) in women.

	Low risk **SCORE <10%†** *n/N (%)*	Intermediate risk **SCORE 10 - 20%†** *n/N (%)*	High risk **SCORE ≥20%†** *n/N (%)*	P value	Low risk **CAC score 0-99** *n/N (%)*	High risk **CAC score 100-399** *n/N (%)*	Very high risk **CAC score ≥400** *n/N (%)*	P value
	3,234/6,009 (53.8)	*1,479/6,009 (24.6)*	*1,296/6,009 (21.6)*		*5,180/6,223 (83.2)*	*754/6,223 (12.1)*	*289/6,223 (4.6)*	
Median age (IQR)	60.0 (5)	67.0 (4)	71.0 (4)	*<0.001*	63.0 (9)	66.5 (8)	68.0 (8)	*<0.001*
Current smoker	371/3,234 (11.5)	255/1,479 (17.2)	201/1,296 (15.5)	*<0.001*	654/5,180 (12.6)	142/754 (18.8)	54/289 (18.7)	*<0.001*
Median BMI (IQR)	25.3 (5.0)	25.7 (5.3)	26.0 (5.1)	*<0.001*	25.5 (5.0)	25.5 (5.3)	25.6 (5.7)	0.653
Median waist circumference* (IQR)	96.0 (13.5)	97.0 (13.5)	98.5 (14.5)	*<0.001*	96.0 (13.5)	97.0 (13.0)	97.5 (14.9)	0.062
Family history of CHD#	1,352/2,968 (45.6)	598/1,325 (45.1)	501/1,144 (43.8)	0.596	2,008/4,684 (42.9)	359/666 (53.9)	151/264 (57.2)	*<0.001*
Diabetes Mellitus	21/3,234 (0.6)	37/1,479 (2.5)	94/1,296 (7.3)	*<0.001*	114/5,180 (2.2)	49/754 (6.5)	15/289 (5.2)	*<0.001*
Hypertension in past year	443/3,173 (14.0)	236/1,445 (16.3)	269/1,246 (21.6)	*<0.001*	786/5,065 (15.5)	151/737 (20.5)	68/278 (24.5)	*<0.001*
Hypercholesterolemia in past year	475/3,147 (15.1)	267/1,413 (18.9)	196/1,242 (15.8)	0.005	774/5,004 (15.5)	141/717 (19.7)	59/273 (21.6)	*0.001*
Baseline medical treatment								
Antihypertensive	573/3,227 (17.8)	360/1,474 (24.4)	373/1,288 (29.0)	*<0.001*	1,077/5,166 (20.8)	195/750 (26.0)	98/287 (34.1)	*<0.001*
Lipid-lowering	186/3,226 (5.8)	132/1,472 (9.0)	131/1,289 (10.2)	*<0.001*	340/5,153 (6.6)	107/750 (14.3)	43/286 (15.0)	*<0.001*

A P value of < 0.005 was considered statistically significant after application of the Bonferroni correction.

† SCORE calculation according to the 2011 edition of the Cardiovascular Risk Management protocol of the Dutch College of General Practitioners (7).

* Waist circumference in centimetres.

Family history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives.

The risk distribution categories in intervention arm A are as in the Dutch Cardiovascular Risk Management protocol, and those in intervention arm B are as cut-offs from literature.

BMI: body mass index; CAC: coronary artery calcium; CHD: coronary heart disease; IQR: interquartile range; SCORE: systematic coronary risk evaluation

Table 3. Distributions of cardiovascular risks by baseline characteristics in intervention arm A (Dutch SCORE calculation) and intervention arm B (CAC quantification) in men.

	Low risk **SCORE <10%**† *n/N (%)*	Intermediate risk **SCORE 10 - 20%**† *n/N (%)*	High risk **SCORE ≥20%**† *n/N (%)*	P value	Low risk **CAC score 0-99** *n/N (%)*	High risk **CAC score 100-399** *n/N (%)*	Very high risk **CAC score ≥400** *n/N (%)*	P value
	2,262/6,176 (36.6)	*1,751/6,176 (28.4)*	*2,163/6,176 (35.0)*		*4,659/6,727 (69.3)*	*1,200/6,727 (17.8)*	*868/6,727 (12.9)*	
Median age (IQR)	52.0 (6)	60.0 (7)	68.0 (7)	*<0.001*	56.0 (12)	63.0 (11)	66.0 (9)	*<0.001*
Current smoker	432/2,262 (19.1)	441/1,751 (25.2)	652/2,163 (30.1)	*<0.001*	1,198/4,659 (25.7)	318/1,200 (26.5)	220/868 (25.3)	0.811
Median BMI (IQR)	26.6 (4.3)	27.1 (4.3)	26.9 (4.2)	0.012	26.9 (4.3)	27.0 (4.6)	26.9 (4.4)	0.605
Median waist circumference* (IQR)	104.0 (12.0)	104.5 (11.5)	105.0 (11.0)	*<0.001*	104.0 (12.0)	104.5 (11.0)	104.5 (12.0)	0.259
Family history of CHD#	1,046/2,141 (48.9)	755/1,640 (46.0)	836/1,937 (43.2)	*0.001*	1,880/4,341 (43.3)	512/1,119 (45.8)	420/802 (52.4)	*<0.001*
Diabetes Mellitus	19/2,262 (0.8)	24/1,751 (1.4)	157/2,163 (7.3)	*<0.001*	138/4,659 (3.0)	52/1,200 (4.4)	67/868 (7.7)	*<0.001*
Hypertension in past year	264/2,202 (12.0)	324/1,706 (19.0)	376/2,112 (17.8)	*<0.001*	694/4,550 (15.3)	237/1,169 (20.3)	188/842 (22.3)	*<0.001*
Hypercholesterolemia in past year	298/2,208 (13.5)	289/1,694 (17.1)	330/2,095 (15.8)	0.007	648/4,546 (14.3)	209/1,156 (18.1)	144/839 (17.2)	*0.002*
Baseline medical treatment								
Antihypertensive	198/2,258 (8.8)	305/1,746 (17.5)	514/2,153 (23.9)	*<0.001*	647/4,648 (13.9)	288/1,196 (24.1)	252/866 (29.1)	*<0.001*
Lipid-lowering	124/2,258 (5.5)	132/1,741 (7.6)	237/2,153 (11.0)	*<0.001*	323/4,649 (6.9)	135/1,194 (11.3)	127/866 (14.7)	*<0.001*

A P value of < 0.005 was considered statistically significant after application of the Bonferroni correction.

† SCORE calculation according to the 2011 edition of the Cardiovascular Risk Management protocol of the Dutch College of General Practitioners (7).

* Waist circumference in centimetres.

Family history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives.

The risk distribution categories in intervention arm A are as in the Dutch Cardiovascular Risk Management protocol, and those in intervention arm B are as cut-offs from literature.

BMI: body mass index; CAC: coronary artery calcium; CHD: coronary heart disease; IQR: interquartile range; SCORE: systematic coronary risk evaluation

In both women and men, apart from the factors included in SCORE calculation, larger waist circumference, diabetes mellitus, and use of blood pressure or cholesterol lowering medication were associated with a higher SCORE. Additionally, a higher BMI was associated with a higher SCORE in women. In contrast, BMI and waist circumference were not associated with an increase in CAC score in women (p=0.653 and p=0.062, respectively). A higher BMI was not associated with a higher SCORE, nor with a higher CAC score in men (p=0.012 and p=0.605, respectively). Waist circumference and current smoking in men were not associated with an increase in CAC score (p=0.259 and p=0.811, respectively; Table 2 and 3).

In addition to the SCORE calculations based on the Dutch CVRM guideline, Table B in the Supplementary data presents the converted SCORE risks according to the European model from the European Society of Cardiology (6).

Difference in risk and preventive treatment

The absolute reduction in the number of increased risk individuals was 29.4% in women and 32.7% in men when CAC scoring was used as screening tool. The subsequent rate ratios (RR) were 0.363 (95% confidence interval (CI): 0.341-0.386) for women and 0.485 (95% CI: 0.466-0.505) for men. This resulted in relative reductions of increased-risk individuals of 63.7% and 51.5% in women and men respectively.

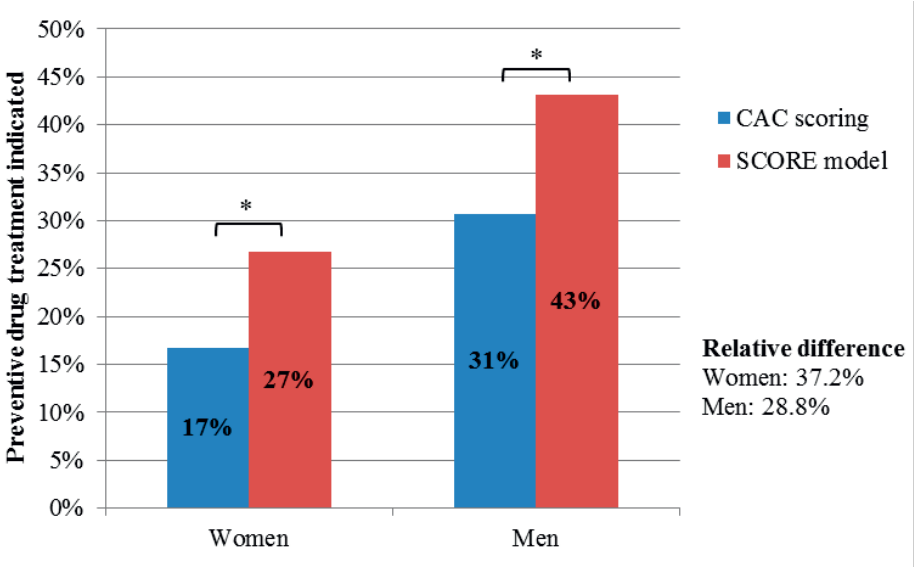

Figure 2. Individuals indicated to consult their general practitioner for preventive drug treatment in intervention arm A and B based on estimated risks and the absolute and relative difference between both intervention arms.

* Level of significance: p<0.001

The difference in the number of individuals indicated for preventive treatment between the intervention arms were analysed and are presented as absolute and relative differences.

CAC: coronary artery calcium; SCORE: systematic coronary risk evaluation

These large differences in CVD risk distributions between the screening modalities in both women and men caused statistically significant differences in the number of individuals indicated to consult their GP for preventive drug treatment (Figure 2). Potential preventive drug treatment was indicated for 1,604 out of 6,009 (26.7%) women according to the SCORE model, compared to 1,043 out of 6,223 (16.8%) women according to CAC scoring ($p<0.001$; absolute reduction of 9.9%). The relative reduction in the number of women indicated for preventive drug treatment was estimated to be 37.2% when using CAC scoring compared to SCORE calculation (based on RR 0.628, 95% CI: 0.586-0.673). Among men, 2,666 out of 6,176 (43.2%) were advised to start preventive drug treatment based on SCORE calculation, whereas 2,068 out of 6,727 (30.7%) received preventive drug treatment advice based on CAC score ($p<0.001$; absolute reduction of 12.4%). Risk estimation using CAC scoring caused a relative reduction in the number of preventive drug treatment indications of 28.8% in men (based on RR 0.712, 95% CI: 0.680-0.746).

Discussion

In this population-based screening RCT for the early detection and treatment of an increased risk for CVD, 25,135 asymptomatic participants were screened by means of either applying the SCORE model or CAC scoring. As expected, the CVD risk distributions differed significantly between the two screening modalities. Risk assessment through CAC scoring identified more low-risk individuals compared to the SCORE model. Follow-up analyses should establish whether the indicated high-risk individuals were treated correctly.

The associations between traditional risk factors and a higher SCORE are a natural result of the SCORE model being based on these risk factors. However, similar associations were not observed in intervention arm B: higher CAC score categories were not associated with increasing waist circumference in women and men, nor with current smoking in men, nor with increasing BMI in women. In men, BMI was not associated with a higher SCORE, nor a higher CAC score. Regarding BMI, previous studies indeed reported that BMI does not predict CAC, which is largely related to the inability of BMI to differentiate between fat and muscle and the assumption that CAC scores can be underestimated in women with large chest size and large patients (19, 20). In contrast, the lack of an association between waist circumference and CAC contradicts earlier findings indicating that waist circumference is associated with CAC beyond traditional risk factors (21). As there is no unambiguous evidence on this subject yet, future research should focus more on this potential association. Further, the proportion of male current smokers did not increase with higher CAC score categories. This is in line with previous research that concluded that the effect of current smoking on CAC might decrease with age (22). Discrepancies in presence of CAC and absence of traditional risk factors, and vice versa, might influence the decision on whether to start preventive drug treatment or not. In particular, current preventive treatment in people with zero CAC may be considered as overtreatment, since this score represents a minimal risk (23). Current preventive treatment decisions are largely based on traditional risk prediction models, whereas CAC scoring is thought to be better at correctly identifying individuals who would benefit the most from preventive treatment (24).

The SCORE model has several limitations, including the limited adaptation for different ethnic groups and age ranges, and the lack of incorporating risk modifiers that potentially reclassify CVD risk, such as socio-economic status, CVD family history and obesity, and therefore lacks discriminative power (4, 8). CAC scoring has superior discrimination and risk reclassification as compared with other risk indicators (25). Previous studies showed that asymptomatic intermediate-risk individuals were more often downgraded to a lower risk category after adding CAC scoring to risk prediction, which is in line with our results (11, 12). Additionally, the review of Greenland et al., which summarized the results of population-based cohorts, convincingly showed the value of CAC scoring as a single predictive cardiovascular risk marker beyond traditional risk factors (9). Furthermore, recent literature described that shared decision making guided by CAC scoring in intermediate-risk individuals can be a cost-effective strategy to avoid years of preventive medication (9, 14). Future analyses on CVD-related events in the ROBINSCA trial might add important evidence on the extent to which preventive treatment decisions should be based on CAC screening.

The observed reduction in the number of individuals indicated to consult their GP for preventive treatment after screening by CAC scoring compared to screening using the SCORE model will potentially influence prevention strategies. However, future analyses on CVD-related events are needed to determine whether the indicated high-risk individuals were treated correctly. Within the screening setting of the current study, the results might imply a reduction in burden for both screening participants and GPs. The improved estimate of a CAC-based CVD risk status might reduce unnecessary stress that participants may experience upon receiving an unfavourable test result, while it might increase adherence to preventive treatment (26). For GPs, risk management in intervention arm B participants is less time consuming since the treatment indication in intervention arm A is not solely based on the SCORE model, but also on additional risk-increasing factors that are not known in the ROBINSCA trial. Furthermore, a potential reduction in unnecessary treatment will reduce costs. However, as CT scanning is more expensive compared to using the SCORE model, the effectiveness of CT screening should first be confirmed (14, 27).

The strength of this study is its large study population that was randomly selected from the national population registry. The aimed sample size was reached and therefore there should be sufficient power to show a reduction in CHD events of at least 15% (15). Furthermore, screening results were consistently obtained by adequately trained research personnel. A main limitation was that the presented data analysis is cross-sectional. Therefore, conclusions on the reduction of preventive overtreatment cannot be drawn yet. Future analyses on this subject are required. Another limitation was that recall bias might have caused some inaccuracies in the population characteristics data obtained from the self-reported baseline questionnaire. However, multiple questions were used per health topic to increase the reliability of the answers. Therefore, self-reported questionnaires are the preferred and most cost-effective method for obtaining data in large study populations. Another point is that the described treatment indications in intervention arm A are not completely comparable with preventive treatment based on the SCORE model in current practice. To maintain feasibility, not all risk-increasing factors that co-determine the

treatment indication were incorporated in the screening as they are not part of the SCORE calculation itself. Lastly, the final decision regarding preventive treatment was made in consultation with the GP as GPs have access to participants' medical background. The role of GPs in the risk management of increased-risk individuals is important in the feasibility of a potential CVD screening program.

Within this first population-based RCT on screening for a high risk of CHD, CAC scoring classified significantly fewer individuals at intermediate and high-risk in both women and men compared to applying the SCORE model. Subsequently, the potential expected reduction in preventive overtreatment favours the use of CAC scoring in screening. However, future analyses are required to confirm the effectiveness of CVD screening for reduction of CHD and to incorporate costs of CT scanning and preventive treatment. Should screening for a high risk of CVD be net-effective, large health gains will be achieved.

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Supplementary data

Table A. Baseline characteristics of screened and non-screened individuals.

	Intervention arm A, **SCORE** *n/N (%)*		P value	Intervention arm B, **CAC score** *n/N (%)*		P value
	Screened N=12185	Not screened N=2293		Screened N=12950	Not screened N=1500	
Sex			*<0.001*			0.200
Women	6009/12185 (49.3)	1013/2293 (44.2)		6223/12950 (48.1)	747/1500 (49.8)	
Men	6176/12185 (50.7)	1280/2293 (55.8)		6727/12950 (51.9)	753/1500 (50.2)	
Median age (IQR)	61.0 (10)	59.0 (11)	*<0.001*	60.0 (11)	61.0 (12)	*0.001*
Educational level			*0.036*			*<0.001*
Low	4592/12152 (37.8)	928/2284 (40.6)		4756/12905 (36.9)	685/1494 (45.9)	
Medium	3294/12152 (27.1)	585/2284 (25.6)		3564/12905 (27.6)	372/1494 (24.9)	
High	4266/12152 (35.1)	771/2284 (33.8)		4585/1295 (35.5)	437/1494 (29.3)	
Smoker at baseline	2352/12185 (19.3)	623/2293 (27.2)	*<0.001*	2586/12950 (20.0)	410/1500 (27.3)	*<0.001*
Median BMI (IQR)	26.3 (4.9)	26.5 (5.3)	*0.002*	26.3 (4.8)	26.3 (5.6)	0.488
Median waist circumference (IQR)	101.5 (14.5)	102.0 (15.0)	*0.002*	101.5 (14.5)	101.5 (15.5)	0.197
Family history of CHD	5088/11155 (45.6)	945/2068 (45.7)	0.944	5330/11876 (44.9)	549/1337 (43.3)	0.272
Diabetes mellitus	352/12185 (2.9)	117/2293 (5.1)	*<0.001*	436/12950 (3.4)	65/1500 (4.3)	0.053
Hypertension in past year	2912/11884 (16.1)	433/2229 (19.4)	*<0.001*	2124/12641 (16.8)	260/1449 (17.9)	0.273
Hypercholesterolemia in past year	1855/11799 (15.7)	737/2209 (16.9)	0.170	1975/12535 (15.8)	207/1444 (14.3)	0.159

CAC: coronary artery calcium; CHD: coronary heart disease; IQR: interquartile range; SCORE: systematic coronary risk evaluation

Table B Distributions of cardiovascular risks by baseline characteristics in intervention arm A in women (a) and men (b) according to the European SCORE model as described by Conroy et al (1).

	Low risk **SCORE <1%** *n/N (%)*	Intermediate risk **SCORE ≥1 - <5%** *n/N (%)*	High risk **SCORE ≥5 - <10%** *n/N (%)*	Very high risk **SCORE ≥10%** *n/N (%)*	P value
a) Women	*886/6009 (14.7)*	*4112/6009 (68.4)*	*831/6009 (13.8)*	*180/6009 (3.0)*	
Median age (IQR)	57.0 (3)	64.0 (6)	71.0 (5)	72.0 (4)	*<0.001*
Current smoker	62/886 (7.0)	550/4112 (13.4)	148/831 (17.8)	67/180 (37.2)	*<0.001*
Median BMI (IQR)	25.0 (4.9)	25.5 (5.2)	25.9 (5.2)	26.1 (5.1)	*<0.001*
Median waist circumference* (IQR)	95.0 (12.5)	97.0 (13.0)	98.0 (14.5)	98.0 (15.0)	*<0.001*
Family history of CHD#	389/825 (47.2)	1677/3715 (45.1)	322/741 (43.5)	63/156 (40.4)	0.306
Diabetes Mellitus	19/886 (2.1)	101/4112 (2.5)	29/831 (3.5)	3/180 (1.7)	†
Hypertension in past year	82/869 (9.4)	646/4023 (16.1)	175/801 (21.8)	45/171 (26.3)	*<0.001*
Hypercholesterolemia in past year	104/856 (12.1)	682/3978 (17.1)	127/794 (16.0)	25/174 (14.4)	*0.004*
Baseline use blood pressure lowering medication	132/885 (14.9)	881/4098 (21.5)	238/827 (28.8)	55/179 (30.7)	*<0.001*
Baseline use of cholesterol lowering medication	49/881 (5.6)	320/4099 (7.8)	64/828 (7.7)	16/179 (8.9)	0.115
b) Men	*564/6176 (9.1)*	*3602/6176 (58.3)*	*1495/6176 (24.2)*	*515/6176 (8.3)*	
Median age (IQR)	48.0 (3)	57.0 (8)	67.0 (7)	70.0 (6)	*<0.001*
Current smoker	84/564 (14.9)	806/3602 (22.4)	393/1495 (26.3)	242/515 (47.0)	*<0.001*
Median BMI (IQR)	26.6 (4.7)	26.9 (4.3)	26.9 (4.2)	26.6 (4.5)	0.123
Median waist circumference* (IQR)	103.8 (13.5)	104.5 (12.0)	104.5 (11.0)	105.0 (11.5)	*0.003*
Family history of CHD#	257/533 (48.2)	1593/3379 (47.1)	630/1356 (46.5)	157/450 (34.9)	*<0.001*
Diabetes Mellitus	12/564 (2.1)	111/3602 (3.1)	57/1495 (3.8)	20/515 (3.9)	0.190
Hypertension in past year	56/544 (10.3)	535/3515 (15.2)	273/1467 (18.6)	100/494 (20.2)	*<0.001*
Hypercholesterolemia in past year	63/555 (11.4)	567/3494 (16.2)	212/1450 (14.6)	75/498 (15.1)	*0.023*
Baseline use blood pressure lowering medication	42/564 (7.4)	487/3590 (13.6)	363/1491 (24.3)	125/512 (24.4)	*<0.001*
Baseline use of cholesterol lowering medication	31/563 (5.5)	295/3590 (8.2)	133/1486 (9.0)	34/513 (6.6)	*0.044*

* Waist circumference in centimeters.

