Cardiovascular risk prediction in the Netherlands

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Cardiovascular risk prediction in the Netherlands

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ABSTRACT

Background

In clinical practice, Systematic COronary Risk Evaluation (SCORE) risk prediction functions and charts are used to identify persons at high risk for cardiovascular diseases (CVD), who are considered eligible for drug treatment of elevated blood pressure and serum cholesterol levels. These functions use classical risk factors (age, sex, smoking, blood pressure and the ratio of total-to-HDL-cholesterol) to predict absolute 10-year risk of CVD mortality rather than total (fatal plus nonfatal) CVD. The aim of this thesis was to improve cardiovascular risk prediction in the Netherlands, and to correctly classify high-risk persons.

Methods

We primarily used data from the Monitoring Project on Chronic Disease Risk Factors (MORGEN project) of the National Institute for Public Health and the Environment (RIVM). Risk factor data of more than 20,000 men and women aged 20-65 years were collected between 1993 and 1997. Ten-year follow up data on CVD mortality and morbidity were obtained from Statistics Netherlands and the National Hospital Discharge Register, respectively. Risk functions were developed using multivariable Cox proportional hazard models.

Results

The SCORE risk function for low-risk countries was the best predictor of CVD mortality in the Netherlands. Total CVD was approximately four times higher than CVD mortality. Obesity (BMI ≥ 30 kg/m^2) and parental history of myocardial infarction before age 70 were independent predictors of total CVD. Risk functions predicting risk of CVD mortality and total CVD, and their ability to discriminate between future cases and non-cases, did not differ. Of the high-risk persons with a CVD mortality risk of at least 5%, approximately 20% developed a nonfatal or fatal CVD event during 10 years of follow-up. When a cut-off point of 2% CVD mortality was used, approximately 10% of the high-risk persons developed a CVD event. When obesity and parental history of MI were added to the classical risk factor function, correct risk classification improved by 5%. This improvement in risk prediction was mainly due to obesity.

Conclusions

Discrimination between future cases and non-cases did not improve by expanding the endpoint of risk prediction from fatal CVD to total CVD. Adding obesity and parental history to the classical risk factor functions slightly increased the number of correctly classified persons.

Contents

1

Introduction

The Health Council of The Netherlands led the way on cardiovascular risk management 30 years ago by issuing advice on treatment of hypertension,[1,2] followed by an advice on cholesterol.[3] Almost at the same time, guidelines for hypertension and cholesterol were developed by the former Institute of Health Care Improvement (CBO) in cooperation with the Netherlands Heart Foundation (NHF).[4,5] The Netherlands College of General Practitioners (NHG) developed guidelines specifically for general practitioners.[6,7] In 2006, the first guideline on integrated cardiovascular risk management was released, a collaborative activity involving CBO, NHG and NHF.[8-10] Revision of guidelines took place after 2-8 years, depending on new developments e.g. publication of landmark studies on new generations of drugs, or inspired by publications or updates of WHO, American or European guidelines. In the past 30 years, eight guidelines on hypertension,[1,2,4,6,11-14] seven on cholesterol,[3,5,15-18] and two on cardiovascular risk management have been published in the Netherlands (Figure 1.1).[8-10,19]

An historic overview is presented of Dutch guideline development on hypertension and cholesterol, lately integrated into cardiovascular risk management. Emphasis is on consensus guidelines for primary prevention, in high-risk persons without manifest cardiovascular diseases (CVD). The focus is on changes in blood pressure levels for drug treatment of hypertension, on cholesterol levels for drug treatment of hypercholesterolemia and on the introduction of risk charts to identify persons at high risk of CVD.

Guidelines on hypertension 1978–2003

The first advice on treatment of hypertension was published by the Health Council (1978, 1983).[1,2] Hypertension was defined as a diastolic blood pressure of 115 mmHg or higher. Persons with hypertension were advised to change their lifestyle and were eligible for drug treatment. Persons with blood pressure values between 100–115 mmHg were eligible for drug treatment, when lifestyle measures did not effectively lower blood pressure. First choice of drugs were diuretics (thiazides) and beta-blockers. These recommendations were based on the results of the Hypertension Detection and Follow-up Program from the USA[20] and the Australian therapeutic trial in mild hypertension.[21]

New insights into the risk of moderately elevated blood pressure levels,[22] were the justification for the lower thresholds of drug treatment in the 1990 CBO/NHF-consensus[4] and the 1991 NHG-guideline.[6] Now persons with diastolic blood pressure levels exceeding 105 mmHg were eligible for drug treatment. Persons with levels between 95–104 mmHg were treated only when additional risk factors were present, e.g. smoking, diabetes, hypercholesterolemia, high body mass index (BMI) or a positive family history of CVD. The presence of one additional risk factor was recommended in the CBO-guideline, and two in the NHG-guideline. For pharmacological treatment, four classes of drugs were available: diuretics, beta-blockers, (ACE)-inhibitors and calcium-antagonists. At that time,

Treatment levels (mmHg)		Hypertension		Year		Hypercholesterolemia	Treatment levels (mmol/l)
DBP ≥ 115		Health Council advice	→	1978			
DBP ≥ 115		Health Council advice	→	1983			
				1987	←	CBO-consensus	≥ 8
DBP ≥ 105		CBO-consensus	→	1990	←	Health Council advice	≥ 8 and ≥ 1 additional risk factor
DBP ≥ 105		NHG-guideline	→	1991	←	CBO-consensus 1st revision	≥ 8
				1991	←	NHG-guideline	8-10 and ≥ 1 additional risk factor
DBP ≥ 105	SBP ≥ 180	NHG-guideline 1st revision	→	1997			
				1998	←	CBO-consensus 2nd revision	Age-dependent CHD risk
DBP ≥ 105	SBP ≥ 180	NHG-guideline 2nd revision	→	1999	←	NHG-guideline 1st revision	Age-dependent CHD risk
DBP > 100	SBP > 180	CBO-consensus 1st revision	→	2000	←	Health Council advice	Risk score of 8:
CVD risk ≥ 20%							Ratio total/HDL cholesterol + number of elevated risk factors
DBP > 100	SBP > 180	NHG-guideline 3rd revision	→	2003			
CVD risk ≥ 20%							
SBP > 180		2006					> 8 or ratio total/HDL-cholesterol > 8
CVD mortality risk ≥ 10%		CBO/NHG-guideline on Cardiovascular Risk Management					CVD mortality risk ≥ 10%
SBP > 180		2011					Ratio total/HDL-cholesterol > 8
Total CVD risk ≥ 20%		CBO/NHG-guideline on Cardiovascular Risk Management, 1st revision					Total CVD risk ≥ 20%

Figure 1.1 Overview of guidelines on hypertension, hypercholesterolemia, and cardiovascular risk management by year, and treatment levels. CBO, Dutch Institute for Healthcare Improvement (Utrecht); NHG, Dutch College of General Practitioners (Utrecht); NHF, Netherlands Heart Foundation (The Hague). CHD, coronary heart disease; CVD, cardiovascular diseases; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL-cholesterol, high density lipoprotein-cholesterol.

there was only definitive evidence that the first two classes of antihypertensives reduced CVD incidence in patients with hypertension.

In the 1990s, several meta-analyses of trials in persons with hypertension were published.[23,24] Evidence was accumulating, that treatment of systolic hypertension reduced CVD incidence, also in the elderly. The 1997 and 1999 NHG-guidelines (first and second revisions)[11,12] proposed also that persons with systolic blood pressure levels of 180 mmHg or higher were eligible for drug treatment.

The scientific evidence for elevated systolic blood pressure as a CVD risk factor, the release of the WHO-criteria for management of hypertension[25] and growing interest in integrated risk factor management, were reasons for the revision of the CBO-guideline on high blood pressure, which was released in 2000.[13] In the meantime, the focus on treatment of diastolic shifted to systolic blood pressure and on total cholesterol to the ratio of total to HDL cholesterol. The Framingham risk tables were introduced as a first step towards multifactorial risk management (Figure 1.2).[26] Risk assessment was based on age, sex, smoking status, systolic blood pressure, total to HDL-cholesterol ratio and diabetes. Classification of those at high risk was based on a combination of elevated levels of systolic blood pressure with a high absolute risk of CVD, and on elevated serum cholesterol levels with a high absolute risk of CHD. A positive family history of CVD below age 60 was an additional risk factor and a reason to start drug treatment at a lower level of risk. The following stepwise approach for treatment of patients with absolute risk of CVD ≥ 20% or hypertension (≥ 180 mmHg) was recommended: 1. diuretics (thiazides), 2. beta-blocker, 3. RAS-inhibitors. The first choice for diuretics was based on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial.[27] In elderly people, diuretics are most effective, with less adverse effects. The 2003 NHG-guideline (third revision)[14] was based on the 2000 CBO/NHF-guideline.[13]

Guidelines on high cholesterol 1987-1999

The first guidelines on serum total cholesterol were characterised by a unifactorial approach. Important evidence on the relationship between serum cholesterol and coronary heart disease (CHD) mortality came from the 350,000 screenees of the Multiple Risk Factor Intervention Trial.[28] This study showed that this relationship was strong and graded. Soon thereafter, the results of the Lipid Research Clinic-trial were published on the effect of the first generation of cholesterol lowering drugs, the bile acid sequestrant resins.[29] This trial showed a mean decrease of 8% in serum total cholesterol and 12% in LDL-cholesterol resulting in a 19% CHD incidence reduction. These results formed the basis of the first consensus report on cholesterol in the Netherlands, published in 1987.[5] Total cholesterol levels of at least 6.5 mmol/l were considered elevated and levels of 8 mmol/l and higher strongly elevated. The cornerstone of treatment of high cholesterol levels was a healthy

diet. Cholesterol-lowering medication could be considered, but prescription was restricted mainly to those with strongly elevated cholesterol levels.

Anticipating the introduction of statins, a new generation of cholesterol synthesis inhibitors, the Health Council performed a cost-effectiveness analysis in 1990.[3] Costs per life year gained were higher for cholestyramin than for simvastatin, and costs for both drugs were much higher than that of a cholesterol-lowering diet. The Health Council advice and the NHG 1991 guideline[7] used the same cut-off points for elevated serum cholesterol levels as recommended by the 1991 first revision of the CBO cholesterol consensus (≥ 8 mmol/l).[15] Additionally, their advice on prescription of cholesterol-lowering medication depended for the first time not only on these elevated serum cholesterol levels, but also on the presence of at least one additional risk factor. Statins (simvastatin and pravastatin) became the first choice of drugs for patients with cholesterol levels above 8 mmol/l. For those with lower cholesterol levels the bile acid sequestrant resins remained first choice. At that time, it was demonstrated that statins lowered LDL-cholesterol levels by 25–35%, and could induce regression of atherosclerosis.[30] However, evidence on the effect on CHD incidence had still to be obtained.

In the mid 1990s results of important milestone studies on cholesterol treatment were published: 4S, CARE, WOSCOPS, LIPID and AFCAPS trials.[31-33] These trials showed that statins reduced CHD incidence by 25–35%. This led to revision of the CBO cholesterol consensus in 1998.[16] The Framingham risk tables predicting 10-year CHD risk, were used to identify high risk persons (Figure 1.2). These tables were derived from the ones used by the European Societies of Cardiology, Atherosclerosis and Hypertension.[34,35] Risk prediction was based on age, sex, smoking status, total-to-HDL cholesterol ratio, diabetes and hypertension. Indication for drug treatment of hypercholesterolemia was no longer based on serum cholesterol levels alone, but also on age-specific risk scores. Age-specific cut-off points for drug treatment were formulated, based on cost-effectiveness analyses. The cut-off point of 10-year CHD incidence increased from > 25% at age 40 to 35–40% at age 70. In case of a positive family history of CHD at age < 60, medication could already be prescribed at a 5% lower cut-off point of CHD risk. The first choice of drugs were statins. The first revision of the NHG guideline, published in 1999[17] was based on the 1998 CBO-consensus.[16]

In 2000, the Health Council advised the Minister of Health on indications for cholesterol treatment with statins.[18] The Council recommended to use a 'risk score of 8' as cut-off point for treatment with statins. This means that persons with a total-to-HDL cholesterol ratio higher than 8, or those with a ratio higher than 7 plus one additional risk factor, or a ratio of 6 with two additional risk factors (e.g. smoking and hypertension) qualified for statin treatment. The major reason not to recommend risk tables was that the Council preferred a simplified method to select high risk persons, without the need to consult tables. Only a minority of the committee was in favour of considering costs for determining indications for cholesterol-lowering therapy.

Guidelines on cardiovascular risk management 2006-2011

In the first decade of the 21st century, the shift from unifactorial to multifactorial risk factor management was completed. In 2003, the results of the first large trial on the effects of a powerful new statin, atorvastatin were published.[36] This statin was tested in persons with hypertension, average or below average serum cholesterol levels, and at least three additional risk factors. Atorvastatin treatment reduced major cardiovascular events by 35%, major cerebrovascular events by 48% and all-cause mortality by 15%. In 2006, the CBO and NHG released the first 'Multidisciplinary Guideline on CardioVascular Risk Management in clinical practice'.[9] In line with the European guideline on Cardiovascular Disease Prevention in Clinical Practice,[37,38] the earlier used US Framingham risk tables were replaced by those of the European based Systematic COronary Risk Evaluation (SCORE)-system (Box 1.1).[37] The SCORE-group adapted the risk function for the Netherlands (Figure 1.2). The risk factors in the SCORE tables were the same as those in the Framingham risk tables, except for diabetes.

The introduction of the SCORE-risk charts meant a change from predicting 10-year risk of CHD incidence to 10-year risk of CVD mortality. The cut-off point for identifying those who needed drug treatment for elevated blood pressure and cholesterol was a 10-year CVD mortality risk of ≥ 10%.[9] This was higher than the cut-off point used in the European guidelines (≥ 5%).[38,39] This higher cut-off point was based on cost-effectiveness analyses and on preventing an increase in the work load of general practitioners. At a risk between 5% and 10%, drug treatment could be started when additional risk factors – such as clinical signs of organ damage, a positive family history of CVD < 60 years, a BMI > 30 kg/m^2 or a waist circumference > 88 cm for women and > 102 cm for men – were present. Based

Box 1.1 SCORE risk charts

Risk charts of the SCORE (Systematic COronary Risk Evaluation) project were derived from a large database of prospective studies including over 200,000 persons in Europe. Risk equations for high-risk countries were based on data collected in cohorts from Denmark, Finland and Norway and for low-risk countries from Belgium, Italy and Spain.[37] Almost all participants in these cohorts were recruited in the 1970s and early 1980s. At the time of construction of these SCORE charts, the Netherlands was considered a high-risk country. The SCORE-group adapted the risk function for the Netherlands, using the national percentage of smokers and average systolic blood pressure and serum total and HDL-cholesterol levels derived from a Dutch survey carried out between 1998 and 2001 (Regenboog-project; RIVM) and using national CVD mortality statistics from 2000 (WHO mortality database).

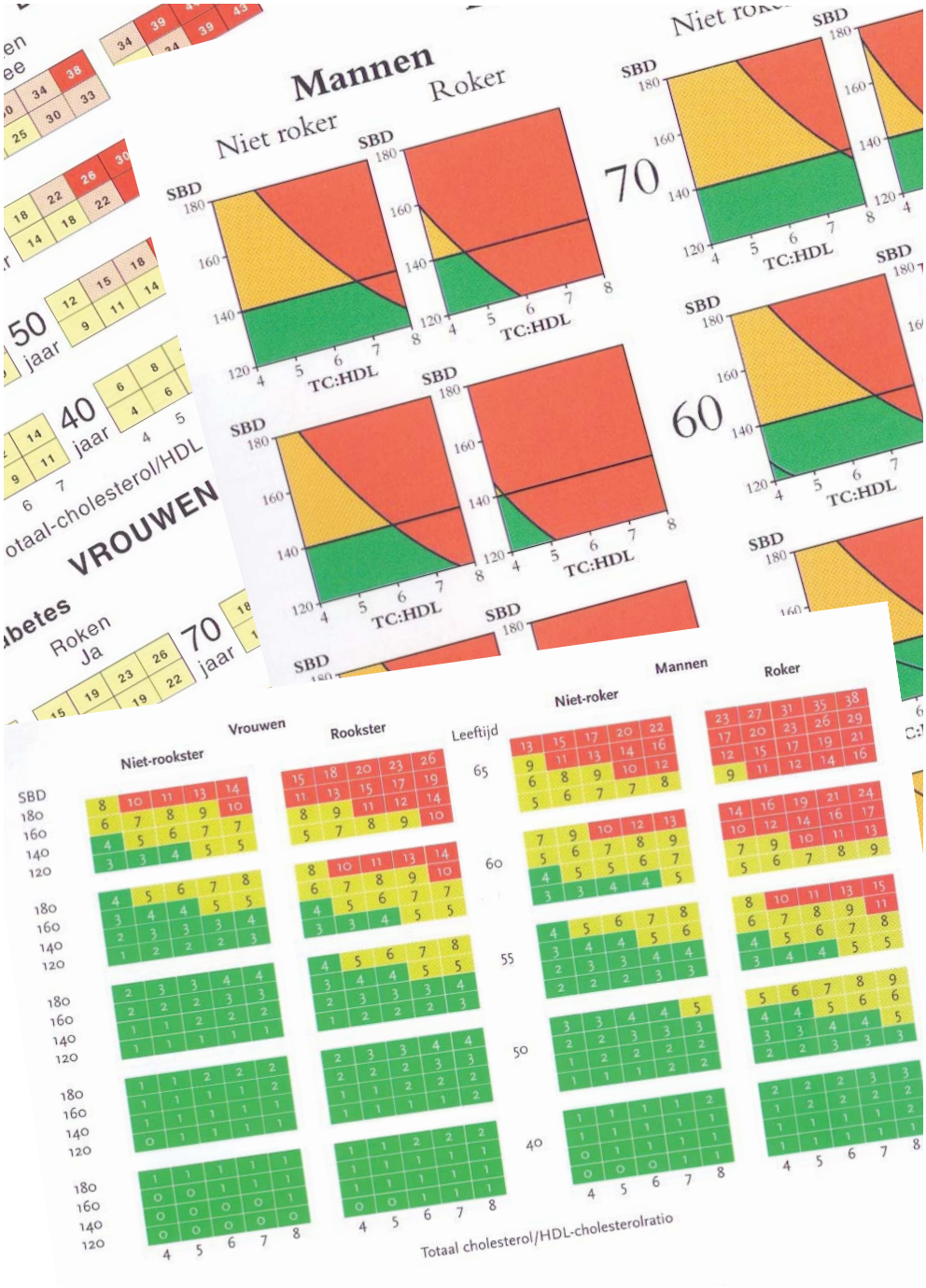

Figure 1.2 Impression of risk charts in the 1998 Guideline on Cholesterol, the 2000 Guideline on High blood pressure and the 2006 Guideline on Cardiovascular Risk Management.

on cost-effectiveness, drug treatment of elevated blood pressure was started with a low dose of a diuretic and, if the targets were not reached, other classes of antihypertensive drugs could be added. Treatment of elevated serum cholesterol started with simvastatin or pravastatin. When the targets were not reached, atorvastatin was not recommended for those without CVD or type II diabetes, because of the limited evidence for an effect on CVD endpoints and on safety.

After the 2006 guideline on CVRM, results on the effectiveness of drug treatment of blood pressure and serum cholesterol cumulated exponentially, and several meta-analyses were published. The effectiveness of blood pressure-lowering drugs in the prevention of CVD was demonstrated in 27 randomised clinical trials in more than 100,000 persons with no history of CHD, all classes of antihypertensive drugs showed similar effects in reducing CVD events.[40] The benefit of statin therapy in about 70,000 persons without CVD was investigated in a meta-analysis including trials with the first generations of statins: simvastatin (HPS), lovastatin (AFCAPS/TexCAPS) and pravastatin (WOSCOPS, PROSPER, ALLHATT-LTT, MEGA), and with the more recently developed statins, atorvastatin (ASCOT-LLA, CARDS, ASPEN) and rosuvastatin (JUPITER).[41] Major coronary events were reduced by 30%, major cerebrovascular events by 19%, and all-cause mortality by 12%. However, CHD mortality was not significantly reduced.

The first revision of the multidisciplinary guideline on cardiovascular risk management will be published in 2011.[19] A shift was made from risk tables with CVD mortality to total CVD incidence. Nonfatal endpoints included were myocardial infarction, stroke and heart failure. This also meant a shift in cut-off points for high risk to ≥ 20%, for intermediate risk to 10–20%, and for low risk to < 10%. For those at intermediate risk, one strongly and two or more moderately elevated CVD risk factors can be an indication for drug treatment. Among the strongly elevated risk factors were having at least two family members with a history of CVD below age 65 or at least one with a history of CVD below age 60, BMI > 35 kg/m^2 and a sedentary lifestyle. The mildly elevated risk factors included having one family member with a history of CVD below age 65, BMI 30–35 kg/m^2 and less than 30 minutes physical activity on five or less days a week. Also diminished kidney function is considered an additional risk factor. For treatment of elevated blood pressure levels, all classes of drugs can be used, with a mild preference for diuretics in those without CVD. A stepwise approach was recommended. Based on cost-effectiveness, drug treatment of elevated serum cholesterol levels started with simvastatin. If the treatment goal of LDL ≤ 2.5 mmol/l is not reached, a switch to rosuvastatin, or atorvastatin is recommended.

Conclusion

Cardiovascular risk management has changed over the past 30 years from unifactorial treatment of severe hypertension (diastolic blood pressure ≥ 115 mmHg) and severe hypercholesterolemia (≥ 8 mmol/l), to multifactorial risk factor treatment based on overall cardiovascular risk and treatment of elevated systolic blood pressure and/or serum total and HDL-cholesterol levels. Nowadays, the concept that "the lower the risk factors, the lower the absolute risk" is the leading paradigm in CVD prevention.

AIM AND RESEARCH QUESTIONS

The overall aim of this thesis is to improve cardiovascular risk prediction in the Netherlands and to correctly identify persons at high risk for CVD, who are eligible for drug treatment of elevated blood pressure and/or serum cholesterol levels. This thesis deals with the following questions raised during the development of the first multidisciplinary guideline on Cardiovascular Risk Management in clinical practice (CVRM),[8] published in 2006:

1. Which SCORE risk function fits best for the Netherlands?
2. What are the consequences of a change from predicting CVD mortality to total CVD (fatal plus nonfatal) for identifying high-risk persons?
3. What is the added value for risk prediction of including additional risk factors (obesity and parental history of myocardial infarction) in the classical risk function with total CVD as endpoint?

To answer these questions data were used from two monitoring studies of the National Institute for Public Health and the Environment (RIVM): the Monitoring Project on Cardiovascular Disease Risk Factors, of which the risk factor data were collected in 1987–1992 and the Monitoring Project on Chronic Disease Risk Factors of which the risk factors were collected in 1993–1997.[42,43] The latter project is the RIVM contribution to the EPIC study.[44] Mortality and morbidity data were collected until 2006. Also data from the EPIC-NL cohort were analysed, a combined database of the EPIC cohort of the RIVM and the PROSPECT cohort of the University Medical Centre of Utrecht.[44]

To deal with the first question, we examined how well 10-year CVD mortality observed in Dutch cohorts is predicted by three different risk functions: the SCORE risk functions for low-risk European regions, the SCORE risk function for high-risk European regions (including the Netherlands) and the nationally adapted Dutch SCORE risk function, prepared by the SCORE group for the 2006 guideline on CVRM (**Chapter 2**).

To improve cardiovascular risk prediction and correctly classify high-risk persons for CVD, we investigated the impact of expanding the endpoint of risk prediction from CVD

mortality to CVD incidence and of adding additional risk factors to the risk function. Two promising risk factors are obesity and a parental history of myocardial infarction (MI). First, we conducted studies to examine the associations between measures of overweight and risk of CVD (**Chapter 3**) and between parental history of MI and CVD risk (**Chapter 4**). We used different definitions of these risk factors to obtain the best predictor.

