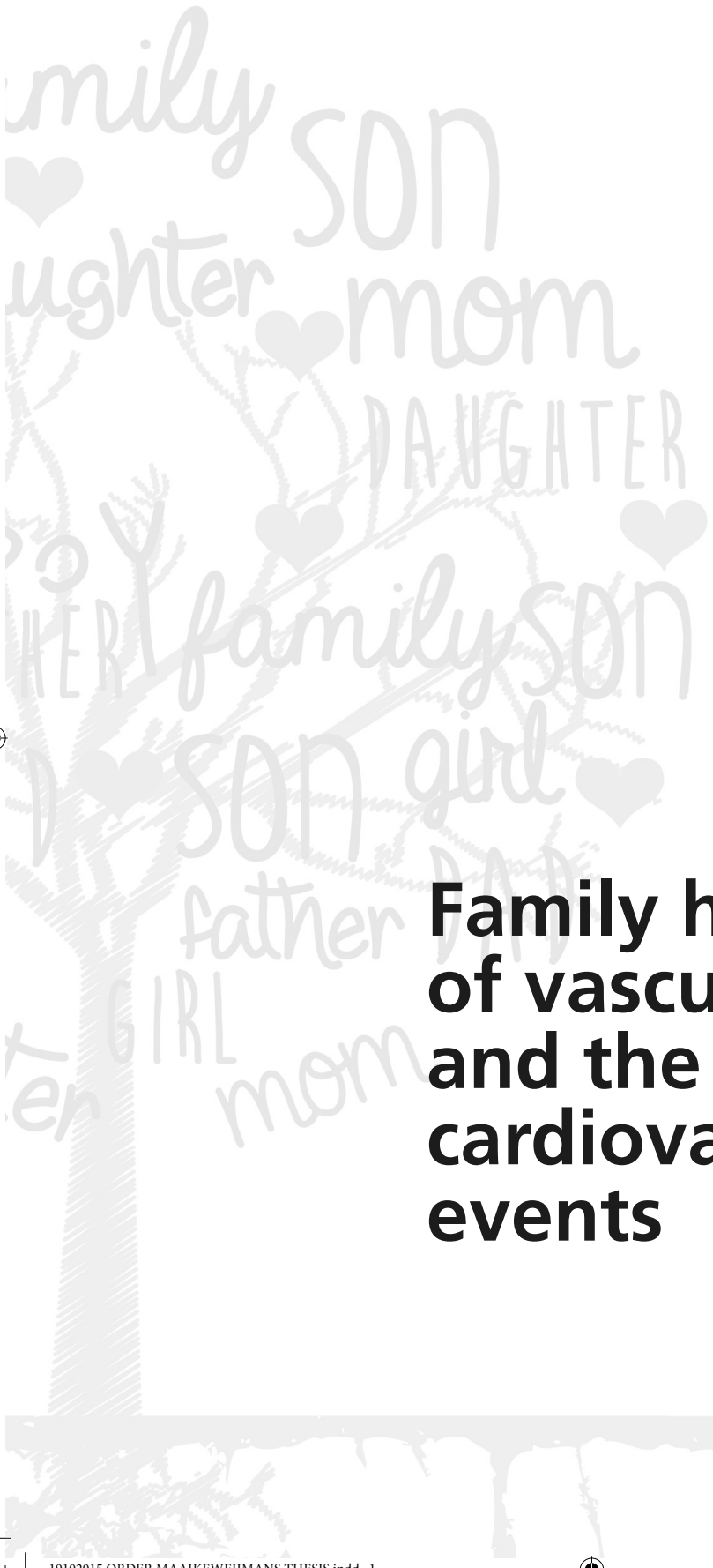

Family history of vascular disease and the risk of cardiovascular events

Maaike Weijmans

Family history of vascular disease and the risk of cardiovascular events

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Family history of vascular disease and the risk of cardiovascular events

Belaste familieanamnese voor hart- en vaatziekten en het risico op cardiovasculaire events

(met een samenvatting in het Nederlands)

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geboren op 3 september 1988
te Nieuwegein

Promotoren: Prof. dr. F.L.J. Visseren
Prof. dr. Y. van der Graaf

CONTENTS

1

General introduction

Does cardiovascular disease run in the family?

Family history of disease is one of the most used traditional diagnostic tools in medicine for several diseases such as cancer, depression, Alzheimer's disease and cardiovascular disease. Nowadays, awareness of the increased likelihood of developing a specific disease having a positive family history stretches beyond the medical world and is well-known to the public. In fact, 'Does it run in the family?' has definitely moved into the public domain as a household phrase for anyone inquisitive about disease, medical professional or not. The diagnostic use of family history was already acknowledged by Hippocrates, thus predating the science of genetics by a long margin. However, not only genetic factors are important for clustering of disease in families. A positive family history of disease can be regarded as the combined genetic and environmental predisposition for a specific disease[1].

For cardiovascular disease, the importance of family history for the development of cardiovascular events has also been established[2-6]. Clustering of vascular events has been demonstrated in 122,155 Utah families[7]. Of these families, 14% had a family history of coronary heart disease. However, these 14% accounted for over 72% of the persons who developed early coronary heart disease. For stroke the familial clustering was even more impressive, a family history of stroke prevalent in almost 11% of the families, accounted for 86% of the early stroke cases[7]. The effects of this familial risk can already be seen in childhood. Young children of parents with cardiovascular disease or risk factors already have early metabolic changes related to an increased vascular risk in later life, such as decreased insulin sensitivity[8], decreased beta-cell function[9], high-normal blood pressure[10] and increased leptin plasma levels[11].

The assessment of a family history provides a unique opportunity to identify families who actually develop cardiovascular disease. An extreme level of serum LDL-cholesterol or an extremely high blood pressure strongly increases a person's risk of developing cardiovascular events. However, the attributive risk of these extreme levels in the population is low, since most events occur in patients with moderately elevated levels of risk factors. Therefore, a positive family history may help identifying persons at increased risk, as it is able to capture factors, known and unknown, that interact to cause cardiovascular disease. However, there is growing evidence that by simply dividing a family history of cardiovascular disease into positive or negative, the potential value of family history in risk assessment is not fully exploited. For example, different risks are described for having a positive paternal or positive maternal history of vascular disease[5, 12, 13] (e.g. OR 7.2 for maternal history and 3.4 for paternal history [5]), and for different locations of vascular disease[3, 6, 7, 14] (e.g. OR of myocardial infarction; 3.0 for positive family history of myocardial infarction and 1.2 for positive parental history of stroke[14]).

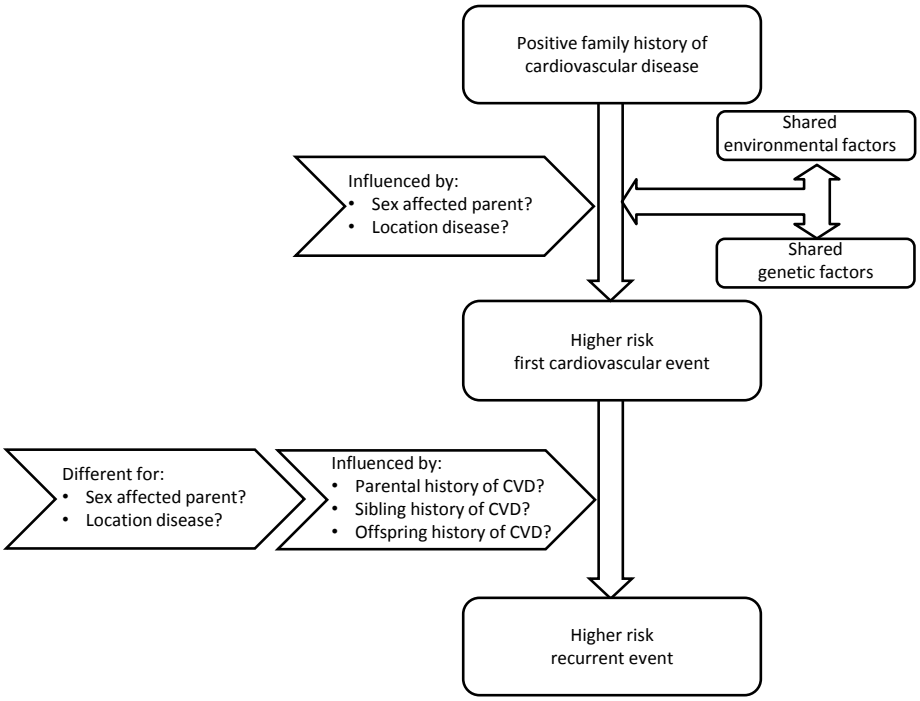
Relevance of family history for patients at increased vascular risk

Although a positive parental history or sibling history of cardiovascular disease is an established risk factor for the development of first cardiovascular events, this is inconclusive for patients with established vascular disease. The number of patients with established vascular disease is growing as a result of improved medical care and aging. In these patients, there is a wide distribution of absolute risks of developing subsequent vascular events, ranging from a low 10-year predicted risk (<10%) to an extremely high 10-year predicted risk (≥40%)[15]. In current practice, all patients with vascular disease are treated similarly according to guidelines. For patients with an (extremely) high risk of subsequent vascular events however, clinicians may consider novel therapies such as new biologicals, immunomodulants and antithrombotics. To improve discrimination of patients at very high or at very low risk for subsequent vascular events, identifying important risk factors for subsequent vascular events is necessary. Previously, a positive relation between a parental history of premature cardiovascular disease and the risk of subsequent cardiac, peripheral artery or cerebrovascular disease was demonstrated in patients with premature cardiovascular disease[16, 17]. However, whether this relation can automatically be translated to all patients with cardiovascular disease, also to patients who developed cardiovascular disease at later age, is unclear. In addition, since familial correlations of cardiovascular risk factors between family members decline with age[18], the presence of cardiovascular disease in offspring may reflect the exposure to (un)known risk factors in a different phase in life. Therefore, a positive offspring history may also, besides parental and sibling history, be a risk factor for the development of subsequent vascular events. A schematic outline of this part of this thesis is given in figure 1 and 2.

Genetic factors and coronary artery calcification

Family history of cardiovascular disease would be less noteworthy if the complete mechanism leading to atherosclerosis and subsequent to cardiovascular events were unraveled. An important pillar in the understanding of the biological mechanisms leading to cardiovascular disease is the identification of genetic factors related to a higher risk of cardiovascular disease. Genome-wide association studies have identified multiple risk loci associated with the development of cardiovascular disease[19-21]. These individual single-nucleotide polymorphisms have typically small effect sizes and are therefore increasingly combined into multi-locus genetic risk scores, demonstrating modest improvements of vascular risk prediction in patients free of vascular disease[22-24]. Another risk factor for first vascular events is the presence of coronary artery calcifications, which can be quantified in a coronary calcium score[25, 26]. Coronary artery calcification can be considered as a surrogate for the lifetime exposure to known and unknown risk factors, including genetic and heritable factors. Genetic factors and coronary

Figure 1. Schematic overview of outline thesis.

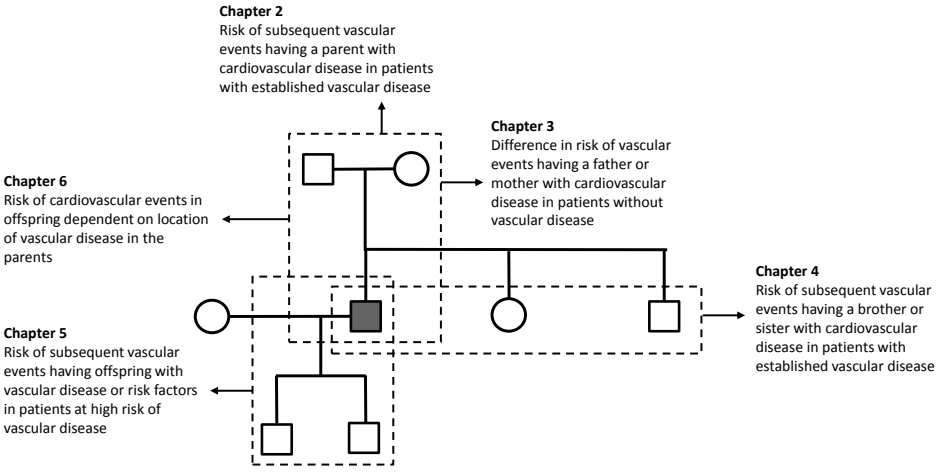


artery calcification may have a particular role in patients with vascular disease, since these patients all deserve treatment of their traditional risk factors (e.g. elevated LDL-cholesterol levels and elevated blood pressure). However, although the LDL-cholesterol levels generally respond well to lipid-lowering medication, the risk associated with having prolonged elevated LDL-cholesterol level does not instantly change by lowering these cholesterol levels. Therefore, evaluating the roles of genetic factors and of coronary artery calcium, which cannot be changed by medical interventions, in patients with established vascular disease may be of real value as they may better reflect the patient's actual vascular risk.

Thesis objectives

The general objectives of this thesis are to evaluate the relation between a positive family history of cardiovascular disease and the risk of cardiovascular events in patients with and without prevalent vascular disease, and to evaluate the clinical value of genetic factors and coronary artery calcification in high risk patients.

Figure 2. Cardiovascular disease in siblings, parents and offspring and risk of vascular events.



Thesis outline

The first part of this thesis focuses on the risk of (subsequent) vascular events having a positive family history. In chapter 2, the relation between having a positive parental history of cardiovascular disease and the development of subsequent vascular events in patients with clinically manifest vascular disease is demonstrated. Furthermore, the role of the sex of the affected parent and the effect of parental vascular disease location were explored. In chapter 3, a systematic review and meta-analysis of current literature was performed to evaluate whether positive paternal and maternal histories confer a different risk of cardiovascular disease in offspring free of vascular disease. In chapter 4 the role of a positive sibling history of cardiovascular disease and subsequent vascular events and mortality is investigated, taking into account the number of affected siblings and the location of vascular disease. Furthermore, it is investigated whether this potential increased vascular risk is dependent on the presence or absence of traditional risk factors. In chapter 5 it is evaluated whether the presence of cardiovascular disease and cardiovascular risk factors in offspring increases the risk of subsequent cardiovascular events in parents already at high vascular risk. In chapter 6 it is evaluated whether prevalence of diabetes mellitus, hypercholesterolemia and hypertension in offspring of patients at increased vascular risk is higher compared with the general population. Furthermore, in the children of patients with manifest vascular disease it is determined whether the risk of cardiovascular events and prevalence of cardiovascular risk factors is dependent on the location of vascular disease in the parents.

The second part of this thesis concerns the potential role of genetic factors and coronary artery calcification in patients with established vascular disease. In chapter 7 it is studied

whether a genetic risk score based on 30-single nucleotide-polymorphisms associated with coronary artery disease can improve risk prediction of new cardiovascular events in patients with vascular disease. In chapter 8 important determinants of coronary artery calcium and the distribution of coronary calcium are assessed in patients with prevalent coronary artery disease.

The main findings of this thesis are discussed in chapter 9 and summarized in chapter 10.

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2

Parental history and the risk of subsequent vascular events in patients with clinically manifest vascular disease: the effects of sex of the parent and vascular disease location

Maaike Weijmans, Yolanda van der Graaf, Gert Jan de Borst, Hendrik M. Nathoe, Ale Algra, Frank L.J. Visseren

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ABSTRACT

Background

Parental history of cardiovascular disease is a risk factor for first vascular events. It is unknown whether this also holds for subsequent events in patients with vascular disease. Also, the role of the location of parental vascular disease and the sex of the affected parent is unidentified.

Methods

In a cohort of 4,529 patients with symptomatic vascular disease enrolled in the Second Manifestations of Arterial Disease (SMART) Study, the relation between parental cardiovascular history under the age of sixty, sex of the parent, location of parental vascular disease (heart, brain, lower extremities) and subsequent myocardial infarction (MI), stroke, vascular death and peripheral artery disease (PAD) was determined by Cox-proportional hazard analyses.

Results

During a median follow-up of 4.9 years (interquartile range 2.5 – 7.0), MI was experienced by 220 patients, stroke by 112, PAD by 297, whereas 371 patients died. A positive parental history of cardiovascular disease, without knowledge of vascular disease location and sex of that particular parent, was not associated with subsequent events (HR 1.0; 95%CI 0.8 – 1.3). For specific types of parental history regarding sex and vascular location, having a father with a history of PAD was related to an increased risk of incident PAD (HR 3.1; 95%CI 2.1 – 4.6).

Conclusions

A positive parental history of cardiovascular disease without information about vascular disease location and sex does not increase the risk of recurrent vascular events in patients with symptomatic vascular disease. Vascular patients with a father with PAD have an increased risk of subsequent peripheral artery disease compared with vascular patients without such a family history.

INTRODUCTION

A positive parental history of cardiovascular disease is related to an increased risk of first cardiovascular events in offspring without vascular disease[1-4]. The clinical use of assessing parental history of myocardial infarction has been proven: a family history of myocardial infarction before the age of sixty is incorporated in several cardiovascular risk scores, used for stratifying patients with a high risk of first cardiovascular events[5-7].

In clinical practice, assessing a parental history of cardiovascular disease is an integral part of a patients' history, irrespective of the fact whether a patient already experienced a vascular event. Intuitively it seems that patients with a history of vascular disease and a positive parental history of cardiovascular disease have an increased risk of recurrent vascular events compared with patients without a parental history of cardiovascular disease. For patients with premature cardiovascular disease, defined as a cardiovascular event before the age of 51 years in men and 56 years in women, there is a positive relation between a parental history of premature cardiovascular disease and the risk of developing a subsequent cardiac, peripheral artery or cerebrovascular event (HR 1.31, 95%CI 1.01 – 1.72)[8, 9].

The question arises whether it is useful to assess a parental history of cardiovascular disease in all patients with clinically manifest vascular disease and to what extent. There is growing evidence that by simply dividing a parental history of cardiovascular disease into positive or negative, the potential value of parental history in risk assessment is not fully utilized[10]. For example, a parental history of peripheral artery disease is related to an increased risk of peripheral artery disease, whereas a parental history of cardiovascular disease in general is not related to incident peripheral artery disease[4].

The sex of the parent with a vascular history may also be worth assessing as it is hypothesized that maternal transmission is related to a higher vascular risk than paternal transmission in offspring, although studies report contradicting findings[11-13]. A possible explanation for an assumed differential transmission of cardiovascular risk from mothers and fathers is the fact that the intra-uterine period is determined by the mother. There is increasing evidence that the intrauterine environment has very important and long lasting effects on risk of cardiovascular events and premature mortality in offspring[14, 15].

The objective of the present study is to evaluate the relation between a positive parental history of cardiovascular disease and subsequent vascular events in patients with clinically manifest vascular disease and to investigate whether, in case of a positive parental history, the location of parental vascular disease and sex of the parent confer different risks.

METHODS

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. The rationale and design of the SMART study have been described previously[16]. In short, the SMART study is an ongoing single-center prospective cohort study that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular disease or a vascular risk factor. The Ethics Committee of the University Medical Centre Utrecht approved the study and all participants gave their written informed consent.

For this study data were used of 4,700 patients who were newly referred to the University Medical Centre between 2001 and 2012 with a history of arterial atherosclerosis (i.e. coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) or abdominal aortic aneurysm (AAA)). Patients were enrolled after a stable situation of their disease was reached. Patients with a terminal malignancy were excluded, as well as those not independent in daily activities, not sufficiently fluent in Dutch language or referred back to the referring specialist immediately after one visit. Of the 4,700 patients included in the analysis, parental history information was not available in 171 patients and these patients were excluded.

CAD was present in 2,898 patients, CVD in 1,289, PAD in 692 and AAA in 313. A total of 663 patients fell into more than one category at baseline. CAD was defined as myocardial infarction, angina pectoris or coronary revascularization (coronary bypass surgery or coronary angioplasty). Patients with CVD had experienced a transient ischemic attack, cerebral infarction, cerebral ischemia, amaurosis fugax, retinal infarction or a history of carotid surgery. PAD was defined as a symptomatic and documented obstruction of distal arteries of the leg or interventions (percutaneous transluminal angioplasty (PTA), bypass or amputation). Patients with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter ≥3 cm, measured with ultrasonography) or a history of AAA surgery.

Baseline examination

All patients underwent a standardized extensive vascular screening. Patients received a uniform questionnaire on medical history, current medication, symptoms of cardiovascular disease and presence of cardiovascular risk factors. Furthermore, patients underwent laboratory assessments and non-invasive screening for manifestations of atherosclerotic disease and risk factors.

Parental history of cardiovascular disease

The questionnaire inquired for parental history of stroke, myocardial infarction, coronary artery stenosis and peripheral artery stenosis. A positive parental history was defined as at least

one parent with cardiovascular disease before the age of sixty, as this definition is frequently used in current literature[5-7]. Subsequently, parental history was divided in four categories: parental history of CAD, parental history of stroke, parental history of PAD and parental history of cardiovascular disease, a combination of the first three categories. Furthermore, a subdivision was made distinguishing the sex of the affected parent.

Because multiple definitions of a positive parental history of cardiovascular disease exist, we performed additional analyses in 3011 patients with the alternative definition of CVD <55 in men and <65 in women, according to the NCEP17 and JNC7 guidelines[18].

Follow-up

During follow-up, patients were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. When a vascular event was suspected, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the treating specialist. All possible events were independently evaluated by three members of the endpoint committee, comprising physicians from different departments. Study outcomes included myocardial infarction, coronary interventions, stroke (ischemic and hemorrhagic), carotid interventions, peripheral artery disease (amputation, operation, PTA or stenting of leg or iliac artery), vascular mortality, a composite of the previous mentioned vascular outcomes and all-cause mortality. The definitions of the several events are shown in table 1.

Follow-up duration (years) was defined as the period between study inclusion and first cardiovascular event or death from any cause, date of loss to follow-up or the preselected date of 1 March 2012. In total, 141 of the 4,529 participants (3%) were lost to follow-up due to migration or discontinuation from the study.

Data analyses

Data are presented as percentages for categorical variables, as mean with standard deviation (SD) for normally distributed variables and as median with interquartile range [IR] for non-normally distributed variables. Cox proportional hazards model analysis was used to estimate the effect of parental history of cardiovascular disease on the risk of subsequent vascular events. Patients with both myocardial infarction and stroke during follow-up contributed to both the myocardial infarction and stroke analyses, but with follow-up time matching the respective outcomes. If patients had multiple events of the same type, the first recorded event was used in the analyses. For the composite vascular outcome, the date of reaching the first vascular outcome was set as the composite outcome date. Results were expressed as hazard ratios (HR) and 95% confidence intervals (95%CI).

Single imputation by weighted probability matching on the basis of multivariate regression using covariate and outcome data was used to reduce missing data for smoking status (n=20; 0.4%), alcohol status (n=25; 0.6%), systolic and diastolic blood pressure (n=30; 0.7%), body

mass index (n=7; 0.2%), waist circumference (n=139; 3.1%), total cholesterol (n=24; 0.5%), triglycerides (n=32; 0.7%), HDL-cholesterol (n=38; 0.8%), LDL-cholesterol (n=41; 0.9%) and eGFR (n=26; 0.6%).

Two models were constructed. Model I included adjustment for age and sex. An additional model (model II) was constructed to assess the influence of hypertension, diabetes mellitus type 2, hypercholesterolemia, body mass index, smoking and use of antiplatelet agents and statins.

As previous studies showed potential effect modification for sex[11, 19] and because the relation between parental history and cardiovascular events may be stronger in younger patients[20], interaction on a multiplicative scale was assessed by adding an interaction term for sex and age to the model. No significant interaction ($p<0.05$) was found.

Additional analyses were performed to determine whether a positive paternal history or maternal history conferred different risks for subsequent events.

The proportional hazards assumptions were formally tested with the Schoenfeld test. No significant non-proportionality ($p<0.05$) was observed. Analyses were performed in SPSS version 20 (SPSS, Chicago, Illinois, USA) and R version 2.15.2.

Table 1. Study outcomes.

Myocardial infarction	Acute chest pain for at least 20 minutes with ST-segment elevation (STEMI)
	Acute chest pain without ST-segment elevation with elevated troponin (NSTEMI)
	Intervention related myocardial infarction
	Typical pain, remaining STT changes on ECG, no documented cardiac enzymes development
	Sudden death: unexpected cardiac death occuring within 1 h after onset of symptoms, or within 24 h given convincing circumstantial evidence
Coronary interventions	Percutaneous coronary interventions
	Coronary artery bypass grafting
Stroke	Relevant clinical features for at least 24 h causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *infarction* on CT or MRI
	Relevant clinical features for at least 24 h causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *hemorrhage* on CT or MRI
	Relevant clinical features for at least 24 h causing an increase in impairment of at least one grade on the modified Ranking scale, *without a new (hemorrhage) cerebral infarction* on CT or MRI
	Hemorrhage demonstrated with CT, MRI or operation
Carotid interventions	Percutaneous transluminal angioplasty or carotid artery stenting
	Carotid endarterectomy
Peripheral artery disease	Amputation of toe, foot, below the knee, above the knee
	Operation of leg or iliac artery
	Percutaneous transluminal angioplasty or stenting of leg or iliac artery
Vascular mortality	Death from stroke, myocardial infarction, congestive heart failure, rupture of abdominal aortic aneurysm and vascular death from other causes
Composite vascular outcome	Composite of myocardial infarction, stroke, retinal infarction, congestive heart failure and vascular mortality
Composite vascular outcome with vascular interventions	Composite of myocardial infarction, coronary interventions, stroke, carotid interventions, peripheral artery disease, abdominal aortic aneurysm, retinal infarction, congestive heart failure and vascular mortality
All-cause mortality	Death from any cause

RESULTS

Baseline characteristics

In table 2 the baseline characteristics of the study population are listed according to the location of parental vascular disease. A positive parental history of vascular disease was present in 1,212 patients (27%). Parental history of CAD was most common: 855 patients had a parental history of CAD (71%), 240 patients a parental history of stroke (20%) and 232 patients had a parental history of PAD (19%).

The only difference between patients with and without a positive parental history was age: patients with a positive parental history were younger than patients without a positive parental history, 57+10 versus 61+10 years.

Relation between a positive parental history of cardiovascular disease and subsequent vascular events and mortality in offspring

During a median follow-up of 4.9 years (interquartile range 2.5 – 7.0 years), 371 patients died of whom 179 patients due to a vascular cause. Myocardial infarction occurred in 220 patients, 112 patients experienced a stroke and 297 peripheral artery disease (170 patients received PTA or stenting, 110 an operation and 17 patients underwent an amputation). The composite outcome of myocardial infarction, stroke or vascular mortality occurred in 392 patients. If vascular interventions were included, the composite outcome occurred in 1,221 patients.

As shown in figure 1, no relations were observed between a positive parental history of cardiovascular disease and vascular mortality, all-cause mortality, stroke, myocardial infarction and for the composite outcome of stroke, myocardial infarction and vascular mortality.

Parental history of cardiovascular disease was related to a slightly increased risk of the composite outcome with vascular interventions (HR 1.2, 95%CI 1.0 – 1.3). The alternative definition of parental history of cardiovascular disease was not related to increased cardiovascular risk (HR 1.1, 95%CI 0.9 – 1.3). The relations between a positive parental history of cardiovascular disease and subsequent events were similar in model II.

Relation between parental vascular disease location and location of subsequent events in offspring

In figure 2, the results of the different parental vascular disease locations in relation to different vascular events are presented. Parental history of CAD was related to the combined outcome of myocardial infarction and coronary interventions (HR 1.3, 95%CI 1.1 – 1.6) and not to myocardial infarction alone (HR 1.1, 95%CI 0.8 – 1.5). An inverse association was found for having a parental history of CAD and subsequent strokes (HR 0.5, 95%CI 0.3 – 1.0). Parental history of stroke did not result in an increased risk of subsequent strokes (HR 1.0, 95%CI 0.4 – 2.4) or other subsequent events. Parental history of PAD was positively related to subsequent peripheral artery disease (HR 2.4, 95%CI 1.7 – 3.5). No relations were found

Table 2. Baseline characteristics according to location of parental history of vascular disease

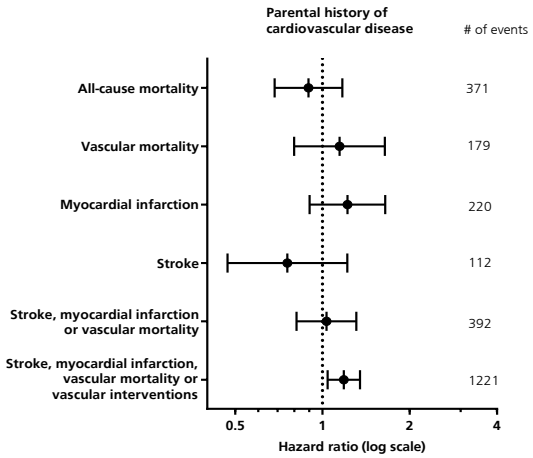
	Parental history of cardiovascular disease		Parental history CAD		Parental history stroke		Parental history PAD	
	yes (n = 1,212)	no (n = 3,317)	yes (n = 855)	no (n = 3,674)	yes (n = 240)	no (n = 4,289)	yes (n = 232)	no (n = 4,297)
Age (years)	57 (10)	61 (10)	56 (10)	61 (10)	57 (10)	60 (10)	55 (10)	60 (10)
Male sex (%)	70	74	71	74	68	73	68	73
Location of vascular disease*								
Coronary artery disease (%)	69	62	74	62	58	64	62	64
Cerebrovascular disease (%)	24	30	21	30	34	28	27	29
Peripheral artery disease (%)	16	15	15	16	19	15	22	15
Abdominal aortic aneurysm (%)	6	7	5	7	8	7	8	7
Diabetes Mellitus type 2 (%)	16	17	16	17	17	17	17	17
Ever smoking (%)	76	79	77	79	71	79	79	78
Current alcohol use (%)	73	72	75	72	72	73	72	73
Blood pressure-lowering agents (%)	79	76	81	76	73	77	73	77
Lipid-lowering agents (%)	80	75	81	75	77	76	77	76
Antiplatelets agents (%)	81	79	83	79	81	80	74	80
Systolic blood pressure (mmHg)	138 (20)	141 (21)	137 (19)	141 (21)	140 (23)	140 (21)	138 (21)	140 (21)
Diastolic blood pressure (mmHg)	82 (11)	82 (12)	82 (11)	82 (12)	83 (11)	82 (11)	83 (12)	82 (11)
Body mass index (kg/m^2)	27.3 (4.4)	27.0 (3.9)	27.3 (4.3)	27.0 (4.0)	27.0 (4.3)	27.1 (4.0)	27.7 (4.3)	27.0 (4.0)
Waist circumference (cm)	95 (13)	96 (12)	95 (13)	96 (12)	95 (14)	96 (12)	97 (13)	96 (12)
Total cholesterol (mmol/l)	4.6 (1.1)	4.6 (1.1)	4.6 (1.1)	4.6 (1.1)	4.6 (1.0)	4.6 (1.1)	4.6 (1.2)	4.6 (1.1)
Triglycerides (mmol/l)	1.3 [1.0-1.9]	1.3 [0.9-1.8]	1.4 [1.0-2.0]	1.3 [0.9-1.8]	1.3 [0.9-1.9]	1.3 [0.9-1.8]	1.4 [1.0-2.0]	1.3 [0.9-1.8]
HDL-cholesterol (mmol/l)	1.2 (0.4)	1.3 (0.4)	1.2 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.4)	1.3 (0.4)
LDL-cholesterol (mmol/l)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)
eGFR (ml/min/1.73 m^2)	78 (19)	76 (17)	79 (19)	76 (18)	77 (20)	77 (18)	78 (19)	76 (18)

Data are expressed as mean (SD), median [interquartile range] or percentage.

eGFR = glomerular filtration rate, estimated by the Chronic Kidney Disease Epdidemiolgoy Collaboration (CKD-EPI) equation.

* Not mutually exclusive, patients can have multiple locations of vascular disease

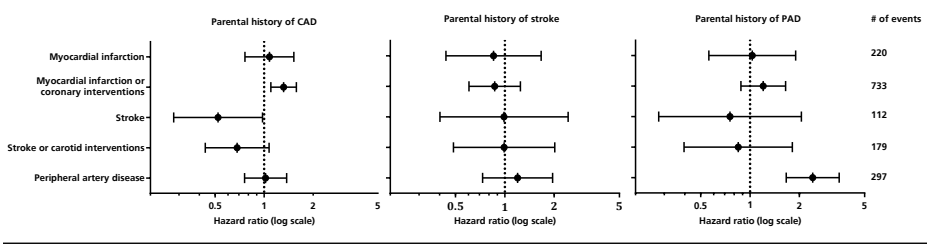
Figure 1. Relation of having a positive parental history of cardiovascular disease and the occurrence of subsequent vascular events and mortality.



Results are expressed as hazard ratios with 95% confidence intervals. Hazard ratios are adjusted for age and sex.

between parental history of PAD and other subsequent events. The relations found did not change in model II. The relations between the different parental vascular disease locations and different vascular events were similar using the alternative definition of a positive parental history of cardiovascular disease.

Figure 2. Relation of different parental disease locations and different subsequent vascular events.

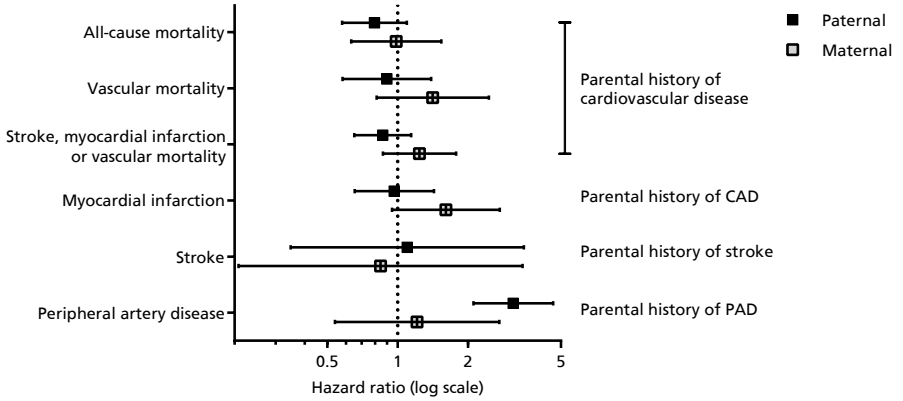


Results are expressed as hazard ratios with 95%CI confidence intervals. Hazard ratios are adjusted for age and sex.

Risk difference between paternal or maternal history

Maternal history of vascular disease did not increase the risk of subsequent vascular events in offspring (figure 3). There was a relation between paternal history of PAD and subsequent peripheral artery disease (HR 3.1, 95%CI 2.1 – 4.6) which was independent of the sex of the offspring. No relations were seen between other paternal vascular disease locations and vascular events in offspring. The relations were the same using the alternative definition of a positive parental history of cardiovascular disease and in the second model.

Figure 3. Risk of subsequent vascular events or mortality according to a paternal or maternal history of vascular disease.



Results are expressed as hazard ratios with 95%CI confidence intervals. Hazard ratios are adjusted for age and sex

DISCUSSION

The present study in patients with various manifestations of atherosclerotic vascular disease demonstrates that a positive parental history of cardiovascular disease before the age of sixty without detailed information about vascular disease location and sex of that particular parent is non-informative of future recurrent vascular events in offspring. Only patients with manifest vascular disease with a father with PAD have an increased risk of subsequent peripheral artery disease.

Only two studies assessed the relation between a family history of cardiovascular disease and the risk of recurrent vascular events in patients with premature cardiovascular disease[8,9]. In the first study it was shown that patients with premature cardiovascular disease more frequently experienced a recurrent event in case of a positive family history of cardiovascular disease (first- and second-degree family members) than patients without such a family history (HR 1.3; 95%CI 1.0 – 1.7)[8]. Vascular events were defined as incident cardiac, cerebrovascular and peripheral artery disease including vascular interventions. These results are therefore most comparable to the composite vascular outcome with vascular interventions used in the present study, showing similar results. The disadvantage to include vascular interventions to the definition of the outcome is the possibility of subjective assessments by the treating physician, who may be more eager to vascularize in case of a positive family history.

In the second study, a positive family history of cardiovascular disease increased the risk of a recurrent arterial thrombotic event in patients who already experienced an arterial thrombotic event (HR 3.0, 95%CI 1.3 – 6.8). A positive family history did not increase the risk of stable atherosclerotic event recurrence in patients with stable atherosclerosis (HR 1.0, 95%CI 0.6

– 1.6)[9]. An arterial thrombotic was defined as an acute myocardial infarction, acute arterial occlusion of the upper or lower peripheral arteries and stroke or TIA without any atherosclerotic abnormalities on duplex of the carotid arteries. Stable atherosclerosis was defined as complaints of angina necessitating elective interventions, peripheral artery disease necessitating interventions and stroke or TIA with atherosclerotic abnormalities on duplex of the carotid arteries. Because the present study did not differentiate between these arterial thrombotic and stable atherosclerotic events, the results cannot simply be compared.

In the present study there was no relation between parental history of cardiovascular disease and subsequent major cardiovascular events and there was no relation found between parental history of stroke or CAD and subsequent stroke or myocardial infarction. Patients already experienced cardiovascular events in the present study, and have already a high baseline risk for subsequent vascular events and on top of that a positive parental history is apparently not informative anymore.

Yet, a parental history of PAD was related with subsequent peripheral artery disease, whereas no differences were seen in smoking and other measured risk factors in patients with a positive or negative parental history. This may suggest a significant genetic contribution for the development of peripheral artery disease, although knowledge of the genetic base of peripheral artery disease is limited. Previous studies have shown that in an elderly population the C allele at rs1333046 on chromosome 9p21 was associated with both a lower mean arterial brachial index level and an increased prevalence of peripheral artery disease, irrespective of the presence of diagnosed myocardial infarction and atherosclerotic risk factors[21]. In addition, a genome-wide association study on 1292 individuals with abdominal aortic aneurysms and 30,503 controls demonstrated that the A allele of rs7025486 on chromosome 9q33 was associated with peripheral artery disease (OR 1.14; p=3.1 x 10-5) independent of traditional atherosclerotic risk factors[22].

There is no clear pathophysiologic explanation for the relation between parental history of PAD and subsequent peripheral artery disease and it is possible that the relation found may be a chance finding. However, smoking is a well-known strong risk factor to the development of peripheral artery disease. Another genome-wide association study identified genetic variants on chromosome 15q24 associated with both nicotine dependence and increased risk of peripheral artery disease[23]. One could speculate that a part of the relation found could be explained by known gene-environment interactions causing patients with a parental history of PAD to have more difficulty quitting smoking and subsequently be more susceptible to the development of peripheral artery disease.

Surprisingly, no increased risk of maternal transmission was found. This difference in the relation between maternal and paternal history of PAD and subsequent PAD cannot easily be explained by knowledge of the genetic base of peripheral artery disease and is probably due to lack of power, as only 6 patients with subsequent peripheral artery disease had a maternal history of PAD. This is the first study showing the importance of paternal history of PAD.

In clinical practice multiple risk stratification models are available to determine which individual has a high risk for developing a first vascular event. Patients with a clinical manifestation of vascular disease are all considered to be at high risk for a subsequent vascular event and there were no algorithms available for risk stratification in these patients. Recently the SMART risk score was developed for risk stratification of patients with arterial disease based on clinical parameters used in the Reynolds risk score and easy to measure characteristics[24]. Parental history of myocardial infarction under the age of sixty was also considered in the development phase of that model, but it appeared to be of no importance for the development of recurrent vascular events (vascular death, myocardial infarction and ischemic stroke). That is in line with the results of the present etiologic analyses only demonstrating a clear relation between parental history of PAD and risk of subsequent peripheral artery disease. Considering the results found in the present study, assessing the presence of a paternal history of PAD may add valuable information to the risk profile of the patient for the development of peripheral artery disease. Knowledge of the parental history and the associated increased risk of peripheral artery disease may stimulate adherence to lifestyle changes and influence clinical decisions regarding monitoring and preventive interventions like supervised exercise programs.

The present study has several strengths. It is an observational cohort study reflecting clinical practice of patients with vascular disease being treated according to national guidelines. The proportion of patients lost to follow-up due to migration or discontinuation of the study was very low, reducing the risk for bias. The adjudication procedure for clinical events is very strict, reducing the chance for subjective assessments. Limitations of the study need to be considered and include the use of self-reported questionnaires for parental history assessment. Misreporting of parental history can lead to an underestimation of the associated risk of subsequent events in offspring. In the present study all patients already experienced cardiovascular events, which may increase the knowledge of the offspring of cardiovascular disease in their parents. Although all patients in the present study have clinically manifest vascular disease, the severity of these manifestations varies. This may neutralize the association between parental history of cardiovascular disease and subsequent events. In addition, one cannot exclude the possibility that having a positive parental history of cardiovascular disease causes patients to receive better secondary prevention, resulting in a diluted association.

In conclusion, parental history of cardiovascular disease without detailed information about vascular disease location or parental sex is not related with an increased risk of recurrent vascular events in patients with clinical manifest vascular disease. For the specific types of parental history regarding sex of the parent and disease location, a paternal history of PAD was related with a higher risk of developing peripheral artery disease.

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3

Paternal or maternal history of cardiovascular disease and the risk of cardiovascular disease in offspring. A systematic review and meta-analysis

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ABSTRACT

Background

Parental history of cardiovascular disease (CVD) is an established risk factor for the development of CVD in offspring. Several studies have suggested that a maternal transmission of CVD is more important for the development of CVD than paternal transmission.

Methods

A systematic search and meta-analysis were conducted, using the Medline and Embase databases. Included were cohort, case-control and cross-sectional studies (n=26) focusing on the relation between paternal and maternal history of cardiovascular disease and offspring CVD (myocardial infarction, stroke or cardiovascular mortality). The pooled estimates were calculated using a random-effects model.

Results

The pooled OR of CVD in offspring having a positive paternal history of CVD compared to not having a positive parental history was 1.91 (95%CI 1.56 – 2.34; I^2 53%), the RR 1.54 (95%CI 1.33 – 1.77; I^2 96%). The OR of a maternal history was 2.16 (95%CI 1.71 – 2.74; I^2 50%), RR 1.59 (95%CI 1.38 – 1.84; I^2 90%). Regarding different age limits, a maternal history <50 years (3.15, 95%CI 2.18 – 4.55) and paternal history <55 years (2.82, 95%CI 2.25 – 3.54) were associated with the highest cardiovascular risk. Additional analyses demonstrated for sons an estimate for a positive paternal history of 1.55 (95%CI 1.39 – 1.71; I^2 74%) and for maternal history 1.56 (95%CI 1.46 – 1.67; I^2 16%). For daughters, the estimate for paternal history was 1.48 (95%CI 1.26 – 1.74; I^2 73%) and for maternal history 1.79 (95%CI 1.50 – 2.13; I^2 68%).

Conclusions

The risk of CVD in offspring was not substantially different between having a positive paternal or maternal history of CVD, the highest risk was observed for maternal history <50 years. Since a positive parental history of CVD involves an increased cardiovascular risk, parental history inquiry is useful in clinical practice. No distinction has to be made whether the affected parent is the mother or the father.

INTRODUCTION

Parental history of cardiovascular disease is a risk factor for the development of cardiovascular events, with reported relative risks ranging from 1.2 to 7.2[1-6]. In clinical practice, assessing parental history of cardiovascular disease is an integral part of a patient's history, which may provide valuable information regarding the risk of cardiovascular disease in patients. In addition, several widely used cardiovascular risk prediction scores, such as the Reynolds Risk Score and the PROCAM, have incorporated parental history of myocardial infarction[7-9]. However, no distinction is made between the sex of the affected parent, while several studies suggest that maternal history of cardiovascular disease confers a higher cardiovascular risk in their offspring than a paternal history of cardiovascular disease[3,10-12] (e.g. 7.2 for maternal history and 3.4 for paternal history[6]). Not all studies though found a difference between paternal and maternal history[13,14] and some even attributed a higher risk to paternal history[15,16]. The lower age-specific incidence causes cardiovascular disease in women to be less common, which may reduce the power of demonstrating a differential risk of paternal and maternal transmission. In addition it is possible that cardiovascular events in mothers occur after the assessment of a paternal or maternal history of cardiovascular disease in offspring which may lead to misclassification of a maternal history. An increased risk for maternal transmission of diabetes mellitus type 2 compared to paternal transmission has also been described[17].
To evaluate whether paternal and maternal history confer different risks of cardiovascular disease in offspring, we conducted a systematic review and summarized the results in a meta-analysis.

METHODS

Search strategy

One investigator (M.W.) identified articles through a systematic search of the Medline (PubMed) and Embase databases up to 7 July 2014 using the following or similar search terms: parental history and cardiovascular events (full search string is provided in supplemental table 1). The references of the retrieved articles were scanned manually. If the full text was unavailable, the authors were contacted by email.

Study selection

Studies were considered eligible if authors reported data from original peer-reviewed studies, if parental history was a specific determinant of the study, if a clear distinction was made between paternal and maternal history of cardiovascular disease in the reporting of results and if the outcome consisted of cardiovascular events. Articles which provided insufficient data for the analyses were excluded.

Data extraction and quality assessment

One author (M.W.) extracted the data and two other authors (F.V. and Y.G.) independently extracted the data from the relevant studies. Discrepancies between the authors were discussed and resolved. From each included study the following information was extracted: first author surname, year of publication, country, study design, population, gender distribution, follow-up years, mean age or age range, number of cardiovascular events, number of participants, definition exposure, definition outcome, all reported risk estimates and their measures of precision (e.g. standard error or confidence intervals) and the number and type of confounders included in the analyses (table 1 and supplemental table 2). Studies using the same study population for different outcomes and definitions of parental history were both included. Studies were included if they reported on one or a combination of the following outcomes: coronary artery disease, cerebrovascular disease or cardiovascular death.

The methodological quality of each included study was evaluated using the Newcastle-Ottawa quality assessment scales (NOS) for cohort, case-control and cross-sectional studies[18]. These scales comprised standard criteria assessing the risk of bias using four main themes: selection, comparability, exposure and outcome. A summary score can be calculated ranging from 0 to 9 points with higher scores indicating to lower risk of bias.