Family history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives.

† Too small numbers.

CHD: coronary heart disease; IQR: interquartile range; SCORE: systematic coronary risk evaluation

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Chapter 5

Screening for coronary artery calcium in a high-risk population: the ROBINSCA trial

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Research letter

Cardiovascular disease (CVD) remains the main cause of death worldwide, accounting for 44% of all noncommunicable disease deaths, of which most are attributable to coronary heart disease (CHD) (1). Coronary artery calcification (CAC) has a strong association with major cardiovascular events and mortality, and has a high risk-predictive value of CHD in asymptomatic individuals (2, 3). It has been argued that the amount of CAC, expressed in the CAC score, can be used in population-based screening.
The Dutch Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial is the first large-scale population-based randomized controlled trial (RCT) to investigate whether CAC screening followed by preventive treatment is effective in reducing CHD-related morbidity and mortality in asymptomatic individuals (4, 5). The aim of this study was to investigate the CAC prevalence and predictors in the ROBINSCA trial, which included an asymptomatic high-risk potential target population from the general population.

The rationale and design of the ROBINSCA trial have been described before (5). Briefly, 43,447 potential high-risk women (55-74 years) and men (45-74 years) from the national population registry who completed a baseline questionnaire to assess sociodemographic and health characteristics and gave informed consent were randomized (1:1:1) to either the control arm, intervention arm A (screening according to traditional risk factors) or intervention arm B (CAC screening). The current study focuses on the CAC screening arm (Figure 1). The Minister of Health authorized the ROBINSCA trial in 2013.

CAC screening was performed using computed tomography scanning to identify CVD risk according to the CAC score, which represents the total amount of any CAC (6). CAC scores were categorized into low (Agatston 0-99), high (Agatston 100-399) and very high (Agatston ≥400) risk (2).

The effects of baseline characteristics on CAC score were analyzed using a two-step approach regression analyses for modeling presence, both any CAC and CAC score of 400 or higher (multivariable backward logistic regression), and extent (multivariable backward linear regression of the log-transformed CAC score) of CAC in women and men separately. Variables included in the models were age, educational level, waist circumference cut-off (88 cm for women and 102 cm for men), BMI cut-off (30 kg/m^2), family history of CHD, smoking, diabetes mellitus, hypertension and/or hypercholesterolemia in the past year, and baseline use of either antihypertensive or lipid-lowering medication (according to self-reported data from baseline questionnaire). A P value of < 0.05 was considered statistically significant. All analyses were performed with IBM SPSS Statistics Version 24.0.

Of the 12,950 screened participants, 48.1% were female and 94.2% were born in the Netherlands. Median age was 64 years in women and 62 years in men. Regarding CVD risk factors, 20.0% were current smokers at baseline, 3.4% reported diabetes mellitus, 16.4% and 15.3% reported being diagnosed with respectively hypertension and hypercholesterolemia in the year before baseline, and 44.9% reported a family history of CHD.

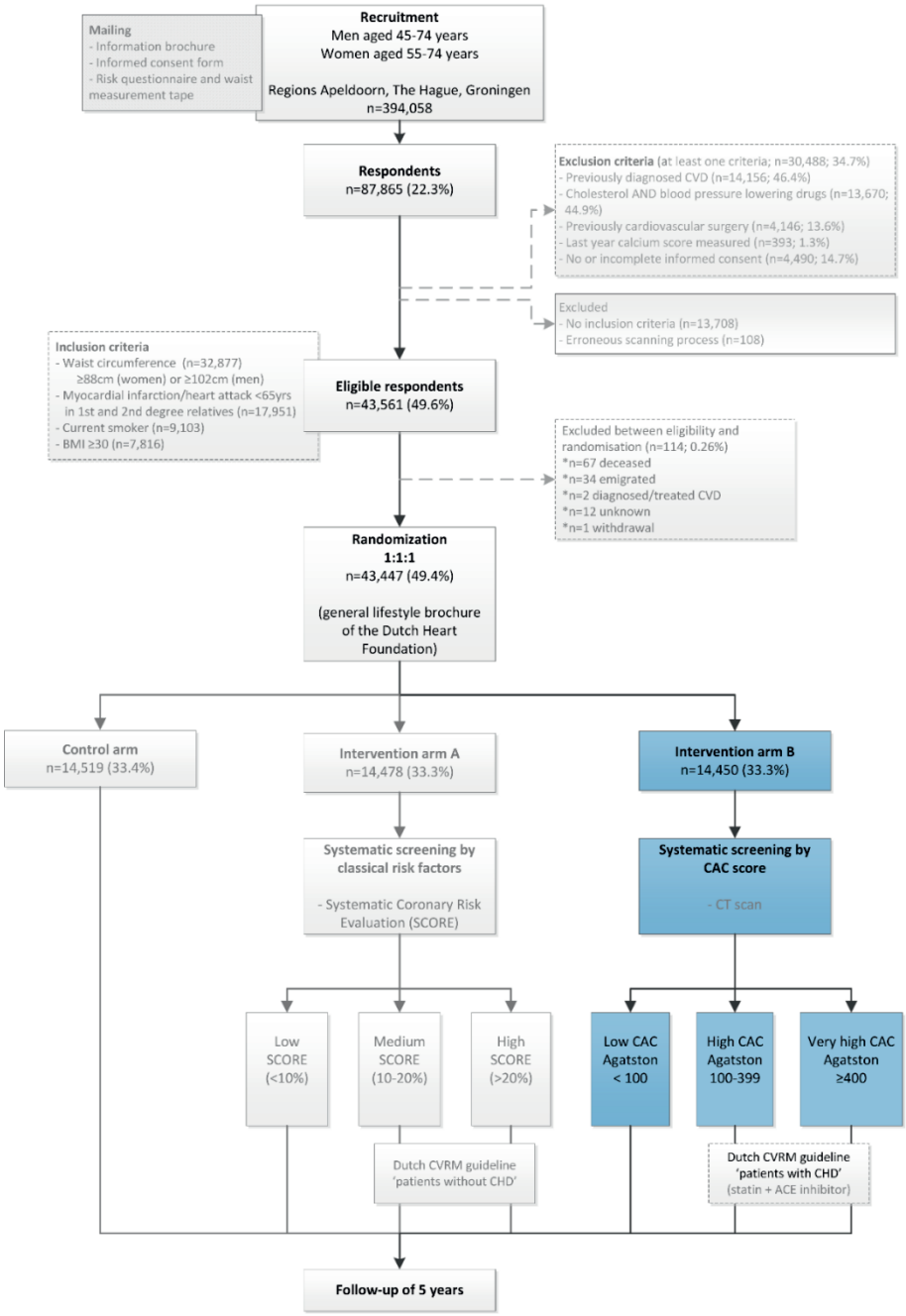

Figure 1. Flowchart of the ROBINSCA trial study design in which CAC scoring is performed in intervention arm B. Abbreviations: BMI, Body Mass Index; CAC, Coronary Artery Calcium; CHD, Coronary Heart Disease; CT, Computed Tomography; CVD, Cardiovascular Disease; CVRM, Cardiovascular Risk Management; SCORE, Systematic Coronary Risk Evaluation

CAC was absent in 39.2% of the total study population. Overall, 48% of women had a zero CAC score compared to 20.7% of men in the same age category and 31.2% of all men. Further, 16.8% of women had a CAC score of 100 or higher compared to 40.0% of men in the same age category and 30.7% of all men. The CAC distribution in the ROBINSCA trial is compared to the German Heinz Nixdorf Recall Study and the American Multi Ethnic Study of Atherosclerosis in the Supplemental Material.

Age, high waist circumference, family history of CHD, smoking at baseline, diabetes mellitus, self-reported hypertension or hypercholesterolemia at baseline, and baseline use of either antihypertensive or lipid-lowering medication were all selected as predictors in the backward regression analysis of the presence of CAC and CAC ≥ 400, and in the linear regression for predicting the log-transformed CAC extent in women (Table 1a). Age, educational level, high BMI, family history of CHD, smoking at baseline, diabetes mellitus, self-reported hypercholesterolemia at baseline, and baseline use of either antihypertensive or lipid-lowering medication were selected as predictors in the analyses for men (Table 1b). A higher educational level predicted a lower CAC score in men. The composition of the predictors differed moderately in the models for women and men.

The associations of age, male sex, diabetes mellitus and smoking with higher CAC scores are well-known (7). A lower socioeconomic status, indicated by educational level, significantly predicted a higher extent of CAC in men. This association is possibly a result of a less favorable lifestyle in terms of smoking, diet and physical activity (8). Diabetes mellitus was one of the strongest predictors for CAC presence in women. This is in line with previous research where diabetes mellitus was identified to have a greater impact in women compared to men (9). Moreover, diabetes mellitus was a strong predictor for CAC extent in both sexes, suggesting that it is the most important risk factor for CAC development after sex and age. Regarding BMI and waist circumference, our results confirm earlier findings that BMI is not a strong predictor for presence of CAC, while waist circumference is more predictive of CAC presence (10). The predictive value of baseline use of either antihypertensive or lipid-lowering medication in CAC development was also seen in previous research. However, statins have been associated with increased CAC scores, but not with more CVD events. It is suggested that statins induce CAC progression and, at the same time, plaque repair (11).

This study contributes to evidence on identifying the optimal target population for screening from the general population that will gain most healthy life-years from screening and subsequent treatment. All inclusion criteria for the ROBINSCA trial (smoking, waist circumference, BMI and a family history of CHD) were statistically significant predictors of CAC. Future analyses should provide evidence on whether the study population includes individuals who benefit most.

A main limitation is that the ROBINSCA population is not representative of all ethnic groups as a result of a homogeneous distribution, though ethnicity is known to affect CAC prevalence and severity. Another possible limitation is that study participants tend to be generally healthier than similar individuals not responding to the participation invitation (healthy volunteer effect). However, the inclusion- and exclusion criteria should have minimized this effect. Furthermore, participants using both cholesterol-lowering and antihypertensive medication were

excluded from the trial, which might have affected the found associations of CAC with CVD medication. Finally, baseline data was obtained using a self-reported questionnaire, rather than diagnostic test measures, and might entail some inaccuracies.

In conclusion, this currently largest population-based RCT for CAC screening in asymptomatic middle-aged Caucasian individuals showed that 30.7% of men and 16.8% of women with a CAC score of ≥100 urgently require preventive treatment. To a large extent, male sex and increasing age, followed by diabetes mellitus and smoking, influence CAC distribution. These results can therefore help determine the best risk prediction and prevention strategy should screening for a high risk of developing CVD be (cost)-effective.

Table 1. Baseline predictors for the presence and extent of coronary artery calcium and for a coronary artery calcium score of 400 or higher.

	Logistic regression for CAC presence (CAC score = 0 vs. >0)		**Linear regression for log-transformed CAC extent [a]**		**Logistic regression for CAC ≥ 400**	
	Odds ratio (95% CI)	P value	**Coefficient** (95% CI)	P value	**Odds ratio** (95% CI)	P value
a) Women						
Age, per 10 years	2.74 (2.46-3.05)	<0.001***	0.48 (0.36-0.59)	<0.001***	3.58 (2.79-4.64)	<0.001***
Waist circumference cut-off [b]	1.22 (1.03-1.46)	0.024*				
Family history of CHD [c]	1.63 (1.45-1.84)	<0.001***	0.20 (0.08-0.31)	0.001**	1.70 (1.31-2.21)	<0.001***
Smoker at baseline	2.00 (1.69-2.37)	<0.001***	0.35 (0.19-0.51)	<0.001***	2.18 (1.55-3.05)	<0.001***
Diabetes mellitus	2.26 (1.51-3.39)	<0.001***	0.33 (0.04-0.63)	0.026*		
Hypertension in past year (self-reported)	1.27 (1.06-1.51)	0.008**				
Hypercholesterolemia in past year (self-reported)	1.15 (0.98-1.36)	0.097				
Antihypertensive medication	1.28 (1.09-1.49)	0.002**	0.28 (0.14-0.42)	<0.001***	1.93 (1.46-2.57)	<0.001***
Lipid-lowering medication	1.81 (1.41-2.32)	<0.001***	0.22 (0.02-0.42)	0.033*	2.25 (1.54-3.30)	<0.001***
	Area under the curve: 0.685		**Adjusted R^2: 0.043**		**Area under the curve: 0.744**	
b) Men						
Age, per 10 years	2.97 (2.52-3.46)	<0.001***	0.70 (0.60-0.80)	<0.001***	3.02 (2.57-3.52)	<0.001***
Educational level [d]						
Low						
Medium			-0.15 (-0.30- -0.002)	0.046*	0.85 (0.68-1.05)	0.132
High			-0.15 (-0.29- -0.02)	0.026*	0.77 (0.63-0.93)	0.007**
Body Mass Index cut-off [e]			0.23 (0.07-0.38)	0.004**	1.33 (1.07-1.66)	0.011*
Family history of CHD [c]	1.38 (1.18-1.62)	<0.001***	0.27 (0.15-0.38)	<0.001***	1.57 (1.32-1.87)	<0.001***
Smoker at baseline	1.35 (1.12-1.64)	0.002**	0.30 (0.16-0.44)	<0.001***	1.52 (1.24-1.86)	<0.001***
Diabetes mellitus			0.39 (0.13-0.66)	0.004**	1.39 (0.96-2.03)	0.085
Hypercholesterolemia in past year (self-reported)	1.25 (0.99-1.59)	0.063				
Antihypertensive medication	1.94 (1.55-2.43)	<0.001***	0.32 (0.18-0.46)	<0.001***	1.47 (1.21-1.79)	<0.001***
Lipid-lowering medication	1.48 (1.10-2.00)	0.011*	0.40 (0.21-0.58)	<0.001***	1.49 (1.14-1.95)	0.004**
	Area under the curve: 0.686		**Adjusted R^2: 0.077**		**Area under the curve: 0.698**	

Abbreviations: CAC, Coronary Artery Calcium; CHD, Coronary Heart Disease; CI, Confidence Interval

[a] Log-transformation in individuals with CAC score > 2 because transforming CAC score > 0 did not result in a normal distribution.

[b] Trial inclusion criteria cut-off for waist circumference: ≥88 cm for women and ≥102 cm for men.

[c] Family history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives.

[d] Educational levels: low; primary, lower secondary general or lower vocational education, medium; intermediate vocational or higher secondary education, high; higher vocational education or university.

[e] Trial inclusion criteria cut-off for Body Mass Index: ≥30 kg/m^2.

*P<0.05, **P<0.01, ***P<0.001.

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The authors would like to thank the European Union for funding the ROBINSCA trial and the Ministry of Health, Welfare and Sports for the ethical approval to perform the trial. Naturally, we thank all participants for their participation. Furthermore, we would like to thank M. Quak for the extensive research assistance, RADventure for developing the data management system and IVA group for handling all questionnaires and letters. Lastly, we thank all employees of the radiology departments of the screening centers (Gelre Hospital Apeldoorn, Bronovo Hospital The Hague and University Medical Centre Groningen) for scanning participants.

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SUPPLEMENTAL MATERIAL

The coronary artery calcification (CAC) distribution in the ROBINSCA trial can be compared to other large studies like the American Multi Ethnic Study of Atherosclerosis (MESA) and the German Heinz Nixdorf Recall Study (HNR) (1). The Pearson's Chi-squared test was used to compare CAC score 0 vs. >0 distributions in the ROBINSCA trial, MESA and HNR. To match for age and ethnicity, a subset of Caucasians of the total MESA population was used (data not shown, adapted from Erbel et al.(1)). The ROBINSCA population included slightly fewer individuals with diagnosed diabetes mellitus based on self-report. The distributions of absolute CAC scores for women and men in the MESA (n=2,220), HNR (n=3,126) and the ROBINSCA trial followed the same trend (Figure 1). However, overall differences in the presence of CAC were statistically significant between ROBINSCA and both MESA and HNR ($p<0.001$). Zero CAC scores were most prevalent in MESA (47.5%) followed by ROBINSCA (39.2%) and then HNR (33.0%). Regarding sex-specific distributions, presence of CAC was comparable between ROBINSCA and HNR in women (respectively 52.0 vs. 53.8%; $p=0.206$) and CAC presence in men was comparable between ROBINSCA and MESA (68.8 vs. 67.6%; $p=0.423$).

Comment

We compared CAC distribution in the ROBINSCA trial to those in the Caucasian individuals of the MESA and HNR asymptomatic populations (1). An important population selection difference was the age of women; the ROBINSCA trial included women aged 55-74 years, whereas MESA and HNR included women aged 45-75 years. Furthermore, the exclusion criteria of MESA and HNR were slightly more selective in terms of excluding among others individuals with medical conditions preventing follow-up, with active cancer treatment and living in a nursing home. On the other hand, individuals using both cholesterol- and blood pressure-lowering medication were excluded in the ROBINSCA trial. The MESA population had the best CVD risk factor profiles (e.g. lowest number of current smokers). However, among this population were the most antihypertensive and lipid-lowering medication users, which is potentially a result from a high prevalence of hypertension and hypercholesterolemia. The same CAC distribution pattern was seen; however, overall differences in CAC presence were statistically significant. This is probably related to a different prevalence of risk factors, since MESA had the healthiest population which can possibly be a result of excluding individuals with any serious medical condition that would prevent long-term participation. Another important explanation is the discrepancy in the age range of the women, since MESA and HNR included also younger women. Regarding the women-specific comparison, the ROBINSCA distribution would presumably approach the MESA distribution if the same age categories were included. In contrast, a comparison was possible for men and a difference in CAC presence was seen between ROBINSCA and HNR. In the HNR study, CAC scores were higher, possibly as a result of less favorable risk factor levels (1).

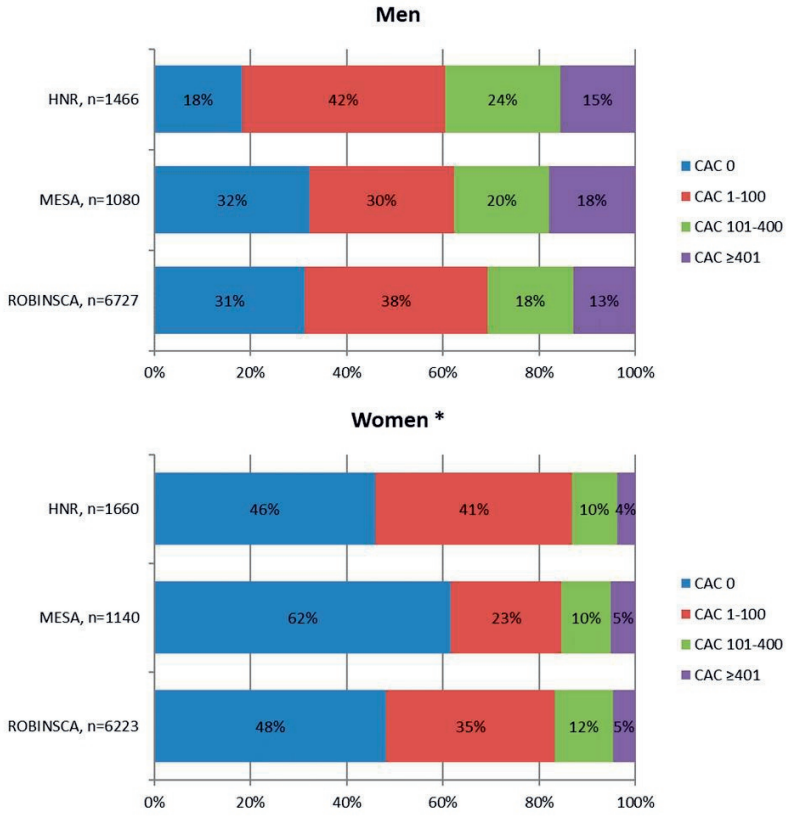

Figure 1. Comparison of distributions of absolute coronary calcium scores in the Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial, the Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall (HNR) study.
Data on CAC scores in MESA and HNR from Erbel, et al (1).
* Different age categories for women: ROBINSCA; 55-77 years, MESA and HNR; 45-75 years.
Abbreviations: CAC = Coronary Artery Calcium, HNR = Heinz Nixdorf Recall study, MESA = Multi-Ethnic Study of Atherosclerosis, ROBINSCA = Risk Or Benefit IN Screening for CArdiovascular disease

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Appendix: full article

Screening for coronary artery calcium in a high-risk population: the ROBINSCA trial

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Abstract

Objectives: Presence of coronary artery calcium (CAC) is a strong predictor of coronary heart disease (CHD). The Dutch population-based randomized-controlled Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial incorporates CAC quantification as screening modality to identify individuals at high cardiovascular disease (CVD) risk. This study presents CAC prevalence and its predictors in the ROBINSCA screening trial.
Methods: Asymptomatic individuals with an increased risk (n=14,450) were selected from the general population. CAC scores were measured using computed tomography scanning in 12,950 (89.6%) men (aged 45-74 years) and women (aged 55-74 years, 48.1%) (median age 62 years). Absolute distributions by baseline characteristics were calculated and a two-step regression approach was used to identify relevant predictors.
Results: CAC was absent in 48% of the women compared to 31.2% of men and CAC score was ≥100 (Agatston) in respectively 16.8% and 30.7%. Men had substantially higher median CAC scores, respectively 1 and 17. Logistic regression results indicated that age, diabetes mellitus and smoking were the strongest predictors for CAC presence in women, and age, antihypertensive and lipid-lowering medication use in men. In the linear model for predicting the extent of CAC, age was the strongest predictor for both women and men, followed by smoking for women and lipid-lowering medication use for men.
Conclusion: This is currently the largest population-based CAC screening study in asymptomatic middle-aged individuals, showing that 30.7% of men and 16.8% of women from the general population with a CAC score of ≥100 are recommended for preventive treatment.

