

Public health aspects of serum cholesterol

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Gezondheidsaspecten van serum cholesterol

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Contents

1. Introduction	9
2. Trends in total and HDL cholesterol and their determinants in The Netherlands between 1993 and 1997	17
3. Smoking and elevated blood pressure at low, medium and high serum cholesterol levels and 20-year mortality in men and women aged 30-54	35
4. Serum cholesterol is a risk factor for myocardial infarction in elderly men and women: the Rotterdam Study	47
5. Total but not HDL cholesterol is consistently associated with coronary heart disease mortality in elderly men in Finland, Italy and The Netherlands	63
6. Predicting cardiovascular risk in the elderly in different European countries	77
7. Primary prevention of coronary heart disease through serum cholesterol lowering: quantifying the impact of different population strategies and a high-risk strategy	89
8. General discussion	107
Summary	127
Samenvatting	133
Dankwoord	139
About the author	141

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Chapter 2

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Chapter 5

Houterman S, Verschuren WMM, Giampaoli S, Nissinen A, Feskens EJM, Menotti A, Kromhout D. Total but not high-density lipoprotein cholesterol is consistently associated with coronary heart disease mortality in elderly men in Finland, Italy, and the Netherlands. *Epidemiology* 2000;11:327-332.

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Other publications by the author

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CHAPTER 1

Introduction

In the beginning of this century Anitschkow and De Langen started pioneering work concerning the relation between cholesterol and coronary heart disease.^{1,2} Both showed that there was a possible relation between cholesterol in the diet, blood cholesterol levels and atherosclerosis. It took until the second half of the twentieth century before large-scale population based studies, like the Framingham Study and the Seven Countries Study, were started to investigate the relation between serum cholesterol levels and coronary heart disease. These studies showed positive associations between serum cholesterol and incidence of and mortality from coronary heart disease in middle-aged men.³⁻⁶ Since then, other large epidemiological studies have shown that serum total cholesterol is positively associated and HDL cholesterol inversely associated with coronary heart disease mortality in middle-aged men.⁷⁻⁹

Quantifying the effect of cholesterol lowering interventions on for example incidence of coronary heart disease in The Netherlands is an important public health issue. Total cholesterol levels in the Dutch population are relatively high and did not substantially decrease until the beginning of the nineteen nineties.^{10,11} To quantify the amount of health gain that can be achieved through cholesterol lowering, additional information has to be gathered. First, recent levels of and trends in total and HDL cholesterol and prevalences of hypercholesterolemia and low HDL cholesterol levels in the Dutch population have to be described. Second, more evidence on the impact of total and HDL cholesterol on coronary heart disease in elderly men and women has to be collected. It is well known that serum total and HDL cholesterol are associated with coronary heart disease in middle-aged men and women, but it is still unclear whether this relation holds in the elderly.¹²⁻¹⁸ Third, risk functions to predict absolute risk of coronary heart disease in middle-aged men and women are well developed.¹⁹ However, in the elderly it is not clear whether these risk functions are a valid tool for risk prediction. This is important to know because cholesterol lowering treatment is nowadays based on the absolute level of risk, taking the total risk profile of an individual into account.

Coronary heart disease

Despite the declining trend in age-adjusted coronary heart disease mortality since 1972, it is still the most important cause of death in The Netherlands and other

developed countries.²⁰⁻²² Almost 20,000 persons died from coronary heart disease in 1997 in The Netherlands, of which more than 14,000 died from myocardial infarction.²⁰ The declining trend in coronary heart disease mortality may, at least in part, be attributed to changes in the classical risk factors and to improvements in medical care. In a descriptive study based on literature data it was tried to explain the declining trend in coronary heart disease mortality in The Netherlands between 1974 and 1992.²³ The largest part of the decline in coronary heart disease mortality seems to be explained by changes in mainly smoking in the 1970's and improvements in therapy in the 1980's.²³ Hunink et al.²⁴ estimated that in the United States 25% of the decline in coronary heart disease mortality between 1980 and 1990 was explained by changes in risk factors like serum cholesterol, blood pressure and smoking and 71% of the decline by improvements in the treatment of patients with coronary heart disease.

The declining trend in coronary heart disease mortality in The Netherlands contrasts with the increasing trend in number of hospital admissions for coronary heart disease. In the Dutch elderly (aged 65 years and over) the hospitalisation rate for coronary heart disease almost doubled between 1972 and 1997.²⁰ This is due to a strong increase in the number of hospital admissions for the more chronic forms of coronary heart disease, because the hospitalisation rate for acute myocardial infarction has declined since 1972. Healthier life-styles (less smoking and better nutrition) and better treatment of hypercholesterolemia and hypertension cause this decline.^{20,21} The rising number of hospital admissions for the more chronic forms of coronary heart disease can be explained by an improvement in technology and treatment leading to a better prognosis after an acute myocardial infarction.²¹ Due to better treatment and the increasing number of elderly in the Dutch population in the future, the prevalence of coronary heart disease will increase. The expectation is that the prevalence of coronary heart disease will increase with 35-45% between 1994 and 2015.²¹ This means that coronary heart disease remains one of the biggest public health problems in The Netherlands, as is the case in other affluent countries.