Subsequently, the impact of expanding the endpoint from CVD mortality to total CVD in classical cardiovascular risk factor models is described (**Chapter 5**). The added value for risk prediction was examined of including obesity and parental history of MI into classical risk factor functions (**Chapter 6**). In the final chapter the contribution of our research to cardiovascular risk management in the Netherlands is described and promising future developments in cardiovascular risk prediction are discussed (**Chapter 7**).

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Evaluation of cardiovascular risk predicted by different SCORE equations: The Netherlands as an example

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ABSTRACT

Background: In Europe, for primary prevention of cardiovascular diseases (CVD), the Systematic COronary Risk Evaluation (SCORE) risk charts for high-risk and low-risk regions (SCORE-high and SCORE-low, respectively) are used. For the Dutch 'Clinical Practice Guideline for Cardiovascular Risk Management' an adapted SCORE risk chart (SCORE-NL) was developed in collaboration with the SCORE group. We evaluated these three SCORE equations using risk factor and mortality data of a Dutch prospective cohort study with 10 year follow-up.

Methods: Baseline data were collected between 1987 and 1997 in 32,885 persons aged 37.5–62.5 years. Vital status was checked and causes of death were obtained from Statistics Netherlands. On the basis of the level of risk factors, the expected number of CVD deaths was calculated by applying the three SCORE equations and compared with the observed number.

Results: The observed CVD mortality was three-fold higher in men (n = 242; 1.6%) than in women (n = 83; 0.5%). On the basis of SCORE-NL, 8.5% of the men and 0.8% of the women had a CVD mortality risk of 5% or more. The ratio of the observed-to-expected number of CVD deaths was 0.75 for men and 0.55 for women using SCORE-NL, 0.54 and 0.56 using SCORE-high and 1.11 and 0.95 using SCORE-low.

Conclusion: At the population level, SCORE-low predicts the number of CVD deaths well, whereas both SCORE-NL and SCORE-high overestimate the number of CVD deaths by a factor 1.5–2.

INTRODUCTION

Current guidelines for primary prevention of cardiovascular disease (CVD), recommend treatment of hypercholesterolemia and hypertension based on the estimated 10-year absolute risk for fatal CVD, taking into account an individual's overall risk profile, assessed on sex, age, smoking, systolic blood pressure and serum total cholesterol or total /HDL-cholesterol ratio.[1-3]

In the European Union (EU)-funded Systematic COronary Risk Evaluation (SCORE) project, a CVD risk function was developed based on European risk factor and CVD mortality data.[4] Risk charts were presented to estimate 10-year absolute risk of fatal CVD in populations at low and high-CVD risk. The Netherlands was regarded as a high-risk region. On request, the SCORE-group adapts its risk functions to recent national risk factor levels and CVD mortality statistics of European countries. Such a nationally adapted risk chart for The Netherlands was presented in the Dutch Clinical Practice Guideline for Cardiovascular Risk Management.[3]

On the basis of data from two large longitudinal population-based studies carried out in the late 1980s and 1990s, we evaluated the performance of the SCORE risk equations for the Dutch situation. We compared the observed CVD mortality with the expected CVD mortality based on the SCORE risk equations, both the equation for high-risk regions (SCORE-high) and that for low-risk regions (SCORE-low), and the risk function adapted to more recent national risk factor data and CVD mortality statistics (SCORE-NL). Implications for use and adaptation of risk charts in European countries are discussed.

METHODS

Study populations and data collection

Two monitoring projects on CVD risk factors, using the same methods, were carried out in The Netherlands between 1987 and 1997. Baseline cardiovascular risk factor data were collected in about 42,000 men and women aged 20–59 years during 1987–1992 in the Monitoring Project on Cardiovascular Disease Risk Factors and in approximately 21,000 men and women aged 20–65 years during 1993-1997 in the Monitoring Project on Chronic Disease Risk Factors (MORGEN-Project).[5,6]

The surveys were approved by the Medical Ethics Committees of the Academic Hospital Leiden and TNO Prevention and Health, Leiden, respectively. Participants signed an informed consent form for collecting additional medical information. The projects were carried out in random population samples of Amsterdam and Maastricht (response rates 33% and 43%, respectively). In Doetinchem, during 1993–1997 participants of the first survey in 1987–1992, were reinvited. In this analysis for Doetinchem only risk factor data collected

in 1993–1997 were used (response rate 68%). To enable comparison with SCORE, this analysis included data of 32,887 persons aged 37.5–62.5 years at baseline and excluded 577 persons with a self-reported history of myocardial infarction.

Information on demographic variables, disease history, use of medication, and lifestyle factors was obtained by standardized questionnaires. Serum total and HDL-cholesterol were measured at a laboratory that is a permanent member of the international Cholesterol Reference Method Laboratory Network (Erasmus Medical Centre, Rotterdam).[7,8] Blood pressure was measured twice by a trained technician at the right upper arm with the participant in sitting position using a random zero sphygmomanometer. Systolic blood pressure was recorded at the first and diastolic blood pressure at the fifth Korotkoff phase. The second measurement was taken after counting the resting heart rate for 30s. The mean of both measurements was used in the analyses. Information on smoking status was obtained from a questionnaire and dichotomized into 'current' and 'non-smoker'.

Vital status was checked through record linkage with the national population register. Only 66 persons were lost to follow up, 694 persons emigrated and were censored at the date of emigration. Data on CVD mortality during follow-up were obtained from Statistics Netherlands. Cases were censored at the date of death. Other participants were censored at the end of follow-up (at a maximum of 11 years), with an average of 10 years. Until January 1, 1996 we used the same International Classification of Diseases (ICD) 9 codes as applied in the SCORE project and thereafter corresponding ICD 10 codes.

SCORE project

The aim of the SCORE project was to construct risk equations for estimating an individual's 10-year risk of fatal CVD, based on a combination of risk factors[4] to assist clinicians in cardiovascular risk management for primary prevention. SCORE equations for high-risk regions were based on baseline survival data collected in cohorts from Denmark, Finland and Norway (SCORE-high) and for low-risk regions from Belgium, Italy and Spain (SCORE-low). Almost all participants in these cohorts were recruited in the 1970s and early 1980s. At the time of construction of these SCORE charts, The Netherlands was considered a high-risk region. For the Dutch Clinical Guideline on Cardiovascular Risk Management, the SCORE group adapted the SCORE equation as described by Conroy et al.[4] in 2006 by using the national percentage of smokers and average systolic blood pressure and serum total and HDL-cholesterol levels derived from a Dutch survey carried out by municipal health services in approximately 4,000 participants between 1998 and 2001 (REGENBOOG-project).9 For this purpose, national CVD mortality statistics of 2000 were obtained from the WHO mortality database. The nationally adapted SCORE risk function (SCORE-NL) calculates risk based on age, sex, smoking, systolic blood pressure, and the natural log of the ratio of total/HDL-cholesterol.[3]

In the SCORE project, CVD mortality was defined as a combination of coronary heart disease (CHD) (ICD 9: 401–414, 798.1 and 798.2) and noncoronary CVD (ICD 9: 426–443, with the exception of 426.7, 429.0, 430.0, 432.1, 437.3, 437.4 and 437.5). Noncoronary CVD includes ischemic cerebrovascular accident, congestive heart failure and peripheral arterial disease.

Statistical analysis

The cumulative 10-year incidence of fatal CVD (observed CVD mortality) was calculated. For all respondents, their individual 10-year risk for fatal CVD was calculated as follows, using the nationally adapted risk function SCORE-NL:

$$\text{Expected CVD risk} = \left(1-\text{Survival}_{\text{baseline}}{}^{*e^{[\beta_1*(\text{smoking status})+\beta_2*(\text{systolic blood pressure}-140)+\beta_3*(\ln \text{ratio total/HDL-cholesterol}-\ln 5)]}}\right)*100.$$

Age-dependent and sex-dependent baseline survival coefficients, and the β-coefficients were provided by the SCORE group. Subsequently, the expected total number of CVD deaths based on this nationally adapted SCORE risk equation (expNL) was calculated.

To estimate the risk according to SCORE-high and SCORE-low, the expected 10-year risk estimates for fatal CVD were based on baseline survival coefficients for CHD and noncoronary CVD from SCORE low-risk and high-risk regions separately, and on coefficients for men and women from a pool of 12 European cohorts participating in the SCORE project (Appendix A, Table A; Conroy et al., 2003).[4] The total effect of smoking, serum total cholesterol, and systolic blood pressure was calculated by applying the β-coefficients of the SCORE equation as mentioned in Table B.[4] More detailed coefficients were provided by the SCORE group. The expected 10-year risk for fatal CVD was obtained by applying the SCORE equations for high-risk and low-risk regions (expH, expL) on the individually measured systolic blood pressure value, the serum total cholesterol levels, and the smoking status of all respondents of the Dutch cohort.

The observed number of fatal CVD in the Dutch cohort (observed) and the expected number of fatal CVD based on the nationally adapted SCORE risk equation (expNL) and the SCORE equations for high-risk and low-risk regions (expH, expL), were plotted by categories of absolute risk according to the nationally adapted SCORE-NL function. Subsequently, the ratio observed/expected number of fatal CVD was calculated for the different risk functions.

To evaluate the impact of applying the different risk functions and thresholds for treatment on the number of persons eligible for pharmacological treatment, we present the percentage of respondents with a risk of 5–10 % and 10% or higher. These thresholds are frequently applied in European guidelines for cardiovascular risk management[1,2] and in the Netherlands.[3] In addition, risk charts for men and women aged 55 years, based on three different risk functions are presented.

For all analyses SAS 9.1 by SAS Institute Inc. (Cary, North Carolina, USA) 2002–2003 was used.

RESULTS

Description of the study population

Of the total study population of 32,885 persons, 60% was examined between 1987 and 1992 and 40% between 1993 and 1997; 47% was men and 53% women (Table 2.1). The differences in risk factors levels between men and women were small with the exception of a 5 mmHg higher mean systolic blood pressure and a 0.3 mmol/l lower mean HDL-cholesterol in men. Almost 40% of the men and women smoked.

Table 2.1 Baseline CVD risk factors [1987–1997, mean (SD) or percentage] and absolute 10-year CVD mortality risk in 32,887 men and women aged 37.5–62.5 years without a history of myocardial infarction in two Dutch population-based cohorts

	Men (n = 15,385)	Women (n = 17,500)
Age (years)	49 (6.5)	49 (6.6)
Body mass index (kg/m^2)	26.0 (3.4)	25.6 (4.3)
Overweight (BMI ≥ 25 kg/m^2) (%)	59.1	48.0
Serum total cholesterol (mmol/l)	5.7 (1.1)	5.7 (1.1)
Hypercholesterolemia (≥ 6.5 mmol/l) (%)	22.3	22.0
Cholesterol lowering medication (%)	1.0	0.8
HDL-cholesterol (mmol/l)	1.1	1.4
Systolic blood pressure (mmHg)	126 (15.9)	121 (17.0)
Hypertension (SBP ≥ 160 mmHg) (%)	8.0	6.3
Blood pressure lowering medication (%)	6.0	7.3
Current smokers (%)	38	37
Self-reported diabetes mellitus (%)	1.6	1.4
CVD deaths, n (%)	242 (1.57)	83 (0.48)
CHD deaths, n (%)	166	52
Noncoronary CVD deaths*, n	76	31
SCORE-NL risk 5–10 (%)	7.4	0.7
SCORE-NL risk > 10% (%)	1.2	0.05
SCORE-high risk 5–10 (%)	13.1	0.8
SCORE-high risk > 10% (%)	3.3	0.09
SCORE-low risk 5–10 (%)	2.9	0.1
SCORE-low risk > 10% (%)	0.2	0.02

BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; SCORE-NL, Systematic COronary Risk Evaluation nationally adapted; SBP, systolic blood pressure.
*Noncoronary CVD includes stroke, peripheral arterial disease and heart failure.

Observed 10-year incidence of fatal CVD

During 10 years of follow-up, 1,459 persons died, of whom 325 died from CVD (Table 2.1). CVD mortality was three-fold higher in men than in women. Ten-year CVD mortality was almost twice as high in persons recruited in the period 1987–1992 compared with those recruited in the period 1993–1997 both in men (1.9% versus 1.1%) and in women (0.6% versus 0.3%), whereas age distributions were similar in both study populations.

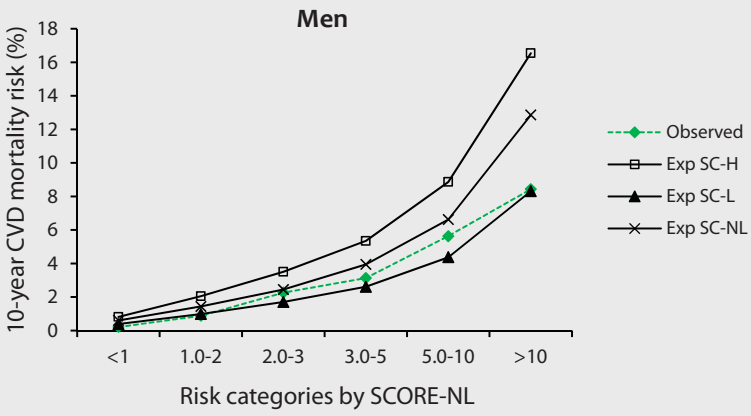
Observed and expected CVD mortality risk

The observed number of CVD deaths in this Dutch cohort was only half the number of CVD deaths expected by SCORE-NL in women (Obs/ExpNL = 0.55) and three-quarters in men (Obs/ExpNL = 0.74). The observed number of CVD deaths was half that predicted by SCORE-high (Obs/ExpH = 0.54 for men and 0.56 for women) (Figure 2.1). This overestimation by SCORE-NL and SCORE-high was present in almost all risk categories and in both men and women. The observed CVD mortality risk compared well with the expected risk based on SCORE-low (Obs/ExpL = 1.1 for men and 0.95 for women) (Figure 2.1).

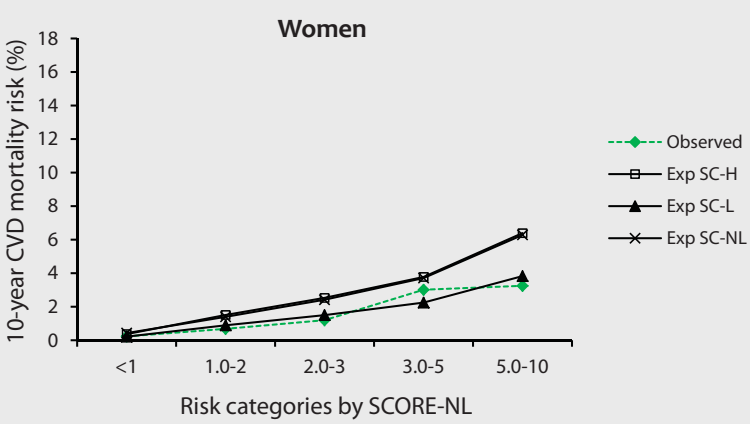
Implications for risk factor treatment

On the basis of different SCORE equations, the percentage of persons with a risk above 5% varied in men between 3% for SCORE-low and 16% for SCORE-high (Table 2.1). For women these percentages were 0.1% and 0.8%. When a risk of 10% as cut-off point for treatment was taken, the percentage of men eligible for treatment varied between 0.2% for SCORE-low and 3.2% for SCORE-high. In women these percentages were 0.02% and 0.09%. The number of persons with risk above 5% and 10%, respectively, based on SCORE-NL was in between that of SCORE-low and SCORE-high. Using SCORE-high, 16 times more men and 4.5 times more women had a risk of 10% or higher, as compared with using SCORE-low. A similar pattern was found for men with a risk of 5% or higher, whereas for SCORE-NL and SCORE-high in women no difference was observed.

Figure 2.2 shows the 10-year absolute CVD mortality risk charts for men and women aged 55 years by smoking, the ratio of serum total /HDL-cholesterol (SCORE-NL) or serum total cholesterol (SCORE-high and SCORE-low), and systolic blood pressure based on SCORE-NL, SCORE-high and SCORE-low. According to the Dutch Clinical Guideline, based on SCORE-NL, a male smoker aged 55 years with a systolic blood pressure of 160 mmHg, has a risk of more than 10% when the ratio total /HDL cholesterol is 8 or higher and should therefore be pharmacologically treated. On the basis of SCORE-high he should be treated when serum total cholesterol is 6 mmol/l or higher. By applying SCORE-low a men with these characteristics would not be eligible for pharmacological treatment.



# at risk	5,666	4,086	2,341	1,979	1,135	178
O/E SC-H	0.26	0.43	0.65	0.59	0.64	0.51
O/E SC-L	0.55	0.89	1.33	1.20	1.29	1.01
O/E SC-NL	0.35	0.61	0.92	0.82	0.85	0.66



# at risk	12,619	3,217	1,001	531	123
O/E SC-H	0.62	0.45	0.46	0.80	0.51
O/E SC-L	1.07	0.77	0.80	1.34	0.85
O/E SC-NL	0.54	0.49	0.50	0.81	0.52

Figure 2.1 Observed and expected absolute 10-year cardiovascular disease (CVD) mortality risk (%) in 15,385 men and 17,502 women from two Dutch population based cohorts, examined in 1987–1997, by risk categories based on the nationally adjusted risk equation (SCORE-NL).
E, expected; O, observed; SC-H, SCORE-high; SC-L, SCORE-low; SC-NL, SCORE-nationally adjusted.

Men

Nonsmoker, aged 55 years						Smoker, aged 55 years				
SCORE-NL					SBP					
4	5	6	7	8	180	8	10	11	13	15
3	4	4	5	6	160	6	7	8	9	11
2	3	3	4	4	140	4	5	6	7	8
2	2	2	3	3	120	3	4	4	5	5
4	5	6	7	8	Ratio	4	5	6	7	8
SCORE-high										
6	7	8	10	12	180	12	13	16	19	22
4	5	6	7	8	160	8	9	11	13	16
3	3	4	5	6	140	5	6	8	9	11
2	2	3	3	4	120	4	4	5	6	8
4	5	6	7	8	Chol	4	5	6	7	8
SCORE-low										
3	4	4	5	6	180	6	7	8	10	12
2	2	3	3	4	160	4	5	6	7	8
1	2	2	2	3	140	3	3	4	5	6
1	1	1	2	2	120	2	2	3	3	4
4	5	6	7	8	Chol	4	5	6	7	8

Women

Nonsmoker, aged 55 years						Smoker, aged 55 years				
SCORE-NL					SBP					
2	3	3	4	4	180	4	5	6	7	8
2	2	2	3	3	160	3	4	4	5	5
1	1	2	2	2	140	2	3	3	3	4
1	1	1	1	1	120	1	2	2	2	3
4	5	6	7	8	Ratio	4	5	6	7	8
SCORE-high										
2	2	3	3	4	180	4	5	5	6	7
1	2	2	2	3	160	3	3	4	4	5
1	1	1	1	2	140	2	2	2	3	3
1	1	1	1	1	120	1	1	2	2	2
4	5	6	7	8	Chol	4	5	6	7	8
SCORE-low										
1	1	2	2	2	180	3	3	3	4	4
1	1	1	1	1	160	2	2	2	3	3
1	1	1	1	1	140	1	1	1	2	2
0	0	1	1	1	120	1	1	1	1	1
4	5	6	7	8	Chol	4	5	6	7	8

risk ≥ 10% risk 5–10% risk < 5%

Figure 2.2 Ten-year risk chart of fatal cardiovascular disease (CVD) in male and female smokers and nonsmokers aged 52.5–57.5 years by serum total cholesterol or ratio total/HDL-cholesterol and systolic blood pressure category based on the nationally adjusted risk equation (SCORE-NL), SCORE-high, and SCORE-low risk regions.
SBP, systolic blood pressure in mmHg; chol, serum total cholesterol in mmol/l (SCORE-low, SCORE-high); ratio, serum total cholesterol (mmol/l)/HDL-cholesterol (mmol/l) (SCORE-NL).

DISCUSSION

The observed number of CVD deaths during 10 years of follow-up in Dutch men and women was overestimated by a factor 1.5–2 by SCORE-NL and by a factor 2 by SCORE-high, but was adequately predicted by SCORE-low. Applying SCORE-NL and especially SCORE-high can lead to pharmacological overtreatment. Nowadays, the SCORE function for low-risk regions fits best in the Dutch situation.

For this study, we used data from two monitoring projects with a large number of men and women (15,385 and 17,500 respectively). Risk factor data were measured with standardized methodology and mortality follow-up was almost complete. However, because of the decline in CVD mortality in the past decades in The Netherlands, the total number of CVD deaths during 10-year follow-up was low, especially among women. Even during a 10-year follow-up period we observed a two-fold higher CVD mortality rate in the cohort with respondents recruited between 1987 and 1992 compared with those recruited between 1993 and 1997. Therefore, in the development and adaptation of risk charts based on national data, the period in which participants are recruited should be taken into account.

The Dutch SCORE function published in 2006 was calibrated using risk factor data of the REGENBOOG-project.[9] These risk factor data were collected more recently (1998–2001) than the ones in this study (1987–1997). The number of smokers was 1% lower in men and 6% in women, average blood pressure level was 7 mmHg higher in men and 6 mmHg in women, but serum total and HDL-cholesterol levels were similar (data provided by L. Viet, May 2009). Baseline survival coefficients for the calibrated SCORE-NL function were derived from national CVD mortality statistics of 2000; whereas CVD mortality data in this study were collected between 1987 and 2007. Therefore, the national CVD mortality data are not representative for the entire follow-up period of our cohort. Furthermore, in contrast to this study, the national CVD mortality data were derived from the whole population including persons with pre-existing CVD. This could contribute to the discrepancy between the expected CVD mortality risk based on SCORE-NL and observed risk in this study.

Similar studies, in which nationally adapted SCORE charts were evaluated in cohorts with a 10-year CVD mortality follow-up, have been published for the high-risk country, Sweden, and the low-risk country, Belgium.[10,11] As in The Netherlands, also in Sweden, the calibrated SCORE risk function overestimated the number of CVD deaths, whereas in Belgium the calibrated function performed well. Both in Sweden and The Netherlands, CVD mortality has strongly declined in the past decades, whereas the decrease in Belgium was less pronounced.[12,13] Thus, in countries with decreasing CVD mortality rates such as Sweden and The Netherlands, calibration removes only part of the overestimation.

We also evaluated the performance of the SCORE-high and SCORE-low functions in The Netherlands and compared our results with those of other cohort studies with a 10-year

CVD mortality follow up. SCORE-high also overestimated the number of CVD deaths in the high-risk countries such as Iceland[14] and Norway.[15] As in The Netherlands, SCORE-low performed much better in Iceland and Norway. Again, the most important explanation for these overestimations of the number of CVD deaths in high risk countries are the strong decreasing CVD mortality trends in these countries.[13] The consequence of these overestimations is, that persons who did not qualify for treatment based on SCORE-low will also be treated.

The 2007 European guidelines on cardiovascular prevention recommended an absolute risk of 5% as cut-off point for treatment.[2] According to the Framingham Study a 5% fatal CVD risk equals a 20% nonfatal and fatal CHD risk.[16] The Dutch 2006 guideline proposed a cut-off point of 10% fatal CVD risk for pharmacological treatment based on cost-effectiveness and a limited capacity of health care workers.[3] As nowadays the number of persons with such a high risk is low, the European cut-off points might be reconsidered. However, all these cut-off points are arbitrary and in discussion; issues such as the balance between treatment and side effects, costs, health care capacity, and medicalisation also need to be considered.