Introduction

Cardiovascular disease (CVD) remains the main cause of death worldwide, accounting for 44% of all noncommunicable disease deaths, of which most are attributable to coronary heart disease (CHD) (1-3). Coronary artery calcification (CAC) has a strong association with major cardiovascular events and CHD-related and all-cause mortality (4, 5). The CHD risk-predictive value of presence of CAC is high in asymptomatic individuals, independent from the traditional risk factors including age, male sex, smoking, hypertension, hypercholesterolemia, and diabetes mellitus (4, 6, 7). It has been argued that the amount of CAC, expressed in the CAC score, can be used in population-based screening. However, there is not yet solid evidence from randomized controlled trials (RCT) that population-based CAC screening followed by preventive treatment is effective in reducing CVD-related morbidity and mortality (8, 9).

The Dutch Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial is the first large-scale population-based screening RCT. It included 43,447 asymptomatic individuals to investigate whether screening for CVD risk followed by subsequent risk reducing treatment can reduce CHD-related morbidity and mortality by at least 15% compared to no screening (10). Individuals with an expected increased CVD risk, based on a questionnaire and measured waist circumference, were selected for participation. Screening is carried out by CAC quantification using computed tomography (CT) scanning (10).

Some smaller prospective studies have investigated CAC prevalence in different sexes, age categories, socioeconomic status (educational level) categories and ethnicities (11, 12). However, the ROBINSCA trial provides detailed information on CAC prevalence, distribution and predictors in the general high-risk population. Moreover, the sample size allows for explicit examination of predictors of high CAC scores (≥400). The ROBINSCA trial is sufficiently powered to show whether screening will reduce CHD-related morbidity and mortality, but the trial needs longer follow-up. The results will contribute to evidence of the highest level on selecting those individuals who are expected to benefit most from screening and subsequent treatment. RCTs such as the ROBINSCA trial are essential to optimize guidelines and policy regarding CAC screening.

The aim of this study was to investigate the CAC prevalence and predictors in the large ROBINSCA trial, which included an asymptomatic high-risk potential target population for CAC screening from the general population.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study population

The rationale and design of the ROBINSCA trial have been described before (10). In brief, 394,058 women (55-74 years) and men (45-74 years) from the national population registry received an information brochure, a waist circumference measurement tape, a baseline questionnaire to assess sociodemographic and (CVD-related) health characteristics and a form to obtain written informed consent. Asymptomatic respondents free of diagnosed CVD were found eligible for participation when a potentially increased CVD risk was observed based on traditional CVD risk factors. All eligible respondents who gave informed consent were randomized (1:1:1) to either the control arm, intervention arm A (screening according to the Systematic Coronary Risk Evaluation (SCORE) model) or intervention arm B (CAC screening). Five year follow-up is required to investigate the effect of screening on CHD events compared to the control arm (Figure 1). The current study focuses on the CAC screening arm. The Minister of Health, Welfare and Sports authorized the ROBINSCA trial after positive advice from the Dutch Health Council in 2013.

CAC quantification and preventive treatment

The design and technical background of the CAC imaging protocol have been described elsewhere (13). A second-generation dual-source CT system was used to identify CVD risk according to the CAC score, which represents the total amount of any CAC (SOMATOM Flash, Siemens Healthineers, Erlangen, Germany). Prospective ECG triggering was used to acquire images at 60% of the inter-beat interval during an inspiratory breath-hold. Experienced technicians performed the scans and were blinded from clinical data of the participants. Images were reconstructed with a slice thickness of 3.0 mm by default and analyzed with semiautomatic selection of calcifications per coronary artery using dedicated CAC scoring software (CaSc, Syngo.via, Siemens, Erlangen, Germany). A calcification was defined as an area with a density of ≥130 Hounsfield units and ≥2 adjacent voxels, resulting in a CAC score according to Agatston (14). CAC scores were categorized into low (Agatston 0-99), high (Agatston 100-399) and very high (Agatston ≥400) risk (4). The result was communicated to both participants and their general practitioners (GP) along with preventive treatment advice for (very) high-risk individuals. The advice for CAC scores of ≥100 consisted of prescription of ACE inhibitors and statins, which is in accordance with the Dutch guideline for Cardiovascular Risk Management (CVRM) for "patients with CVD" of the Dutch College of General Practitioners (15). This specific advice was formulated based on recent literature and in consultation with the researchers and local cardiologists and GPs.

Statistical analysis

Study population characteristics are shown as frequencies or medians (interquartile range; IQR) for skewed variables. Baseline variables are evaluated for statistically significant differences using Pearson's Chi-squared test or the Mann-Whitney U-test, as appropriate. Differences between CAC distributions by age category, educational level, smoking status, diabetes mellitus status, and self-reported hypertension and hypercholesterolemia in the past year were tested using Pearson's Chi-squared test. Percentiles of CAC scores were calculated for the total study population and for age categories for both women and men. The effects of baseline

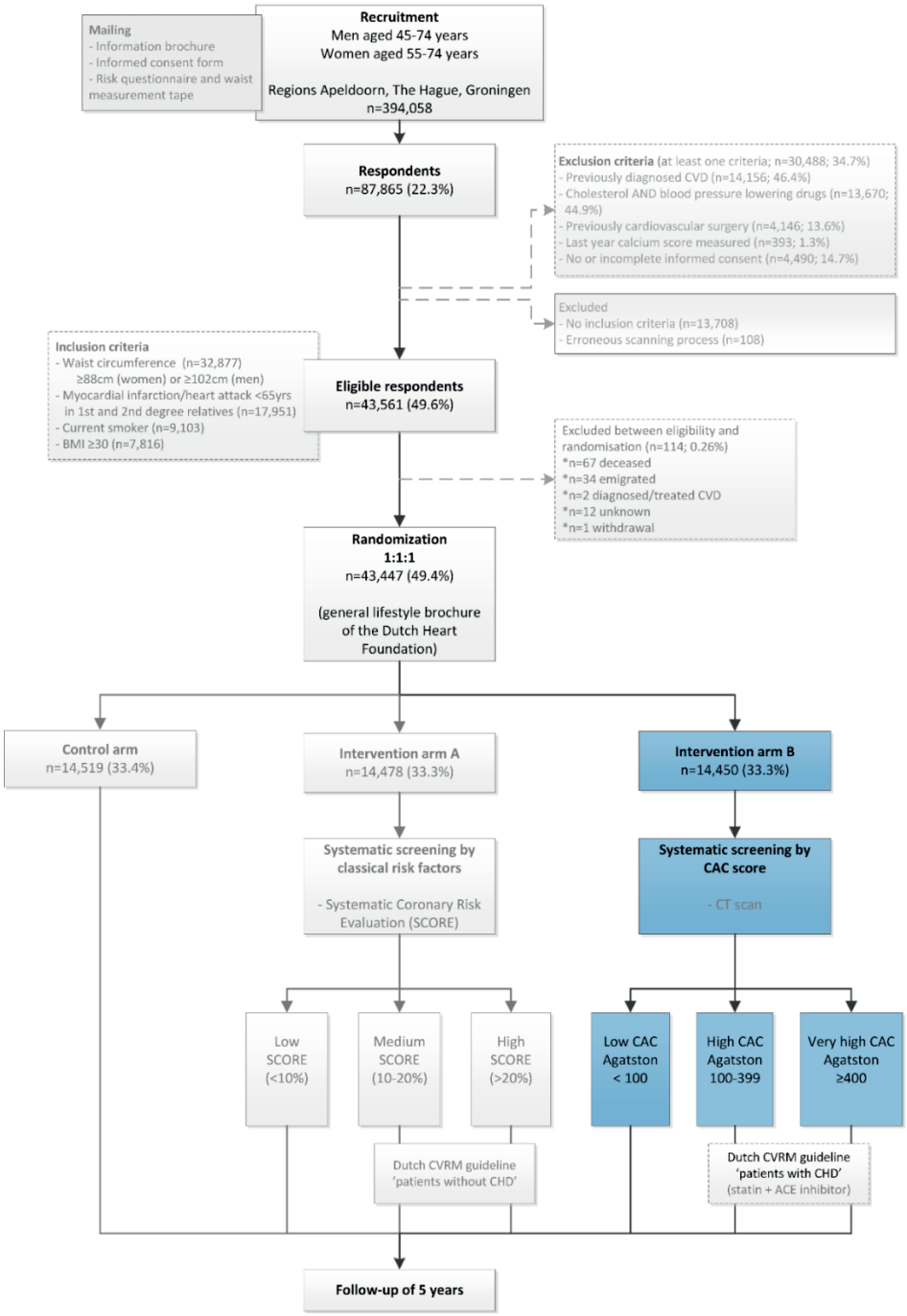


Figure 1. Flowchart of the ROBINSCA trial study design in which CAC scoring is performed in intervention arm B. Abbreviations: BMI, Body Mass Index; CAC, Coronary Artery Calcium; CHD, Coronary Heart Disease; CT, Computed Tomography; CVD, Cardiovascular Disease; CVRM, Cardiovascular Risk Management; SCORE, Systematic Coronary Risk Evaluation

characteristics on CAC score were analyzed using regression analyses for women and men separately. Since the CAC score distribution is heavily right skewed, we used a two-step approach for modeling both presence and extent of CAC. Presence of CAC (CAC score 0 vs. >0) was predicted using multivariable backward logistic regression, and the extent of CAC was predicted using multivariable backward linear regression of the log-transformed CAC score >2 (since log-transformed CAC score >0 did not approach normal distribution). Variables included in the models were age, educational level, waist circumference cut-off (88 cm for women and 102 cm for men), BMI cut-off (30 kg/m^2), family history of CHD, smoking, diabetes mellitus, hypertension in the past year, hypercholesterolemia in the past year, baseline use of antihypertensive medication and baseline use of lipid-lowering medication (all according to self-reported data from baseline questionnaire). The same variables were included in a multivariable backward logistic regression model to predict a CAC score of 400 or higher. A P value of < 0.05 was considered statistically significant. All analyses were performed with IBM SPSS Statistics Version 24.0.

Results

Study population

In total, 14,450 individuals were randomized to CAC scoring. Screening attendance was 89.6% (12,950) and was comparable for men and women, respectively 89.9% and 89.3% (p=0.159). Non-screened participants were more often smokers (27.3% vs 20%), lower educated (45.9% vs. 36.9%) and median age was one year higher. Sex, CHD family history, diabetes mellitus, and hypertension and hypercholesterolemia in the year before baseline were comparable for screened and non-screened participants. Of the screened participants, 48.1% were female and 94.2% were born in the Netherlands. Median age at CAC quantification was 64 (IQR 8) years in women and 62 (IQR 13) years in men. Regarding CVD risk factors, 20.0% were current smokers at baseline, 3.4% reported diabetes mellitus, 16.4% and 15.3% reported being diagnosed with respectively hypertension and hypercholesterolemia in the year before baseline, and 44.9% reported a family history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives (Table 1).

CAC distribution

CAC was absent in 39.2% of the total study population. Furthermore, 36.7% had a CAC score between 1 and 99, 15.1% between 100 and 399, and 8.9% had a CAC score of 400 or higher. Overall, 48% of women had a zero CAC score compared to 20.7% of men in the same age category and 31.2% of all men. Further, 16.8% of women had a CAC score of 100 or higher compared to 40.0% of men in the same age category and 30.7% of all men (Table 1). Statistically significant higher CAC scores were observed with higher age, lower educational level, current smoking, having diabetes, and hypertension and hypercholesterolemia in the past year (Figure 2). The specific CAC score percentiles in Table 2 accentuate the wide variations of CAC among sexes and age categories; in particular, CAC development seems to differ approximately by ten years and therefore possibly progresses slower in women. The CAC distribution in the

Table 1. Baseline characteristics study population (ROBINSCA intervention arm B participants).

	Total n/N (%)	Women n/N (%)	Men (age 55+)[a] n/N (%)	Men (total) n/N (%)	P value [b]
Age (at screening)					0.019*
45-54 years	2,190/12,950 (16.9)	n/a	n/a	2,190/6,727 (32.6)	
55-64 years	5,913/12,950 (45.7)	3,360/6,223 (54.0)	2,553/4,537 (56.3)	2,553/6,727 (38.0)	
65-77 years	4,847/12,950 (37.4)	2,863/6,223 (46.0)	1,984/4,537 (43.7)	1,984/6,727 (29.5)[c]	
Educational level [d]					<0.001***
Low	4,756/12,905 (36.9)	2,699/6,200 (43.5)	1,493/4,522 (33.0)	2,057/6,705 (30.7)	
Medium	3,564/12,905 (27.6)	1,552/6,200 (25.0)	1,227/4,522 (27.1)	2,012/6,705 (30.0)	
High	4,585/12,905 (35.5)	1,949/6,200 (31.4) [c]	180/4,522 (39.8) [c]	2,636/6,705 (39.3)	
Country of birth					0.005**
The Netherlands	12,139/12,882 (94.2)	5,808/6,185 (93.9)	4,296/4,514 (95.2)	6,331/6,697 (94.5)	
Other	743/12,882 (5.8)	377/6,185 (6.1)	218/4,514 (4.8)	366/6,697 (5.5)	
Smoker at baseline					<0.001***
Non-smoker	4,877/12,950 (37.7)	2,603/6,223 (41.8)	1,360/4,537 (30.0)	2,274/6,727 (33.8)	
Former smoker	5,487/12,950 (42.4)	2,770/6,223 (44.5)	2,124/4,537 (46.8)	2,717/6,727 (40.4)	
Current smoker	2,586/12,950 (20.0)	850/6,223 (13.7)	1,053/4,537 (23.2)	1,736/6,727 (25.8)	
Body Mass Index (median (IQR))	26.3 (4.9)	25.5 (5.0)	26.8 (4.3)	26.9 (4.4)	<0.001***
Waist circumference (median (IQR))	101.5 (14.5)	96.5 (13.5)	104.5 (11.5)	104.5 (12.0)	<0.001***
Chronic disease [e]	7,374/12,950 (56.9)	4,233/6,223 (68.0)	2,247/4,537 (49.5)	3,141/6,727 (46.7)	<0.001***
Diabetes mellitus	436/12,950 (3.4)	178/6,223 (2.9)	202/4,537 (4.5)	258/6,727 (3.8)	<0.001***
Hypertension in past year (self-reported)	2,124/12,919 (16.4)	1,005/6,207 (16.2)	820/4,525 (18.1)	1,119/6,712 (16.7)	0.009**
Hypercholesterolemia in past year (self-reported)	1,975/12,910 (15.3)	974/6,201 (15.7)	710/4,525 (15.7)	1,001/6,709 (14.9)	0.981
Baseline CVD medication					
Antihypertensive medication	2,557/12,913 (19.8)	1,370/6,203 (22.1)	992/4,523 (21.9)	1,187/6,710 (17.7)	0.850
Lipid-lowering medication	1,075/12,898 (8.3)	490/6,189 (7.9)	473/4,522 (10.5)	585/6,709 (8.7)	<0.001***
Family history of CHD [f]	5,330/11,876 (44.9)	2,518/5,614 (44.9)	1,913/4,220 (45.3)	2,812/6,262 (44.9)	0.636
CAC score categories					<0.001***
0	5,082/12,950 (39.2)	2,984/6,223 (48.0)	940/4,537 (20.7)	2,098/6,727 (31.2)	
1-99	4,757/12,950 (36.7)	2,196/6,223 (35.3)	1,781/4,537 (39.3)	2,561/6,727 (38.1)	
100-399	1,954/12,950 (15.1)	754/6,223 (12.1)	1,010/4,537 (22.3)	1,200/6,727 (17.8)	
400-999	763/12,950 (5.9)	215/6,223 (3.5)	503/4,537 (11.1)	548/6,727 (8.1)	
≥1000	394/12,950 (3.0)[c]	74/6,223 (1.2)[c]	303/4,537 (6.7)	320/6,727 (4.8)	

Abbreviations: CHD, Coronary Heart Disease; CVD, Cardiovascular Disease; IQR, Interquartile Range

[a] Age range comparable with women.

[b] Between comparable ages; both women and men aged 55 years or older.

[c] Percentages do not add up to exactly 100% due to rounding differences.

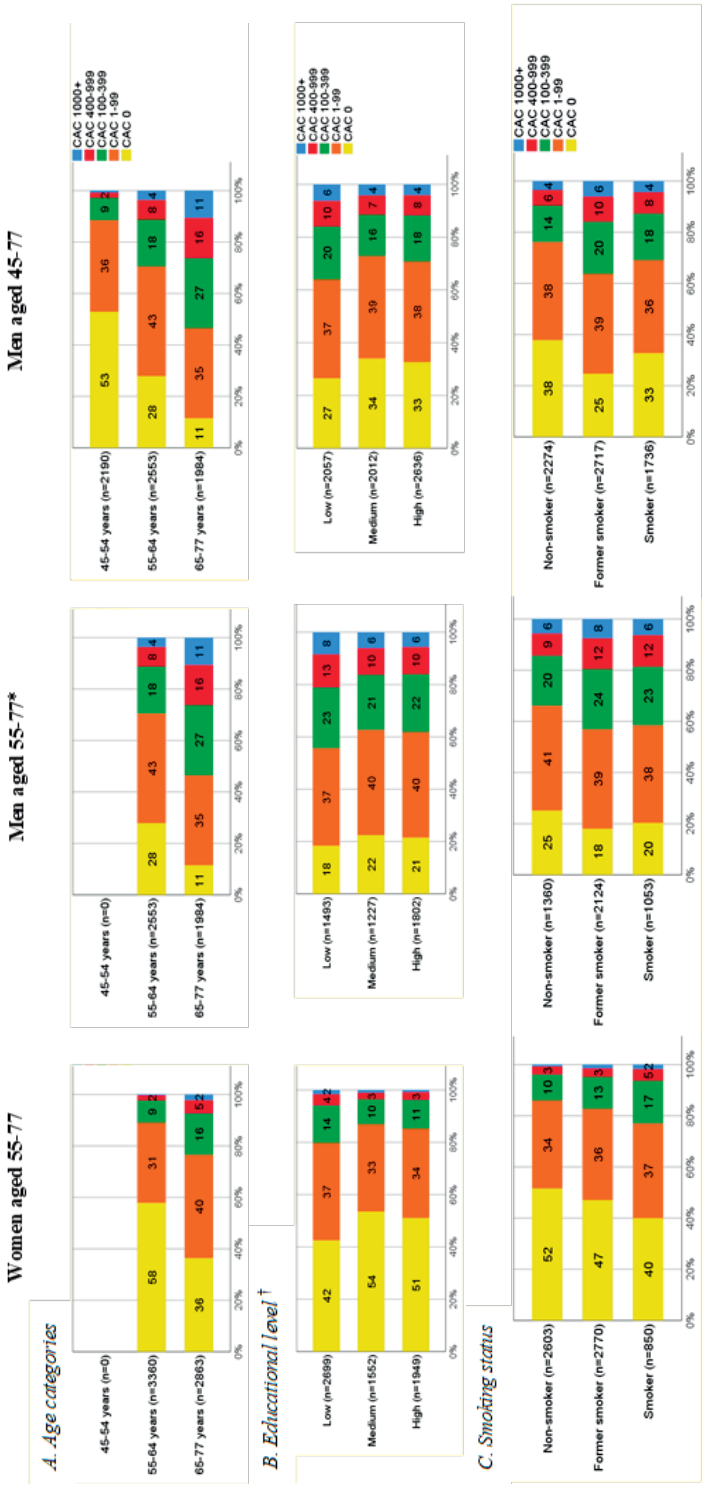
[d] Educational levels: low; primary, lower secondary general or lower vocational education, medium; intermediate vocational or higher secondary education, high; higher vocational education or university.

[e] Chronic diseases include cardiovascular diseases (which were no exclusion criteria), diabetes mellitus, cancer, renal disease, arthrosis, rheumatic disease, osteoporosis, epilepsy, migraine, dementia, Parkinson's disease, psychotic diseases, asthma and chronic obstructive pulmonary disease.

[f] Family history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives.

n/a: women aged 45-54 years old are not part of the ROBINSCA study population

*P<0.05, **P<0.01, ***P<0.001.