Data analyses

The comparator of having a paternal history or maternal history of cardiovascular disease in the different studies was not having a paternal or maternal history of cardiovascular disease or not having a parental history of cardiovascular disease. The summary relative risks and odds ratios were calculated using the generic inverse variance method and using the random-effects model of DerSimonian-Laird[19] to incorporate heterogeneity in results between studies. If studies reported results for several age limits of parental history, the results of the highest age limit of parental history were used.

A mixture of regression techniques can be used in longitudinal association studies (e.g. logistic regression, Cox or parametric survival models, Poisson regression) leading to different types of effect measures including odds ratios (OR), hazard ratios (HR), and relative risks (RR). Because the rare disease assumption might not hold, the odds ratios were first displayed separately from the other effect estimates (rate ratios and hazard ratios) for the main analyses and pooled afterwards. Different adjustments for potential confounders were performed across the included studies. The pooled effect estimates of two types of models were presented: a model with adjustment for age and sex (if available), and a model adjusted for age, sex, lifestyle and traditional risk factors. For studies reporting results only stratified for sex, the risk estimates were pooled first, using a fixed-effects model, before including the study in the overall analysis. To explore heterogeneity, the I^2 statistic ([Q – df]/Q x 100) was used, reflecting the proportion of observed variance due to real differences in effect sizes. Values of 25%, 50%, and 75% were considered as low, moderate and high heterogeneity. Since several large studies were included

which may influence the I^2 statistic, visual inspection of the forest plots was also performed. To assess potential publication bias, Egger regression tests and visual inspection of funnel plots were performed. Additional analyses were also performed. It was evaluated whether a younger age at which the parent experienced a cardiovascular event further increased the risk of cardiovascular events in offspring. Therefore, the risk estimates were pooled according to age limits of parental history. Studies were divided according to the age limits used: no age limit of parental history, parental history <65 years, parental history <60 years, parental history <55 years and parental history <50 years. Categories were not mutually exclusive; studies using a parental history <55 years were also included in parental history <65 years and <60 years. As previous studies demonstrated potential effect modification between parental history and sex of offspring, we performed stratified analyses for men and women. Studies reporting stratified results for sex of offspring or studies which only comprised men or only women were included in these analyses.

Sensitivity analyses were performed to assess whether there was a difference for the relation between having a positive parental history of coronary artery disease or cerebrovascular disease and cardiovascular events in offspring. In addition, subgroup analyses were performed for studies which presented risk estimates adjusted for age, sex and lifestyle factors (without adjustment for traditional risk factors) and for studies which received full points for the ascertainment of exposure.

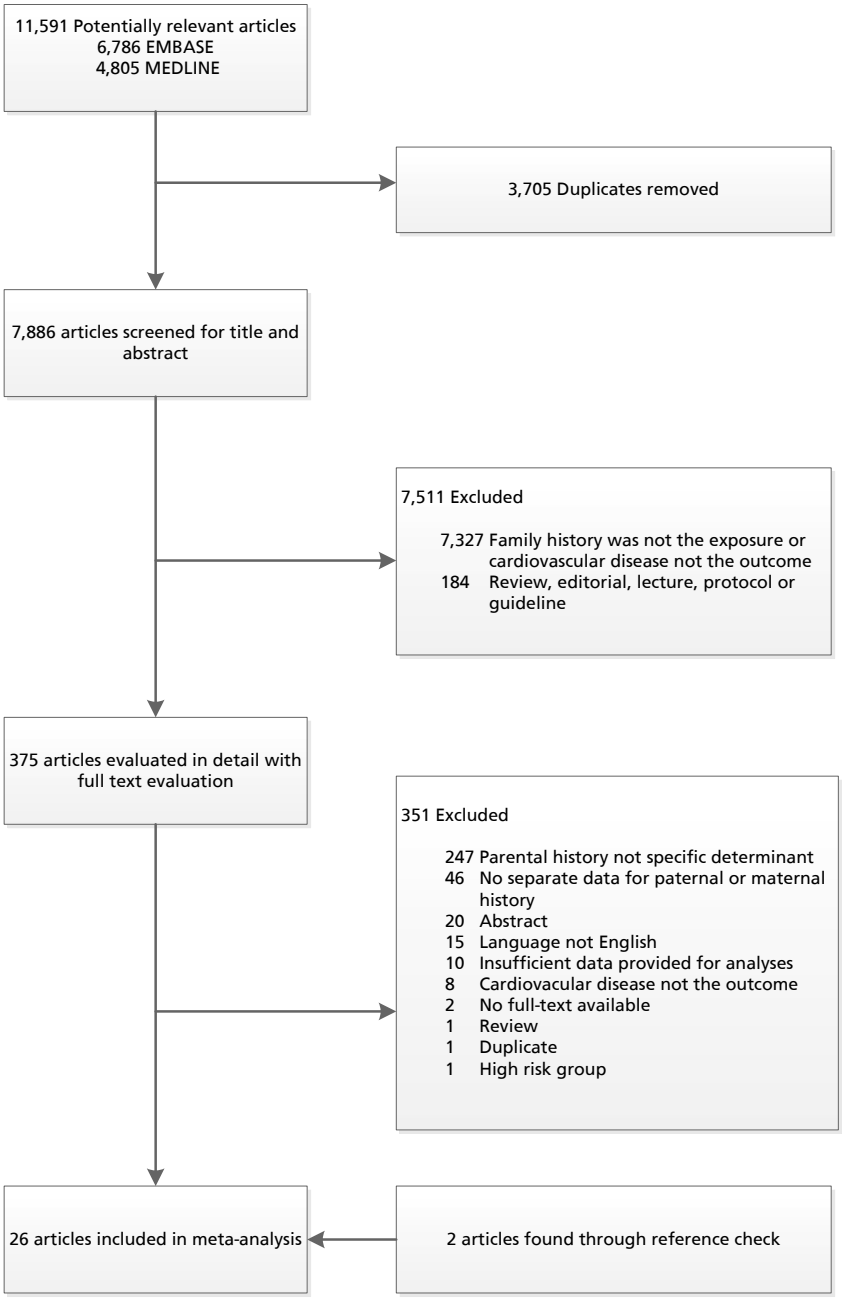
The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were used in the reporting of this systematic review[20].

Statistical analyses were conducted with Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012 and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

RESULTS

The search strategy identified 7886 potentially relevant studies. Initial screening based on title and abstracts left 375 articles for further evaluation. After examining those articles in more detail, 351 articles were excluded for reasons shown in figure 1. An additional two articles were found through manual reference check, resulting in 26 articles included in the meta-analysis[1,3,5,6,10-16,21-35]. Of these 26 articles, four were based upon data derived from the Framingham cohort (two of offspring cohort[1,15] and two of original cohort[14,16]) and two articles were derived from the same Finnish population[28,29]. Because these articles used different outcomes, different definitions of parental history and different time periods of execution, they were not excluded. The results from one particular study were included in multiple analyses as it separately evaluated the relation between parental history of myocardial infarction and stroke and different outcomes[34]. If studies reported results for cardiovascular events, and

Figure 1. Flowchart of study selection.



for stroke and myocardial infarction separately, results for cardiovascular events were used.

Description of studies

Included articles were published in the period 1989 – 2012 and were case-control (n=8[21-24,27,31,33,34]), cross-sectional (n=2[6,30]) and cohort studies (n=16[1,3,5,10-16,25,26,28,29,32,35]). The number of included participants ranged from 106 to 248,490 with a median of 4,933 participants (interquartile range 1699 – 24483). The studies had been conducted in the United States of America (n=11), Europe (n=12), Asia (n=2) and South America (n=1). The study characteristics of the selected studies are shown in table 1. Of the included articles, 13 studies specifically reported results for the relation between a parental history of coronary heart disease and coronary artery disease as outcome, 8 studies reported results for a parental history of stroke and strokes as outcome, 4 studies evaluated the relation between parental history of cardiovascular events and cardiovascular events as outcome and 1 study assessed the relation between a parental history of myocardial infarction and cardiovascular events as outcome. Combined results for men and women were presented in 13 studies, 12 studies reported results for men and women separately, 3 studies only included men and 3 studies only included women.

Several analytic techniques were used in the studies, including logistic regression (n=11), cox proportional hazards regression (n=12), Poisson regression (n=2) and generalized estimating equation models (n=1) (supplemental table 3).

Regarding adjustment for potential confounding factors, 23 studies reported results adjusted for age and 19 studies reported results adjusted for age, sex, lifestyle factors and traditional risk factors.

Quality varied across studies, the scores of the New-Ottawa Scale (NOS) quality assessment ranged from 5 to 9 points (supplemental table 4). In general, a high risk of bias was observed for the ascertainment of the parental history (figure 2), as this was often assessed by written self-reports of offspring instead of using secure records or by a structured interview. In case-control studies, most studies used hospital controls instead of community controls, inducing a risk of bias.

Risk difference between paternal and maternal transmission of cardiovascular disease

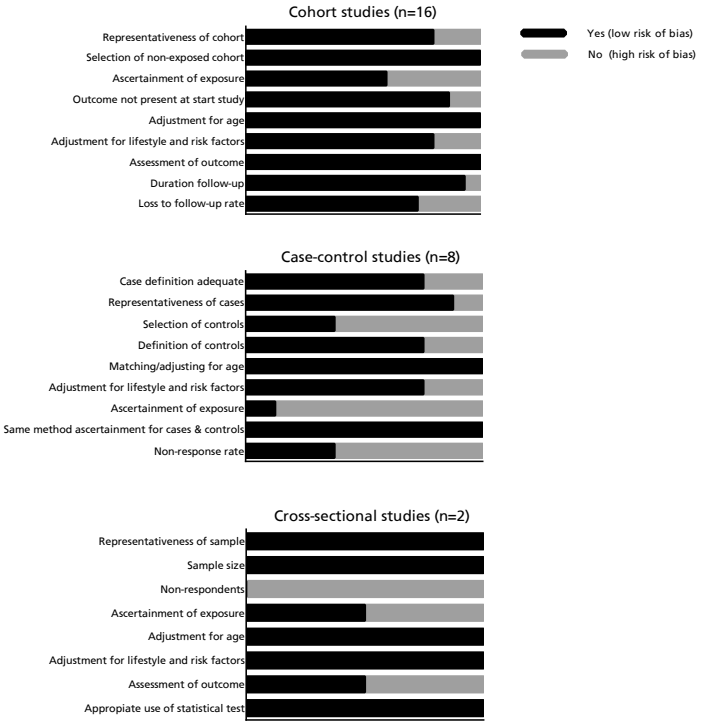
Twenty-three studies demonstrated results adjusted for age and sex (if available) and were included in the age-adjusted analysis of paternal and maternal transmission of cardiovascular disease (supplemental table 3). The pooled OR of cardiovascular events was 1.91 (95%CI 1.56 – 2.34; I^2 53%) for a positive paternal history and 2.16 (95%CI 1.71 – 2.74; I^2 50%) for a positive maternal history (figure 3). No evidence of publication bias using the Egger regression test was observed (p 0.83 and p 0.24).

The pooled RR for paternal history was 1.54 (95%CI 1.33 – 1.77; I^2 96%), and for maternal history 1.59 (95%CI 1.38 – 1.84; I^2 90%). Again, no evidence of publication bias was ob

Table 1. Characteristics of the included studies.

Author / year / country	Study design	Population	Men (%)	Follow-up years	Mean age/age distribution	Definition exposure	Outcome	# Events / # Participants
Colditz / 1986 / USA	Cohort	Nurses' Health Study	0	141,982 py	30 - 55	MI	Nonfatal MI	132 / 117,156
Schildkraut / 1989 / USA	Cohort	Framingham Study (original)	Not stated	Not stated	46	Coronary heart disease	Coronary heart disease	988 / 3933
Colditz / 1991 / USA	Cohort	Health Professionals Follow-up Study	100	72454 py	40 - 75	MI	MI or sudden death	370 / 45317
Kiely / 1993 / USA	Cohort	Framingham Study (original)	Not stated	16	36	Death due Stroke	Stroke or TIA	604 / 4933
Wannamethee / 1996 / UK	Cohort	British Regional Heart study	100	15	40-59	Fatal stroke	Stroke	278 / 7683
Jousilahti / 1996 / Finland	Cohort	Eastern Finland	49	12	43	Premature CHD	Nonfatal MI or coronary death	1046 / 15620
Jousilahti / 1997 / Finland	Cohort	Eastern Finland	49	149896 py	25-64	Stroke	Stroke	453 / 14371
Sesso / 2001 / USA	Cohort	Physicians' & Women's Health Study	36	13 & 6	53	MI	Cardiovascular events	3217 / 61947
Kinra / 2003 / UK	Cohort	University of Glasgow	100	43	21	Coronary heart disease	Fatal coronary heart disease	373 / 8402
Lloyd-Jones / 2004 / USA	Cohort	Framingham Study (offspring)	49	8	44	Cardiovascular events	Cardiovascular events	243 / 2302
Nilsson / 2004 / Sweden	Cohort	Malmo Preventive project	67	Not stated	47	Cardiovascular mortality	Cardiovascular events	2677 / 33346
Sundquist / 2006 / Sweden	Cohort	The Multigeneration Register	Not stated	192.7 million py	Not stated	Coronary heart disease	Coronary heart disease	76575 / ?
Seshadri / 2010 / USA	Cohort	Framingham Study (offspring)	47	77534 py	48	Stroke	Stroke	128 / 3443
van Dis / 2011 / The Netherlands	Cohort	MORGEN-project	46	10	40-65	MI and stroke	MI, unstable angina, ischemic stroke	914 / 10524
Eguchi / 2012 / Japan	Cohort	Japan Collaborative Cohort Study	42	15,9	57	Stroke	Stroke-related mortality	1502 / 53691
Nielsen / 2013 / Denmark	Cohort	Danish registries	Not stated	Not stated	Not stated	MI	MI	? / 248,490
Roncaglioni / 1992 / Italy	Case-control	GISSI-2 trial	89	NA	56	MI	MI	916 /2022
Castro-Beiras / 1993 / Spain	Case-control	Spain	80	NA	57	Coronary heart disease	Coronary heart disease	106 / 212
Ciruzzi / 1997 / Argentinia	Case-control	Various clinical centers in Argentina	74	NA	60	CAD	MI	1060 / 2031
Friedlander / 2001 / USA	Case-control	Western Washington State	0	NA	38	MI	MI	107 / 633
Bertuzzi / 2003 / Italy	Case-control	Milan area, northern Italy	69	NA	60	Ischemic heart disease	First nonfatal AMI	507 / 985
MacClellan / 2006 / USA	Case-control	SPYW Study	0	NA	39	Stroke	Stroke	487 / 1102
Choi / 2009 / Korea	Case-control	Jeju National University Hospital	57	NA	70	Stroke	Ischemic stroke	400 / 800
Siegerink / 2012 / The Netherlands	Case-control	RATIO study	0	NA	39	MI and stroke	MI or ischemic stroke	451 / 1376
Liao / 1997 / USA	Cross-sectional	Family Heart Study	50	NA	60	Stroke	Stroke	105 / 3144
Brown / 2002 / USA	Cross-sectional	NHANES IIII	49	NA	39	MI	MI	237 / 11307

Figure 2. Overview of risk of bias based on the Newcastle-Ottawa Scale.



Overview of the quality of the studies based on the total of individual scores of the studies using the Newcastle-Ottawa Scale (Supplemental table 4). The results are displayed separately for cohort, case-control and cross-sectional studies, as different scoring schemes for these types of studies were used.

served (Egger regression tests p 0.57 and p 0.80).

Pooling the 23 studies resulted in a summary effect estimate of 1.66 (95%CI 1.48 – 1.87; I^2 92%) for paternal history and 1.76 (95%CI 1.56 – 1.99; I^2 84%) for maternal history.

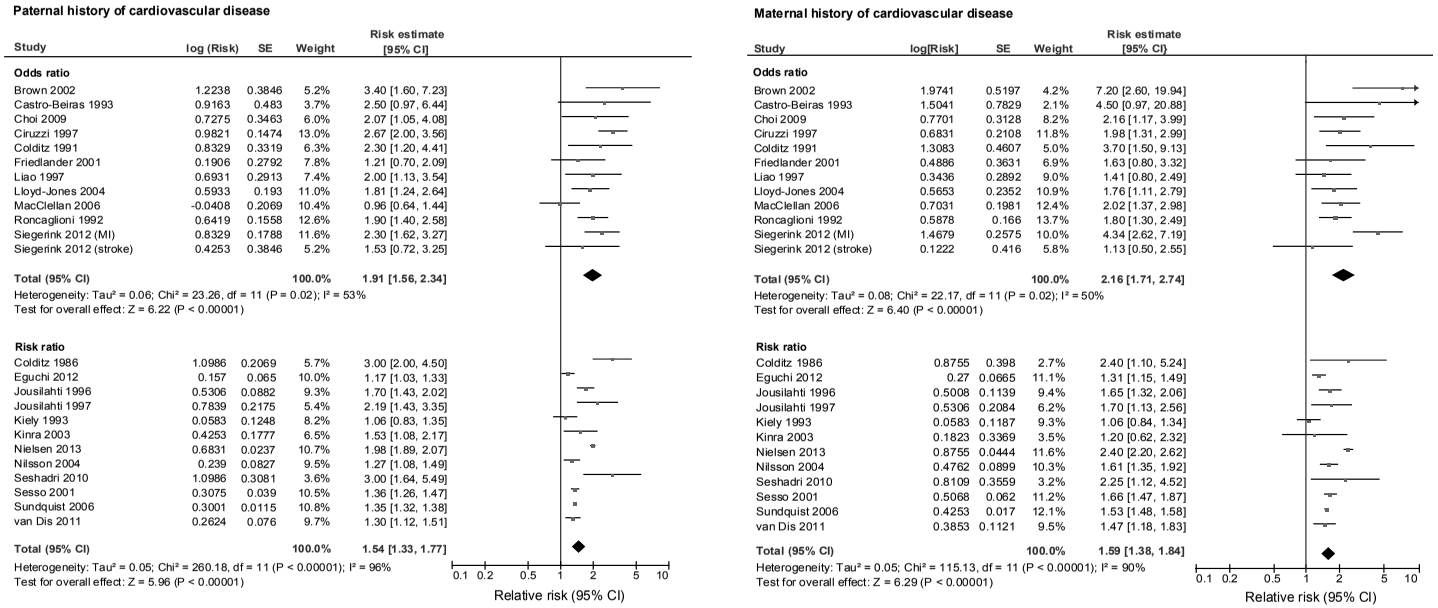
A slight attenuation of the pooled effect estimates was seen in the analyses adjusted for age, sex, lifestyle and traditional risk factors (supplemental figure 1).

Risk difference using several age limits of parental history of cardiovascular disease

For studies using no age limit (supplemental table 6) in the definition of parental history, a maternal history of cardiovascular disease had a slightly higher risk of offspring cardiovascular events (RR 1.65, 95%CI 1.43 – 1.81; I^2 88%) than a paternal history of cardiovascular disease (RR 1.52, 95%CI 1.32 – 1.75; I^2 95%) (figure 4).

The risk of cardiovascular events in offspring increased for both paternal and maternal history of cardiovascular disease using an age limit of <65 years (paternal 2.38, 95%CI 1.94 – 2.92; I^2 85% and maternal 2.51, 95%CI 2.00 – 3.16; I^2 79%). For paternal history of

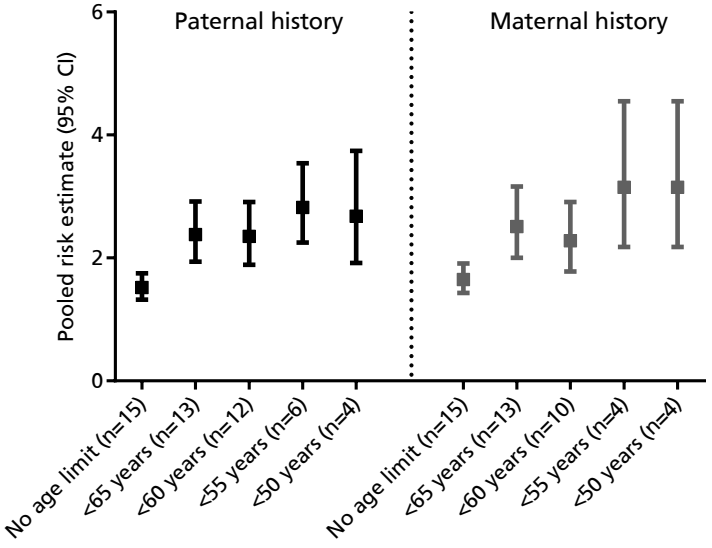
Figure 3. Paternal and maternal histories of cardiovascular disease and the risk of cardiovascular disease in offspring.



Results are age adjusted and sex adjusted if available.

cardiovascular disease the highest risk was observed using the definition of paternal history <55 years (2.82, 95%CI 2.25 – 3.54; I^2 73%). For maternal history, the highest risk was observed with a definition of maternal history <50 years (3.15, 95%CI 2.18 – 4.55; I^2 46%). Adjustment of age, sex, lifestyle factors and traditional risk factors resulted in an attenuation of all observed effects, especially for paternal history <65 and <60 years (1.71, 95%CI 1.41 – 2.07; I^2 68% and 1.76, 95%CI 1.46 – 2.13; I^2 44%). For maternal history of cardiovascular disease <50 years, adjustment of sex, age, lifestyle and traditional risk factors resulted in a further increased risk of offspring cardiovascular events, namely 5.68 (95% CI 2.86 – 11.29; I^2 0%). However, this was only based on 2 studies.

Figure 4. Pooled risk estimates of different age limits of paternal and maternal history of cardiovascular disease and risk of cardiovascular events in offspring.



Age limits for parental history stratified for paternal or maternal history. The groups are not mutually exclusive. Several studies performed analyses for different age limits of parental history of cardiovascular disease. If studies used an age limit of <55 years, these studies are also included in parental history <65 years and parental history <60 years. Studies presenting results for parental history at any age and for parental history <50 years, were included for both categories. Results are adjusted for age (and sex) of offspring.

Risk difference between paternal and maternal transmission of cardiovascular disease stratified for sex of offspring

For men, the age-adjusted pooled estimate for having a paternal history of cardiovascular disease and risk of cardiovascular events was 1.55 (95%CI 1.40 – 1.72; I^2 74%) which was almost identical for having a maternal history of cardiovascular disease (1.56, 95%CI 1.46 – 1.67; I^2 17%) (figure 5).

For women, the pooled estimate for paternal history was 1.48 (95%CI 1.26 – 1.75; I^2 73%) and for maternal history 1.79 (95%CI 1.50 – 2.14; I^2 68%). Adjustment for age, sex, lifestyle

and traditional risk factors resulted in a risk of cardiovascular events of 1.59 (95%CI 1.36 – 1.86; I^2 68%) for men having a paternal history of cardiovascular disease and 1.48 (95%CI 1.29 – 1.69; I^2 35%) for men having a maternal history of cardiovascular disease (supplemental figure 2). For women, the risk estimates for paternal and maternal history of cardiovascular disease were slightly attenuated to 1.35 (95%CI 1.13 – 1.61, I^2 38%) and 1.51 (95%CI 1.23 – 1.87, I^2 45%).

Sensitivity analyses

Restricting the analyses to studies focusing on paternal history of coronary artery disease resulted in a pooled OR of 2.19 (95%CI 1.78 – 2.69; I^2 30%) and a pooled RR of 1.62 (95%CI 1.35 – 1.94; I^2 97%). Including only studies on paternal history of cerebrovascular disease resulted in a pooled OR of 1.49 (95%CI 0.98 – 2.27; I^2 51%) and a pooled RR of 1.53 (95%CI 1.08 – 2.18; I^2 83%).

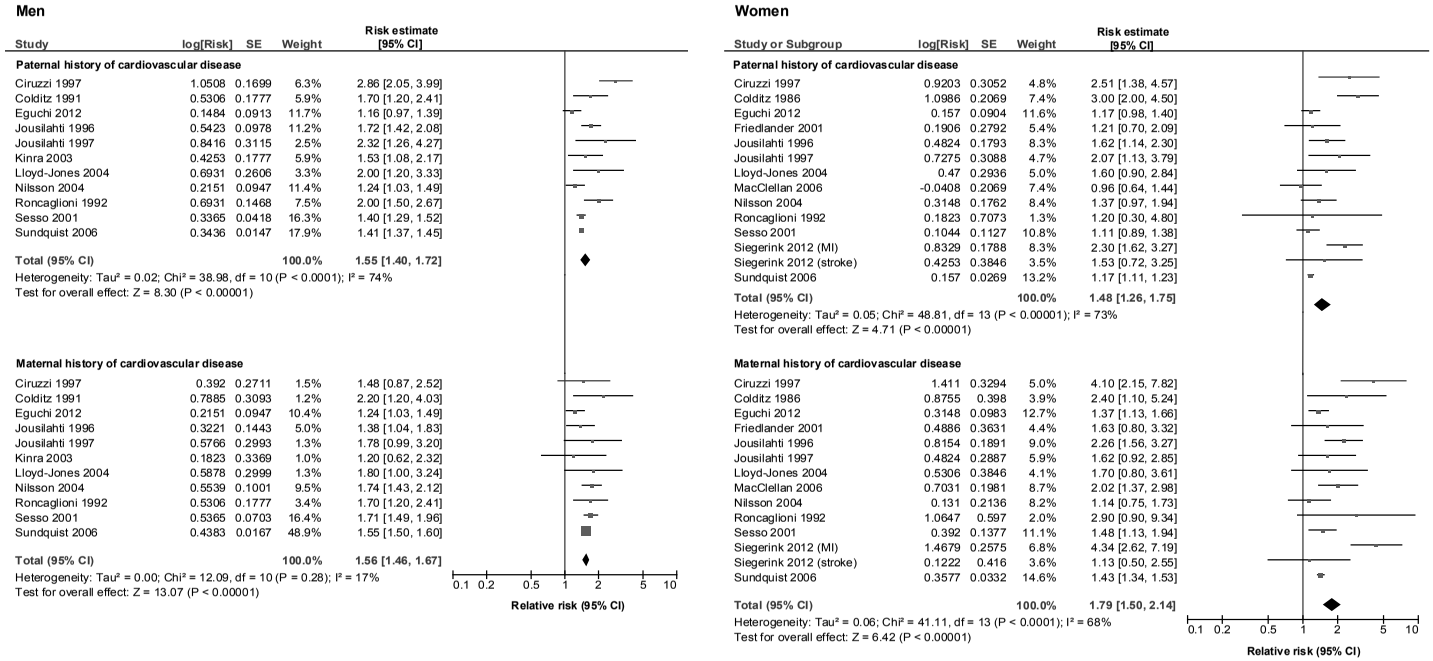
For maternal history of coronary artery disease the pooled OR was 2.74 (95%CI 1.86 – 4.05, I^2 63%) and the pooled RR was 1.76 (95%CI 1.39 – 2.22; I^2 94%). A maternal history of cerebrovascular disease resulted in a pooled OR of 1.77 (95%CI 1.36 – 2.32; I^2 0%) and a pooled RR of 1.34 (95%CI 1.08 – 1.67; I^2 57%). Restricting the analyses for studies presenting risk estimates adjusted for age, sex and lifestyle factors (n=4), resulted in a pooled estimate of 1.31 (95%CI 1.17 – 1.47; I^2 58%) for paternal history of cardiovascular disease and 1.48 (95%CI 1.30 – 1.68; I^2 45%) for maternal history of cardiovascular disease.

Sensitivity analyses were also performed for studies which received maximum points for the ascertainment of parental history (using secure records or structured interviews, supplemental table 4). Having a paternal history of cardiovascular disease resulted in a pooled age-adjusted estimate of 1.57 (95%CI 1.27 – 1.94; I^2 97%) and having a maternal history resulted in a pooled age-adjusted estimate of 1.66 (1.31 – 2.11; I^2 93%).

DISCUSSION

The present meta-analysis based on cohort, case-control and cross-sectional studies demonstrates no substantial difference between the risks of cardiovascular events in offspring having a paternal history of cardiovascular disease and offspring having a maternal history of cardiovascular disease. A parental history <65 years was related to a higher risk compared to parental history at any age, irrespective of the sex of the affected parent. The highest risk was observed for a maternal history of cardiovascular disease <50 years. For sons, the risk of cardiovascular events was similar for having a positive paternal and maternal history of cardiovascular disease. For daughters, a higher risk was observed for maternal history of cardiovascular disease than for paternal history.

Figure 5. Paternal and maternal histories of cardiovascular disease and risk of cardiovascular disease in offspring stratified for sex.



Results are age adjusted.

A priori, the hypothesis of the present meta-analysis was that a positive maternal history of cardiovascular disease was more important than a positive paternal history of cardiovascular disease. Three causal mechanisms have been described that may play a role[36,37]. In genomic imprinting, epigenetic modifications of parental DNA occur, silencing one allele from the mother or father resulting in gene expression from the other allele. Mitochondrial effects may be a second mechanism as the mitochondrial genome in offspring is determined solely by maternally inherited mitochondrial genes. The third mechanism involves the intrauterine environment. As the intrauterine environment is determined by the mother, the mothers' genes influence offspring independent of whether these genes are passed to the offspring[36,37.] In addition, it has been demonstrated that the intrauterine environment has substantial and long lasting effects on risk of cardiovascular events and premature mortality in offspring[38]. Although a higher risk was observed for maternal history compared to paternal history of cardiovascular disease, the higher risk was small, less than expected a priori and probably not clinically relevant.

In all studies regarding parental history of cardiovascular events and offspring cardiovascular events it remains questionable which age limit of a positive parental history should be used. In the Reynolds Risk score[7,8] and the PROCAM risk score[9] an age limit of 60 years is used whereas the Dutch guidelines of cardiovascular risk management (based on the SCORE[39]) recently adjusted the age limit from a parental history <60 years to a parental history <65 years. The present meta-analysis demonstrated a clear difference between the risk estimates for studies using or not using an age limit for parental history. No differences in risk estimates were seen in the analyses for studies with a parental history <65 years and <60 years; not for paternal, nor for maternal history of cardiovascular disease. An age limit of parental history <60 years is probably too strict and may result in losing important information regarding parental history of cardiovascular disease. A higher risk was observed in daughters having a maternal history of cardiovascular disease compared to paternal history. Unfortunately, we could not test whether these risk estimates were significantly different. Studies presented separate risk estimates for having a paternal and maternal history of cardiovascular disease using a reference group of not having a parental history of cardiovascular disease. Therefore the same reference group was used twice, resulting in a positive correlation between the estimates of paternal and maternal history. An estimate of this correlation per study was never reported. If we could take this positive correlation into account, this would result in a smaller p-value. It is known that the magnitude of the correlation is inversely related to the number of events and non-events in the reference group that is used twice. In other words, the larger the reference group, the smaller the correlation. As the majority of studies included in the meta-analysis were quite large, the effect of taking the covariance into account is probably limited. Although we would prefer a proper statistical test, the clinical implication of this differential transmission is probably small, as there is also a substantial increased risk

of cardiovascular events in daughters having a paternal history of cardiovascular disease. Some limitations and remarks of this meta-analysis need to be considered. The first is the heterogeneity across studies. Different definitions of parental history were used regarding the types (e.g. parental history of myocardial infarction, parental history of stroke, parental history of cardiovascular disease) and age limits of parental history (e.g. <60, <50, no age limit). Another potential cause for heterogeneity is the difference in follow-up time and the use of different outcomes in the included studies; cerebrovascular disease, coronary artery disease, cardiovascular death and coronary interventions. The different effect measures used in the included studies (e.g. RR, HR, OR) may also have caused increased heterogeneity in the exact magnitude of the association, however not in the direction of the association. Although the quality of the included studies was generally high, the ascertainment of parental history, the ascertainment of cardiovascular events and the selection of controls were suboptimal in several studies, inducing a potential risk of bias.

To account for the (expected) heterogeneity, several analytic techniques were used to give insight of the effect of heterogeneity on the pooled estimate calculated in the present meta-analysis. A priori we decided to use a random effects model expecting different real effect sizes between the studies. We also performed several sensitivity analyses and subgroup analyses regarding type of parental history (e.g. myocardial infarction or stroke), sex of offspring, and age limits used in the definitions of parental history. We also performed a sensitivity analysis including only those studies presenting effect estimates adjusted for age, sex and lifestyle factors. Most studies presented effect estimates which were additionally adjusted for traditional risk factors. However, adjustment for these traditional risk factors (e.g. hypertension, diabetes mellitus) may result in over-adjustment as part of the mechanism of parental history of cardiovascular disease leading to cardiovascular events may involve the development of hypertension or diabetes mellitus. As expected, the results slightly attenuated adjusting also for traditional risk factors. Therefore, a model with for sex, age and lifestyle factors would be more preferable, unfortunately only four studies presented these results. In addition, it would be valuable to have information regarding the pre- or postmenopausal status of the mothers at the time the mothers experienced their cardiovascular event, since age of menopause is associated with increased cardiovascular risk[40]. Having a mother who experienced cardiovascular disease premenopausal could theoretically be associated with higher cardiovascular risk in offspring compared to having a mother who experienced a cardiovascular event postmenopausal. This information was however not available.

We decided to use all peer-reviewed original studies, irrespective of whether the studies were cross-sectional of prospective of nature. In general, cohort studies are the preferable studies for answering etiologic questions, and cross-sectional and case-control studies are often excluded in meta-analyses. For answering the current question however, cohort studies are not necessarily more favourable. In cohort studies, the presence of a positive parental history is determined at baseline and cardiovascular events in offspring are determined over time. How-

ever, the parental status may also change over time, as parents may develop clinical manifest vascular disease during follow up, and therefore misclassification of parental history may occur. Determining the presence of a parental history and cardiovascular events in offspring at the same time, as performed in cross-sectional studies, leaves no chance of misclassification. In addition, we interpreted the determinant-outcome relation for these cross-sectional studies prospectively as we are confident that the parental history of cardiovascular disease is related to cardiovascular events in offspring and not vice versa. However, the disadvantage of cross-sectional studies is the possibility that patients who experienced a cardiovascular event are more aware of whether their parents experienced a vascular event than patients without cardiovascular disease, which may induce a risk of recall bias.

For the systematic search we chose to only include studies that specifically studied the relation between a parental history of cardiovascular disease and cardiovascular events in offspring. Studies assessing parental history of cardiovascular disease as a potential factor of cardiovascular events along with other factors were not included to avoid selection bias; studies with a positive relation between parental history and cardiovascular events are more likely to report this result in their abstract than studies which did not find a relation. In conclusion, the risk of cardiovascular events in offspring was not substantially different between having a positive paternal or maternal history of cardiovascular disease. Since a positive parental history is related to an increased cardiovascular risk, inquiring after a parental history of cardiovascular disease is useful in clinical practice. No distinction has to be made whether the affected parent is the mother or the father.

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SUPPLEMENTARY INFORMATION

Supplemental table 1. Search strategy in Medline and Embase.

Medline
("family history"[Title/Abstract] OR "parental history"[Title/Abstract]) OR "paternal history"[Title/Abstract]) OR "maternal history"[Title/Abstract]) OR "maternal transmission"[Title/Abstract]) OR "paternal transmission"[Title/Abstract]) AND ("cardiovascular disease"[Title/Abstract] OR "cardiovascular event"[Title/Abstract]) OR "coronary disease"[Title/Abstract]) OR "coronary ischemia"[Title/Abstract]) OR "coronary ischaemia"[Title/Abstract]) OR "coronary artery disease"[Title/Abstract]) OR "coronary heart disease"[Title/Abstract]) OR "myocardial infarction"[Title/Abstract]) OR "heart infarction"[Title/Abstract]) OR "stroke"[Title/Abstract]) OR "cerebrovascular disease"[Title/Abstract]) OR "cerebrovascular event"[Title/Abstract]) OR "cerebrovascular ischemia"[Title/Abstract]) OR "cerebrovascular ischaemia"[Title/Abstract]) OR "cerebrovascular accident"[Title/Abstract]) OR "cerebrovascular hemorrhage"[Title/Abstract]) OR "cerebrovascular infarction"[Title/Abstract]) OR "cerebral disease"[Title/Abstract]) OR "cerebral event"[Title/Abstract]) OR "cerebral ischemia"[Title/Abstract]) OR "cerebral ischaemia"[Title/Abstract]) OR "cerebral accident"[Title/Abstract]) OR "cerebral hemorrhage"[Title/Abstract]) OR "cerebral haemorrhage"[Title/Abstract]) OR "cerebral infarction"[Title/Abstract]) OR "brain infarction"[Title/Abstract]) OR "brain hemorrhage"[Title/Abstract]) OR "brain haemorrhage"[Title/Abstract]) OR "brain ischemia"[Title/Abstract]) OR "brain ischaemia"[Title/Abstract]) OR "transient ischemic attack"[Title/Abstract]) OR "transient ischaemic attack"[Title/Abstract]) OR "abdominal aortic aneurysm"[Title/Abstract]) OR "peripheral artery disease"[Title/Abstract]) OR "peripheral arterial disease"[Title/Abstract]) OR "peripheral artery occlusive disease"[Title/Abstract]) OR "percutaneous coronary intervention"[Title/Abstract]) OR "percutaneous transluminal angioplasty"[Title/Abstract]) OR "percutaneous transluminal coronary angioplasty"[Title/Abstract]) OR "coronary artery bypass graft"[Title/Abstract]) OR "carotid endarterectomy"[Title/Abstract]) OR "carotid artery stenting"[Title/Abstract]) OR atherosclerosis[Title/Abstract]) OR ("myocardial infarction"[MeSH Terms] OR "stroke"[MeSH Terms]).
Embase
('family history':ab,ti OR 'family medical history':ab,ti OR 'parental history':ab,ti OR 'paternal history':ab,ti OR 'maternal history':ab,ti OR 'maternal transmission':ab,ti OR 'paternal transmission':ab,ti AND [embase]/lim AND 'cardiovascular disease':ab,ti OR 'vascular disease':ab,ti OR 'cardiovascular event':ab,ti OR 'coronary disease':ab,ti OR 'coronary ischemia':ab,ti OR 'coronary ischaemia':ab,ti OR 'coronary artery disease':ab,ti OR 'coronary heart disease':ab,ti OR 'myocardial infarction':ab,ti OR 'heart infarction':ab,ti OR 'heart infarction'/exp OR stroke:ab,ti OR 'cerebrovascular disease':ab,ti OR 'cerebrovascular event':ab,ti OR 'cerebrovascular ischemia':ab,ti OR 'cerebrovascular ischaemia':ab,ti OR 'cerebrovascular accident':ab,ti OR 'cerebrovascular hemorrhage':ab,ti OR 'cerebrovascular haemorrhage':ab,ti OR 'cerebrovascular infarction':ab,ti OR 'cerebral disease':ab,ti OR 'cerebral event':ab,ti OR 'cerebral ischemia':ab,ti OR 'cerebral ischaemia':ab,ti OR 'cerebral accident':ab,ti OR 'cerebral hemorrhage':ab,ti OR 'cerebral haemorrhage':ab,ti OR 'cerebral infarction':ab,ti OR 'brain infarction'/exp OR 'brain infarction':ab,ti OR 'brain hemorrhage':ab,ti OR 'brain haemorrhage:ti:ab' OR 'brain ischemia':ab,ti OR 'brain ischaemia':ab,ti OR 'transient ischemic attack':ab,ti OR 'transient ischaemic attack':ab,ti OR 'abdominal aorta aneurysm'/exp OR 'abdominal aortic aneurysm':ab,ti OR 'abdominal aorta aneurysm':ab,ti OR 'peripheral artery disease':ab,ti OR 'peripheral arterial disease':ab,ti OR 'peripheral artery occlusive disease':ab,ti OR 'peripheral occlusive artery disease'/exp OR 'percutaneous coronary intervention':ab,ti OR 'percutaneous transluminal angioplasty':ab,ti OR 'percutaneous transluminal coronary angioplasty':ab,ti OR 'coronary artery bypass graft':ab,ti OR 'carotid endarterectomy':ab,ti OR 'carotid artery stenting':ab,ti OR atherosclerosis:ab,ti OR 'atherosclerosis'/exp AND [embase]/lim)

Supplemental table 2. Risk estimates per study.

Author	Effect measure	Model	Paternal history	Maternal history	Confounders adjusted for
Bertuzzi (2013)	Odds ratio	1	2.1 (1.4 - 3.0)	2.1 (1.2 - 3.4)	Age, sex, education, BMI, total cholesterol, smoking, coffee, alcohol, physical activity, diabetes, hypertension and number of siblings
Men	Odds ratio	1	2.4 (1.5 - 3.9)	2.3 (1.3 - 4.2)	Age, sex, education, BMI, total cholesterol, smoking, coffee, alcohol, physical activity, diabetes, hypertension and number of siblings
Women	Odds ratio	1	1.8 (0.9 - 3.9)	1.7 (0.6 - 4.9)	Age, sex, education, BMI, total cholesterol, smoking, coffee, alcohol, physical activity, diabetes, hypertension and number of siblings
Brown (2002)	Odds ratio	1	2.2 (1.1 - 4.5)	6.7 (2.9 - 15.8)	Crude
		2	3.4 (1.6 - 7.2)	7.2 (2.6 - 19.9)	Age, race, sex
		3	3.1 (1.5 - 6.3)	6.1 (2.1 - 17.4)	Model 2 covariates + education, current smoking, body mass index, diabetes, hypertension and total cholesterol concentration
Castro-Beiras (1993)	Odds ratio	1	2.50 (0.97 - 6.44)	4.50 (0.97 - 20.83)	Matched for age and sex
Choi (2009)	Odds ratio	1	2.07 (1.05 - 4.09)	2.16 (1.17 - 3.99)	Crude (matched age)
		2	2.40 (1.15 - 5.02)	2.00 (1.03 - 3.87)	Age, sex, BMI, hypertension, diabetes mellitus, heart disease, blood cholesterol and smoking
Ciruzzi (1997)	Odds ratio	1	2.67 (2.00 - 3.59)	2.17 (1.46 - 3.24)	Age in decades, sex
		2	2.13 (1.57 - 2.90)	1.98 (1.31 - 2.99)	Model 1 covariates + cholesterolemia, smoking, diabetes, hypertension, body mass index, education, social class and physical exercise
Men	Odds ratio	1	2.86 (2.05 - 4.08)	1.48 (0.87 - 2.51)	Age in decades
		2	2.22 (1.56 - 3.17)	1.56 (0.92 - 2.64)	Model 1 covariates + cholesterolemia, smoking, diabetes, hypertension, body mass index, education, social class and physical exercise
Women	Odds ratio	1	2.51 (1.38 - 4.58)	4.10 (2.15 - 8.22)	Age in decades
		2	1.95 (1.04 - 3.66)	3.00 (1.46 - 6.17)	Model 1 covariates + cholesterolemia, smoking, diabetes, hypertension, body mass index, education, social class and physical exercise
Colditz (1986)	Relative risk	1	3.0 (2.0 - 4.5)	2.4 (1.1 - 5.3)	Age using five-years age categories
Colditz (1991)					
FH < 70 years	Relative risk	1	1.7 (1.2 - 2.3)	2.2 (1.2 - 3.8)	Age
FH < 50 years	Relative risk	1	2.3 (1.2 - 4.3)	3.7 (1.5 - 9.3)	Age
		2	2.2 (1.2 - 4.1)	5.4 (2.2 - 13.6)	Model 1 covariates + body mass index, smoking habits, diabetes mellitus, hypertension, hypercholesterolemia, alcohol use, health profession, dietary energgy, saturated, polysaturated and monounsaturated fat and cholesterol intake
Eguchi (2012)	Hazard ratio	1	1.17 (1.03 - 1.32)	1.31 (1.15 - 1.50)	Age
		2	1.16 (1.03 - 1.32)	1.33 (1.16 - 1.52)	Model 1 covariates + sex, healthy-lifestyle score, perceived mental stress, educational level and regular employment
		3	1.08 (0.95 - 1.23)	1.21 (1.06 - 1.39)	Model 2 covariates + hypertension and diabetes mellitus
Men	Hazard ratio	1	1.16 (0.97 - 1.38)	1.24 (1.03 - 1.50)	Age
		2	1.17 (0.99 - 1.40)	1.26 (1.05 - 1.53)	Model 1 covariates + sex, healthy-lifestyle score, perceived mental stress, educational level and regular employment
		3	1.09 (0.91 - 1.30)	1.17 (0.97 - 1.42)	Model 2 covariates + hypertension and diabetes mellitus
Women	Hazard ratio	1	1.17 (0.98 - 1.40)	1.37 (1.13 - 1.66)	Age
		2	1.15 (0.96 - 1.37)	1.40 (1.15 - 1.70)	Model 1 covariates + sex, healthy-lifestyle score, perceived mental stress, educational level and regular employment
		3	1.08 (0.90 - 1.30)	1.28 (1.06 - 1.56)	Model 2 covariates + hypertension and diabetes mellitus
Friedlander (2001)	Odds ratio	1	1.49 (0.88 - 2.53)	2.21 (1.12 - 4.35)	Crude
		2	1.21 (0.70 - 2.09)	1.63 (0.80 - 3.32)	Age
		3	0.91 (0.44 - 1.86)	1.22 (0.47 - 3.14)	Model 2 covariates + education, diabetes, hypertension, hypercholesterolemia, smoking, physical activity, coffee and fat consumption, and body mass index
		4	0.47 (0.15 - 1.44)	1.81 (0.17 - 19.11)	Model 3 covariates + total cholesterol, triglyceride, HDL-C, Lp(a), LDL subclass, and polymorphisms in the genes for factor V, prothrombin, MTHFR and platelet glycoprotein IIb

Supplemental table 2 continued.