Cholesterol metabolism and atherosclerosis

Cholesterol is an essential component of cell membranes and serum lipoproteins and it is a precursor of bile acids, adrenal steroids and sex hormones.²⁵ Cholesterol enters the body through the diet or is produced in the liver. The transport of cholesterol from the intestine to the liver occurs through triglyceride-rich lipoproteins called chylomicrons. The liver secretes triglyceride-rich lipoproteins called very low-density lipoproteins (VLDLs), which are degraded by lipoprotein lipase to VLDL remnants. These remnants can be taken up by the liver or transformed into low-

density lipoproteins (LDLs). Most cholesterol (70%) is carried in the plasma in LDL particles. The majority of circulating LDL is removed from plasma via LDL receptors on the liver cells and the remainder part is cleared by the extrahepatic tissues, like the endothelium. High-density lipoproteins (HDLs) are synthesised in the liver and small intestine. HDLs transport cholesterol from peripheral tissues back to the liver where it can be degraded and excreted into bile acids or incorporated again in LDL and VLDL particles. About 20% of cholesterol is transported in HDL particles.^{25,26}

Atherosclerosis is the most common pathophysiological condition that underlies coronary heart disease. It is a progressive disease characterised by the accumulation of lipids and fibrous elements in the large arteries.^{27,28} Cholesterol, in particular LDL, plays an important role in the process of atherosclerosis. A primary initiating event in the atherosclerotic process is the accumulation of LDL in the subendothelial matrix. When the levels of LDL in the circulation are raised, accumulation and retention of LDL increased in the intima of the vessel wall.^{27,29} The infiltration of LDL may be accelerated by endothelial injury, which removes a natural barrier to the entrance of LDL into the vessel wall.²⁵ LDL can be modified in the vessel wall through oxidation, lipolysis, proteolysis and aggregation. Especially oxidised LDL plays an important role in the process of atherosclerosis.²⁹ The oxidised LDL particles can be taken up by macrophages to form foam-cells.²⁷⁻²⁹ These foam cells together with platelet thrombi release growth factors that cause proliferation of smooth muscle cells and deposition of monocytes. The plaques can be divided in several types. The unstable lesions characterised by a high concentration of extracellular lipids are most prone to rupture.²⁸ HDL cholesterol can have a positive influence on the process of atherosclerosis through removing cholesterol from macrophages, thus preventing the formation of foam cells and through increasing plaque stability. HDL can possibly also prevent the oxidation of LDL, the adhesion of monocytes to the endothelium and HDL prolongs the half-life of prostacycline and preserves its vasodilatory effect.²⁶

Dietary and lifestyle determinants of serum cholesterol

From results of the Seven Counties Study it became clear that at the population level a large part of the variation in serum cholesterol levels is related to diet.³ Controlled dietary experiments have shown that saturated fat is one of the most important dietary factors that increase serum total cholesterol.^{30,31} Increasing the intake of saturated fatty acids by 1 percent of energy causes an increase in the total cholesterol level by 0.07 mmol/L, largely due to changes in LDL cholesterol. Saturated fatty acids suppress the activity of the LDL receptor, which increases the serum LDL cholesterol level. Trans fatty acids increase serum total and LDL

cholesterol and decrease HDL cholesterol.³² An increase in the intake of trans fatty acids by 1 percent of energy results in an increase in total cholesterol by 0.026 mmol/L, an increase in LDL cholesterol by 0.037 mmol/L and a decrease in HDL cholesterol by 0.017 mmol/L. If the intake of polyunsaturated fatty acids is increased with 1 percent of energy, serum total cholesterol decreases by 0.06 mmol/L, of which most is due to a decline in LDL cholesterol.³⁰ The intake of dietary cholesterol doesn't have a large impact on the serum cholesterol level. An increase in dietary cholesterol of 5 mg/day results in an increase in total cholesterol of 0.0065 mmol/L.³⁰

Lifestyle factors can also affect serum total and HDL cholesterol levels. Obesity increases total cholesterol and decreases HDL cholesterol levels. Every kilogram decrease in body weight is associated with a 0.05 mmol/L decrease in total cholesterol and a 0.009 mmol/L increase in HDL cholesterol.³³ Smoking has also an unfavourable effect on serum cholesterol. Smokers have on average 3% higher serum total cholesterol levels, 2% higher LDL cholesterol levels and 6% lower HDL cholesterol levels compared to non-smokers.³⁴ Physical activity increases HDL cholesterol and decreases total and LDL cholesterol. Aerobic exercise training is associated with a 0.05 mmol/L higher HDL cholesterol level, a 0.10 mmol/L lower total cholesterol level and a 0.10 mmol/L lower LDL cholesterol level.³⁵ Moderate alcohol consumption increases HDL cholesterol. Increasing alcohol intake by 1 gram of alcohol per day was associated with an increase in HDL cholesterol of 0.003 mmol/L.³⁶