Women aged 55-77
Men aged 55-77*
Men aged 45-77
A. Age categories
45-54 years (n=0)
55-64 years (n=3360)
65-77 years (n=2863)
45-54 years (n=0)
55-64 years (n=2553)
65-77 years (n=1984)
45-54 years (n=2190)
55-64 years (n=2553)
65-77 years (n=1984)
B. Educational level†
Low (n=2699)
Medium (n=1552)
High (n=1949)
Low (n=1493)
Medium (n=1227)
High (n=1802)
Low (n=2057)
Medium (n=2012)
High (n=2636)
C. Smoking status
Non-smoker (n=2603)
Former smoker (n=2770)
Smoker (n=850)
Non-smoker (n=1360)
Former smoker (n=2124)
Smoker (n=1053)
Non-smoker (n=2274)
Former smoker (n=2717)
Smoker (n=1736)
CAC 1000+
CAC 400-999
CAC 100-399
CAC 1-99
CAC 0
0%
20%
40%
60%
80%
100%

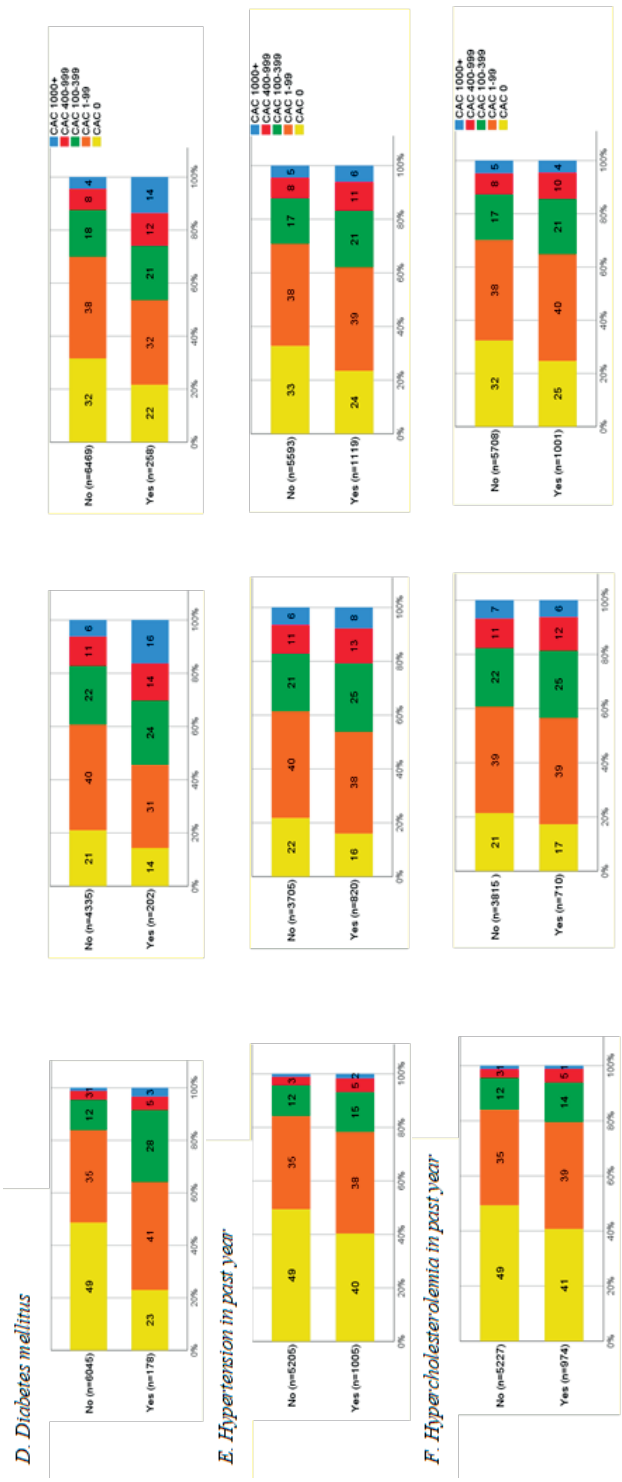


Figure 2. Distribution of coronary artery calcium score categories by age (a), educational level (b), smoking status (c), diabetes mellitus (d), hypertension in the past year (e) and hypercholesterolemia in the past year (f) for women aged 55-77, men aged 55-77 and men aged 45-77.
Abbreviations: CAC, Coronary Artery Calcium
* Age range comparable with women.
† Educational levels: low; primary, lower secondary general or lower vocational education, medium; intermediate vocational or higher secondary education, high; higher vocational education or university

Table 2. Coronary artery calcium score percentiles estimated by sex and age.

	Total	**Women**				**Men**			
		Total	45-54 y	55-64 y	65-77 y	Total	45-54 y	55-64 y	65-77 y
	n=12,950	*n=6,223*	*n=0*	*n=3,360*	*n=2,863*	*n=6,727*	*n=2,190*	*n=2,553*	*n=1,984*
Percentiles	CACS	CACS	CACS	CACS	CACS	CACS	CACS	CACS	CACS
25th	0	0	*n/a*	0	0	0	0	0	16
50th	6	1		0	9	17	0	20	124
75th	92	48		23	87	156	21	136	424
90th	356	200		115	303	530	122	468	1,034
95th	691	379		230	567	966	240	801	1,568

Abbreviations: CACS, Coronary Artery Calcium Score; y, years

n/a: women aged 45-54 years old are not part of the ROBINSCA study population

ROBINSCA trial is compared to the American Multi Ethnic Study of Atherosclerosis (MESA) and the German Heinz Nixdorf Recall Study (HNR) in the Supplemental Material.

Predictors for CAC presence and extent

Backward regression analysis of the presence of CAC in women included age, high waist circumference, family history of CHD, baseline smoking, diabetes mellitus, self-reported hypertension, self-reported hypercholesterolemia (not statistically significant; p=0.097), and baseline use of either antihypertensive or lipid-lowering medication as predictors in the model (Table 3a). This model had an area under the curve (AUC; model indicator for discrimination between CAC score 0 vs. >1) of 0.685. Highest odds ratios were found for age per 10 years (2.74; confidence interval (CI) 2.46-3.05; p<0.001), diabetes mellitus (2.26; 95% CI 1.51-3.39; p<0.001) and smoking at baseline (2.00; 95% CI 1.69-2.37; p<0.001). The linear regression for predicting the log-transformed CAC extent selected age, family history of CHD, smoking, diabetes mellitus, and baseline use of either antihypertensive or lipid-lowering medication. The explanation of variation, by means of the adjusted R-square, was 0.043. Extent of CAC was predominantly predicted by age (coefficient 0.48; 95% CI 0.36-0.59; p<0.001) and smoking (coefficient 0.35; 95% CI 0.19-0.51; p<0.001) (Table 3a). For men, the backward logistic regression analysis for presence of CAC selected age, family history of CHD, smoking, self-reported hypercholesterolemia (not statistically significant; p=0.063), and baseline use of either antihypertensive or lipid-lowering medication as predictors in the model (AUC: 0.686). Age had the highest odds ratio (2.97; 95% CI 2.52-3.46; p<0.001), followed by antihypertensive medication (1.94; 95% CI 1.55-2.43; p<0.001) and lipid-lowering medication (1.48; 95% CI 1.10-2.00; p=0.011) (Table 3b). The linear regression analysis included age, educational level, BMI, family history of CHD, smoking, diabetes mellitus, and baseline use of either antihypertensive or lipid-lowering medication (adjusted R-square: 0.077). Again, age had the highest coefficient (0.70; 95% CI 0.60-0.80; p<0.001), followed by lipid-lowering medication (0.40; 95% CI 0.21-0.58; p<0.001).

A CAC score of 400 or higher was predicted by age, use of lipid-lowering medication, smoking, use of antihypertensive medication and family history of CHD (from highest to lowest odds ratio) in women according to logistic regression analysis (AUC: 0.744). Age had also the highest odds ratio in the logistic regression model for men, followed by family history of CHD, smoking, use of lipid-lowering medication, use of antihypertensive medication, diabetes mellitus (not

Table 3. Baseline predictors for the presence and extent of coronary artery calcium.

	Logistic regression for CAC presence (CAC score = 0 vs. >0)		**Linear regression for log-transformed CAC extent** [a]	
	Odds ratio (95% CI)	P value	**Coefficient** (95% CI)	P value
a) Women				
Age, per 10 years	2.74 (2.46-3.05)	<0.001***	0.48 (0.36-0.59)	<0.001***
Waist circumference cut-off [b]	1.22 (1.03-1.46)	0.024*		
Family history of CHD [c]	1.63 (1.45-1.84)	<0.001***	0.20 (0.08-0.31)	0.001**
Smoker at baseline	2.00 (1.69-2.37)	<0.001***	0.35 (0.19-0.51)	<0.001***
Diabetes mellitus	2.26 (1.51-3.39)	<0.001***	0.33 (0.04-0.63)	0.026*
Hypertension in past year (self-reported)	1.27 (1.06-1.51)	0.008**		
Hypercholesterolemia in past year (self-reported)	1.15 (0.98-1.36)	0.097		
Antihypertensive medication	1.28 (1.09-1.49)	0.002**	0.28 (0.14-0.42)	<0.001***
Lipid-lowering medication	1.81 (1.41-2.32)	<0.001***	0.22 (0.02-0.42)	0.033*
	Area under the curve: 0.685		**Adjusted R^2: 0.043**	
b) Men				
Age, per 10 years	2.97 (2.52-3.46)	<0.001***	0.70 (0.60-0.80)	<0.001***
Educational level [d]				
Low				
Medium			-0.15 (-0.30- -0.002)	0.046*
High			-0.15 (-0.29- -0.02)	0.026*
Body Mass Index cut-off [e]			0.23 (0.07-0.38)	0.004**
Family history of CHD [c]	1.38 (1.18-1.62)	<0.001***	0.27 (0.15-0.38)	<0.001***
Smoker at baseline	1.35 (1.12-1.64)	0.002**	0.30 (0.16-0.44)	<0.001***
Diabetes mellitus			0.39 (0.13-0.66)	0.004**
Hypercholesterolemia in past year (self-reported)	1.25 (0.99-1.59)	0.063		
Antihypertensive medication	1.94 (1.55-2.43)	<0.001***	0.32 (0.18-0.46)	<0.001***
Lipid-lowering medication	1.48 (1.10-2.00)	0.011*	0.40 (0.21-0.58)	<0.001***
	Area under the curve: 0.686		**Adjusted R^2: 0.077**	

Abbreviations: CAC, Coronary Artery Calcium; CHD, Coronary Heart Disease; CI, Confidence Interval

[a] Log-transformation in individuals with CAC score > 2 because transforming CAC score > 0 did not result in a normal distribution.

[b] Trial inclusion criteria cut-off for waist circumference: ≥88 cm for women and ≥102 cm for men.

[c] Family history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives.

[d] Educational levels: low; primary, lower secondary general or lower vocational education, medium; intermediate vocational or higher secondary education, high; higher vocational education or university.

[e] Trial inclusion criteria cut-off for Body Mass Index: ≥30 kg/m².

*P<0.05, **P<0.01, ***P<0.001.

statistically significant; p=0.085) and BMI (AUC: 0.698). A high educational level was selected as significant predictor for a CAC score lower than 400 (odds ratio 0.77; 95% CI 0.63-0.93; p=0.007) (Table 4).

Table 4. Logistic regression analysis of baseline predictors for a coronary artery calcium score of 400 or higher.

	Women		**Men**	
	Odds ratio (95% CI)	P value	**Odds ratio** (95% CI)	P value
Age, per 10 years	3.58 (2.79-4.64)	<0.001***	3.02 (2.57-3.52)	<0.001***
Educational level [a]				
Low				
Medium			0.85 (0.68-1.05)	0.132
High			0.77 (0.63-0.93)	0.007**
Body Mass Index cut-off [b]			1.33 (1.07-1.66)	0.011*
Family history of CHD [c]	1.70 (1.31-2.21)	<0.001***	1.57 (1.32-1.87)	<0.001***
Smoker at baseline	2.18 (1.55-3.05)	<0.001***	1.52 (1.24-1.86)	<0.001***
Diabetes mellitus			1.39 (0.96-2.03)	0.085
Antihypertensive medication	1.93 (1.46-2.57)	<0.001***	1.47 (1.21-1.79)	<0.001***
Lipid-lowering medication	2.25 (1.54-3.30)	<0.001***	1.49 (1.14-1.95)	0.004**
	Area under the curve: 0.744		**Area under the curve: 0.698**	

Abbreviations: CHD, Coronary Heart Disease; CI, Confidence Interval

[a] Educational levels: low; primary, lower secondary general or lower vocational education, medium; intermediate vocational or higher secondary education, high; higher vocational education or university.

[b] Trial inclusion criteria cut-off for waist circumference: ≥88 cm for women and ≥102 cm for men.

[c] Family history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives.

*P<0.05, **P<0.01, ***P<0.001.

Discussion

This large-scale population-based study investigated the prevalence and extent of CAC, and identified predictive baseline characteristics in an asymptomatic Dutch population that is part of the ROBINSCA trial. This trial aims to investigate whether CAC screening is effective in reducing CHD-related morbidity and mortality in a high-risk population. This study contributes to evidence on identifying the optimal target population for screening that will gain most healthy life-years from screening and subsequent treatment.

The well-known effect of age and male sex causing higher CAC scores is also seen in the ROBINSCA trial (11, 16). Furthermore, socioeconomic status, indicated by educational level, was related to CAC and significantly predicted the extent of CAC in men. Our results support the limited existing evidence that a lower educational level is related to an increased CAC (17, 18). This is possibly a result of a less favorable lifestyle in terms of smoking, diet and physical activity (19).

CAC score percentiles in the ROBINSCA trial emphasize the substantial differences in extent of coronary calcification between asymptomatic men and women in the same age groups. Notably, our results showed that the CAC score percentiles of women aged 55-64 years were similar to men of one age category younger (45-54 years). This outcome was even more profound at higher ages; women of the highest age category (65-77 years) had considerably lower CAC scores compared to men of a younger age category, possibly indicating an accelerated progression of CAC in men. A recent study showed that men have a higher net reclassification index from CAC scoring and thus benefit more from adding CAC to risk assessment compared

to women (20). Therefore, it seems appropriate to select women for CVD screening at approximately ten years higher age compared to men. However, another study found no differences in reclassification between men and women, and there are some female-specific risk factors that substantially increase CVD risk, including preeclampsia and menopause onset (7, 21). Future research should focus more on CVD risk assessment strategies in women with these risk factors. Although CAC score percentile ranks are described to be less capable in risk stratification than sex- and age-specific absolute scores, they can be useful to assess the level of CVD risk relative to other persons with the same age and sex (22).

The investigated predictive value of several cardiovascular risk factors was similar to previous studies. Diabetes mellitus was one of the strongest predictors for CAC presence in women. This is in line with previous research where diabetes mellitus was identified to have a greater impact in women compared to men (23). Moreover, diabetes mellitus was a strong predictor for CAC extent in both sexes. This confirms the idea that diabetes mellitus is the most important risk factor for CAC development after sex and age (24). The results are also consistent with those of Kronwal et al. and Pletcher et al. who showed that diabetes mellitus is a major risk factor for CAC in MESA participants (16, 25). Another important risk

factor in the development of CAC is smoking behavior, as current smoking predicted both the presence and the extent of CAC in women and men. The smoking prevalence is higher among men, however, the reduction of smoking prevalence declined more slowly among women over the past decades and prolonged smoking is more harmful for women regarding CVD outcomes (21, 26). The regression analyses showed that a high waist circumference predicted CAC presence in women, but not the extent of CAC. This partly contradicts previous research that described a high waist circumference as a risk factor for CAC accumulation (27). Regarding BMI, no predictive value was observed in women and it only predicted the extent of CAC in men. These results confirm earlier findings that showed that BMI is not a strong predictor for presence of CAC, and that waist circumference is more predictive of CAC (28, 29).

Baseline use of either antihypertensive or lipid-lowering medication were other predictive variables selected by the regression models. In contrast, self-reported hypertension and hypercholesterolemia were less or not predictive of calcifications. However, these variables are likely to have some overlap, as individuals using antihypertensive or lipid-lowering medication probably faced elevated levels of blood pressure or cholesterol in earlier years. In previous research, statins have been associated with increased CAC scores, but not with more CVD events. It is suggested that statins induce CAC progression and, at the same time, plaque repair (30). Largely the same baseline variables also significantly predicted CAC scores of 400 or higher. Interestingly, diabetes mellitus was not selected in the female-specific model and not statistically significant in the analysis for men, contradicting previous research (24). However, another study showed that age, male sex, smoking, hypertension and hypercholesterolemia were all predictive of a CAC score of 400 or higher, and not diabetes mellitus (31).

With respect to the target population for CVD screening, it is important to select the optimal population that includes individuals who gain the most healthy life-years from screening and subsequent treatment. All inclusion criteria for the ROBINSCA trial (smoking, waist circumference, BMI and a family history of CHD) were statistically significant predictors of the presence of CAC. Furthermore, the extent of calcifications was predicted by a family history of CHD and smoking. Overall, it seems that a large proportion of the targeted high-risk population can be identified from the general population using these inclusion criteria. Future analyses of morbidity and mortality will provide more evidence on the (cost-) effectiveness of CVD screening in the ROBINSCA trial.

A strength of this study is its population-based selection of asymptomatic individuals from the national population registry. Through this approach, many individuals were reached and selected for participation. Furthermore, all CT-scans were analyzed in one analyzing center expert in CAC scoring, allowing for consistent review of CAC. However, the generalizability of our results is subject to certain limitations. For instance, the ROBINSCA population is not representative of all ethnic groups. The study population consisted mainly of native Dutch individuals (94%), whereas 18% of the general population within the same age range in the Netherlands have a migration background (32). As a result of this homogeneous distribution, ethnicity could not be included in the regression analyses, even though ethnicity is known to affect prevalence and severity of CAC. Another possible limitation is that study participants tend to be generally healthier than similar individuals not responding to the participation invitation (healthy volunteer effect). Participants were however selected on having at least one risk factor for developing CVD and the use of our inclusion- and exclusion criteria should have minimized this effect. Finally, baseline data was obtained using a self-reported questionnaire including a self-measurement of waist circumference, rather than diagnostic test measures, and might entail some inaccuracies. However, self-reported questionnaires remain the preferred method for obtaining data from an extensive population as in the ROBINSCA trial, where 394,058 individuals were approached and invited to participate.

This study summarizes CAC prevalence in a large sample of asymptomatic individuals derived from the general 'at risk' Caucasian population. To a large extent, male sex and increasing age, followed by diabetes mellitus and smoking, influence CAC distribution. This is currently the largest population-based CAC screening study in asymptomatic middle-aged men and women. It shows that 30.7% of men and 16.8% of women with a CAC score of ≥100 are recommended for preventive treatment. These results can therefore help determine the best risk prediction and prevention strategy should screening for a high risk of developing CVD be (cost)-effective.

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Part III

Cardiovascular health behavior

Chapter 6

Impact of a cardiovascular disease risk screening result on preventive behavior in asymptomatic participants of the ROBINSCA trial

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Abstract

Introduction: A teachable moment for preventive behavioural change can occur when asymptomatic individuals receive their cardiovascular disease screening result. This study investigated prevention-seeking behaviour and compliance with preventive treatment of participants of the population-based Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial after receiving a screening result.

Methods: Asymptomatic Dutch individuals (n = 43,447) were randomly assigned (1:1:1) to screening for cardiovascular disease by either traditional risk assessment (intervention arm A), or determining the amount of coronary artery calcification (intervention arm B), or to usual care (control arm). A random sample (n = 600) of ROBINSCA participants with a screening result (arms A and B) received an online questionnaire (in 2017) to measure the impact of a cardiovascular disease screening result in low and increased (arm A: risk > 10%; arm B: Agatston ≥ 100) risk groups.

Results: Of all respondents (438/600; 73%) 63.5% were men and the mean age (± standard deviation) was 63.8 ± 6.9 years. Individuals with an increased coronary artery calcification score consulted their general practitioner more often compared to increased risk individuals from arm A: 140/149 (94%) and 86/137 (62.8%), respectively ($P < 0.001$). Current use of blood pressure and cholesterol-lowering drugs was significantly higher in the increased coronary artery calcification score group (108/140; 77.1%), compared to the group with an increased traditional risk (35/80, 43.8%; $P < 0.001$). Self-reported compliance was high (98.1–100%).

Conclusion: Receiving the screening result might be a teachable moment that can enhance cardiovascular disease prevention-seeking behaviour through consulting a general practitioner and high compliance with preventive treatment. The impact of the screening result was more profound in the increased coronary artery calcification score group.

Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD), has an enormous global burden in terms of both morbidity and mortality, annually accounting for over 30% of all deaths worldwide (1, 2). CVD has a long asymptomatic period and is often only diagnosed in a progressive phase when serious events occur. This stresses the importance of early detection (screening) and subsequent risk-reducing treatment of asymptomatic people to stop or delay subclinical disease progression (3). Risk stratification is currently based on risk prediction models including the main traditional risk factors, and distinguishes low, intermediate and high-risk individuals (4-7). However, the amount of coronary artery calcification (CAC), which is strongly related to all-cause and CHD-related mortality, is suggested to be more accurate in risk stratification (8-10). In addition, recent evidence suggests a high external validity of CAC screening in a population-based prospective cohort in terms of cardiovascular risk (11). The availability of risk stratification tools and effective preventive measures, such as modifying lifestyle behaviour and preventive medication, suggests that population-based screening might be a promising strategy in secondary prevention (3, 12). The Dutch Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial is the first large population-based randomised controlled screening trial designed to investigate whether screening for a high CVD risk by means of either traditional risk assessment (arm A) or quantifying CAC using computed tomography (CT) scanning (arm B) followed by preventive treatment can reduce CHD-related morbidity and mortality in asymptomatic high-risk individuals compared to a control group.