Author	Effect measure	Model	Paternal history	Maternal history	Confounders adjusted for
Jousilahti (1996)					
Men	Risk ratio	1	1.72 (1.42 - 2.07)	1.38 (1.04 - 1.83)	Age and study year
		2	1.63 (1.35 - 1.97)	1.34 (1.01 - 1.77)	Model 1 covariates + smoking, serum cholesterol, systolic blood pressure, diabetes and body mass index
		3	1.65 (1.36 - 1.99)	1.34 (1.01 - 1.77)	Model 2 covariates + number of school years and total family income
Women	Risk ratio	1	1.62 (1.14 - 2.28)	2.26 (1.56 - 3.28)	Age and study year
		2	1.57 (1.11 - 2.22)	2.20 (1.51 - 3.20)	Model 1 covariates + smoking, serum cholesterol, systolic blood pressure, diabetes and body mass index
		3	1.58 (1.12 - 2.24)	2.21 (1.52 - 3.22)	Model 2 covariates + number of school years and total family income
Jousilahti (1997)					
Men	Risk ratio	1	2.32 (1.26 - 4.24)	1.78 (0.99 - 3.17)	Age and study year
		2	2.07 (1.13 - 3.81)	1.83 (1.02 - 3.27)	Model 1 covariates + smoking, serum cholesterol, systolic blood pressure, diabetes and relative length of education
Women	Risk ratio	1	2.07 (1.13 - 3.81)	1.62 (0.92 - 2.84)	Age and study year
		2	2.15 (1.17 - 3.96)	1.67 (0.95 - 2.94)	Model 1 covariates + smoking, serum cholesterol, systolic blood pressure, diabetes and relative length of education
Kiely (1993)	Relative risk	1	1.03 (0.81 - 1.30)	1.06 (0.84 - 1.33)	Crude
		2	1.06 (0.83 - 1.34)	1.06 (0.84 - 1.34)	Age and sex
		3	0.996 (0.78 - 1.27)	1.00 (0.78 - 1.27)	Model 2 covariates + systolic blood pressure + serum cholesterol + ciagerettes smoked per day + left ventricular hypertrophy by ECG and glucose intolerance or diabetic status
Kinra (2003)	Hazard ratio	1	1.59 (1.12 - 2.26)	1.26 (0.65 - 2.45)	Crude
		2	1.53 (1.08 - 2.17)	1.20 (0.62 - 2.33)	Year of birth
		3	1.53 (1.08 - 2.18)	1.19 (0.61 - 2.32)	Model 2 covariates + cigarette smoking, father's social class, height, body mass index and systolic blood pressure
Liao (1997)	Odds ratio	1	2.17 (1.23 - 3.82)	1.68 (0.96 - 2.95)	Crude
		2	2.00 (1.13 - 3.54)	1.41 (0.80 - 2.50)	Proband age, ethnicity and sex
		3	2.01 (1.10 - 3.69)	1.35 (0.73 - 2.48)	Model 2 covariates + history of elevated cholesterol level, ciagerette smoking status, history of coronary heart disease, hypertension, diabetes mellitus and sampling strata
Lloyd-Jones (2004)					
Men (premature parental CVD)	Odds ratio	1	3.0 (1.7 - 5.0)	3.4 (2.1 - 5.6)	Crude
		2	2.7 (1.6 - 4.7)	2.4 (1.5 - 4.0)	Age
		3	2.5 (1.4 - 4.3)	2.2 (1.3 - 3.7)	Age and SBP and antihypertensive therapy
		4	2.8 (1.6 - 4.9)	2.1 (1.2 - 3.4)	Age and total/HDL cholesterol ratio
		5	2.4 (1.4 - 4.1)	2.2 (1.4 - 3.7)	Age and smoking
		6	2.5 (1.4 - 4.3)	2.2 (1.3 - 3.7)	Age and diabetes and body mass index
		7	2.2 (1.2 - 3.9)	1.7 (1.0 - 2.9)	Age, total/HDL cholesterol ratio, SBP, antihypertensive therapy, diabetes, body mass index, and current smoking
Women (premature parental CVD)	Odds ratio	1	2.7 (1.3 - 5.8)	3.2 (1.7 - 6.0)	Crude
		2	2.8 (1.3 - 6.1)	2.3 (1.2 - 4.5)	Age
		3	2.3 (1.1 - 5.1)	1.9 (0.9 - 3.7)	Age and SBP and antihypertensive therapy
		4	1.9 (0.8 - 4.3)	2.0 (1.0 - 3.9)	Age and total/HDL cholesterol ratio
		5	2.8 (1.3 - 6.0)	2.3 (1.2 - 4.4)	Age and smoking
		6	2.4 (1.1 - 5.3)	2.2 (1.1 - 4.3)	Age and diabetes and body mass index
		7	1.7 (0.7 - 3.9)	1.7 (0.8 - 3.4)	Age, total/HDL cholesterol ratio, SBP, antihypertensive therapy, diabetes, body mass index, and current smoking

Supplemental table 2 continued.

Author	Effect measure	Model	Paternal history	Maternal history	Confounders adjusted for
Men (nonpremature parental CVD)	Odds ratio	1	3.0 (1.9 - 4.6)	4.1 (2.4 - 6.8)	Crude
		2	2.0 (1.2 - 3.1)	1.8 (1.0 - 3.2)	Age
		3	1.8 (1.1 - 2.8)	1.5 (0.8 - 2.8)	Age and SBP and antihypertensive therapy
		4	1.8 (1.2 - 2.9)	1.8 (1.0 - 3.3)	Age and total/HDL cholesterol ratio
		5	1.9 (1.2 - 2.9)	1.6 (0.9 - 2.9)	Age and smoking
		6	1.8 (1.2 - 2.9)	1.6 (0.8 - 2.9)	Age and diabetes and body mass index
		7	1.6 (1.0 - 2.5)	1.3 (0.7 - 2.4)	Age, total/HDL cholesterol ratio, SBP, antihypertensive therapy, diabetes, body mass index, and current smoking
Women (nonpremature parental CVD)	Odds ratio	1	2.6 (1.5 - 4.6)	3.5 (1.7 - 6.9)	Crude
		2	1.6 (0.9 - 3.0)	1.7 (0.8 - 3.7)	Age
		3	1.4 (0.7 - 2.6)	1.3 (0.6 - 3.0)	Age and SBP and antihypertensive therapy
		4	1.4 (0.7 - 2.6)	1.4 (0.6 - 3.2)	Age and total/HDL cholesterol ratio
		5	1.5 (0.8 - 2.8)	1.7 (0.8 - 3.9)	Age and smoking
		6	1.6 (0.9 - 3.0)	1.7 (0.8 - 3.9)	Age and diabetes and body mass index
		7	1.1 (0.6 - 2.1)	1.2 (0.5 - 2.9)	Age, total/HDL cholesterol ratio, SBP, antihypertensive therapy, diabetes, body mass index, and current smoking
MacClellan (2006)	Odds ratio	1	0.96 (0.64 - 1.42)	2.02 (1.37 - 2.99)	Matched age
		2	0.66 (0.39 - 1.12)	1.67 (1.05 - 2.66)	Age, race, smoking, myocardial infarction and relative age
Nielsen (2013)					
FH any age	Rate ratio	1	1.98 (1.89 - 2.09)	2.40 (2.20 - 2.60)	Age (5-year interval), sex and calender time (5-year interval)
		2	1.64 (1.55 - 1.72)	2.06 (1.89 - 2.23)	Diabetes, hypertension, use of statins, use of acetyl-salicyclic acid, chronic obstructive lung disease, cerebrovascular disease, peripheral vascular disease and renal disease
FH < 50 years	Rate ratio	1	3.30 (2.92 - 3.72)	3.23 (2.56 - 4.10)	Age (5-year interval), sex and calender time (5-year interval)
		2	2.46 (2.18 - 2.79)	2.60 (2.21 - 3.05)	Diabetes, hypertension, use of statins, use of acetyl-salicyclic acid, chronic obstructive lung disease, cerebrovascular disease, peripheral vascular disease and renal disease
Nilsson (2004)					
Men	Risk ratio	1	1.24 (1.03 - 1.48)	1.74 (1.43 - 2.11)	Age
		2	1.22 (1.02 - 1.47)	1.51 (1.23 - 1.84)	Model 1 covariates + social class, body mass index, systolic blood pressure, blood lipids (cholesterol, triglycerides), fasting glucose and smoking at baseline screening
Women	Risk ratio	1	1.37 (0.97 - 1.92)	1.14 (0.75 - 1.75)	Age
		2	1.20 (0.83 - 1.73)	0.87 (0.54 - 1.41)	Model 1 covariates + social class, body mass index, systolic blood pressure, blood lipids (cholesterol, triglycerides), fasting glucose and smoking at baseline screening
Roncaglioni (1992)	Odds ratio	1	1.9 (1.4 - 2.4)	1.8 (1.3 - 2.6)	Age in decades
		2	1.9 (1.4 - 2.5)	1.9 (1.3 - 2.7)	Age, sex, smoking, cholesterol levels, diabetes, body mass index, hypertension, hyperlipidemia, and total number of relatives
Men	Odds ratio	1	2.0 (1.5 - 2.7)	1.7 (1.2 - 2.5)	Age in decades
		2	2.1 (1.5 - 2.8)	1.8 (1.2 - 2.6)	Age, sex, smoking, cholesterol levels, diabetes, body mass index, hypertension, hyperlipidemia, and total number of relatives
Women	Odds ratio	1	1.2 (0.3 - 4.5)	2.9 (0.9 - 8.9)	Age in decades
		2	0.8 (0.3 - 2.1)	2.6 (0.7 - 8.9)	Age, sex, smoking, cholesterol levels, diabetes, body mass index, hypertension, hyperlipidemia, and total number of relatives

Supplemental table 2 continued.

Author	Effect measure	Model	Paternal history	Maternal history	Confounders adjusted for
Schildkraut	Relative risk	1	1.0 (1.0 - 1.1)	1.2 (1.0 - 1.4)	Crude
		2	1.2 (1.1 - 1.5)	1.3 (1.1 - 1.5)	Age, sex, systolic blood pressure, cholesterol, glucose intolerance, cigarettes smoked per day, relative body weight, left ventricular hypertrophy, mother age's of death, father's age of death and interactions between cholesterol and age, cholesterol and systolic blood pressure, cholesterol and cigarettes smoked per day at exam
Men	Relative risk	1	1.2 (0.9 - 1.8)	1.4 (1.1 - 1.8)	Crude
		2	1.2 (1.0 - 1.5)	1.4 (1.1 - 1.8)	Age, sex, systolic blood pressure, cholesterol, glucose intolerance, cigarettes smoked per day, relative body weight, left ventricular hypertrophy, mother age's of death, father's age of death and interactions between cholesterol and age, cholesterol and systolic blood pressure, cholesterol and cigarettes smoked per day at exam
Women	Relative risk	1	1.0 (0.8 - 1.3)	1.1 (0.8 - 1.4)	Crude
		2	1.3 (1.0 - 1.7)	1.3 (1.0 - 1.7)	Age, sex, systolic blood pressure, cholesterol, glucose intolerance, cigarettes smoked per day, relative body weight, left ventricular hypertrophy, mother age's of death, father's age of death and interactions between cholesterol and age, cholesterol and systolic blood pressure, cholesterol and cigarettes smoked per day at exam
Seshadri (2010)	Hazard ratio	1	3.00 (1.64 - 5.51)	2.25 (1.12 - 4.52)	Age, sex and sibship
		2	2.56 (1.37 - 4.76)	1.93 (0.92 - 4.07)	Model 1 covariates + systolic blood pressure, history of nonstroke cardiovascular disease, smoking, diabetes mellitus, atrial fibrillation and LVH
Men	Hazard ratio	2	2.26 (1.01 - 5.10)	1.34 (0.47 - 3.84)	Age, sex, sibship, systolic blood pressure, history of nonstroke cardiovascular disease, smoking, diabetes mellitus, atrial fibrillation and LVH
Women	Hazard ratio	2	3.50 (1.30 - 9.45)	2.51 (0.98 - 6.45)	Age, sex, sibship, systolic blood pressure, history of nonstroke cardiovascular disease, smoking, diabetes mellitus, atrial fibrillation and LVH
Sesso (2001)					
Men - Total CVD	Relative risk	1	1.40 (1.29 - 1.53)	1.71 (1.49 - 1.97)	Age
		2	1.40 (1.28 - 1.53)	1.71 (1.48 - 1.97)	Model 1 covariates + BMI, smoking status, exercise, and alcohol intake. Randomized aspirin and beta-carotene treatment
Men - Myocardial infarction	Relative risk	1	1.57 (1.32 - 1.87)	2.15 (1.65 - 2.79)	Age
		2	1.58 (1.33 - 1.89)	2.14 (1.64 - 2.79)	Model 1 covariates + BMI, smoking status, exercise, and alcohol intake. Randomized aspirin and beta-carotene treatment
Men - Stroke	Relative risk	1	1.06 (0.87 - 1.28)	1.28 (0.93 - 1.74)	Age
		2	1.05 (0.87 - 1.27)	1.26 (0.92 - 1.72)	Model 1 covariates + BMI, smoking status, exercise, and alcohol intake. Randomized aspirin and beta-carotene treatment
Women - Total CVD	Relative risk	1	1.11 (0.89 - 1.37)	1.48 (1.13 - 1.94)	Age
		2	1.15 (0.92 - 1.42)	1.46 (1.11 - 1.92)	Model 1 covariates + BMI, smoking status, exercise, and alcohol intake. Randomized aspirin and vitamine E treatment, postmenopausal status and postmenopausal hormone use
Women - Myocardial infarction	Relative risk	1	0.88 (0.57 - 1.37)	1.86 (1.17 - 2.96)	Age
		2	0.93 (0.60 - 1.45)	1.76 (1.09 - 2.87)	Model 1 covariates + BMI, smoking status, exercise, and alcohol intake. Randomized aspirin and vitamine E treatment, postmenopausal status and postmenopausal hormone use
Women - Stroke	Relative risk	1	1.13 (0.80 - 1.60)	1.11 (0.67 - 1.84)	Age
		2	1.15 (0.81 - 1.63)	1.14 (0.69 - 1.90)	Model 1 covariates + BMI, smoking status, exercise, and alcohol intake. Randomized aspirin and vitamine E treatment, postmenopausal status and postmenopausal hormone use

Supplemental table 2 continued.

Author	Effect measure	Model	Paternal history	Maternal history	Confounders adjusted for
Men - Total CVD - History <50 years	Relative risk	1	2.22 (1.80 - 2.75)	1.05 (0.40 - 2.81)	Age
		2	2.19 (1.77 - 2.72)	1.00 (0.38 - 2.68)	Model 1 covariates + BMI, smoking status, exercise, and alcohol intake. Randomized aspirin and vitamine E treatment, postmenopausal status and postmenopausal hormone use
Women - Total CVD - History <50 years	Relative risk	1	1.76 (1.22 - 2.55)	2.59 (1.52 - 4.41)	Age
		2	1.63 (1.12 - 2.39)	2.57 (1.51 - 4.37)	Model 1 covariates + BMI, smoking status, exercise, and alcohol intake. Randomized aspirin and vitamine E treatment, postmenopausal status and postmenopausal hormone use
Siegerink (2012)					
Parental history MI - MI	Odds ratio	1	2.30 (1.62 - 3.28)	4.34 (2.62 - 7.17)	Area of residence, year of event and age (continuous)
Parental history Stroke - Stroke	Odds ratio	1	1.53 (0.72 - 3.25)	1.13 (0.50 - 2.51)	Area of residence, year of event and age (continuous)
Sundquist (2006)					
Men	SIR	1	1.41 (1.37 - 1.45)	1.55 (1.50 -1.60)	Age (per 10 years), occupation and region
Women	SIR	1	1.17 (1.11 - 1.23)	1.43 (1.34 - 1.51)	Age (per 10 years), occupation and region
Men (premature parental CHD)	SIR	1	3.82 (2.91 - 4.91)	3.39 (2.97 - 3.85)	Age (per 10 years), occupation and region
Women (premature parental CHD)			1.54 (0.76 - 2.76)	3.63 (2.94 - 4.44)	Age (per 10 years), occupation and region
	SIR	1			
van Dis (2011)					
PH Myocardial infarction	Hazard ratio	1	1.33 (1.14 - 1.55)	1.47 (1.18 - 1.84)	Age and gender
		2	1.33 (1.14 - 1.55)	1.41 (1.13 - 1.76)	Model 1 covariates + smoking, alcohol intake, BMI and education
		3	1.30 (1.12 - 1.52)	1.33 (1.06 - 1.66)	Model 2 covariates + systolic blood pressure + serum total and HDL-cholesterol, self reported diabetes mellitus
PH Myocardial infarction <60 years	Hazard ratio	1	1.47 (1.20 - 1.81)	2.20 (1.59 - 3.04)	Age and gender
		2	1.42 (1.16 - 1.75)	2.10 (1.52 - 2.90)	Model 1 covariates + smoking, alcohol intake, BMI and education
		3	1.37 (1.11 - 1.68)	2.05 (1.48 - 2.84)	Model 2 covariates + systolic blood pressure + serum total and HDL-cholesterol, self reported diabetes mellitus
Wannamethee (1996)	Relative risk	1	1.5 (1.0 - 2.2)	1.6 (1.0 - 2.4)	Age, social class, smoking, physical activity, alcohol intake, recall of stroke, diabetes and preexisting ischemic
		2	1.4 (0.9 - 2.0)	1.4 (0.9 - 2.0)	Model 1 covariates + systolic blood pressure and use of antihypertensive treatment

Supplemental table 3. Characteristics of the included studies with regard to study design and data analyses.

	Bertuzzi 2003	Brown 2002	Castro-Beiras 1993	Choi 2009	Ciruzzi 1997	Colditz 1986	Colditz 1991	Eguchi 2012	Friedlander 2001	Jousilahti 1996	Jousilahti 1997	Kiely 1993	Kinra 2003	Liao 1997	Lloyd-Jones 2004	Macclellan 2006	Nielsen 2013	Nilsson 2004	Roncaglioni 1992	Schildkraut 1989	Seshadri 2010	Sesso 2001	Siegerink 2012	Sundquist 2006	van Dis 2011	Wannamethee 1996
Type of study																										
Case control	×		×	×	×				×							×			×				×			
Cohort						×	×	×		×	×	×	×		×		×	×		×	×	×		×	×	×
Questionnaire		×												×												
Results presented for																										
Men and women combined	×	×	×	×	×			×				×		×			×		×	×	×				×	
Men	×				×		×	×		×	×		×		×			×	×	×	×		×			×
Women	×				×	×		×	×	×	×				×	×		×	×	×	×	×	×			
Type of model																										
Logistic regression model	×	×	×	×	×		×		×					×	×				×				×			
Mantel-Haenszel procedure																			×							
Cox regression model						×		×		×	×	×	×					×		×	×	×			×	×
Poisson regression model																	×							×		
Generalized Estimating Equations model																×										
Effect measure																										
Odds ratio	×	×	×	×	×				×					×	×	×			×				×			
Hazard ratio								×					×								×				×	
Rate ratio																	×									
Standardized Incidence Ratio																								×		
Relative risk						×	×					×								×		×				×
Risk ratio										×	×							×								
Included confounders																										
Crude		×										×	×	×	×					×						
Age						×	×	×	×	×	×		×		×	×		×	×			×	×	×		
Age + sex		×	×	×	×							×		×			×				×				×	
Age + sex + lifestyle factors								×							×							×			×	
Age + sex + traditional risk factors															×											
Age + sex + lifestyle factors + traditional risk factors	×	×		×	×		×	×	×	×	×	×	×	×	×			×	×	×	×				×	×
Total number of confounders included in full model	12	9	3	8	10	1	11	9	20	9	7	8	7	9	7	5	8	7	9	10	9	7	3	3	9	10

Adjustment for lifestyle factors if results were adjusted for one or more of the following factors: smoking, alcohol use, physical activity, body mass index, social class, education. Adjustment for traditional risk factors if results were adjusted for one or more of the following factors: blood pressure, antihypertensive therapy, diabetes mellitus, cholesterol levels or use of statins.

Supplemental table 4. Newcastle-Ottawa scale per study.

Cohort studies	Selection				Comparability		Outcome			Total quality score
	Representativeness of exposed cohort	*Selection of non-exposed cohort*	*Ascertainment of exposure*	*Outcome absent at start of study*	*Adjustment for age*	*Adjustment for lifestyle & traditional risk factors*	*Outcome assessment*	*Follow-up length*	*Loss to follow-up rate*	
Colditz 1986	0	1	0	1	1	0	1	0	1	5
Colditz 1991	0	1	0	1	1	1	1	0	1	6
Eguchi 2012	1	1	0	1	1	1	1	1	1	8
Jousilahti 1996	1	1	0	1	1	1	1	1	1	8
Jouisilahti 1997	1	1	0	1	1	1	1	1	1	8
Kiely 1993	1	1	1	1	1	1	1	1	0	8
Kinra 2003	0	1	1	1	1	1	1	1	0	7
Lloyd-Jones 2004	1	1	1	1	1	1	1	1	0	8
Nielsen 2013	1	0	1	0	1	0	1	1	1	6
Nilsson 2014	1	1	1	0	1	1	1	1	0	7
Schildkraut 1989	1	1	1	1	1	1	1	1	0	8
Seshadri 2010	1	1	1	1	1	1	1	1	1	9
Sesso 2001	0	1	0	1	1	0	1	1	1	6
Sundquist 2006	1	1	1	0	0	0	1	1	1	6
van Dis 2011	1	1	0	1	1	1	1	1	1	8
Wannemethee 1996	1	1	1	1	1	1	1	1	1	9
Case-control studies	**Selection**				**Comparability**		**Exposure**			**Total quality score**
	Case definition adequate	*Representativeness of the cases*	*Selection of controls*	*Definition of controls*	*Adjustment for age*	*Adjustment for lifestyle & traditional risk factors*	*Ascertainment of exposure*	*Uniform method of ascertainment*	*Non-response rate*	
Bertuzzi 2013	0	1	0	1	1	1	0	1	1	6
Castro-Beiras 1993	1	0	0	1	1	0	1	1	0	5
Choi 2009.	1	3	0	1	1	1	0	1	0	6
Ciruzzi 1997	1	1	0	1	1	1	0	1	1	7
Friedlander 2001	1	1	1	0	1	1	0	1	1	7
MacClellan 2006	1	1	1	0	1	1	0	1	0	6
Roncaglioni 1992	0	1	0	1	1	1	0	1	0	5
Siegerink 2012	1	1	1	1	1	0	0	1	0	6
Cross-sectional studies	**Selection**				**Comparability**		**Outcome**			**Total quality score**
	Representativeness of sample	*Sample size*	*Non-respondents*	*Ascertainment of exposure**	*Adjustment for age*	*Adjustment for lifestyle & traditional risk factors*	*Outcome assessment**	*Appropiate use of statistical tests*		
Brown 2002	1	1	0	1	1	1	1	1		7
Liao 1997	1	1	0	1	1	1	1	1		7

The quality of the included studies was assessed using the Newcastle-Ottawa scale. Studies can be awarded one point per item unless stated otherwise (*). As different items are important for cohort studies, case-control studies and cross-sectional studies, adapted Ottawa-Newcastle scales were used for the different type of studies. The term exposure refers to parental history of cardiovascular disease. A point for ascertainment of exposure was given if secure records or structured interviews were used to assess the parental history of cardiovascular disease. If studies used only a written self-report of the participants or if no description of the ascertainment was given, no point was received.

A point for adjustment of age was given if the results of the study were adjusted for age. Studies using age categories based on >5 years received no point. For case-control studies the difference in age between the case patients and control patients should not exceed >5 years. Regarding lost to follow-up, the lost to follow-up should not exceed >5% or there should be a clear statement that the lost to follow-up was independent of exposure. * Optimal ascertainment is indicated by a score of 2 points.

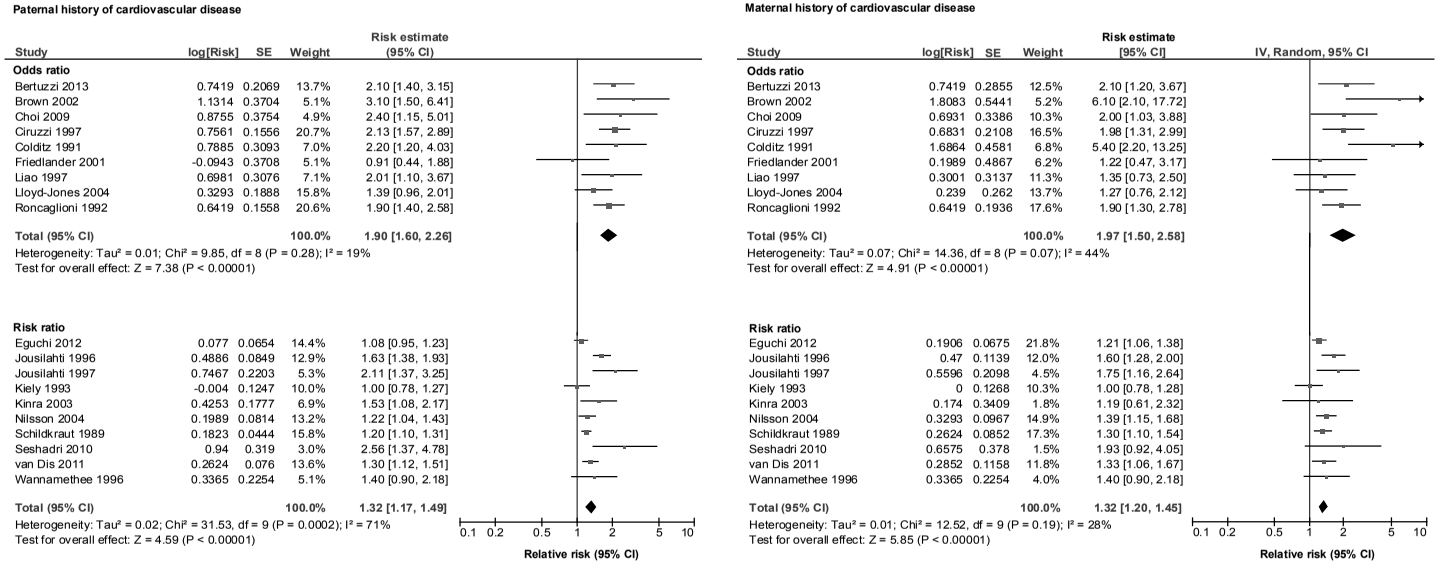
Supplemental table 5. Definitions for parental history of cardiovascular disease and cardiovascular events.

Study	Definition parental history	Definition cardiovascular disease
Bertuzzi 2013	Ischemic heart disease assessed by interview	First episode of nonfatal acute myocardial infarction (ICD-9, 410)
Brown 2002	Early-onset myocardial infarction (<50 years) assessed by questionnaire	Myocardial infarction <65 years assessed by questionnaire
Castro-Beiras 1993	Coronary heart disease; positive when two cardiologist, blind to the condition of the cases or control, labelled a parent as having definite or probable heart disease	Angina pectoris or acute myocardial infarction based on clinical, enzymatic and electrocardiographic criteria. Angina diagnosed when patient presented typical chest pain and at least one of the following three criteria: a) documented ECG evidence of transient ischaemic during pain, b) positive treadmill test; c) angiographic evidence of a narrowing of at least 50% in at least one coronary artery.
Choi 2009	Stroke defined as episode of abrupt speech difficulty, motor or sensory deficit of more than 24 hours assessed by questionnaire	Acute stroke based on neurological examinations, cranial CT or MRI
Ciruzzi 1997	Coronary artery disease, including acute myocardial infarction assessed by questionnaire	First episode of acute myocardial infarction (ICD-9, 410)
Colditz 1986	Myocardial infarction <60 years assessed by questionnaire	Nonfatal myocardial infarction. If reported on follow-up questionnaire, medical records were reviewed by physicians without knowledge of exposure. Myocardial infarctions were classified if they met the criteria of WHO.
Colditz 1991	Myocardial infarction <50 years and <70 years assessed by questionnaire	Fatal and nonfatal myocardial infarction. MI classified according to WHO through medical records. Death considered due to MI if confirmed by hospital records or autopsy
Eguchi 2012	Stroke assessed by questionnaire	Stroke mortality (ICD-10, 160-169). Reviewing death certificates.
Friedlander 2001	Myocardial infarction assessed by questionnaire	First nonfatal or fatal myocardial infarction identified through the review of hospital discharge diagnoses, incident reports from emergency medical service systems and death certificates. Criteria MI defined by evidence of symptoms, elevated enzymes and electrocardiographic changes.
Jousilahti 1996	(Non)fatal or angina pectoris <60 years assessed by questionnaire	Coronary mortality (ICD-9, 410-414) obtained from the Central Statistical Office of Finland. Data on nonfatal acute myocardial infarction received from National Hospital Discharge Register (ICD-9, 410-411)
Jousilahti 1997	(Non)fatal stroke <60 years assessed by questionnaire	Mortality data obtained from Central Statistical Office of Finland. Data on nonfatal stroke events received from National Hospital Discharge register. Incident case of stroke, defined as either the first nonfatal cerebrovascular event or stroke death without a history of nonfatal attack.
Kiely 1993	Death due to stroke reported by the subjects and updated biannaually	Stroke defined as the first occurence of atherothrombotic brain infarction, cerebral embolism, subarachnoid hemorrhage, intracerebral hemorrhage, or other type.
Kinra 2003	Angina or (non)fatal myocardial infarction reported by participant	Death from coronary heart disease determined from death certificates (ICD-9, 410-414; ICD-10, 120-125)
Liao 1997	Stroke assessed by questionnaire	History of stroke assessed by questionnaire
Lloyd-Jones 2004	Cardiovascular events; coronary death, myocardial infarction, coronary insufficiency, angina pectoris, atherothrombotic stroke, intermittent claudication, or cardiovascular death assessed by follow-up evaluations. Premature if validated parental event occurred prior to an offspring baseline examination and <55 years in father or <65 years in a mother	Cardiovascular events defined as the occurence of coronary death, myocardial infarction, coronary insufficiency, angina pectoris, atherothrombotic stroke, intermittent claudication, or cardiovascular death assessed by follow-up evaluations
MacClellan 2006	Stroke assessed by standardized interview	Clinical diagnosis of first non-traumatic ischemic stroke, identified by discharge surveillance and through direct referral by regional neurologist
Nielsen 2013	Myocardial infarction identified through the Danish National Patient registry defined as first-time diagnosis of myocardial infarction (ICD-10, 121-122 and ICD-8, 410). Different categories used; parental history at any age, <50 years and >50 years	Myocardial infarction identified through the Danish National Patient registry (fatal or nonfatal)
Nilsson 2004	Cardiovascular disease mortality before age 75 years determined via register linkage analysis	Cardiovascular disease events (morbidity and mortality) collected from national registers
Roncaglioni 1992	Myocardial infarction assessed by asking offspring by interviewer	Patiens under 75 years of age with their first confirmed acute myocardial infarction admitted to coronary care units
Schildkraut 1989	Death due to coronary heart disease <65 years assessed by interview	Coronary artery disease defined as the first occurence of angina pectoris, coronary insufficiency, myocardial infarction or death due to coronary artery disease
Seshadri 2010	Verified clinical stroke by 65 years of age	Stroke defined as an acute-onset focal neurological deficit of presumed vascular origin persisting for >24hours. All events were adjudicated by a panel of 2 neurologists
Sesso 2001	Myocardial infarction assessed by questionnaire	Cardiovascular events consisting of myocardial infarction, CABG, PTCA, stroke or cardiovascular death assessed by questionnaire and reviewing of medical records
Siegerink 2012	Myocardial infarction or stroke <60 years assessed by questionnaire	Myocardial infarction and ischemic stroke
Sundquist 2006	Non(fatal) coronary heart disease (ICD-9, 410-414; ICD-10, 120-125) conducted via the Multigeneration Register. No age limit and CHD <55 years in fathers and <65 years in mothers	(Non)fatal coronary heart disease (ICD-9, 410-414; ICD-10, 120-125) conducted via the Multigeneration Register
van Dis 2011	Myocardial infarction assessed by questionnaire. No age limit and <60 years	(Non)fatal cardiovascular events defined as CHD, PAD, stroke, heart failure and hypertensive IHD obtained by National Hospital Discharge Register and Statistics Netherlands
Wannamethee 1996	Death due stroke asked at screening	(Non)fatal stroke. Nonfatal were those that produced a neurological deficit than 24 hours. Evidence from GP, semiannual reviews and medical records

Supplemental table 6. Definitions parental history and age limits used per study.

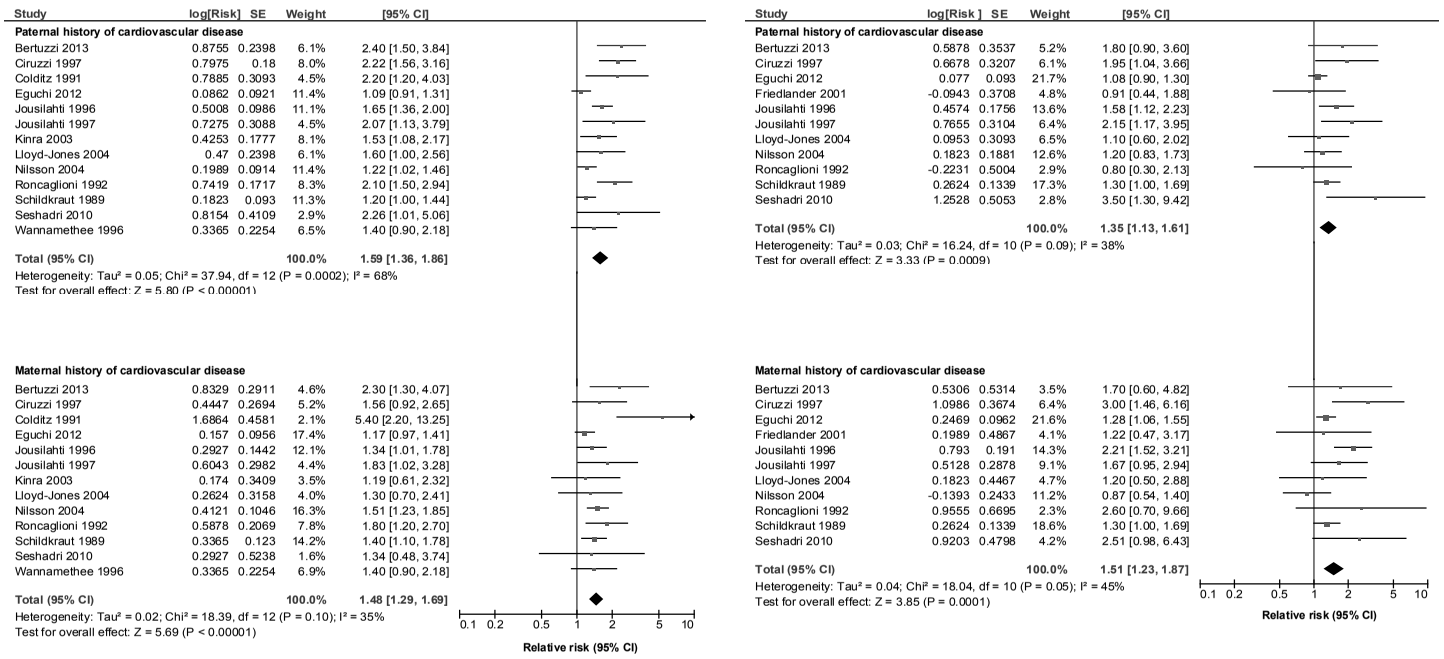
	Bertuzzi 2003	Brown 2002	Castro-Beiras 1993	Choi 2009	Ciruzzi 1997	Coldiz 1986	Coldiz 1991	Eguchi 2012	Friedlander 2001	Jousilahti 1996	Jousilahti 1997	Kiely 1993	Kim 2004	Kinra 2003	Liao 1997	Lloyd-Jones 2004	Maclellan 2006	Nielsen 2013	Nilsson 2004	Roncaglioni 1992	Schildkraut 1989	Seshadri 2010	Sesso 2001	Siegerink 2012	Sundquist 2006	van Dis 2011	Wannamethee 1996
Definition parental history	×	×	×		×	×	×		×	×				×				×		×	×		×	×	×	×	×
Coronary artery disease				×				×			×	×	×		×		×										
Cerebrovascular disease																×			×								
Composite of coronary artery disease & cerebrovascular disease																											
Age limits paternal history	×		×	×	×			×	×			×	×	×	×	×	×	×		×			×		×	×	×
No age limit																			×								
< 75 years							×																				
< 70 years																						×					
< 65 years						×																					
< 60 years							×			×	×													×			
< 55 years																×									×		
< 50 years		×					×											×					×			×	×
Age limits maternal history	×		×	×	×			×	×			×	×	×	×	×	×	×		×			×		×	×	×
No age limit																			×								
< 75 years							×																				
< 70 years						×																×					
< 65 years																											
< 60 years							×			×	×													×			
< 55 years																×									×		
< 50 years		×					×											×					×			×	×

Supplemental figure 1. Paternal and maternal history of cardiovascular disease and risk of cardiovascular events in offspring.



Results are adjusted for sex, age, lifestyle and traditional risk factors.

Supplemental figure 2. Paternal and maternal history of cardiovascular disease and risk of cardiovascular events in offspring stratified for sex.



Results are adjusted for sex, age, lifestyle and traditional risk factors.

4

Sibling history of cardiovascular disease is a risk factor for subsequent vascular events dependent on traditional risk factor presence in patients with vascular disease

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Submitted

ABSTRACT

Background

A positive sibling history of cardiovascular disease may be related to subsequent vascular events in patients with established vascular disease. The underlying mechanism for this potential increased vascular risk may be shared genetic or traditional and behavioral risk factors leading to increased cardiovascular risk which may be modified by the level of risk factor control.

Methods

In a cohort of 4,662 patients with symptomatic vascular disease enrolled in the SMART study, the relation between a positive sibling history of cardiovascular disease (≥1 sibling with vascular disease <60 years) and subsequent events (myocardial infarction (MI), stroke, interventions for PAD) and (vascular) mortality was determined by Cox-proportional hazard analyses. Effect modification by presence of ≤1 versus ≥2 traditional cardiovascular risk factors despite treatment (hypertension, smoking, low physical activity, elevated LDL-cholesterol and overweight or obesity) was examined.

Results

During a median follow-up of 5.3 years (interquartile range 2.9-7.8), the composite outcome of MI, stroke or vascular mortality occurred in 434 patients. In patients with ≥2 risk factors (n=3,277) no relation between positive sibling history (n=809) and subsequent events and mortality was observed, as opposed to patients with ≤1 risk factor (n=1,385) where a positive sibling history (n=328) was related to an increased risk of vascular mortality (HR 2.6, 95%CI 1.2 – 5.4) (p-interaction = 0.01), MI (HR1.9, 95%CI 1.0 – 3.7) (p-interaction = 0.29), composite outcome (HR 1.6, 95%CI 1.0 – 2.6) (p-interaction = 0.12), all-cause mortality (HR 1.6, 95%CI 1.0 – 2.6) (p-interaction = 0.05) and PAD (HR 1.8, 95%CI 1.0 – 3.3) (p-interaction = 0.03), but not to stroke (HR 0.9, 95%CI 0.4 – 2.3) (p-interaction = 0.90).

Conclusions

In patients with established vascular disease and ≤1 traditional risk factor, a positive sibling history of cardiovascular disease was a risk factor for the development of subsequent vascular events. No increased risk due to a positive sibling history was observed in patients with uncontrolled cardiovascular risk factors.

INTRODUCTION

A positive family history of cardiovascular disease is considered a strong risk factor for the occurrence of symptomatic cardiovascular disease[1-8]. This clustering of cardiovascular disease in families was aptly demonstrated in 122,155 families where the 14% of the families having a positive family history of coronary heart disease (CHD) remarkably accounted for >72% of the persons developing early CHD. A family history of stroke was prevalent in 11% of the families, accounting for 86% of the early stroke cases[9]. However, in patients with already clinically manifest vascular disease we could not demonstrate a relation between a positive parental history of cardiovascular disease and recurrent cardiovascular events (HR 1.0, 95%CI 0.8 – 1.3)[10]. Notwithstanding, a positive sibling history of cardiovascular disease for subsequent events could be of importance as siblings share more environmental factors than parents and offspring[11], and previous studies describe an up to two times higher relative risk for sibling history compared with parental history[1-3, 12]. Furthermore it was demonstrated that the risk of cardiovascular disease increases with the number of siblings with cardiovascular disease (≥2 affected siblings incidence ratio 6.6 – 8.2)[5] and also depends on the location of vascular disease in siblings[3].

The increased cardiovascular risk aggregating in families can be explained by shared environmental and genetic factors and their interplay[13]. These shared factors may lead to the development of traditional risk factors such as hypertension, overweight and increased serum LDL-cholesterol levels and subsequently to increased cardiovascular risk. But independent of these traditional risk factors, shared genetic factors associated with cardiovascular disease by other pathophysiologic pathways (e.g. left ventricular wall thickness) or still unknown mechanisms may also play a role. Therefore, patients with vascular disease with multiple traditional risk factors despite treatment could have a genetic predisposition for traditional risk factors and their risk of subsequent vascular events may be determined by the presence of (uncontrolled) risk factors. In patients with established vascular disease with no or just one risk traditional risk factor (e.g. hypertension or overweight), a positive sibling history could indicate a genetic predisposition for other pathophysiologic pathways with a potential different associated cardiovascular risk.

The aim of the present study is to determine in patients with symptomatic vascular disease whether a positive sibling history of cardiovascular disease is related to the development of subsequent cardiovascular events dependent on the presence or absence of traditional cardiovascular risk factors.

METHODS

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. The rationale and design of the SMART study have been described previously[14]. In short, the SMART study is an ongoing single-center prospective cohort study designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular disease or a vascular risk factor. The Ethics Committee of the University Medical Centre Utrecht approved the study and all participants gave their written informed consent.

For this study, data were used from 5,023 patients who were newly referred to the University Medical Center between 2001 and 2013 with a history of clinically manifest vascular disease (i.e. coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) or abdominal aortic aneurysm (AAA)). Patients without siblings (n=351) and patients without information regarding siblings (n=10) were excluded, resulting in 4,662 patients. CAD was defined as myocardial infarction, angina pectoris or coronary revascularization (coronary bypass surgery or coronary angioplasty). Patients with CVD had experienced a transient ischemic attack, cerebral infarction, cerebral ischemia, amaurosis fugax, symptomatic carotid artery stenosis, retinal infarction or a history of carotid surgery. PAD was defined as a symptomatic and documented obstruction of distal arteries of the leg or interventions (Fontaine classification II-IV confirmed with ankle brachial index (ABI) ≤0.90 in rest or decrease of ABI >20% after exercise, percutaneous transluminal angioplasty, bypass or amputation). Patients with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter ≥3 cm, measured with ultrasonography) or a history of AAA surgery. Patients with a terminal malignancy were not included, as well as those not independent in daily activities or not sufficiently fluent in Dutch language.

Baseline examinations

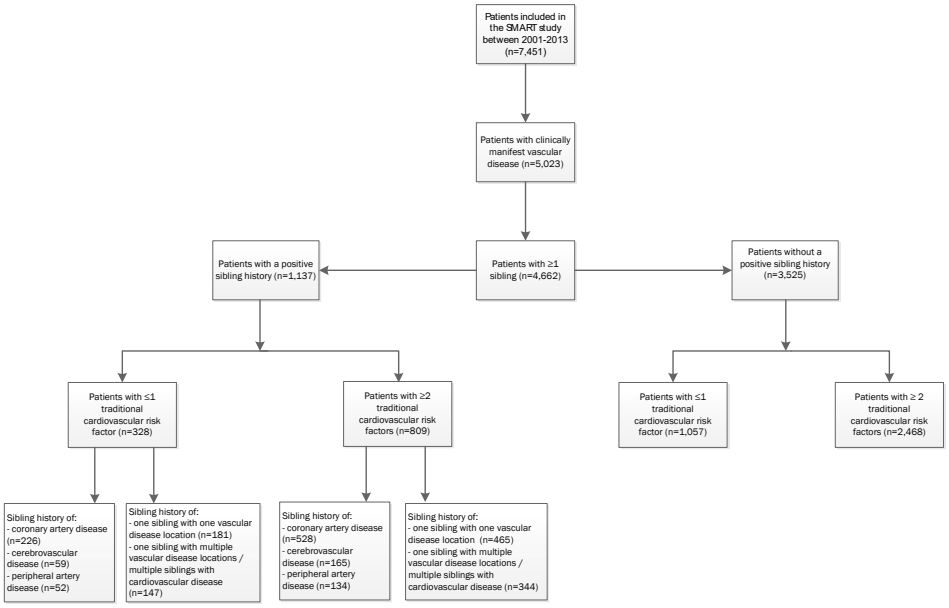
All patients underwent a standardized extensive vascular screening including a uniform questionnaire on medical history, symptoms of cardiovascular disease and presence of traditional cardiovascular risk factors, physical examination (height, weight, waist circumference, systolic and diastolic blood pressure) and laboratory tests to determine fasting serum lipid, glucose and creatinine levels. In addition, patients were screened non-invasively for presence of asymptomatic atherosclerotic diseases other than the qualifying diagnosis, by measuring the ABI at rest, ultrasonography of the abdominal aorta and duplex ultrasound of the common and internal carotid arteries. Body mass index (BMI) was calculated as weight divided by height squared. Waist circumference was measured halfway between the lower rib and iliac crest.

Sibling history of cardiovascular disease

The questionnaire inquired for sibling history of myocardial infarction, coronary artery stenosis, stroke, AAA, peripheral artery stenosis and death due to cardiovascular cause. A positive sibling history of cardiovascular disease was defined as having at least one sibling with cardiovascular disease occurring before the age of sixty (n=1,137).

Subsequently patients were categorized according to number of siblings with cardiovascular disease. Patients were divided into three categories: no sibling history of cardiovascular disease (reference), patients with a positive sibling history of one sibling with one vascular disease location (e.g. only CAD), and patients with a positive sibling history of one sibling with multiple vascular disease locations (e.g. CVD and CAD) or of multiple siblings with cardiovascular disease (figure 1). In addition, separate positive sibling histories dependent on vascular disease location were determined: a positive sibling history of CAD (myocardial infarction and coronary artery stenosis), of CVD and of PAD.

Figure 1. Flowchart study population.



Presence of traditional cardiovascular risk factors

To determine whether the relation between sibling history of cardiovascular disease and subsequent vascular events is modified by the presence of traditional risk factors, patients were divided according to the number of these traditional risk factors based on the treatment targets according to the AHA/ACCF guideline[15]. The following risk factors were scored at baseline: current smoking (n=1,375; 29%), systolic blood pressure >140 mmHg or diastolic

blood pressure >90 mmHg (n=2,266; 49%), LDL-cholesterol >2.5 mmol/l (n=2,337; 50%), physical activity less than 30 minutes, 7 days per week (minimum of 5 days a week) (n=486; 10%) and body mass index <18.5 kg/m^2 or >25 kg/m^2 (n=3,173; 68%).
Of the patients, 1,385 had ≤1 traditional risk factor and 3,277 had ≥2 traditional risk factors. In patients with elevated blood pressure and elevated LDL-cholesterol levels, no difference in use of antihypertensive and lipid-lowering agents was observed for patients with ≤1 and ≥2 traditional risk factors (supplemental table 1).
The presence of ≥2 traditional risk factors was similar in the patients with (n=809 (71%)) and without (n=2,468 (70%)) a positive sibling history.