CONCLUSION

The results of this study show that overestimation of CVD mortality risk may result in pharmacological overtreatment. Therefore, SCORE risk functions need to be adapted regularly in countries where CVD mortality rates are changing, using recent risk factor and mortality data. Owing to the strongly improved survival of CVD patients, emphasis will shift from a focus on CVD mortality to morbidity. Therefore, new risk charts are needed based on both nonfatal and fatal CVD.[3,14]

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3

Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20,000 Dutch men and women aged 20-65 years

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ABSTRACT

Aims: Body mass index (BMI) and waist circumference (WC) are both predictors of cardiovascular diseases (CVD). We compared absolute risk, hazard ratio (HR), and (population) attributable risk of nonfatal and fatal CVD for BMI and WC in a large prospective cohort study with an average follow-up of 10 years.

Methods and results: Anthropometric data were measured between 1993 and 1997 in a general population sample of over 20,000 men and women aged 20–65 years in The Netherlands. All risks were adjusted for age and sex. Absolute risk of nonfatal CVD was on average 10 times higher than that of fatal CVD. In obese respondents (BMI ≥ 30 kg/m^2), relative risk of fatal CVD was four-fold higher [HR = 4.0 95% confidence interval (CI) = 2.4–6.6], whereas risk of nonfatal CVD was two-fold higher (HR = 1.8 95% CI = 1.6–2.2) than in normal weight respondents. Similar associations were observed for WC (≥ 88 vs. < 80 cm in women and ≥ 102 vs. 94 cm in men). In persons with overweight or obesity (BMI ≥ 25 kg/m^2), half of all fatal CVD (attributable risk = 54%, 95% CI = 30–70) and a quarter of nonfatal CVD was ascribed to their overweight. On the population level, one-third of all fatal CVD cases could be attributed to overweight and obesity (population attributable risk = 35%, 95% CI = 14–52), and about one in seven of nonfatal CVD cases.

Conclusion: The associations of BMI and WC with CVD risk were equally strong. Overweight and obesity had a stronger impact on fatal CVD than on nonfatal CVD.

INTRODUCTION

Overweight and obesity are a major public health problem and contribute substantially to the burden of chronic diseases worldwide. Currently, more than 1.6 billion adults are overweight and at least 400 million are obese. In 2015, the number of overweight persons is expected to increase to 2.3 billion and the number of obese to 700 million.[1]

Body mass index (BMI) and waist circumference (WC), a measure of abdominal obesity, are associated with risk factors for cardiovascular diseases (CVD)[2-6] and are predictors of CVD mortality.[7-11] As CVD mortality rates are strongly declining in Western countries,[12,13] the burden of CVD is nowadays more strongly determined by CVD morbidity. Therefore, information on the strength of the association of BMI and WC and on the contribution of overweight and obesity to the occurrence of nonfatal CVD is needed.[14-16]

Data on the associations of overweight and obesity with nonfatal CVD are mainly obtained from large prospective cohorts in which height and weight were self-reported and WC was self-measured.[8,11,17,18] Visscher et al.[19] showed that self-reported BMI data underestimate the true prevalence of obesity by at least 25%. For a correct estimation of the strength of the associations of BMI and WC with nonfatal and fatal CVD, anthropometric data measured by trained staff are needed.

In The Netherlands, in the Monitoring Project on Chronic Disease Risk Factors (MORGEN), cardiovascular risk factors were measured between 1993 and 1997 in a large cohort of over 20,500 respondents. We studied both BMI and WC in relation to absolute risk, hazard ratio (HR), attributable risk (AR), and population attributable risk (PAR) for 10-year fatal and nonfatal CVD.

METHODS

Study population

In the MORGEN project, cardiovascular risk factor data were collected in about 20,500 men and women aged 20-65 years during the period 1993-1997.[20] The survey was carried out in a general population sample from the towns of Amsterdam (response rate 33%), Doetinchem (68%), and Maastricht (43%). The MORGEN project is one of the two Dutch cohorts participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) project.[7] The MORGEN project was approved by the Medical Ethics Committee of TNO Prevention and Health, Leiden and participants signed an informed consent form.

Data collection

Body weight, height, and WC were measured according to the WHO recommendations[21] by trained staff. Body weight was measured to the nearest 100 g on calibrated scales. As participants were weighed wearing light indoor clothing (with empty pockets and no shoes), 1 kg was subtracted from the measured body weight. Height was measured to the nearest cm. Body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in meters) squared. WC was measured at the level midway between the lower rib margin and the iliac crest at the end of gentle expiration, with participants in standing position. The mean of two measures was used for analysis.

Nonfasting blood samples were taken and serum total cholesterol was measured by the CHOD-PAP method.[22] HDL-cholesterol was determined in the supernatant after precipitation of apolipoprotein B-containing lipoproteins with magnesium phosphotungstate.[23] All cholesterol determinations were done in a laboratory that is a permanent member of the international Cholesterol Reference Method Laboratory Network (Erasmus Medical Centre, Rotterdam, The Netherlands).

Blood pressure was measured twice by a trained technician at the right upper arm with the participant in sitting position using a random zero sphygmomanometer. Systolic blood pressure was recorded at the first, and diastolic blood pressure at the fifth Korotkoff phase. The second measurement was carried out after counting resting heart rate for 30s. The mean of both measurements was used in the analyses.

Information on demographic variables, disease history, educational level, and lifestyle factors was obtained by standardized questionnaires. Smoking was dichotomized as 'current smoker' or 'non-smokers'. The prevalence of myocardial infarction and diabetes mellitus at baseline was based on self-report. Educational level was assessed at seven levels ranging from primary education or less to university education. For the present analyses education was divided into three categories: low (intermediate secondary education or less), medium (intermediate vocational or higher secondary education), or high (higher vocational or university education).

Nonfatal and fatal cardiovascular diseases

Vital status was checked through record linkage with the national population register. Only 556 persons were lost to follow-up, of whom 538 persons emigrated. Data on fatal CVD were obtained from Statistics Netherlands (till 1 January 2006) and patients with nonfatal CVD were identified through linkage with the National Hospital Discharge Register (till 1 January 2006). On the national level, 88% of the hospital admissions could be uniquely linked to a single person.[24] Cases were censored at the date of the first hospital discharge or date of death. Other subjects were censored at the time of emigration or at the end

of follow-up (at a maximum of 11 years), with an average of 10 years. As this study was carried out in collaboration with the SCORE project, the same International Classification of Diseases (ICD) codes for nonfatal and fatal CVD[25] were used: coronary heart disease (ICD 9: 401–414, 798.1 and 798.2) and noncoronary CVD (ICD 9: 426–443; with the exception of 426.7, 429.0, 430.0, 432.1, 437.3, 437.4 and 437.5). After January 1996, corresponding ICD 10 codes were used for fatal CVD.

Data and statistical analyses

We excluded 242 persons with a self-reported history of myocardial infarction. In addition, we excluded 120 pregnant women, 44 persons with missing data on anthropometric measures, 161 persons with missing information on confounders, and the second record of 48 persons measured twice. We also excluded 289 persons with a BMI of less than 18.5 kg/m^2. The remaining study population consisted of 9,062 men and 10,572 women. On account of the limited number of CVD deaths, we did not stratify for sex. There were no significant interactions with sex and age. Therefore, we combined data and adjusted for sex and age.

Normal weight was defined as a BMI of 18.5–24.9 kg/m^2, overweight as a BMI of 25–29.9 kg/m^2, and obesity as a BMI of 30 kg/m^2 or more (WHO criteria). Cut-off points for WC for normal weight, overweight and abdominal obesity were defined in men at less than 94 cm, 94–101.9 cm, and ≥ 102 cm, respectively, and in women at less than 80 cm, 80–87.9 cm, and ≥ 88 cm, respectively.[21,26]

Absolute risks (cumulative incidence rates during 10-years of follow-up) were calculated using general linear models, adjusted for sex and age. Associations of BMI and WC with risk of fatal and nonfatal CVD were analyzed with Cox proportional hazard models, adjusted for sex and age (model 1), sex, age, smoking behavior, and educational level (model 2) and additionally adjusted for systolic blood pressure, serum total cholesterol, HDL-cholesterol and self-reported diabetes mellitus (model 3). The proportionality of the hazards was verified by plotting the log-log survival curves and graphical inspection of parallelism of the curves. Data are presented as HR with confidence intervals (95% CI). Two-sided P-values of less than 0.05 were considered statistically significant.

The AR fraction in persons with obesity or who were overweight was calculated with the formula: AR = $[HR_{ov}-1]/HR_{ov}$, in which HR_{ov} = the hazard ratio in overweight or obese respondents versus normal weight respondents. The PAR for overweight and obesity was calculated with the formula: PAR = $[P_{ov}(HR_{ov}-1)]/[P_{ov}(HR_{ov}-1)+1]$,[27] in which P_{ov} = proportion of overweight or obese persons in cohort and HR_{ov} = the hazard ratio of overweight or obese respondents versus normal weight respondents. The confidence intervals of the HRs for nonfatal and fatal CVD were applied to calculate the confidence intervals of the PARs.

For all analyses SAS 9.1 by SAS Institute Inc. (Cary, North Carolina, USA) 2002–2003 was used.

RESULTS

On the basis of BMI, 42% of the men and 30% of the women were overweight, whereas 10% of the men and 11% of the women were obese (Table 3.1). On the basis of WC (≥ 88 cm in women and ≥ 102 cm in men), 19% of the men and 26% of the women had abdominal obesity. Obese persons smoked less, had a lower educational level, and more unfavorable CVD risk factor levels compared with persons with a healthy weight. BMI and WC were strongly correlated (Pearson's r = 0.86 in men and r = 0.84 in women). During an average follow-up of 10 years, 728 men and 403 women were hospitalized for nonfatal CVD and 81 men and 30 women died from CVD.

In this cohort, with an average age of 43 years, the incidence of a first nonfatal CVD was approximately 10 times more frequent than that of fatal CVD (Figure 3.1). The absolute

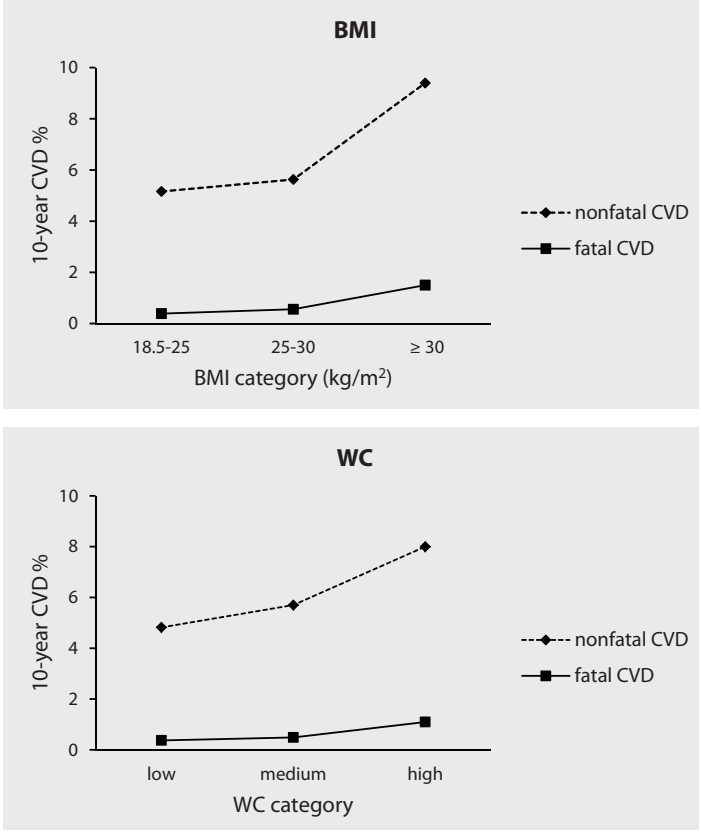

Figure 3.1 Age- and sex-adjusted absolute 10-year nonfatal and fatal cardiovascular disease rates by BMI (kg/m²) and waist circumference (cm) category in men and women aged 20–65 years.
WC categories: low: men < 94, women < 80 cm; medium: men 94–102 cm, women 80–88 cm; high: men ≥ 102 cm, women ≥ 88 cm.
BMI, body mass index; CVD, cardiovascular disease; WC, waist circumference.

Table 3.1 Risk factor levels (mean, SD or %) and crude percentage of nonfatal and fatal CVD in men and women without a history of myocardial infarction aged 20–65 years by BMI category in the MORGEN project, 1993–1997

	Men (n = 9,062)			Women (n = 10,572)		
	BMI (kg/m^2)			BMI (kg/m^2)		
	18.5–25	25–30	≥ 30	18.5–25	25–30	≥ 30
Number	4,340 (48)	3,849 (42)	873 (10)	6,282 (59)	3,150 (30)	1,140 (11)
Age (years)	40 (11)	46 (10)	47 (9)	40 (11)	46 (11)	47 (11)
BMI (kg/m^2)	22.7 (1.6)	27.0 (1.4)	32.4 (2.7)	22.2(1.6)	27.0 (1.4)	33.6 (3.4)
Waist circumference (cm)	85.0 (6.7)	97.0 (6.6)	110.5 (8.9)	75.6 (6.6)	87.2 (7.3)	101.2 (9.7)
Smokers, %	39	32	32	39	31	31
Low education, %	35	49	64	44	66	77
Serum total cholesterol (mmol/l)	5.0 (1.0)	5.6 (1.0)	5.7 (1.2)	5.1 (1.0)	5.5 (1.1)	5.5 (1.0)
Serum HDL-cholesterol (mmol/l)	1.3 (0.3)	1.1 (0.3)	1.0 (0.2)	1.6 (0,4)	1.4 (0.4)	1.3 (0.3)
Systolic blood pressure (mmHg)	121 (13.3)	128 (15.1)	134 (17.0)	114 (14.2)	122 (16.4)	129 (18.8)
Self reported diabetes mellitus, %	0.8	1.3	3.0	0.6	1.3	3.3
Nonfatal CVD, %	5.9	8.7	16.0	2.6	5.1	6.8
Fatal CVD, %	0.4	1.1	2.6	0.2	0.3	0.9

BMI, body mass index; CVD, cardiovascular diseases; HDL, high-density lipoprotein; MORGEN, Monitoring Project on Chronic Disease Risk Factors.

Table 3.2 Hazard ratios for risk of 10-year nonfatal and fatal cardiovascular diseases in men and women aged 20–65 years

	HR (95% CI) nonfatal CVD				HR (95% CI) fatal CVD			
BMI (kg/m²)	no. of cases/ no. at risk	Model 1	Model 2	Model 3	no. of cases/ no. at risk	Model 1	Model 2	Model 3
18.5–25	254/4340	1	1	1	16/4340	1	1	1
25–29.9	334/3849	1.1 (1.0–1.3)	1.2 (1.0–1.3)	1.0 (0.8–1.1)	42/3849	1.7 (1.0– 2.7)	1.8 (1.1–2.9)	1.4 (0.9–2.3)
≥ 30	140/873	1.8 (1.6–2.2)	1.9 (1.6–2.2)	1.3 (1.1–1.5)	23/873	4.0 (2.4–6.6)	4.7 (2.9–7.9)	2.9 (1.7–5.1)
WC (cm)								
M* < 94, W < 80	273/5147	1	1	1	19/5147	1	1	1
M 94–102, W 80–88	214/2232	1.2 (1.1–1.4)	1.2 (1.1–1.4)	1.1 (0.9–1.2)	24/2232	1.4 (0.8–2.4)	1.5 (0.9–2.6)	1.2 (0.7–2.1)
M ≥ 102, w ≥ 88	241/1683	1.7 (1.5–1.9)	1.7 1.4–2.0)	1.2 (1.0–1.4)	38/1683	2.9 (.8–4.7)	3.2 (1.9–5.1)	2.1 (1.3–3.5)

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking and educational level. Model 3: adjusted for age, sex, smoking, educational level, systolic blood pressure, total serum cholesterol, HDL-cholesterol and self reported diabetes mellitus.
BMI, body mass index; CI, confidence interval; HR, hazard ratio; M, men; W, women; WC, waist circumference.

Table 3.3 Prevalence, hazard ratios, attributable risk and population attributable risk (95% CI) in overweight and obese men and women aged 20–65, based on BMI and WC

	Prevalence (%)	HR for nonfatal CVD (95% CI)	HR for fatal CVD (95% CI)	AR for nonfatal CVD (95% CI)	AR for fatal CVD (95% CI)	PAR for nonfatal CVD (95% CI)	PAR for fatal CVD (95% CI)
BMI ≥ 25 kg/m²	45.9	1.3 (1.1–1.4)	2.2 (1.4–3.4)	22% (12–31)	54% (30–70)	12% (6–17)	35% (15–52)
WC men ≥ 94, women ≥ 80 cm	47.4	1.4 (1.3–1.6)	2.1 (1.4–3.3)	30% (21–39)	53% (26–70)	17% (10–23)	35% (14–52)

AR, attributable risk; BMI, body mass index; CI, confidence interval; CVD, cardiovascular diseases; HR, hazard ratio; M, men; PAR, population attributable risk; WC, waist circumference; W, women.

risks of nonfatal and fatal CVD for categories of BMI as well as of WC were similar and the absolute risks increased from the normal weight category to the obesity category, with the largest increase from the overweight to the obesity category.

For obesity, HR for fatal CVD adjusted for age and sex [BMI = 4.0 (2.4–6.6), WC = 2.9 (1.8–4.7)] were approximately twice as strong as for nonfatal CVD [BMI = 1.8 (1.6–2.2), WC = 1.7 (1.5–1.9)] after adjustment for sex and age (Table 3.2). Adjustment for potential intermediate risk factors (systolic blood pressure, total cholesterol, HDL-cholesterol and self-reported diabetes mellitus), reduced the observed HR for fatal CVD by 50% and nonfatal CVD by 70% (Table 3.2).

In overweight or obese respondents, 53% of all fatal CVD (based on BMI or WC) and 22%–30% of nonfatal CVD (based on BMI respectively WC) is ascribed to their overweight (Table 3.3). Given a prevalence of 46% for overweight and obesity in our population, 35% of all fatal CVD cases and 12%–17% (based on BMI respectively WC) of all nonfatal CVD cases can be attributed to overweight and obesity (Table 3.3).

DISCUSSION

In our population, the incidence of nonfatal CVD was on average 10 times higher than that of fatal CVD. Risk estimates for overweight were similar for BMI and WC. However, the strengths of the associations of obesity were approximately twice as strong for fatal compared with nonfatal CVD. Intermediate risk factors explained a large part of the association, especially for nonfatal CVD. One-third of all fatal CVD cases and about one-seventh of all nonfatal CVD cases could be attributed to overweight and obesity.

Our cohort was relatively young (20–65 years) compared with other populations.[10,11] As the relationship of BMI and WC with CVD mortality decreases with age,[10,28] our findings may not be generalisable to older populations.

Information on nonfatal CVD was obtained from hospital discharge data through linkage with the National Hospital Discharge Register. On a national level, 88% of the hospital admissions could be uniquely linked to a single person on basis of sex, date of birth and the numeric part of the postal code.[24] Through this procedure, in 9% of the cases more than one person was merged to the same set of linkage variables and 4% could not be linked. Since almost all persons in the MORGEN-project had a unique combination of linkage variables and persons who emigrated were censored at the date of emigration, successful record linkage in our cohort was higher than 88%. Successful linkage was probably not related to BMI and WC, and we therefore believe that differential bias has not affected our findings.

BMI and WC were strongly correlated in both men and women. The magnitude of the correlation was similar to that in other studies.[7,8,11,14,29,30] A recent editorial concluded that

BMI and WC are similar indexes of body composition, which could explain the similar results for the associations of BMI and WC with all-cause mortality.[31] This study extends this to the associations with nonfatal and fatal CVD.

Owing to the strongly improved survival of CVD patients in many Western countries,[12,13] the burden of CVD is nowadays strongly determined by CVD morbidity. Therefore it is important to establish the strength of the associations of BMI and WC with nonfatal CVD. We found a 10 times higher incidence of nonfatal CVD compared with fatal CVD in this relatively young cohort. This implies that only taking fatal CVD into account for risk prediction in individuals as assessed by e.g. SCORE risk charts,[25] is only the tip of the iceberg, especially in young persons.

We observed a four-fold increased risk of fatal CVD for obesity based on BMI and a three-fold increased risk for obesity based on WC. These hazard ratios are higher than those reported by most other studies. In the EPIC project with 359,387 participants, that also included data of our cohort, the relative risks (RR) from circulatory causes of death (ICD 10 codes I00–I99) were similar for BMI and WC categories,[7] but they were lower than those in this study (in EPIC men: HR = 1.6 for BMI and HR = 1.8 for WC; in EPIC women: HR = 1.3 for BMI and HR = 2.3 for WC). Men and women in EPIC were on average 10 years older. Furthermore, in this study, the HR in older respondents of our cohort (40–65 years) was lower than that in respondents aged 20–40 years (HR = 3.2 and HR = 12.5, respectively for BMI; HR = 2.8 and HR = 3.4, respectively for WC), but this could not completely explain the difference with EPIC.

In the large prospective study collaboration (PSC) with almost 1 million persons at risk with subsequently about 30,000 vascular deaths during an average follow-up of 8 years (deaths in first 5 years excluded), obese persons (BMI 30–35 vs. 22.5–25 kg/m^2) had a two-fold risk of ischemic heart disease, stroke or other vascular diseases in the 35–59 years age group (web table 10). Although the age range of the PSC study is comparable with the present study and in most studies BMI was measured, RR for vascular deaths was lower. In studies with self-reported anthropometric data, RRs are generally lower for BMI as well as WC (range RR 1.6–2.7),[8,11,32] except in the Health Professionals Follow-up Study (RR = 3.9 for obesity based on BMI and HR = 2.9 based on WC in men aged 40-64 years).[10] These lower risks are very likely the result of underreporting of body weight and overreporting of height, especially in overweight persons,[19] leading to attenuation of the relationship between obesity and CVD. In most epidemiological studies with incident CVD as an endpoint, data were presented for the combined endpoint of nonfatal and fatal CVD. RRs of nonfatal and fatal CVD of 1.5–2 were observed for obesity based on either BMI or WC.[15,17,18,29] These findings are in line with the results of this study for nonfatal CVD.

In the present study, adjustment for the intermediate classical CVD risk factors (systolic blood pressure, total-cholesterol and HDL-cholesterol and self-reported diabetes)

explained about 70% of the association of obesity based on BMI or WC with nonfatal CVD and 50% of the association with fatal CVD. In a meta-analysis of 21 cohort studies, about 45% of the increased risk of fatal or fatal and nonfatal CHD events in overweight and obese persons was explained by higher blood pressure and cholesterol levels.[33] The results of these studies suggest that major CVD risk factors explain the increased CVD risk caused by obesity by about 50%. The results of this study suggest that the intermediate CVD risk factors explain even a larger part of the occurrence of nonfatal CVD risk caused by obesity.

In this relatively young cohort, in overweight or obese respondents, half of all fatal CVD and a quarter of nonfatal CVD was ascribed to their overweight. On the population level, one-third of all fatal CVD cases and one in seven of all nonfatal CVD cases could be attributed to overweight and obesity. The impact of overweight and obesity on fatal CVD for BMI is two times and for WC three times stronger than the impact on nonfatal CVD. Overweight and obesity explain the occurrence of fatal CVD to a large extent than that of nonfatal CVD.

We conclude that in adults aged 20–65 years, the burden of CVD is changing from fatal to nonfatal cardiovascular diseases. For overweight and obesity based on BMI as well as on WC, similar associations were obtained for nonfatal and fatal CVD. These associations were approximately twice as strong for fatal than for nonfatal CVD. Especially for nonfatal CVD, the impact of obesity was to a large extent attributable to intermediate risk factors. One out of three of fatal and one out of seven of nonfatal CVD cases can be attributed to overweight and obesity in the population. This emphasizes the importance of overweight prevention in CVD prevention. Measuring overweight has the advantage that it does not require medical investigations and can be based on self-identification by persons at risk.