For preventive measures to be effective, individuals need to comply with preventive advice consistently. Unfortunately, many individuals experience an inability to do so, especially caused by the asymptomatic character of CVD (13, 14). However, the moment individuals receive a screening result might be a so-called teachable moment; a health event that motivates individuals to seek prevention for their increased risk status (15). Previous research on teachable moments has shown that participation in a screening programme creates valuable opportunities to advise participants about a risk-reducing lifestyle (15, 16). Receiving an unfavourable result can cause concern which can change the perceived susceptibility and seriousness of being at risk. The higher perceived threat can result in intention for or actual behavioural change by means of seeking and complying with preventive measures (13, 17).

In the ROBINSCA trial, risk stratification is communicated to both participants and their general practitioners (GPs). Participants with an increased CVD risk are advised to consult their GP for preventive treatment. It is currently unknown whether receiving a CVD screening result is a teachable moment to seek prevention and to comply with given advice. It is also unknown whether there is a difference in impact from receiving the result between two different screening methods (arms A and B within the ROBINSCA trial). Finally, health behaviour change is also crucial in determining the potential effect of screening in the ROBINSCA trial. Therefore, this study investigated the prevention-seeking behaviour after receiving the screening result and compliance with preventive treatment of high-risk ROBINSCA participants.

Methods

ROBINSCA trial

The trial was approved by the Minister of Health of The Netherlands after positive advice of the Dutch Health Council. Participating centres also gave their approval for conducting the study.

Study population

ROBINSCA trial

This study was conducted in a subsample of participants of the ROBINSCA trial (Figure 1). The aim of this randomised controlled trial was to assess whether screening for a high risk of CVD reduces CHD morbidity and mortality with 15%. Based on the national population registry, a total of 394,058 men aged 45–74 years and women aged 55–74 years from the regions Apeldoorn, The Hague and Groningen in The Netherlands were invited to participate between 2014 and 2016. They were asked to complete a baseline questionnaire and measure waist circumference to check eligibility and to sign the informed consent form. Selection of asymptomatic individuals took place based on the following inclusion criteria: (a) a waist circumference of 88 cm or greater for women or 102 cm or greater for men; (b) a body mass index of 30 kg/m^2 or more; (c) a family history of myocardial infarction or sudden death before the age of 65 years in first or second degree relatives; and/or (d) current smoking. Individuals were not eligible when they: (a) were already diagnosed with CVD or had had a CVD surgery; (b) received a CAC score measurement in the previous year; (c) use both cholesterol and blood pressure-lowering drugs; and/or (d) did not complete the informed consent. In total, 43,447 eligible individuals were randomly assigned (1:1:1) to the control arm, intervention arm A or intervention arm B, and received generic healthy lifestyle recommendations of the Dutch Heart Foundation at randomisation. No screening was offered in the control arm. In arm A, the 10-year risk for fatal and non-fatal CVD was calculated using the systematic coronary risk evaluation (SCORE) risk table as adapted for Dutch practice in the Dutch guideline for cardiovascular risk management (CVRM) by the Dutch College of General Practitioners (18). This risk prediction model is based on age, sex, smoking status, systolic blood pressure and total cholesterol/high-density lipoprotein cholesterol ratio. A SCORE of less than 10% indicates low CVD risk, 10–20% indicates intermediate risk and 20% or higher indicates high risk. Participants in arm B underwent multi-detector CT scanning for CAC scoring, which is expressed as the total amount of any coronary calcifications (Agatston score) (19). CAC scores were stratified into low risk (Agatston < 100), high risk (Agatston 100–399) and very high risk (Agatston ≥ 400). After screening, both participants and their GPs received the screening result. Participants at increased CVD risk were advised to consult a GP for preventive treatment. The treatment study protocol was formulated corresponding to current literature and in consultation with the research team and local cardiologists and GPs. This treatment protocol advised GPs to treat participants of intervention arm A as 'patients without CVD' according to the CVRM guideline of the Dutch College of General Practitioners consisting of lifestyle advice with complementary lipid and/or blood pressure-lowering drug treatment. In intervention arm B, angiotensin-converting enzyme inhibitors and statins were recommended for participants at increased risk, which is in line with

the CVRM guideline for treating 'patients with CHD' (18). All participants are followed for 5 years to investigate the effect of screening on CHD-related morbidity and mortality as primary outcomes.

Substudy

A random sample of 600 screened participants was recruited from the ROBINSCA trial: 100 participants per risk stratification category from both intervention arms (Figure 1). The selected population received an online questionnaire in which prevention-seeking behaviour and compliance with preventive treatment were questioned. Prevention-seeking behaviour was considered as behavioural practices regarding (the motivation of) seeking healthcare from a GP after receiving the screening result. Compliance was defined as consistently taking prescribed preventive medication that should lower CHD-related risk.

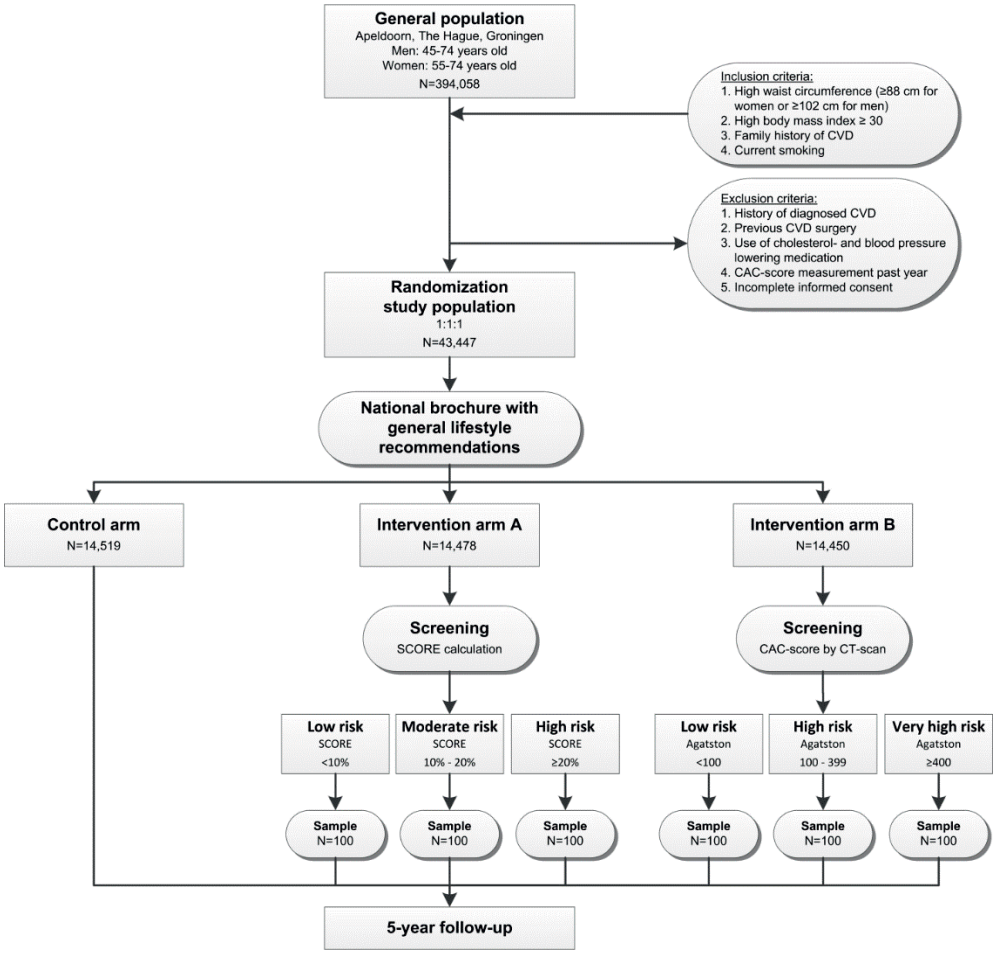

Figure 1. Flowchart of the study design of the ROBINSCA trial.
Abbreviations: CAC = Coronary Artery Calcium, CT = Computed Tomography, CVD = Cardiovascular Disease, SCORE = Systematic Coronary Risk Evaluation

Questionnaire

In 2017, participants received an invitation to complete a questionnaire by email including a link directing them to the online questionnaire. In this environment, it was possible to skip questions because participants might consider some answers as sensitive private data. Participants had at least to state their study identification number, date of birth and sex to be able to verify identity. Respondents were only included when these background characteristics were filled in as well as whether a GP was consulted or not. The questionnaire first asked participants to state their study arm and screening result, even though these data were known to the researchers, to investigate possible recall bias and the impact of participation. Prevention-seeking behaviour was defined as consulting a GP, either on one's own initiative or following a call from the GP. In addition, multiple choice questions, including open space to type, were asked about the reasons for consulting a GP and the timeframe after receiving the screening result in which this was done. There was also a question asked about the reasons for not consulting a GP. Regarding preventive measures, it was questioned whether the GP advised on lifestyle changes such as starting a healthy diet, reducing weight, increasing physical activity, ceasing smoking and/or reducing alcohol consumption. Furthermore, current prescriptions of CVD medication were asked to compare with self-reported baseline medication. To measure compliance with preventive treatment participants were asked whether they use the current prescribed medication.

Statistical analysis

Population characteristics from the baseline questionnaire are presented as mean ± standard deviation (SD) or median (interquartile range; IQR) as appropriate. Differences in characteristics distributions between intervention arm A and B participants and risk subgroups were analysed using Pearson's chi-squared test, differences in means of two groups were analysed using the independent t-test, and differences in medians between two groups were analysed using the Mann–Whitney U-test. Differences in recall of participation, GP visits and preventive CVD medication prescriptions after receiving the screening result between low and increased risk groups (arm A: SCORE > 10%; arm B: Agatston ≥ 100) were analysed using Pearson's chi-squared test. A P value of 0.05 or less was considered to be statistically significant. All analyses were performed using IBM SPSS Statistics version 24.0.

Results

Study population characteristics

The 600 selected participants received the online questionnaire after a mean ± SD follow-up of 14.8 ± 3.4 months after screening. The total response rate was 73% (438/600) and the response rates of 71% in arm A and 75% in arm B were comparable (P = 0.270). Of all respondents, 63.5% were men, mean age (±SD) was 63.8 ± 6.9 years, and 43.6% were highly educated. Comparing increased-risk and low-risk groups, an increased CVD risk was reported more often by men and individuals of higher mean age. About one-third had been diagnosed with hypertension (31.5%) or hypercholesterolemia (30.3%) in the past 5–10 years. Both diagnoses were reported more often among increased-risk individuals who underwent traditional risk screening (arm A). As to health behaviour, 18% were current smokers and 26.7% reported either

cholesterol or blood pressure-lowering medication at baseline. The relative amount of smokers was higher among individuals at increased risk compared to low risk (arm A: 26.3 vs. 10.5%; P = 0.007). There was slightly more self-reported baseline CVD medication use among the increased-risk groups compared to low-risk groups (cholesterol-lowering drug use in arm B: 14.9 vs. 5.3%; P = 0.034) (Table 1).

Prevention-seeking behaviour and compliance with preventive treatment

Correct recall of the received screening intervention was reported by 82% of the respondents from arm A and did not differ between low and increased CVD risk groups (P = 0.859), whereas adequate recall in arm B was substantially higher (90.6%) in the increased-risk group compared to having a low risk (77.6%; P = 0.008). Recall was significantly higher in the increased CAC score group than in the increased SCORE group (P = 0.043). For the screening result, recall was higher in low-risk individuals from both intervention arms compared to increased-risk individuals (87% vs. 55.6% in arm A; P < 0.001 and 80% vs. 56.1% in arm B; P < 0.001) (Table 2). Reported recall in the original increased CAC score risk categories was with 38.9% also significantly lower in the highest risk group (Agatston ≥ 400) compared to 72.4% in the high-risk group (Agatston 100–399) (P < 0.001).

As intended, almost no low-risk individuals consulted their GP after receiving the screening result (7.9% and 3.9% in arms A and B, respectively). More individuals with an increased CAC score (140/149; 94%) consulted their GP compared to individuals with an increased SCORE (86/137; 62.8%) (P < 0.001). The most common stated reason for GP consults was the wish to reduce CVD risk, especially reported by increased CAC score individuals (86/138; 62.3%) compared to increased SCORE individuals (39/86; 46.4%; P = 0.021). Within the increased SCORE group, the majority of individuals (52.3%) consulted a GP within one month after receiving the screening result. For the increased CAC score group the most stated timeframe was one week (48.6%). Increased-risk individuals who did not consult a GP mostly reported no health complaints as the reason for not consulting a GP (25/43; 58.1% in arm A and 6/9; 66.7% in arm B) (Table 2).

Concerning preventive measures, approximately half of the individuals with an increased-risk result received lifestyle advice during the GP consult with no differences between both intervention arms (P = 0.350). Initiation of any CVD medication after screening was reported by 65 out of 140 (46.4%) increased CAC score individuals, which was significantly higher than the 16 out of 80 (20%) individuals with an increased SCORE who had an indication for preventive medication based on blood pressure and cholesterol levels (P < 0.001). Total current prescriptions of a combination of antihypertensive and cholesterol-lowering drugs were more prevalent among individuals with an increased CAC score (67/140; 47.9%) compared to individuals with an increased SCORE for whom this medication was indicated (10/80; 12.5%; P < 0.001). Also, the total amount of any current CVD medication prescription was significantly higher in the increased CAC score group, 108 out of 140 (77.1%), compared to the increased SCORE group (35/80; 43.8%; P < 0.001). Self-reported compliance with this preventive CVD

Table 1. Study population characteristics.

	Overall population	Intervention arm A SCORE		Intervention arm B CAC-score		p-value arm A: low vs. increased risk	p-value arm B: low vs. increased risk	p-value low risk: arm A vs. arm B	p-value increased risk: arm A vs. arm B
		Low risk n/N (%)	Increased risk[a] n/N (%)	Low risk n/N (%)	Increased risk[a] n/N (%)				
Sex						0.001**	<0.001***	0.330	0.134
Male	278/438 (63.5)	33/76 (43.4)	93/137 (67.9)	39/76 (51.3)	113/149 (75.8)				
Female	160/438 (36.5)	43/76 (56.6)	44/137 (32.1)	37/76 (48.7)	36/149 (24.2)				
Mean age (SD)	63.8 (6.9)	58.4 (5.5)	66.4 (5.6)	61 (7.4)	65.7 (6.3)	<0.001***	<0.001***	0.018*	0.315
Educational level [b]						0.139	0.216	0.064	0.332
Low	127/438 (29.0)	28/76 (36.8)	39/137 (28.5)	15/76 (19.7)	45/149 (30.2)				
Medium	120/438 (27.4)	21/76 (27.6)	30/137 (21.9)	27/76 (35.5)	42/149 (28.2)				
High	191/438 (43.6)	27/76 (35.5)	68/137 (46.9)	34/76 (44.7)	62/149 (41.6)				
Current smoker	79/438 (18.0)	8/76 (10.5)	36/137 (26.3)	7/76 (9.2)	28/149 (18.8)	0.007**	0.061	0.786	0.129
Diagnosis in past years									
Hypertension	138/438 (31.5)	17/76 (22.4)	55/137 (40.1)	18/76 (23.7)	48/149 (32.2)	0.009**	0.184	0.847	0.163
Hypercholesterolemia	132/438 (30.3)	15/76 (19.7)	47/137 (34.3)	24/76 (31.6)	46/147 (31.3)	0.025*	0.965	0.095	0.589
Baseline CVD medication									
Blood pressure lowering	81/435 (18.6)	10/76 (13.2)	26/135 (19.3)	13/76 (17.1)	32/148 (21.6)	0.258	0.424	0.497	0.623
Cholesterol lowering	37/436 (8.5)	0/76 (0)	11/136 (8.1)	4/76 (5.3)	22/148 (14.9)	[c]	0.034*	[c]	0.075
Ever consulted cardiologist	71/437 (16.2)	8/76 (10.5)	27/137 (19.7)	13/75 (17.3)	23/149 (15.4)	0.083	0.715	0.227	0.342
Median follow-up since randomization in months (IQR)	16.8 (5.6)	16.9 (8.1)	16.8 (8.1)	16.1 (5.6)	16.8 (4.2)	0.408	0.617	0.492	0.634
Mean follow-up since screening (SD)	14.8 (3.4)	15.1 (3.6)	14.7 (3.6)	15 (3.1)	14.7 (3.2)	0.459	0.456	0.854	0.903

*P<0.05, **P<0.01, ***P<0.001

[a] Combined increased risk categories (intervention arm A; intermediate and high risk, intervention arm B; high and very high risk)

[b] Educational levels: low; primary, lower secondary general or lower vocational education, medium; intermediate vocational or higher secondary education, high; higher vocational education or university

[c] Small numbers

Abbreviations: CAC = Coronary Artery Calcium, CVD = Cardiovascular Disease, IQR = Interquartile Range, SCORE = Systematic Coronary Risk Estimation, SD = Standard Deviation

Table 2. Prevention-seeking behavior after receiving the screening result.

	Intervention arm A SCORE			Intervention arm B CAC-score			Between increased risk in arm A and B
	Low risk n/N (%)	Increased risk[a] n/N (%)	p-value	Low risk n/N (%)	Increased risk[a] n/N (%)	p-value	p-value
Recall correct study arm	62/76 (81.6)	113/137 (82.5)	0.869	59/76 (77.6)	135/149 (90.6)	0.008**	0.043*
Recall correct risk category [b]	60/69 (87)	69/124 (55.6)	<0.001***	60/75 (80)	83/148 (56.1)	<0.001***	0.943
GP consult	6/76 (7.9)	86/137 (62.8)	<0.001***	3/76 (3.9)	140/149 (94)	<0.001***	<0.001***
<70 years	6/76 (7.9)	61/102 (59.8)	<0.001***	n/a	n/a	n/a	n/a
Reason GP consult [b]							
Wish for (repeated) risk assessment	2/5 (40)	14/84 (16.7)	[c]	0	6/138 (4.3)	[c]	0.002**
Wish to reduce risk	0	39/84 (46.4)	[c]	1/3 (33.3)	86/138 (62.3)	[c]	0.021*
Need for explanation	2/5 (40)	24/84 (28.6)	[c]	1/3 (33.3)	42/138 (30.4)	[c]	0.768
Other	1/5 (20)	7/84 (8.3)	[c]	1/3 (33.3)	4/138 (2.9)	[c]	0.070
Timeframe GP consult							
Within 1 week	2/6 (33.3)	33/86 (38.4)	[c]	0	68/140 (48.6)	[c]	0.134
Within 1 month	2/6 (33.3)	45/86 (52.3)	[c]	3/3 (100)	60/140 (42.9)	[c]	0.166
>1 month	2/6 (33.3)	8/86 (9.3)	[c]	0	12/140 (8.6)	[c]	0.851
Reason no GP consult							
Low risk result	44/59 (74.6)	5/43 (11.6)	<0.001***	49/68 (72.1)	1/9 (11.1)	[c]	[c]
No health complaints	11/59 (18.6)	25/43 (58.1)	<0.001***	12/68 (17.6)	6/9 (66.7)	[c]	[c]
Other/unknown	4/59 (6.8)	13/43 (30.2)	0.002**	7/68 (10.3)	2/9 (22.2)	[c]	[c]

*P<0.05, **P<0.01, ***P<0.001

[a] Combined increased risk categories (intervention arm A; intermediate and high risk, intervention arm B; high and very high risk)

[b] Numbers do not match total number because some participants skipped questions

[c] Small numbers

Abbreviations: CAC = Coronary Artery Calcium, GP = General Practitioner, SCORE = Systematic Coronary Risk Estimation

medication was high in both increased-risk groups (100% and 98.1% in arms A and B) (Table 3).

Discussion

Receiving a screening result when participating in a screening intervention trial such as the ROBINSCA trial can introduce a teachable moment to change risk behaviour and seek for and comply with preventive measures (15). In the current study, many individuals at increased CVD risk indeed showed prevention-seeking behaviour by consulting their GP. This potential teachable moment should to be used optimally for CVD prevention by discussing healthy lifestyle and preventive treatment options. The Dutch Prevention Consult Cardio Metabolic Risk study recently reported on the prevention-seeking behaviour of participants who were invited to complete an online CVD risk questionnaire and visit their GP when the questionnaire indicated a high-risk result (20). Prevention-seeking behaviour appeared to be twice as low (36%) compared to the ROBINSCA trial (63% and 94% in arms A and B) suggesting a potential teachable moment after a screening intervention result compared to an online questionnaire outcome without testing. As expected in the ROBINSCA trial, CT screening, which is uncommon in asymptomatic individuals, was taken more seriously than traditional risk assessment resulting in more prevention-seeking behaviour. The traditional assessment includes frequently used measures that are part of standard procedure in Dutch general practices, which

Table 3. Preventive measures and compliance with preventive treatment of participants who consulted their general practitioner.