Follow-up

During follow-up, patients were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. When a vascular event was suspected, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the treating specialist. All possible events were independently evalu
ated by three members of the endpoint committee, comprising physicians from different departments. Study outcomes included myocardial infarction, stroke (ischemic and hemorrhagic), vascular mortality, composite vascular outcome (composite of the previous mentioned outcomes), all-cause mortality and peripheral artery disease (amputation, operation, PTA or stenting of leg or iliac artery). The definitions of the several events are shown in table 1.
Follow-up duration (years) was defined as the period between study inclusion and first cardiovascular event or death from any cause, date of loss to follow-up or the preselected date of 1 March 2013. In total, 182 of the 4,662 participants (4%) were lost to follow-up due to migration or withdrawal from the study.

Data analyses

Data are presented as percentages for categorical variables, as mean with standard deviation (SD) for normally distributed variables and as median with interquartile range [IR] for non-normally distributed variables. To reduce bias and increase statistical rigour, missing data (<3.0%) were singly imputed using predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming these values were missing at random[16].
Cox proportional hazards model analysis was used to estimate the effect of having a positive sibling history of cardiovascular disease on the risk of subsequent vascular events and mortality. Results were expressed as HR and 95%CI. Patients with both myocardial infarction and stroke during follow-up contributed to both the myocardial infarction and stroke analyses, but with follow-up time matching the respective outcomes. If patients had multiple events of the same type, the first recorded event was used in the analyses. Adjustments were performed for age, sex and total numbers of siblings. Interaction on a multiplicative scale was assessed by

Table 1. Study outcomes.

Outcome events	Definition
Myocardial infarction	At least two of the following criteria (I) Chest pain for at least 20 minutes, not disappearing after administration of nitrates (II) ST-elevation > 1 mm in two following leads or a left bundle branch block on the electrocardiogram (III) Troponin elevation above clinical cut-off values or creatinine kinase (CK) elevation of at least two times the normal value of CK and a myocardial band-fraction > 5% of the total CK. Sudden death: unexpected cardiac death occurring within one hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
Stroke	Relevant clinical features for at least 24 hours causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *infarction* on CT or MRI Relevant clinical features for at least 24 hours causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *hemorrhage* on CT or MRI Relevant clinical features for at least 24 hours causing an increase in impairment of at least one grade on the modified Ranking scale, *without a new (hemorrhage) cerebral infarction* on CT or MRI Cerebral hemorrhage demonstrated with CT, MRI or operation
Vascular mortality	Death from stroke, myocardial infarction, congestive heart failure, rupture of abdominal aortic aneurysm and vascular death of other causes
Composite vascular outcome	Composite of myocardial infarction, stroke, retinal infarction, congestive heart failure, sudden death and vascular mortality
All-cause mortality	Death from any cause
Peripheral artery disease	Amputation of toe, foot, below the knee, above the knee Operation of leg or iliac artery Percutaneous transluminal angioplasty or stenting of leg or iliac artery

CK: creatinine kinase, CT: computed tomography, MRI: magnetic resonance imaging

adding a product term between sibling history of cardiovascular disease and presence of ≤1 traditional risk factor or ≥2 traditional risk factors with p-value <0.05 considered significant. Because of low number of patients having ≤1 traditional risk factor with a positive sibling history, we determined only in patients with ≥2 traditional risk factors whether the number of siblings with cardiovascular disease and the vascular disease location was relevant for the risk of subsequent events. First, patients were divided into three groups: patients with no sibling history of cardiovascular disease (reference group), patients with a sibling history of one sibling with one vascular disease location, and patients with a positive sibling history of one sibling with multiple vascular disease locations or of multiple siblings with cardiovascular disease. Second, the relation between different positive sibling histories of CAD, CVD and PAD with subsequent vascular events and mortality was assessed, with no positive history of

cardiovascular disease as reference category. Two models were constructed. The first model included age and sex, the second model included additionally total number of siblings, smoking (pack years), body mass index, systolic blood pressure, physical activity, diabetes mellitus type 2, hypercholesterolemia, lipid-lowering medication, antihypertensive medication and antiplatelets agents.

The proportional hazards assumptions were formally tested with the Schoenfeld test. No significant non-proportionality ($p<0.05$) was observed. Analyses were performed in R version 3.1.1.

RESULTS

Baseline characteristics

A total of 4,662 patients with vascular disease was included with a mean age of 60±10, of whom 3,389 (73%) were male. Patients with a positive sibling history of cardiovascular disease had coronary artery disease more often compared with patients without a positive sibling history (79% versus 68% in patients with ≤1 traditional risk factor and 68% versus 59% in patients with ≥2 traditional risk factors). In patients with a positive sibling history the use of blood pressure and lipid-lowering agents was slightly more frequent compared with patients without a sibling history, although no differences in LDL cholesterol levels and systolic blood pressure were observed (table 2).

Follow-up

During a median follow-up of 5.3 years (interquartile range 2.9 – 7.8), 410 patients died, of whom 199 due to a vascular cause. Myocardial infarction occurred in 246 patients, stroke in 122 patients and interventions for PAD in 321 patients. The composite vascular outcome of myocardial infarction, stroke and vascular mortality occurred in 434 patients (event rate 1.8% per year). In patients with ≤1 traditional risk factor the composite vascular outcome occurred in 82 patients (event rate 1.2% per year) and in patients with ≥2 traditional risk factors in 352 patients (event rate 2.0% per year).

Relation between positive sibling history of cardiovascular disease and risk of subsequent vascular events and mortality

In patients with ≤1 traditional risk factor, a positive sibling history was related to a higher risk of vascular mortality (HR 2.6, 95%CI 1.2 – 5.4) (p=0.01 for interaction), myocardial infarction (HR 1.9, 95%CI 1.0 – 3.7) (p=0.29 for interaction), the composite vascular outcome (HR 1.6, 95%CI 1.0 – 2.6) (p=0.12 for interaction), all-cause mortality (HR 1.6, 95%CI 1.0 – 2.6) (p=0.05 for interaction) and PAD (HR 1.8, 95%CI 1.0 – 3.3) (p=0.03 for interaction). No increased risk was observed for stroke (HR 0.9 , 95%CI 0.4 – 2.3) (p=0.90 for interaction)

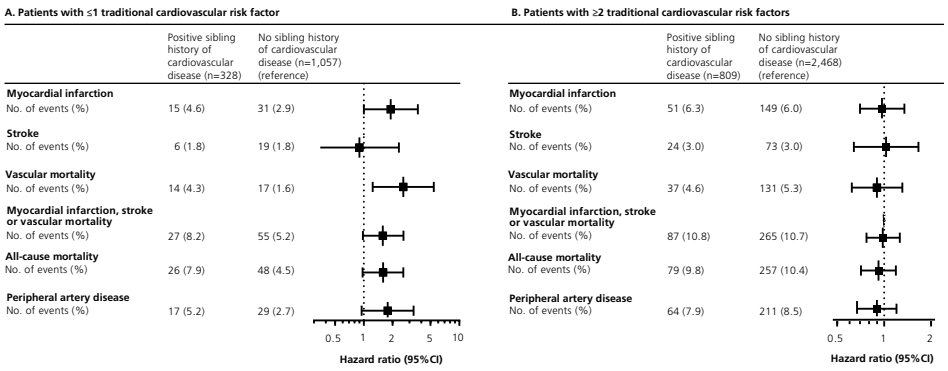
Table 2. Baseline characteristics according to presence of a positive sibling history of cardiovascular disease stratified for patients with ≤1 traditional cardiovascular risk factor and patients with ≥2 traditional risk factors.

	Positive sibling history of cardiovascular disease (n=1,137)		No positive sibling history of cardiovascular disease (n=3,525)	
	≤1 traditional risk factor (n=328)	≥2 traditional risk factors (n=809)	≤1 traditional risk factor (n=1,057)	≥2 traditional risk factors (n=2,468)
Age (years)	62 (8)	61 (9)	60 (10)	59 (11)
Male sex (%)	240 (73)	558 (69)	769 (73)	1,822 (74)
Location of vascular disease*				
Coronary artery disease (%)	258 (79)	549 (68)	719 (68)	1,443 (59)
Cerebrovascular disease (%)	72 (22)	205 (25)	321 (30)	746 (30)
Peripheral artery disease (%)	23 (7)	139 (17)	92 (9)	461 (19)
Abdominal aortic aneurysm (%)	19 (6)	54 (7)	54 (5)	189 (8)
Diabetes Mellitus type 2	52 (16)	164 (20)	151 (14)	422 (17)
Current smoking (%)	19 (6)	303 (37)	88 (8)	967 (39)
Blood pressure-lowering agents (%)	278 (85)	644 (80)	814 (77)	1,828 (74)
Lipid-lowering agents (%)	288 (88)	737 (79)	893 (84)	1,757 (71)
Antiplatelets agents (%)	287 (88)	639 (79)	880 (83)	1,914 (78)
Systolic blood pressure (mmHg)	130 (15)	144 (20)	129 (16)	144 (21)
Diastolic blood pressure (mmHg)	77 (9)	84 (11)	77 (9)	84 (12)
Body mass index (kg/m^2)	25.3 (3.5)	27.8 (4.1)	25.4 (3.6)	27.7 (4.0)
Waist circumference (cm)	91 (12)	97 (12)	91 (12)	98 (12)
Total cholesterol (mmol/l)	4.0 (0.9)	4.8 (1.1)	4.0 (0.9)	4.8 (1.1)
Triglycerides (mmol/l)	1.1 [0.9 - 1.5]	1.4 [1.0 - 1.9]	1.1 [0.8 - 1.5]	1.4 [1.0 - 2.0]
HDL-cholesterol (mmol/l)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.4)
LDL-cholesterol (mmol/l)	2.2 (0.8)	2.8 (0.9)	2.2 (0.7)	2.8 (1.0)

Data are expressed as mean (SD), median [interquartile range] or number (percentage); * not mutually exclusive, patients can have multiple locations of vascular disease. Traditional risk factors defined as current smoking, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, LDL-cholesterol >2.5 mmol/l, physical activity less than 30 minutes, 7 days per week (minimum of 5 days a week) and body mass index <18.5 kg/m^2 or >25 kg/m^2.

(figure 2).

Figure 2. Relation between sibling history of cardiovascular disease and subsequent vascular events and mortality stratified for patients with ≤1 traditional cardiovascular risk factor and patients with ≥2 traditional cardiovascular risk factors.



Results are expressed as hazard ratios with 95% confidence intervals. Data are n (%). Results are adjusted for age, sex and number of siblings.

In patients with ≥2 traditional risk factors, there was no relation between a positive sibling history of cardiovascular disease and subsequent vascular events or mortality.

Furthermore, in patients with ≥2 traditional risk factors, having a positive sibling history of a sibling with cardiovascular disease at one vascular location did not increase the risk of subsequent vascular events (composite vascular outcome HR 1.1, 95%CI 0.8 – 1.5) and all-cause mortality (HR 1.0, 95%CI 0.7 – 1.4) compared with patients without a positive sibling history of cardiovascular disease (figure 3).

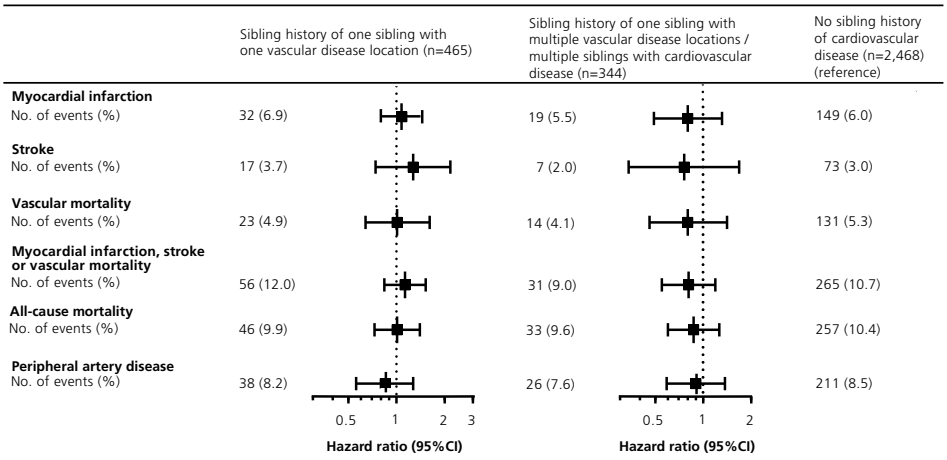
Also no increased risk of subsequent vascular events (HR 0.8, 95%CI 0.6 – 1.2) and all-cause mortality (HR 0.9, 95%CI 0.6 – 1.3) was observed in patients with a positive sibling history of a sibling with cardiovascular disease at multiple vascular locations or of multiple siblings with cardiovascular disease.

The vascular disease location of the siblings, demonstrated no relation between a positive sibling history of CAD (HR varying between 0.9 – 1.1), positive sibling history of CVD (HR varying between 0.4 – 1.3), and a positive sibling history of PAD (HR varying between 0.5 – 1.3) and subsequent vascular events and mortality compared with patients without a sibling history (figure 4). The HR estimates were similar after additional adjustment for risk factors and use of medication.

DISCUSSION

A positive sibling history of cardiovascular disease in patients with manifest vascular disease is related to a higher risk of subsequent vascular events among patients with ≤1 traditional

Figure 3. Relation between number of siblings with a history of cardiovsacular disease or number of vascular disease locations in siblings and the risk of subsequent vascular events and mortality in patients with ≥2 traditional cardiovascular risk factors.



Results are expressed as hazard ratios with 95% confidence intervals. Data are n (%). Results are adjusted for age, sex and number of siblings, , smoking (pack years), body mass index, systolic blood pressure, physical activity, diabetes mellitus type 2, hypercholesterolemia, lipid-lowering medication, anti-hypertensive medication and antiplatelets.

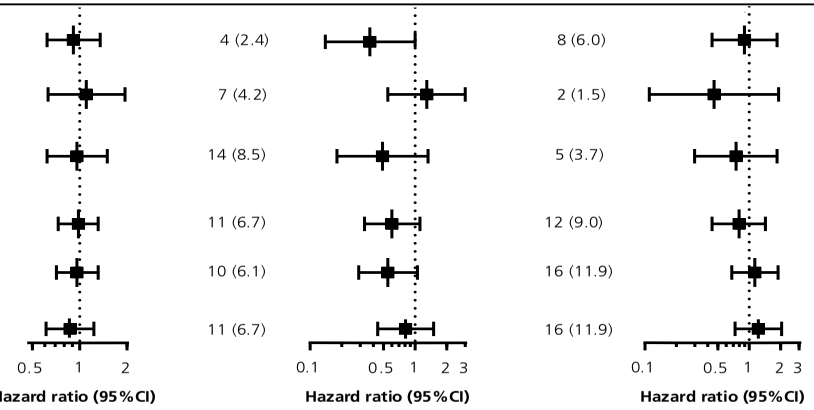
risk factor. In patients with ≥2 traditional risk factors there was no such relation, even after taking into account the number of siblings with cardiovascular disease and sibling vascular disease location.

Previous studies evaluating the relation between a positive sibling history of cardiovascular disease and development of vascular events focused on patients without prevalent vascular disease. In these studies, with in general younger patients, sibling history of vascular disease increased the risk of first vascular events[1, 2, 12]. Since relations between cardiovascular risk factors[11] and genetic effects between siblings become weaker with increasing age[17, 18], one might argue that the older age of the current study population largely neutralizes the effect of a positive sibling history. However, studies in older adults (mean age >70 years) demonstrated an increased risk of prevalent and incident coronary heart disease (HR 1.3, p<0.001)[19] and incident stroke (OR 2.5, 95%CI 1.7 – 7.4)[3] in patients with a positive sibling history. In our study there was no difference in age between patients with ≤1 and ≥2 traditional risk factors, which makes the argument of age even more unlikely.

Regarding familial aggregation of cardiovascular risk, shared genetic factors probably contribute substantially to this risk. The difference in vascular risk observed in patients with ≤1 and ≥2 traditional risk factors having a positive sibling history strengthens our hypothesis that the risk of subsequent events in patients with ≥2 traditional risk factors with a positive sibling history is caused by a genetic predisposition for developing cardiovascular risk factors. While patients with ≤1 traditional risk factor and a positive sibling history have a genetic predispo-

Figure 4. Relation between location of vascular disease in siblings and the risk of subsequent vascular events and mortality in patients with ≥2 traditional cardiovascular risk factors.

	Sibling history of coronary artery disease (n=528)	Sibling history of cerebrovascular disease (n=165)	Sibling history of peripheral artery disease (n=134)	No sibling history of cardiovascular disease (n=2,468) (reference)
Myocardial infarction No. of events (%)	33 (6.3)	4 (2.4)	8 (6.0)	149 (6.0)
Stroke No. of events (%)	16 (3.0)	7 (4.2)	2 (1.5)	73 (3.0)
Vascular mortality No. of events (%)	26 (4.9)	14 (8.5)	5 (3.7)	131 (5.3)
Myocardial infarction, stroke or vascular mortality No. of events (%)	59 (11.2)	11 (6.7)	12 (9.0)	265 (10.7)
All-cause mortality No. of events (%)	54 (10.2)	10 (6.1)	16 (11.9)	257 (10.4)
Peripheral artery disease No. of events (%)	38 (7.2)	11 (6.7)	16 (11.9)	211 (8.5)



Results are expressed as hazard ratios with 95% confidence intervals. Data are n (%). Model 1: age and sex. Model 2: model 1 with additionally number of siblings, smoking (pack years), body mass index, systolic blood pressure, physical activity, diabetes mellitus type 2, hypercholesterolemia, lipid-lowering medication, anti-hypertensive medication and anti-platelets.

sition for other different (unknown) atherosclerotic mechanisms independent of these risk factors. Since all patients have clinically manifest vascular disease, obviously patients already receive medication. Apparently, patients with >2 traditional risk factors are more difficult to treat since there were no differences in use of antihypertensive and lipid-lowering agents between patients with ≤1 and >2 traditional risk factors while there were differences in blood pressure and LDL-cholesterol levels.

Based on the results of the present study we conclude that assessment of a positive sibling history of cardiovascular disease is useful in patients with ≤1 traditional risk factor. In this group the event rate was 1.2% per year, but for patients with a positive sibling history 1.7% per year, almost comparable with patients with ≥2 traditional risk factors (event rate 2.0% per year). Therefore a positive sibling history of cardiovascular disease may help to discriminate between patients with a low or high risk of subsequent vascular events despite the absence of traditional risk factors. Apparently, management of these patients is difficult as most treatment goals with conventional therapy are already achieved. Further research for identification of important mechanisms leading to the development of cardiovascular disease and identification of important genes associated with cardiovascular disease may help to elucidate this increased risk in these patients, which may help in developing new therapeutic options.

Notable strengths of our study include its prospective design, the low lost to follow-up due to migration or discontinuation of the study which reduces the risk of bias, and the strict procedure for clinical event adjudication which reduces the chance of subjective assessment. In addition, the included patients reflect clinical practice of patients with vascular disease being treated according to national guidelines.

Limitations of our study need to be considered too. Determination of a positive sibling history of cardiovascular disease was based on self-reported questionnaires. This may have resulted in misreporting of sibling history which can lead to an underestimation of the observed effects because of non-differential misclassification. In the group of patients with ≤1 traditional risk factor the low number of events may have led to limited statistical power resulting in limited precision of HR estimates. In addition, because of the low number of events the number of confounders which could be included in the analyses was limited too. However, we are confident that the effect of potential confounding is negligible because HRs remained essentially similar after full adjustment. It would also have been interesting to determine in patients with ≤1 traditional risk factor whether the sibling vascular disease location and number of siblings with cardiovascular disease influenced the risk of subsequent vascular events. Unfortunately, because of low number of patients in these several groups of sibling history, these analyses could not be performed.

The risk factor diabetes mellitus was not included as traditional risk factor since HbA1c levels ≤7% are only important for patients with diabetes and not for the whole study population, and were therefore not available for all patients.

Although all patients in the present study have clinically manifest vascular disease, the severity

of these manifestations varies, resulting in a heterogeneous study population.

In conclusion, a positive sibling history of cardiovascular disease is related to a higher risk for the development of subsequent vascular events in patients with clinically manifest vascular disease with ≤1 traditional risk factor. For patients with vascular disease with ≥2 traditional risk factors there was no relation between a positive sibling history and subsequent vascular events.

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SUPPLEMENTARY INFORMATION

Supplemental table 1. Frequencies of traditional risk factors for patients with ≤1 traditional cardiovascular risk factor and for patients with ≥2 traditional cardiovascular risk factors.factor and patients with ≥2 traditional cardiovascular risk factors.

	≤1 traditional risk factor	≥2 traditional risk factors
	(n=1,385)	(n=3,277)
Current smoking	107 (8%)	1,270 (39%)
Physical inactivity	16 (1%)	470 (14%)
Body mass index <18.5 kg/m^2 or >25 kg/m^2	578 (42%)	2,674 (82%)
Blood pressure >140/90 mmHg	214 (15%)	2,052 (63%)
Treated with antihypertensive agents	165 (77%)	1,600 (78%)
LDL-cholesterol >2.5 mmol/l	231 (17%)	2,106 (64%)
Treated with lipid-lowering agents	148 (64%)	1,353 (64%)
0 traditional risk factor	268 (19%)	
1 traditional risk factor	1,117 (81%)	
2 traditional risk factors		1,769 (54%)
3 traditional risk factors		1,089 (33%)
4 traditional risk factors		378 (12%)
5 traditional risk factors		41 (1%)

5

The relation between the presence of cardiovascular disease and vascular risk factors in offspring and the occurrence of new vascular events in their parents already at high vascular risk

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ABSTRACT

Background

For parents at high risk for cardiovascular events, presence of cardiovascular disease or risk factors in their offspring may be an indicator of their genetic load or exposure to (unknown) risk factors, and might be related to the development of new or recurrent vascular events.

Methods

In 4,267 patients with vascular disease, hypertension, diabetes or hypercholesterolemia enrolled in the SMART cohort, the presence of cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking or overweight) and cardiovascular disease (CAD, CVD, PAD or AAA) was assessed in their 10,564 children. The relation between presence of cardiovascular disease or vascular risk factors in their offspring, and new or recurrent vascular events was determined by Cox-proportional hazard analyses.

Results

Of the patients, 506 (12%) had offspring with cardiovascular disease, hypertension, hypercholesterolemia or diabetes. Smoking in offspring was present in 1,972 patients (46%) and overweight in 845 patients (20%). During a median follow-up of 7.0 years (interquartile range 3.7 – 10.4), the composite outcome of myocardial infarction (MI), stroke or vascular mortality occurred in 251 patients. Patients with offspring with cardiovascular disease, hypertension, hypercholesterolemia or diabetes had an increased risk of vascular mortality (HR 2.9; 95%CI 1.2 – 7.1), MI (HR 1.6; 95%CI 1.1 – 2.5) and the composite outcome (HR 1.5; 95%CI 1.1 – 2.2). Diabetes in offspring was related to an increased risk of the composite outcome (HR 2.7; 95%CI 1.5 – 5.0), MI (HR 3.3; 95%CI 1.7 – 6.6) and vascular mortality (HR 3.4; 95%CI 0.8 – 14.8). Smoking and overweight in offspring were not related to increased vascular risk in parents.

Conclusions

Presence of cardiovascular disease, hypertension, hypercholesterolemia and diabetes in offspring, with diabetes mellitus being the most contributing vascular risk factor, is related to an increased risk of developing new or subsequent vascular events in patients already at high vascular risk.

INTRODUCTION

Having a parent or sibling who experienced a cardiovascular event increases the risk of developing cardiovascular disease[1-6]. A positive family history of cardiovascular disease is considered an important risk factor and is part of various risk prediction algorithms such as the Reynolds Risk score and PROCAM risk score for estimating the risk of first vascular events[7-9]. In clinical practice it is not standard to also assess the presence of cardiovascular disease in offspring of patients. Documenting presence of vascular disease in offspring may not be customary because the prevalence is likely to be low as children are often too young to have developed cardiovascular disease yet. Parental and sibling history of cardiovascular disease are already established risk factors for first vascular events, which makes it questionable whether a positive offspring history adds to this information. However, parental and sibling history of cardiovascular disease are not established risk factors in patients who already have clinical manifest vascular disease. Recently, we demonstrated in patients with clinically manifest vascular disease that parental history of cardiovascular disease is not related to an increased risk of subsequent stroke, myocardial infarction and vascular mortality[10]. Patients with a clearly elevated risk of new or recurrent vascular events are generally older and their offspring may also be older and thus at higher vascular risk themselves. One may hypothesize that having a child with clinically manifest vascular disease or with hypertension, diabetes or hypercholesterolemia, reflects a genetic base of cardiovascular disease or reflects exposure to (unknown) traditional risk factors in the patient. In addition, the smoking status and weight of the offspring can be seen as a proxy for healthy behavior earlier in life. Therefore, patients with children with cardiovascular disease or cardiovascular risk factors may be at higher risk of developing new vascular events compared with patients without affected children.

The objective of the present study is to evaluate the relation between the presence of cardiovascular disease and cardiovascular risk factors in offspring, and new or subsequent events in patients with clinically manifest vascular disease or cardiovascular risk factors.

METHODS

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. The rationale and design of the SMART study have been described previously[11]. In short, the SMART study is an ongoing single-center prospective cohort study, designed to establish the presence of additional arterial disease and risk factors for cardiovascular disease in patients with manifest vascular disease or a vascular risk factor. The Ethics Committee of the University Medical Centre Utrecht approved the study and all participants gave their written consent.

For this study data were used of patients who were newly referred to the University Medical Centre between 1996 and 2013 with a history of clinically manifest vascular disease (i.e. coronary artery disease, cerebrovascular disease, peripheral artery disease or abdominal aortic aneurysm (AAA)) or presence of a cardiovascular risk factor (diabetes mellitus type 1 or 2, hyperlipidemia or hypertension). Coronary artery disease was defined as myocardial infarction, angina pectoris or coronary revascularization (coronary bypass surgery or coronary angioplasty). Patients with cerebrovascular disease had experienced a transient ischemic attack, cerebral infarction, cerebral ischemia, amaurosis fugax, symptomatic carotid artery stenosis, retinal infarction or a history of carotid surgery. Peripheral artery disease was defined as a symptomatic and documented obstruction of distal arteries of the leg or interventions (Fontaine classification II-IV confirmed with ankle brachial index (ABI) ≤0.90 in rest or decrease of ABI >20% after exercise, percutaneous transluminal angioplasty, bypass or amputation). Patients with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter ≥3 cm, measured with ultrasonography) or a history of AAA surgery.
Diabetes mellitus was defined as fasting serum glucose ≥7.0 mmol/l, serum glucose ≥11.1 mmol/l or the use of oral anti-hyperglycemic agents or insulin. Hyperlipidemia was defined as a total cholesterol >5.0 mmol/l or low-density lipoprotein cholesterol >3.2 mmol/l or the use of lipid-lowering drugs. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or the use of blood pressure-lowering agents.
Patients with a terminal malignancy were not included, as well as those not independent in daily activities or not sufficiently fluent in Dutch language.

Baseline examinations

All patients underwent a standardized extensive vascular screening including a uniform questionnaire on medical history, education level, symptoms of cardiovascular disease and presence of cardiovascular risk factors, physical examination (height, weight, waist circumference, systolic and diastolic blood pressure) and laboratory tests to determine fasting serum lipid, glucose and creatinine levels. In addition, patients were screened non-invasively for presence of asymptomatic atherosclerotic diseases other than the qualifying diagnosis, by measuring the ABI at rest, ultrasonography of the abdominal aorta and duplex ultrasound of the common and internal carotid arteries. Body mass index (BMI) was calculated as weight divided by height squared. Waist circumference was measured halfway between the lower rib and iliac crest.

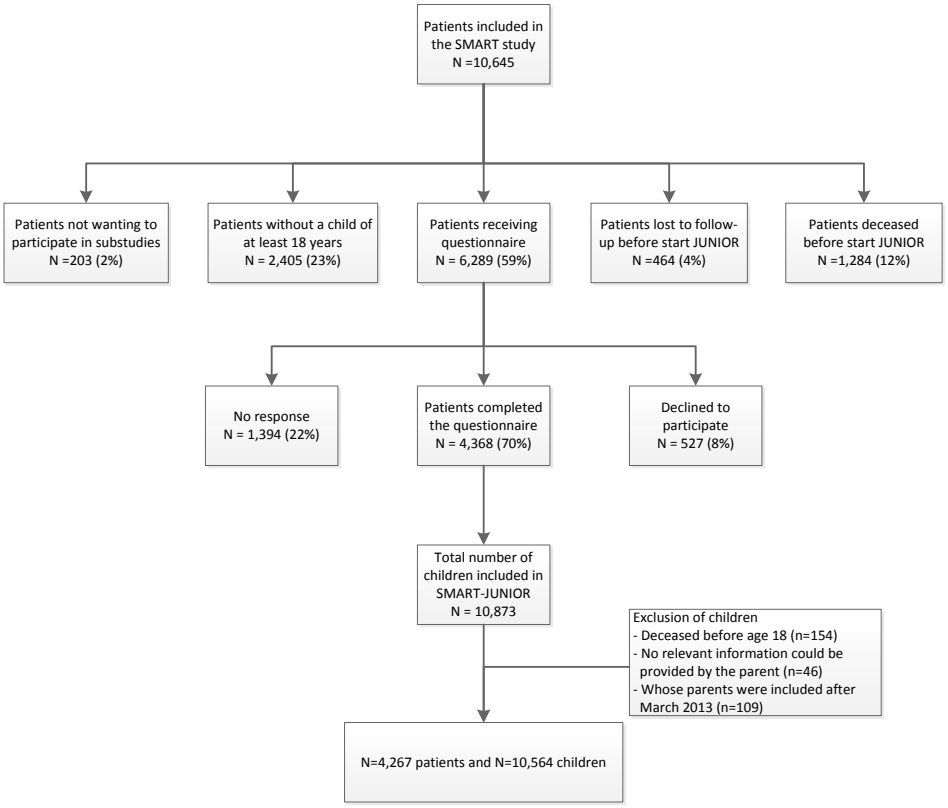
Cardiovascular disease and vascular risk factors in offspring

After a median follow-up of 6 years (interquartile range 4 – 8 years), all eligible patients included in the SMART study received a standardized questionnaire in the period 2009 -2013, inquiring about the presence of cardiovascular risk factors and cardiovascular events in their children. Cardiovascular risk factors and cardiovascular events in offspring which occurred

before the inclusion of the parent in the SMART study were considered eligible for counting. Regarding cardiovascular risk factors, information was obtained about the presence of diabetes mellitus, hypertension, hypercholesterolemia, smoking behavior and weight of the offspring. Regarding cardiovascular events, the questionnaire inquired whether offspring had experienced myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), stroke, peripheral artery disease or AAA. The questionnaire also comprised the dates of cardiovascular event occurrences and risk factor diagnoses, thus indicating whether an offspring event or diagnosis took place before the inclusion of the patient in SMART. For weight only the present weight of the offspring was available.

Of the 10,645 patients included in the SMART study, 1,284 (12%) patients had already died before the start of SMART-junior, 1,523 (14%) had no children and 882 (8%) patients did not have children of at least eighteen years (figure 1).

Figure 1. Flowchart of data collection SMART-junior.



A total of 6,289 patients (59%) were eligible to participate in the SMART-junior study. In order to maximize the response rate, a second mail was sent to non-responders. In case of incomplete questionnaires or inaccuracies, patients were contacted for further information. A total of 4,368 patients (70%) completed the questionnaire and 1,921 patients (30%) did not response or declined to participate. There were no substantial differences in characteristics between patients willing to participate and patients not willing to participate (supplemental table 1). Information of 10,873 children was obtained. Children deceased before the age of 18 were excluded (n=154), as well as those whose parents could not provide any relevant information (n=46). As mentioned, only patients included before 2013 were used in the present study, resulting in a cohort of 4,267 patients and their 10,564 children.

Follow-up

During follow-up, patients were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. If a vascular event was suspected, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the treating specialist. All possible events were independently evaluated by three members of the endpoint committee, comprising physicians from different departments. Study outcomes included myocardial infarction, stroke (ischemic and hemorrhagic), vascular mortality, all-cause mortality, peripheral artery disease and a composite of myocardial infarction, stroke or vascular mortality. The definitions of the study outcomes are shown in supplemental table 2. Follow-up duration (years) was defined as the period between study inclusion and first cardiovascular event or death from any cause, date of loss to follow-up or the preselected date of 1 March 2013. In total, 34 of the 4,267 participants (0.8%) were lost to follow-up due to migration or discontinuation from the study.

Data analyses

Data are presented as percentages for categorical variables, as mean with standard deviation (SD) for normally distributed variables and as median with interquartile range [IR] for non-normally distributed variables. Cox proportional hazards model analysis was used to estimate the effect of having offspring with cardiovascular disease or risk factors, and the risk of new vascular events in patients. The date of the first vascular outcome was set as composite outcome date. Results were expressed as HR and 95%CI. Patients with both myocardial infarction and stroke during follow-up contributed to both the myocardial infarction and stroke analyses, but with follow-up time matching the respective outcomes. If patients had multiple events of the same type, the first recorded event was used in the analyses. For the composite vascular outcome, the date of the first vascular outcome was set as composite outcome date.

Missing data (<1%) were singly imputed using predictive mean matching (aregImpute-algorithm in R, Hmisc-package) assuming these values were missing at random[12], only education

level was missing in 41% of the patients.

Multiple models were constructed to adjust the results for confounding. Model I included positive offspring history, age and sex. Model II included additionally body mass index, systolic blood pressure, hypercholesterolemia, history of diabetes mellitus, smoking (pack years), physical activity, history of hypertension, family size, age oldest child at baseline and difference in age between youngest and oldest child. Further adjustment for education level was performed in model III.

To test the robustness of our findings we performed sensitivity analyses restricted to patients with clinically manifest vascular disease (n=3,206). To take the severity of atherosclerosis into account, another model was constructed adjusting for the recently developed SMART risk score and family size[13]. The SMART risk score was developed for risk prediction of recurrent vascular events in patients with clinically manifest vascular disease and was based on easy-to-measure patient characteristics (age, sex), traditional risk factors (current smoking, systolic blood pressure, diabetes mellitus, high-density lipoprotein cholesterol, total cholesterol, eGFR and hs-CRP) and vascular disease history of the patient (CAD, CVD, PAD, AAA and years since first vascular event).

The proportional hazards assumptions were formally tested with the Schoenfeld test. No significant non-proportionality ($p<0.05$) was observed. Analyses were performed in SPSS version 20 (SPSS, Chicago, Illinois, USA) and R version 2.15.2. No extramural funding was used to support this work.

RESULTS

Of the patients, 127 (3%) had at least one child with cardiovascular disease. Seventy-eight patients (2%) had offspring with diabetes mellitus, 189 patients (4%) had offspring with hypercholesterolemia and 247 (6%) patients had offspring with hypertension. Smoking in offspring was present in 1,972 patients (46%) and 845 patients (20%) had offspring who were overweight.

In total, 506 patients had at least one child with cardiovascular disease or a traditional cardiovascular risk factor (diabetes mellitus, hypertension or hypercholesterolemia) (mean age first born 38±9 years). Of the patients with offspring with cardiovascular disease or a traditional risk factor, 43% (n=217) were female, compared with 29% (n=1,107) in the group without offspring with cardiovascular disease or traditional risk factors (mean age first born 31±10 years) (table 1). A history of coronary artery disease and diabetes mellitus was more common in patients with offspring with cardiovascular disease or risk factors than in patients without offspring with cardiovascular disease or traditional risk factors.

During a median follow-up of 7.0 years (interquartile range 3.7 – 10.4), 90 patients died, of whom 31 due to a vascular cause. Myocardial infarction occurred in 164 patients, stroke in

Table 1. Baseline characteristics according to presence of cardiovascular disease or risk factors in offspring.

	Patients with cardiovascular disease or diabetes, hypertension or hypercholesterolemia in offspring	**Patients without cardiovascular disease or diabetes, hypertension or hypercholesterolemia in offspring**
	(n = 506)	(n = 3,761)
Age (years)	63 (9)	59 (9)
Male sex (%)	289 (57)	2654 (71)
Location of vascular disease*		
Coronary artery disease (%)	290 (57)	1850 (49)
Cerebrovascular disease (%)	88 (17)	740 (20)
Peripheral artery disease (%)	45 (9)	396 (11)
Abdominal aortic aneurysm (%)	36 (7)	183 (5)
Diabetes Mellitus type 2 (%)	115 (23)	560 (15)
Ever smoking (%)	357 (71)	2810 (75)
Current alcohol use (%)	309 (61)	2188 (59)
Blood pressure-lowering agents (%)	394 (78)	2666 (71)
Lipid-lowering agents (%)	375 (74)	2319 (62)
Antiplatelets agents (%)	342 (68)	2396 (64)
Systolic blood pressure (mmHg)	143 (22)	141 (21)
Diastolic blood pressure (mmHg)	82 (12)	83 (12)
Body mass index (kg/m^2)	27.1 (4.1)	26.9 (4.1)
Waist circumference (cm)	95 (12)	95 (12)
Total cholesterol (mmol/l)	4.9 (1.4)	5.0 (1.3)
Triglycerides (mmol/l)	1.3 [1.0 - 2.0]	1.4 [1.0 - 2.0]
HDL-cholesterol (mmol/l)	1.3 (0.4)	1.3 (0.4)
LDL-cholesterol (mmol/l)	2.9 (1.2)	3.0 (1.1)
eGFR (ml/min/1.73m^2)	74 (16)	77 (16)

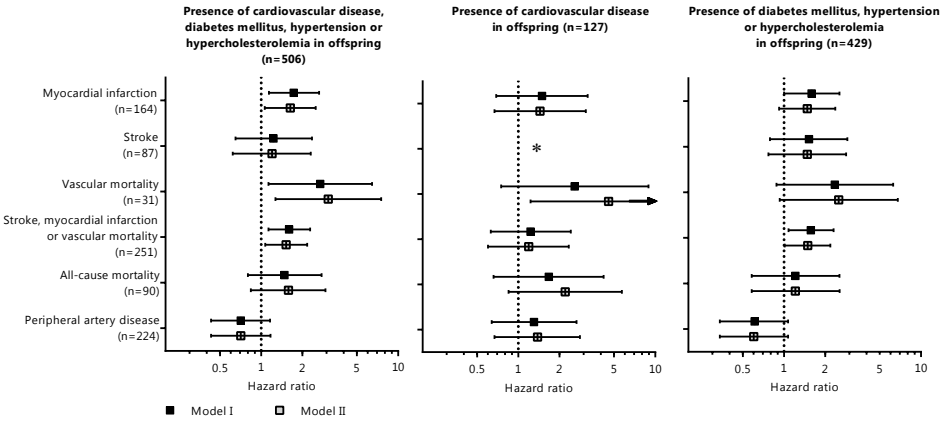
Data are expressed as mean (SD), median [interquartile range] or percentage.
eGFR = glomerular filtration rate, estimated by the Modification of Diet in Renal Disease equation.
* Not mutually exclusive, patients can have multiple locations of vascular disease

87 patients. The composite vascular outcome of myocardial infarction, stroke and vascular mortality occurred in 251 patients.

Relation between presence of cardiovascular disease or risk factors in offspring and the risk of new or subsequent vascular events

Having offspring with cardiovascular disease or traditional risk factors increased the risk of vascular mortality (HR 2.9; 95%CI 1.2 – 7.1), myocardial infarction (HR 1.6; 95%CI 1.1 – 2.5) and the composite outcome of stroke, myocardial infarction or vascular mortality (HR 1.5; 95%CI 1.1 – 2.2) (figure 2). No increased risk was observed for peripheral artery disease

Figure 2. Relation between presence of vascular disease or diabetes mellitus, hypertension or hypercholesterolemia in offspring and the occurrence of subsequent or new vascular events in patients with cardiovascular risk factors or clinically manifest vascular disease.



Results are expressed as HRs with 95%CIs. Model I: age and sex. Model II: model I + BMI, systolic blood pressure, hypercholesterolemia, diabetes mellitus, smoking (pack years), physical activity, hypertension, family size, age oldest child and difference in age between youngest and oldest child. * During follow-up only two strokes occurred in the group of patients with cardiovascular disease in offspring

(HR 0.7; 95%CI 0.4 – 1.2), stroke (HR 1.2; 95%CI 0.6 – 2.3) and all-cause mortality (HR 1.6; 95%CI 0.8 – 2.9).

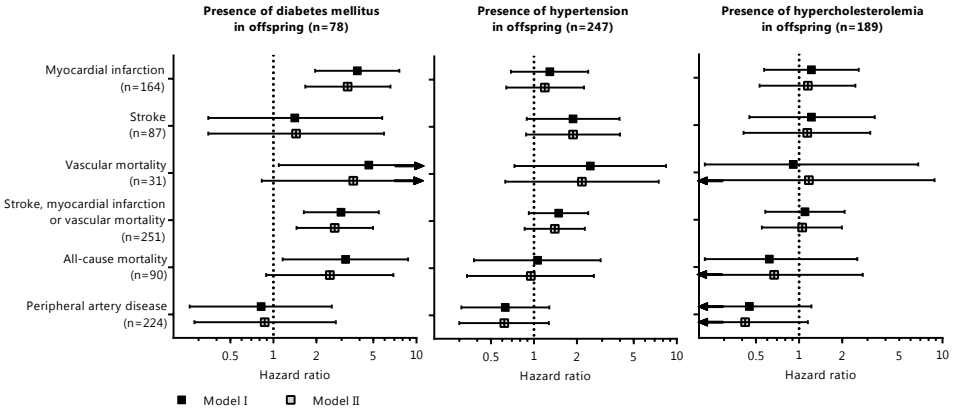
Presence of cardiovascular disease in offspring was related to cardiovascular mortality (HR 4.0; 95%CI 1.1 – 14.9), whereas no significant relation was observed between presence of cardiovascular disease in offspring and other outcomes. Presence of cardiovascular risk factors in offspring was related to an increased risk of the composite vascular outcome (HR 1.5, 95%CI 1.0 – 2.2). Adjustment for potential confounding of education in model III resulted in completely the same risk estimates as in model II (data not shown).

Sensitivity analyses in patients with clinically manifest vascular disease demonstrated similar results (supplemental table 3). Adjustment for the SMART risk score yielded in general similar results.

Relation between presence of diabetes mellitus, hypertension, hypercholesterolemia, smoking or overweight in offspring and the risk of new or subsequent vascular events

Presence of diabetes mellitus in offspring was related to the composite vascular outcome (HR 2.7; 95%CI 1.5 – 5.0) and myocardial infarction (HR 3.3; 95%CI 1.7 – 6.6) (figure 3). An increased risk was also observed for all-cause mortality (HR 2.5; 95%CI 0.9 – 6.9), although this was not statistically significant. Presence of hypercholesterolemia in offspring was not related with occurrence of subsequent vascular events, and presence of hypertension in offspring

Figure 3. Relation between presence of diabetes mellitus, hypertension or hypercholesterolemia in offspring and the occurrence of subsequent or new vascular events in patients with cardiovascular risk factors or clinically manifest vascular disease.



Results are expressed as HRs with 95%CIs. Model I: age and sex. Model II: model I + BMI, systolic blood pressure, hypercholesterolemia, diabetes mellitus, smoking (pack years), physical activity, hypertension, family size, age oldest child and difference in age between youngest and oldest child.

was related to a higher risk of stroke (HR 1.9; 95%CI 0.9 – 4.0), although not statistically significant.

Smoking or overweight in offspring were not related to a higher risk of subsequent vascular events (HR 1.1; 95%CI 0.9 – 1.4, HR 0.9; 95%CI 0.6 – 1.2), all-cause mortality (HR 0.8; 95%CI 0.5 – 1.3, HR 0.8; 95%CI 0.5 – 1.3) and peripheral artery disease (HR 1.2; 95%CI 0.9 – 1.5, HR 1.2; 95%CI 0.9 – 1.7) (figure 4).

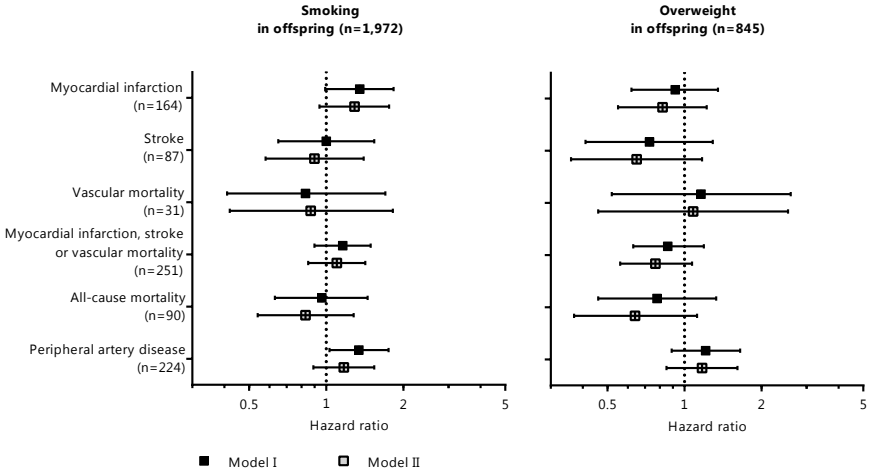
Again adjustment for education level in model III did not change the risk estimates (data not shown). Sensitivity analyses in patients with clinically manifest vascular disease also demonstrated the importance of the presence of diabetes mellitus in offspring and the risk for subsequent vascular events (supplemental table 3).

DISCUSSION

The present study demonstrates that the presence of vascular disease and hypertension, hypercholesterolemia or diabetes mellitus in offspring is related to a higher risk of new vascular events in patients with clinically manifest vascular disease and cardiovascular risk factors. The presence of diabetes mellitus in offspring was also related to vascular events in patients already at high vascular risk. Smoking or overweight in offspring were not related to a higher risk of vascular events.