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4

Various definitions of parental history of myocardial infarction and 10-year cardiovascular diseases incidence in a Dutch cohort of middle-aged men and women

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ABSTRACT

Background: A positive parental history of myocardial infarction (MI) is an independent risk factor for cardiovascular diseases (CVD). However, different definitions of parental history have been used. We evaluated the impact of parental gender and age of onset of MI on CVD incidence.

Methods: Baseline data were collected between 1993 and 1997 in 10,524 respondents aged 40-65 years. CVD events were obtained from the National Hospital Discharge Register and Statistics Netherlands. We used proportional hazard models to calculate hazard ratios (HR) and 95% confidence intervals (CI) for CVD incidence and adjusted for lifestyle and biological risk factors.

Results: At baseline, 36% had a parental history of MI. During 10-year follow-up, 914 CVD events occurred. The age and gender adjusted HR was 1.3 (95% CI 1.1-1.5) for those with a paternal MI, 1.5 (1.2-1.8) for those with a maternal MI and 1.6 (1.2-2.2) for those with both parents with an MI. With decreasing parental age of MI, HR increased from 1.2 (1.0-1.6) for age ≥ 70 years to 1.5 (1.2-1.8) for age < 60 years for a paternal MI and from 1.1 (0.9-1.5) to 2.2 (1.6-3.0) for a maternal MI. The impact of having a mother with MI before age 60 significantly differed in women [2.9 (1.8-4.6)] and men [1.5 (0.9-2.6)]. Adjustment only slightly influenced HRs for maternal MI.

Conclusions: Respondents with a parental history of MI have an increased CVD incidence, in particular with parental onset of MI before age 70. A maternal history of MI before age 60 was the strongest predictor of CVD incidence.

INTRODUCTION

A positive parental history of a myocardial infarction (MI) is an independent risk factor for cardiovascular diseases (CVD). This relationship was already demonstrated in the 1970s in men[1] and in the 1980s in women,[2] and has been confirmed in many prospective studies. However, most studies were conducted in men only and parental history was not uniformly defined. Simple definitions were used as having a parent, a father or a mother, or both parents with a history of MI, regardless of the age of onset. Relative risks of 1.0-2.2 in men and women were found.[3-13] Some studies showed a slightly stronger paternal[4,12,13] and others a stronger maternal transmission[3,5,6,9] in men. In women, only a few studies were conducted.[6,8,9] For both parents with a history of MI, regardless of the age of onset, a relative risk of approximately 2 was observed.[6]

In most studies on the risk of premature parental MI, the cut-off for the age of onset of the MI was fixed and ranged from a parental MI before the age of 65 to before age 50.[1,5,9,14-17] The National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III) recommended that cut-off points should be age of onset before age 65 in the father and before age 55 in the mother.[18] These different cut points for men and women were applied in several studies.[19-21] Relative risks of premature parental history of MI amounted to 1.2-2.8 in men and women. As for parental history irrespective of age of onset, differences between paternal and maternal transmission were inconsistent, and for those with both parents who had had a premature MI, relative risks of 1.5-4.1 were found.[4,16,21,22]

The age of onset of MI was studied in more detail in two large US cohorts.[6,22] These studies showed a continuous increase in relative risks of CVD with decreasing paternal or maternal age of onset of the MI. In men, a paternal and maternal MI before age 70[6,22] conferred a greater risk of CVD (RR 1.7-2.6) compared to those with a higher parental age of MI. For women this was the case for a paternal and maternal MI below age 50.[6]

An important question is, whether the positive relationship between parental history of MI can be explained by lifestyle factors such as smoking, alcohol intake and physical inactivity and/or risk factors such as blood pressure and serum cholesterol. In most studies, adjusting for lifestyle[4,5,6] and risk factors[14,15,16,19-21] only slightly lowered the relative risk in respondents with (premature) parental MI.

The aim of the present study was to investigate the relationship between various definitions of parental history of MI and CVD incidence in the offspring, with emphasis on the impact of a maternal and paternal MI and on older or younger parental age of onset of the MI. Furthermore we investigated the impact of lifestyle and risk factors on the association between parental history and CVD incidence.

METHODS

Study population

In the Monitoring Project on Chronic Disease Risk Factors (MORGEN-project), baseline cardiovascular risk factor data were collected in 1993-1997 in about 23,000 men and women aged 20-65 years.[23,24] The project was carried out in random population samples of Amsterdam, Maastricht and Doetinchem in the Netherlands. We used only data of respondents aged 40-65 years, because many younger respondents will have parents who were too young to have experienced an MI. The survey was approved by the Medical Ethics Committee of TNO Prevention and Health, Leiden and respondents signed an informed consent form.

Data collection

Information on parental history of MI, demographic variables, lifestyle factors, educational level and disease history was obtained by standardized questionnaires. Parental history of MI was ascertained using the questions 'did your father ever experience an MI' and 'did your mother ever experience an MI', followed by a question about the age of onset for those reporting a parental MI. We categorized respondents into four categories of parental history: both parents without MI (reference group), a father only with MI, a mother only with MI or both parents with MI. In order to study the effect of age of onset of MI, and to define premature MI, the age of onset of the parental MI was classified as ≥ 70 years, 60-69 years and < 60 years for both the mother and the father. In a reproducibility study in part of our respondents, 75% of respondents were classified into the same parental history group again (no, one or two parents with MI < 60 years in men and < 65 years in women). Smoking was dichotomized as 'current smoker' or 'non-smokers' (including ex-smokers). Alcohol consumption was defined as none, moderate (male: ≤ 2 glasses/female ≤ 1 glass per day) and high (male: > 2 glasses/female > 1 glass per day). Physical activity was assessed by a validated questionnaire in respondents recruited between 1994 and 1997. For this subset, we calculated whether respondents practised cycling and sports with a metabolic equivalent score ≥ 4 (yes/no).[25] Educational level was classified into three categories: low (intermediate secondary education or less), intermediate (intermediate vocational or higher secondary education) or high (higher vocational or university education). The prevalence of MI or diabetes mellitus at baseline (yes/no) was based on self-report.

Body weight and height were measured by trained staff according to the WHO recommendations. BMI was calculated by dividing weight (in kg) by height (in m) squared.[26] Non-fasting blood samples were taken and serum total cholesterol was measured by the CHOD-PAP method. HDL-cholesterol was determined in the supernatant after precipitation

of apo B-containing lipoproteins with magnesium phosphotungstate.[27] All cholesterol determinations were done in a standardized laboratory.[23] Blood pressure was measured twice by a trained technician at the right upper arm with the participant in sitting position using a random zero sphygmomanometer. Systolic blood pressure was recorded at the first, and diastolic blood pressure at the fifth Korotkoff phase. The mean of both measurements was used in the analyses.

Mortality and morbidity follow-up

The cohort was linked to three registries. Vital status was checked by the national population register. Data on CVD mortality during follow-up were obtained from Statistics Netherlands (till 1 January 2006). CVD morbidity was identified through linkage with the National Hospital Discharge Register (till 1 January 2006) based on information on the date of birth, gender and postal code using a validated probabilistic method.[24] Total CVD was defined as the first event during 10-year follow-up, either nonfatal or fatal, whichever came first. Cases were censored at the first date of hospital admission for CVD or at the date of death. Other subjects were censored at the date of emigration, date of death, at the end of follow-up or at a maximum of 11 years, resulting in a mean follow-up of 10 years. We defined fatal and nonfatal events identical to the ICD-codes used in the SCORE-project: CVD (ICD 9: 401-414, 426-443, 798.1, 789.2, ICD 10: I10-I25, I46, I47-I51, I61-I65, G45, I67-I69, I70-I72, R96).[28] In total, 914 events occurred, of which 40 were fatal without a previous nonfatal event. Most events were due to coronary heart diseases (557), peripheral arterial diseases (128), stroke (125), heart failure (60) and hypertensive ischemic heart diseases (40).

Data and statistical analyses

We excluded respondents without informed consent for linkage with registries, respondents under the age of 40, prevalent cases of MI and respondents with missing data on parental history of MI and age of onset, on lifestyle and risk factors. This left 10,524 respondents, 4,878 men and 5,646 women for analysis. First we investigated whether there was interaction between gender and parental history of MI. Since there was no significant interaction ($p = 0.22$) for most definitions of parental history of MI, we pooled the data of men and women and adjusted for gender. There was interaction with gender only for those respondents whose mother had an MI before age 60 ($p = 0.04$).

Baseline characteristics of the study population by parental MI – subdivided by paternal, maternal or both parents with MI – were described as mean and standard deviation for normally distributed continuous variables and numbers and percentages for categorical variables. The 10-year cumulative incidence rates according to parental history of MI were calculated.

Associations between parental history of MI and CVD incidence were analyzed with Cox proportional hazard models. The proportionality of the hazards was verified by plotting the log-log survival curves and graphical inspection of parallelism of the curves. In all analyses respondents with 'both parents without an MI' were used as the reference category. All hazard ratios (HR) were adjusted for age and gender. The HR's for maternal MI were stratified by gender, adjusted for paternal MI and included an interaction term mother*gender in the model. We additionally adjusted for education and the following lifestyle-related factors: current smoking status, alcohol intake and BMI. In the main analyses we did not adjust for physical activity because this variable was not estimated in respondents recruited in 1993 and adjustment for physical activity in the respondents recruited from 1994-1997 only slightly attenuated the HRs. Furthermore, we adjusted for the risk factors serum total and HDL-cholesterol, systolic blood pressure (continuously) and for self-reported diabetes mellitus (dichotomously).

For all analyses SAS 9.2 by SAS Institute Inc. (Cary, North Carolina, USA) 2002-2008 was used.

RESULTS

At baseline, 36% of the men and women had one or two parents who experienced an MI (23% only a father with MI, 8% only a mother with MI and 4% both parents) (Table 4.1). Age of respondent was not associated with parental history of MI, while average systolic blood pressure and serum total cholesterol and the prevalence of self-reported diabetes were highest in those with two parents with an MI. The number of current smokers was lowest in men with two parents with an MI. A high level of education was more common in respondents with parents without MI and those with a father with MI. Fathers experienced their MI at a mean age of 63, mothers at age 67.

All three groups with a positive parental history of MI had an increased CVD risk compared to those without a parental history of MI (Table 4.2, Figure 4.1). The age and gender adjusted pooled HR was 1.3 (95% CI 1.1-1.5) for having only a father, 1.5 (1.2-1.8) for having only a mother and 1.6 (1.2-2.2) for having both parents with MI. With decreasing parental age of MI, the HR for a paternal MI increased from 1.2 (1.0-1.6) for age ≥ 70 years to 1.5 (1.2-1.8) for age < 60 years and for a maternal MI from 1.1 (0.9-1.5) to 2.2 (1.6-3.0).

No interaction between gender and parental history of MI was found, except an interaction between gender and maternal history of MI at age below 60 ($p = 0.04$). Compared to women without a parental history of MI, the HR was 1.0 (0.6-1.6) for women having a mother with age of onset of MI above 70 years, 1.9 (1.2-3.1) at age 60-69 years and 2.9 (1.8-4.6) at age below 60 (Figure 4.2). Compared to men without a parental history of MI, these HRs were 1.2 (0.8-1.7), 1.6 (1.0-2.5) and 1.5 (0.9-2.6) respectively in men.

Table 4.1 Baseline characteristics (mean, SD or %) and observed percentage of CVD events during an average follow-up of 10 years in 4,878 men and 5,646 women by parental MI in the MORGEN-cohort in the Netherlands

	Men				Women			
Parents MI	No parents	Father only	Mother only	Both parents	No parents	Father only	Mother only	Both parents
Number	3,149	1,210	342	177	3,618	1,260	511	257
Age (years, sd)	50.6 (6.2)	49.6 (6.0)	50.6 (5.9)	50.7 (5.8)	50.3 (6.3)	49.8 (6.0)	51.2 (6.3)	51.0 (5.8)
High education, %	29	29	23	20	19	18	12	15
Smokers, %	33.0	31.8	34.5	27.7	31.9	36.8	35.6	37.0
Moderate alcohol intake, %	53.5	54.8	51.8	53.7	54.1	52.5	56.2	51.4
Cycling, %	74.9	72.2	71.2	76.7	77.6	75.6	75/7	71.5
Sports, %	38.1	37.4	35.6	28.6	36.9	38.8	31.5	33.2
BMI (kg/m^2, sd)	26.1 (3.5)	26.2 (3.5)	26.3 (3.4)	26.3 (3.3)	25.5 (4.3)	25.4 (4.0)	25.8 (4.5)	25.6 (4.4)
Systolic blood pressure (mmHg, sd)	127.3 (16.3)	127.5 (15.2)	129.4 (16.5)	128.9 (15.4)	121.7 (17.5)	122.2 (17.2)	123.5 (17.8)	124.4 (17.0)
Serum total cholesterol (mmol/l, sd)	5.57 (0.99)	5.67 (1.03)	5.65 (0.99)	5.77 (0.92)	5.55 (1.04)	5.59 (1.04)	5.72 (1.00)	5.78 (1.05)
Serum HDL-cholesterol (mmol/l, sd)	1.21 (0.31)	1.17 (0.31)	1.16 (0.31)	1.15 (0.27)	1.53 (0.39)	1.55 (0.40)	1.49 (0.37)	1.46 (0.36)
Self-reported diabetes, %	1.6	1.2	1.8	2.3	1.3	1.1	1.6	2.0
CVD, n, %	353 (11.2)	173 (14.3)	48 (14.0)	26 (14.7)	177 (4.9)	68 (5.4)	43 (8.4)	26 (10.1)

CVD, cardiovascular diseases; MI, myocardial infarction.

Table 4.2 Hazard ratio of CVD [HR (95% CI)], adjusted for age, gender, education, lifestyle and biological risk factors for CVD in respondents aged 40-65 years by parental gender and parental age at onset of MI

	No parental history	Father MI only	Mother MI only	Both parents MI	Father MI ≥ 70 y	Father MI 60-69 y	Father MI < 60 y	Mother MI ≥ 70 y	Mother MI 60-69 y	Mother MI < 60 y
n	6,767	2,470	853	434	852	962	1,090	612	400	275
Model 1	1	1.33 (1.14-1.55)	1.47 (1.18-1.84)	1.64 (1.24-2.18)	1.24 (0.98-1.56)	1.41 (1.14-1.74)	1.47 (1.20-1.81)	1.14 (0.87-1.50)	1.82 (1.34-2.46)	2.20 (1.59-3.04)
Model 2	1	1.33 (1.14-1.55)	1.41 (1.13-1.76)	1.66 (1.25-2.21)	1.27 (1.01-1.60)	1.43 (1.16-1.77)	1.42 (1.16-1.75)	1.16 (0.88-1.52)	1.65 (1.21-2.23)	2.10 (1.52-2.90)
Model 3	1	1.30 (1.12-1.52)	1.33 (1.06-1.66)	1.55 (1.16-2.06)	1.27 (1.01-1.60)	1.38 (1.11-1.71)	1.37 (1.11-1.68)	1.09 (0.83-1.43)	1.52 (1.12-2.07)	2.05 (1.48-2.84)

Model 1: adjusted for age and gender.
Model 2: model 1 + adjusted for smoking, alcohol intake, BMI and education.
Model 3: model 2 + adjusted for systolic blood pressure, serum total and HDL-cholesterol, self-reported diabetes mellitus.

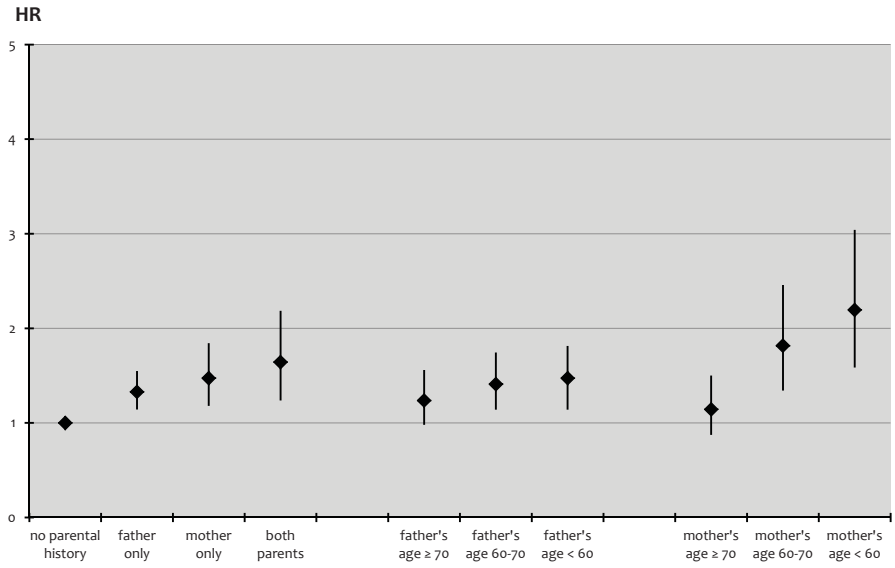
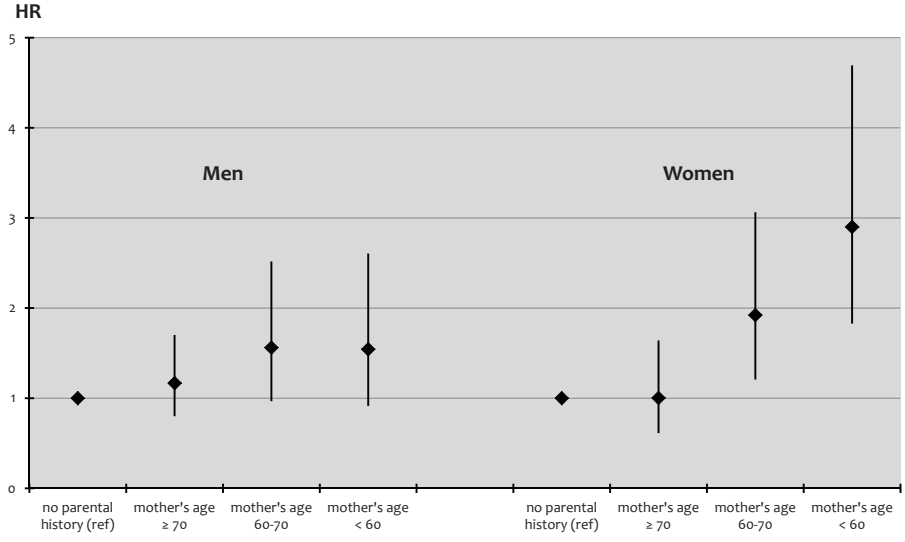


Figure 4.1 Hazard ratio of CVD and 95% confidence intervals, adjusted for age and gender in respondents aged 40-65 years by parental age of onset of MI.



n	**3,149**	**271**	**143**	**105**	**3,618**	**341**	**257**	**170**
CVD n	353	37	21	16	177	21	25	23
CVD %	11.21	13.65	14.69	15.24	4.89	6.16	9.73	13.53

Figure 4.2 Age and father's age of onset of MI adjusted hazard ratio of CVD and 95% confidence intervals in men and women aged 40-65 years by mother's age of onset of MI.

In multivariable analyses - adjusting for age, gender, education and lifestyle-related factors such as smoking, physical activity (in subset), alcohol intake and BMI - HRs for paternal MI were of the same magnitude compared to those adjusted only for age and gender, and slightly lower for maternal MI. Additional adjustment for biological risk factors yielded similar HRs for paternal MI and slightly attenuated the HRs for maternal MI at age of onset below 60 years (Table 4.2).

DISCUSSION

Respondents with a parental history of MI had a 30-60% higher CVD risk, after adjustment for age and gender, regardless of the age at which their parents had an MI. In cases of premature parental MI (defined as onset of MI before age 70), a maternal transmission of CVD risk was twice as strong (80-120% increased risk) as paternal transmission (40-50%). The impact of a maternal MI at age below 60 was twice as strong as in women (HR 2.9) than in men (HR 1.5). These associations could not be explained by higher levels of lifestyle and biological risk factors in respondents with a paternal history of MI and only to a small extent in those with a maternal history of MI.

The strength of the present study was that we had detailed information on parental history of MI for men and women. The vast majority of studies on the relationship of parental history of MI with CVD incidence reported on men only. We did not find an interaction between gender and parental history of MI, so our data suggest that results did not differ between men and women. We had also information available on the age of onset of MI in both fathers and mothers. Only a few studies investigated parental MI according to the age of onset of parental MI and CVD incidence beyond cut-off points for premature history of MI.[6,22] We reported on respondents aged 40-65 years, because younger respondents had parents who were too young to have experienced an MI. However, even in the selected age group of respondents, some parents were too young to have experienced an MI, especially mothers. Mean age of MI in mothers was four years lower than in fathers.

Information on nonfatal CVD was obtained from hospital discharge data through record linkage with the National Hospital Discharge Register. The linkage success rate for cardiovascular endpoints was 97.6%.[24] Comparison of hospital discharge diagnoses for a sub sample from the Maastricht area with a cardiology information system in this region, showed that 14.2% of the cases of acute myocardial infarction were not registered in the hospital discharge register.[29] The reliability of the cause-of-death coding was examined by Statistics Netherlands. The inter-coder agreement of the underlying cause of death by ICD-10 code was 89.1% for acute myocardial infarction and 78.5% for stroke.[30] This minor underestimation and misclassification of nonfatal and fatal endpoints probably did not affect the association between parental history of MI and CVD incidence.

We studied the impact of parental history of MI on nonfatal and fatal CVD incidence. This broad endpoint definition was the same as the one used in the SCORE-project[28] and included myocardial infarction (21%), angina pectoris (20%), cerebrovascular accidents (14%), peripheral arterial diseases (14%), congestive heart failure (7%) and hypertensive heart diseases (4%). Similar broad definitions of CVD were also used in some studies,[6,14,21] while almost all studies included nonfatal and fatal CHD.[5,9,12,13,16,22] However, similar relative risks were observed for parental history of MI in relation to different definitions of CVD endpoints, suggesting similar impacts on CHD and CVD incidence.

As in most studies, in the present study parental history of MI was based on self-report by the respondents. We only conducted a reproducibility study and found a 75% agreement. Several validation studies were carried out by others, in which parental events were confirmed by medical records.[31-33] Parental history of MI or CHD was correctly reported by 68%-89% of respondents. In the Framingham Heart Study, in which both off-spring and parental CVD events were validated, higher relative risks for a parental history of MI were found.[21] This suggests that stronger relative risks are obtained when more accurate information on parental history of MI is used.

Our results confirm previous findings of an independent relationship between parental history of MI and CVD incidence. For the 'simple' definitions of having a father, a mother or both parents with a history of MI, we found HRs of 1.3, 1.5 and 1.6 respectively, which were in the same order of magnitude as observed in other studies (RR 1.2-2.2).[3-13] Furthermore, we showed a strong gradient of CVD incidence with decreasing parental age of onset of MI. CVD incidence was significantly increased when a father or a mother experienced an MI under the age of 70. This cut-off point of a premature parental history of MI was comparable to that found in US Physicians' Health and Health Professionals studies[6,22] However, the cut-off points for increased CHD risk set by the NCEP expert panel (fathers who were younger than 65 at the age of onset and mothers who were under 55 at the age of onset)[18] and the fixed cut-off points used in most other studies for premature parental MI (at or before the age of 65)[1,9,14-16,21] are at younger age compared to the present study, especially those for women. We observed a stronger maternal than paternal transmission of risk for different ages of onset of an MI. However, other studies on (premature) parental MI found either a stronger paternal transmission,[4,7,12,15,16] stronger maternal transmission[3,5,6,9] or no difference[21,22] in men. So definitive conclusions cannot be drawn on this issue.