	Intervention arm A SCORE	Intervention arm B CAC-score	
	Increased risk [a] n/N (%)	Increased risk [a] n/N (%)	p-value
Lifestyle advice [b c]	45/84 (53.6)	65/138 (47.1)	0.350
Initiation of CVD medication [c d]	16/80 (20) [e]	65/140 (46.4)	<0.001***
Total current CVD medication (after screening)			
Blood pressure lowering	27/80 (33.8) [e]	82/140 (58.6)	<0.001***
Cholesterol lowering	18/80 (22.5) [e]	93/140 (66.4)	<0.001***
Both CVD medication	10/80 (12.5) [e]	67/140 (47.9)	<0.001***
Any CVD medication	35/80 (43.8) [e]	108/140 (77.1)	<0.001***
Compliance to current CVD medication [c]	35/35 (100) [e]	104/106 (98.1)	[f]

***P<0.001

[a] Combined increased risk categories (intervention arm A; intermediate and high risk, intervention arm B; high and very high risk)

[b] Lifestyle advice: healthy diet and/or weight reduction and/or increase physical activity and/or smoking cessation and/or reduce alcohol consumption

[c] Numbers do not match total number because some participants skipped questions

[d] Comparison of any baseline and current CVD medication

[e] This group includes only individuals with an indication for preventive treatment based on systolic blood pressure (≥140 mmHg) or total cholesterol (≥5 mmol/L) levels.

[f] Small numbers

Abbreviations: CAC = Coronary Artery Calcium, CVD = Cardiovascular Diseases, SCORE = Systematic Coronary Risk Estimation

might have diminished the impact of the screening result. Other reasons for not seeking prevention from a GP despite being at increased CVD risk are denial or underestimation of being at high risk, not understanding the principle of secondary prevention – the early detection and treatment of an increased risk for developing CHD before symptoms occur – and subsequent reluctance of medication. Underestimation might also explain that low-risk individuals recalled their CVD risk status better compared to individuals at high risk. Misperception of a high CVD risk was also reported by Johnson et al. who investigated the effect of knowledge of the CAC score on risk perception and health-promoting behaviour change (13).

Regarding preventive CVD medication, relatively more medication initiation and current medication was seen in intervention arm B; a possible result from the more serious impact a CT result has on willingness to take preventive medication. The greater amount of prescriptions of a combination of CVD medication in arm B is a logical result from the treatment study protocol in which it was recommended to treat individuals with both angiotensin-converting enzyme inhibitors and statins. An explanation for this drug combination being prescribed to only half of the individuals with an increased CAC score might be reluctance of individuals to take different kinds of medication without health complaints or reluctance of the GP to prescribe based only on CAC score. High compliance with prescribed preventive CVD medication is possibly caused by increased consciousness and understanding of being at risk of developing CVD. It is important to note that the described numbers are relative; the increased CAC score group is in fact smaller than the increased SCORE group (data not shown). Therefore fewer participants from the first group are advised to consult their GP and consequently absolute CVD medication prescription is lower.

Studies investigating the effect of knowledge on the CAC score showed results similar to ours. Gupta et al. investigated the relationship between the identification of CAC and starting with and adhering to preventive measures (21). The authors concluded that the presence of CAC significantly changed health behaviour in terms of an increase in the initiation and continuation of preventive medication and healthy lifestyle interventions. Comparable results were also found by Johnson et al. when the authors demonstrated that knowledge of the CAC score improves health-promoting behaviour in a relatively highly educated population, underlining the potential of this teachable moment (13). Besides, they showed that perceived barriers and quality of life are significant predictors for behaviour change. McNaughton and Shucksmith (22) reported on compliance with lifestyle advice and preventive medication in high CVD risk individuals identified during the National Health Service health check in the UK. Here, CVD risk assessment is targeted in all asymptomatic individuals between 40 and 74 years old and is carried out by calculating a risk score that is comparable with the SCORE model. Out of 23 interviewed individuals with a high risk who initiated statin therapy, 18 (78%) were compliant with taking the statin after one year. The higher compliance of ROBINSCA participants might be explained by the much smaller sample size in the UK study or by the fact that ROBINSCA participants are volunteers in a scientific trial with possibly a higher level of health consciousness (healthy volunteer effect) (23).

A possible limitation is the use of self-reported questionnaires in which social desirability bias might occur (24). However, we assume this risk to be limited because of the created casual setting which allows the respondent to complete the questionnaire at any time and place. A limitation might be the relatively long follow-up since screening that might have caused recall bias. Another limitation is that it was not investigated to what extent individuals adhere to lifestyle advice from their GP. This should be a subject in future behavioural research in the field of CVD screening. Another future research topic should focus on health literacy, as previous research showed that chronic disease patients are more likely to have lower health literacy (25). Low health literacy often involves less healthcare-seeking behaviour, which might have occurred in the ROBINSCA trial but was not investigated in the current study. The main strength of this research is the conduct of the study. The design of the online questionnaire was convenient for obtaining reliable information and its simplicity led to a high response.

Despite the promising results of receiving a screening result as a teachable moment for starting prevention, future studies should focus on increasing prevention-seeking behaviour in those who are expected to benefit from preventive treatment when CVD screening is demonstrated to be cost-effective. Furthermore, research on the health-related quality of life of participants is needed as receiving a high-risk result might cause anxiety and even depression (26).

In conclusion, prevention-seeking behaviour among individuals with an increased CVD risk was high, especially when the CAC score was quantified. CVD medication prescription following GP consultation differed between screening methods and was relatively high with good compliance. These results imply that receiving a CVD risk screening result has an important role in health behaviour change and therefore the prevention of disease.

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Part IV

Discussion and summary

Chapter 7

General discussion

General discussion

In the Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) trial, the primary aim is to investigate whether screening for a high cardiovascular disease (CVD) risk and subsequent preventive treatment in a high-risk population can reduce cardiovascular morbidity and mortality. The success or failure of such a population screening program depends on several factors as the risk-based selection and randomization of a high-risk population for participation, the screening protocol, careful analysis of screening results, screening uptake and treatment acceptance and compliance. The general aim of this thesis was to evaluate these secondary outcomes of the ROBINSCA trial. This chapter discusses all major findings with its strengths and limitations. The chapter also reviews challenges within this research topic and future perspectives. Finally, conclusions will be drawn.

Main findings and interpretation

Part 1: The ROBINSCA trial

In this first part, the ROBINSCA trial and its rationale, study design and recruitment process are described in **Chapter 2**. The research question was: *How to conduct a population-based randomized-controlled screening trial to obtain evidence on the effectiveness of screening for cardiovascular risk in an asymptomatic high-risk population?*

Findings

Chapter 2 presented the study protocol of the ROBINSCA trial, which includes a power analysis, the predefined inclusion and exclusion criteria for participating in the trial, study protocols for the screening tests and the advised preventive treatment. According to the power analysis, a sample size of 13,028 per study arm should be sufficient to show a reduction of 15% or more in morbidity and mortality, which corresponds to 100,000 CHD-related death and 500,000 CHD-related hospital admissions in Europe annually (at the time of writing the research proposal). After approval by the Minister of Health, 394,058 potential participants based on population registries were invited of which 87,866 responded to the questionnaire (response rate of 22.3%). In total, 43,447 eligible respondents (49.4%) were randomized (1:1:1) to intervention arm A for screening according to the SCORE model (n=14,478; 33.3%), intervention arm B for CAC scoring (n=14,450; 33.3%), or the control arm (n=14,519; 33.4%). Baseline characteristics (sex, age, educational level, region, BMI, waist circumference, family history of myocardial infarction, smoking status, and diabetes mellitus) of the study participants were comparable ($p>0.05$) between the three study arms.

Interpretation

The sample size fulfilled the requirements of the power analysis, indicating that recruitment was successful. This implies that there are sufficient participants in the trial to be able to draw reliable conclusions from the results that are not based on coincidence. Future similar studies are needed to obtain independent results. Furthermore, the results implied adequate randomization, since baseline characteristics between the three study arms were comparable. The population-based

design of the trial reduced the risk of self-selection. As a result, potential differences in background variables (such as morbidity and mortality, general health e.g.) between the study population and the target population who is at high risk for developing CHD are minimized.

Evidence from large-scale RCTs, indicating that CAC screening for CHD can reduce CHD-related mortality and morbidity, is lacking so far. As a consequence, current (inter)national guidelines do not yet recommend systematic population-based CAC screening in an asymptomatic population. The European Society of Cardiology recommends systematic assessment of SCORE in increased risk individuals and additional CAC scoring in individuals with moderate SCORE (1). The new 2019 guideline on primary prevention of CVD of the American College of Cardiology/American Heart Association recommends considering CAC scoring to guide (statin) therapy decisions in adults of 40-75 years of age at intermediate 10-year atherosclerotic CVD risk rather than a screening test for all (2). However, if screening for cardiovascular risk turns out to be successful, CAC screening is estimated to prevent up to 15% of the current CHD-related morbidity and mortality. This corresponds to approximately 94,800 CHD-related deaths and 460,000 CHD-related hospital admissions in the European Union yearly, based on 2015 statistics (3). Data from the ROBINSCA trial will ultimately provide more insight in the balance between the harms and benefits of screening for CVD.

In conclusion, evidence for net-effectiveness of population-based screening for cardiovascular risk in an asymptomatic population will possibly enable large-scale implementation with large health gains.

Chapter 3 focused on contamination, or in other words, mixing of interventions between study arms. Contamination can diminish the estimated potential effectiveness of screening. The contamination rate was investigated in a sample of the study population to assure statistical power to evaluate the screening effectiveness. The research question was: *What is the contamination rate in the study arms of the ROBINSCA trial?*

Findings

A random sample (n=700) of 600 screened participants (300 per screening arm and 100 per risk stratification category) as well as 100 participants from the control arm received an online questionnaire after a median follow-up (interquartile range) of 16.8 (4.7) months. Contamination in the ROBINSCA trial was defined as performing an off-study CVD screening intervention in randomized participants: measuring CAC score in intervention arm A or in the control arm, and measuring both cholesterol and blood pressure in the control arm (examinations are part of traditional risk assessment in the SCORE risk model). Measuring both cholesterol and blood pressure in intervention arm B was not considered as contamination since these measurements can be part of monitoring preventive CVD treatment. The power calculation was based on 20% potential contamination. The overall response to the contamination questionnaire was 497 (71%). Response rates in the intervention arms were significantly higher, with 71% in intervention arm A (p=0.026) and 75% in intervention arm B (p=0.002), compared to a response rate of 59% in the control arm. The results suggested the contamination rate begin negligible. CAC score measurements or a combination of cholesterol and blood pressure measurements as part of traditional risk assessment were reported by none of the 59 respondents from the control

arm indicating a contamination rate of 0%. Within intervention arm A, one out of 213 respondents indicated an off-study CAC score measurement resulting in a contamination rate of 0.5%. In intervention arm B, 80 out of 225 (35.6%) answers reported a combination of cholesterol and blood pressure. However, it is unknown whether this is contamination or treatment monitoring.

Interpretation

There was a substantial risk of contamination in the ROBINSCA trial, because participants of the different study arms can be family or neighbors who discuss the screening interventions, visit the same GP practice or because of familiarity with the SCORE model or unfamiliarity with CAC scoring. A possible explanation for the low contamination rate of 0.5% in the SCORE arm is that CAC scoring is not part of standard procedure in CVD prevention. An explanation of the absence of contamination in the control arm is that controls were not advised to consult their GP and subsequently barely did so. Any GP consults of participants from the control arm were on own initiative. The maximum potential contamination rate in intervention arm B was 35.6%: a combination of blood pressure and cholesterol measurements was reported by 35.6% of the respondents. However, instead of indicating contamination, these measurements can also indicate initiation or monitoring of preventive drug treatment. The general treatment advice for elevated CAC scores include ACE-inhibitors and statins, as derived from the current guideline for 'patients with CHD' for Dutch general practice. The reason for following the guideline for 'patients with CHD' is that screening demonstrated coronary disease, even though participants with elevated CAC may still be asymptomatic. Regarding potential contamination, GPs might have performed a blood pressure or cholesterol measurement to check the diagnostic status of blood pressure or lipids at treatment initiation. Furthermore, ACE-inhibitors are contra-indicated in case of hypotension and therefore, blood pressure needs to be monitored regularly. The most common stated reason to consult the GP among intervention arm B participants who underwent blood pressure measurements, was the wish to reduce the CVD risk. This might indicate that the GP started preventive treatment including treatment monitoring. Our hypothesis is that part of the GPs indeed performed a full SCORE assessment as a consequence of unfamiliarity with CAC scoring and that another part performed the measurements only for treatment monitoring routine after acting on the CAC score result. We expect this distribution to be within the limit of 20% contamination. Our results of limited observed contamination are in line with those of the lung cancer screening trials Danish Lung Cancer Screening Trial (DLCST) and the Dutch-Belgian randomized-controlled lung cancer screening trial (NELSON) (4, 5). The researchers conclude that the contamination rate might be underestimated because it is possible that some participants who received an off-study intervention do not fulfill the questionnaire as they understand that off-study interventions may affect the outcomes of the trial. This might have happened within our study as well, although the exact purpose of the questionnaire was obviously not mentioned in the general introduction in the invitation to prevent social desirable responses.

In conclusion, the contamination rate in the ROBINSCA trial is expected to be below the acceptable predefined rate and therefore is unlikely to affect the power to demonstrate a potential effect of early detection and treatment of a high CVD risk.

Part 2: Cardiovascular disease screening results

Chapter 4 described the CVD risk distributions in the screening arms of the ROBINSCA trial. The potential reduction in preventive overtreatment was estimated based on the expected difference in risk distributions. The research question was: *What are the differences in cardiovascular risk distributions and the number of preventive treatment indications between screening using traditional risk factor assessment or coronary artery calcium scoring in asymptomatic participants of the ROBINSCA trial?*

Findings

Screening attendance rate was high, but different as expected for both intervention arms; 12,185 out of 14,478 (84.2%) participants underwent a SCORE assessment and 12,950 out of 14,450 (89.6%) participants underwent CT scanning for CAC quantification ($p<0.001$). Based on the Dutch SCORE, 53.8% (3,234/6,009) of women were classified as low-risk, 24.6% (1,479) as intermediate and 21.6% (1,296) as high-risk. A substantial different CVD risk distribution was observed using CAC scoring: more low-risk individuals were identified. A zero CAC score was measured in 48.0% of the women (2,984/6,223), and 35.3% (2,196) had a low CAC score (Agatston 1-99), 12.1% (754) had a high CAC score (Agatston 100-399) and 4.6% (289) had a very high CAC score (Agatston ≥400). The absolute reduction in the number of high-risk women was 29.4% when CAC scoring was used as screening tool and the relative reduction was 63.7%. Regarding men, 36.6% (2,262/6,176) were assessed as being at low risk, 28.4% (1,751) as intermediate risk and 35.0% (2,163) as high-risk based on the SCORE model. A total of 31.2% (2,098/6,727) had a zero CAC score, 38.1% (2,561) had a low CAC score, followed by 17.8% (1,200) and 12.9% (868) with a high and very high CAC score respectively. The absolute reduction in the number of high-risk men was 32.7% and the relative reduction was 51.5% when CAC scoring was used as screening tool. These large differences in CVD risk distributions between the screening modalities in both women and men caused statistically significant differences in the number of individuals indicated to consult their GP for preventive drug treatment. Eventually, the GP will consider drug treatment based on medical background and when systolic blood pressure is >140 mmHg and/or LDL-cholesterol >2.5 mmol/L. Preventive treatment was indicated for 26.7% of women according to the SCORE model, compared to 16.8% of women according to CAC scoring ($p<0.001$). This caused an absolute reduction of 9.9% and relative reduction of 37.2% in the number of women indicated for preventive treatment when using CAC scoring compared to SCORE calculation. Among men, 43.2% were advised to start preventive treatment according to the SCORE model, whereas 30.7% received a preventive treatment advice according to CAC scoring ($p<0.001$). The absolute reduction was 12.4% and the relative reduction was 28.8%.

Interpretation

As expected, the results show that the CVD risk distributions differed largely between the two screening modalities. CAC scoring identified more low-risk individuals compared to the SCORE model. Traditional risk prediction using the SCORE model has several limitations, including the limited adaptation for different ethnic groups, the limited age range, and the lack of incorporating risk modifiers that potentially reclassify CVD risk, such as socio-economic status, CVD family history and obesity (1). Furthermore, it identifies many intermediate-risk individuals for whom

the decision to start preventive treatment is often debatable based solely on SCORE assessment (6). As stated before, current European and American guidelines recommend considering additional CAC scoring to guide preventive therapy decisions in intermediate-risk adults (1, 2). A reason for this is that CAC scoring has superior discrimination and risk reclassification as compared with other risk indicators (7). Previous studies showed that asymptomatic intermediate-risk individuals were more often downgraded to a lower risk category after adding CAC scoring to risk prediction (8, 9). There are no results yet of CAC score and SCORE estimates within one individual in the ROBINSCA trial. Future analyses will focus on that. However, as baseline characteristics are comparable and the study population size is sufficient, it might be reasonably assumed that risk estimates based on SCORE are comparable over the three study arms, as well as risk distributions based on CAC score. Therefore, our results are in line with the previous studies. Additionally, a review summarized the results of population-based cohorts that showed the convincing value of CAC scoring beyond traditional risk factors as a single predictive cardiovascular risk marker (10). Recent literature also described that shared-decision making guided by CAC scoring in intermediate-risk individuals can be a cost-effective strategy to avoid years of preventive medication (10, 11). However, there is no evidence yet on using CAC scoring as a screening tool for all.

The substantial reduction in the number of individuals indicated for preventive treatment after CAC scoring will potentially influence prevention strategies significantly. The CAC score is considered to be an improved estimate of CVD risk status, however, this should first be confirmed. If proven, it might minimize unnecessary and unjustified stress that potentially occurs when participants receive an unfavorable test result (12). It will also reduce the burden for GPs, as risk management based on CAC scoring should be less time consuming since the indication for treatment is more clear. Furthermore, the potential reduction in preventive overtreatment will reduce potential harmful side effects in participants and costs of drug treatment and cardiovascular risk management. However, the effectiveness of CT screening in reducing CVD-related morbidity and mortality should first to be confirmed, as CT scanning is more expensive compared to using the SCORE model. Moreover, participants are exposed to radiation which might cause side effects. We developed a protocol to keep the radiation dose as low as possible. The protocol also included a description of clinically relevant incidental findings which could be detected on the CT scan. There were few incidental findings during screening, as the scans were zoomed in as closely as possible on only the coronary arteries. Future analyses on CVD-related events in the ROBINSCA trial might add important evidence on whether CVD screening is effective in reducing CHD-related events and to what extent a preventive treatment decision should be based on CAC screening.

In conclusion, CAC scoring classified significantly fewer individuals at high-risk for CVD in both women and men compared to applying the SCORE model. Subsequently, the potential reduction in preventive overtreatment might favor the use of CAC scoring in screening for cardiovascular risk in the asymptomatic, potential high-risk, population.

Chapter 5 provides more insight in CAC prevalence, distribution and predictors in a high-risk potential target population for screening from the general population. The research question

was: *What is the coronary artery calcium prevalence and what are predictors in an asymptomatic potential high-risk target population for coronary artery calcium screening?*

Findings

CAC was absent in 39.2% of the total screened study population (n=12,950), in 48% of women (n=6,223), in 20.7% of men in the same age category as women (n=4,537) and in 31.2% of all men (n=6,727). Further, 16.8% of women had a CAC score of 100 or higher compared to 40.0% of men in the same age category and 30.7% of all men. Statistically significant higher CAC scores were observed with higher age, low educational level, current smoking, having diabetes, and hypertension and hypercholesterolemia in the past year. A low educational level was defined as primary, lower secondary general or lower vocational education, medium level as intermediate vocational or higher secondary education, and a high educational level was defined as higher vocational education or university. The specific CAC score percentiles accentuated the wide variations of CAC among sexes and age categories; in particular, CAC development seems to differ approximately by ten years and possibly progresses slower in women. Age, educational level, high waist circumference, high BMI, family history of CHD, smoking at baseline, diabetes mellitus, self-reported hypertension or hypercholesterolemia at baseline, and baseline use of either antihypertensive or lipid-lowering medication were all selected as predictors in the backward regression analysis of the presence of CAC and in the linear regression for predicting the log-transformed CAC extent. The composition of the predictors differed moderately in the models for women and men.

Interpretation

The associations of age, male sex, diabetes mellitus and smoking with higher CAC scores are well-known (13-15). In our results, diabetes mellitus was one of the strongest predictors for CAC presence in women. This is in line with previous research where diabetes mellitus was identified to have a greater impact in women compared to men (16). Moreover, diabetes mellitus was a strong predictor for CAC extent in both sexes, suggesting that it is the most important risk factor for CAC development after sex and age (17). Current smoking predicted both the presence and the extent of CAC in women and men. It is important to realize that the reduction of smoking prevalence declined more slowly among women over the past decades and that prolonged smoking is more harmful for women regarding CVD outcomes, which therefore requires extra awareness (18, 19). Another important predictor besides current smoking might be smoking history in terms of pack-years. However, as smoking history of ROBINSCA participants was not questioned in the baseline questionnaire, a future study might focus on the potential predictive value of this variable. Furthermore, socioeconomic status, indicated by educational level, was related to CAC development. A potential explanation for this association might be a less favorable lifestyle in terms of smoking, diet and physical activity (20-22). Regarding BMI and waist circumference, our results confirm earlier findings that showed that BMI is not a strong predictor for presence of CAC, while waist circumference is more predictive of CAC presence (23, 24). The predictive value of baseline use of either antihypertensive or lipid-lowering medication in CAC development was also seen in previous research. High dose and long-term statin therapy is associated with increased CAC scores. However, statin therapy is not associated

with more CVD events. It is suggested that statins induce plaque repair, which is associated with stabilization of CVD events (25). Future research is required to elaborate on this hypothesis, for example by making a follow-up CT scan.