Family history of cardiovascular disease is usually evaluated 'upward' in the family tree to-

Figure 4. Relation between smoking or overweight in offspring and the occurrence of subsequent or new vascular events in patients with cardiovascular risk factors or clinically manifest vascular disease



Results are expressed as HRs with 95%CIs. Model I: age and sex. Model II: model I + BMI, systolic blood pressure, hypercholesterolemia, diabetes mellitus, smoking (pack years), physical activity, hypertension, family size, age oldest child and difference in age between youngest and oldest child.

5

wards parents and horizontally towards brothers and sisters. In the present study, family history is assessed 'downward' towards children of patients which is a new approach. For primary prevention, determining presence of cardiovascular disease and risk factors in offspring is probably not useful because of the low prevalence simply due to young age of the offspring. Recently, a novel family history definition was evaluated in a random population sample, additionally taking later onset of disease, second-degree relatives, number of affected relatives and presence of cardiovascular disease in offspring into account[14]. It was demonstrated that this extended definition of family history was superior to a conventional definition of family history (presence of premature cardiovascular disease in first-degree relatives) in predicting prevalent atherosclerosis (carotid or femoral IMT ≥0.9mm or presence of carotid or femoral plaque). However, in that study, the mean participant age of 46 years was probably too low for their offspring to be at an high enough age to already have developed cardiovascular disease.

In the current study population of older patients with an elevated risk of vascular events, determining the presence of cardiovascular disease or diabetes, hypercholesterolemia or hypertension in offspring proved to be useful as this is related to a higher risk of vascular events. The mechanism behind this increased risk remains speculative. A possible explanation is that a positive offspring history reflects the severity of atherosclerosis or the degree of exposure of traditional, and also yet unknown, vascular risk factors. To evaluate this risk, we performed multiple adjustments for potential risk factors in the causal pathway. In one model traditional

risk factors were incorporated and in another model the SMART risk score. In the SMART risk score several traditional risk factors are included (e.g. smoking, blood pressure, cholesterol levels), as well as the vascular burden of the patient (e.g. coronary artery disease, peripheral artery disease or multiple vascular manifestations)[13]. Adjusting for the SMART risk score did not substantially change the risk estimates compared with the model adjusted for traditional risk factors. The risk increase can therefore not simply be explained by the severity of atherosclerosis in a patient or presence of conventional risk factors.

In general, the heritable risk of cardiovascular disease is determined by genetic factors, shared environmental factors and gene-environment interactions[15, 16]. "Environmental factors" is a generic term and comprises lifestyle factors such as smoking and obesity, but also true environmental factors like air pollution[17]. An example of a gene-environment interaction is the difference in cardiovascular risk seen in patients with the 9p21 risk allele following a healthy diet (OR 1.02, 95%CI 0.92 – 1.14) and patients following a less healthy diet (OR 1.32, 95%CI 1.18 – 1.48)[18]. Adjustment of lifestyle factors and traditional risk factors did not lead to substantial attenuations of the observed risks although residual confounding cannot be ruled out. The risk increase remained after adjustment for known risk factors which suggests that genetic factors, gene-environmental interactions and exposure to yet unknown risk factors contribute to the relation of having offspring with vascular disease or having offspring with traditional cardiovascular risk factors and new vascular events. Therefore we interpreted a positive offspring history as a proxy of the genetic base of the patient and of the degree of exposure to (unknown) risk factors of cardiovascular disease of the patient. The risk related having offspring with diabetes mellitus and subsequent events is probably due to aggregation of insulin resistance within families.

In patients with clinically manifest vascular disease there is a wide range of absolute risks of developing subsequent vascular events, ranging from a low 10-year predicted risk (<10%) to an extremely high 10-year predicted risk (≥40%)[13]. As people in general become older and survival of acute cardiovascular events has improved[19, 20], this group of patients becomes increasingly important. Although all patients should be treated according to guidelines, clinicians may consider novel therapy such as new biologicals, immunomodulants and antithrombotics for patients with an extremely high risk of vascular events. For these treatments, which may become increasingly available in clinical practice, it is important to treat patients with the highest estimated effect. Determining a positive offspring history, especially cardiovascular events and diabetes mellitus, could be valuable for this identification and is easy to add as part of a patient's (family) history. Whether adding information on offspring history to a prediction model improves risk prediction of (recurrent) vascular events should still be evaluated.

The present study has several strengths. This is a large observational cohort study reflecting clinical practice of patients with vascular disease and risk factors being treated according to national guidelines. We were able to study a large number of offspring. The procedure for clinical event adjudication of the patients is very strict, which reduces the chance of subjective

assessment. The response rate for participation in the present study was high, which reduces the chance of bias.

Study limitations need to be considered. Notably, the SMART cohort is a dynamic cohort and the SMART junior study started in the period 2009-2013 whereas the SMART study started in 1996. Of the patients who died or were lost to follow-up in the period 1996 – 2009, no information could be obtained regarding the health of their children which may have led to an underestimation of the observed effects as these patients had the worst prognosis. In addition, the low number of patient who died may have led to low statistical power for these analyses and therefore false-negative results.

Assessment of presence of risk factors and cardiovascular disease in offspring was performed by sending a questionnaire to the patients. Although we assume good knowledge regarding the health of offspring by parents, non-differential misclassification may occur which may lead to dilution of the observed effects. This could be especially the case for the presence of hypercholesterolemia in offspring, of which the offspring is not even aware of. Therefore the relation between the presence of hypercholesterolemia in offspring and subsequent events may be diluted as well as the relation between the presence of diabetes mellitus, hypertension and hypercholesterolemia and subsequent events. In addition, no information was available of marital status and health literacy of the patient which may have affected the knowledge of offspring's health.

Since the study population comprises patients with established vascular disease and patients with cardiovascular risk factors, it is possible that patients with vascular disease have a higher recollection and awareness of the presence of vascular disease and risk factors in their offspring which may have biased the results. Therefore sensitivity analyses were performed only in patients with clinically manifest vascular disease and similar results were found as for the whole study population. Adjustment for the SMART risk score was performed as well, taking the extent of atherosclerosis and degree of cardiovascular risk factors into account. Again, the results were comparable with the results not adjusted for the SMART risk score. These results point towards robustness of the data and limited recall bias.

Regarding the presence of diabetes mellitus in offspring it would have been preferable to make a distinction between diabetes mellitus type 1 and type 2, as a higher risk of vascular events in parents would be expected for having offspring with diabetes mellitus type 2, but this information was not available.

In conclusion, presence of vascular disease and risk factors in offspring is related to an increased risk of developing new or subsequent vascular events in parents already at high risk for developing vascular events.

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SUPPLEMENTARY INFORMATION

Supplemental table 1. Characteristics of patients willing to participate and of patients not willing to participate.

	Patients willing to participate	**Patients not willing to participate / non-responders**
	(n = 4,368)	(n = 1,921)
Age (years)	60 (10)	59 (10)
Male sex (%)	2982 (70)	1182 (63)
Location of vascular disease*		
Coronary artery disease (%)	2156 (50)	760 (40)
Cerebrovascular disease (%)	839 (20)	349 (19)
Peripheral artery disease (%)	450 (10)	252 (13)
Abdominal aortic aneurysm (%)	218 (5)	88 (5)
Diabetes Mellitus type 2 (%)	684 (16)	390 (21)
Ever smoking (%)	3227 (75)	1414 (75)
Current alcohol use (%)	2541 (59)	937 (50)
Blood pressure-lowering agents (%)	3092 (72)	1319 (70)
Lipid-lowering agents (%)	2728 (63)	1079 (57)
Antiplatelets agents (%)	2767 (64)	1084 (58)
Systolic blood pressure (mmHg)	141 (21)	144 (22)
Diastolic blood pressure (mmHg)	83 (12)	84 (12)
Body mass index (kg/m^2)	27 (4)	27 (4)
Waist circumference (cm)	95 (12)	95 (13)
Total cholesterol (mmol/l)	5.0 (1.3)	5.2 (1.4)
Triglycerides (mmol/l)	1.4 [1.0 - 2.0]	1.4 [1.0 - 2.1]
HDL-cholesterol (mmol/l)	1.3 (0.4)	1.3 (0.4)
LDL-cholesterol (mmol/l)	3.0 (1.1)	3.2 (1.2)
eGFR (ml/min/1.73m^2)	77 (16)	77 (18)

Data are expressed as mean (SD), median [interquartile range] or percentage.
eGFR = glomerular filtration rate, estimated by the Modification of Diet in Renal Disease equation.
* Not mutually exclusive, patients can have multiple locations of vascular disease

Supplemental table 2. Study outcomes.

Outcome events	Definition
Myocardial infarction	At least two of the following criteria (I) Chest pain for at least 20 minutes, not disappearing after administration of nitrates (II) ST-elevation > 1 mm in two following leads or a left bundle branch block on the electrocardiogram (III) Troponin elevation above clinical cut-off values or creatinine kinase (CK) elevation of at least two times the normal value of CK and a myocardial band-fraction > 5% of the total CK. Sudden death: unexpected cardiac death occurring within one hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
Stroke	Relevant clinical features for at least 24 hours causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *infarction* on CT or MRI Relevant clinical features for at least 24 hours causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *hemorrhage* on CT or MRI Relevant clinical features for at least 24 hours causing an increase in impairment of at least one grade on the modified Ranking scale, *without a new (hemorrhage) cerebral infarction* on CT or MRI Cerebral hemorrhage demonstrated with CT, MRI or operation
Vascular mortality	Death from stroke, myocardial infarction, congestive heart failure, rupture of abdominal aortic aneurysm and vascular death of other causes
Composite vascular outcome	Composite of myocardial infarction, stroke, retinal infarction, congestive heart failure, sudden death and vascular mortality
All-cause mortality	Death from any cause
Peripheral artery disease	Amputation of toe, foot, below the knee, above the knee Operation of leg or iliac artery Percutaneous transluminal angioplasty or stenting of leg or iliac artery

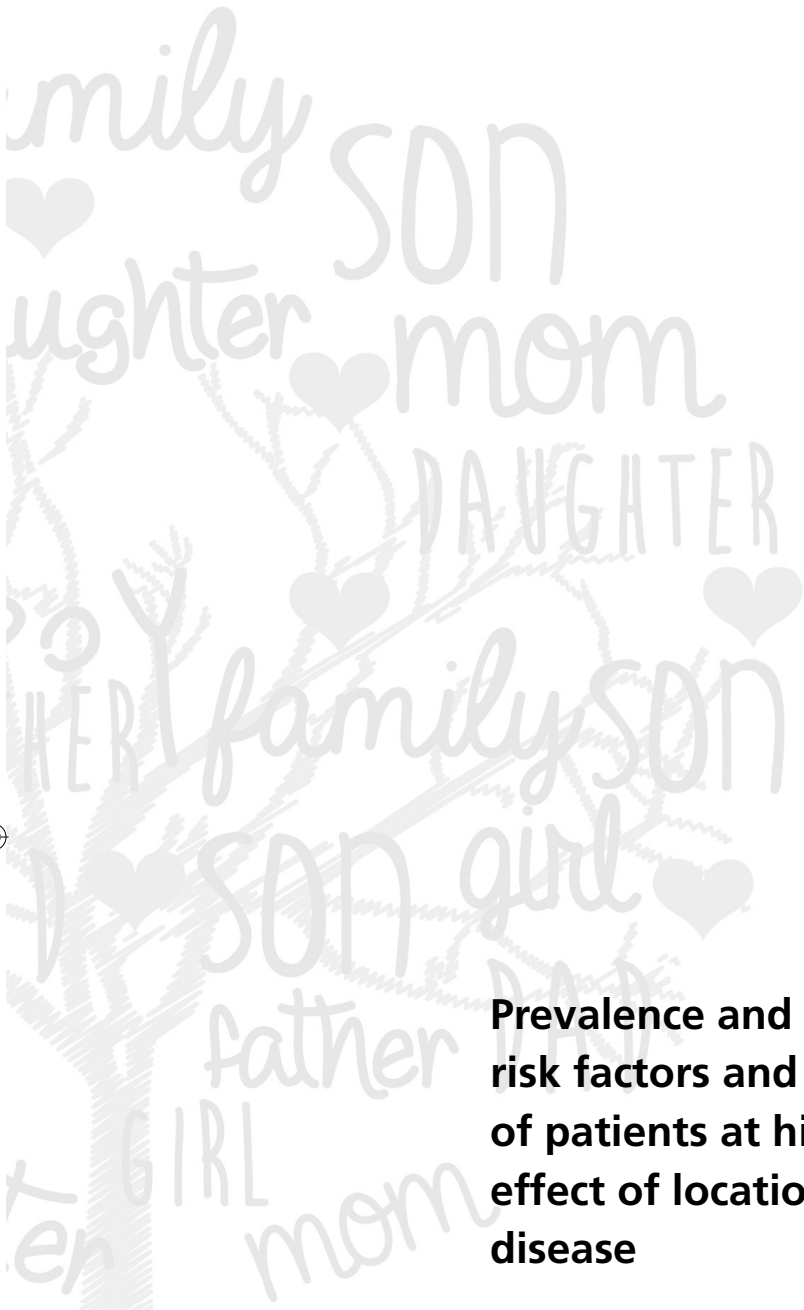
CK: creatinine kinase, CT: computed tomography, MRI: magnetic resonance imaging

Supplemental table 3. Relation between presence of vascular disease or vascular risk factors in offspring and risk of subsequent vascular events in patients with clinically manifest vascular disease (n=3,206).

	Model	Myocardial infarction (n=148)	Stroke (n=75)	Vascular mortality (n=26)	Stroke, myocardial infarction & vascular mortality (n=220)	All-cause mortality (n=75)	Peripheral artery disease (n=210)
Presence of cardiovascular disease or cardiovascular risk factors in offspring	1	1.78 (1.13 - 2.80)	1.23 (0.60 - 2.52)	3.17 (1.27 - 7.92)	1.64 (1.12 - 2.39)	1.50 (0.78 - 2.91)	0.71 (0.43 - 1.18)
	2	1.61 (1.02 - 2.54)	1.19 (0.58 - 2.45)	3.15 (1.22 - 8.16)	1.51 (1.03 - 2.22)	1.50 (0.78 - 2.95)	0.73 (0.44 - 1.21)
	3	1.54 (0.97 - 2.43)	1.18 (0.57 - 2.44)	2.76 (1.07 - 7.09)	1.46 (1.00 - 2.14)	1.32 (0.68 - 2.59)	0.64 (0.38 - 1.06)
Presence of cardiovascular disease in offspring	1	1.38 (0.60 - 3.16)	NA	2.97 (0.84 - 10.42)	1.20 (0.59 - 2.46)	1.42 (0.51 - 3.98)	1.14 (0.53 - 2.44)
	2	1.33 (0.58 - 3.06)	NA	3.50 (0.91 - 13.43)	1.16 (0.56 - 2.37)	1.71 (0.59 - 4.92)	1.29 (0.60 - 2.78)
	3	1.23 (0.53 - 2.82)	NA	2.96 (0.77 - 11.31)	1.08 (0.53 - 2.23)	1.38 (0.48 - 3.97)	1.13 (0.53 - 2.44)
Presence of cardiovascular risk factors in offspring	1	1.57 (0.94 - 2.61)	1.55 (0.76 - 3.17)	2.64 (0.96 - 7.30)	1.56 (1.03 - 2.36)	1.34 (0.63 - 2.84)	0.60 (0.33 - 1.08)
	2	1.40 (0.84 - 2.33)	1.49 (0.72 - 3.08)	2.58 (0.92 - 7.27)	1.43 (0.94 - 2.17)	1.26 (0.59 - 2.69)	0.59 (0.33 - 1.07)
	3	1.35 (0.81 - 2.25)	1.49 (0.72 - 3.07)	2.38 (0.86 - 6.60)	1.39 (0.91 - 2.10)	1.23 (0.58 - 2.61)	0.53 (0.29 - 0.96)
Presence of diabetes mellitus in offspring	1	4.66 (2.35 - 9.25)	0.85 (0.12 - 6.18)	5.08 (1.17 - 22.05)	3.27 (1.72 - 6.21)	3.59 (1.29 - 9.98)	0.87 (0.28 - 2.74)
	2	3.76 (1.87 - 7.57)	0.84 (0.11 - 6.12)	4.09 (0.92 - 18.22)	2.84 (1.48 - 5.45)	2.73 (0.96 - 7.73)	0.93 (0.29 - 2.95)
	3	3.98 (2.01 - 7.87)	0.81 (0.11 - 5.88)	5.54 (1.28 - 23.90)	2.88 (1.52 - 5.47)	3.77 (1.37 - 10.39)	0.86 (0.27 - 2.70)
Presence of hypertension in offspring	1	1.12 (0.56 - 2.23)	1.92 (0.86 - 4.31)	2.44 (0.70 - 8.52)	1.37 (0.81 - 2.30)	1.04 (0.37 - 2.93)	0.54 (0.25 - 1.16)
	2	1.00 (0.50 - 2.00)	1.94 (0.86 - 4.39)	2.13 (0.59 - 7.61)	1.26 (0.75 - 2.14)	0.91 (0.32 - 2.56)	0.55 (0.25 - 1.17)
	3	0.93 (0.47 - 1.86)	1.79 (0.79 - 4.03)	1.70 (0.49 - 5.93)	1.17 (0.69 - 1.98)	0.81 (0.29 - 2.24)	0.44 (0.20 - 0.94)
Presence of hypercholesterolemia in offspring	1	1.23 (0.54 - 2.80)	1.20 (0.38 - 3.85)	0.99 (0.13 - 7.48)	1.07 (0.52 - 2.17)	0.67 (0.16 - 2.76)	0.50 (0.19 - 1.36)
	2	1.10 (0.48 - 2.52)	1.12 (0.35 - 3.59)	1.13 (0.15 - 8.62)	0.98 (0.48 - 2.00)	0.67 (0.16 - 2.79)	0.47 (0.17 - 1.26)
	3	1.12 (0.49 - 2.55)	1.24 (0.39 - 3.96)	1.21 (0.16 - 9.18)	1.00 (0.49 - 2.04)	0.74 (0.18 - 3.07)	0.52 (0.19 - 1.40)

Results are expressed as hazard ratios with 95% confidence intervals. Model 1: age and sex. Model 2: Model 1 + BMI, systolic blood pressure, hypercholesterolemia, diabetes mellitus, smoking, physical activity, hypertension and antihypertensive agents, family size and age of oldest child. Model 3: SMART risk score* and family size.

* The SMART risk score contains the following variables: age, sex, smoking status, systolic blood pressure, diastolic blood pressure, diabetes mellitus, history of coronary artery disease, history of cerebrovascular disease, history of abdominal aortic aneurysm, history of peripheral artery disease, years since first diagnosis of vascular disease, HDL-cholesterol levels, total cholesterol levels, eGFR (as estimated by the modification of diet in renal disease equation) and CRP-levels.



6

Prevalence and risk of cardiovascular risk factors and events in offspring of patients at high vascular risk and effect of location of parental vascular disease

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ABSTRACT

Background

Offspring of patients with cardiovascular disease are at increased risk of developing cardiovascular events. We evaluated whether prevalence of risk factors in offspring of patients with increased cardiovascular risk is higher compared with the general population and whether the risk of cardiovascular events and prevalence of cardiovascular risk factors in offspring is dependent on parental vascular disease location.

Methods

Of 4,270 patients enrolled in the SMART cohort we assessed after a follow-up of 7 years (interquartile range 4 – 8) the presence of cardiovascular risk factors and disease in their 10,572 children by questionnaire. The SMART patients had symptomatic vascular disease (coronary artery disease (CAD) (n=1,826), cerebrovascular disease (CVD) (n=637), peripheral artery disease (PAD) (n=275), abdominal aortic aneurysm (AAA) (n=98), polyvascular disease (≥2 vascular manifestations) (n=371)) or risk factors (hypercholesterolemia, diabetes, hypertension) (n=1,063). The prevalence of risk factors in offspring was compared with the general population and stratified for parental vascular disease location. The relation between parental vascular disease location and cardiovascular events in offspring was determined by Poisson regression.

Results

The offspring had higher prevalence of in particular hypercholesterolemia and hypertension compared with the general population, irrespective of the parental vascular disease location. Higher risks of cardiovascular events compared with offspring of patients without manifest vascular disease were observed in offspring of patients with CAD (PR 1.8, 95%CI 0.9 – 3.4), CVD (PR 2.4 ,95%CI 1.2 – 4.8), PAD (PR 2.8, 95%CI 1.3 – 6.4), polyvascular disease (PR 2.5, 95%CI 1.2 – 5.2), but not with AAA (PR 1.7; 95%CI 0.5 – 6.1).

Conclusions

In offspring from patients with cardiovascular disease or risk factors, the prevalence of traditional risk factors was higher compared with the general population, independent of the location of vascular disease of the parent. Offspring of patients with PAD had the highest risk of developing vascular disease.

INTRODUCTION

Parental history of cardiovascular disease is an established risk factor for developing cardiovascular events[1-4]. Recently it was demonstrated that hypertensive patients having a parental history of premature coronary artery disease (CAD) and stroke were earlier referred and treated compared with hypertensive patients without such parental history[5]. Despite earlier referral, earlier treatment, lower cardiovascular risk factor burden and similar blood pressure reduction compared with patients without a positive parental history, subjects with a positive parental history retained an increased risk of all-cause and cardiovascular mortality (HR 1.1; 95%CI 1.0 – 1.3 and HR 1.2; 1.0 – 1.4). The effects of this heritable risk can already be seen in childhood. Several studies demonstrated that young children with a parent with cardiovascular disease or risk factors show early signs of insulin resistance[6], glucose intolerance[7], high-normal blood pressure[8], endothelial dysfunction and decreased mitochondrial function[9, 10]. Whether the prevalence of hypercholesterolemia, diabetes mellitus and hypertension is increased for offspring of affected parents at a young age, and whether this depends on the vascular disease location of the parent is unclear.

After experiencing a cardiovascular event, patients may wish to be informed about their own health, but also about the vascular risk in their children. This may also be an opportunity for the physician to convey information regarding preventive measures for their offspring. The potentially increased risk may cohere with the location of vascular disease in the patient. There is evidence for increased vascular risk in children of parents with clinical manifest CAD[2, 11-14] and stroke[13, 15-17], but little is known about the vascular risk of children of parents with peripheral artery disease (PAD)[4, 18].

The objective of the present study is to compare the prevalence of cardiovascular risk factors in offspring of patients at high vascular risk with the general population. In addition, we determine whether location of vascular disease in patients influences the risk of cardiovascular events and the presence of risk factors in their offspring.

METHODS

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. The rationale and design of the SMART study have been described previously[19]. In short, the SMART study is an ongoing single-center prospective cohort study that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular disease or a vascular risk factor. The Ethics Committee of the University Medical Centre Utrecht approved the study and all participants gave their written consent.

For this study data were used of patients who were newly referred to the University Medical Centre between 1996 and 2013 with a history of arterial atherosclerosis (i.e. coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) or abdominal aortic aneurysm (AAA)) or with a cardiovascular risk factor (diabetes mellitus type I or II, hyperlipidemia or hypertension). CAD was defined as myocardial infarction, angina pectoris or coronary revascularization. Patients with CVD had experienced a transient ischemic attack, cerebral infarction, cerebral ischemia, amaurosis fugax, retinal infarction or a history of carotid surgery. PAD was defined as a symptomatic and documented obstruction of distal arteries of the leg or interventions (Fontaine classification II-IV confirmed with ankle brachial index (ABI) ≤0.90 in rest or decrease of ABI >20% after exercise, percutaneous transluminal angioplasty, bypass or amputation). Patients with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter ≥3 cm, measured with ultrasonography) or a history of AAA surgery. Diabetes mellitus type I and II was defined as fasting serum glucose ≥7.0 mmol/l, serum glucose ≥11.1 mmol/l or the use of oral anti-hyperglycemic agents or insulin. Hyperlipidemia was defined as a total cholesterol >5.0 mmol/l, low-density lipoprotein cholesterol >3.2 mmol/l or the use of lipid-lowering drugs. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or the use of antihypertensive agents.

Patients were enrolled after a stable situation of their disease was reached. Patients with a terminal malignancy were excluded, as well as those not independent in daily activities, not sufficiently fluent in Dutch language or referred back to the referring specialist immediately after one visit.

Baseline examination

All patients underwent a standardized extensive vascular screening including a uniform questionnaire on medical history, symptoms of cardiovascular disease and presence of cardiovascular risk factors, physical examination (height, weight, waist circumference, systolic and diastolic blood pressure) and laboratory tests to determine fasting serum lipid, glucose and creatinine levels. In addition, patients were screened non-invasively for presence of asymptomatic atherosclerotic diseases other than the qualifying diagnosis, by measuring the ABI at rest, ultrasonography of the abdominal aorta and duplex ultrasound of the common and internal carotid arteries. Body mass index (BMI) was calculated as weight divided by height squared. Waist circumference was measured halfway between the lower rib and iliac crest.

During follow-up patients were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. A detailed description of the follow-up procedure can be found elsewhere[19]. For the present study only baseline measurements were used.

SMART-junior

SMART-junior is a sub-study of the SMART study, designed to investigate the presence of

cardiovascular risk factors and vascular disease in offspring of patients participating in the SMART cohort. A secondary objective was to identify a risk profile of the parent prognostic for the development of traditional cardiovascular risk factors or cardiovascular events in their children.

All eligible patients included in the SMART study received after a median follow-up of 7 years (interquartile range 4 – 8 years) a standardized questionnaire in the period 2009 -2013, inquiring about the presence of cardiovascular risk factors and cardiovascular events in their children. Regarding cardiovascular risk factors, information was obtained about the presence of diabetes mellitus, hypertension, hypercholesterolemia, smoking behavior and weight of the offspring. Regarding cardiovascular events, the questionnaire inquired whether offspring had experienced myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), stroke, PAD or AAA.

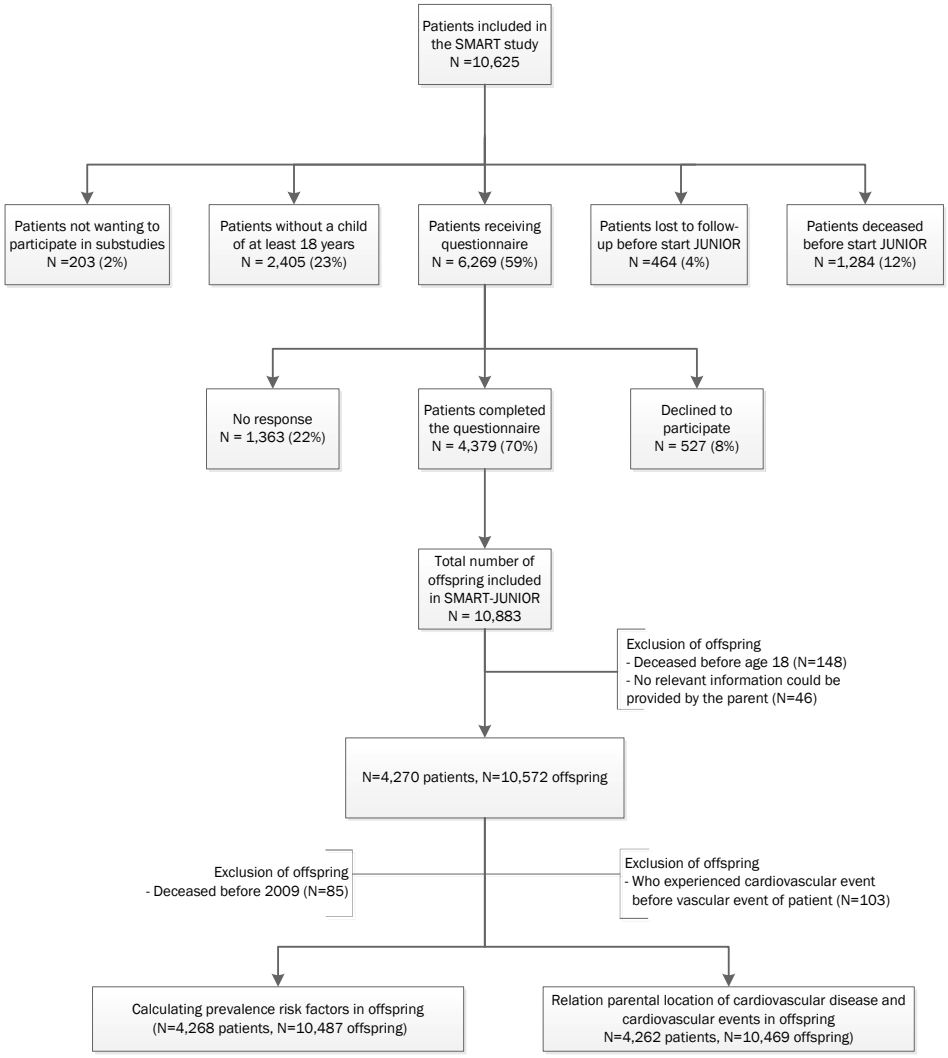
Of the 10,625 patients included in the SMART study, 1523 (14.3%) had no children, 882 (8.3%) patients did not have children of at least eighteen years and 1284 (12%) patients had already died before the start of SMART-junior (figure 1). A total of 6269 patients (59%) were eligible to participate in the SMART-junior study. In order to maximize the response rate, a second mail was sent to non-responders. In case of incomplete questionnaires or inaccuracies, patients were contacted for further information. A total of 4379 patients (70%) completed the questionnaire and information of 10,883 children was obtained. There were no substantial differences in characteristics between patients willing to participant and patients not willing to participate. Offspring deceased before the age of 18 were excluded (n=148), as well as those whose parents could not provide relevant information (n=46). Eventually, of 4270 patients (69% male, 31% female) information of their 10,572 offspring (51% male, 49% female) was available. The mean age of the offspring was 37 (±10) years.

Data analyses

Data are presented as percentages for categorical variables, as mean with standard deviation (SD) for normally distributed variables and as median with interquartile range [IR] for non-normally distributed variables.

To compare the prevalence of the cardiovascular risk factors hypertension, diabetes mellitus and hypercholesterolemia in children of patients with cardiovascular disease or vascular risk factors to the general population, point prevalence values were calculated. The prevalence values of risk factors of the general population were based on the Dutch Central Bureau of Statistics (www.cbs.nl). In the Netherlands all people are registered with one general practitioner (GP). The presence of a risk factor was recorded if diagnosed by the GP. As these values were based on the entire Dutch population, no confidence intervals were presented. For the calculation of risk factor prevalence in the SMART-junior population, the offspring was divided into age categories of five years according to the Dutch registry. In the younger age categories, age categories were pooled because of the low number of offspring in these

Figure 1. Flowchart SMART-junior.



groups. Since offspring information was obtained in the period 2009-2013, prevalence values were compared to those of the general population registered in 2011. Offspring deceased before 2009 were excluded (n=85) (figure 1). Point prevalence (per 1,000) per age category was calculated using the following formula: point prevalence = number of existing cases / number of people in the population * 1000. The corresponding 95% confidence intervals were calculated as follows; CI = $p \pm 1.96 * \sqrt{((p * (1 - p)) / n)}$. The difference in prevalence values between the SMART-junior population and the general population was calculated using Confidence Interval Analysis (CIA) calculator version 2.2.0 (University of Southampton, Southampton, United Kingdom). If patients could not give a clear indication regarding the presence of diabetes mellitus, hypertension or hypercholesterolemia, the offspring was not included in prevalence calculation (diabetes mellitus n=85; 0.8%, hypertension n=1144; 11%, hypercholesterolemia n=2552; 24.4%). Missing data for smoking (n=21; 0.5%), BMI (n=6; 0.1%), alcohol intake (n=23; 0.6%) and physical activity (n=16; 0.4%) were singly imputed using predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming that these values were missing at random[20].

To evaluate the relation between vascular disease location in patients and cardiovascular events in their offspring, prevalence ratios and corresponding 95% confidence intervals (PR, 95%CI) were calculated using Poisson regression models with robust variance. Patients were divided in categories according to presence of clinically manifest vascular disease at inclusion of the study: CAD, CVD, PAD, AAA, polyvascular disease (two or more vascular manifestations) and patients without manifest vascular disease but with a cardiovascular risk factor (reference category). The outcome was a cardiovascular event (coronary interventions, myocardial infarction, stroke, PAD or AAA) in offspring. Offspring who experienced a cardiovascular event earlier in time than their parent were excluded (n=103) (figure 1).

Three models were constructed. Model I included vascular disease location of the patient, age, sex and age oldest child. Model II included model I with smoking, body mass index, alcohol intake, physical activity and family size. Model III included model II with hypertension, diabetes mellitus type 2 and hypercholesterolemia.

Analyses were performed in SPSS version 20 (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline characteristics of patients

In table 1 the baseline characteristics of the patients are listed according to the location of clinically manifest vascular disease. Patients with cardiovascular risk factors were younger, had diabetes mellitus more often, had higher blood pressure, and higher total cholesterol and LDL-cholesterol levels compared with patients with clinically manifest vascular disease. Of the patients with CAD, AAA or polyvascular disease more than 78% were male, compared to

Table 1. Baseline characteristics of patients (n = 4270) according to location of manifest vascular disease.

	Cardiovascular risk factor (n=1063)	Coronary artery disease (n=1826)	Cerebrovascular disease (n=637)	Peripheral artery disease (n=275)	Abdominal aortic aneurysm (n=98)	Polyvascular disease (n=371)
Age (years)	56 (9)	61 (9)	59 (9)	57 (9)	64 (8)	63 (8)
Male sex (%)	50	82	57	64	85	78
Location of vascular disease						
Coronary artery disease (%)	0	100	0	0	0	85
Cerebrovascular disease (%)	0	0	100	0	0	52
Peripheral artery disease (%)	0	0	0	100	0	45
Abdominal aortic aneurysm (%)	0	0	0	0	100	33
Diabetes Mellitus type 2 (%)	20	15	11	11	14	20
Ever smoking (%)	64	74	76	90	87	89
Current alcohol use (%)	55	63	62	47	53	57
Blood pressure-lowering agents (%)	56	91	51	39	55	85
Lipid-lowering agents (%)	37	81	57	42	42	79
Antiplatelets agents (%)	18	89	73	43	37	83
Systolic blood pressure (mmHg)	148 (23)	137 (19)	141 (20)	143 (19)	143 (19)	142 (21)
Diastolic blood pressure (mmHg)	89 (13)	81 (11)	82 (11)	83 (11)	85 (11)	80 (11)
Body mass index (kg/m^2)	27 (5)	27 (4)	26 (4)	27 (4)	26 (4)	27 (4)
Waist circumference (cm)	93 (14)	97 (11)	92 (12)	95 (12)	98 (11)	98 (12)
Total cholesterol (mmol/l)	5.8 (1.4)	4.5 (1.0)	4.9 (1.2)	5.5 (1.2)	5.4 (1.6)	4.7 (1.1)
Triglycerides (mmol/l)	1.5 [1.0 - 2.3]	1.3 [1.0 - 1.9]	1.2 [0.9 - 1.7]	1.5 [1.1 - 2.2]	1.5 [1.1 - 2.0]	1.5 [1.1 - 2.2]
HDL-cholesterol (mmol/l)	1.4 (0.4)	1.2 (0.3)	1.4 (0.4)	1.3 (0.4)	1.2 (0.3)	1.2 (0.3)
LDL-cholesterol (mmol/l)	3.6 (1.3)	2.6 (0.9)	2.9 (1.0)	3.4 (1.1)	3.4 (1.2)	2.7 (0.9)
eGFR (ml/min/1.73 m^2)	77 (17)	77 (15)	77 (16)	79 (17)	76 (19)	72 (16)

Data are expressed as mean (SD), median [interquartile range] or percentage. eGFR = glomerular filtration rate, estimated by the Modification of Diet in Renal Disease (MDRD) equation.

57% and 66% in patients with CVD or PAD. Most frequent use of blood pressure-lowering, lipid-lowering and antiplatelet agents was seen in patients with coronary artery and polyvascular disease.

Characteristics of offspring

Of the 10,572 offspring, 71 children experienced a myocardial infarction, 62 children a stroke, 95 children received a PCI or CABG, 45 children had a history of PAD and 16 children a history of AAA. A history of hypertension, hypercholesterolemia or diabetes mellitus was present in 1113 offspring. Taking vascular disease location of their parents into account, offspring of patients with a cardiovascular risk factor were youngest (33±11 years) and offspring of patients with AAA were oldest (42±9 years) (table 2). A history of hypertension (9.4%), hypercholesterolemia (6.1%), diabetes mellitus (1.9%), stroke (1.1%), myocardial infarction (1.8%), PCI (1.8%) and CABG (0.7%) was most common in offspring of patients with polyvascular disease. Cardiovascular events occurred least in offspring of patients with a cardiovascular risk factor (e.g. PCI in 0.3%, CABG in 0.1%).

Prevalence of cardiovascular risk factors in offspring compared with the general population

The offspring of patients with clinically manifest vascular disease and cardiovascular risk factors had a higher prevalence of diabetes mellitus, hypertension and hypercholesterolemia for most age categories compared to the general population, most notably for hypertension and hypercholesterolemia (figure 2). Higher prevalence values (all per 1000 persons) were observed for all three risk factors for the age category 25-29; diabetes mellitus had a prevalence of 11 (95%CI 6 – 19), hypertension of 32 (95%CI 23 – 45) and hypercholesterolemia of 48 (95%CI 35 – 64) compared to prevalence values of 4, 6 and 6 in the general population.
Taking the vascular disease location of the parents into account, higher prevalence values of hypertension and hypercholesterolemia were observed for the offspring population for almost all age categories and for all different vascular manifestations of the parents (table 3). There was no clear pattern between vascular disease location of the parent and diabetes prevalence in offspring.

Risk of vascular events in offspring of patients with vascular disease according to vascular disease location

Of the 4262 patients, 113 patients had at least one child who experienced a cardiovascular event. Myocardial infarction, PCI and stroke were the most common events in offspring. Offspring of patients with clinically manifest vascular disease had an increased risk of cardiovascular events compared to offspring of patients with a cardiovascular risk factor (PR 1.9, 95%CI 1.1 – 3.6), adjusted for age, sex, age oldest child, BMI, alcohol intake, smoking, physical activity, family size, hypertension, diabetes mellitus type 2 and hypercholesterolemia.

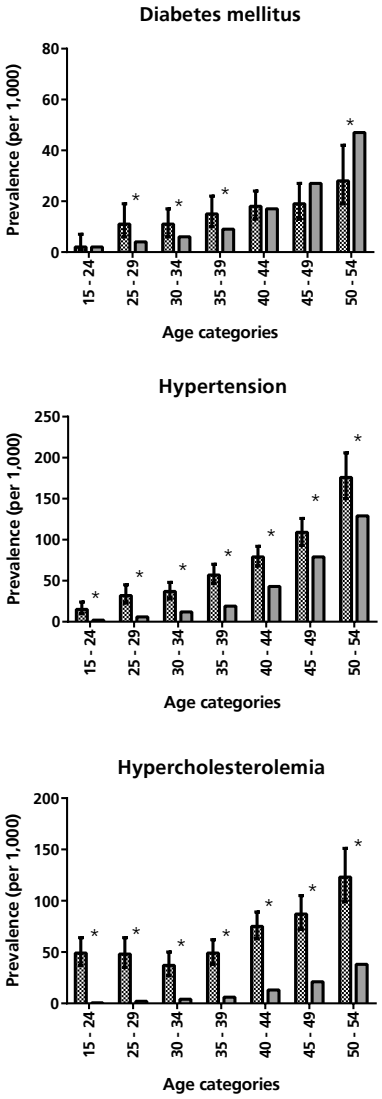
Table 2. Cardiovascular risk factors and cardiovascular events in the children (n = 10,572) of patients with clinically manifest vascular disease or cardiovascular risk factor according to the vascular disease location of the parent.

	Offspring of patients with cardiovascular risk factor (n=2546)	Offspring of patients with coronary artery disease (n=4624)	Offspring of patients with cerebrovascular disease (n=1588)	Offspring of patients with peripheral artery disease (n=613)	Offspring of patients with abdominal aortic aneurysm (n=257)	Offspring of patients with polyvascular disease (n=944)
Age (years)	33 (11)	38 (10)	37 (10)	37 (10)	42 (9)	40 (11)
Male sex, n (%)	1295 (51)	2379 (51)	816 (51)	317 (52)	114 (44)	450 (48)
Cardiovascular risk factors						
Ever smoking, n (%)	939 (37)	1788 (39)	643 (41)	298 (49)	115 (45)	436 (47)
Hypertension, n (%)*	125 (5.6)	289 (7.0)	90 (6.3)	33 (5.9)	16 (7.1)	89 (10.3)
Hypercholesterolemia, n (%)*	145 (7.8)	228 (6.5)	59 (4.7)	20 (4.3)	7 (3.7)	61 (8.3)
Diabetes Mellitus, n (%)*	38 (1.5)	78 (1.7)	14 (0.9)	7 (1.1)	3 (1.2)	18 (1.9)
Overweight, n (%)	458 (18)	871 (19)	273 (17)	108 (18)	59 (23)	200 (22)
Cardiovascular events						
Percutaneous coronary interventions, n (%)	7 (0.3)	38 (0.8)	7 (0.4)	4 (0.7)	2 (0.8)	17 (1.8)
Coronary artery bypass graft, n (%)	3 (0.1)	8 (0.2)	1 (0.1)	1 (0.2)	0 (0)	7 (0.7)
Myocardial infarction, n (%)	11 (0.4)	30 (0.6)	6 (0.4)	4 (0.7)	3 (1.2)	17 (1.8)
Stroke (hemorrhagic / ischemic), n (%)	14 (0.5)	23 (0.5)	9 (0.6)	5 (0.8)	1 (0.4)	10 (1.1)
Abdominal aortic aneurysm, n (%)	4 (0.2)	7 (0.2)	4 (0.3)	1 (0.2)	0 (0)	0 (0)
Peripheral artery disease, n (%)	5 (0.2)	22 (0.5)	8 (0.5)	6 (1.0)	1 (0.4)	3 (0.3)
Deceased, n (%)	18 (0.7)	58 (1.3)	12 (0.8)	4 (0.7)	4 (1.2)	18 (1.9)

Data are expressed as number (percentages) or as mean (standard deviation).

* Based on offspring population with clear indication of the presence or absence of cardiovascular risk factor.

Figure 2. Prevalence of diabetes mellitus, hypertension and hypercholesterolemia in offspring of patients with clinically manifest vascular disease or cardiovascular risk factors and in the general population.



Prevalence (per 1000 subjects) in age categories of children of patients with clinically manifest vascular disease or cardiovascular risk factors ( ) with 95%CI intervals (error bars) and prevalence of the general population ( ).
* Indicates a significant difference between the prevalence of the SMART-junior population and the general population.

Offspring of patients with PAD had the highest risk (PR 2.8, 95%CI 1.3 – 6.4), followed by offspring of patients with polyvascular disease (PR 2.5, 95%CI 1.2 – 5.2), cerebrovascular disease (PR 2.4, 95%CI 1.2 – 4.8) and CAD (PR 1.8, 95%CI 0.9 – 3.4) (table 4).

Table 3. Prevalence of diabetes mellitus, hypertension and hypercholesterolemia in offspring compared to the general population stratified according to vascular disease location of the parent.

	Prevalence per 1000 (95% CI)						
	Age categories						
	15 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	50 - 54
Offspring of patients with vascular risk factors	n = 547	n = 377	n = 388	n = 363	n = 383	n = 256	n = 126
Hypertension	14 (7 - 29)*	24 (12 - 46)*	54 (34 - 83)*	66 (44 - 99)*	80 (55 - 113)*	93 (61 - 139)	196 (131 - 284)*
Diabetes mellitus	4 (1 - 13)	19 (9 - 38)*	8 (3 - 23)	22 (11 - 43)*	16 (7 - 34)	31 (16 - 61)	16 (4 - 56)
Hypercholesterolemia	67 (46 - 97)*	63 (40 - 99)*	64 (41 - 99)*	70 (45 - 107)*	92 (64 - 131)*	85 (53 - 133)*	176 (110 - 271)*
Offspring of patients with CAD	n = 458	n = 425	n = 638	n = 781	n = 995	n = 726	n = 398
Hypertension	12 (5 - 29)*	45 (28 - 70)*	30 (19 - 47)*	48 (34 - 67)*	86 (69 - 106)*	115 (93 - 142)*	150 (117 - 191)
Diabetes mellitus	2 (0 - 12)	9 (4 - 24)*	14 (7 - 27)*	12 (6 - 22)	21 (14 - 32)	17 (10 - 29)	36 (21 - 59)
Hypercholesterolemia	39 (23 - 65)*	56 (36 - 87)*	41 (27 - 62)*	40 (27 - 59)*	81 (64 - 103)*	95 (73 - 123)*	103 (72 - 145)*
Offspring of patients with CVD	n = 194	n = 185	n = 209	n = 268	n = 331	n = 223	n = 110
Hypertension	22 (9 - 55)*	35 (16 - 74)*	43 (22 - 82)*	70 (44 - 109)*	56 (36 - 89)	116 (78 - 170)	117 (67 - 198)
Diabetes mellitus	0	0	0	15 (6 - 38)	6 (2 - 22)	23 (10 - 52)	28 (10 - 79)
Hypercholesterolemia	0	20 (7 - 58)*	6 (1 - 35)	52 (29 - 91)*	61 (38 - 95)*	67 (38 - 117)*	145 (85 - 236)*
Offspring of patients with PAD	n = 77	n = 60	n = 91	n = 115	n = 142	n = 76	n = 32
Hypertension	0	18 (3 - 93)	34 (12 - 97)*	28 (10 - 79)	61 (31 - 116)	143 (77 - 250)	250 (138 - 411)*
Diabetes mellitus	0	17 (3 - 89)	22 (6 - 77)*	18 (5 - 62)	7 (1 - 39)	13 (2 - 71)	0
Hypercholesterolemia	68 (27 - 162)*	22 (4 - 116)*	0	26 (7 - 90)*	75 (38 - 141)*	52 (18 - 141)	87 (24 - 268)
Offspring of patients with AAA	n = 8	n = 14	n = 9	n = 41	n = 72	n = 52	n = 54
Hypertension	125 (22 - 471)*	0	0	63 (17 - 201)	31 (9 - 107)	43 (12 - 145)	226 (114 - 398)
Diabetes mellitus	0	0	0	0	28 (8 - 97)	19 (3 - 101)	0
Hypercholesterolemia	0	0	0	69 (19 - 220)*	34 (10 - 117)	47 (13 - 155)	40 (7 - 195)
Offspring of patients with polyvascular disease	n = 54	n = 73	n = 98	n = 156	n = 198	n = 199	n = 147
Hypertension	19 (3 - 101)*	16 (3 - 85)	11 (2 - 60)	81 (47 - 136)*	115 (77 - 170)*	101 (65 - 153)	252 (180 - 342)*
Diabetes mellitus	0	0	10 (2 - 56)	19 (7 - 55)	25 (11 - 58)	10 (3 - 36)	35 (14 - 86)
Hypercholesterolemia	106 (46 - 226)*	20 (4 - 105)*	14 (2 - 74)	48 (22 - 101)*	56 (30 - 103)*	109 (69 - 168)*	184 (116 - 278)*
General population (reference group)							
Hypertension	2	6	12	19	43	79	129
Diabetes mellitus	2	4	6	9	17	27	47
Hypercholesterolemia	0.5	2	4	6	13	21	38

* Indicates a significant difference between the prevalence values of the SMART-junior population and the general population.