In the present study, adjusting for education, lifestyle and risk factors did not influence the CVD incidence for paternal MI, and only slightly attenuated the CVD incidence associated with maternal MI. Similar results were found in other studies on lifestyle[4-6] and risk factors[5,14-17,19-21] This means that the relationship between a positive family history and CVD incidence is largely independent from known lifestyle and risk factors. Therefore, this

relationship may be due to genetic factors. However, influence of unknown or unmeasured lifestyle and biological factors cannot be excluded.

In conclusion, individuals with a parental history of MI had an increased CVD incidence of similar magnitude in men and women. CVD risk increased gradually with decreasing parental age of onset of MI. Based on our results, a premature parental MI can be defined as having a father and/or a mother with MI before the age of 70. Higher age cut-off points for defining premature parental MI might be warranted. The strongest associations were observed in persons with a mother who had an MI before age 60, especially in women.

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5

Effect of including nonfatal events in cardiovascular risk prediction, illustrated with data from the Netherlands

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ABSTRACT

Aims: European physicians use SCORE risk charts to predict a patient's 10-year risk of cardiovascular disease (CVD) mortality. We examined whether the inclusion of nonfatal events improved risk prediction and the identification of high risk persons.

Methods and results: In the EPIC-NL cohort, risk factor data were collected between 1993 and 1997 in 6,772 men and 9,108 women aged 35-65 years. During 10 years of follow-up, 540 total (fatal + nonfatal) CVD events occurred, of which 122 (23%) were fatal. Risk equations were developed using Cox proportional hazard models. Discriminating ability and hazard ratios for CVD risk factors did not differ between the two endpoints. Absolute risks for total CVD were approximately four times higher than for CVD mortality. Using the current 5% CVD mortality threshold or the 20% total CVD threshold for identification of high risk persons leaves more than 84% of all male and 98% of all female future cases untreated. Of those exceeding these thresholds, 20% and 27% of the men, respectively, and 16% and 19% of women will experience a CVD event in the next 10 years. Cut-off points of 2% for CVD mortality, corresponding to 10% for total CVD, will identify high-risk persons of whom approximately 10% will experience a CVD event in the next 10 years.

Conclusion: CVD mortality comprises a quarter of all total CVD events. Risk functions and the discriminating ability did not differ between the two endpoints. Cut-off points of 2% for CVD mortality or 10% for total CVD could be considered to identify high-risk persons.

INTRODUCTION

In 1994, the first Task Force of the European Societies of Cardiology, Atherosclerosis and Hypertension recommended the estimation of coronary heart disease (CHD) risk based on the Framingham risk charts for CHD prevention in clinical practice. They advised intensive treatment of all risk factors when the absolute 10-year risk of nonfatal and fatal CHD exceeded 20%.[1] However, in several European countries the Framingham risk charts overestimated CHD risk, potentially leading to overtreatment.[2,3]

In 2003, the third Joint European Societies Task Force on cardiovascular disease (CVD) prevention introduced risk charts of the SCORE (Systematic COronary Risk Evaluation) project.[4,5] The SCORE risk charts were derived from a large database of prospective studies including over 200,000 persons in Europe. These charts predicted 10-year CVD mortality risk, whereas the previously used Framingham risk charts predicted both fatal and nonfatal CHD events. Consequently, the cut-off point for increased risk was changed, from ≥ 20% previously used in Framingham charts for incident CHD[1,6-8] to ≥ 5% for CVD mortality in the SCORE risk charts.[4,5,9]

Risk charts predicting CVD mortality do not reflect the total burden of CVD.[10] In high income countries, CVD mortality rates are continuously decreasing,[11] which might be interpreted as an indication that CVD is no longer an important public health problem.[12] However, low CVD mortality is accompanied by a high incidence of nonfatal CVD.[13] Therefore, a change in risk prediction from CVD mortality to total (fatal plus nonfatal) CVD has been advocated.[4,9,14]

In 2008, an updated Framingham Heart Study general CVD risk function was developed with an expanded CVD endpoint.[10] The threshold previously used for high CHD risk (≥ 20% in 10 years, ATP III guidelines[7]) is now used for total CVD.[6,8,10] The 2011 Guideline of the American Heart Association for CVD prevention in women recommended a cut-off point of ≥ 10% for high total CVD risk.[15] Based on recent analyses of clinical trials the American Heart Association concluded that generic statins are already cost-effective at this threshold.[15]

The purpose of this article is to investigate the effect of including nonfatal events in the equation used for cardiovascular risk prediction, on identifying high-risk persons. We evaluated also the discriminating ability of a risk function based on either CVD mortality or total CVD, and the implications of a change from CVD mortality to total CVD for the identification of high-risk persons eligible for drug treatment in clinical practice.

SUBJECTS AND METHODS

Study population and data collection

We used data from the EPIC-NL study, consisting of the two Dutch cohorts (MORGEN and PROSPECT) that comprise the Dutch contribution to the European EPIC study. These cohorts started separately in 1993-1997 and were later merged into the EPIC-NL-cohort.[16] For the present analysis, data of participants aged 35-65 years at baseline were used. We excluded 5,579 persons aged < 35 years, 2,576 women aged > 65 years, 605 patients with a history of myocardial infarction, stroke or heart failure based on self-report or hospital discharge data, and those with missing data on smoking, serum total and HDL cholesterol or systolic blood pressure. In total, 6,772 men and 9,108 women were included in the analysis. All participants provided informed consent before they were included in the study. The study complies with the Declaration of Helsinki and was approved by two medical ethics committees.

Vital status of EPIC-NL participants was obtained through record linkage with the municipal population registries. Data on morbidity were obtained from the National Medical Registry (NMR), a digital database of hospital discharge diagnoses (until 1 January, 2006). In the NMR all diagnoses were coded according to the 9th revision of the International Classification of Diseases (ICD). The EPIC-NL cohort was linked to the NMR using a validated probabilistic method.[17] Causes of death were obtained through linkage with 'Statistics Netherlands' (follow-up completed until 1 January, 2006). ICD-9 codes were used until 1 January, 1996, and corresponding ICD-10 codes thereafter. Cases were censored at the first date of hospital admission for CVD, the date of death or emigration, or at the end of follow-up (at a maximum of 11 years), whichever came first. Loss to follow-up was less than 2% among respondents who gave informed consent.[16]

CVD mortality and total CVD

We defined fatal CVD events identical to the ICD codes used in the SCORE-project, ICD-9: 401-414, 426-443, 798.1 and 798.2. After January 1996 corresponding ICD-10 codes were used. For nonfatal CVD we included nonfatal acute myocardial infarction, stroke and heart failure (ICD-9 codes: 410, 427.5, 428, 430, 431, 433, and 436).

The reliability of the cause of death coding was examined by Statistics Netherlands. The inter-coder-agreement of the underlying cause of death by ICD-10 code was 89% for MI, 79% for stroke and 76% for heart failure.[18] The success rate for linking nonfatal cardiovascular events was 98%.[16] Comparison of hospital discharge diagnoses with diagnoses from a cardiology information system showed a sensitivity of 84% for myocardial infarction and 43% for heart failure.[19]

Data analysis

We defined total CVD as fatal plus nonfatal CVD. A case of fatal or nonfatal CVD could only be included once and was censored at the time of a first nonfatal event or death, whichever came first. The observed 10-year cumulative incidence rates were calculated for CVD mortality and total CVD. Subsequently we calculated the ratio of the observed total CVD to CVD mortality and 95% confidence intervals (CI).

To estimate 10-year CVD mortality risk we used the risk function composed for the Netherlands (SCORE-NL) by the SCORE-group[20] and published in the Dutch Clinical Guideline on Cardiovascular Risk Management.[21] We used the following basic risk function:

$$\text{CVD risk} = 1\text{-Survival}_{\text{baseline}}{}^{*}\exp[\beta 1{*}\text{gender} + \beta 2{*}\text{age} + \beta 3{*}\text{smoking status} + \beta 4{*}(\text{systolic blood pressure} - \text{mean SBP}) + \beta 5\,{*}(\ln \text{ratio total/HDL-cholesterol} - \text{mean ln ratio})].$$

Cox regression was used to estimate the betas for each endpoint as well as the baseline survival function. For the two endpoints, baseline survival was used to estimate the 10-year risk of a 35-year-old, non-smoking woman. We assessed the statistical significance of interactions between the classical risk factors and gender. As the interaction terms were not statistically significant, we fitted a single model for both men and women. Subsequently, we tested whether the coefficients for the risk factors differed between the two risk prediction functions.[22]

The risk discriminating ability, a measure to distinguish future cases from noncases, was expressed as the Area Under the ROC-curve (AUROC) including a 95%-confidence interval (CI). The AUROC ranks persons according to their risk. Future cases were the observed fatal plus nonfatal CVD cases. An AUROC of 0.5 means no discrimination, 0.7 acceptable discrimination and 1.0 perfect discrimination.[23]

We also cross-tabulated different categories of risk predicted by the model with CVD mortality as endpoint against a broader range of risk categories predicted by the model with total CVD as endpoint. We calculated the proportion of future cases among those at high risk and eligible for drug treatment, using the European 5% CVD mortality treatment thresholds,[4,9] the US Framingham 20% global CVD treatment thresholds[10] and, for women, the recently proposed American Heart Association treatment thresholds of 10%.[15] We defined corresponding thresholds for CVD mortality and total CVD for identification of similar proportions of 10% future CVD cases among those at high risk.

For all analyses SAS 9.2 (SAS Institute Inc., Cary, North Carolina, USA) 2002-2008 was used.

RESULTS

This study included 15,880 persons, of whom 43% were men (Table 5.1). Men had, on average, a 5 mmHg higher SBP, and a 0.3 mmol/l lower HDL-cholesterol level than women (Table 5.1). During, on average, 10 years of follow-up approximately twice as many men experienced a CVD event as women. The ratio of observed total CVD to CVD mortality was 4.0 (95% CI 3.4-5.0) in men and 5.2 (95% CI 4.1-7.2) in women.

In Table 5.2, the hazard ratios and 95% CIs for the risk factors included in the models predicting 10-year risk of CVD mortality and total CVD, respectively, are presented for men and women combined. These hazard ratios were similar for CVD mortality and total CVD. The area under the ROC curve was of the same magnitude for CVD mortality and total CVD, suggesting that the discrimination between future cases and non-cases did not differ between the risk function for CVD mortality and the function for total CVD (Figure 5.1).

In Table 5.3, the risk categories of CVD mortality are cross-tabulated against the risk categories of total CVD. Absolute risk levels for total CVD were approximately four fold higher than absolute risk levels for CVD mortality. Using the 5% CVD mortality threshold, of the 224 men with this high risk, 50 (22%) developed a CVD event during the next10 years (Table 5.3A). Using the 20% total CVD threshold, 31 (27%) out of 119 men developed an

Table 5.1 Baseline risk factor levels (1993-1997), and 10-year fatal and total CVD, in Dutch men and women aged 35-65 years, without a history of CVD (MORGEN cohort)

	Men (n = 6,772)	Women (n = 9,108)
Age (years)	48.2 (7.4)	49.2 (7.6)
Systolic blood pressure (mmHg)	127 (16)	122 (18)
Serum total cholesterol (mmol/l)	5.5 (1.0)	5.5 (1.0)
Serum HDL-cholesterol (mmol/l)	1.2 (0.3)	1.5 (0.4)
Serum total-to-HDL-cholesterol ratio	5.0 (1.7)	3.9 (1.2)
Body mass index (kg/m^2)	26.0 (3.5)	25.3 (4.3)
Smokers (%)	34	34
Fatal CVD[1] cases	80 (1.2%)	42 (0.5%)
Total CVD[2] cases	321 (4.7%)	219 (2.4%)

Values are mean (SD) for continuous variables. HDL, high-density lipoprotein; CVD, cardiovascular diseases.
[1]Fatal CVD: ICD-9: 401-414, 426-443, ICD-10: I10-I25, I46, I47-I51, I61-I65, G45, I67-I69, I70-I72, R96.
[2]Total CVD: fatal CVD codes + nonfatal myocardial infarction, stroke and heart failure (ICD-9 codes: 410, 427.5, 428, 430, 431, 433, 436).

event. Using the 10% total CVD threshold, 116 (13%) events occurred in 871 high risk men. This corresponded to 156 (12%) CVD events in 1,314 men with a CVD mortality risk of 2% or higher. During 10 years of follow-up, 84% of all future CVD cases among men occurred below the 5% CVD mortality threshold and 49% below the 2% CVD mortality threshold (Table 5.3A).

Table 5.2 Hazard ratios (95% confidence intervals) for 10-year risk of CVD mortality and total CVD in Dutch men and women combined, aged 35-65 years

	CVD mortality	Total CVD	P-value*
Male gender	2.14 (1.45-3.18)	1.65 (1.37-1.98)	0.22
Age, per 10 years	2.30 (1.73-3.04)	1.93 (1.70-2.20)	0.16
Smoking (y/n)	2.17 (1.52-3.12)	1.99 (1.68-2.40)	0.59
SBP, per 20 mmHg	1.61 (1.35-1.92)	1.47 (1.35-1.61)	0.60
Serum total-to-HDL cholesterol, per unit	2.75 (1.56-4.87)	2.78 (2.11-3.62)	0.68

SBP, systolic blood pressure; HDL, high density lipoprotein.
*P-value for the difference between the hazard ratios for CVD mortality and total CVD.

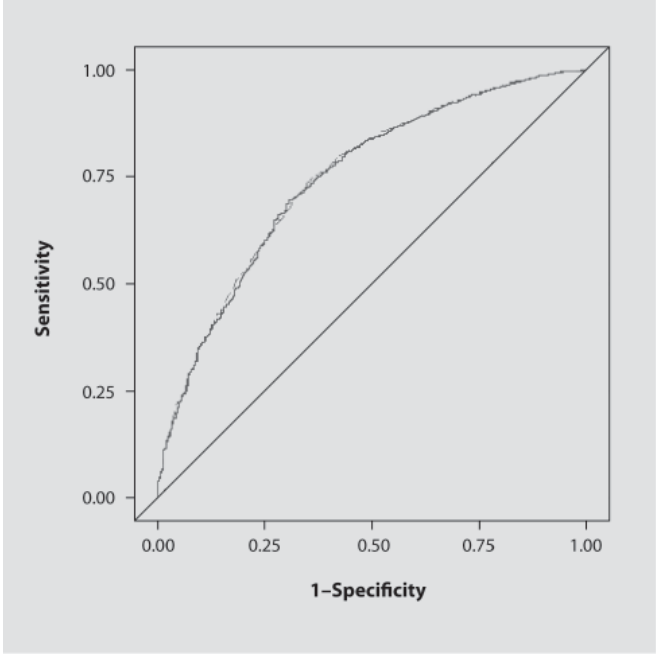

Figure 5.1 Receiver Operating Characteristics (ROC) curves for 10-year CVD mortality and total CVD in Dutch men and women of the MORGEN cohort. — CVD mortality (AUROC 0.7457); – – Total CVD (AUROC 0.7472).

Table 5.3 Classification of the observed total CVD cases according to predicted risk of CVD mortality by risk of total CVD in men (A) and women (B)

(A) men

		Risk of total CVD							
Risk of CVD mortality		0-3%	3-5%	5-7%	7-10%	10-20%	≥ 20%	Total	Ratio all/ cases
0-2%	Cases (n)	37	42	59	27			165	33
	All (n)	2,537	1,630	974	317	1,756		5,458	
2-3%	Cases (n)			1	39	12		52	12
	All (n)			10	428	188		626	
3-4%	Cases (n)					37		37	9
	All (n)				5	310		315	
4-5%	Cases (n)					17		17	9
	All (n)					149		149	
≥ 5%	Cases (n)					19	31	50	4
	All (n)					105	119	224	
Total	Cases (n)	37	42	60	66	85	31	321	21
	All (n)	2,537	1,630	984	750	752	119	6,772	
Ratio	All/ cases	69	39	16	11	9	4	21	

(B) women

		Risk of total CVD							
Risk of CVD mortality		0-3%	3-5%	5-7%	7-10%	10-20%	≥ 20%	Total	Ratio all/ cases
0-2%	Cases (n)	89	48	31	15			183	48
	All (n)	6,417	1,479	612	232			8,740	
2-3%	Cases (n)				10	9		19	12
	All (n)				136	84		220	
3-4%	Cases (n)					9		9	10
	All (n)					87		87	
4-5%	Cases (n)					3		3	10
	All (n)					29	1	30	
≥ 5%	Cases (n)					1	4	5	6
	All (n)					11	20	31	
Total	Cases (n)	89	48	31	25	22	4	219	42
	All (n)	6,417	1,479	612	368	211	21	9,108	
Ratio	All/ cases	72	31	20	15	10	5	42	

All, cases + non-cases.

Using the 5% CVD mortality threshold, during 10 years of follow-up, of the 31 women with this high risk, 5 (16%) developed a CVD event during the next 10 years (Table 5.3B). Using the 20% total CVD threshold, 4 (19%) out of 21 women experienced an event. Using the 10% total CVD threshold, 26 (11%) events occurred in 232 high risk women. This percentage corresponded to 36 (10%) CVD events in 368 women with a CVD mortality risk of 2% or higher. In women, 98% of all future CVD cases occurred below the 5% CVD mortality threshold and 84% below the 2% CVD mortality threshold (Table 5.3B).

DISCUSSION

In the EPIC-NL cohort of middle-aged persons, about a quarter of all total CVD events were fatal events. The strengths of the associations of the risk factors did not differ between the models predicting CVD mortality and total CVD. Also the models for the two endpoints discriminated equally well between future CVD cases and non-cases. The currently used cut-off point of 5% for CVD mortality leaves a very large proportion of future cases untreated. When using a cut-off point of 2% for CVD mortality, or 10% for total CVD, similar proportions of 10% of future cases in high-risk men and women will be identified.

To the best of our knowledge, this is the first prospective study that provides insight into how total CVD relates to CVD mortality. Older studies reported on CHD only and did not distinguish between first and recurrent events.[24,25] In several primary prevention trials the ratio of total to fatal major cardiovascular events varied between 3.2 and 4.5 (WOSCOPS, JUPITER and CARDS).[26] These trials included slightly older age groups, and only a few women. The ratio of 4 in men in our middle-aged population-based sample is in line with these data.

In the present study, the relationships between risk factors and CVD mortality did not differ significantly from their relationship with total CVD. Similar results were obtained in other prospective cohort studies using CHD as endpoint.[5] The two equations also discriminated equally well between future CVD cases and non-cases. Other studies did not compare risk discrimination between future CVD cases and non-cases in models with these two endpoints. The AUROC for predicting CVD mortality risk in the SCORE data set was 0.763 in men and 0.807 in women.[27,28] In our study the AUROC for CVD mortality was 0.749 in men and 0.710 in women. An explanation for the different results in the two studies could be that the AUROCs for men and women in the SCORE study were based on risk factor data collected in the 1970s and 1980s, when the absolute CVD mortality risk was higher than in the present study, in which risk factor data were collected around 1995.

Risk prediction tools and guidelines for CVD risk assessment use different definitions of CVD endpoints.[14,27,29] Thresholds for drug treatment depend on the diseases included in the definition of nonfatal CVD events.[5] The updated Framingham risk score included a broad

range of CVD endpoints, e.g. angina pectoris and peripheral vascular disease.[6,10] Since risk tables are used to identify high risk persons who will benefit from drug treatment, we included only vascular diseases such as non-fatal myocardial infarction, stroke and heart failure for which there is sufficient evidence that blood pressure and cholesterol lowering will reduce the number of CVD events.[26,30,31]

Any threshold for defining high-risk persons is arbitrary, but necessary for decision-making in clinical practice. In current European guidelines, intensive treatment is recommended for CVD mortality risk ≥ 5%.[4,9] In US guidelines predicting total CVD or global CVD risk, cut-points for drug treatment were set at ≥ 20%.[6,10] In the present study, within the group exceeding the 5% threshold for CVD mortality and the corresponding threshold of 20% for total CVD, approximately 20% of the men and women developed a CVD event. Only a small number of persons had such a high risk. These cut-off points leave a large proportion of high-risk persons untreated. If the threshold of 10% for total CVD, as recommended by the American Heart Association for women,[15] will be used for both women and men, still 1 in 10 of these high-risk persons would develop a fatal or nonfatal event in the next 10 years. To decide whether or not this 10% total CVD threshold, or the equivalent threshold of 2% CVD mortality, could be used, not only depends on the level of risk, but also on the results of cost-effectiveness analyses.

We conclude that about a quarter of total CVD is due to fatal events. To discriminate between future CVD cases, the risk function predicting CVD mortality performed as well as the risk function predicting total CVD. Both the 5% CVD mortality threshold and the 20% total CVD threshold for high risk leaves a very large number of persons untreated. The present study showed that cut-off points of 2% for CVD mortality and 10% for total CVD identify high-risk persons of whom approximately 10% will develop a CVD event in 10 years. With such a high yield of cases that can be adequately treated with blood pressure and cholesterol lowering drugs, consideration should be given to lowering the thresholds for treatment which are currently in use.

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6

Do obesity and parental history of myocardial infarction improve cardiovascular risk prediction?

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ABSTRACT

Background: In clinical practice, individuals at increased risk of cardiovascular diseases (CVD) are identified on the basis of age, sex, smoking status, blood pressure and serum total and HDL-cholesterol. We examined whether CVD risk prediction improved when obesity (BMI ≥ 30 kg/m^2) and premature (< 70 y) parental myocardial infarction (MI) were added to the classical risk factor model.

Methods: Risk factors were measured in 1993-1997 in 12,818 participants (53% female) aged 35-65 in the Dutch MORGEN project. Cases of fatal and nonfatal CVD during 10 years of follow-up were identified through record linkage. Classical risk factor equations, obtained by Cox proportional hazard analysis, were extended with obesity, paternal MI and maternal MI. We calculated the Net Reclassification Index (NRI), a measure for correct reclassification of subjects, to check improvement in risk prediction using 5% and 10% increments in absolute CVD risk.

Results: A CVD event occurred in 280 men and 140 women. Obesity and maternal MI were positively and significantly related to total CVD after adjustment for classical risk factors (both hazard ratios ~1.5). Adding obesity and parental MI to CVD risk prediction yielded a significant NRI of 4.5% in men and a non-significant NRI of 2.6% in women when 5% risk categories were used. For 10% categories, the NRIs were slightly larger (5.5% and 3.3%, respectively). The improvements in risk prediction were mainly due to obesity.

Conclusion: Modest improvements in CVD risk prediction can be obtained when obesity and, to a lesser extent, parental MI were added to the risk function.