The target population for CVD screening should include those individuals who are most likely to gain healthy life-years from screening and subsequent treatment. All inclusion criteria for the ROBINSCA trial (smoking, waist circumference, BMI and a family history of CHD) were statistically significant predictors of either the presence of CAC or the severity of the calcifications. Furthermore, CAC score percentiles emphasized the substantial differences between women and men. A recent study showed that men might benefit more than women from adding CAC scores, since men have a higher net reclassification index from adding CAC scoring to the traditional risk assessment (26). Therefore, it seems appropriate in CVD screening to select women at approximately ten years higher age compared to men. However, there are some female-specific risk factors that substantially increase CVD risk, including preeclampsia and menopause onset, which should be recommended for future research topics (18). Overall, it seems that a large proportion of the targeted high-risk population can be identified from the general population using the current inclusion criteria. Future analyses of morbidity and mortality will provide more evidence on the (cost-)effectiveness of CVD screening in the ROBINSCA trial.

The CAC score is also associated with an increased risk for noncardiovascular disease, including cancer, chronic kidney disease, and chronic obstructive pulmonary disease (COPD) (27). A recent review summarized evidence and technical considerations of combined CT protocols for early detection of lung cancer, COPD, and CVD, the "Big-3" diseases, with low-dose chest CT. Combined screening could be feasible since a single CT scan of the chest area can detect the biomarkers for these three diseases: lung nodule growth rate for lung cancer, emphysema for COPD and CAC for CVD. Even though smoking cessation remains the most effective measure to decrease Big-3 disease burden, the authors stated that lung cancer screening might be extended with screening for COPD and CVD to significantly improve the cost-effectiveness of low-dose lung cancer screening in the future (28).

In conclusion, the currently largest population-based RCT for CAC screening in asymptomatic middle-aged individuals showed that 30.7% of men and 16.8% of women with a CAC score of ≥100 urgently require preventive treatment. These results can help select the optimal target population for screening and determine the best risk prediction and prevention strategy should screening for a high risk of developing CVD be (cost-)effective.

Part 3: Cardiovascular health behavior

Receiving a screening result of cardiovascular screening might be a teachable moment to seek preventive health care for a high risk and comply to preventive measures. **Chapter 6** described the impact of receiving the screening result on prevention-seeking behavior. The research question was: *What is the impact of receiving a cardiovascular disease risk screening result on preventive behavior and compliance to subsequent preventive treatment in asymptomatic participants of the ROBINSCA trial?*

Findings

A sample of 600 screened participants received an online questionnaire after a mean follow-up of almost 15 months of which 438 responded (73%). The response rates of 71% in intervention arm A (SCORE) and 75% in intervention arm B (CAC scoring) were comparable (p=0.270). In intervention arm A, 82% of the respondents correctly remembered the received screening intervention and recall did not differ between low and increased CVD risk groups (p=0.859). In contrast, adequate recall in intervention arm B was substantially higher (90.6%) in the increased risk group compared to having a low risk (77.6%; p=0.008). Moreover, recall was significantly higher in the increased CAC score-group (90.6%) than in the increased SCORE-group (82.5%; p=0.043). Furthermore, recall of the correct risk category was higher in low risk individuals from both intervention arms compared to increased risk individuals (87 vs. 55.6% in arm A; p<0.001 and 80 vs. 56.1% in arm B; p<0.001). Regarding prevention-seeking behavior, almost no low risk individuals consulted their GP after receiving the screening result as intended (7.9 and 3.9% in arm A and B). More individuals with an increased CAC score (140/149; 94%) consulted their GP compared to individuals with an increased SCORE (86/137; 62.8%) (p<0.001). The most common stated reason for GP consults was the wish to reduce CVD risk, which was especially reported by increased CAC score individuals (86/138; 62.3%) compared to increased SCORE individuals (39/86; 46.4%; p=0.021). Increased risk individuals who did not consult a GP mostly reported no health complaints as reason for not consulting a GP (25/43; 58.1% in arm A and 6/9; 66.7% in arm B). Concerning preventive measures, 53.6% of the individuals with an increased SCORE and 47.1% with an increased CAC score received lifestyle advice during the GP consult (p=0.350). There were more total current prescriptions of a combination of antihypertensive and cholesterol lowering drugs according to the study protocol among individuals with an increased CAC score (67/140; 47.9%) compared to individuals with an increased SCORE for whom this medication was indicated (10/80; 12.5%; p<0.001). Moreover, the total number of any current CVD medication prescription was also significantly higher in the increased CAC score-group (108/140; 77.1%) compared to the increased SCORE-group (35/80; 43.8%; p<0.001). Self-reported compliance with preventive CVD medication was high in both increased risk groups (100 and 98.1% in arm A and B). The described numbers are relative; the increased CAC score-group is smaller than the increased SCORE-group (data shown in Chapter 4). Therefore fewer participants from the first group are advised to consult their GP and consequently absolute CVD medication prescription is lower.

Interpretation

These results showed that a vast majority of the individuals at increased CVD risk showed prevention-seeking behavior by consulting their GP. This potential teachable moment should be used optimally for CVD prevention by discussing healthy lifestyle and preventive treatment options (29). However, the results showed that approximately half of the increased risk individuals did not recall their correct CVD risk status. Underestimation might explain that low risk individuals had better recall of their CVD risk status compared to individuals at high risk. The letter with the screening test result should be as clear and specific as possible to prevent denial, underestimation and misperception of being at high risk, as well as not understanding the principle of secondary prevention and reluctance of subsequent treatment (12). Compared to a

previously performed pilot study, the potential effect of a teachable moment after a physical screening intervention was at least twice as high as after completing an online CVD risk questionnaire (30). This suggests that performing tests to measure CVD risk has more impact than answering questions about the potential risk. As expected, especially CT screening resulted in relatively more prevention-seeking behavior compared to traditional risk assessment. This might be explained by CT scanning being high-quality equipment compared to blood testing and a blood pressure monitor. Furthermore, CT scanning is uncommon in asymptomatic individuals. The traditional risk assessment includes frequently used measures that are part of standard procedure in Dutch general practices which might have diminished the impact of the SCORE screening result. Another possible result from the more serious impact of a CT result is the increase in willingness to take preventive medication. Relatively more intervention arm B participants reported CVD medication initiation and current medication. At-risk individuals with prescribed preventive CVD medication reported high compliance rates. The explanation could be an increased consciousness and understanding of being at risk for developing CVD. This is in line with previous research that showed that knowledge of CAC presence increased health-promoting behavior and initiation and continuation of preventive medication and healthy lifestyle interventions (12, 31). However, an important note when measuring compliance is the potential role of the healthy volunteer effect. Volunteers in a scientific trial possibly have a higher level of health consciousness. For example, compliance to preventive treatment was lower after CVD risk assessment in asymptomatic individuals in the National Health Service health check in the UK (32).

In conclusion, prevention-seeking behavior among individuals with an increased CVD risk was high, especially when the CAC score was quantified. CVD medication prescription following GP consultation differed between screening methods and was relatively high with good compliance. These results imply that receiving a CVD risk screening result is a potential teachable moment and therefore has an important role in health behavior change and prevention of CVD.

Strengths and limitations

The major strength of the research in this thesis is the setting of the ROBINSCA trial. The trial is a population-based randomized-controlled screening trial. Only this type of research can provide evidence of the highest level on effectiveness of screening. The recruitment process of participants through the national population registry reached a large population. This strategy aims to limit self-selection bias and to stimulate selection of a representative study population. Moreover, the random allocation of study participants to study arms minimizes the effect of potential confounding factors. The characteristics of randomized participants will be compared with Dutch national data to measure generalizability.

Furthermore, the contamination rate in the study arms and compliance to preventive treatment were measured with a convenient and straightforward online questionnaire. This allowed participants to complete the questionnaire at any time and place they wanted. As a result, the response was high and assumed to be reliable.

Another strength of this research is the screening protocol. Participants that were randomized to the intervention arms received an invitation for screening, either SCORE assessment or CAC scanning, at a local screening site. Blood pressure was measured by centrally trained lab staff with blood pressure monitors according to the study protocol. Blood samples were also taken by trained lab staff and analyzed in an experienced regional laboratory. Furthermore, CT scans were made according to a scanning protocol with the lowest radiation dose as possible (33). CT images were transmitted to the analyzing center through a secure online environment. This prominent center has extensive experience with CAC scans and assessed all scans for the presence of CAC. All results were ultimately entered into the data management system. Through this system, result letters were sent to participants and GPs in the most error-free manner possible.

Despite these strengths, there are some limitations that need to be addressed. The recruitment of a high-risk study population was based on self-reported health data rather than diagnostic tests. Self-reported data are prone to recall bias and might entail some inaccuracies (34). However, each health topic was examined with multiple different questions to determine the reliability of answers with more certainty. Therefore, this strategy remains the preferred method for recruitment of and data collection from an extensive population like in the ROBINSCA trial. In total, 394,058 individuals from the national population registry were invited to participate. It would have been unfeasible and not cost-effective to diagnostically verify baseline health characteristics of all these individuals.

Regardless the wide reach of potential study participants, the healthy volunteer effect may have occurred, making the study population less representative than the target population. It is known that study participants tend to be generally healthier than non-responders. Previous research showed that individuals who might gain most from screening are least likely to participate (35). However, the ROBINSCA inclusion- and exclusion criteria selected participants based on having at least one risk factor for developing CVD. This strategy should have minimized the healthy volunteer effect as much as possible. An additional related determinant is health literacy. Low health literacy is associated with presence of risk factors, poor adherence to treatment and low screening attendance and might result in exacerbating health inequalities (36). Health literacy was not investigated in this thesis.

Further, the ROBINSCA population is not representative of all ethnic groups. First, only self-reported data on country of birth of both the participants as well as their parents are known. This information provides a reasonable estimate of ethnicity, but classification based on country of birth is not always correct. Second, the majority of the study population was native Dutch, whereas 18% of the general population within the same age range in the Netherlands have a migration background (37). Ethnicity plays an important role as it is known that CAC distributions differ among ethnicities (13). As a result, the outcomes may be less generalizable to other ethnicities.

An additional limitation is the potential social desirability bias that might have occurred in the questionnaire (34). In particular, the questions on the use of prescribed medication or other preventive measures might be prone to this type of bias, since individuals understand that preventive measures might improve risk status. However, self-reported adherence measures through computer administration are the preferred method to obtain reliable data as it reduces the risk of biases (38). Furthermore, recall bias was another potential source of bias in the questionnaire on contamination and impact of receiving a screening test result. A relatively long follow-up since screening may have caused problems in recalling whether or not participants consulted their GP after receiving the screening test result. In contrast, it seems reasonable to expect that a GP consult following participation in a screening program will have some impact on participants, as participating in a screening program is not a common activity. Communication to participants is of great importance to achieve sufficient impact and to encourage participants to act appropriately on the screening result.

Finally, the contamination rate and the impact of a CVD risk screening result were investigated in a relatively small sample of the total ROBINSCA study population. However, we assume that the results are relatively generalizable to the study population, since they do not differ on baseline characteristics and the response rate was sufficient.

Challenges and future directions

The final analyses of the ROBINSCA trial aim to establish whether population-based screening for a high risk of CVD and subsequent early treatment can reduce CHD-related morbidity and mortality. After completion of at least 5-years follow-up, data on CHD-related events will be obtained through linkages with the national Causes of Death registry and the National Hospital Discharge Registry of Statistics Netherlands. Primary outcome analysis of these data allows for investigation of screening effectiveness. This analysis should also include subgroup analyses for specific risk groups, such as women with female-specific risk factors, diabetics and smokers. The risk-based recruitment of participants selected an asymptomatic population who is expected to benefit most from screening and early treatment. This selection method attempts to ensure that those who do not benefit from screening are not exposed to the potential harmful effects of participation. The subgroup analyses should confirm whether the selected risk groups indeed benefit most from participating in cardiovascular screening. Future research on the effect of ethnicity is recommended as well. Moreover, morbidity and mortality data are necessary to verify the reduction in overtreatment when using CAC scoring as screening tool. In this thesis, the reduction in the number of individuals indicated for preventive treatment was estimated based on their CVD risk status. However, morbidity and mortality analyses should demonstrate whether individuals who were indicated for preventive treatment actually have fewer CHD-related events. These results might add important evidence about whether CAC screening should guide decisions on preventive treatment.

As described before, participants of screening trials might be slightly healthier compared to nonparticipants which is known as the healthy-volunteer effect. This effect may impair the

generalizability of the study results to the target population. Therefore, it should be investigated whether there are differences between the baseline and mortality characteristics of trial participants and nonparticipants.

The potential effectiveness of CVD screening program depends on several factors. After the screening performance itself, it is essential that GPs act according to the advice for treatment. Participants at (very) high risk for developing CVD are advised to consult their GP who has access to their medical background with potential indicators for treatment or contra-indicators that should impede treatment as advised. More protocoled treatment options are needed for a high-standard screening program, although in this stage the first step is to investigate whether the early detection of a high risk in the asymptomatic population is feasible. The final decision regarding preventive treatment is made in consultation with the GP and not solely based on the ROBINSCA advice for treatment. Shared-decision making is important in a screening program, as each individual has an unique medical background that either indicates or contraindicates drug treatment. However, this may have consequences for demonstrating the effect of screening. The final outcomes not only depend on the effectiveness of the screening modality, but also on appropriate subsequent response in terms of preventive (drug) treatment. The shared-decision making process increases the workload of GPs as cardiovascular risk management might be time consuming. On the other hand, accurate risk management will reduce morbidity and will therefore provide long-term benefits. Clear information and evidence should be communicated to GPs to explain importance. Adherence to the protocol is important to ensure that those who are expected to benefit most from screening and early treatment actually receive preventive treatment. Future research should investigate the adherence of GPs to the advice for treatment. Second, as previously described in this thesis, prevention-seeking behavior and compliance to preventive measures of participants are also crucial in achieving a reduction in CHD-related events. Since it was not investigated to what extent participants adhered to lifestyle advice, this should be explored in future research. This research should also include improving strategies to stimulate prevention-seeking behavior and the role of health literacy in compliance to preventive measures.

Should CVD screening be effective, potential adverse side effects need to be considered before implementing a screening program. First, screening can cause psychological side effects, such as discomfort, anxiety and distress related to screening. The impact of screening on health-related quality of life (HRQoL) should be included in balancing the overall favorable and unfavorable effects of screening. HRQoL and general anxiety will be assessed in a subsample of the ROBINSCA trial. Second, individuals are exposed to a radiation dose in CAC screening. To avoid side effects from radiation, the effective dose should be as low as possible. An imaging protocol was developed for the ROBINSCA trial (33). However, validation of the protocol is needed and the impact on CAC score of different CT generations should be investigated.

Finally, a cost-effectiveness analysis should be performed after the above analyses have been completed. A microsimulation screening analysis (MISCAN) model will be developed for the CVD screening setting. The MISCAN model allows to estimate the effect of screening in various

dynamic populations, to explain results of screening trials, to predict and compare the (cost-) effectiveness of different screening policies and to monitor the results of population screening programs (39). The HRQoL measures will be used to calculate quality-adjusted life-years gained for implementation in the cost-effectiveness analysis. Furthermore, direct and indirect costs for all the phases (screening, diagnosis, preventive treatment, advanced disease) will be obtained and used in the micro-simulation model to estimate the cost-effectiveness of cardiovascular screening. Cost-effectiveness is calculated as the difference in total costs between a situation with screening and a situation without screening, divided by the difference in life-years. Cost-effectiveness should be calculated for different screening scenarios, varying in screening interval, screening age, screening modality and target group. As described in this thesis, only one screening round is performed in the ROBINSCA trial. Additional research should focus on whether multiple screening rounds might improve individualized risk prediction.

Final conclusions and recommendations

Conclusions following the research in this thesis are:

- Evidence for net-effectiveness of population-based screening for cardiovascular risk in an asymptomatic population is lacking. However, the ROBINSCA trial was designed adequately to provide evidence on the effectiveness of screening, which is expected to enable large-scale implementation with large health gains if effective.

- The contamination rate in the ROBINSCA trial is expected to be below the acceptable predefined rate. Since an adequate randomization and a sufficient sample size were also achieved, it is likely that the trial has sufficient power to demonstrate a potential effect of early detection and treatment of a high CVD risk.

- CAC scoring classified significantly fewer individuals at high-risk in both men and women, as compared to using the SCORE model. Subsequently, fewer individuals were indicated for preventive drug treatment, which potentially indicates a substantial reduction in preventive care. The risk-based selection of participants detected those who benefit most from screening and early treatment.

- The ROBINSCA trial showed that male sex and increasing age, followed by diabetes mellitus and smoking, influence CAC distribution to a large extent. Further, 30.7% of men and 16.8% of women with a CAC score of ≥100 are recommended for preventive treatment. A large proportion of the targeted high-risk population will be identified using the defined inclusion criteria for participation in the trial.

- Receiving a CVD risk screening result is a potential teachable moment and results in high prevention-seeking behavior among individuals with an increased CVD risk, especially when the CAC score was quantified. CVD medication prescription following GP consultation was higher after CAC quantification but was relatively high with good compliance in both screening arms.

Specific recommendations based on these conclusions are:

- The primary outcome analysis using data on CHD-related morbidity and mortality needs to be performed after at least 5-years of follow-up. This analysis should preferably include analyses of subgroups such as postmenopausal women, diabetics, smokers, and different ethnic groups.

- To examine the generalizability of the results, it is required to compare baseline and mortality characteristics of the trial participants and nonparticipants.

- The potential effectiveness of CVD screening partly depends on adherence of GPs to the advice for treatment. It should be monitored whether tools are required for improved communication of background information and clinical relevance. Education of GPs on the treatment protocol is essential.

- Given the low costs of lifestyle changes compared to preventive drug treatment, future research should investigate the impact of screening on willingness to adhere to lifestyle changes. This research should also include the role of health literacy in compliance to preventive measures.

- Cardiovascular screening can cause adverse side effects. Research on health-related quality of life and general anxiety is needed to balance favorable and unfavorable effects of screening.

- Follow-up CT scan might add important knowledge on progression of CAC after CAC scanning and potential subsequent preventive treatment. Funding for these follow-up scans is urgently needed.

- Ultimately, a cost-effectiveness analysis should be performed after the above analyses have been completed.

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Chapter 8

Summary

Summary

Cardiovascular disease (CVD) is the main cause of death worldwide and is responsible for 45% of all annual deaths in Europe. Approximately one fourth of the CVD burden is caused by coronary heart disease (CHD). Improving the modifiable lifestyle risk factors or starting preventive drug treatment can reduce the risk of developing CVD. However, a problem in preventing cardiovascular events is that a large proportion of the population is missed for preventive measures.

CHD is often asymptomatic for a long time until serious events occur and effective and affordable risk-reducing medication is available. This offers opportunities for early detection (screening) and subsequent treatment of an increased risk of CVD. However, large-scale randomized controlled trials (RCT) to investigate the effectiveness of screening for a high CVD risk are lacking. Furthermore, there is no evidence yet on what the most suitable screening tool should be. The first population-based RCT on screening for a high risk of CVD (ROBINSCA trial) was initiated to investigate the effectiveness of cardiovascular screening by means of risk assessment based on traditional risk factors or coronary artery calcium (CAC) quantification using computed tomography (CT) scanning. The purpose of this thesis was to evaluate several secondary outcomes of the ROBINSCA trial in terms of investigating the conduct of the risk-based selection and randomization of a high-risk population for participation, the screening protocol, careful analysis of screening results, screening uptake and treatment acceptance and compliance.

Part 1: The ROBINSCA trial

In **Chapter 2**, the rationale, study design, and the recruitment process of the ROBINSCA trial were described. The detailed descriptions included a power analysis, the predefined inclusion and exclusion criteria for participating in the trial, study protocols for the screening tests and the advised preventive treatment. The results implied a successful recruitment, since the sample size fulfilled the requirements of the power analysis, and adequate randomization, since baseline characteristics between the three study arms were comparable. If screening for cardiovascular risk turns out to be successful, CAC screening is estimated to prevent up to 15% of the current CHD-related morbidity and mortality. Evidence from the ROBINSCA trial will ultimately provide more insight in the balance between the harms and benefits of screening for CVD and will possibly enable large-scale implementation with large health gains for an asymptomatic population.

The aim of the second research question was to investigate the contamination rate in the study arms of the ROBINSCA trial (**Chapter 3**). Contamination, or in other words mixing of interventions between study arms can diminish the estimated potential effectiveness of screening. A random sample of participants (n=700) of the control arm, intervention arm A with screening by traditional risk assessment and intervention arm B with screening by CAC quantification received an online questionnaire about medical examinations that were performed by general practitioners (GP) after screening. The contamination rates in the control arm and

intervention arm A were (almost) zero. The maximum potential contamination rate in intervention arm B was 35.6%, however, the performed measurements can also indicate initiation or monitoring of preventive drug treatment. Future results of the ROBINSCA trial should demonstrate the potential effect of screening for a high risk of CVD.