Table 4. Risk of cardiovascular events in offspring of patients with clinically manifest vascular disease according to vascular disease location of the parents.

Vascular disease location	# Patients	# Offspring	Patients with ≥ 1 offspring with vascular event (%)	Model	PR (95%CI)
Cardiovascular risk factor	1060	2524	12 (1.1)	I/II/III	Reference category
Coronary artery disease	1823	4575	48 (2.6)	I	1.82 (0.97 - 3.43)
				II	1.87 (1.01 - 3.48)
				III	1.77 (0.93 - 3.39)
Cerebrovascular disease	636	1580	21 (3.3)	I	2.37 (1.19 - 4.71)
				II	2.45 (1.24 - 4.83)
				III	2.44 (1.24 - 4.80)
Peripheral artery disease	275	607	11 (4.0)	I	2.37 (1.00 - 5.63)
				II	2.64 (1.17 - 5.96)
				III	2.82 (1.26 - 6.35)
Abdominal aortic aneurysm	97	254	3 (3.1)	I	1.65 (0.47 - 5.87)
				II	1.61 (0.44 - 5.84)
				III	1.68 (0.47 - 6.08)
Polyvascular disease	371	929	18 (4.9)	I	2.85 (1.39 - 5.85)
				II	2.63 (1.28 - 5.42)
				III	2.49 (1.19 - 5.21)

Results are expressed as prevalence ratios (PR) with 95% confidence intervals.
Model I: age, sex and age oldest child.
Model II: model I with body mass index, smoking, alcohol intake, physical activity and family size.
Model III: Model II with hypertension, diabetes mellitus type 2 and hypercholesterolemia.

DISCUSSION

In the present study it is shown that offspring of patients with increased cardiovascular risk or manifest vascular disease have a higher prevalence of hypertension, hypercholesterolemia and diabetes mellitus at young age compared with the general population, irrespective of the vascular disease location of the parent. Offspring of patients with manifest vascular disease have an increased risk for developing vascular disease compared with offspring of patients without overt vascular disease in the presence of cardiovascular risk factors. The highest vascular risk was observed in offspring of patients with manifest PAD.

Several studies demonstrated that young children having at least one parent with a cardiovascular risk factor or disease, have early metabolic changes related to an increased risk of vascular events later in life. Offspring of parents with diabetes mellitus appeared to have early signs of decreased insulin sensitivity[6, 21,] decreased beta-cell function[22] and endothelium dysfunction[9]. Offspring of parents with hypertension more often showed signs of hyperinsulinemia[23], high-normal blood pressure, increased serum CRP and leptin plasma levels compared with offspring without such parental history[8, 24-27]. In addition, it was recently demonstrated that family histories of premature and late coronary artery disease are associated with a pro-

gression of coronary artery calcium in offspring[28]. In offspring of patients who experienced a heart attack, increased levels of total cholesterol, VLDL cholesterol and LDL cholesterol from the age of 18 years were demonstrated previously[29]. In the present study, offspring in the age category 15-24 years of patients with cardiovascular risk factors or disease had increased prevalences of hypercholesterolemia and hypertension.

Summarizing, persons with a positive parental history have early features suggestive of increased risk of atherosclerosis seen in otherwise young and healthy persons, increased prevalence of risk factors present from young age and increased risk of mortality despite earlier treatment[5]. Therefore, early lifestyle counselling and screening for the presence of risk factors in offspring of patients with clinical manifest vascular disease and risk factors may be considered. Recent guidelines regarding cardiovascular health and risk reduction in children and adolescents recommend to take a detailed family history of cardiovascular disease, defined as a family member with heart attack, treated angina, CABG/stent/angioplasty, stroke or sudden cardiac death at <55 years in males and <65 years in females[30]. If a positive family history is identified, the subject should be evaluated for other cardiovascular risk factors (e.g. dyslipidemia, hypertension, diabetes). Although in guidelines and risk prediction scores for first cardiovascular events family history of CAD is frequently incorporated[31-33], the smallest increased risk of cardiovascular events was seen in offspring of patients with CAD whereas the highest risk was observed in patients with PAD. Therefore offspring of patients with PAD might be an especially relevant group for early screening and intervention. The risk of events in offspring of patients with PAD was even higher compared with offspring of patients with polyvascular disease, probably because of the high portion of patients with CAD included in this group.

Regarding genetic factors, genome-wide association studies have identified multiple risk loci associated with increased cardiovascular risk, especially for CAD[34-36]. Knowledge regarding the genetic base of PAD is limited, although the C allele at rs1333046 on chromosome 9p21[37] and the A allele of rs7025486 on chromosome 9q33 were associated with PAD[38]. Previously we demonstrated in patients with manifest vascular disease that only a parental history of PAD was related to an increased risk of subsequent PAD[39]. This strengthens the hypothesis that a parental history of PAD is even more important than a parental history of coronary artery disease or cerebrovascular disease.

The present study has several strengths, including the prospective cohort design with a large group of patients with various clinical manifestations of vascular disease enabling direct comparisons between groups of patients with different locations of vascular disease. In most studies regarding parental history and cardiovascular risk in offspring, the parental history is assessed by information obtained from the offspring. This may lead to an underestimation of the risk of cardiovascular events. In the present study information about vascular diseases and vascular risk factors in parents was accurately measured, eliminating the risk of misreporting. In addition, this also enabled proper adjustment for potential confounders.

Limitations of the study need to be considered and include the lack of information of the

spouses of the patients. This information would be available in clinical practice and could have been of value as a covariate for the analysis. Information on the presence of cardiovascular risk factors and events in the children was assessed by questionnaires completed by the patients. The assumption is that parents have accurate knowledge regarding the health of their children and therefore know whether their child has a cardiovascular risk factor or has experienced a cardiovascular event. To reduce the chance of misclassification, children were excluded from analyses if patients could not indicate whether the child was alive or if patients were not able to answer any other question. Still, a large proportion of the patients could not indicate whether their offspring had hypercholesterolemia. However, this seems logical as it could very well be that in the offspring the cholesterol levels have never been measured given their younger age.

It would have been interesting to have information regarding the birth weight and birth status of the offspring since these are related with increased cardiovascular risk[40]. Unfortunately, this information was not available.

The sub-study SMART-junior started in the period 2009-2013, whereas the SMART study started in 1996. Of patients who were already lost to follow-up or deceased, no information could be obtained of their children which may have led to selection bias and to an underestimation of the observed effects as these patients had the worst prognosis. Except for the calculation of the prevalence of risk factors in the offspring, the reference group consisted of patients with a cardiovascular risk factor, which also may have resulted in underestimation of the observed effects as the reference group already has an increased risk of cardiovascular events. Although all included patients have an increased cardiovascular risk, the severity of the different clinical manifestations of vascular disease and risk factors varies. Furthermore, the mean age of the offspring was 37 years, therefore most offspring was too young to have already developed cardiovascular disease.

In conclusion, offspring of patients with cardiovascular risk factors or manifest vascular disease have a higher prevalence of hypertension, hypercholesterolemia and diabetes mellitus compared with the general population, from a young age and independent of the location of vascular disease of the parent. The highest risk for developing vascular disease was observed for offspring of patients with manifest PAD.

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Incremental value of a genetic risk score for the prediction of new vascular events in patients with clinically manifest vascular disease

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ABSTRACT

Background

Several genetic markers are related to incidence of cardiovascular events. We evaluated whether a genetic risk score (GRS) based on 30 single-nucleotide-polymorphisms associated with coronary artery disease (CAD) can improve prediction of 10-year risk of new cardiovascular events in patients with clinically manifest vascular disease.

Methods

In 5742 patients with symptomatic vascular disease enrolled in the SMART study, we developed Cox regression models based on the SMART Risk Score (SRS) and based on the SRS plus the GRS in all patients, in patients with a history of acute arterial thrombotic events and in patients with a history of more stable atherosclerosis and without CAD. The discriminatory ability was expressed by the c-statistic. Model calibration was evaluated by calibration plots. The incremental value of adding the GRS was assessed by net reclassification index (NRI) and decision curve analysis.

Results

During a median follow-up of 6.5 years (interquartile range 4.0 – 9.5), the composite outcome of myocardial infarction, stroke, or vascular death occurred in 933 patients. Hazard ratios of GRS ranging from 0.86 to 1.35 were observed. The discriminatory capacity of the SRS for prediction of 10-year risk of cardiovascular events was fairly good (c-statistic 0.70, 95%CI 0.68 – 0.72), similar to the model based on the SRS plus the GRS. Calibration of the models based on SRS and SRS plus GRS was adequate. No increase in c-statistics, categorical NRIs and decision curves was observed when adding the GRS. The continuous NRI improved only in patients with stable atherosclerosis (0.14, 95%CI 0.03 – 0.25), increasing further excluding patients with a history of CAD (0.21, 95%CI 0.06 – 0.36).

Conclusions

In patients with symptomatic vascular disease, a GRS did not improve risk prediction of 10-year risk of cardiovascular events beyond clinical characteristics. The GRS might improve risk prediction of first vascular events in the subgroup of patients with a history of stable atherosclerosis.

INTRODUCTION

Prediction of the risk for development of cardiovascular disease in individual patients is widely used in clinical practice. As patients are treated according to their absolute risks of developing vascular events, accurate risk prediction is very important. Various risk stratification models are available to determine the individual absolute cardiovascular risk in patients without clinical manifest vascular disease[1-4]. In patients with clinical manifest vascular disease there is a wide range of absolute risks for developing new acute vascular events[5]. Recently we developed the SMART Risk Score, based on easy-to-measure patient characteristics and traditional risk factors, for risk prediction of vascular events in patients with clinically manifest vascular disease[6]. Although this risk score predicts new events fairly well, addition of other predictors may further optimize this prediction model. Genome-wide association studies (GWAS) have identified multiple risk loci associated with the development of coronary artery disease (CAD)[7-10], including rs1122608 at the LDLR gene, rs4977574 at 9p21 and rs11206510 at the PCSK9 gene. These individual single-nucleotide polymorphisms (SNPs) provide valuable insight into the underlying biological pathways, but their effect sizes are typically small and individually contribute little to the heritable risk[11]. Associated risk alleles are therefore increasingly combined into multi-locus genetic risk scores for the purpose of prediction[12-14], showing modest improvements in risk prediction of first cardiovascular events in patients free of prevalent vascular disease[12, 15]. Because traditional risk factors of cardiovascular disease are easy to measure and frequently available in clinical practice, it is more meaningful to assess the value of a genetic risk score on top of these traditional risk factors than to assess a genetic risk score separately. In addition, traditional risk factors may change over time due to treatment, whereas a genetic risk score remains constant. In patients with diabetes a relation was found between a genetic risk score and cardiovascular mortality (HR 1.46, 95%CI 1.08 – 1.96)[16] and in patients with clinical manifest vascular disease there was a relation between a genetic risk score and incident myocardial infarction (HR 1.13, 95%CI 1.00 – 1.28)[14]. Furthermore, a genetic risk score improved risk prediction for individuals at intermediate cardiovascular risk in a two-stage risk screening[17], suggesting a potential role of a genetic risk score in risk prediction of patients with a high risk of cardiovascular disease.

The aim of the present study was to evaluate whether a genetic risk score improves the SMART Risk Score for the prediction of absolute risk of developing new vascular events in patients with clinically manifest vascular disease.

METHODS

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. The rationale and design of the SMART study have been described previously[18]. In short, the SMART study is an ongoing single-center prospective cohort study that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular diseases or a vascular risk factor. The Ethics Committee of the University Medical Center Utrecht approved the study and all participants gave their written informed consent.

For this study data were used of 6580 patients who were newly referred to the University Medical Center between 1996 and 2012 with established clinical manifest arterial disease (i.e. coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) or abdominal aortic aneurysm (AAA)). Patients were enrolled after a stable situation of their disease was reached. Patients with a terminal malignancy were not included, as well as those dependent in daily activities, insufficiently fluent in Dutch language or referred back to the referring physician immediately after one visit.

Of the 6580 patients included in SMART, DNA for genotyping was available of 5742 patients. A history of CAD was present in 3450 patients, of CVD in 1665, of PAD in 1160 and of AAA in 507. A total of 1040 patients fell into more categories because of the presence of more than one clinical manifestation of vascular disease. CAD was defined as myocardial infarction, angina pectoris or coronary revascularization (coronary bypass surgery or coronary angioplasty). Patients with CVD had experienced a transient ischemic attack, cerebral infarction, cerebral ischemia, amaurosis fugax, retinal infarction or a history of carotid artery surgery. PAD was defined as symptomatic and documented obstruction of distal arteries of the lower extremity or interventions (percutaneous transluminal angioplasty (PTA), bypass or amputation). Patients with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter ≥3 cm, measured with ultrasonography) or a history of AAA surgery.

Baseline measurements

All patients underwent a standardized extensive vascular screening. Patients received a uniform questionnaire on medical history, current medication, symptoms of cardiovascular disease and presence of cardiovascular risk factors. Furthermore, patients underwent laboratory assessments and non-invasive screening for manifestations of atherosclerotic disease and risk factors. Based on the questionnaire, the time since first diagnosis of clinically manifest atherosclerosis was calculated. If the patients' first vascular event occurred in the preceding year, the duration of disease was rounded down to zero years.

Follow-up

During follow-up, patients were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. The outcome of interest was occurrence of major cardiovascular events, defined as cardiovascular death, ischemic or hemorrhagic stroke or myocardial infarction (table 1). If a vascular event was reported, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the treating specialist. All possible events were independently evaluated by three members of the endpoint committee, comprising physicians from different clinical departments. Follow-up duration (years) was defined as the period between study inclusion and first cardiovascular event or death from any cause, date of loss to follow-up or the preselected date of 1 March 2012. In total, 225 of the 5742 participants (4%) were lost to follow-up due to migration or discontinuation from the study.

Table 1. Study outcomes.

Myocardial infarction	Acute chest pain for at least 20 minutes with ST-segment elevation (STEMI)
	Acute chest pain without ST-segment elevation with elevated troponin (NSTEMI)
	Intervention related myocardial infarction
	Typical pain, remaining STT changes on ECG, no documented cardiac enzymes development
	Sudden death: unexpected cardiac death occuring within one hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
Stroke	Relevant clinical features for at least 24 hours causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *infarction* on CT or MRI
	Relevant clinical features for at least 24 hours causing an increase in impairment of at least one grade on the modified Ranking scale, with a new cerebral *hemorrhage* on CT or MRI
	Relevant clinical features for at least 24 hours causing an increase in impairment of at least one grade on the modified Ranking scale, *without a new (hemorrhage) cerebral infarction* on CT or MRI
	Hemorrhage demonstrated with CT, MRI or operation
Vascular mortality	Death from stroke, myocardial infarction, congestive heart failure, rupture of abdominal aortic aneurysm and vascular death of other causes
Composite vascular outcome	Composite of myocardial infarction, stroke and vascular mortality

Development of the genetic risk score

An extensive review of the literature provided a list of 31 SNPs reported as significant for CAD. The CARDIoGRAM study identified 25 SNPs[10], the Coronary Artery Disease Genetics Consortium identified three SNPs[9] and three other SNPs were identified by three independent studies[19-21]. Two SNPs were associated with a Japanese population or a Chinese population. One SNP (rs12936587) was out of Hardy-Weinberg equilibrium, with no heterozygotes called for this SNP, and was therefore not included in the analyses. Therefore, the genetic risk score was based on 30 SNPs (Supplementary table 1). The effect sizes employed for the calculation of the genetic risk score were obtained from the original papers (the odds ratios for the risk

alleles ranged from 1.06 to 1.65).

Genotyping

Wet-lab genotyping for single-nucleotide polymorphism analysis was carried out by KBiosciences, Hertfordshire, UK (www.kbioscience.co.uk), whose personnel was blinded to patient status, using their proprietary KASPar PCR technique TaqMan. Genotype calling was carried out using an automated system, the results of which were checked manually by study personnel using the SNPviewer software.

Data analyses

Data are presented as percentages for categorical variables, as mean with standard deviation (SD) for normally distributed variables and as median with interquartile range (IQR) for non-normally distributed variables. Missing data for hs-CRP (n=70; 0.01%) were singly imputed using predictive mean matching (aregImpute-algorithm in R, Hmisc-package) assuming that these values were missing at random[22]. Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers. To estimate the individual patients' 10-year cardiovascular disease risk, a prediction model was constructed based on the previously published SMART Risk Score using a Cox proportional hazards risk model6. The model was updated to ensure an optimal fit in this population[23]. The SMART Risk Score contains the following parameters: age, sex, current smoking, systolic blood pressure, diabetes mellitus, history of CAD, history of cerebrovascular disease, history of peripheral artery disease, history of aortic abdominal aneurysm, years since first vascular event, high-density lipoprotein cholesterol, total cholesterol, eGFR and hs-CRP.

Next, two new Cox proportional hazards risk models for the occurrence of major cardiovascular events (myocardial infarction, stroke or vascular mortality) were developed. One model was based on the SMART Risk Score with addition of the genetic risk score, the second model was only based on the genetic risk score. Procedures similar to the aforementioned were followed to estimate the individual patients' 10–year risk of vascular events. Because the SNPs used in the genetic risk score are associated with coronary artery disease, the same analyses were repeated to estimate the 10-year absolute risk for the occurrence of a myocardial infarction (fatal and non-fatal). These analyses were performed for all patients (n= 5742) and separately for patients with a history of CAD (n=3450).

Because of the heterogeneity of the study population we performed subgroup analyses in patients with a history of an acute arterial thrombotic event (myocardial infarction or stroke (n=2645)), and in patients with a history of more stable atherosclerosis (e.g. angina pectoris and peripheral artery disease (n=3097)). In addition, to exclude the possibility that the effect of the genetic risk score is masked by the large proportion of patients with CAD, a sensitivity analysis was performed in patients with a history of stable atherosclerosis without a history of CAD (n=1550).

The discriminatory ability of the different prediction models was expressed by the c-statistic for survival data. Model calibration was demonstrated by calibration plots and tested with the Gronnesby-Borgan goodness-of-fit statistic based on the likelihood ratio test.
The categorical net reclassification index (NRI) was calculated to assess improvement of adding the genetic risk score to the SMART Risk Score based on the 10-year risk of vascular events for low (<10%), moderate (10-20%), high (20-30%), very high (30-40%) and extremely high (>40%) risk categories. The continuous NRI (cNRI) was also calculated. The 95% confidence intervals were estimated by bootstrapping.
All analyses were conducted with R statistical software version 2.15.2. (http://www.R-project.org).

Net benefit

The incremental value on a group level of adding the genetic risk score to the SMART Risk Score was determined using the net benefit assessment method described by Vickers et al[24]. Traditional measures such as the c-statistic have limited value in clinical practice for decisions that result from using a prediction model. Therefore it is possible that no effect on the c-statistics is observed, but it can be of clinical relevance for prediction models[25]. In the net benefit assessment, the adverse effects are incorporated. This means that a weight for detecting true positives versus false positives is taken into account reflected by the decision threshold. In general, a low decision threshold can be applied if a false positive result is not harmful, for example in case of statin treatment. If a false positive result indicates a potentially hazardous intervention, such as a surgical operation, the decision threshold should be high. To assess the incremental value of a marker, the net benefit (demonstrated on the y-axis) of the model should be higher compared to the model without the marker. If decision curves are completely overlapping there is no incremental value, making the simplest model preferable. If there is incremental value of a marker the decision curves for the two models would show divergence. However, if the model with the marker shows divergence compared to the model without the marker, it depends on the decision threshold whether this is of clinical relevance. If a false positive result is not harmful (e.g. decision threshold of 10%), and the models with and without the marker show divergence for decision thresholds of 30%, the model with the marker is not necessarily better.
The decision curves of the two models used in the present study (model based on the SMART Risk Score and the model based on the SMART Risk Score and the genetic risk score) are presented together with the net benefit of making the same decisions for all patients (all positive or all negative).

RESULTS

The baseline characteristics of the study population are listed according to the genetic risk score (table 2). The genetic risk score was normally distributed with a mean of 0.061 (±0.008). Patients in the fourth quartile of the genetic risk score (0.072 ± 0.004) more often had a history of CAD, compared with patients in the lowest quartile (0.050 ± 0.004) (65% versus 54%). During a median follow-up of 6.5 years (interquartile range 4.0 – 9.5 years), 1031 patients died of whom 560 patients due to a vascular cause. Myocardial infarction occurred in 330 patients and 267 patients experienced a stroke. The composite outcome of myocardial infarction, stroke or vascular death occurred in 933 patients. In table 3 the risks of the lowest versus the highest quartile of genetic risk score are presented as well as the risks per standard deviation higher genetic risk score for the composite outcome and myocardial infarction. No statistical significant risk increase was observed for the composite vascular outcome (HR 1.00, 95%CI 0.83 – 1.20) or for myocardial infarction (HR 1.26, 95%CI 0.92 – 1.70).

Model performance

The discriminatory capacity of the SMART Risk Score to predict the 10-year risk of major cardiovascular events was reasonable (c-statistic 0.70, 95%CI 0.68 – 0.72), identical to the model with the SMART Risk Score and genetic risk score (c-statistic 0.70, 95%CI 0.68 – 0.72) (table 4). The c-statistic of the SMART Risk Score to predict 10-year risk of myocardial infarction was 0.65 (95%CI 0.63 – 0.68), the same as the model with the SMART Risk Score and genetic risk score (c-statistic 0.66, 95%CI 0.63 – 0.69). In patients with a history of CAD the prediction of myocardial infarction with the SMART Risk Score had a c-statistic of 0.63 (95%CI 0.59 – 0.66). Addition of the genetic risk score to the SMART Risk Score did not improve the discriminatory capability (c-statistic 0.63, 95%CI 0.59 – 0.66). The models with only the genetic risk score to predict 10-year risk of major cardiovascular events or myocardial infarction had no discriminatory capability (c-statistics ranging from 0.50 to 0.54). The calibration plots of 10-year predicted versus observed free survival are shown in figure 1 for the models based on the SMART Risk Score with and without addition of the genetic risk score. The Gronnesby-Borgan confirmed goodness-of-fit for all models (0.97> p >0.53).
In the subgroup analyses no substantial increase in c-statistic was observed for the prediction of major cardiovascular events and myocardial infarction (supplemental table 2). Calibration plots are shown in supplemental figure 1.

Net Reclassification Index (NRI)

The categorical NRI for adding the genetic risk score to the SMART Risk Score was -0.01 (95%CI -1.05 – 1.75) to predict the 10-year risk of major cardiovascular events and -1.44 (95%CI -3.06 – 0.07) for predicting the 10-year risk of a myocardial infarction, thus demonstrating no improvement of reclassification by adding the genetic risk score to the SMART Risk

Table 2. Baseline characteristics stratified according to the genetic risk score (GRS).

	1st quartile of GRS	2nd quartile of GRS	3rd quartile of GRS	4th quartile of GRS
	Mean: 0.050 (0.004)	Mean: 0.058 (0.002)	Mean: 0.063 (0.002)	Mean: 0.072 (0.004)
	n = 1,435	n = 1,436	n = 1,436	n = 1,435
Age (years)	61 (11)	60 (10)	60 (10)	60 (10)
Male sex (%	74	74	75	75
Location of vascular disease*				
Cerebrovascular disease (%)	32	29	29	27
Coronary artery disease (%)	54	59	63	65
Peripheral artery disease (%)	21	22	19	19
Abdominal aortic aneurysm (%)	10	8	9	8
Years since first vascular event	3.3 (6.7)	3.8 (7.2)	3.8 (7.0)	3.6 (6.5)
Diabetes Mellitus Type 2 (%)	15	16	19	17
Current smoking (%)	32	34	33	32
Blood-pressure-lowering agents (%)	70	74	76	75
Lipid-lowering agents (%)	61	63	64	67
Antiplatelets agents (%)	72	72	76	76
Systolic blood pressure (mmHg)	142 (21)	141 (22)	141 (21)	141 (21)
Diastolic blood pressure (mmHg)	82 (11)	82 (12)	81 (11)	82 (11)
Body mass index (kg/m$^{2)}$	27 (4)	27 (4)	27 (4)	27 (4)
Total cholesterol (mmol/l)	4.9 (1.2)	5.0 (1.2)	4.9 (1.2)	4.9 (1.3)
Triglycerides (mmol/l)	1.4 [1.0 - 2.0]	1.4 [1.1 - 2.1]	1.4 [1.0 - 2.1]	1.4 [1.0 - 2.0]
HDL-cholesterol (mmol/l)ǂ	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)
LDL-cholesterol (mmol/l)‡	3.0 (1.0)	3.0 (1.0)	2.9 (1.0)	2.9 (1.0)
hs-CRP (mg/l)§	2.2 [1.0 - 4.5]	2.1 [1.0 - 4.8]	2.0 [1.0 - 4.2]	2.1 [1.0 - 4.7]
eGFR (ml/min/1.73 m^{2})ǁ	75 (18)	76 (19)	76 (18)	76 (18)

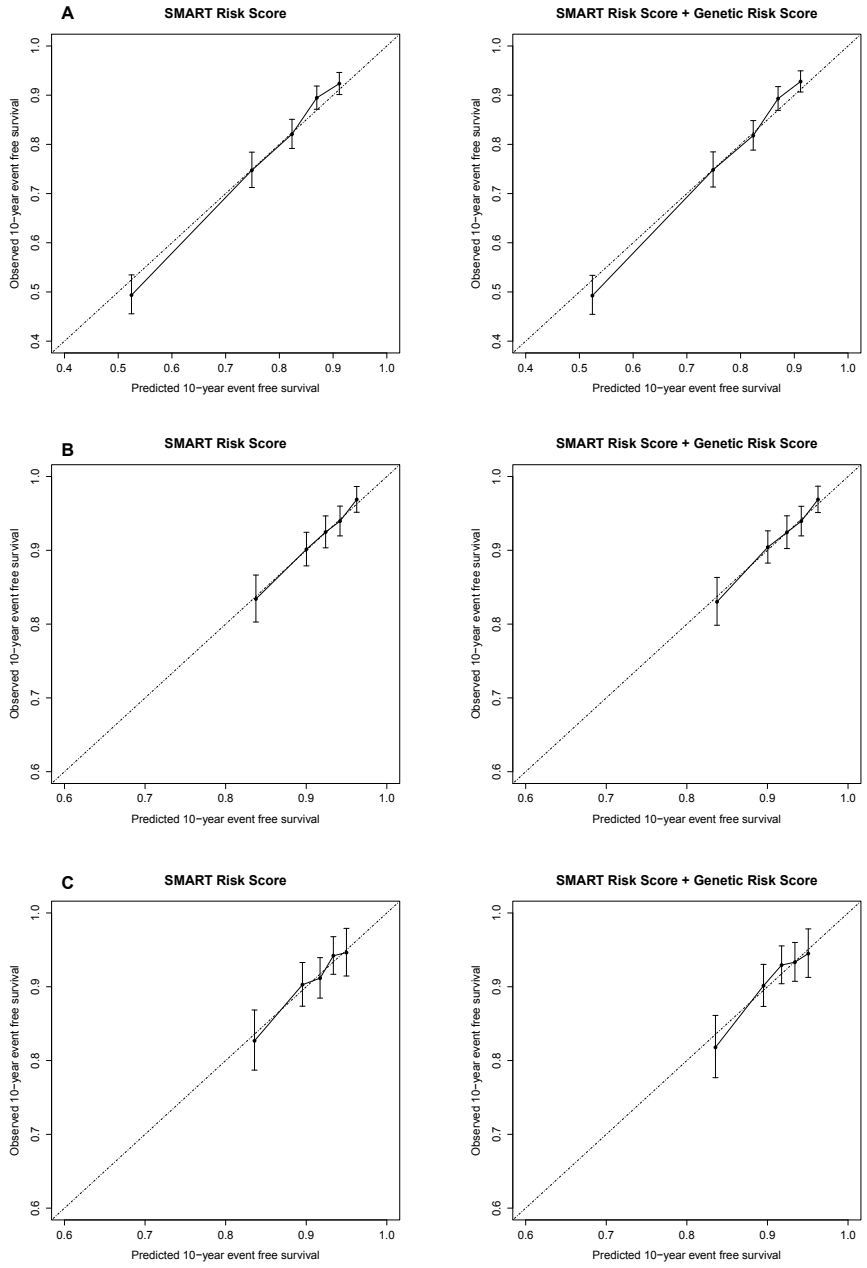
Data are expressed as mean (SD), median [interquartile range] or percentage. * Not mutually exclusive, patients can have multiple locations of vascular disease. HDL = high-density lipoprotein. LDL = low-density lipopreotein. hs-CRP = high-sensitivity C-reactive protein. eGFR = Glomerular Filtration Rate as estimated by the Modification of Diet in Renal Disease (MDRD) equation.

Table 3. Hazard ratios for risk of major cardiovascular events and myocardial infarction for the highest versus the lowest quartile of the genetic risk score and per standard deviation increase of the genetic risk score.

Included patients	Cardiovascular outcome	Model	HR (95%CI) lowest versus highest quartile	HR (95%CI) per SD increase
All patients	Composite outcome (n=933)	I	1.00 (0.83 - 1.20)	0.98 (0.92 - 1.05)
(n=5,742)		II	0.98 (0.83 - 1.20)	0.98 (0.92 - 1.05)
	Myocardial infarction (n=330)	I	1.26 (0.92 -1.70)	1.08 (0.97 - 1.21)
		II	1.18 (0.87 - 1.60)	1.05 (0.95 - 1.18)
Patients with CAD at baseline	Composite outcome (n=517)	I	1.09 (0.86 - 1.40)	1.02 (0.93 - 1.11)
(n=3,450)		II	1.02 (0.87 - 1.32)	1.00 (0.92 - 1.09)
	Myocardial infarction (n=218)	I	1.35 (0.92 - 1.96)	1.11 (0.98 - 1.27)
		II	1.27 (0.87 - 1.86)	1.09 (0.96 - 1.25)
Patients with stable atherosclerosis at baseline (n=3,097)	Composite outcome (n=474)	I	0.93 (0.72 - 1.10)	0.93 (0.85 - 1.02)
		II	0.94 (0.72 - 1.21)	0.95 (0.86 - 1.04)
	Myocardial infarction (n=182)	I	1.24 (0.81 - 1.87)	1.06 (0.92 - 1.23)
		II	1.16 (0.76 - 1.76)	1.04 (0.89 - 1.20)
Patients with acute arterial thrombotic events at baseline	Composite outcome (n=459)	I	1.08 (0.83 - 1.40)	1.02 (0.94 - 1.12)
(n=2,645)		II	1.02 (0.78 - 1.33)	1.01 (0.92 - 1.11)
	Myocardial infarction (n=148)	I	1.28 (0.82 - 2.00)	1.11 (0.95 - 1.30)
		II	1.20 (0.76 - 1.88)	1.08 (0.91 - 1.26)
Patients without acute vascular events & without CAD (n=1,550)	Composite outcome (n=300)	I	0.93 (0.68 - 1.29)	0.93 (0.83 - 1.05)
		II	0.86 (0.62 - 1.20)	0.92 (0.82 - 1.03)
	Myocardial infarction (n=92)	I	1.11 (0.61 - 2.02)	1.05 (0.85 - 1.29)
		II	1.03 (0.56 - 1.89)	1.03 (0.84 - 1.27)

Model I: crude model. Model II: variables included in the SMART Risk Score (age, sex, current smoking, systolic blood pressure, diabetes mellitus, history of cerebrovascular disease, history of coronary artery disease, history of peripheral artery disease, history of abdominal aortic aneurysm, years since first vascular event, HDL-cholesterol, total cholesterol, total cholesterol, hs-CRP and eGFR).

Figure 1. Calibration plots.



Predicted versus observed 10-year survival within quintiles of predicted survival. Calibration is presented for all patients and major cardiovascular events as the outcome (A), for all patients and myocardial infarction as the outcome (B) and for patients with a history of coronary artery disease and myocardial infarction as the outcome (C).

Score. Also no increase in cNRI was observed for major cardiovascular events (0.02, 95%CI -0.59 – 0.11) and myocardial infarction (-0.01, 95%CI -0.14 – 0.13).
Adding the genetic risk score to the SMART Risk Score to predict the 10-year risk of a myocardial infarction in patients included with CAD revealed an NRI of 0.74 (95%CI -3.92 – 5.09). For various subgroups, no improvements in categorical NRI were observed. Adding the genetic risk score improved the cNRI for the combined outcome of major cardiovascular events (0.14, 95%CI 0.03 – 0.25) in patients with a history of stable atherosclerosis and in the subgroup of patients without a history of CAD (0.21, 95%CI 0.06 – 0.36) (supplemental table 2).

Table 4. Discriminatory ability of the different models on different vascular outcomes.

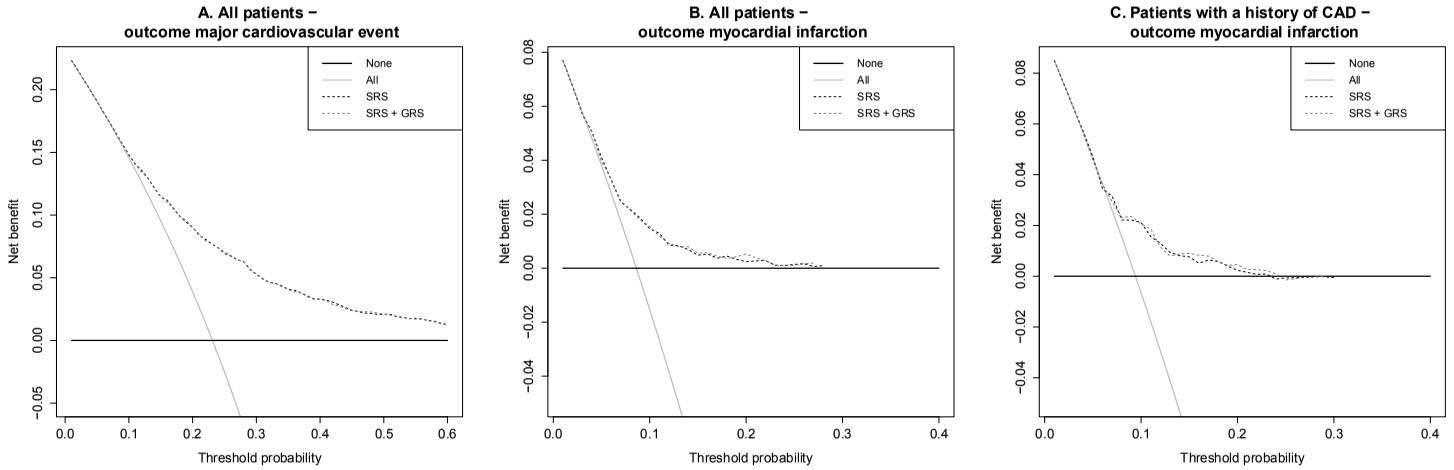
Prediction model	Patients	Outcome	C-statistic (95%CI)
SMART Risk Score	All patients (n=5742)	Composite vascular outcome (n=933)	0.70 (0.68 - 0.72)
SMART Risk Score and Genetic Risk Score			0.70 (0.68 - 0.72)
Genetic Risk Score			0.50 (0.48 - 0.52)
SMART Risk Score	All patients (n=5742)	Myocardial infarction (n=330)	0.65 (0.63 - 0.68)
SMART Risk Score and Genetic Risk Score			0.66 (0.63 - 0.69)
Genetic Risk Score			0.53 (0.49 - 0.56)
SMART Risk Score	Patients with a history of CAD (n=3450)	Myocardial infarction (n=218)	0.64 (0.60 - 0.67)
SMART Risk Score and Genetic Risk Score			0.64 (0.60 - 0.68)
Genetic Risk Score			0.54 (0.49 - 0.57)

Results are expressed as c-statistics with 95% confidence intervals.

Net benefit

The decision curves of the models based on the SMART Risk Score and on the SMART Risk Score with the addition of the genetic risk score for prediction of the 10-year risk of major cardiovascular events are displayed in figure 2a. Incremental value of adding the genetic risk score to the SMART Risk Score would show divergence of the decision curves for these two models. We observed that the decision curves of the two models were completely overlapping, demonstrating that adding the genetic risk score to the SMART Risk Score did not improve prediction-based decisionmaking, irrespective of the decision threshold.
As the genetic risk score was based on SNPs associated with CAD, the incremental value of adding the genetic risk score to the SMART Risk Score was also assessed for prediction of the 10-year risk of myocardial infarction for patients with a history of CAD. As illustrated in figure 2b and 2c, the decision curves for the model with the SMART Risk Score alone and for the model with the SMART Risk Score and genetic risk score were similar, again demonstrating no incremental value of adding the genetic risk score to the SMART Risk Score to predict the 10-year risk of myocardial infarction. The decision curves in the subgroup analyses were also similar of the model with solely the SMART Risk Score compared to the model with the SMART Risk Score and the genetic risk score (supplemental figure 2).

Figure 2. Decision curves.



Graphical representation of net benefit at a range of decision-thresholds of clinical relevance for the models based on the SMART Risk Score (SRS) and based on the SMART Risk Score with addition of the genetic risk score (GRS). Incremental value of the genetic risk score would result in divergence of the model with and without the genetic risk score. If decision curves are overlapping, there is no incremental value of the genetic risk score.

DISCUSSION

The present study demonstrates that adding a genetic risk score, based on 30 SNPs known to be related to the development of coronary artery disease, to a risk score with clinical characteristics and traditional risk factors does not have incremental value for the prediction of 10-year risk for new vascular events in patients with clinical manifest vascular disease (no increase in c-statistic, no improved net benefit, categorical NRI -0.01 (95%CI -1.05 – 1.75) and cNRI 0.02 (95%CI -0.59 – 0.11)). For patients with stable atherosclerosis, the predictive performance improved by adding genetic information to the risk score with only clinical variables, as measured by better continuous reclassification (0.14, 95%CI 0.03 – 0.25).

Previous studies evaluating the incremental value of using genetic risk scores for prediction of cardiovascular disease demonstrate contradicting results. As genetic risk scores are very different in content and composition, direct comparisons are difficult to make. One study demonstrated that a genetic risk score based on 13 SNPs significantly improved reclassification with respect to prediction of incident coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study, whereas no such improvements were seen in the Rotterdam and Framingham Offspring Studies[12]. In a recently published outline of how to combine a clinical risk score with a genetic risk, improved discrimination and calibration was also demonstrated in ARIC[26]. In two studies based on 2,963 and 3,014 patients, modest improvement in risk classification of weighted genetic risk scores based on 29 SNPs and 13 SNPs was found for the prediction of incident coronary heart disease[27, 28]. A recently performed study showed incremental value of a genetic risk score in a two-stage risk assessment in patients with intermediate coronary heart disease risk (10-20%)[17]. Adding a genetic risk score based on 28 SNPs (24 SNPs also included in the genetic risk score of the present study) to a model with traditional risk factors improved the reclassification (NRI of 5%). Two other independent studies demonstrated no additional value of adding a genetic risk score (based on 101 and 13 SNPs) to a model with traditional risk factors for the prediction of vascular events[13, 15]. One study was performed in 19,313 women for the prediction of incident myocardial infarction, stroke, arterial revascularization and cardiovascular death[13], while the other study was performed in 52,726 participants for the prediction of coronary heart disease[15].

A possible explanation for the observed lack of predictive capacity of the genetic risk score in the present study in most patients, may be that the genetic effects are already captured by clinical characteristics already part of the SMART Risk Score. For example, SNP rs599839 at the SORT1 locus and SNP rs3184504 at the SH2B3 locus are associated with CAD, but also with decreased HDL-cholesterol[8] and increased systolic blood pressure[29]. As HDL-cholesterol concentration and systolic blood pressure are already incorporated in the prediction model, adding these particular SNPs, or other similar SNPs affecting HDL-cholesterol or blood pressure, may not improve the predictive capacity of the model. Nevertheless, we argue that the lack of incremental value of adding a genetic risk score to the SMART Risk Score cannot only

be explained by the fact that important traditional risk factors are already incorporated in the SMART model. Traditional risk factors were equally distributed over the different quartiles of the genetic risk score, suggesting no relationship between the genetic risk score and traditional risk factors. However, the proportion of patients with a history of CAD increased across the quartiles of the genetic risk score. Therefore we performed subgroup analyses in patients with a history of stable atherosclerosis not being prevalent CAD, demonstrating additional value as measured by improvement of cNRI of adding the genetic risk score to the SMART risk score.

The patients included in the present study all have prevalent vascular disease, whereas most studies are performed in patients without prevalent vascular disease. However, the group of patients with prevalent vascular disease becomes increasingly important as people in general become older and survival of acute cardiovascular events has improved. Still, guidelines consider all patients with clinical manifest cardiovascular disease to be at high risk of vascular events neglecting a wide distribution of this risk ranging from a low 10-year predicted risk (<10%) to an extremely high 10-year predicted risk (≥40%) of developing recurrent cardiovascular events[6]. Although these patients should be monitored and treated to reduce the risk of cardiovascular events, it could be valuable to identify patients with an extremely high risk of new vascular events as for these patients more aggressive treatment such as with new biologicals, combined antithrombotics therapy and lower treatment goals for LDL-cholesterol monitoring may be considered. The present study shows that adding a genetic risk score does not add predictive information beyond clinical characteristics for the prediction of recurrent vascular events. To further optimize the SMART Risk Score other potentially important predictors, like biomarkers or imaging, need to be identified and evaluated for improvement of prediction.

The present study has several strengths including the large observational cohort study design reflecting clinical practice of patients with vascular disease being treated according to national guidelines. The proportion of patients lost to follow-up due to migration or discontinuation of the study was very low, reducing the risk for bias. The adjudication procedure for clinical events is very strict, reducing the chance for subjective assessments and bias. Limitations of the study also need to be considered. In the present study a genetic risk score was used based on 30 different SNPs known to be related to the development of coronary artery disease in a population with prevalent vascular disease.

In future studies, additional SNPs, related to different atherosclerotic mechanisms and CHD, may be identified and may add to the predictive capacity of the genetic risk score with respect to vascular events.

Subsequently, one might argue that these SNPs are especially related to the development of acute coronary events (as some of the GWAS studies looked specifically at early-onset myocardial infarction). We used a composite vascular outcome including myocardial infarction, stroke and vascular death, which may have limited the predictive capacity of the genetic risk

score as combining different vascular endpoints may dilute the predictive power. Additional analyses revealed that adding the genetic risk score to the SMART Risk Score did not increase the predictive capacity for predicting the 10-year risk of myocardial infarction. Although all patients in the present study have clinically manifest vascular disease, the severity and the location of these clinical manifestations varies (e.g. patients could be included with a PCI or with an acute myocardial infarction). In addition, patients included in the present study are of European descent, which may limit the generalizability.

In conclusion, in this prospective cohort of patients with clinically manifest vascular disease, a literature-based weighted CAD-associated genetic risk score did not improve prediction of 10-year risk of new cardiovascular events beyond clinical characteristics. The genetic risk score might improve risk prediction of first vascular events in the subgroup of patients with a history of stable atherosclerosis.

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Supplemental table 1. Compostion of the genetic risk score based on coronary artery disease associated SNPs.