INTRODUCTION

European guidelines on cardiovascular disease (CVD) prevention in clinical practice recommend individual risk assessment based on classical risk factors (CRF), such as smoking status, blood pressure, and serum cholesterol.[1] Persons at high risk are eligible for intensive treatment, both pharmacological and lifestyle. Although CVD risk increases exponentially, cut-off points are needed for treatment decisions in clinical practice. From a cost-effectiveness perspective, it is necessary to optimise ranking of persons according to their risk and, if possible, to limit the use of laboratory measurements.[2]

There is great interest in improving risk prediction by adding additional risk factors to the classical models.[2-6] Models have been extended with risk factors such as heart rate, educational level, body mass index (BMI), family history of myocardial infarction (MI), C-Reactive Protein and fibrinogen, and measures of atherosclerosis such as carotid intima-media thickness.[3-6,7] These risk factors are generally independently associated with the occurrence of CVD. Traditionally, the added value of incorporating new risk factors into CRF models was evaluated by measuring the improvement in risk discrimination by the Area Under the Receiver Operating Characteristics Curve (AUROC). However, additional risk factors hardly improve risk discrimination beyond the CRF models.[4,8] A new and more relevant method to evaluate improvement in risk prediction in clinical practice, is the net reclassification index (NRI).[8] This measure provides information on reclassification of persons to more appropriate CVD risk categories.[5,8] The NRI depends on the thresholds chosen for the risk categories.[8]

In Europe, risk prediction is frequently based on the European Systematic COronary Risk Evaluation (SCORE) equations.[9] These models include age, sex, smoking status, systolic blood pressure, and serum total and HDL-cholesterol. Obesity and parental history of MI are not included, although these are easy to measure risk factors, which do not require laboratory measurements.[7,9] Obesity, defined as a BMI ≥ 30 kg/m^2, is an independent predictor of CVD risk.[10-14] Since the SCORE risk function does not include diabetes, obesity may add to improve risk prediction. So far, for treatment decisions, obesity is considered as an additional risk factor, but is not included in most risk prediction equations.[2,7] The reason that obesity is not included in CRF models in the US, is that BMI did not or only slightly improved CVD risk discrimination.[15,16]

Parental history of MI is also an independent risk factor, but associations may differ for paternal and maternal MI.[17] Information on this risk factor can easily been obtained by asking whether the father or the mother experienced an MI before a certain age. Parental history of premature MI or CVD is incorporated in several risk score systems.[7,18-20] However, to the best of our knowledge, there is no information available on improvement of risk prediction by adding parental history of MI alone to a model containing the SCORE classical risk factors.

The SCORE risk models predict 10-year risk of CVD mortality. However, CVD mortality does not reflect the total burden of CVD.[21] In high income countries, CVD mortality rates are continuously decreasing,[22] but a low CVD mortality is accompanied by a high incidence of CVD.[23] Therefore, a change in risk prediction from CVD mortality to total (fatal plus nonfatal) CVD has been advocated.[1-3] In 2008, an updated Framingham Heart Study general CVD risk function was developed with an expanded CVD endpoint and a cut-off point for high total CVD risk of ≥ 20% in 10 years was used.[4,21] The 2011 Guideline of the American Heart Association for CVD prevention in women recommended a lower cut-off point for total CVD risk of ≥ 10%.[24] Although BMI and parental MI have been added to CHD risk prediction models,[5] they were not added to models with CVD endpoints and evaluated by the NRI.

In the present study we assessed how obesity and parental MI relate to total CVD risk, and examined whether inclusion of these factors in the CRF model improved risk prediction.

METHODS

Study population

In the Monitoring Project on Chronic Disease Risk Factors (MORGEN project), baseline cardiovascular risk factor data were collected between 1993 and 1997 in about 23,000 men and women aged 20-65 years.[25,26] The project was carried out in random population samples of Amsterdam, Maastricht and Doetinchem in the Netherlands. The study was approved by the medical ethics committee of TNO Prevention and Health, Leiden, and respondents signed an informed consent form.

Data collection

Information on demographic variables, smoking status, parental history of MI and disease history was obtained by standardised questionnaires.[25] Smoking was dichotomised into 'current smoker' or 'non-smoker' (including ex-smokers). Parental history of MI was assessed using the questions 'did your father ever experience an MI' and 'did your mother ever experience an MI', followed by a question about the age of onset for those reporting a parental MI. We found in an earlier study that parental history of MI before age 70 independently predicted total CVD.[27] Therefore we defined premature MI as having a father and/or a mother with MI before age 70.

Body weight and height were measured by trained staff according to the WHO recommendations. BMI was calculated as weight (in kilograms) divided by height (in metres) squared. Obesity was defined as a BMI of 30 kg/m^2 or higher, based on WHO criteria. We excluded persons with a BMI < 18.5 kg/m^2. Non-fasting blood samples were taken and

serum total cholesterol was measured by the CHOD-PAP method. HDL-cholesterol was determined in the supernatant after precipitation of apo B-containing lipoproteins with magnesium phosphotungstate. All cholesterol determinations were done in a certified laboratory.[25] Blood pressure was measured twice by a trained technician at the right upper arm with the participant in sitting position using a random zero sphygmomanometer. Systolic blood pressure (SBP) was recorded at the first Korotkoff phase. The mean of both measurements was used in the analyses.

Mortality and morbidity follow-up

Vital status was checked through record linkage with the national population register. Data on CVD mortality during follow-up were obtained from Statistics Netherlands. CVD morbidity was identified through linkage with the National Hospital Discharge Register, using a validated probabilistic method.[26] Follow-up was completed until 1 January, 2006. Total CVD was defined as the first event during 10-year follow-up, either nonfatal or fatal. Cases were censored at the date of first hospital admission for CVD, the date of death or emigration, or at the end of follow-up.

CVD mortality was defined as in the SCORE project according to the International Classification of Diseases (ICD) 9th revision (401-414, 426-443, 798.1 and 798.2) or 10th revision (I10-I25, I46-I51, I61-I65, G45, I67-I72 and R96).[9] CVD morbidity included nonfatal MI, stroke and heart failure (ICD-9 codes 410, 427.5, 428, 430, 431, 433, 434 and 436). This definition of nonfatal CVD was used by the Dutch Working Group on Revision of the Guidelines for Cardiovascular Risk Management of 2006,[28] and includes only those forms of CVD for which sufficient evidence exists that in high-risk individuals the risk can be reduced by antihypertensive and/or cholesterol lowering treatment.

Data analysis

We selected 7,746 men and 8,968 women aged 35-65 years and subsequently excluded respondents without informed consent for linkage with registries (< 5%), without successful record linkage (< 2%), prevalent cases of MI, stroke or heart failure, and respondents with missing risk factor data, leaving 5,967 men and 6,851 women for statistical analyses.

To estimate 10-year risk of CVD, we used the basic risk function prepared for the Netherlands (SCORE-NL) by the SCORE-group[29] and published in the Dutch Clinical Guideline on Cardiovascular Risk Management.[28] This function included the classical risk factors for CVD: age, sex, smoking status, SBP and the ratio of total/HDL-cholesterol. This model was subsequently extended with dummy variables for obesity, and/or paternal and maternal MI. Cox proportional hazard models were used to estimate the regression coefficients for all risk factors. Baseline survivals were calculated for a non-smoking woman aged 35 years,

without obesity and/or parental MI. We present the hazard ratios (HRs) with confidence intervals (95% CI) for the risk factors included in the different models, and tested whether these HRs differed.[30] Ten-year estimated risk of total CVD was categorised using 5% cut-off values (0-<5%, 5-<10% , ≥ 10%), or 10% cut-off values (0-<10%, 10-<20% and ≥ 20%).

The performance of the different models was assessed by the NRI, with positive values indicating correct reclassification.[8] Respondents with a CVD event and those without a CVD event (non-events) were classified according to their estimated CVD risk. Risk categories based on the classical risk factors and the extended models were cross-tabulated, after which the NRI was calculated. Basically, the NRI shows the improvement in risk prediction by taking the 'net' proportion of events (more correctly) reclassified into a higher risk category, minus the 'net' proportion of nonevents (incorrectly) reclassified in a higher risk category. Significance was tested assuming independence between events and nonevents ($z > 1.96$) with the null hypothesis of NRI = 0. We calculated the NRI both for 5% and 10% risk cut-off values. For all analyses SAS 9.2 (SAS Institute Inc., Cary, North Carolina, USA) 2002-2008 was used.

RESULTS

The study comprised 12,818 subjects (53% female) with a mean age of 48 ± 7 years at baseline (Table 6.1). Mean risk factor levels were similar in men and women, except for a lower SBP and a higher HDL-cholesterol level in women. BMI ≥ 30 kg/m^2 was present in 11% of the men and 12% of the women. The percentage of respondents with a father or mother who suffered from an MI before age 70 was 20% and 6%, respectively. During 10-year follow up, 280 men (4.7%) and 140 women (2.0%) experienced a fatal or nonfatal CVD event.

Table 6.1 Baseline risk factor levels in 12,818 Dutch men and women aged 35-65 years without a history of myocardial infarction, stroke or heart failure

	Men (n = 5,967)	Women (n = 6,851)
Age (y)	48.0 (7.4)	48.9 (7.4)
Systolic blood pressure (mmHg)	127 (16)	120 (17)
Serum total cholesterol (mmol/l)	5.5 (1.0)	5.5 (1.0)
Serum HDL-cholesterol (mmol/l)	1.2 (0.3)	1.5 (0.4)
Total/HDL cholesterol ratio	5.0 (1.7)	3.8 (1.2)
Current smokers (%)	34	34
BMI (kg/m^2)	25.9 (3.4)	25.3 (4.1)
Obesity (%)	11.1	12.2
Maternal MI < 70 y (%)	5.0	7.3
Paternal MI < 70 y (%)	20.9	19.0

Values are mean (SD) or percentages.
BMI, body mass index; HDL, high-density lipoprotein; MI, myocardial infarction; Obesity, BMI ≥ 30 kg/m^2.

Approximately a quarter of the total CVD cases in men and a fifth in women were fatal. Obesity and maternal MI were independent predictors of total CVD (Table 6.2). The HR of 1.2 for a paternal MI was not statistically significant. Adding obesity, and/or paternal and maternal MI to the CRF model did not change the HRs of the risk factors (Table 6.2).

Using the CRF model and categorising CVD risk in 5% categories, 10-year estimated CVD risk increased from 1.9% for the risk category of 0-5% risk to 12.6% for the category ≥ 10% in men, and from 1.5% to 12.3% in women, respectively. Extending the CRF model with obesity resulted in a NRI of 2.2% in men and 1.1% in women (Table 6.3A). Extending the CRF model with paternal MI and maternal MI also improved risk prediction in men (2.5%) but not in women (-0.7%). Including both risk factors improved risk prediction by 4.5% in men (significant) and 2.6% in women.

Using the CRF model and categorising CVD risk in 10% categories, 10-year estimated CVD risk increased from 3.5% for the risk category of 0-10% to 23.4% for the risk category ≥ 20% in men, and from 1.9% for the risk category of 0-10% to 13.2% for the risk category of 10-20% in women. Only 8 women had an estimated CVD risk ≥ 20%, but none of them actually experienced an event during follow-up. Extending the CRF model with obesity resulted in a NRI of 3.8% in men (significant) and 2.7% in women. Extending the CRF model with parental MI improved risk prediction by 2.0% in men and 0.6% in women (Table 6.3B). After adding both risk factors, risk prediction improved by 5.5% in men (significant) and 3.3% in women.

More detailed information on reclassification of CVD events and non-events by extending the CRF model with obesity and/or parental MI is provided in Appendix 6.1.

Table 6.2 Hazard ratios for total CVD during 10 years of follow-up, using a classical risk factor model (CRF) and CRF models extended with obesity and parental MI

	Hazard ratio (95% confidence interval)			
	CRF model	CRF model with obesity*	CRF model with parental MI**	CRF model with obesity and parental MI**
Male gender	1.71 (1.38-2.12)	1.79 (1.44-2.22)	1.74 (1.41-2.16)	1.82 (1.47-2.26)
Age (per 10 years)	1.95 (1.69-2.25)	1.96 (1.70-2.27)	1.97 (1.71-2.28)	1.99 (1.72-2.30)
Smoking (y/n)	1.91 (1.57-2.32)	1.96 (1.61-2.38)	1.90 (1.56-2.31)	1.95 (1.61-2.37)
SBP (per 20 mmHg)	1.49 (1.35-1.65)	1.44 (1.30-1.60)	1.48 (1.34-1.64)	1.43 (1.29-1.59)
Total/HDL cholesterol ratio (per unit)	2.85 (2.11-3.86)	2.61 (1.91-3.55)	2.77 (2.04-3.74)	2.53 (1.86-3.45)
Obesity (y/n)*		1.52 (1.19-1.93)		1.51 (1.19-1.93)
Maternal MI < 70 y (y/n)			1.45 (1.03-2.03)	1.44 (1.03-2.02)
Paternal MI < 70 y (y/n)			1.17 (0.93-1.48)	1.18 (0.93-1.48)

CVD, cardiovascular diseases; SBP, systolic blood pressure; MI, myocardial infarction.
*BMI ≥ 30 kg/m^2 vs BMI 18.5-30 kg/m^2; **Both maternal MI and paternal MI are included in the model.

Table 6.3 Reclassification of CVD events and non-events, and net reclassification index (NRI) for a classical risk factors model and models extended with obesity and parental MI, using 5% risk categories (A) and 10% risk categories (B)

	Number of events			Number of non-events			NRI		
	Total	Up	Down	Total	Up	Down	%	z	P-value
A. Risk categories 0-5%, 5-10% and ≥ 10%									
Men									
CRF model with obesity	280	18	12	5,687	201	206	2.2	1.1	0.3
CRF model with parental MI*	280	11	5	5,587	158	177	2.5	1.7	0.09
CRF model with obesity and parental MI*	280	24	13	5,587	270	303	4.5	2.0	0.04
Women									
CRF model with obesity	140	8	6	6,711	135	114	1.1	0.4	0.7
CRF model with parental MI	140	4	5	6,711	81	82	-0.8	-0.4	0.7
CRF model with obesity and parental MI	140	13	9	6,711	171	155	2.6	0.8	0.4
B. Risk categories 0-10%, 10-20% and ≥ 20%									
Men									
CRF model with obesity	280	20	9	5,687	107	101	3.8	2.0	0.05
CRF model with parental MI	280	8	3	5,587	64	75	2.0	1.6	0.1
CRF model with obesity and parental MI	280	24	9	5,587	135	134	5.5	2.6	0.01
Women									
CRF model with obesity	140	6	2	6,711	37	24	2.7	1.3	0.2
CRF model with parental MI	140	2	1	6,711	22	16	0.6	0.5	0.6
CRF model with obesity and parental MI	140	9	4	6,711	50	35	3.3	1.3	0.2

CVD, cardiovascular diseases; CRF, classical risk factors; MI, myocardial infarction; NRI, net reclassification index.
*Both maternal MI and paternal MI are included in the model.

DISCUSSION

In the present study, obesity and maternal MI were independent risk factors for total CVD in both men and women. In men, obesity, but not parental MI significantly improved risk prediction (at 10% increments in CVD risk). An additive effect of obesity and parental MI was found and together they improved risk prediction strongest (at 5% and 10% increments in CVD risk). In women, no significant improvements in risk prediction were obtained after adding obesity and/or parental MI to the risk function.

In the present study, obesity is an independent risk factor of total CVD and obese persons had a 50% higher CVD risk compared to non-obese persons. In a large prospective cohort study,[12] and in meta-analyses of prospective studies[11,16] similar or slightly higher risks were found. These higher risks were adjusted for age, sex and smoking status only, but became lower when adjustments were made for intermediate risk factors, e.g. systolic blood pressure and total cholesterol.[16] In the present study, relative risks for obese persons with a BMI ≥ 30 kg/m^2 were calculated with non-obese persons as reference category (BMI 18.5-30 kg/m^2). In other studies, relative risks of obese persons with BMI 30-35 kg/m^2 were compared with lower BMI values as reference category (e.g. BMI 23.5-25 kg/m^2). These differences might explain the lower relative risks observed in the present study.

Adding obesity to a model including similar risk factors as the SCORE model improved risk classification significantly by 3.8% in men (10% increments in CVD risk). No other publications reported on the NRI of adding obesity to the CRF model. However, in a subset of about 50,000 men and women from pooled data of 58 studies (58% from Europe, 56% women), adding BMI (per SD) to the Framingham risk factor model, did not improve risk prediction of CVD (NRI = -0.19%, p = 0.5; risk categories < 5%, 5-10%, 10-20% and ≥ 20%).[16] A similar analysis of our data, also showed a non-significant improvement in NRI in men and women. These results suggest that a proper operationalisation of BMI is essential. When a continuous analysis is done expressing BMI per SD, the NRI did not improve. However the NRI improved, when the BMI was dichotomised in those who were, or were not obese.

A positive family or parental history of premature MI, is generally defined as a parent who experienced an event before age 60. Many prospective studies have shown that a positive family history is an independent risk factor of CVD in men and women.[17] We found in our population that the definition of premature family history could be extended to an event before age 70.[27] A maternal MI before age 70 increased CVD risk by 40% and a paternal history of MI increased CVD risk by 20%. The literature is inconsistent on the specific effects of maternal and paternal history of MI on CVD.[17,27,31,32] Therefore, we included both maternal and paternal history of MI in our risk function, although the latter was not statistically significant.

We are not aware of other studies that calculated the NRI for adding a positive family history only to a CRF model. Ridker et al. included a positive family history together with C-Reactive Protein into a CRF model.[6] They found an improvement in the NRI of 5.3% in men. In other studies, adding CRP alone to the Framingham CRF model, improved correct risk classification by 3%-9%, depending on the thresholds of the risk categories.[33] Therefore, we conclude that only modest improvements of the NRI can be expected of adding parental history to CRF models.

The improvements in risk prediction by adding obesity and parental MI to the CRF model were not significant in women. Although our cohort consisted of a large number of women, their absolute CVD risk was very low. In the CRF model, 98% of the women had a CVD risk between 0 and 10% and in 0.1% CVD risk was ≥ 20%. Using the 5% increments in CVD risk, still 90% of the women had a risk between 0 and 5% and only 2% exceeded risk of 10% and higher, the new cut-off point for high CVD risk in women, proposed in the 2011 American Heart Association guideline for CVD prevention.[24] In case of both the 5% and 10% increments in CVD risk, only a few women could potentially have moved to a higher risk category and this is the most likely explanation for the observation that adding these two risk factors did not improve the NRI. Cohorts with more events are needed before statements can be made about the effect of these additional factors on the correct classification of high-risk women.

In general, the NRI depends on the choice of cut-off points.[8] A threshold for defining persons at low, intermediate and high risk is arbitrary, but necessary for clinical decision making. In men the 5% and 10% increments in CVD risk, provided similar improvements in risk prediction by adding obesity and parental history of MI to the CRF model (NRI = 4.5% at 5% and 5.5% at 10% risk categories). However, risk improvement by adding obesity alone attenuated when the 5% risk categories were used instead of the 10% risk categories. This suggests that adding obesity to the CRF model is meaningful for risk prediction in men at highest risk.

To the best of our knowledge, the present study is the first to show that adding obesity to the CRF model modestly improved risk prediction in men. Risk prediction improved further when parental history of MI was added to the model, although the impact of the latter risk factor was not statistically significant in itself. Risk prediction in women did not improve. Using 5% instead of 10% increments in absolute CVD risk, leads to similar conclusions.

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APPENDIX 6.1

Reclassification of CVD events and non-events, and net reclassification index (NRI) for a classical risk factors model (CRF) and models extended with obesity and parental MI, using increments of 5% (A) and 10% (B) in absolute CVD risk.

CVD, cardiovascular diseases; CRF, classical risk factors; MI, myocardial infarction; NRI, net reclassification index. Both maternal and paternal MI are included in the model.

A. Men , risk categories 0-5%, 5-10% and ≥ 10%

Men	CRF model with obesity					
CRF model	0-5%	5-10%	≥ 10%	Total	Number up	Number down
Events						
0-5%	66	4	0	70		
5-10%	5	94	14	113		
≥ 10%	0	7	90	97		
Total	71	105	104	280	18	12
Non-events						
0-5%	3,521	117	0	3,638		
5-10%	122	1,171	84	1,377		
≥ 10%	0	84	588	672		
Total	3,643	1,372	672	5,687	201	206

NRI = (18/280 – 12/280) – (201/5,687 – 206/5,687) = 0.022 (z = 1.122, P-value = 0.26).

Men	CRF model with parental MI					
CRF model	0-5%	5-10%	≥ 10%	Total	Number up	Number down
Events						
0-5%	66	4	0	70		
5-10%	3	103	7	113		
≥ 10%	0	2	95	97		
Total	69	109	102	280	11	5
Non-events						
0-5%	3,536	102	0	3,638		
5-10%	110	1,211	56	1,377		
≥ 10%	0	67	605	672		
Total	3,646	1,380	661	5,687	158	177

NRI = (11/280 – 5/280) – (158/5,687 – 177/5,687) = 0.025 (z = 1.691, P-value = 0.091).

Men	CRF model with obesity and parental MI					
CRF model	0-5%	5-10%	≥ 10%	Total	Number up	Number down
Events						
0-5%	63	7	0	70		
5-10%	7	89	17	113		
≥ 10%	0	6	91	97		
Total	70	102	108	280	24	13
Non-events						
0-5%	3,471	166	1	3,638		
5-10%	183	1,091	103	1,377		
≥ 10%	0	120	552	672		
Total	3,654	1,377	656	5,687	270	303

NRI = (24/280 – 13/280) – (270/5,687 – 303/5,687) = 0.045 (z = 2.037, P-value = 0.042).

A. Women, risk categories 0-5%, 5-10% and ≥ 10%

Women	CRF model with obesity					
CRF model	0-5%	5-10%	≥ 10%	Total	Number up	Number down
Events						
0-5%	93	2	0	95		
5-10%	4	20	6	30		
≥ 10%	0	2	13	15		
Total	97	24	19	140	8	6
Non-events						
0-5%	5,962	102	0	6,064		
5-10%	93	414	33	540		
≥ 10%	0	21	86	107		
Total	6,055	537	119	6,711	135	114

NRI = (8/140 – 6/140) – (135/6,711 – 114/6,711) = 0.0112 (z = 0.416, P-value = 0.68).

Women	CRF model with parental MI					
CRF model	0-5%	5-10%	≥ 10%	Total	Number up	Number down
Events						
0-5%	92	3	0	95		
5-10%	4	25	1	30		
≥ 10%	0	1	14	15		
Total	96	29	15	140	4	5
Non-events						
0-5%	6,002	62	0	6,064		
5-10%	67	454	19	540		
≥ 10%	0	15	92	107		
Total	6,069	531	111	6,711	81	82

NRI = (4/140 – 5/140) – (81/6.711 – 82/6.711) = - 0.0077 (z = -0.361, P-value = 0.72).

Women	CRF model with obesity and parental MI					
CRF model	0-5%	5-10%	≥ 10%	Total	Number up	Number down
Events						
0-5%	90	5	0	95		
5-10%	5	17	8	30		
≥ 10%	0	4	11	15		
Total	95	26	19	140	13	9
Non-events						
0-5%	5,936	128	0	6,064		
5-10%	122	375	43	540		
≥ 10%	0	33	74	107		
Total	6,058	536	117	6,711	171	155

NRI = (13/140 – 9/140) – (171/6,711 – 155/6,711) = 0.026 (z = 0.779, P-value = 0.44).

B. Men, risk categories 0-10%, 10-20% and ≥ 20%

Men	CRF model with obesity					
CRF model	0-10%	10-20%	≥ 20%	Total	Number up	Number down
Events						
0-10%	169	14	0	183		
10-20%	7	59	6	72		
≥ 20%	0	2	23	25		
Total	176	75	29	280	20	9
Non-events						
0-10%	4,931	84	0	5,015		
10-20%	84	483	23	590		
≥ 20%	0	17	65	82		
Total	5,015	584	88	5,687	107	101

NRI = (20/280 – 9/280) – (107/5,687 – 101/5,687)= 0.0382 (z=1.970, P-value = 0.049).

Men	CRF model with parental MI					
CRF model	0-10%	10-20%	≥ 20%	Total	Number up	Number down
Events						
0-10%	176	7	0	183		
10-20%	2	69	1	72		
≥ 20%	0	1	24	25		
Total	178	77	25	280	8	3
Non-events						
0-10%	4,959	56	0	5,015		
10-20%	67	515	8	590		
≥ 20%	0	8	74	82		
Total	5,026	579	82	5,687	64	75

NRI = (8/280 – 3/280) – (64/5,687 – 75/5,687) = 0.020 (z = 1.645, P-value = 0.10).