Part 2: Cardiovascular disease screening results

In **Chapter 4**, the CVD risk distributions in both screening arms were investigated, based on risk categories for the screening setting for early detection of preclinical disease. The risk distributions based on traditional risk assessment using the systematic coronary risk evaluation (SCORE) model and CAC screening were compared. The subsequent potential reduction in preventive overtreatment was estimated based on the expected shift in CVD risk distribution. Screening uptake was 84.2% in the traditional risk assessment arm and 89.6% in the CAC scoring arm. According to CAC screening, significantly more asymptomatic individuals were at low risk for developing CVD compared to SCORE screening. This resulted in relative reductions of increased-risk individuals of 63.7% and 51.5% in women and men respectively. Subsequently, CAC scoring significantly reduced the number of individuals indicated to consult their GP for preventive treatment compared to SCORE (relative reduction women: 37.2%; men: 28.8%). Future analyses are required to confirm the effectiveness of CAC screening for reduction of CHD and to what extent a preventive treatment decision should be based on CAC screening.

In the next chapter (**Chapter 5**), the CAC prevalence and its predictors in the asymptomatic high-risk ROBINSCA-population were investigated. A total of 12,950 men and women (median age 62 years) underwent CT scanning for CAC scoring. Absolute CAC score distributions were calculated by sex, age and education. A two-step regression approach, including logistic regression for presence of any CAC and linear regression of the log-transformed CAC score for the severity of CAC present, was used to identify relevant predictors. CAC was absent in 48% of the women compared to 31.2% of all men and CAC score was ≥100 (Agatston) in respectively 16.8% and 30.7%. Men had substantially higher CAC scores: median CAC score was respectively 17 and 1. Diabetes mellitus, age and smoking were the strongest predictors for presence of CAC in women, and age, hypertension and CHD family history in men. Age per ten years and diabetes mellitus were the strongest predictors in both women and men for the severity of CAC. These results from currently the largest population-based CAC screening study in asymptomatic middle-aged men and women, showed that 30.7% of men and 16.8% of women with a CAC score of ≥100 urgently require preventive treatment. The results are important to determine the best risk prediction and prevention strategy should screening for a high risk of developing CVD be (cost)-effective.

Part 3: Cardiovascular health behavior

The last research question aimed to investigate the impact of receiving a cardiovascular disease screening result on preventive behavior and compliance to preventive treatment in asymptomatic participants of the ROBINSCA trial (**Chapter 6**). A random sample (n=600) of participants with a screening result received an online questionnaire to measure the impact of a cardiovascular disease screening result in low and increased (arm A: risk > 10%; arm B: Agatston ≥ 100) risk

groups. The response rate was 73%. Individuals with an increased CAC score consulted their general practitioner more often compared to increased risk individuals from arm A: 94% and 62.8%, respectively. Current use of blood pressure and cholesterol-lowering drugs was significantly higher in the increased CAC score group (77.1%), compared to the group with an increased traditional risk (43.8%). Self-reported compliance was high (98.1–100%). The results indicate that receiving a CVD risk screening result might be a potential teachable moment. The impact was more profound in the increased CAC score group. Therefore, risk communication has an important role in health behavior change and prevention of CVD.

Discussion and conclusions

The main findings and answers to the research questions were discussed in **Chapter 7**. Furthermore, strengths and limitations of the research were discussed in this chapter, as well as challenges and future perspectives. Based on these considerations, specific recommendations were described. The first part of this thesis described that evidence for net-effectiveness of population-based screening for cardiovascular risk in an asymptomatic population is lacking. Therefore, the ROBINSCA trial was designed adequately to provide evidence on the effectiveness of screening. This is expected to enable large-scale implementation with large health gains if effective. Furthermore, the results showed that the contamination rate in the trial is expected to be below the acceptable predefined rate. Since an adequate randomization and a sufficient sample size were also achieved, it is likely that the trial has sufficient power to demonstrate a potential effect of early detection and treatment of a high CVD risk. In the second part of this thesis, the first cardiovascular disease screening results were shown. The results indicated that CAC scoring classified significantly fewer individuals at high-risk in both men and women, as compared to using the SCORE model based on traditional risk factors. Subsequently, fewer individuals were indicated for preventive drug treatment, which potentially indicates a substantial reduction in preventive care. The risk-based selection of participants detected those who benefit most from screening and early treatment. Furthermore, results from the ROBINSCA trial showed that male sex and increasing age, followed by diabetes mellitus and smoking, influence CAC distribution to a large extent. 30.7% of men and 16.8% of women with a CAC score of ≥100 are recommended for preventive treatment. A large proportion of the targeted high-risk population will be identified using the defined inclusion criteria for participation in the trial. The research in the third part of this thesis showed that receiving a CVD risk screening result is a potential teachable moment and results in high prevention-seeking behavior among individuals with an increased CVD risk, especially when the CAC score was quantified. CVD medication prescription following GP consultation was higher after CAC quantification but was relatively high with good compliance in both screening arms.

Chapter 9

Nederlandse samenvatting

Samenvatting

Hart- en vaatziekten ziekten (HVZ) zijn wereldwijd de voornaamste doodsoorzaak en veroorzaken 45% van alle jaarlijkse sterfgevallen in Europa. Ongeveer een kwart van de cardiovasculaire ziektelast wordt veroorzaakt door coronaire hartziekten (CHZ). Het verbeteren van de aanpasbare risicofactoren in de leefstijl of het starten van preventieve medicamenteuze behandeling kan het risico op het ontwikkelen van HVZ verminderen. Echter het feit dat een groot deel van de bevolking gemist wordt voor preventieve maatregelen geeft een probleem bij de preventie van cardiovasculaire aandoeningen.

CHZ zijn vaak lange tijd asymptomatisch totdat zich een ernstige ziekte voordoet. Er is effectieve en betaalbare risico verlagende medicatie beschikbaar. Dit samen biedt kansen voor vroege opsporing (screening) en behandeling van een verhoogd risico op HVZ. Grootschalige gerandomiseerde gecontroleerde studies (RCT) ontbreken echter die de effectiviteit van screening op een hoog risico op HVZ aantonen. Bovendien zijn er nog geen aanwijzingen over wat de meest geschikte screeningstool zou moeten zijn. Het eerste gerandomiseerde bevolkingsonderzoek naar screening op een hoog cardiovasculair risico (de ROBINSCA studie) is geïnitieerd om de effectiviteit van cardiovasculaire screening te onderzoeken. Hierbij is screening uitgevoerd door middel van enerzijds een risicobeoordeling op basis van traditionele risicofactoren of anderzijds kwantificering van kransslagaderverkalking (CAC) met behulp van een CT scan. Het doel van dit proefschrift was om verschillende secundaire resultaten van de ROBINSCA studie te evalueren, waaronder het onderzoeken van het wervingsproces (risico-gebaseerde selectie en randomisatie) van de onderzoekspopulatie met een mogelijk verhoogd risico en het screeningprotocol, en het zorgvuldig analyseren van de screeningresultaten, de aanvaarding van screening en de acceptatie en naleving van preventieve behandeling.

Deel 1: De ROBINSCA studie

In **hoofdstuk 2** zijn de aanleiding, de onderzoeksopzet en het wervingsproces van de ROBINSCA studie beschreven. De gedetailleerde beschrijvingen omvatten een power analyse, de gedefinieerde in- en exclusiecriteria voor deelname aan de studie, de studieprotocollen voor de screeningstests en de geadviseerde preventieve behandeling. De resultaten duidden een succesvolle werving, gezien het feit dat de steekproefomvang voldeed aan de vereisten van de power analyse, en een adequate randomisatie, aangezien de baseline-kenmerken tussen de drie studiearmen vergelijkbaar waren. Als screening op cardiovasculair risico effectief blijkt te zijn, zal naar schatting tot 15% van de huidige CHZ-gerelateerde morbiditeit en mortaliteit voorkomen kunnen worden door CAC screening. Bewijs uit de ROBINSCA studie zal uiteindelijk meer inzicht geven in de balans tussen de voor- en nadelen van screening op HVZ. Bewijs van effectiviteit kan een grootschalige implementatie mogelijk maken met veel gezondheidswinst voor een asymptomatische populatie.

Het doel van de tweede onderzoeksvraag was om het percentage van contaminatie in de studiearmen van de ROBINSCA studie te onderzoeken (**hoofdstuk 3**). Contaminatie, of met andere woorden, het mengen van interventies tussen studiearmen kan de geschatte potentiële

effectiviteit van screening aantasten. Een willekeurige steekproef van deelnemers (n=700) uit de controle arm, interventie arm A met screening door traditionele risicobeoordeling en interventie arm B met screening door CAC kwantificatie ontving een online vragenlijst over medische onderzoeken die uitgevoerd zijn door hun huisarts na de screening. De contaminatie percentages in de controle arm en interventie arm A waren (bijna) nul. Het maximale mogelijke contaminatie percentage in interventie arm B was 35,6%. Echter, de uitgevoerde metingen kunnen ook duiden op initiatie of monitoring van preventieve medicamenteuze behandeling. Toekomstige resultaten van de ROBINSCA studie moeten het potentiële effect van screening op een hoog risico op HVZ aantonen.

Deel 2: Resultaten van cardiovasculaire screening

In **hoofdstuk 4** zijn de HVZ-risicoverdelingen in beide screeningsarmen onderzocht. De hiervoor gebruikte risicocategorieën zijn gebaseerd op de screeningsetting voor vroege detectie van preklinische aandoeningen. De risicoverdelingen op basis van traditionele risicobeoordeling met behulp van het systematische coronaire risicobeoordelingsmodel (SCORE) en CAC-screening zijn vergeleken. Vervolgens is de daaropvolgende mogelijke vermindering van preventieve overbehandeling geschat op basis van de verwachte verschuiving in de risicoverdeling. In interventie arm A onderging 84,2% de traditionele risicobeoordeling en in interventie arm B onderging 89,6% CAC screening. Volgens CAC screening liepen significant minder asymptomatische personen risico op het ontwikkelen van HVZ in vergelijking met SCORE screening. Er werd een relatieve vermindering van mensen met een verhoogd risico berekend van 63,7% bij vrouwen en 51,5% bij mannen. Hierdoor werden ook aanzienlijk minder mensen geadviseerd om hun huisarts te raadplegen voor preventieve behandeling op basis van CAC screening in vergelijking met SCORE (relatieve reductie vrouwen: 37,2%; mannen: 28,8%). Toekomstige analyses moeten aantonen of CAC screening daadwerkelijk effectief is in het verminderen van CHZ en in hoeverre een beslissing over preventieve behandeling gebaseerd moet worden op CAC screening.

In het volgende hoofdstuk (**hoofdstuk 5**) zijn de prevalentie en voorspellers van CAC onderzocht in de asymptomatische ROBINSCA-populatie. In totaal kregen 12.950 mannen en vrouwen (mediaan leeftijd 62 jaar) een CT scan om de CAC score te bepalen. De verdelingen van de absolute CAC scores zijn berekend voor geslacht, leeftijd en opleiding. Een tweestaps regressie benadering (logistische regressie voor de aanwezigheid van een CAC en lineaire regressie van de log-getransformeerde CAC score voor de mate van de aanwezige CAC) is gebruikt om relevante voorspellers te identificeren. CAC was afwezig bij 48% van de vrouwen en 31,2% van alle mannen. De CAC score was ≥100 (Agatston) in 16,8% van de vrouwen en 30,7% van de mannen. Mannen hadden aanzienlijk hogere CAC scores: de mediane CAC score was respectievelijk 17 en 1. Diabetes mellitus, leeftijd en roken waren de krachtigste voorspellers voor de aanwezigheid van CAC bij vrouwen, en leeftijd, hypertensie en CHD familiegeschiedenis bij mannen. Leeftijd en diabetes mellitus waren de voornaamste voorspellers bij zowel vrouwen als mannen voor de mate van CAC. Deze resultaten van momenteel het grootste bevolkingsonderzoek naar CAC screening bij asymptomatische mannen en vrouwen van middelbare leeftijd toonden aan dat 30,7% van de mannen en 16,8% van de vrouwen met een

CAC score van ≥100 dringend preventieve behandeling nodig hebben. De resultaten zijn belangrijk om optimale risicovoorspelling en preventie te bepalen als screening op een hoog risico op het ontwikkelen van HVZ (kosten-)effectief blijkt.

Deel 3: Cardiovasculair gezondheidsgedrag

De laatste onderzoeksvraag richtte zich op het onderzoeken van de impact van het ontvangen van een screeningresultaat op preventief gedrag en de naleving van preventieve behandeling bij asymptomatische deelnemers van de ROBINSCA studie (**hoofdstuk 6**). Een willekeurige steekproef (n=600) van deelnemers met een screeningresultaat ontving een online vragenlijst om de impact van het ontvangen van het screeningresultaat te meten in de lage en verhoogde (arm A: risico> 10%; arm B: Agatston ≥ 100) risicogroepen. Het responspercentage was 73%. Personen met een verhoogde CAC score raadpleegden vaker hun huisarts in vergelijking met personen met verhoogd risico uit arm A: respectievelijk 94% en 62,8%. Het huidige gebruik van bloeddruk- en cholesterolverlagende medicijnen was significant hoger in de groep met een verhoogde CAC score (77,1%), vergeleken met de groep met een verhoogd traditioneel risico (43,8%). Zelf gerapporteerde compliance was hoog (98,1–100%). Deze resultaten impliceren dat het ontvangen van een HVZ-risico screeninguitslag een potentieel leerzaam moment kan zijn. De impact was groter in de groep met een verhoogde CAC score. Risicocommunicatie speelt daarom een belangrijke rol bij de verandering van gezondheidsgedrag en de preventie van HVZ.

Discussie en conclusies

De belangrijkste bevindingen en antwoorden op de onderzoeksvragen zijn in **hoofdstuk 7** besproken. Verder zijn in dit hoofdstuk de sterke punten en beperkingen van het onderzoek besproken, evenals uitdagingen en toekomstperspectieven. Op basis van deze overwegingen zijn specifieke aanbevelingen gegeven. Het eerste deel van dit proefschrift beschrijft dat er nog geen bewijs is voor de effectiviteit van een bevolkingsonderzoek voor de vroege opsporing van een hoog cardiovasculair risico in een asymptomatische populatie. Daarom is de ROBINSCA studie geïnitieerd om bewijs te leveren voor de effectiviteit van screening. Wanneer screening effectief blijkt, zal grootschalige implementatie van een bevolkingsonderzoek naar verwachting veel gezondheidswinst opleveren. Bovendien hebben de resultaten aangetoond dat de mate van contaminatie in de ROBINSCA studie naar verwachting onder de acceptabele vooraf gedefinieerde waarde ligt. Aangezien de randomisatie ook adequaat bleek en de onderzoekspopulatie groot genoeg is, heeft de studie hoogstwaarschijnlijk voldoende power om een potentieel effect van vroege opsporing en behandeling van een hoog HVZ-risico aan te tonen. In het tweede deel van dit proefschrift zijn de eerste screeningsresultaten beschreven. De resultaten lieten zien dat het gebruik van de CAC score significant minder mensen als een hoog risico classificeerde bij zowel mannen als vrouwen, vergeleken met het gebruik van het SCORE-model op basis van traditionele risicofactoren. Als logisch gevolg hiervan werden er minder personen geïndiceerd voor preventieve medicamenteuze behandeling, wat mogelijk duidt op een substantiële vermindering van preventieve zorg. Door de risico-gebaseerde selectie van deelnemers zijn diegenen opgespoord die het meest baat hebben bij screening en vroege behandeling. Bovendien hebben de resultaten van de ROBINSCA studie laten zien dat het mannelijk geslacht en toenemende leeftijd, gevolgd door diabetes mellitus en roken, de CAC-

distributie in grote mate beïnvloeden. 30,7% van de mannen en 16,8% van de vrouwen met een CAC score van ≥ 100 hebben preventieve behandeling nodig. Zoals verwacht zal een groot deel van de beoogde hoog risico populatie worden geïdentificeerd met behulp van de gedefinieerde in- en exclusiecriteria voor deelname aan het bevolkingsonderzoek. Het onderzoek in het derde deel van dit proefschrift heeft aangetoond dat het ontvangen van een HVZ-screeningresultaat een potentieel leerzaam moment teweeg brengt. Dit resulteerde in een hoge mate van preventief gedrag bij personen met een verhoogd HVZ-risico, vooral wanneer de CAC score werd bepaald. Er waren meer HVZ medicatievoorschriften na CAC-kwantificering, maar het aantal voorschriften was relatief hoog in beide screeningsarmen met goede therapietrouw.

Appendices

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Lieve **Jeroen**. Alsof ons master-diploma nog niet genoeg was, hadden we allebei het ambitieuze plan om nog maar eens 'even' voor het volgende diploma gaan. En het lijkt ons nog te lukken ook. Wie had dat gedacht! Samen slepen we elkaar erdoorheen. Want dat was soms nodig. Jouw onvoorwaardelijke liefde, vertrouwen en positiviteit had ik niet kunnen missen tijdens mijn promotietraject. Jij laat mij altijd inzien dat alles relatief is en dat we het heel goed hebben samen met al onze mooie reizen. You're the best!

About the author

Sabine Denissen was born on the 9th of January 1992 in Roosendaal, the Netherlands and grew up at her parents' farm in Nispen. In 2010, she completed her Gymnasium at the Gertrudiscollege in Roosendaal. She continued her education at the Radboud University in Nijmegen where she started the bachelor Biomedical Sciences. During the bachelor curriculum, Sabine did an internship at the department of Anatomy in the Radboud University Medical Center in Nijmegen. After finishing the bachelors' degree, she started the master Biomedical Sciences in which she focused on Epidemiology and Science Communication. She completed internships at the GGD Hart voor Brabant, the Ndlovu Research Center in Elandsdoorn, South-Africa, and the RIVM. She obtained her Master of Science degree in March 2016. Sabine lived in Nijmegen during her university education and moved to Tilburg in 2015. In April 2016, Sabine started working as a junior researcher at the department of Public Health of the Erasmus Medical Center in Rotterdam. Her research focused on population-based cardiovascular screening in the ROBINSCA trial and resulted in this PhD-thesis. After her PhD-period, she started working for the three GGD's in Brabant as an environmental health expert. Currently, Sabine lives with her partner Jeroen in Breda.

PhD portfolio

Name PhD candidate:	Sabine J.A.M. Denissen
PhD period:	April 2016 – September 2019
Erasmus MC department:	Public Health
Promotor:	Prof. dr. Harry J. de Koning
Co-promotor:	Dr. Carlijn M. van der Aalst

	Year	Workload (Hours/ECTS)
Courses		
Research Integrity	Apr 2017	0.3 ECTS
BROK 'Basiscursus Regelgeving Klinisch Onderzoek'	Jul 2019	1.5 ECTS
Time management course	Nov 2016	3.5 hours
Systematisch literatuuronderzoek 1-2	Jan 2019	16 hours
Sex and Gender in Cardiovascular Research (COEUR)	Feb 2018	8 hours
HS05 Planning and evaluation of screening (NIHES)	Mar 2018	1.4 ECTS
EP20 Cardiovascular epidemiology (NIHES)	May 2018	0.7 ECTS
HS02a Public health research: analysis of population health (NIHES)	Oct 2018	1.9 ECTS
Seminars and workshops		
Workshop 'Go your own way' for junior epidemiologists	Mar 2017	16 hours
Seminars / research meetings of the department of Public Health	2016-2019	140 hours
Symposium 'De goede health check'	Jan 2018	4 hours
Grant proposal writing	Jul 2018	2 hours
Webinars European Society of Cardiology	Feb 2019	24 hours
COEUR PhD course + symposium: vascular clinical epidemiology	Jan 2019	8 hours
Employability (outside) academia	Apr-Jul 2019	40 hours
Oral presentations		
Presentation for Certe lab, Groningen	Jan 2017	16 hours
Presentation in NIHES course, Rotterdam	Mar 2018	20 hours
Section (VO) meeting, Rotterdam	Jun 2018	24 hours
Section (VO) meeting, Rotterdam	Jan 2019	24 hours
Rapid fire abstract presentation at EuroPrevent congress, Lisbon	Apr 2019	28 hours
Poster presentations		
Poster presentation at EuroPrevent congress, Ljubljana	Apr 2018	20 hours
Poster presentation at EuroPrevent congress, Lisbon	Apr 2019	20 hours
Poster presentation for ESC congress, Paris	Aug 2019	20 hours

(Inter)national conferences

Nationale Lipidendagen, Zeist	May 2016	16 hours
ESC congress, Rome	Aug 2016	40 hours
PULS 2018 Hartstichting, Nieuwegein	Feb 2018	16 hours
EuroPrevent congress, Ljubljana	Apr 2018	24 hours
EuroPrevent congress, Lissabon	Apr 2019	24 hours

Teaching

Examining bachelor essays Medicine students	Jul 2017	32 hours
Supervising 3rd year medical students community projects	Feb-Mar 2018	32 hours
Examining bachelor essays Medicine students	Jun 2018	32 hours
Supervising 3rd year medical students community projects	Feb-Mar 2019	32 hours