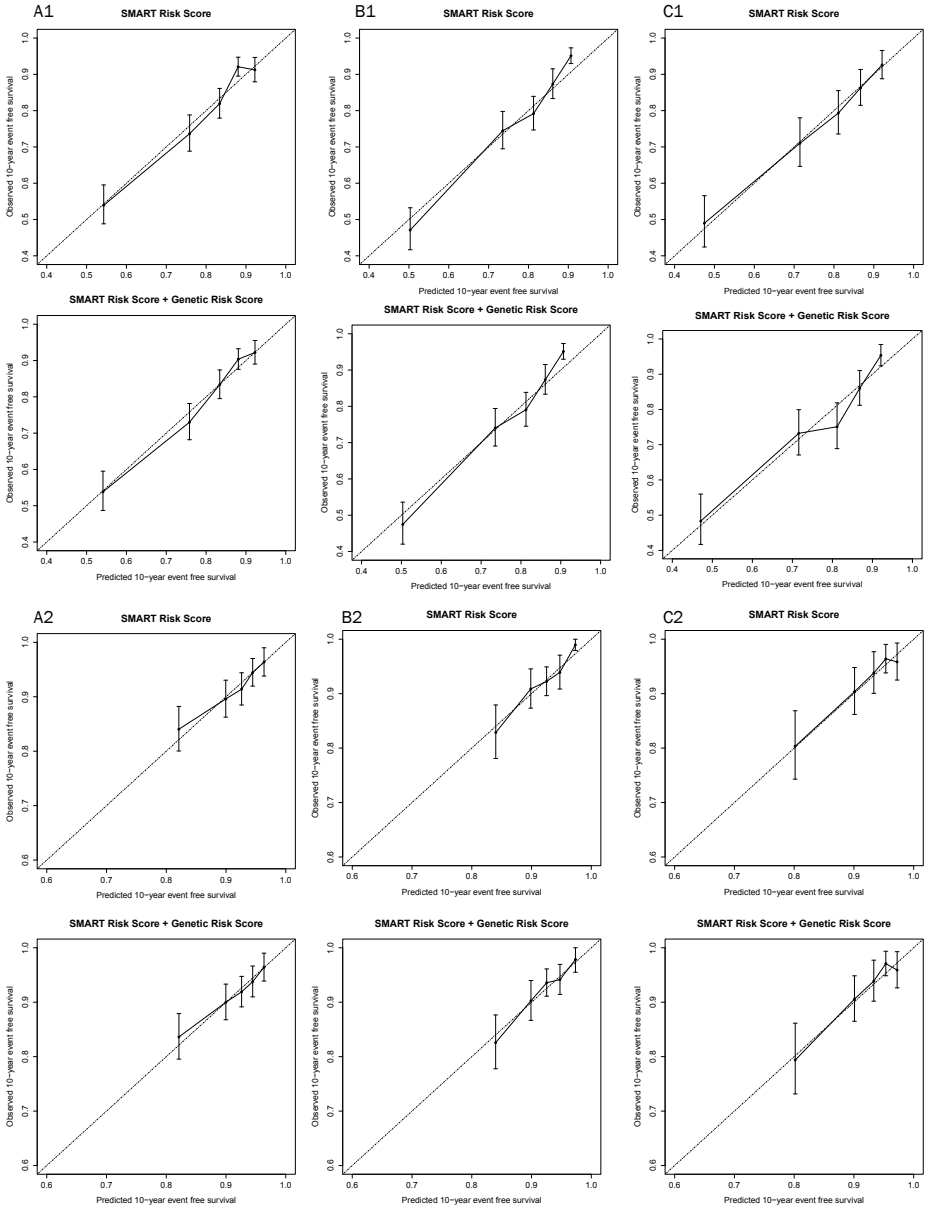
	Reported by literature							
Locus	**SNP**	**Chromosome**	**Effect allele**	**Other allele**	**Effect allele frequency**	**Odds ratio**	**P-value**	**Reference**
PCSK9	rs11206510	1	T	C	0,82	1,08	9.10×10^{-8}	Schunkert et al.[10]
PPAP2B	rs17114036	1	A	G	0,91	1,17	1.43×10^{-8}	Schunkert et al.[10]
MIA3	rs17465637	1	C	T	0,74	1,14	1.36×10^{-8}	Schunkert et al.[10]
SORT1	rs599839	1	A	G	0,78	1,11	2.89×10^{-10}	Schunkert et al.[10]
WDR12	rs6725887	2	C	T	0,15	1,14	1.12×10^{-9}	Schunkert et al.[10]
MRAS	rs2306374	3	C	T	0,18	1,12	3.34×10^{-8}	Schunkert et al.[10]
5p15	rs11748327	5	C	T	0,70	1,25	5.30×10^{-13}	Aoki et al.[19]
TCF21	rs12190287	6	C	G	0,62	1,08	4.64×10^{-11}	Schunkert et al.[10]
PHACTR1	rs12526453	6	C	G	0,67	1,10	1.15×10^{-9}	The CAD Genetics Consortium[9]
ANKS1A	rs17609940	6	G	C	0,75	1,07	2.21×10^{-6}	Schunkert et al.[10]
LPA	rs3798220	6	C	T	0,02	1,51	3.00×10^{-11}	Schunkert et al.[10]
C6orf105	rs6903956	6	A	G	0,08	1,65	2.55×10^{-13}	Wang et al.[21]
7q22	rs10953541	7	C	T	0,75	1,08	3.12×10^{-8}	The CAD Genetics Consortium[9]
ZC3HC1	rs11556924	7	C	T	0,62	1,09	2.22×10^{-9}	Schunkert et al.[10]
CDKN2A, CDKN2B	rs4977574	9	G	A	0,46	1,29	1.35×10^{-22}	Schunkert et al.[10]
ABO	rs579459	9	C	T	0,21	1,10	1.16×10^{-7}	Schunkert et al.[10]
CYP17A1, CNNM2, NT5C2	rs12413409	10	G	A	0,89	1,12	1.47×10^{-6}	Schunkert et al.[10]
LIPA	rs1412444	10	T	C	0,34	1,09	2.76×10^{-13}	Schunkert et al.[10]
CXCL12	rs1746048	10	C	T	0,87	1,09	2.93×10^{-10}	Schunkert et al.[10]
KIAA1462	rs3739998	10	C	G	0,45	1,15	1.27×10^{-11}	Erdmann et al.[20]
APOA5-A4-C3-A1	rs964184	11	G	C	0,13	1,13	8.02×10^{-10}	Schunkert et al.[10]
PDGFD	rs974819	11	T	C	0,29	1,07	2.41×10^{-9}	The CAD Genetics Consortium[9]
SH2B3	rs3184504	12	T	C	0,44	1,07	6.35×10^{-6}	Schunkert et al.[10]
COL4A1, COL4A2	rs4773144	13	G	A	0,44	1,07	4.15×10^{-7}	Schunkert et al.[10]
HHIPL1	rs2895811	14	C	T	0,43	1,07	2.67×10^{-7}	Schunkert et al.[10]
ADAMTS7	rs3825807	15	A	G	0,57	1,08	9.63×10^{-6}	Schunkert et al.[10]
SMG6, SRR	rs216172	17	C	G	0,37	1,07	6.22×10^{-7}	Schunkert et al.[10]
UBE2Z, GIP, ATP5G1, SNF8	rs46522	17	T	C	0,53	1,06	3.57×10^{-6}	Schunkert et al.[10]
LDLR	rs1122608	19	G	T	0,77	1,14	9.73×10^{-10}	Schunkert et al.[10]
MRPS6	rs9982601	21	T	C	0,15	1,18	4.22×10^{-10}	Schunkert et al.[10]

Supplemental table 2. Discrimination and reclassification after adding the genetic risk score to the SMART risk score for the prediction of the composite vascular outcome and myocardial infarction for specific subgroups of patients.

	C-statistic SRS	C-statistic SRS + GRS	Categorical NRI*	Continuous NRI
Stable atherosclerosis at baseline				
Composite vascular outcome	0.71 (0.69 - 0.74)	0.71 (0.69 - 0.74)	0.01 (-0.02 - 0.04)	0.14 (0.03-0.25)
Myocardial infarction	0.67 (0.63 - 0.71)	0.67 (0.63 - 0.71)	0.06 (-0.02 - 0.03)	-0.07 (-0.24 - 0.11)
Acute arterial thrombotic events at baseline				
Composite vascular outcome	0.69 (0.67 - 0.72)	0.69 (0.67 - 0.72)	0.00 (-0.01 - 0.02)	0.02 (-0.10 - 0.13)
Myocardial infarction	0.68 (0.64 - 0.71)	0.68 (0.64 - 0.72)	0.04 (-0.01 - 0.08)	0.08 (-0.12 - 0.26)
Stable atherosclerosis without CAD				
Composite vascular outcome	0.72 (0.69 - 0.76)	0.73 (0.70 - 0.76)	0.03 (-0.01 - 0.07)	0.21 (0.06 - 0.36)
Myocardial infarction	0.70 (0.64 - 0.76)	0.70 (0.64 - 0.76)	0.01 (-0.01 - 0.03)	-0.05 (-0.28 - 0.19)

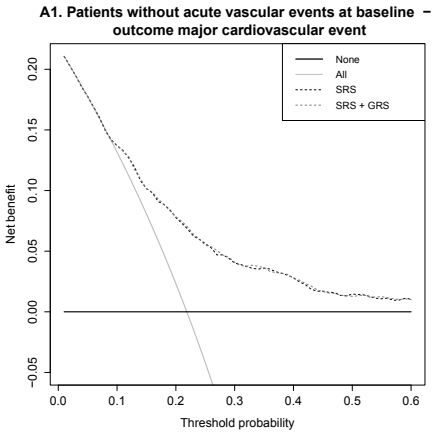
* Five 10-year risk categories were constructed: 0-10%, 10-20%, 20-30%, 30-40%, >40%.

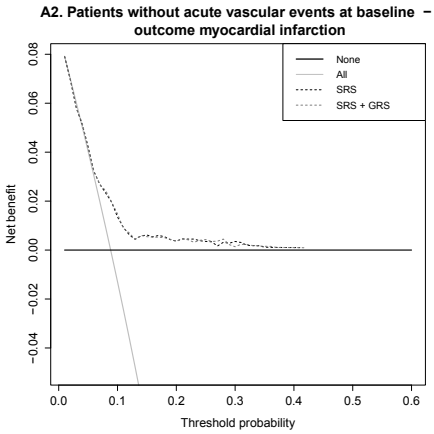
Supplemental figure 1. Calibration plots for the prediction of the composite vascular outcome and myocardial infarction for specific subgroups of patients.

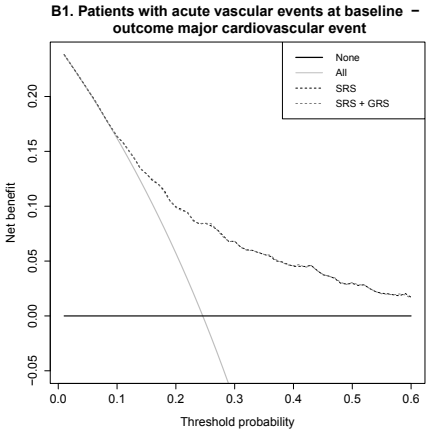


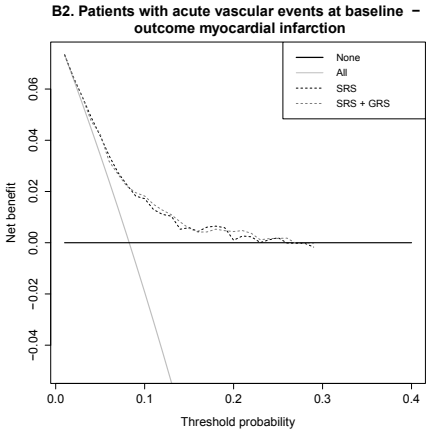
Predicted versus observed 10-year survival within quintiles of predicted survival.
Calibration is presented for patients without acute vascular events at baseline for major cardiovascular events as the outcome (A1) and myocardial infarction as the outcome (A2), for patients with acute arterial thrombotic events at baseline (composite vascular outcome=B1 and myocardial infarction=B2) and for patients with stable atherosclerosis at baseline without a history of coronary artery disease (composite vascular outcome=C1 and myocardial infarction=C2).

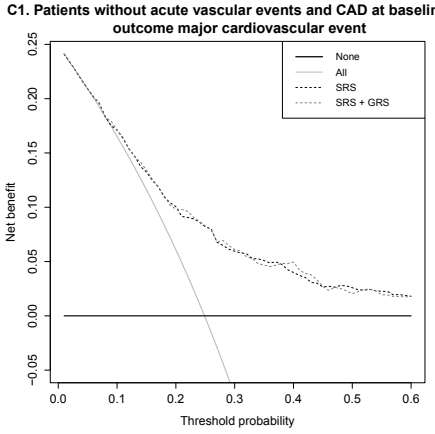
Supplemental figure 2. Decision curves.

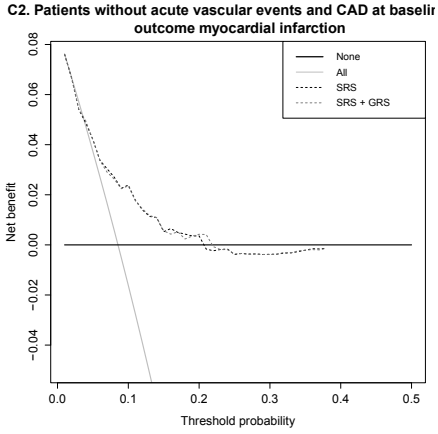












8

Distribution and determinants of coronary artery calcium scores in patients with established coronary artery disease

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Submitted

ABSTRACT

Background

Coronary artery calcium (CAC) can be considered a surrogate for the lifetime exposure to known and unknown risk factors. In patients with established coronary artery disease (CAD), little is known regarding the determinants, distribution, and prognosis of CAC. CAC may be a tool to estimate risk and to tailor risk factor management in these patients.

Methods

CAC scores were measured by computed tomography in patients with established CAD enrolled in the SMART Study. The association between clinical variables and CAC categories (0-100, 101-400, 401-1000 and >1000) was assessed using ordinal logistic regression analyses. Furthermore, the association between the number of risk factors (current smoking, LDL-cholesterol >1.8 mmol/l, SBP >140 mmHg or DBP >90 mmHg, diabetes mellitus and BMI <18.5 or >25 kg/m^2), and CAC scores was determined.

Results

A total of 193 patients was included with a mean age of 60±8 years of whom 168 (87%) were male. The median CAC score was 375 [101-1021], 48 patients (25%) had CAC scores between 0-100 (median 21 [4 – 52]) and 50 patients (25%) had CAC scores >1000. Determinants for increasing CAC scores were multi-vessel coronary disease (two-vessel disease OR 1.8 (95%CI 0.9 – 3.5), three-vessel disease OR 4.9 (95%CI 2.5 – 9.7)), age (OR 1.6 per 5 years, 95%CI 1.4 – 1.9), ever smoking (OR 3.1, 95%CI 1.6 – 5.9), body mass index (BMI) (OR 1.1 per 1 kg/m^2, 95%CI 1.0 – 1.1), intima-media thickness (OR 1.1 per 0.1 mm, 95%CI 1.0 – 1.3) and ankle brachial index (ABI) (OR 0.8 per 0.1, 95%CI 0.7 – 1.0). No association was found between the number of risk factors and CAC (2 risk factors; OR 1.4 (95%CI 0.7 – 2.8), 3 risk factors; OR 1.1 (95%CI 0.5 – 2.3), 4-5 risk factors; OR1.1 (95%CI 0.4 – 2.9), compared with 0-1 risk factors).

Conclusions

In patients with established CAD, a wide distribution of CAC is present. Determinants for increasing CAC scores were multi-vessel coronary disease, age, smoking, BMI, IMT and ABI. The number of risk factors did not influence the risk of higher CAC scores.

INTRODUCTION

Coronary artery calcium (CAC) is an accepted surrogate measure for the presence and extent of atherosclerosis in the coronary arteries. The clinical value of CAC in asymptomatic and symptomatic patients without established vascular disease has been studied extensively, demonstrating substantially increased risks with higher CAC scores and improved risk prediction of coronary heart disease beyond traditional risk factors[1-8].

The group of patients with prevalent coronary artery disease (CAD) has not yet been the focus of studies investigating the value of CAC. This is probably due to the fact that these patients are all considered at high risk of recurrent vascular events[9, 10]. However, recently a wide risk distribution, ranging from very low to very high, for the development of recurrent vascular events was demonstrated in these patients[11]. Therefore, identifying patients with the most severe forms of CAD or identifying patients with lowest risk of recurrent vascular events may be important to consider further differentiation in therapy, such as the use of novel lipid-lowering therapy to further reduce LDL cholesterol or the use of immunomodulants[12]. CAC maybe helpful in classification of risk of new vascular events and thus in individualized management, since patients with very high CAC and therefore more extensive atherosclerosis in the coronary arteries may be at higher risk of recurrent vascular events compared with patients with low CAC. If variation in CAC exists in patients with established coronary artery disease (CAD), the assessment of CAC may be especially important since these patients all deserve treatment of their traditional risk factors according to current guidelines. Nevertheless, risk estimation using traditional risk factors is challenging in these patients. For example, LDL-cholesterol levels generally respond well to lipid-lowering medication, but the risk associated with prolonged elevated LDL-cholesterol levels does not change instantly. Since CAC can be considered the result of lifetime exposure to known and unknown risk factors, and cannot directly be influenced by medical interventions, it may better reflect the actual risk in vascular territories.

To gain more insight in the clinical relevance of the presence of CAC in patients with established CAD, the aim of the present study is to determine the CAC distribution, also in relation to risk factors and predicted risk of recurrent vascular events, and to identify important determinants of CAC in these patients.

METHODS

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. The rationale and design of the SMART study have been described previously[13]. In short, the SMART study is an ongoing single-center prospective cohort study

that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular disease or a vascular risk factor. A subgroup of patients received CT-scanning, with the primary objective to quantify the additional prognostic value of advanced CT-based imaging techniques over traditional risk factors as well as existing risk prediction models for future cardiovascular events.

For this study data were used of consecutive patients who were newly referred to the University Medical Center between 2013-2015 with a history of clinically manifest CAD. CAD was defined as myocardial infarction, angina pectoris or coronary revascularization (coronary bypass surgery or coronary angioplasty). Patients were enrolled after stabilization of their coronary disease. Main exclusion criteria were: terminal malignancy, not independent in daily activities or not sufficiently fluent in Dutch language. Additional exclusion criteria related to CT angiography were: renal failure (eGFR<45 ml/min/1.73m^2), need for intravenous fluid pre-hydration and known contrast allergy. The Ethics Committee of the University Medical Center Utrecht approved the study and all participants gave their written informed consent.

Baseline examination and definitions

All patients underwent a standardized extensive vascular screening including a uniform questionnaire on medical history, symptoms of cardiovascular disease and presence of cardiovascular risk factors, physical examination (height, weight, waist circumference, systolic and diastolic blood pressure) and laboratory tests to determine fasting serum lipid, glucose and creatinine levels. In addition, patients were screened non-invasively for presence of asymptomatic atherosclerotic diseases other than the qualifying diagnosis, by measuring the ankle brachial index at rest, ultrasonography of the abdominal aorta and duplex ultrasound of the common and internal carotid arteries.

Multi-vessel coronary disease was defined as a history of hemodynamically significant stenoses (70% or a fractional flow reserve <0.75) in at least two of the three major epicardial coronary arteries. Reduced left-ventricular ejection fraction was defined as left ventricular ejection fraction of <55%.

Polyvascular disease was defined in the presence of additional arterial disease in one or more other vascular territories such as cerebrovascular disease (CVD), peripheral artery disease (PAD) or the presence of an abdominal aortic aneurysm (AAA). The presence of cerebrovascular disease was defined as a history of a transient ischemic attack, cerebral infarction, cerebral ischemia, amaurosis fugax, retinal infarction or a history of carotid surgery. Peripheral artery disease was defined as a symptomatic and documented obstruction of distal arteries of the lower extremity or interventions (Fontaine classification II-IV confirmed with ankle-brachial index (ABI) ≤0.90 in rest or decrease of ABI >20% after exercise, percutaneous transluminal angioplasty, bypass or amputation). The presence of abdominal aortic aneurysm was defined as a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter ≥3 cm, measured with ultrasonography) or a history of AAA surgery.

A positive family history was defined as at least one parent or sibling with cardiovascular disease before the age of sixty. diabetes mellitus type 2 was defined as fasting serum glucose ≥7.0 mmol/l, non-fasting serum glucose ≥11.1 mmol/l or the use of oral anti-hyperglycemic agents or insulin. Body mass index (BMI) was calculated as weight divided by height squared. Waist circumference was measured halfway between the lower rib and iliac crest. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or the use of blood pressure-lowering drugs. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Hyperlipidemia was defined as total cholesterol >5.0 mmol/l, low-density lipoprotein cholesterol >2.5 mmol/l or the use of lipid-lowering drugs.

Risk factors and predicted 10-year risk of recurrent vascular events

To determine risk distribution of CAC in patients with different cardiovascular health profiles, the number of risk factors was scored according to the targets of risk factors which should be attained according to the guidelines[9, 10]. Risk factors were defined as: current smoking, LDL-cholesterol >1.8 mmol/l, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, presence of diabetes mellitus and BMI <18.5 or >25 kg/m^2.

To determine risk distribution of CAC in patients with different risks of recurrent vascular events, the absolute 10-year risk of recurrent vascular events (myocardial infarction, stroke or vascular mortality) was estimated with the SMART risk score (supplemental table 1)[11]. This risk score was developed specifically in patients with clinically manifest vascular disease and was based on easy-to-measure patient characteristics (age, sex), traditional risk factors (current smoking, systolic blood pressure, diabetes mellitus, HDL-cholesterol, total cholesterol, eGFR and hs-CRP) and vascular disease history of the patient (CAD, CVD, PAD, AAA and years since first vascular event).

Coronary artery calcium measurement

Non-contrast enhanced coronary artery calcium scoring was performed using an ECG gated 256-slice Multi-Detector CT scanner (Philips Healthcare, Best, the Netherlands) using a vendor recommended protocol with 120 kVp and automated choice of mAs value based on patients weight. Slice thickness was 3.0 mm. CAC scores were calculated on a dedicated workstation (EBW, Philips Healthcare) and expressed as Agatston scores. With the Agatston score, coronary artery calcium is quantified by multiplying the area of a calcified lesion by a cofactor that depends on the lesions peak CT number[14]. Scores of all the calcified lesions are summed to determine the Agatston score.

Data analyses

Data are presented as percentages for categorical variables, as mean with standard deviation (SD) for normally distributed variables and as median with interquartile range [IR] for non-nor-

mally distributed variables. CAC was categorized into four groups based on the Agatston scores: 0-100, 101-400, 401-1000 and >1000. Patients characteristics were categorized according to these CAC categories and also according to the number of risk factors (0-1, 2, 3, 4-5).

To reduce selection bias and increase statistical rigor, missing data (<3.0%) were singly imputed using predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming these values were missing at random[15].

The association between clinical variables (multi-vessel coronary disease, reduced left ventricular ejection fraction, age, sex, positive family history of cardiovascular disease, polyvascular disease, history of hypertension, systolic blood pressure, hyperlipidemia, LDL-cholesterol, HDL-cholesterol, BMI, diabetes mellitus type 2, ever smoking, smoking (pack years), pulse pressure, ankle brachial index, intima media thickness) and higher CAC categories was assessed using ordinal logistic regression analyses. The parallel-lines assumption was not violated. The odds ratio can be interpreted as the odds of being in a higher CAC category with a higher independent variable. Two models were constructed. Model I included only the clinical variable. Model II included age and sex. Sensitivity analyses were performed in men (n=168), and in patients with a history of myocardial infarction (n=108).

Ordinal logistic regression analyses were also performed to determine the association between the number of risk factors, 10-year risk of myocardial infarction, stroke or vascular mortality, and CAC. In addition, a bar plot was used to demonstrate the percentage of patients for different cutoff points of number of risk factors (0-1, ≥2, ≥3, ≥4, not mutually exclusive) and different cutoff points of predicted vascular risk (0-10%, ≥10%, ≥15%, ≥20%, not mutually exclusive), stratified for CAC categories and compared using the chi-square test or Fisher's exact test. Analyses were performed with R statistical software V.3.1.1 (http://R-project.org).

RESULTS

Baseline characteristics

A total of 193 patients with established CAD was included with a mean age of 60±8 years of whom 168 (87%) patients was male (table 1). Multi-vessel coronary disease was present in 123 (64%) of the patients. Most patients received blood-pressure lowering treatment (n=157, 81%), lipid-lowering treatment (n=163, 85%) and oral anticoagulants (n=173, 90%).

The median CAC score was 375 [101 – 1021]. In men, the median CAC score was 389 [116 – 1066] and in women 264 [22 – 698]. Forty-eight patients (25%) had CAC scores between 0-100 (median 21 [4 – 52]), of whom 6 (3%) had a CAC score of 0. CAC scores between 101-400 (median 235 [146 – 320]) were present in 52 (27%) patients, CAC scores between 401-1000 (median 592 [476 – 730]) in 43 (22%) patients and 50 (26%) patients had a CAC score >1000 (median 1687 [1308 – 3136]) (figure 1). Stratifying the baseline characteristics accord-

Table 1. Baseline characteristics study population.

	Patients with coronary artery disease (n = 193)
Age (years)	60 (8)
Male sex (%)	168 (87)
Multi-vessel coronary disease	127 (66)
Reduced left ventricular ejection fraction	32 (17)
Polyvascular disease (%)	19 (10)
Positive family history of cardiovascular disease (%)	92 (48)
Diabetes Mellitus type 2	30 (16)
Ever smoking (%)	148 (77)
Current smoking (%)	50 (26)
Pack years	14 [1 - 32]
Blood pressure-lowering agents (%)	157 (81)
Lipid-lowering agents (%)	163 (85)
Anti-thrombotic agents (%)	173 (90)
Systolic blood pressure (mmHg)	130 (15)
Diastolic blood pressure (mmHg)	77 (9)
Body mass index (kg/m2)	27 (4)
Waist circumference (cm)	98 (11)
Total cholesterol (mmol/l)	4.3 (1.0)
Triglycerides (mmol/l)	1.4 [1.1 - 1.9]
HDL-cholesterol (mmol/l)	1.2 (0.3)
LDL-cholesterol (mmol/l)	2.4 (0.9)
eGFR (ml/min/1.73m2)	88 (12)

Data are expressed as mean (SD), median [interquartile range] or number (percentage); eGFR = Glomerular Filtration Rate as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

ing to these CAC categories, demonstrated higher age (56±9 years in CAC category 0-100 versus 63±7 years in CAC category >1000), higher proportion of patients with multi-vessel coronary disease (38% in CAC category 0-100 versus 84% in CAC category >1000), increasing number of patients with a history of smoking (60% in CAC category 0-100 versus 88% in CAC category >1000), higher number of patients with diabetes mellitus (10% in CAC category 0-100 versus 20% in CAC category >1000) with higher CAC scores (table 2).
For the categories of number of risk factors, no increase in CAC was observed over the categories (supplemental table 2).

Determinants of coronary artery calcium

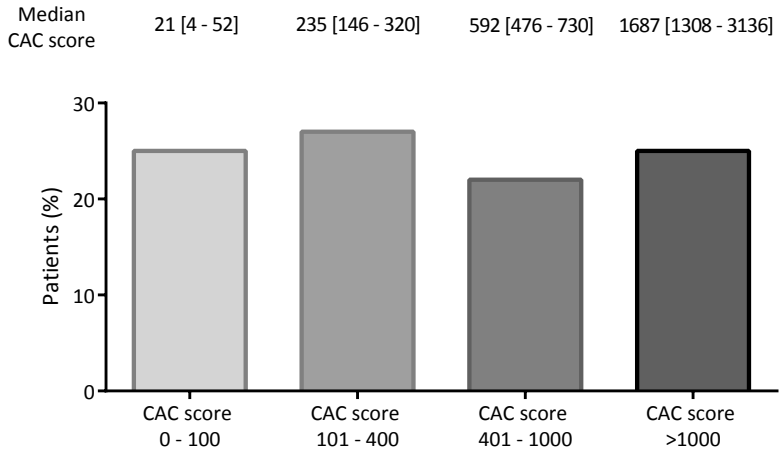
Two- and three-vessel disease, compared with one-vessel disease, were both associated with CAC (OR 1.8, 95%CI 0.9 – 3.5 and 4.9, 95%CI 2.5 – 9.7), whereas no association was found for reduced left ventricular ejection fraction (OR 1.0, 95%CI 0.5 – 2.0) (table 3). Regarding

Table 2. Baseline characteristics stratified for categories of CAC scores.

	CAC scores 0 - 100 Median: 21 [4 - 52] (n = 48)	CAC scores 101 - 400 Median: 235 [146 - 320] (n = 52)	CAC scores 401 - 1000 Median: 592 [476 - 730] (n = 43)	CAC scores >1000 Median: 1687 [1308 - 3136] (n = 50)
Age (years)	56 (9)	59 (7)	64 (7)	63 (7)
Male sex (%)	38 (79)	47 (90)	38 (88)	45 (90)
Multi-vessel coronary disease	21 (44)	31 (60)	33 (77)	42 (84)
Reduced left ventricular ejection fraction	5 (10)	10 (19)	9 (21)	8 (16)
Polyvascular disease (%)	1 (2)	7 (13)	4 (9)	7 (14)
Positive family history of cardiovascular disease	26 (53)	26 (50)	18 (42)	22 (45)
Diabetes Mellitus type 2	5 (10)	8 (15)	7 (16)	10 (20)
Ever smoking (%)	29 (60)	38 (73)	37 (86)	44 (88)
Current smoking (%)	19 (40)	8 (15)	15 (35)	8 (16)
Pack years	10 [0 - 28]	15 [0 - 33]	13 [6 - 33]	22 [7 - 34]
Blood pressure-lowering agents (%)	37 (77)	42 (81)	36 (84)	42 (84)
Lipid-lowering agents (%)	39 (81)	42 (81)	39 (91)	43 (86)
Anti-thrombotic agents (%)	42 (88)	47 (90)	39 (91)	45 (90)
Systolic blood pressure (mmHg)	127 (15)	130 (14)	130 (14)	132 (15)
Diastolic blood pressure (mmHg)	76 (9)	79 (10)	77 (9)	76 (8)
Body mass index (kg/m^2)	26 (4)	27 (4)	27 (4)	27 (4)
Waist circumference (cm)	94 (13)	99 (12)	99 (11)	98 (10)
Total cholesterol (mmol/l)	4.6 (1.1)	4.3 (1.0)	4.2 (0.9)	4.2 (1.1)
Triglycerides (mmol/l)	1.5 [1.2 - 2.0]	1.5 [1.1 - 1.8]	1.4 [1.1 - 1.9]	1.4 [1.1 - 1.9]
HDL-cholesterol (mmol/l)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)	1.2 (0.4)
LDL-cholesterol (mmol/l)	2.6 (0.9)	2.5 (0.8)	2.3 (0.9)	2.3 (0.9)
eGFR (ml/min/1.73m^2)	89 (13)	90 (13)	84 (10)	87 (12)

Data are expressed as mean (SD), median [interquartile range] or number (percentage); eGFR = Glomerular Filtration Rate as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Figure 1. Distribution of CAC scores in patients with established CAD.



unmodifiable risk factors, only age was a determinant for the presence of CAC (OR per 5 years: 1.6, 95%CI 1.4 – 1.9). For the traditional risk factors, ever smoking (OR 3.1, 95%CI 1.6 – 5.9), pack years (OR per 10 pack years: 1.1, 95%CI 1.0 – 1.3) and BMI (OR 1.1, 95%CI 1.0 – 1.1) were associated with higher CAC scores. The measures of subclinical end-organ damage were all associated with CAC: carotid intima-media thickness (OR 1.1; 95%CI 1.0 – 1.3) was positively associated whereas ankle brachial index (OR 0.8, 95%CI 0.7 – 1.0) was inversely associated with CAC. Sensitivity analyses in men and in patients with a history of myocardial infarction yielded in general similar results (supplemental table 3).

Association between CAC and number of risk factors and predicted 10-year risk of recurrent vascular events.

The predicted 10-year risks (for each cutoff point) estimated using the SMART risk score did increase with higher CAC scores (all p-values <0.01). The number of risk factors was not related to higher CAC scores (p-values ranging from 0.4-0.9) (figure 2). After adjustment for age and sex, no association was found between number of risk factors and higher CAC scores (table 4). A graded association was found between the 10-year predicted risk of recurrent vascular events and the amount of CAC. The ORs of higher CAC were 3.0 (95%CI 1.5 – 6.2) in patients with a predicted 10-year risk of 10-15% (n=65), 3.5 (95%CI 1.6 – 7.6) in patients with a predicted 10-year risk of 15-20% (n=30), and 5.7 (95%CI 2.7 – 12.3) in patients with a 10-year risk of >20% (n=47), when compared with patients with a predicted 10-year risk of 0-10% (n=51).

Table 3. Determinants of CAC in patients with established coronary artery disease.

	Odds ratio (95%CI)	
	Model 1	Model 2
Heart disease		
2-vessel disease (compared with 1-vessel)	2.30 (1.23 - 4.37)	1.78 (0.92 - 3.46)
3-vessel disease (compared with 1-vessel)	5.84 (3.03 - 11.49)	4.88 (2.50 - 9.73)
Reduced left ventricular ejection fraction (yes)	1.11 (0.56 - 2.20)	0.96 (0.48 - 1.95)
Unmodifiable risk factors		
Age (per 5 years)	1.63 (1.37 - 1.95)	1.62 (1.36 - 1.94)
Male sex	1.79 (0.82 - 3.96)	1.50 (0.68 - 3.37)
Family history of CVD (yes)	0.79 (0.47 - 1.31)	0.96 (0.57 - 1.62)
Polyvascular disease (yes)	1.97 (0.86 - 4.62)	2.01 (0.87 - 4.79)
Traditional risk factors		
Hypertension (yes)	1.34 (0.81 - 2.24)	1.16 (0.69 - 1.94)
Systolic blood pressure (per 10 mmHg)	1.15 (0.96 - 1.37)	1.06 (0.89 - 1.28)
Hypercholesterolemia (yes)	0.62 (0.33 - 1.16)	0.83 (0.44 - 1.57)
LDL (per 0.1 mmol/l)	0.97 (0.95 - 1.00)	0.98 (0.95 - 1.01)
HDL (per 0.1 mmol/l)	0.97 (0.89 - 1.06)	0.96 (0.87 - 1.05)
BMI (per kg/m^2)	1.03 (0.96 - 1.11)	1.06 (0.99 - 1.14)
Diabetes Mellitus type II (yes)	1.57 (0.78 - 3.18)	1.02 (0.49 - 2.12)
Ever smoking (yes)	3.07 (1.66 - 5.78)	3.06 (1.62 - 5.88)
Smoking (per 10 pack years)	1.12 (0.99 - 1.28)	1.12 (0.98 - 1.28)
Pulse pressure (per 1 mmHg)	1.03 (1.00 - 1.05)	1.00 (0.98 - 1.03)
Asymptomatic atherosclerotic disease		
Ankle brachial index (per 0.1)	0.79 (0.65 - 0.96)	0.80 (0.65 - 0.97)
Carotid intima-media thickness (per 0.1 mm)	1.18 (1.04 - 1.34)	1.10 (0.97 - 1.26)

Results are expressed as odds ratios with 95% confidence intervals. Model 1: crude. Model 2: age and sex.

DISCUSSION

The present study demonstrates a wide distribution of CAC in patients with established CAD. Determinants for higher CAC scores are multi-vessel coronary disease, age, ever smoking, pack years, body mass index, IMT and ABI. Furthermore, higher CAC scores were associated with higher estimated 10-year risks of recurrent vascular events, whereas there was no relation between the number of risk factors and CAC.

To determine the potential diagnostic or predictive value of CAC in patients with established CAD, the first question to answer is whether a distribution of CAC scores exists in these patients. We demonstrated that patients were almost equally divided across the CAC categories of 0-100, 101-400, 401-1000 and >1000, which are the categories important for the risk of

Table 4. Association between CAC scores and number of risk factors and estimated 10-year risk of cardiovascular events.

A

Number of risk factors	Odds ratio (95%CI)	
	Model I	Model II
0-1	1.0 (ref)	1.0 (ref)
2	1.33 (0.69 - 2.61)	1.43 (0.73 - 2.83)
3	1.10 (0.52 - 2.30)	1.07 (0.50 - 2.29)
4-5	1.08 (0.39 - 2.99)	1.05 (0.37 - 2.94)

B

Estimated 10-year risk cardiovascular events	Odds ratio (95%CI)
0-10%	1.0 (ref)
10-15%	2.97 (1.45 - 6.18)
15-20%	3.47 (1.60 - 7.62)
>20%	5.68 (2.67 - 12.32)

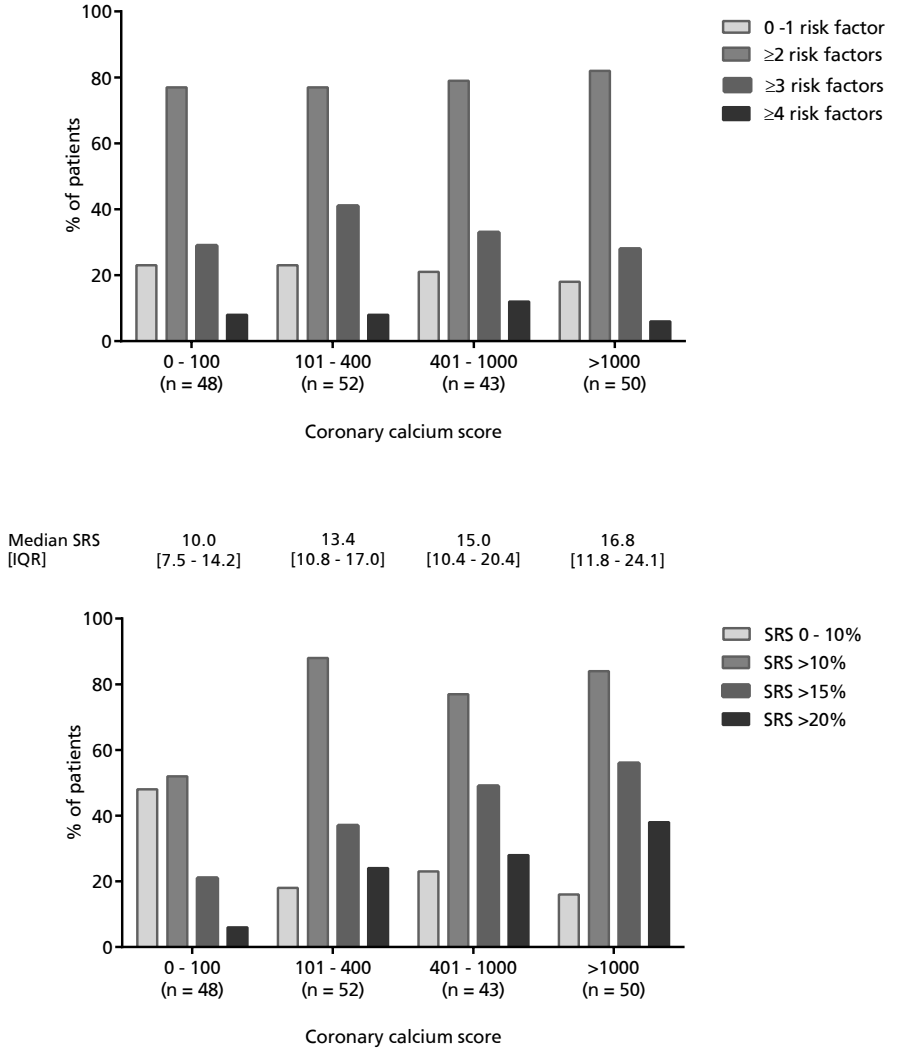
Model I: crude. Model II: age and sex.

first vascular events. Whether these CAC score categories are of similar importance for risk assessment for recurrent vascular events as for the risk of first vascular events[2, 16, 17] should be investigated prospectively.

In the identification of determinants of higher CAC scores, multi-vessel coronary disease was found to be an important determinant for CAC, indicating a greater atherosclerotic burden. Furthermore, increasing age was found to be an important determinant for CAC, which is in agreement with studies performed in asymptomatic and symptomatic patients[17-19]. Moreover, ever smoking conferred a threefold risk of higher CAC scores compared with patients who never smoked. The importance of smoking is in concordance with previous research, demonstrating a 10-year difference in the calcification process between smokers and non-smokers[20]. For the measures of subclinical end-organ damage, IMT was positively associated with higher CAC which was expected since higher risks of stroke have been described for higher CAC scores[7, 21, 22]. ABI was negatively associated with CAC, meaning that decreasing ABI results in a higher risk of CAC, which was also demonstrated in a study population of patients free of vascular disease[23]. Because of these findings, CAC may be considered an indicator of generalized atherosclerosis, and not only an indicator of atherosclerosis in the coronary arteries.

The number of known risk factors was equally distributed over the CAC strata and no association was found between the number of risk factors and the presence of CAC. Two of these risk factors were serum LDL-cholesterol levels and blood pressure. Since patients are all treated according to national guidelines, most patients (>80%) received lipid-lowering and blood pressure-lowering agents. Therefore, the measured values of cholesterol and blood pressure may not be true indicators of the degree of risk factors to which patients have been

Figure 2. Distribution of number of risk factors and predicted 10-year risk of recurrent cardiovascular events over strata of CAC scores.



SRS = SMART risk score; predicted 10-year risk of recurrent vascular events.

exposed to in the past. Patients with low LDL-cholesterol serum levels may be patients with high cholesterol levels in the past who receive intensive lipid-lowering treatment, or patients whose LDL-cholesterol levels were never elevated. Taking this into account, one can imagine that risk stratification in patients with established CAD could be improved by adding CAC scores, as these scores are not directly influenced by recently initiated medical interventions targeting risk factors or recent changes in lifestyle.

Guidelines all consider patients with a history of coronary artery disease at high risk of recur-

rent vascular events (10-year risk >20%). In the present study using a risk score specifically developed for estimating the risk of recurrent vascular events in patients with established vascular disease, demonstrated a 10-year risk of recurrent vascular events of >20% in merely 47 patients (24%) and a 10-year risk of <10% in 51 patients (26%). Therefore, simply stating that all patients with CAD have a recurrent vascular risk of >20% is probably unjustified. Further risk stratification in patients with CAD may be useful to consider further differentiation in therapy, such as PCSK9 inhibitors, for a specific group of patients with CAD. High CAC is probably an important risk factor for the development of recurrent vascular events because of the strongly graded association found between the SMART risk score and CAC scores. Still, there are patients who are considered at low risk for recurrent vascular events using this risk score but with very high CAC scores and vice versa. Therefore it would be worthwhile to determine whether CAC scoring provides additional information beyond clinical characteristics in patients with CAC, which should be evaluated prospectively. Besides the fact that risk prediction of subsequent vascular events might be improved by adding CAC, information on their CAC score may give patients insight in the severity of their vascular disease and thus the importance of risk factor management and lifestyle changes[24, 25].

A more detailed assessment of coronary calcification in addition to the Agatston score might be valuable in the light of our finding that a wide distribution of CAC in patients with established CAD exists. Scoring of the amount of calcium in the coronary arteries using the Agatston score involves an upward weighted score with higher plaque density. However, recently it was demonstrated that CAC density was inversely related with incident cardiovascular disease[26], as denser calcified plaques may indicate more stable plaques and less calcified (soft) plaques more instable plaques. Furthermore, the regional distribution of coronary calcifications may also be of importance since increase in CAC in individual coronary arteries (independent of the total Agatston score) was related with different risks of all-cause mortality (e.g. left main: HR 1.2 (95%CI 1.1 – 1.3), right coronary artery: HR 1.0 (95%CI 1.0 – 1.0))[27]. In addition, more diffuse coronary calcifications are related with a higher risk of cardiovascular events compared with focal coronary calcifications[28].

The present study has several strengths, including the evaluation of CAD patients from routine clinical practice being treated according to national guidelines. Furthermore extensive information is available regarding risk factors related with cardiovascular events. Limitations need to be considered as well. The study population consisted of 193 patients with different severity of their clinically manifest CAD, which may have led to limited statistical power resulting in limited precision of OR estimates. To test the robustness of our findings, sensitivity analyses were performed in patients with a history of acute myocardial infarction, demonstrating similar results. Previously it was demonstrated that the degree of CAC depends on national and ethnic influences, with the highest prevalence of CAC found in Caucasian and the lowest in Chinese groups[18]. Since the current study population consists mainly of Caucasian persons, these results may not be generalizable to all patients with CAD. The present study was a

cross-sectional study. To evaluate the prognostic value of CAC in patients with established CAD a prospective cohort study is needed.

In conclusion, in patients with CAD there is a wide distribution of CAC. Determinants of increasing CAC scores were multi-vessel coronary disease, age, smoking, BMI, IMT and ABI. Furthermore, increasing CAC scores were observed in patients with a higher predicted risk of recurrent vascular events, whereas there was no relation between CAC and the number of risk factors.

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SUPPLEMENTARY INFORMATION

Supplemental table 1. Calculation of the SMART risk score.

10-year cardiovascular disease risk (%) = (1- 0.81066 $^{\exp[A + 2.099])}$ x 100%, where

A = -0.0850 x age in years + 0.00105 x (age in years)^2 + 0.156 [if male] + 0.262 [if current smoker] + 0.00429 x systolic blood pressure in mmHg + 0.223 [if diabetic] + 0.140 [if history of coronary artery disease] + 0.406 [if history of cerebrovascular disease] + 0.558 [if abdominal aortic aneurysm] + 0.283 [if peripheral artery disease] + 0.0229 x years since first diagnosis of vascular disease - 0.426 x HDL-cholesterol in mmol/L + 0.0959 x total cholesterol in mmol/L - 0.0532 x eGFR in mL/min/1.73m² + 0.000306 x (eGFR in mL/min/1.73m²)2 + 0.139 x log(hs-CRP in mg/dL)

Supplemental table 2. Baseline characteristics stratified according to number of risk factors.

	0-1 risk factor Median CAC: 357 [90 - 671] (n = 41)	2 risk factors Median CAC: 419 [80 - 1099] (n = 89)	3 risk factors Median CAC: 340 [112 - 825] (n = 47)	4-5 risk factors Median CAC: 320 [100 - 673] (n = 16)
Age (years)	61 (7)	60 (9)	61 (8)	61 (8)
Male sex (%)	35 (85)	77 (87)	42 (89)	14 (88)
Multi-vessel coronary disease	25 (61)	54 (61)	37 (79)	11 (69)
Reduced left ventricular ejection fraction	5 (12)	17 (19)	9 (19)	1 (6)
Polyvascular disease (%)	3 (7)	7 (8)	7 (15)	2 (13)
Positive family history of cardiovascular disease (%)	19 (46)	41 (46)	22 (47)	10 (63)
Diabetes Mellitus type 2	0 (0)	7 (8)	12 (26)	11 (67)
Ever smoking (%)	23 (56)	75 (84)	38 (81)	12 (75)
Current smoking (%)	0 (0)	24 (27)	16 (34)	10 (63)
Pack years	10 [0 - 28]	15 [0 - 33]	13 [6 - 33]	22 [7 - 34]
Blood pressure-lowering agents (%)	38 (93)	66 (74)	37 (79)	16 (100)
Lipid-lowering agents (%)	39 (95)	73 (82)	37 (79)	14 (88)
Anti-thrombotic agents (%)	40 (98)	74 (83)	41 (87)	16 (100)
Systolic blood pressure (mmHg)	120 (11)	128 (12)	137 (14)	147 (13)
Diastolic blood pressure (mmHg)	73 (8)	77 (8)	79 (9)	85 (9)
Body mass index (kg/m^2)	24 (2)	27 (4)	28 (2)	30 (5)
Waist circumference (cm)	88 (8)	98 (11)	101 (8)	109 (13)
Total cholesterol (mmol/l)	3.9 (1.1)	4.2 (1.0)	4.7 (0.9)	4.8 (1.0)
Triglycerides (mmol/l)	1.2 [0.9 - 1.7]	1.4 [1.1 - 2.0]	1.6 [1.3 - 1.9]	1.8 [1.5 - 2.2]
HDL-cholesterol (mmol/l)	1.2 (0.4)	1.2 (0.3)	1.2 (0.3)	1.1 (0.2)
LDL-cholesterol (mmol/l)	2.1 (0.9)	2.3 (0.8)	2.7 (0.8)	2.8 (1.0)
eGFR (ml/min/1.73m^2)	85 (11)	89 (12)	90 (12)	84 (17)

Data are expressed as mean (SD), median [interquartile range] or number (percentage); eGFR = Glomerular Filtration Rate as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Supplemental table 3. Determinants of coronary calcium score in men and in patients with a history of myocardial infarction.