Men	CRF model with obesity and parental MI					
CRF model	0-10%	10-20%	≥ 20%	Total	Number up	Number down
Events						
0-10%	166	17	0	183		
10-20%	6	59	7	72		
≥ 20%	0	3	22	25		
Total	172	79	29	280	24	9
Non-events						
0-10%	4,911	104	0	5,015		
10-20%	120	439	31	590		
≥ 20%	0	14	68	82		
Total	5,031	557	99	5,687	135	134

NRI = (24/280 – 9/280) – (135/5,687 – 134/5,687) = 0.0533 (z = 2.577, P-value = 0.010).

B. Women, risk categories 0-10%, 10-20% and ≥ 20%

Women	CRF model with obesity					
CRF model	0-10%	10-20%	≥ 20%	Total	Number up	Number down
Events						
0-10%	19	6	0	125		
10-20%	2	13	0	15		
≥ 20%	0	0	0	0		
Total	120	20	0	140	6	2
Non-events						
0-10%	6,571	33	0	6,604		
10-20%	21	74	4	99		
≥ 20%	0	3	5	8		
Total	6,592	110	9	6,711	37	24

NRI = (6/140 – 2/140) – (37/6,711 – 24/6,711) = 0.0266 (z = 1.316, P-value = 0.19).

Women	CRF model with parental MI					
CRF model	0-10%	10-20%	≥ 20%	Total	Number up	Number down
Events						
0-10%	124	1	0	125		
10-20%	1	13	1	15		
≥ 20%	0	0	0	0		
Total	125	14	1	140	2	1
Non-events						
0-10%	6,585	9	0	6,604		
10-20%	15	81	3	99		
≥ 20%	0	1	7	8		
Total	6,600	101	10	6,711	22	16

NRI = (2/140 – 1/140) – (22/6.711 – 16/6.711) = 0.0062 (z = 0.504, P-value = 0.62).

Women	CRF model with obesity and parental MI					
CRF model	0-10%	10-20%	≥ 20%	Total	Number up	Number down
Events						
0-10%	117	8	0	125		
10-20%	4	10	1	15		
≥ 20%	0	0	0	0		
Total	121	18	1	140	9	4
Non-events						
0-10%	6,561	43	0	6,604		
10-20%	33	59	7	99		
≥ 20%	0	2	6	8		
Total	6,594	104	13	6,711	50	35

NRI = (9/140 – 9/140) – (50/6,711 – 35/6,711) = 0.0334 (z = 1.298, P-value = 0.20).

7

General discussion

In the second part of the 20th century, major risk factors for developing cardiovascular diseases (CVD) were identified.[1] Risk factors, such as age, sex, smoking, high blood pressure, hyperlipidaemia and diabetes are now widely accepted.[2] The first risk charts and multivariable risk prediction functions that included these risk factors were constructed in the 1970s in the USA, based on the Framingham Heart Study.[3] The risk charts intended to aid clinicians in assessing patients' risk of developing coronary heart disease (CHD) and facilitate treatment decisions.[1,2] The Framingham risk charts were introduced in Europe with the 1994 Guidelines on the prevention of CHD in clinical practice.[4] Since these charts overestimated CHD risk in several European countries,[5,6] the SCORE (Systematic COronary Risk Evaluation) risk charts were introduced in 2003.[7] Persons with an estimated 10-year risk of CVD mortality of 5% or more were called high risk, and were eligible for pharmacological treatment. The SCORE risk charts have been implemented in clinical practice in many European countries, including the Netherlands.

In the past 30 years, unifactorial treatment of hypertension or hypercholesterolaemia shifted towards integrated cardiovascular risk management. The first – Framingham based – risk charts were introduced in the Netherlands in the 1998 Cholesterol Consensus[8] and the 2000 Guideline on high blood pressure.[9] Three years after the European guidelines, a nationally adapted SCORE risk chart was introduced in the 2006 Guideline on Cardiovascular Risk Management (CVRM).[10] Furthermore, a web-based HEART SCORE calculator became available.[11] However, it was not known how well the underlying risk functions fitted the Dutch situation. These SCORE risk functions predicted CVD mortality risk. Although CVD mortality rates in the Netherlands are continuously decreasing, a low CVD mortality is accompanied by a high nonfatal CVD incidence (Figure 7.1).[12,13] Therefore, clinicians requested a change in risk prediction from CVD mortality to total (fatal plus nonfatal) CVD. Pharmacological treatment of high levels of blood pressure or serum cholesterol were recommended for high-risk persons, and for those with an intermediate risk combined with

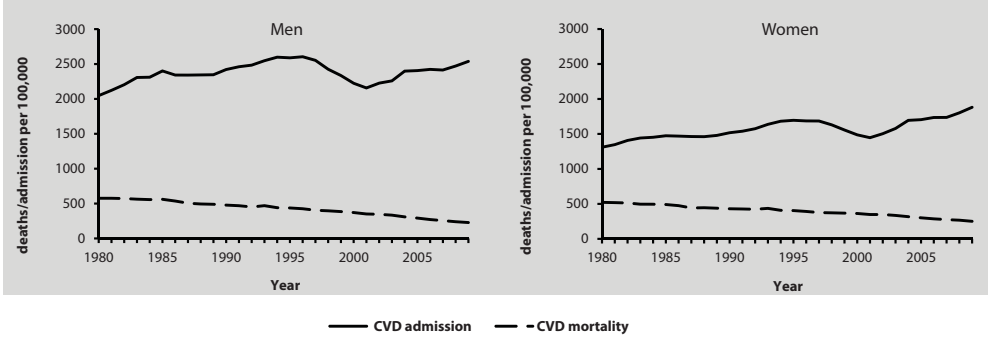

Figure 7.1 Trends in standardised CVD mortality and CVD hospital admissions in the Netherlands per 100,000. Year of standardisation is 2009.[13]

additional risk factors. Obesity and a parental history of MI before age 60 were considered additional risk factors. However, it was not known whether these additional risk factors improved risk prediction when added to the classical risk factor function.

The aim of this thesis was to improve cardiovascular risk prediction in the Netherlands. The following research questions were raised during the development of the first Guideline on Cardiovascular Risk Management (CVRM, 2006):[14]

1. Which SCORE risk function fits best for the Netherlands?
2. What are the consequences of a change from predicting CVD mortality to total CVD (fatal plus nonfatal) for identifying high-risk persons?
3. What is the added value for risk prediction of including additional risk factors (obesity and parental history of myocardial infarction) in the classical risk function with total CVD as endpoint?

Main findings

The main findings, summarised in Table 7.1, are:

- The Netherlands was considered a high-risk CVD mortality country, but is now a low-risk country, for which the SCORE low-risk function fits best;
- The change from predicting CVD mortality to total CVD (fatal plus nonfatal) did not improve discrimination between future cases and non-cases;
- Obesity (BMI ≥ 30 kg/m^2) and parental history of myocardial infarction before age 70 were independent predictors of total CVD;
- Adding obesity and parental history to a classical risk factor function modestly improved correct risk classification;
- The currently used cut-off points of 5% CVD mortality and 20% total CVD only identified individuals at very high risk;
- Cut-off points of 2% CVD mortality or 10% total CVD could be considered for identification of high-risk persons.

Several findings contributed to the 2011 revision of the Guideline on CVRM.[15] Since absolute risks of total CVD better reflect the high burden of CVD, the endpoint of risk prediction was changed from predicting CVD mortality to total CVD. Therefore the absolute fatal CVD risks – now calculated with the low-risk SCORE function – were multiplied by age-specific total-to-fatal CVD ratios. The new threshold for high-risk persons became 20% total CVD risk. The decision to include myocardial infarction, stroke and heart failure in the definition

Table 7.1 The added value of the studies described in this thesis compared with the state of the art described in the 2006 guideline on cardiovascular risk management (CVRM)

State of the art in the 2006 guideline on CVRM	Cohorts	Population	CVD outcome	Main findings and what we added in 2011	Chapter
The Netherlands was considered a high-risk CVD mortality country. The SCORE risk prediction function for high-risk European countries and the nationally adapted risk function were used in the Netherlands.	PEILSTATION MORGEN	32,885 M/F 37.5–62.5 y	Fatal	The Netherlands is a low-risk CVD mortality country, comparable to the Mediterranean countries. The low-risk SCORE prediction function fits the Dutch situation best.	2
Waist circumference was a better predictor of CVD compared with body mass index.	MORGEN	20,000 M/F 20–65 y	Fatal Nonfatal	Body mass index and waist circumference are equally strong predictors of CVD. Obesity is a much stronger predictor of CVD risk than overweight.	3
Premature parental history of MI was defined at age of onset of MI < 60 years.	MORGEN	10,524 M/F 40–65 y	Fatal + nonfatal	Total CVD is significantly elevated in persons having a parent with age of onset of MI < 70 years	4
10-year CVD mortality risk was used as the outcome measure for risk prediction in the Netherlands.	MORGEN PROSPECT	15,880 M/F 35–65 y	Fatal Fatal + nonfatal	Fatal CVD is approximately a quarter of total CVD. Risk functions and discrimination between future cases and non-cases by predicting fatal or total CVD risk do not differ. Cut-off points of 2% CVD mortality or 10% total CVD identify a similar 10% percentage of future CVD cases.	5
Risk prediction was based on the classical risk factors for CVD: age, gender, smoking status, systolic blood pressure, ratio total-to-HDL cholesterol	MORGEN	12,818 M/F 35–65 y	Fatal + nonfatal	Adding both obesity and parental history of MI to the classical risk factor model improves risk prediction by about 5%. This improvement is mainly attributable to obesity and only statistically significant in men.	6

M/F, males and females; CVD, cardiovascular diseases; BMI, body mass index; MI, myocardial infarction.

of nonfatal CVD was taken after discussions in the 2011 Guideline working group. We found that body mass index and waist circumference were equally strong predictors of CVD. Therefore, the advice in the 2006 Guideline 'to measure always both body mass index and waist circumference' was changed to 'measuring body mass index and possibly waist circumference' in the 2011 Guideline. This simplification was also prompted by practical reasons. The age for a premature parental history of MI was changed from < 60 years to < 65 years in the 2011 Guideline. However, since improvements in risk prediction of adding obesity and parental history of MI into a classical risk factor model were modest, these risk factors were not incorporated into the risk function predicting total CVD. In the 2011 Guideline, these risk factors are considered to be additional factors, to take into account when considering to prescribe drug treatment for those with an intermediate CVD risk.

An important finding, not included in the 2011 Guideline, was the fact that the cut-off points for 10-year risk of 5% CVD mortality and 20% for total 10-year CVD identified only individuals at very high risk. The results presented in this thesis suggest that thresholds for identification of high-risk persons could be lowered from 5 to 2% for CVD mortality and from 20 to 10% for total CVD. These lower thresholds will identify approximately 10% of future total CVD events. Recently, the American Heart Association lowered the treatment threshold of total CVD to 10% for women, because statins were cost-effective at this threshold.[16] Whether such a lowering of threshold is also cost-effective for Dutch men and women, needs to be investigated.

Strategies to further improve CVD risk prediction

Current risk prediction functions include mostly only classical risk factors. However, risk classification may improve by adding other risk factors[17] such as:

- easy to measure risk factors e.g. obesity, parental history of MI, heart rate,
- markers of inflammation e.g. C-Reactive Protein (CRP), Interleukin-6,
- markers of endothelial function e.g. intercellular and vascular cell adhesion molecules (ICAM, VCAM),
- markers of thrombosis e.g. fibrinogen,
- vascular markers of atherosclerosis e.g. carotid intima-media thickness (CIMT), coronary artery calcium score (CACS),
- CHD-related genetic variants e.g. on chromosome 10q11 or 9p21.

We added obesity and parental history of premature myocardial infarction to a classical risk function. In men, adding obesity, improved the Net Reclassification Index (NRI) significantly by 3.8% and parental history of myocardial infarction not-significantly by

2.7% using risk categories of 10%. For women these percentages were not significant and amounted to 2.7% and 0.6%. Similar percentage of improvements were found in studies in which the effect was assessed of 45 potential predictors.[17] The most common predictors included CRP and genetic variants such as on chromosome 9p21. In 38 studies, the NRI was calculated and ranged from -3.2% to 39% after adding biomarkers alone or combined. In studies with information on confidence intervals, the NRI was 2% (95% CI 0.5%–3.5%) in studies with an adequate baseline model versus 0.7% (0.2%–1.3%) in other studies. The NRI was 0.7% (0.1%–1.2%) in studies with justified risk thresholds versus 1.9% (0.5%–3.4%) in other studies. The highest NRIs were found for CRP.

Imaging techniques such as ultrasound measurements and computed tomography have been used to measure CIMT and CACS in order to quantify atherosclerosis. Eight studies investigated the added value of CIMT to classical risk factor functions and observed small, but sometimes significant improvements in area under the ROC curve.[18] A recent study showed a 10% improvement in CHD risk prediction when CIMT and the presence of plaque were added.[19] Adding CACS resulted in a NRI of 25%.[20] Although these results are promising, additional data are required on the relationship between these measures and future CVD events before definitive conclusions can be drawn about the usefulness of adding these markers to risk functions.[21]

Implications of risk stratification for public health

An important finding of this thesis was the low number of high-risk persons in the participants in the Dutch MORGEN and PEILSTATION cohorts (aged 20–65 years). Less than 10% of the men and 1% of the women exceeded the 5% CVD mortality threshold for increased risk (Figures 2.1 and 5.3). These low numbers cannot fully be explained by the 'healthy cohort' effect. Although in this high-risk group, about one in four individuals will develop a future CVD event, more than 84% of all male and 98% of all female future cases occurred in those at low or intermediate risk. Using the current thresholds, many future cases remain untreated, unless additional risk factors are present. Therefore to reduce the burden of CVD, also a total population strategy is needed.

The population strategy was for the first time described in a classic paper by Geoffrey Rose, published in the 1980s.[22,23] Cooney et al. re-evaluated the population strategy proposed by Rose.[24] A simulation study was carried out using SCORE data of persons aged 24–80 years, assuming 10% reductions in prevalence of smoking and in serum cholesterol and blood pressure levels by preventive interventions. This would save 9,125 lives per million persons. They also showed that treating high-risk individuals (men aged ≥ 40 or women aged ≥ 50 years, and ≥ 5% CVD mortality risk) with a polypill – containing a statin, three half-dose antihypertensives and aspirin – with a 20–80% uptake, would save 1,861–7,452 lives per million persons. This analysis suggests that the high-risk strategy is less effective.

Wald and Law proposed to treat the whole population aged 55 and older with a polypill.[25] They calculated that in theory, 84% of all CVD cases would be prevented. Recent studies showed that the effect of the polypill on CVD risk factors was moderately lower than predicted.[26] Pitfalls in this medical approach to prevention are the potential costs of the polypill, adverse effects and medicalisation.[27] Furthermore, the medical approach does not eliminate the causes of high risk factor levels.

Safer and more sustainable ways of reducing risk factors in the population can be realised by lifestyle and dietary interventions.[27] Examples of such approaches include smoking bans in public offices and restaurants, and salt and *trans* fats reductions in foods. With this type of lifestyle and environmental modifications large scale reductions in CVD and other chronic disease events can be achieved without side effects.[28]

Conclusion

People with a high risk should be correctly identified. Expanding the endpoint of risk prediction from fatal to total CVD did not improve risk discrimination between future cases and non-cases, and adding additional risk factors to the classical risk factor function, modestly improved identification of high risk persons. Those with CVD risks comparable to that of CVD patients, should be adequately treated. This can be done through effective medication to counteract high levels of blood pressure and serum cholesterol, in combination with lifestyle measures. However, to reduce the large burden of CVD in the population, this is not enough, because most CVD cases occur in people with an intermediate or low risk. Therefore, alongside a high-risk strategy, a population approach is also needed. Fortunately, this can be done by diet and lifestyle interventions. Prospective cohort studies have shown that modifiable factors such as smoking, an unhealthy diet, overweight, and physical inactivity account for 80% of the occurrence of CVD.[29] This means that a healthy diet and lifestyle are powerful tools to reduce the burden of CVD in the population.

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Summary

Cardiovascular diseases are the main cause of death in the Netherlands. In 2010, 28% of the men and 30% of the women died from this cause of death. It is estimated that every year, about 85,000 new coronary heart and 46,000 stroke events occur. Risk of cardiovascular diseases can be reduced by a healthy lifestyle and by pharmacological treatment of risk factors such as a high blood pressure and/or a high serum cholesterol. The first Dutch clinical guidelines on the identification and treatment of persons with high levels of these risk factors were developed in the 1980s, and are characterised by separate treatment of individual risk factors.

Over time interest in an integrated approach of treatment of risk factors for cardiovascular diseases increased. Around the year 2000, by implementation of the American Framingham risk charts in the Netherlands, multifactorial treatment of cardiovascular risk factors in clinical practice was introduced. With this tool, clinicians could calculate a patient's risk of developing cardiovascular diseases in the next 10 years. This risk calculation is based on the classical risk factors age, sex, smoking status, systolic blood pressure and the ratio of total-to-HDL cholesterol.

In the Dutch multidisciplinary guideline on cardiovascular risk management (CVRM) in 2006, guidelines on the identification and treatment of high-risk persons were updated according to the scientific state of the art of that time. The American risk charts were replaced by the European SCORE (Systematic Coronary Risk Evaluation) risk charts. This new risk function and chart predicted the risk of dying from cardiovascular diseases in the next 10 years. During the development of this guideline, several questions were raised, which will be treated in the research for this thesis. Some results of this research have been included in the guideline CRVM, which will be published at the end of 2011.

The aim of this thesis was to improve cardiovascular risk prediction in the Netherlands. The research questions investigated in this thesis are:

1. Which SCORE risk function fits best for the Netherlands?
2. What are the consequences of a change from predicting fatal cardiovascular diseases to total (fatal or nonfatal) cardiovascular diseases for the identification of high-risk persons?
3. What is the added value for risk prediction of including the additional risk factors obesity and parental history of myocardial infarction in the classical risk function with total cardiovascular diseases as endpoint?

To deal with the first question, we examined data from two cohorts of the National Institute for Public Health and the Environment (RIVM). Risk factors of 36,000 persons were measured between 1987 and 1992 (Monitoring Project on Cardiovascular Disease Risk Factors; Peilstations project) and of 23,000 persons between 1993-1997 (Monitoring Project on Chronic Disease Risk Factors; MORGEN project). For the second question,

alongside the MORGEN project data, baseline measurements from the PROSPECT cohort of the University Medical Centre of Utrecht were also used. For the third question, MORGEN project data were used. These cohorts have been linked to the national population register (GBA), the Statistics Netherlands (CBS) register of cause of death and the National Hospital Discharge Register (LMR). By linking these data, it is now known which cohort members experienced a cardiovascular disease and who died from cardiovascular diseases.

The introduction to this thesis presents an historical overview of Dutch guideline development on treatment of hypertension and hypercholesterolemia. In particular, the change from an unifactorial to a multifactorial approach (cardiovascular risk management) and the role of risk charts in clinical practice, are described.

Chapter 2 describes how well 10-year cardiovascular disease mortality observed in the Dutch cohorts in the last two decades is predicted by three different SCORE risk functions: the risk function for low risk European countries (e.g. Mediterranean countries), the risk function for high risk European countries (e.g. Scandinavian countries and the Netherlands) and the nationally adapted Dutch SCORE risk function (published in the 2006 CVRM guideline). It turned out that the function for low-risk Mediterranean countries fitted the Dutch situation best. The SCORE risk function for high-risk European regions and the adapted Dutch SCORE risk function overestimated the number of cardiovascular disease deaths by a factor of 1.5-2. Use of these latter risk functions can lead to overtreatment with drugs to lower high blood pressure and high cholesterol levels. The reason for this overestimation is the fact that these risk functions were developed on data collected in the 1970s and early 1980s. Since then there has been a dramatic decline in cardiovascular disease mortality in the Netherlands, which has continued in recent years.

To improve cardiovascular risk prediction to correctly classify high-risk persons for cardiovascular diseases, we investigated the impact of expanding the endpoint of risk prediction from 10-year risk of cardiovascular diseases mortality to 10-year risk of total (fatal + nonfatal) cardiovascular diseases (**chapter 5**), and of adding additional risk factors to the classical risk function (**chapter 6**). Two promising, easy to measure, risk factors are obesity and a parental history of myocardial infarction. Firstly, we conducted studies to examine the associations between measures of overweight and observed cardiovascular diseases (**chapter 3**), and between various definitions of parental history of myocardial infarctions and observed cardiovascular diseases (**chapter 4**).

We studied the association between body mass index (BMI) and waist circumference, and 10-year incidence of fatal and nonfatal cardiovascular diseases in 20,000 men and women aged 20-65 years (**chapter 3**). About half of the men and women had an increased weight (BMI ≥25 kg/m^2) and/or an increased waist circumference (≥94 cm in men and ≥80 cm in women). During a 10-year follow-up period, 5.7% of the participants experienced a cardiovascular disease and 0.6% died from this cause. Nonfatal cardiovascular diseases

occurred 10 times more often than fatal cardiovascular diseases. Obese persons (BMI ≥30 kg/m^2) had a four-fold higher risk of dying from cardiovascular diseases and a two-fold higher risk of developing a cardiovascular disease compared with normal-weight individuals (BMI 18.5-30 kg/m^2). Similar associations were found for persons with a high waist circumference compared to those with a low waist circumference, meaning that both measures of overweight were equally strong predictors of fatal and nonfatal cardiovascular diseases.

Of all 10,524 participants aged 40-65 years at baseline, 36% had one or two parents who had already experienced a myocardial infarction (**chapter 4**). Participants with a father alone, a mother alone or both parents with a history of myocardial infarction (irrespective the age of onset of the myocardial infarction) had a 30%, 50% and 60%, respectively, increased cardiovascular risk themselves compared to those with parents without a history of a myocardial infarction. The age of onset at which the myocardial infarction in the parent occurred, had an impact on the magnitude of the cardiovascular risk. Participants who had a father with a myocardial infarction between age 60 and 70 or below age 60 had an increased cardiovascular risk of 40% and 50% respectively. Those who had a mother with a myocardial infarction between age 60 and 70 or below age 60 had an increased risk of 80% and 120%, respectively. Women, who had a mother with a myocardial infarction below age 60, had the largest cardiovascular risk (200%) compared to women with a mother without a myocardial infarction.

The currently used SCORE risk charts in clinical practice, predict 10-year risk of dying from cardiovascular diseases. Over the last 40 years, mortality from these causes has gradually declined in the Netherlands, while the number of hospital admissions remained high. It is pertinent to ask, therefore, whether risk prediction could be improved by developing risk charts predicting risk of fatal or nonfatal cardiovascular diseases (**chapter 5**).

Firstly, nonfatal cardiovascular diseases were defined by the occurrence of a myocardial infarction, stroke or heart failure only. During a period of 10 years, about four times as many participants experienced a cardiovascular disease event (nonfatal or fatal) than those who experienced a fatal event. Based on the Dutch data, risk functions were developed using Cox proportional hazard models for both endpoints of risk prediction. As measure to express how well these functions predict the patients who will and who will not experience an event (called risk discrimination), the Area Under the ROC curve was calculated. It turned out that both risk functions performed equally well.

Changing from a risk function which predicts fatal to a risk function predicting total cardiovascular diseases will alter the risk threshold for prescribing drug treatment for high blood pressure and/or high serum cholesterol. This threshold for fatal cardiovascular diseases is 5% (European guidelines) and corresponded with a threshold of 20% for total cardiovascular disease. Of all persons with such a high risk, one in five actually will develop

cardiovascular diseases in a period of 10 years. While considering developing cardiovascular diseases in one in ten persons treated with drugs, a threshold of 2% cardiovascular mortality corresponded with a threshold of 10% total cardiovascular diseases. When medical treatment of 10 persons – leading to 1 case of cardiovascular disease – would be cost-effective, lowering treatment thresholds could be proposed.