		Men (n = 168)	History of MI (n = 108)
	Model	Odds ratio	Odds ratio
Heart disease			
2-vessel disease (compared with 1-vessel)	I	2.84 (1.42 - 5.78)	2.09 (0.90 - 4.93)
	II	2.13 (1.04 - 4.39)	1.42 (0.59 - 3.44)
3-vessel disease (compared with 1-vessel)	I	6.63 (3.24 - 13.90)	5.37 (2.23 - 13.37)
	II	5.36 (2.61 - 11.26)	4.00 (1.63 - 10.09)
Reduced left ventricular ejection fraction (yes)	I	1.05 (0.52 - 2.13)	1.27 (0.54 - 2.96)
	II	0.87 (0.42 - 1.81)	0.90 (0.37 - 2.20)
Unmodifiable risk factors			
Age (per year)	I	1.10 (1.06 - 1.14)	1.12 (1.06 - 1.18)
	II	NA	1.11 (1.06 - 1.17)
Male sex	I	NA	2.13 (0.76 - 6.14)
	II	NA	1.59 (0.55 - 4.75)
Family history of CVD (yes)	I	0.88 (0.51 - 1.51)	1.62 (0.82 - 3.22)
	II	1.06 (0.61 - 1.85)	1.72 (0.86 - 3.48)
Polyvascular disease (yes)	I	1.85 (0.76 - 4.80)	1.97 (0.71 - 5.72)
	II	1.67 (0.69 - 4.19)	1.78 (0.62 - 5.33)
Traditional risk factors			
Systolic blood pressure (per 10 mmHg)	I	1.15 (0.95 - 1.40)	1.14 (0.90 - 1.45)
	II	1.07 (0.88 - 1.30)	1.07 (0.84 - 1.37)
Hypertension	I	1.24 (0.72 - 2.14)	1.63 (0.83 - 3.25)
	II	1.10 (0.63 - 1.92)	1.41 (0.70 - 2.85)
LDL (per 0.1 mmol/l)	I	0.97 (0.94 - 1.00)	0.99 (0.96 - 1.03)
	II	0.98 (0.95 - 1.01)	1.00 (0.97 - 1.04)
HDL (per 0.1 mmol/l)	I	0.98 (0.89 - 1.09)	0.93 (0.83 - 1.04)
	II	0.95 (0.86 - 1.06)	0.98 (0.79 - 1.03)
BMI	I	1.01 (0.93 - 1.10)	1.05 (0.97 - 1.15)
	II	1.05 (0.96 - 1.14)	1.05 (0.97 - 1.17)
Diabetes Mellitus type II	I	1.23 (0.60 - 2.53)	1.38 (0.55 - 3.49)
	II	0.81 (0.38 - 1.71)	0.80 (0.29 - 2.16)
Ever smoking	I	2.77 (1.46 - 5.36)	3.48 (1.44 - 8.66)
	II	2.49 (1.29 - 4.88)	4.17 (1.67 - 10.85)
Smoking (per 10 pack years)	I	1.16 (1.00 - 1.39)	1.10 (0.93 - 1.30)
	II	1.14 (0.98 - 1.33)	1.13 (0.95 - 1.35)
Pulse pressure	I	1.03 (1.01 - 1.06)	1.03 (1.00 - 1.06)
	II	1.01 (0.98 - 1.03)	1.01 (0.98 - 1.05)
Asymptomatic atherosclerotic disease			
Ankle brachial index (per 0.1)	I	0.80 (0.65 - 0.98)	0.81 (0.62 - 1.04)
	II	0.82 (0.66 - 1.00)	0.81 (0.61 - 1.04)
IMT (per 0.1)	I	1.17 (1.01 - 1.36)	1.17 (1.01 - 1.36)
	II	1.10 (0.95 - 1.28)	1.20 (0.98 - 1.48)

Results are expressed as odds ratios with 95% confidence intervals. Model I: crude. Model II: age and sex

9

General discussion

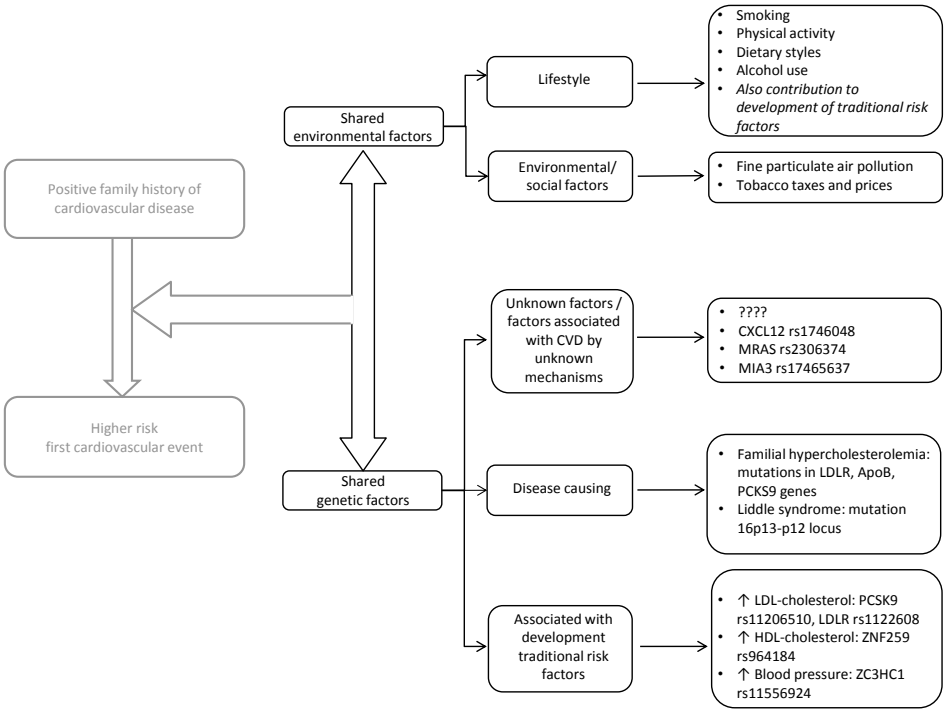
Entire families sometimes show this tendency to early arteriosclerosis. A tendency which cannot be explained in any other way than that in the make-up of the machine bad material was used for the tubing.
(William Osler. The principles and Practice of Medicine. 1892)

Clustering of cardiovascular disease within families was already observed centuries ago. Nowadays, there is strong and consistent evidence of the link between a positive family history and cardiovascular disease[1-8]. This link is due to the fact that family history captures known and unknown factors that interact to cause cardiovascular disease. In addition, since diseases share environmental risk factors and pathophysiologic pathways, family history comprises information on several diseases such as coronary heart disease, but also diseases like diabetes mellitus[9].

UNDERLYING MECHANISM OF CLUSTERING OF CARDIOVASCULAR DISEASE IN FAMILIES

The mechanism underlying clustering of cardiovascular disease is due to shared genetic and environmental factors within families.
One of the best-known genetic disorders leading to cardiovascular disease is the autosomal dominant inherited disorder familial hypercholesterolemia (FH). Familial hypercholesterolemia is caused by a mutation in the apolipoprotein B gene, the PCSK9 gene or – most commonly – in the LDL-receptor gene, leading to strongly elevated plasma cholesterol levels and subsequently a high vascular risk[10]. If a person has a strong family history of premature cardiovascular disease, FH should definitely be considered. Other genetic factors, such as single nucleotide polymorphisms (SNPs) – variations in DNA of one single nucleotide – are also associated with increased cardiovascular risk and occur frequently in the population[11-13]. Although SNPs contribute little to this risk individually, they have a large impact on population level. Shared environmental factors consist of shared lifestyle factors such as smoking and overweight, but also fine particulate air pollution[14] and tobacco prices[15] (figure 1).
Regarding the contribution of shared genetic and environmental factors leading to clustering of cardiovascular disease, opinions are quite divided, varying from: "simply smoking" to "extreme genetic vulnerability of developing cardiovascular disease".
To gain more information regarding the contribution of genetic and environmental factors, twin and adoption studies are of major importance. Twins are a special group of persons as they share the intrauterine environment and age. If a difference exists between the risk of cardiovascular disease for affected monozygote twins and affected dizygote twins, this dif-

Figure 1. Underlying mechanism cardiovascular disease in families



ference would be purely genetic, assuming that the environmental factors for dizygote and monozygote twins are comparable. In adoptees, an increased cardiovascular disease risk for having a biological parent with vascular disease indicates the contribution of shared genetic factors; for having an adoptive parent with vascular disease it indicates the contribution of shared environmental factors.

Several twin studies have been executed. One study consisted of seven thousand monozygotic and fourteen thousand dizygotic twins born between 1886 – 1925[16]. It was observed that if a twin died of coronary heart disease before the age of 55, the risk of death for the other twin increased 4-fold in men and 3-fold in women for dizygotic twins, and 8-fold in men and 15-fold in women for monozygotic twins. Another study, consisting of thousand twins, demonstrated a 2-fold risk of death due to stroke in monozygote twins compared with dizygote twins[17], if their twin died due to stroke. Several adoption studies in Denmark and Sweden demonstrated increased risks of cardiovascular disease or death for having a biological parent with cardiovascular disease (risks ranging from 1.3 – 4.5), while no increased risks were observed for having an adoptive parent with cardiovascular disease (risks ranging from 0.8 – 3.0, all not statistically significant)[18-22].

Taking the results of these twin and adoption studies into account, shared genetic factors

seem to have an important contribution to increased vascular risk in families. However, besides the shared genetic and environmental factors, their interaction also influences vascular risk. For example, in women the odds ratios of myocardial infarction of single exposure to LDL/HDL ≥4.0 and family history of coronary heart disease were 1.8 and 2.1, whereas the combined exposure of these risk factors resulted in an odds ratio of 8.3[23]. In men, the odds ratio of single exposure to diabetes mellitus and family history were 2.0 and 2.4, while the odds ratio of combined exposure was 7.7. Apparently, risk factors are more important in patients with a family history compared with patients without such a history.

INQUIRY OF FAMILY HISTORY OF VASCULAR DISEASE

In clinical practice, the evident relation between the presence of cardiovascular disease in families and first cardiovascular events has resulted in family history being an integral part of a patient's medical history assessment. This is supported by the result described in chapter 3 and 6 of this thesis, which demonstrated increased vascular risk for having a positive parental history compared with subjects not having such a history. Although widely used in clinical practice, there is no strict definition of a positive family history. For example, the Dutch guideline for primary prevention of cardiovascular disease defines a positive family history as cardiovascular disease in ≥1 first-degree relative <65 years. The ACC/AHA guideline on the assessment of cardiovascular risk defines a positive family history of premature cardiovascular disease as the occurrence of cardiovascular disease in ≥1 first-degree relative <65 years in women and <55 in men[24]. The best way to assess family history is yet unknown. For example, does simply asking whether cardiovascular disease runs in the family suffice, or should a more detailed inquiry of family history include disease location, age and sex of affected family members and number of affected siblings?

Family history assessment in first-degree relatives

Although first-degree relatives consist of parents, siblings and offspring, it is not standard in clinical practice to also assess the presence of vascular disease in offspring, probably because offspring are considered too young to have developed cardiovascular disease yet. In chapter 5 we demonstrated that the presence of vascular disease and vascular risk factors (especially diabetes mellitus) in offspring was related to new or recurrent vascular events in patients at higher risk of vascular events, with observed 2-fold higher risks. This positive offspring history may be interpreted as a proxy of the genetic base of the parent and of the degree of shared exposure to (unknown) risk factors. Although in offspring similar genetic information is captured as with parents and siblings, it represents shared environmental factors in a later phase in life of the patient. Therefore, determining the presence of vascular disease or risk factors in offspring should be incorporated in the assessment of family history of cardiovascular disease.

Family history of different vascular locations

The recommendations in guidelines regarding the use of family history are based on studies investigating the relation between family history of coronary artery disease and cerebrovascular disease and cardiovascular events, but lack a foundation in studies concerning peripheral artery disease. Apparently, the influence of family history of stroke and of myocardial infarction in particular on the risk of vascular events has been studied extensively, whereas less studies investigated the influence of peripheral artery disease. However, in the spectrum of cardiovascular disease, peripheral artery disease is also a serious condition with high risks of vascular mortality and all-cause mortality[25]. Since patients with peripheral artery disease evidently are at high risk for subsequent events and mortality, the vascular risk in their offspring may also be high. The importance of family history of peripheral artery disease was demonstrated in chapter 6 of this thesis, where offspring of patients with established peripheral artery disease showed higher risks of developing cardiovascular disease than offspring of patients with cerebrovascular disease and coronary artery disease. Therefore, the occurrence of peripheral artery disease in family members should definitely be part of the definition of family history.

Another reason to determine the location of vascular disease in family members is the observation that the specific location of the disease in the family member conveys the highest risk for the development of a vascular event at that particular location. For example, a parental history of myocardial infarction increases the risk of incident myocardial infarction 4-fold, whereas no increased risk of incident stroke was observed[26]. This was also previously demonstrated for peripheral artery disease, as a positive family history of peripheral artery disease was related with a 2-fold higher risk of incident peripheral artery disease, while no relation was observed between family history of peripheral artery disease and incident cerebrovascular and incident coronary artery disease. Additionally, in chapter 2 we observed a 2-fold higher risk of incident peripheral artery disease, whereas no increased risk was observed for stroke or myocardial infarction in patients with established vascular disease.

Sex and age of the affected family member

Although guidelines do not distinguish between the sex of the affected family members, several studies suggest that cardiovascular disease in female first-degree relatives is more important than cardiovascular disease in male first-degree relatives. In chapter 3 of this thesis we performed a meta-analysis investigating whether paternal and maternal histories of cardiovascular disease confer different risks for vascular events. We demonstrated that there is no substantial difference between the risks of cardiovascular events for having a paternal or maternal history of cardiovascular events. Therefore, there is no indication to take the gender of the affected family member into account.

Several definitions of family history use different age cut-off points for men (e.g. <65 years) and women (e.g. <55 years). Since cardiovascular disease develops ten years later in women compared with men, a low age cut-off point might lead to misclassification of cardiovascular

disease in female family members. However, in chapter 3 we demonstrated that for parental history without an age cut-off point, the risk of cardiovascular events was 1.5 (95%CI 1.3 – 1.8) for having a paternal history and 1.7 (95%CI 1.4 – 1.9) for maternal history. Using the same cut-off point of cardiovascular disease <65 years for both paternal and maternal history resulted in risk estimates of 2.4 (95%CI 1.9 – 2.9) for paternal history and 2.5 (95%CI 2.0 – 3.2) for maternal history. Since the risk estimates for using an age cut-off point are substantially higher compared with not using a cut-off point, the use of age limits in the definition of parental history is defendable. However, the use of different age limits for female and male family members should be avoided.

FAMILY HISTORY IN PATIENTS WITH AND PATIENTS WITHOUT ESTABLISHED VASCULAR DISEASE

A lot of research to identify risk factors for cardiovascular events has been performed in patients without established vascular disease. However, identification of risk factors for recurrent vascular events is also necessary, since patients increasingly survive a first vascular event. Although compelling evidence exists for family history as a risk factor for first vascular events, this evidence is scarce for recurrent vascular events.

In patients with and without established vascular disease the importance of family history inquiry is different. In chapter 2 we demonstrated in patients with established vascular disease that having a positive parental history of myocardial infarction, stroke or vascular mortality did not increase the risk for a subsequent myocardial infarction, stroke or vascular mortality. In chapter 4 no increased risk of subsequent vascular events was observed either for having a sibling history of cardiovascular disease in patients with uncontrolled risk factors, even after taking the number of siblings into account. How can parental and sibling history be such an important risk factor for first events, but appear to be of no importance in the majority of patients with vascular disease?

First, some studies suggest that a family history of cardiovascular disease is a stronger risk factor for fatal vascular events than for non-fatal events. For example, among more than hundred thousand women initially free of vascular disease, the risk of a fatal myocardial infarction was 5-fold and the risk of a nonfatal myocardial infarction almost 3-fold, when having a parental history of myocardial infarction before the age of 60[27]. Second, having a family history of cardiovascular disease may have been an important factor for the development of the first vascular event, but the vascular damage resulting from this event may be of more importance for the development of recurrent vascular events than a positive family history. Third, patients with vascular disease and a positive family history are compared with patients without family history but with vascular disease. Patients without a family history still developed cardiovascular disease due to other factors. Therefore, the baseline risk of developing recurrent events is

high for all patients, and on top of that a family history is not of importance anymore.
However, we cannot conclude that parental and sibling history of cardiovascular disease are not important at all for recurrent vascular events. In patients without or with only one uncontrolled vascular risk factor, a sibling history of cardiovascular disease almost doubled the risk of the composite outcome of myocardial infarction, stroke and vascular mortality, of peripheral artery disease and of all-cause mortality, as demonstrated in chapter 4. Furthermore, in patients with premature vascular disease (defined as a cardiovascular event occurring before the age of 51 in men and 56 years in women) having a positive parental history of premature cardiovascular disease was related to a 30% higher risk of a recurrent vascular event[28].

USE OF FAMILY HISTORY IN CLINICAL PRACTICE

In clinical practice, prediction of the risk for development of cardiovascular disease in patients is widely used, as treatment decisions are based upon these estimated 10-year risks. Because patients are treated according to their individual absolute risks, accurate risk prediction is very important, which may be improved by adding potential important predictors to risk models.
Because of the strong relation between family history and first cardiovascular events, family history of cardiovascular disease could be an important predictor and may improve risk estimations, leading to more selective treatment of high-risk patients. Nevertheless, in cardiovascular risk prediction models, family history of cardiovascular disease is undervalued. In several risk models, such as the widely used Framingham risk score, family history of cardiovascular disease is neither incorporated, nor evaluated. Perhaps the lack of evaluating family history for prediction models is due to under-appreciation of the vascular risk associated with family history independent of traditional risk factors. In other risk scores the definition of family history is suboptimal; in the Reynolds risk score only parental history of myocardial infarction <60 is incorporated[29, 30] and in the PROCAM risk score a positive family history is defined as the presence of myocardial infarction <60 years in first-degree relatives[31]. Therefore, we recommend to determine the additional value of family history containing a full assessment of the presence of vascular disease at different locations in all first-degree relatives, beyond traditional risk factors in order to improve risk prediction in individual patients. Because assessment in further detail of family history is easy to incorporate in a patient's family history and no extra costs are involved, it can easily be implemented in clinical practice.
Although family history is not adequately incorporated in these risk models, it can still guide physicians in assessment of a patient's risk and in making treatment decisions. In patients with an intermediate risk of vascular disease, and consequently an uncertain risk-based treatment decision, the presence of a family history could tip the balance in favour of starting treatment. Since the presence of risk factors is more important in patients with a positive family history compared with patients without such history (because of the gene-environmental interac-

tions), early interventions in these patients may especially be important to reduce vascular risk. Furthermore, because the disease location in family members conveys the highest risk for the development of a vascular event at that particular location, extra local screening may be indicated. For example, in asymptomatic individuals with a family history of myocardial infarction, determining the presence of coronary artery calcium may be useful as an indicator of the presence of coronary artery disease, which is already advised by the American College of Cardiology and American Heart association[32].

In patients with established vascular disease, the clinical value of family history in risk assessment is not as clear as for patients without vascular disease, since the risk for subsequent vascular events did not increase for the majority of patients with vascular disease and a sibling or parental history. In addition, in chapter 7 we demonstrated that adding a genetic risk score did not improve risk prediction beyond clinical characteristics in patients with vascular disease. Since this genetic risk score was only based on 30 SNPs associated with coronary artery disease, and many important genetic factors still need to be discovered, the lack of additional value may be to limitations of this genetic risk score in reflecting genetic vascular risk, but may also points towards limited value of family history in these patients. Determining the presence of vascular disease and risk factors in offspring is useful, because it is related with increased risk of vascular events compared with patients without such history. However, it may feel counterintuitive to assess the presence of vascular disease in offspring for the vascular risk in their parents, since family history of cardiovascular disease is usually evaluated 'upward' in the family tree towards parents and 'horizontally' to brothers and sisters. Although family history assessment 'downwards' towards children of patients is a new approach, substantial risks are observed and increasing awareness of this new approach by physicians may influence further differentiation in therapy, such as further lowering of LDL-cholesterol levels.

Highlights of this thesis

- There is no difference in vascular risk in offspring with a positive paternal or maternal family history.
- The highest increased risk of first cardiovascular events is observed in offspring of patients with peripheral artery disease and the lowest increased risk in offspring of patients with coronary artery disease.
- Offspring of patients with increased vascular risk or vascular disease have a higher prevalence of hypertension, hypercholsterolemia and diabetes mellitus at young age compared with the general population.
- In the majority of patients with established vascular disease with a positive parental or sibling history of cardiovascular disease, the risk of recurrent vascular events is not increased compared with patients without such history.

- In patients with established vascular disease, a genetic risk score does not improve risk prediction of 10-year risk of cardiovascular events beyond clinical characteristics.
- Presence of vascular disease and risk factors in offspring of patients already at high vascular risk should be determined in clinical practice as these patients have a higher risk of new or recurrent vascular events compared with patients without such history.

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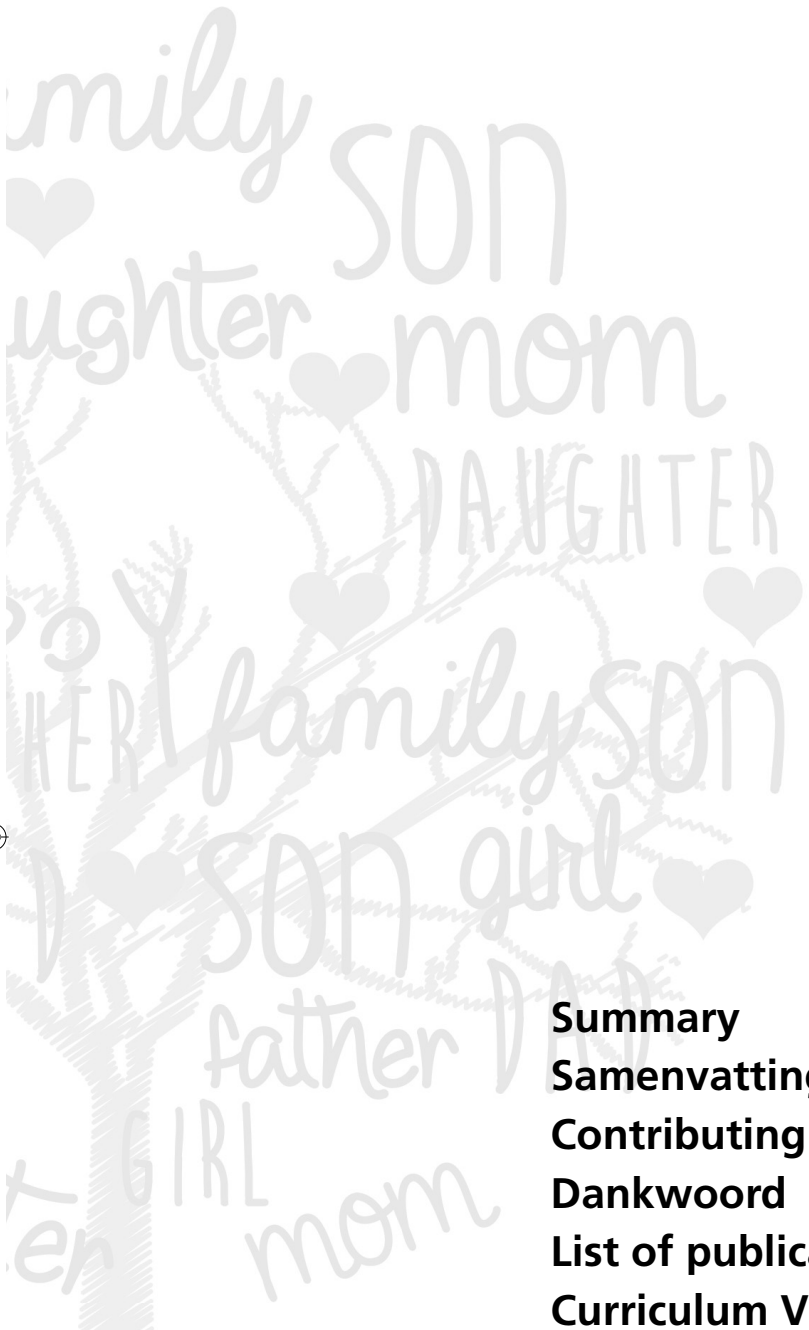

SUMMARY

A positive family history of cardiovascular disease is an established risk factor for the development of first manifestations of symptomatic disease (e.g. myocardial infarction or stroke). The assessment of a family history in clinical practice provides an opportunity to identify families who actually develop symptomatic vascular disease. However, there is growing evidence that by simply dividing a family history of cardiovascular disease into positive or negative, the potential value of family history in risk assessment of cardiovascular disease is not fully exploited. Furthermore, further research is warranted to investigate the risks of vascular disease related with family history in another population; patients with established symptomatic vascular disease. Therefore, in the first part of this thesis, we evaluated the relation between a detailed positive family history of cardiovascular disease and the risk of cardiovascular events in patients with and without prevalent vascular disease.

In **chapter 2** we determined whether there is a relation between a positive parental history of cardiovascular disease and subsequent vascular outcomes (myocardial infarction, stroke, vascular mortality, peripheral artery disease) and all-cause mortality in patients with established vascular disease. Since growing evidence exists that simply dividing a parental history of cardiovascular disease into positive or negative does not use its full potential, we additionally investigated whether, in case of a positive parental history, the location of parental vascular disease and the sex of the parent confer altered risks. We observed that patients with a positive parental history of cardiovascular disease were not at increased risk for developing myocardial infarction, stroke or vascular mortality compared with patients without such history (HR 1.0, 95%CI 0.8 – 1.3). However, having a father with a history of peripheral artery disease increased the risk of incident peripheral artery disease substantially (HR 3.1, 95%CI 2.1 – 4.6).

In literature, the consensus exists that having a mother with cardiovascular disease is more important for the risk of cardiovascular disease compared with having a father with cardiovascular disease. However, conflicting results are reported. In **chapter 3** we describe the results of a systematic review and meta-analysis of current literature to determine whether paternal or maternal histories of cardiovascular disease confer different risks of cardiovascular disease in offspring free of vascular disease. Pooling the results of 26 studies demonstrated no different risk of cardiovascular disease in offspring having a paternal (OR 1.9, 95%CI 1.6 – 2.3; RR 1.5, 95%CI 1.3 – 1.8) or maternal history of cardiovascular disease (OR 2.2, 95%CI 1.7 – 2.7; RR 1.6, 95%CI 1.4 – 1.8). For different age limits the highest cardiovascular risk was demonstrated for a maternal history <50 years (3.2, 95%CI 2.2 – 4.6) and a paternal history <55 years (2.8, 95%CI 2.3 – 3.5). For sons the conferred risk of cardiovascular disease was similar for a positive paternal and maternal history. For daughters a slightly higher risk of vascular events

was observed having a positive maternal history (1.8, 95%CI 1.5 – 2.1) compared with having a positive paternal history (1.5, 95%CI 1.3 – 1.7), although this difference is probably not clinically relevant. We conclude that a positive parental history inquiry of cardiovascular disease is useful in clinical practice since it is related with increased vascular risk in offspring. No distinction however has to be made as to whether the affected parent is the mother or father.

Although no relation was observed in patients with established vascular disease having a positive parental history and the risk of cardiovascular events in chapter 2, a positive sibling history could be of importance as siblings share more environmental factors than parents and offspring. Therefore, we determined in **chapter 4** the relation between a positive sibling history of cardiovascular disease and subsequent myocardial infarction, stroke, peripheral artery disease, vascular and all-cause mortality. We also determined whether the risk of having a positive sibling history depends on the presence or absence of cardiovascular risk factors (hypertension, smoking, low physical activity, elevated LDL-cholesterol and overweight or obesity). In patients with ≥2 risk factors no relation between a positive sibling history and subsequent vascular events was observed. This in contrast to patients with ≤1 risk factor where a positive sibling history was related to increased risk of vascular mortality (HR 2.6, 95%CI 1.2 – 5.4), myocardial infarction (HR 1.9, 95%CI 1.0 – 3.7), peripheral artery disease (HR 1.8, 95%CI 1.0 – 3.3) and all-cause mortality (HR 1.6, 95%CI 1.0 – 2.6). Hence, a positive sibling history of cardiovascular disease may help to discriminate between patients with a low or high risk of subsequent vascular disease despite the absence of traditional risk factors.

In **chapter 5** we studied the relation between the presence of cardiovascular risk factors or disease in offspring and the risk of vascular disease in their parents already at high risk of vascular disease, as this may be an indicator of a patients' genetic load or exposure to (unknown) risk factors. We observed that the presence of vascular disease, hypertension, hypercholesterolemia and diabetes mellitus in offspring is related to a higher risk of vascular mortality (HR 2.9, 95%CI 1.2 – 7.1) and myocardial infarction (HR 1.6, 95CI 1.1 – 2.5). Regarding the presence of cardiovascular risk factors in offspring, diabetes mellitus in particular increased the risk of vascular mortality (HR 3.4, 95%CI 0.8 – 14.8) and myocardial infarction (HR 3.3, 95%CI 1.7 – 6.6). Smoking and overweight in offspring were not related to increased vascular risk in parents. Given these increased risks, determining a positive offspring history, especially cardiovascular events and diabetes mellitus, could be valuable for the identification of patients at high risk of new events enhancing further differentiation in therapy, and is easy to add as part of a patient's (family) history.

In **chapter 6** we investigated the prevalence of cardiovascular risk factors (diabetes mellitus, hypertension and hypercholesterolemia) for several age limits in the offspring of patients at increased vascular risk, and compared these with the prevalence of risk factors in the

general population. It was observed that, from a young age, the offspring population had higher prevalence of in particular hypercholesterolemia and hypertension compared with the general population. Furthermore, it was assessed whether the risk of cardiovascular events and the presence of risk factors in offspring coheres with the location of vascular disease in the parents. The prevalence of risk factors was higher compared with the general population irrespective of the parental vascular disease location. Regarding vascular risk in offspring, the highest risk was observed in offspring of patients with peripheral artery disease (PR 2.8, 95%CI 1.3 – 6.4) and the least increased vascular risk was observed in offspring of patients with coronary artery disease (PR 1.8, 95%CI 0.9 – 3.4). Based on these results we conclude that early lifestyle counseling and screening for the presence of risk factors in offspring of patients with clinically manifest vascular disease and risk factors may be considered. Offspring of patients with peripheral artery disease might be an especially relevant group for early screening and intervention.

One of the mechanism leading to increased vascular risk having a positive family history is shared genetic factors. Nowadays, multiple risk loci are identified which are associated with the development of cardiovascular disease. Another important risk factor for first vascular events is the presence of coronary artery calcium which can be considered as a surrogate for the lifetime exposure to known and unknown risk factors, including genetic risk factors. Therefore, in the second part of this thesis, we evaluated the clinical value of genetic factors and coronary artery calcium in high risk patients.

In **chapter 7** we determined whether a genetic risk score based on 30 single-nucleotide-polymorphisms associated with coronary artery disease can improve prediction of 10-year risk of myocardial infarction, stroke and vascular mortality events in patients with established vascular disease. We demonstrated that in patients with established vascular disease this genetic risk score did not improve prediction of 10-year risk of cardiovascular events beyond clinical characteristics. Therefore, other potentially important predictors like biomarkers or imaging need to be identified to further optimize risk assessment in patients with established vascular disease.

In **chapter 8** we describe the distribution of coronary artery calcium scores (CAC scores) in patients with established coronary artery disease. In a quarter of the patients low CAC scores were observed and in a quarter very high CAC scores, indicating a wide distribution of CAC scores in this specific group of patients. Most important determinants associated with higher CAC scores were multi-vessel coronary disease (two-vessel disease OR 1.8, 95%CI 0.9 – 3.5, three-vessel disease OR 4.9, 95%CI 2.5 – 9.7), age (OR 1.6 per 5 years) and smoking (ever smoking OR 3.1, 95%CI 1.6 – 5.9) Other determinants were body mass index, smoking, ankle brachial index and intima-media thickness. We also demonstrated that higher CAC scores are not associated with the number of patients' risk factors (current smoking, LDL-cholesterol, hypertension, diabetes mellitus or overweight). A strong association exists between higher

CAC scores and higher estimated 10-year risks of recurrent vascular myocardial infarction, stroke or vascular mortality. Therefore, it would be worthwhile to determine whether CAC scoring provides additional information beyond clinical characteristics in predicting patients' recurrent vascular risk, which should be evaluated prospectively.

SAMENVATTING (VOOR NIET INGEWIJDEN)

Het familiair voorkomen van hart- en vaatziekten is een sterke risicofactor voor het ontwikkelen van hart- en vaatziekten. Het bepalen van een belaste familieanamnese (de aanwezigheid van hart- en vaatziekten in familieleden) in de spreekkamer geeft de gelegenheid om families te identificeren waarin daadwerkelijk hart- en vaatziekten voorkomen. Het blijft echter de vraag wat de beste manier is om een belaste familieanamnese te definiëren om zoveel mogelijk informatie over het vasculaire risico van een patiënt te vergaren middels familieanamnese. De simpele vraag of hart- en vaatziekten voorkomen in de familie volstaat waarschijnlijk niet en een gedetailleerdere beoordeling zal wellicht moeten plaatsvinden, met inachtneming van de precieze locatie (hart, brein of benen) en het geslacht van het aangedane familielid. Naast het feit dat de beste manier om familieanamnese te bevragen ter discussie staat, is het ook onduidelijk of een belaste familieanamnese een risicofactor is in patiënten die reeds vaatziekten hebben. Met andere woorden, is het risico op nieuwe hart- en vaatziekten verhoogd indien een belaste familieanamnese aanwezig is in patiënten met eerdere uitingen van vaatziekten in vergelijking met patiënten zonder een belaste familieanamnese? Om deze vragen te beantwoorden, onderzoeken we in het eerste gedeelte van dit proefschrift de relatie tussen gedetailleerde componenten van een belaste familieanamnese voor hart- en vaatziekten en het risico op het ontwikkelen van hart- en vaatziekten in patiënten met en zonder eerdere uitingen van vaatziekten.

In **hoofdstuk 2** hebben we onderzocht of patiënten met reeds bestaande vaatziekten, die minstens één ouder hebben met hart- en vaatziekten voor het zestigste levensjaar, een hogere kans hebben op nieuwe hart- en vaatziekten in vergelijking met patiënten met reeds bestaande vaatziekten zonder belaste familieanamnese. Daarnaast hebben we onderzocht of het risico op nieuwe vaatziekten afhankelijk is van het geslacht van de vader of moeder met vaatziekten en van de locatie van vaatziekten. Hieruit is gebleken dat het hebben van een ouder met hart- en vaatziekten (zonder onderscheid te maken in locatie van vaatziekten en geslacht van de ouder) geen risicofactor is voor het ontwikkelen van nieuwe vaatziekten in deze specifieke patiëntengroep. Indien gekeken werd naar de locatie en geslacht van het vaatlijden, werd een drie keer verhoogd risico gezien op het optreden van vaatziekten in de benen (perifeer vaatlijden) in patiënten die een vader hebben met perifeer vaatlijden.

In bestaande onderzoeken over een belaste familieanamnese van hart- en vaatziekten is steeds meer de consensus ontstaan dat voor het vasculaire risico van het nageslacht een moeder met vaatziekten belangrijker is dan een vader met vaatziekten. De vraag is of deze consensus terecht is aangezien ook onderzoeken bestaan die juist het tegenovergestelde aantonen. In **hoofdstuk 3** beschrijven we de resultaten van een systematische review (systematisch literatuuronderzoek) en meta-analyse (het samenvoegen van alle resultaten uit de beschikbare literatuur). Hierin hebben we onderzocht of het geslacht van de ouder met hart-

en vaatziekten bepalend is voor het risico op het ontwikkelen van hart- en vaatziekten in het nageslacht. De samengevoegde resultaten van 26 studies toonden aan dat het geslacht van de ouder met hart- en vaatziekten niet bepalend is voor dit risico. Wanneer specifiek werd gekeken naar het geslacht van het kind, werden in zonen precies gelijke risico's op hart- en vaatziekten gezien voor vader en moeder, en voor dochters een iets hoger risico indien de aangedane ouder de moeder was. Echter, dit verschil is minimaal en zal in de klinische praktijk geen consequenties zal hebben.

Omgevingsfactoren (bijvoorbeeld roken en overgewicht) die van invloed zijn op het ontwikkelen van hart- en vaatziekten, worden meer gedeeld met broers en zussen dan met ouders. Aangezien deze omgevingsfactoren medeverantwoordelijk zijn voor het clusteren van hart- en vaatziekten in families, kan het zijn dat het hebben van een broer of zus met vaatziekten een hoger risico geeft op nieuwe hart- en vaatziekten in patiënten met reeds bestaande vaatziekten, zoals bekeken in **hoofdstuk 4**. Daarnaast hebben we bekeken of dit risico afhangt van de aan- of afwezigheid van 'traditionele' risicofactoren voor hart- en vaatziekten (hoge bloeddruk, roken, weinig lichamelijke activiteit, verhoogd cholesterol en overgewicht). In patiënten met twee of meer risicofactoren was geen relatie aanwezig tussen het hebben van een broer of zus met hart- en vaatziekten en de ontwikkeling van nieuwe hart- en vaatziekten. Dit in tegenstelling tot patiënten met geen of één risicofactor die een broer of zus met vaatziekten hebben, waarbij een twee tot drie keer hogere kans werd gezien op nieuwe hart- en vaatziekten, in vergelijking met patiënten zonder een broer of zus met vaatziekten. In deze specifieke patiëntengroep zou het vragen naar de aanwezigheid van hart- en vaatziekten in broers en zussen kunnen bijdragen aan het schatten van het risico op nieuwe hart- en vaatziekten aangezien deze patiënten weinig 'traditionele' risicofactoren hebben.

In **hoofdstuk 5** hebben we onderzocht of ouders met een kind met hart- en vaatziekten, diabetes, hypertensie of hoog cholesterol een verhoogd risico hebben op het ontwikkelen van nieuwe hart- en vaatziekten. Deze ouders hadden reeds een verhoogd risico op hart- en vaatziekten, aangezien ze een eerdere manifestatie van hart- en vaatziekten hadden doorgemaakt of een belangrijke risicofactor voor hart- en vaatziekten hadden (diabetes, te hoog cholesterol , te hoge bloeddruk). De hypothese is dat de aanwezigheid van vaatziekten of risicofactoren in kinderen een indicatie geeft van de genetische belasting en de mate van blootstelling aan bekende en onbekende risicofactoren voor hart- en vaatziekten in de ouder. Dit zou vervolgens kunnen leiden tot een hoger risico op vaatlijden. We hebben laten zien dat de aanwezigheid van vaatziekten of risicofactoren (hoge bloeddruk, verhoogd cholesterol of diabetes mellitus) in de kinderen, leidt tot een drie keer hogere kans op overlijden aan een vasculaire oorzaak en een twee keer verhoogd risico op het ontwikkelen van een nieuwe hartaanval in de ouder. De aanwezigheid van diabetes mellitus in de kinderen zorgde voor een drie keer hogere kans op een vasculaire dood en hartaanval in de ouder. De leefstijlfactoren roken en overgewicht in kinderen gaven geen hoger risico op het ontwikkelen van hart- en vaatziekten in de ouder. Gezien het feit dat het hebben van een kind met vaatziekten of ri-

sicofactoren zulk verhoogde risico's geeft op het ontwikkelen van hart- en vaatziekten in de ouder, is het belangrijk om de aanwezigheid hiervan te bepalen in de spreekkamer. Op deze manier kunnen patiënten met een hoog risico worden geïdentificeerd, om zo eventuele behandeling te intensiveren dan wel aan te passen. Aangezien de aanwezigheid van risicofactoren en vaatziekten in kinderen makkelijk te bepalen is door dit toe te voegen aan de definitie van een belaste familieanamnese, kan het snel geïmplementeerd worden in de praktijk.
In **hoofdstuk 6** hebben we onderzocht of risicofactoren voor hart- en vaatziekten vaker voorkomen in kinderen van ouders met een reeds bestaand verhoogd risico op hart- en vaatziekten in vergelijking met de algemene bevolking. De onderzochte risicofactoren verhoogde bloeddruk, verhoogd cholesterol en diabetes mellitus komen al vanaf een jonge leeftijd (vanaf 15 jaar) vaker voor in kinderen met een ouder met een verhoogd risico. De locatie van het vaatlijden van de ouder speelt hierbij geen rol. Een kanttekening moet geplaatst worden voor de risicofactor diabetes aangezien dit verschil op latere leeftijd niet meer aanwezig was. Daarnaast hebben we bekeken of de locatie van het vaatlijden in de ouder, het risico beïnvloedt op het ontwikkelen van hart- en vaatziekten in het kind. Hier kwam uit naar voren dat het risico op hart- en vaatziekten het hoogst is in kinderen van ouders met perifeer vaatlijden (drie keer zo hoog) en het minst hoog in kinderen van ouders met vaatziekten in het hart (twee keer zo hoog), in vergelijking met kinderen die een ouder hebben maar met een belangrijke risicofactor.

Gedeelde genetische factoren zijn een belangrijke schakel in het familiair voorkomen van hart- en vaatziekten. Tot op heden zijn meerdere genetische factoren ontdekt die geassocieerd zijn met het optreden van hart- en vaatziekten. Een andere belangrijke factor voor het ontwikkeling van hart- en vaatziekten is de aanwezigheid van kalk in de kransslagaders van het hart; de kalkscore. Deze kalkscore kan dan ook beschouwd worden als een afspiegeling van alle bekende en onbekende risicofactoren voor hart- en vaatziekten tezamen, gedurende het leven. In het tweede gedeelte van dit proefschrift hebben we de klinische waarde van genetische factoren en kalk in de kransslagaderen onderzocht in patiënten met reeds bestaande vaatziekten.
In de klinische praktijk worden behandelbeslissingen (bijvoorbeeld het starten met een cholesterolverlager) vaak genomen op basis van het geschatte risico op hart- en vaatziekten van een patiënt. De risicomodellen die ten grondslag liggen aan deze schattingen bevatten belangrijke risicofactoren voor het ontstaan van hart- en vaatziekten, zoals bijvoorbeeld leeftijd, geslacht, roken en bloeddruk. Aangezien het belangrijk is om zo precies mogelijk het risico van een patiënt te schatten gezien de therapeutische consequenties, is het zinvol om deze risicomodellen zo goed mogelijk te maken. In **hoofdstuk 7** hebben we gekeken of een risicomodel speciaal voor patiënten met eerdere uitingen van hart- en vaatziekten beter wordt indien daar een genetische risico score aan wordt toegevoegd. Het risicomodel schatte het risico van een patiënt op hart- en vaatziekten niet beter met de genetische risico score – ge-

baseerd op 30 genetische factoren die geassocieerd zijn met vaatlijden van het hart – dan zonder deze score en deze score hoeft daarom niet standaard te worden toegevoegd aan het model. Aangezien het wel belangrijk is dat het risicomodel verder geoptimaliseerd wordt, zullen andere belangrijke factoren moeten worden geïdentificeerd om zo risicoschattingen in deze specifieke patiëntengroep te verbeteren.

In **hoofdstuk 8** hebben we onderzocht of in patiënten met vaatlijden van het hart, een wijde distributie van de kalkscore bestaat en welke factoren van invloed zijn op de hoogte van de kalkscore. Allereerst werd bij een kwart van de patiënten een lage kalkscore gevonden en bij een kwart een heel hoge kalkscore. Factoren die invloed hebben op de hoogte van de kalkscore waren het aantal aangedane kransslagaders, de leeftijd van een patiënt, roken, intima-media dikte (dikte tussen de binnenste lager van de halsslagader) en enkel-arm index (verhouding bovendruk in de onderbenen en armen; maat om te bepalen of iemand vernauwingen heeft in de slagaders van het been). Daarnaast werd een sterk verband gezien tussen het geschatte tienjaars-risico op hart- en vaatziekten en de hoogte van de kalkscore. Dit zou kunnen betekenen dat in patiënten met bestaand vaatlijden van het hart, de kalkscore een belangrijke risicofactor is voor het ontwikkelen van nieuwe hart- en vaatziekten.

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Maaike

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M. Weijmans, Y. van der Graaf, G.J. de Borst, F.W. Asselbergs, M.J. Cramer, A. Algra, F.L.J. Visseren. The relation between the presence of cardiovascular disease and vascular risk factors in offspring and the occurrence of new vascular events in their parents already at high vascular risk. American Heart Journal. 2015 Oct;170(4):744-752.

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M. Weijmans, F.L.J. Visseren, T. Leiner, I.M. Schrover, Y. van der Graaf, H.M. Nathoe. Distribution and determinants of coronary artery calcium scores in patients with established coronary artery disease. In submission.

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Maaike Weijmans was born on the 3rd of September 1988 in Nieuwegein, the Netherlands. After graduating from the Oosterlicht College in Nieuwegein in 2006, she studied Medicine at Utrecht University, the Netherlands. In 2012 she obtained her medical degree. Since then she has been employed as a research physician at the department of Vascular Medicine of the University Medical Center Utrecht. She has worked on the research described in this thesis under supervision of prof. dr. F.L.J. Visseren (Department of Vascular Medicine) and prof. dr. Y. van der Graaf (Julius Center for Health Sciences and Primary Care). She combined her PhD research with a Masters in Clinical Epidemiology at Utrecht University from which she graduated in 2014. In November 2015 she started her training in Internal Medicine in "Gelre Ziekenhuizen" in Apeldoorn under the supervision of dr. C.G. Schaar.