The classical risk function includes the following risk factors: age, sex, smoking status, systolic blood pressure and the ratio of total-to-HDL cholesterol. We expanded this risk function by adding two easy to measure risk factors: the presence or absence of obesity and/or having a father or mother who experienced a myocardial infarction below age 70 (**chapter 6**). Subsequently, the improvement in risk classification was measured by calculating the Net Reclassification Index. Patients who went on to develop a cardiovascular disease within10 years, should be ideally classified into the high-risk category to be eligible for drug treatment for high blood pressure and high serum cholesterol levels. Those who stay free of cardiovascular diseases, should be classified into a low-risk category. It was calculated that about 5% of the men were reclassified in the correct risk category by using the expanded risk function compared to the classical risk function. This moderate improvement was mainly due to adding obesity to the risk function, and, to a lesser extent, by adding having a parent with a myocardial infarction. Risk improvements in women were about 3%, but were not significant.

In **chapter 7**, the contribution of this PhD research to the revision of the 2006 Dutch guideline on cardiovascular risk management is described. In the 2011 guideline a change in risk tables predicting fatal cardiovascular diseases to those predicting total cardiovascular diseases was made, because medical doctors prefer to use risk tables with absolute risks expressing the total burden of cardiovascular diseases. These absolute risks were calculated by using the SCORE risk function for low-risk countries multiplied by age-dependent factors expressing the ratio of total-to-fatal cardiovascular diseases. The choice of this risk function and the multipliers are based on the research described in this thesis. Results from the association studies influenced the preference for using the body mass index in risk assessment and increased the parental age of onset of the myocardial infarction as additional risk factor, from below 60 to below 65 years.

The moderate improvements in risk classification of high-risk persons by adding obesity and parental history of myocardial infarction to the classical risk function in our study were compared with risk improvements in other studies by adding risk factors and biomarkers of inflammation, endothelial function, thrombosis and atherosclerosis. In general, our findings are of the same magnitude as found in other biomarker studies. So far, the most promising results have been found in studies adding biomarkers of inflammation (C reactive-protein) and markers of atherosclerosis e.g. carotid intima-media thickness.

In our study, it was demonstrated that one in five high-risk persons actually developed a cardiovascular disease within a follow-up period of 10 years. However, in our cohorts, the total number of persons with such a high risk was less than 10%. This means that most cases of cardiovascular diseases occur among those at low or moderate risk. Therefore, to reduce the total burden of cardiovascular diseases a population-wide approach is proposed in addition to the high-risk approach as described in this thesis. Such a strategy includes nationwide measures to promote a healthy lifestyle.

The conclusion of this thesis is that current Dutch risk prediction of cardiovascular diseases and identification of the correct persons for drug treatment of high blood pressure and/or high serum cholesterol can be improved by using the SCORE risk function for low-risk countries. Adding the risk factors obesity and parental history of myocardial infarction below age 70 to the classical risk function, will only lead to moderate risk reclassification improvements of high-risk persons.

By a change from predicting risk of fatal cardiovascular disease to risk of fatal or nonfatal cardiovascular disease, thresholds for drug treatment will increase from 5% to 20%. Of all persons with such a high risk, one in five will go on to develop a cardiovascular disease within 10 years. By lowering treatment thresholds to 2% for fatal cardiovascular disease and 10% for fatal or nonfatal cardiovascular disease, one in 10 treated persons will develop a cardiovascular disease in the next 10 years. Cost-effectiveness studies have to demonstrate whether lowering treatment thresholds can be justified.

Samenvatting
(Summary in Dutch)

Hart- en vaatziekten zijn een belangrijke doodsoorzaak in Nederland. In 2010 stierf 28% van de mannen en 30% van de vrouwen hieraan. Naar schatting komen er jaarlijks 85.000 nieuwe gevallen van coronaire hartziekten en 46.000 van een beroerte bij. De kans op hart- en vaatziekten kan verlaagd worden door een gezonde leefwijze en door medicamenteuze behandeling van risicofactoren zoals een hoge bloeddruk en/of een hoog cholesterolgehalte in het bloed. De eerste Nederlandse medische richtlijnen voor de identificatie en behandeling van personen met hoge waarden van deze risicofactoren dateren uit de tachtiger jaren van de vorige eeuw en kenmerken zich door een gescheiden aanpak van de individuele risicofactoren.

De belangstelling voor een integrale aanpak van risicofactoren voor hart- en vaatziekten groeide in de loop der jaren. Met de komst van risicotabellen, gebaseerd op de Amerikaanse Framingham risicofunctie werd rond het jaar 2000 een multifactoriële aanpak van risicofactoren voor hart- en vaatziekten in de medische praktijk geïntroduceerd. Met dit hulpmiddel konden artsen de kans van een patiënt bepalen om in de komende 10 jaar een hart- of vaatziekte te ontwikkelen. Deze risicoschatting ging uit van de klassieke risicofactoren leeftijd, geslacht, het rookgedrag, de systolische bloeddruk en de verhouding totaal-cholesterol/HDL-cholesterol.

In de multidisciplinaire richtlijn Cardiovasculair risicomanagement (CVRM), uitgebracht in 2006, werden de richtlijnen voor de identificatie en behandeling van hoogrisico personen opnieuw aangepast aan de wetenschappelijke stand van zaken van die tijd. De Amerikaanse tabellen werden vervangen door de Europese SCORE (Systematic COronary Risk Evaluation) risicotabellen. Deze nieuwe functie voorspelde de kans om binnen 10 jaar te overlijden aan een hart- of vaatziekte. Tijdens de richtlijnontwikkeling kwamen enkele onderzoeksvragen naar voren, die in dit proefschrift worden behandeld. De bevindingen hebben geleid tot aanpassingen in de richtlijn CVRM die in 2011 wordt uitgebracht.

Doel van dit promotieonderzoek was om het voorspellen van de kans op hart- en vaatziekten in Nederland te verbeteren. De vraagstellingen onderzocht in dit promotieonderzoek zijn:

1. Welke SCORE risicofunctie past het beste bij Nederland?
2. Wat zijn de gevolgen voor het identificeren van hoogrisico personen van een overstap van risicofuncties die de kans op sterfte aan hart- en vaatziekten voorspellen naar risicofuncties die de kans op ziekte of sterfte aan hart- en vaatziekten voorspellen?
3. Kan de kans op ziekte en sterfte aan hart-en vaatziekten beter voorspeld worden door het toevoegen van extra risicofactoren aan de risicofunctie, namelijk ernstig overgewicht en het hebben van ouders die een hartinfarct hebben gehad?

Om antwoord te geven op de eerste vraagstelling zijn gegevens geanalyseerd van een tweetal monitoring-projecten van het Rijksinstituut voor Volksgezondheid en Milieu (RIVM), waarbij de risicofactoren van 36.000 personen werden gemeten in de periode

1987-1992 (Peilstationsproject Hart- en Vaatziekten) en van 23.000 personen tussen 1993 en 1997 (MORGEN-project). Voor de tweede vraagstelling zijn naast de gegevens van het MORGEN-project, ook die van het PROSPECT-cohort van het Universitair Medisch Centrum Utrecht gebruikt. Voor de derde vraagstelling is gebruikgemaakt van het MORGEN-project. De cohorten zijn gekoppeld aan de Gemeentelijke Basis Administratie (GBA), de doodsoorzakenstatistiek van het Centraal Bureau voor de Statistiek (CBS) en aan de landelijke medische registratie van ziekenhuisopnamen (LMR). Daardoor is bekend wie er in de 10 jaar na meting van de risicofactoren een hart- of vaatziekte kreeg en wie daaraan is overleden.

In de introductie van dit proefschrift wordt een historisch overzicht van de ontwikkeling van behandelrichtlijnen voor verhoogde bloeddruk en verhoogde cholesterolgehaltes in Nederland gepresenteerd (**hoofdstuk 1**). In het bijzonder wordt de overstap beschreven van een unifactoriële aanpak naar een multifactoriële aanpak (cardiovasculair risicomanagement) en de rol hierbij van de introductie van risicotabellen in de klinische praktijk.

In **hoofdstuk 2** wordt aangegeven in welke mate de in Nederland waargenomen sterfte aan hart- en vaatziekten in de laatste twee decennia voorspeld kon worden door de drie – door de SCORE groep ontwikkelde – risicofuncties: de functie voor laagrisico landen in Europa (bv. Mediterrane landen), die voor hoogrisico landen (bv. Scandinavische landen en Nederland) en de voor Nederland aangepaste risicofunctie (gepubliceerd in de richtlijn CVRM 2006). Het bleek dat de functie voor Mediterrane landen het best past bij de huidige Nederlandse situatie. De twee andere functies voorspelden 1,5 à 2 maal zoveel sterfgevallen aan hart- en vaatziekten dan daadwerkelijk werd waargenomen. Dit kan leiden tot overbehandeling met medicijnen ter verlaging van verhoogde bloeddruk- en cholesterolwaarden. De reden van de overschatting door twee van de SCORE risicofuncties is dat deze functies opgesteld zijn op basis van gegevens uit de zeventiger en begin tachtiger jaren, terwijl sindsdien de sterfte aan hart- en vaatziekten in Nederland sterk gedaald is en ook in recentere jaren gestaag blijft afnemen.

Om het voorspellen van de kans op hart- en vaatziekten te verbeteren en personen in een juiste risicocategorie in te delen, zijn twee zaken onderzocht. Enerzijds is onderzocht wat de invloed was van het veranderen van het eindpunt van de risicoschatting van de 10-jaars kans op sterfte aan hart- en vaatziekten naar de 10-jaars kans op ziekte en sterfte aan hart- en vaatziekten (**hoofdstuk 5**). Anderzijds is onderzocht wat de invloed was van het toevoegen van extra risicofactoren aan de klassieke risicofunctie (**hoofdstuk 6**). Twee gemakkelijk te meten risicofactoren zijn obesitas en het hebben van ouders die reeds een hartinfarct hebben doorgemaakt. Allereerst onderzochten we het verband tussen verschillende maten van overgewicht (**hoofdstuk 3**) en tussen verschillende definities van het hebben van ouders met een hartinfarct (**hoofdstuk 4**) en de kans op hart- en vaatziekten.

In **hoofdstuk 3** worden de associaties van de body mass index (BMI) en middelomtrek met hart- en vaatziekten beschreven. Van de 20.000 mannen en vrouwen in de leeftijd van 20-65 jaar had ongeveer de helft een te hoog gewicht (BMI ≥25 kg/m^2) en/of te grote middelomtrek (mannen ≥94 cm en vrouwen ≥80 cm). In een periode van 10 jaar kreeg 5,7% van de deelnemers een hart- of vaatziekte en overleed 0,6% hieraan. Niet-fatale hart- en vaatzieken kwamen dus 10 keer vaker voor dan fatale hart- en vaatziekten. Personen met obesitas (BMI ≥30 kg/m^2) hadden een viermaal grotere kans om te sterven aan hart- en vaatziekten en een tweemaal grotere kans om een hart- of vaatziekte te krijgen dan personen met een gezond gewicht (BMI 18.5-25 kg/m^2). Deze hogere risico's golden ook voor personen met een hoge ten opzichte van een lage middelomtrek. Beide maten leverden een vergelijkbare schatting op van de kans op hart- en vaatziekten en -sterfte.

Van de 10.524 deelnemers in de leeftijdsklasse 40-65 jaar had bij de basismeting van risicofactoren 36% één of twee ouders die getroffen waren door een hartinfarct (**hoofdstuk 4**). Het hebben van alleen een vader, alleen een moeder of beide ouders met een hartinfarct (ongeacht de leeftijd waarop) betekende respectievelijk een 30%, 50% of 60% hogere kans voor de deelnemer zelf om een hart- of vaatziekte te krijgen ten opzichte van deelnemers met ouders zonder hartinfarct. Als de vader een hartinfarct had gekregen tussen het 60^{e}en 70^e jaar dan had de deelnemer zelf een 40% hogere kans op hart- en vaatziekten. Kreeg de vader al onder de 60 jaar een hartinfarct, dan was die kans 50% hoger. Als de moeder een hartinfarct had gekregen tussen het 60^e en 70^e jaar dan had de deelnemer zelf een 80% hoger risico op hart- en vaatziekten. Kreeg de moeder een hartinfarct onder de 60 jaar, dan was die kans zelfs 120% hoger. Vrouwen die een moeder hadden met een hartinfarct onder het 60^e jaar liepen het grootste risico op hart- en vaatziekten met een 200% hogere kans ten opzichte van vrouwen met een moeder zonder hartinfarct.

De huidige SCORE risicotabellen die door artsen gebruikt worden, voorspellen de 10-jaars kans op sterfte aan hart- en vaatziekten. Aangezien de sterfte aan hart- en vaatziekten in Nederland in de afgelopen 40 jaar sterk gedaald is, terwijl het aantal ziekenhuisopnamen voor hart- en vaatziekten onverminderd hoog blijft, is de vraag of het schatten van het risico op hart- en vaatziekten verbeterd kan worden door tabellen te ontwikkelen met als eindpunt van de risicoschatting de kans op ziekte of sterfte aan hart- en vaatziekten (**hoofdstuk 5**). Allereerst werd ziekte gedefinieerd als het krijgen van een hartinfarct, beroerte of hartfalen. In een periode van 10 jaar kregen viermaal zo veel personen een hart- of vaatziekte (fataal + niet-fataal) dan er aan hart- en vaatziekten overleden. Op basis van de Nederlandse gegevens werden risicofuncties opgesteld met de kans op sterfte aan hart- en vaatziekten en de kans op ziekte of sterfte aan hart- en vaatziekten als eindpunt. Als maat om uit te drukken hoe goed voorspeld kan worden wie later een hart- of vaatziekte krijgt en wie niet (risicodiscriminatie genaamd), werd de AUROC (Area Under the ROC-curve) berekend. De risicofunctie die de kans op ziekte of sterfte aan hart- en vaatziekten voorspelde bleek echter niet beter in staat onderscheid te maken tussen

personen die later al dan niet een hart- of vaatziekte kregen, dan de functie die alleen de kans op sterfte aan hart- en vaatziekten voorspelde.

Bij een overstap van risicofuncties die de kans op sterfte voorspellen naar risicofuncties die de kans op ziekte of sterfte aan hart- en vaatziekten voorspellen, verandert ook de drempel van het risico waarboven medicamenteuze behandeling ter verlaging van verhoogde waarden van de bloeddruk en/of cholesterol door artsen voorgeschreven wordt. Die behandeldrempel voor de kans op sterfte aan hart- en vaatziekten ligt boven de 5% in Europese richtlijnen en komt overeen met een behandeldrempel voor de kans op ziekte of sterfte aan hart- en vaatziekten boven de 20%. Boven deze drempels ontwikkelden ca. 20% van de personen met zo'n hoog risico in een periode van 10 jaar een hart- of vaatziekte. Als we uit zouden gaan van ca. 10% gevallen van hart- en vaatziekten in een te behandelen groep, komt de drempel voor de kans op sterfte aan hart- of vaatziekten van 2% overeen met een drempel voor de kans op ziekte plus sterfte van 10%. Indien het behandelen van deze 10% nieuwe gevallen van hart- en vaatziekten kosteneffectief zou zijn, kan worden voorgesteld om de behandeldrempels te verlagen.

De klassieke risicofunctie omvat de risicofactoren leeftijd, geslacht, roken, de systolische bloeddruk en de verhouding totaal-cholesterol/HDL cholesterol. Aan deze risicofunctie zijn het al dan niet hebben van obesitas en een familiaire belasting (vader of moeder met hartinfarct voor het 70e jaar) toegevoegd (**hoofdstuk 6**). Deze factoren zijn eenvoudig te meten of na te vragen door artsen. Vervolgens is met de Net Reclassification Index berekend of zo meer personen in een juiste risicocategorie ingedeeld worden. Personen die later daadwerkelijk een hart- of vaatziekte krijgen zouden in een hogere risicocategorie terecht moeten komen om in aanmerking te komen voor medicamenteuze behandeling. Personen die geen hart- en vaatziekte krijgen zouden juist in een lage risicocategorie moeten belanden. Het bleek dat ongeveer 5% van de mannen in een passender risicocategorie terechtkwam indien beide risicofactoren toegevoegd werden aan de klassieke risicofunctie. Deze lichte verbetering was vooral het gevolg van het toevoegen van obesitas, en kwam in mindere mate door het hebben van ouders met een hartinfarct. De verbetering in de indeling in de juiste risicocategorie bij vrouwen was 3%, maar was niet significant.

In **hoofdstuk 7** wordt aangegeven wat dit promotieonderzoek bijgedragen heeft aan de herziene richtlijn Cardiovasculair Risico Management, die eind 2011 uitgebracht wordt. In deze richtlijn wordt de overstap gemaakt van risicotabellen die de kans op sterfte aan hart- en vaatziekten voorspellen naar tabellen die de kans op ziekte of sterfte aan hart- en vaatziekten voorspellen, omdat artsen in de absolute risico's ook de ziektelast van hart- en vaatziekten tot uiting willen laten komen. De absolute risico's om binnen 10 jaar te sterven aan hart- en vaatziekten – berekend met de SCORE-risicofunctie voor laagrisico landen in Europa – werden vermenigvuldigd met een factor die de verhouding

weergeeft tussen ziekte plus sterfte aan hart- en vaatziekten en alleen sterfte aan hart- en vaatziekten. Deze factor verschilde per leeftijdsgroep. De keuze voor de risicofunctie en de omrekeningsfactoren zijn gebaseerd op dit promotieonderzoek. De bevindingen uit de associatiestudies hadden invloed op de keuze van de voorkeursmaat voor overgewicht (van het meten van de BMI én middelomtrek naar de BMI en optioneel de middelomtrek) bij het bepalen van het risicoprofiel. Ook hadden de uitkomsten invloed op de bepalende leeftijd waarop bij de ouder een hartinfarct optrad (van verhoogd risico onder de 60 jaar naar onder de 65 jaar).

De lichte verbetering in indeling van hoogrisico personen in de juiste risicocategorie door het toevoegen van obesitas en het hebben van een ouder met een hartinfarct voor het 70e jaar aan de klassieke risicofunctie werd vergeleken met resultaten van andere studies. Het gaat dan vooral om het toevoegen van biomarkers van ontsteking, endotheelfunctie, trombose en atherosclerose. Onze bevindingen liggen over het algemeen in dezelfde orde van grootte als die in studies waarin naar het additionele effect van biomarkers is gekeken. Veelbelovend zijn ontwikkelingen op het terrein van biomarkers van ontsteking (C-reactive protein) en van de mate van atherosclerose gemeten in de halsslagaders.

In dit onderzoek is aangetoond dat één op de vijf hoogrisico personen binnen een periode van 10 jaar daadwerkelijk een hart- of vaatziekte ontwikkelt. Echter, het totaal aantal personen met een dergelijk risico is minder dan 10%. Dit betekent dat de meeste hart- en vaatziekten optreden bij personen met lage en middelhoge risico's. Derhalve is naast de hoog-risicobenadering, zoals beschreven in dit proefschrift, een populatiebenadering voorgesteld met landelijke maatregelen ter bevordering van een gezonde leefwijze om hart- en vaatziekten verder terug te dringen.

De conclusie van dit promotieonderzoek is dat het voorspellen van de kans op een hart- of vaatziekte en het identificeren van de juiste personen voor medicamenteuze behandeling van een hoge bloeddruk en/of hoog cholesterol in het bloed in Nederland verbeterd kan worden door gebruik van de SCORE risicofunctie voor laagrisico landen. Het toevoegen van de risicofactoren obesitas en het hebben van vader of moeder met hartinfarct voor het 70e jaar aan de klassieke risicofunctie leiden slechts tot geringe verbeteringen in de classificatie van hoogrisico personen.

Bij een overstap van het voorspellen van de kans op sterfte naar de kans op ziekte of sterfte aan hart- of vaatziekten, verandert de behandeldrempel van 5% naar 20%, wat inhoudt dat er 5 personen behandeld worden om 1 toekomstige case te voorkomen. Dit lijkt een vrij 'strenge' drempelwaarde. Het is daarom zinvol om kosteneffectiviteitsstudies uit te voeren om na te gaan of de drempelwaarde verlaagd kan worden naar 2% voor sterfte c.q. 10% ziekte of sterfte aan hart- en vaatziekten.

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About the author

CURRICULUM VITAE

Ineke van Dis graduated in 1975 from secondary school (gymnasium-β) at the Scholengemeenschap professor Casimir in Vlaardingen.

Subsequently, she studied Human Nutrition at Wageningen University with specialisation natural sciences. In 1982 and 1983 she was employed on short-term contracts at the Universities of Wageningen, Nijmegen and Maastricht. In the Department of Epidemiology of Maastricht University, she wrote a textbook with slides on the scientific state of the art on lifestyle and risk factors of cardiovascular diseases.

Since 1983, she is working at the Netherlands Heart Foundation (NHF) as nutritionist, epidemiologist and policymaker. From 1983-1996 she was head of the NHF's group of 10 freelance dieticians and was responsible for health projects in company restaurants, health education meetings, supermarket tours on nutrition labelling and healthy cooking demonstrations. Furthermore, she is in charge of cardiovascular statistics and coordinated the publication of 16 books on cardiovascular statistics. She is also responsible for translating the scientific state of the art on nutrition, lifestyle and risk factors of cardiovascular diseases, into prevention policies and projects, and is spokeswoman on prevention topics. In 2001 and 2005 she was deputy head of the NHF's Department of Prevention and Health Education and from 2002-2006 president of the NHF's union. In 2005, she participated in the NHF management team and was involved in a strategic re-orientation of NHF policy.

In 1991 she became honorary member of the Dutch Association of Dieticians. In 1993 she was registered as epidemiologist A and in 2006 as nutritional scientist A. She has participated in CBO working groups on Dutch guidelines on cholesterol (1987, 1999), cardiovascular risk management (2006, 2011) and obesity (2008), in the Health Council committee on cholesterol (1990) and in the European Heart Network's nutrition working group.

Since 2007, alongside her job as senior policymaker at the Research Department of the NHF, she conducted a PhD project on cardiovascular risk prediction in the Netherlands at the National Institute for Public Health and the Environment (RIVM) in Bilthoven, in collaboration with Wageningen University.

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Van Dis I, Geleijnse JM, Kromhout D, Boer JMA, Boshuizen H, Verschuren WMM. Do obesity and parental history of myocardial infarction improve cardiovascular risk prediction? (submitted)

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OVERVIEW OF COMPLETED TRAINING ACTIVITIES

Courses

- Linear regression, logistic regression, Cox regression and survival analysis. RIVM, Bilthoven, 2007
- Regression analysis by S. Lemeshow. Erasmus Summer Programme, Rotterdam, 2007
- Survival analysis by D. Kleinbaum and M. Klein. Erasmus Summer Programme, Rotterdam, 2006

Meetings

- European Society of Cardiology Congress. Vienna (2007), München (2008), Stockholm (2010), Paris (2011)
- EuroPRevent Congress. Paris (2008), Prague (2010), Geneva (2011)
- 9th Euro Fed Lipids congress, Rotterdam, 2011
- 49th Cardiovascular disease epidemiology and prevention annual conference, and Nutrition, physical activity and metabolism conference. American Heart Association. Florida, USA, 2009
- Prediction in cardiovascular disease. Clinical and methodological perspectives. UMCU, Utrecht, 2009
- World Congress of Cardiology, Barcelona, 2006
- Annual meetings of NWO-nutrition, WEON and EPIC-NL
- Meetings, seminars and conferences of learned societies (14) and universities (5)

General courses

- Team training by Focus. Leidschendam, 2010
- Media training by Burson-Marsteller. The Hague, 2006
- Communication, interaction and management by Van Harte & Lingsma. Leiden, 2002

Optionals

- CBO/NHG Working groups on Cardiovascular risk management (2006 and 2011), and Obesity (2008)
- Nutrition working group, European Heart Network, Brussels

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