Cholesterol lowering in a public health context

In the mid nineteen nineties the first results of the randomised controlled trials with the new generation cholesterol lowering drugs (HMG-CoA reductase inhibitors, the so-called 'statins') were presented. In a recently published meta-analysis of the most important trials it was estimated that treatment with statins was associated with a 20% reduction in total cholesterol, 28% reduction in LDL cholesterol and 5% increase in HDL cholesterol. This results in a 29% reduction in coronary heart disease mortality and a 21% reduction in all-cause mortality.³⁷ The risk reduction calculated in this meta-analysis was comparable for men and women, for elderly (aged 65 years and over) and middle-aged persons and for primary and secondary prevention trials. The conclusion is therefore that treatment with statins is sensible, but the question arises who must be treated with these cholesterol lowering drugs.

In the nineteen eighties guidelines for identification of high risk groups according to their cholesterol level were developed.^{38,39} In these guidelines treatment with cholesterol lowering therapy was based primarily on the cholesterol level. Nowadays treatment decisions are based on the total risk profile of a patient,^{40,41} as described

in the revised version of the Dutch consensus guidelines for cholesterol lowering therapy published in 1998.⁴² According to this consensus, treatment with cholesterol lowering medication in primary prevention is recommended in persons with a combination of risk factors for coronary heart disease leading to a high absolute risk for developing coronary heart disease. The risk factors taken into account are gender, age, serum total and HDL cholesterol, hypertension, diabetes mellitus, smoking and family history of premature coronary heart disease (< 60 years). Cholesterol lowering medication in primary prevention is indicated if the absolute risk for developing coronary heart disease is above a given age- and gender specific cut-off point. In addition, information about a healthy diet and lifestyle should be given: stop smoking, weight reduction if overweight, remain physically active and eat healthy (≤ 10 percent of energy from saturated and trans fatty acids, 400 g fruits and vegetables each day and once or twice a week fish) in order to reduce the incidence of coronary heart disease at the population level.

Outline of the thesis

The aim of the research described in this thesis is to quantify the impact of serum total and HDL cholesterol on public health in The Netherlands. In chapter 2 the prevalence of and trends in total and HDL cholesterol levels in The Netherlands between 1993 and 1997 are described. Furthermore, the extent to which these trends in cholesterol could be explained by changes in lifestyle factors, like body mass index, smoking, alcohol intake, intake of saturated and trans fatty acids is studied. The effect of low, medium and high serum cholesterol levels in combination with elevated blood pressure and smoking on 20-year cause-specific and all-cause mortality in adult men and women is described in chapter 3. In chapter 4 and 5 is reported whether the relations between total and HDL cholesterol and coronary heart disease mortality observed in middle-aged persons still hold in the elderly. In chapter 4 the relation between total and HDL cholesterol and myocardial infarction in men and women aged 55 years and over is analysed. In chapter 5 the relation between total and HDL cholesterol and coronary heart disease mortality in men aged 65-84 years in different European countries is investigated. In chapter 6 risk functions are described for coronary heart disease and cardiovascular diseases mortality for elderly men in different European countries. The impact of different population prevention strategies and a high-risk strategy on the primary prevention of coronary heart disease through cholesterol lowering is presented in chapter 7. A general discussion of the different topics described in this thesis is given in chapter 8.

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Chapter 1

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CHAPTER 2

Trends in total and HDL cholesterol and their determinants in The Netherlands between 1993 and 1997

Abstract

Objective. The aim of this study is to describe trends in plasma total and HDL cholesterol in The Netherlands between 1993 and 1997 and to examine whether these trends in cholesterol could be explained by changes in body mass index, smoking, alcohol intake, use of cholesterol lowering medication, intake of saturated fat, trans fatty acids and dietary cholesterol.

Methods. Each year a random sample of men and women aged 20-59 years living in three towns in The Netherlands was invited to participate in the study. In total more than 21 000 persons were examined.

Results. Between 1993 and 1997 plasma total cholesterol decreased significantly by 0.19 mmol/L in men and by 0.27 mmol/L in women. HDL cholesterol remained stable during this period in both men and women. Small decreases were observed in the intake of saturated fat, trans fatty acids and dietary cholesterol in both men and women. The use of cholesterol lowering medication and for women oral contraceptives and prescribed estrogens increased significantly. After adjustment for these determinants in multivariate analyses the trend in total cholesterol remained highly significant.

Conclusion. Between 1993 and 1997 the mean total cholesterol level decreased significantly while the mean HDL cholesterol remained stable in both men and women in The Netherlands. The observed trend in total cholesterol could only for a small part be explained by changes in the determinants studied.

Introduction

Since 1972, age-adjusted coronary heart disease mortality has declined in The Netherlands by about 40%, but is still a major public health problem.¹ Further decline of coronary heart disease mortality is therefore warranted. A decline in plasma total cholesterol could have a significant impact on mortality. It is known from longitudinal studies that a plasma total cholesterol reduction of 1% results in a decrease of coronary heart disease mortality of 2-3%.² Earlier results of monitoring projects in The Netherlands between 1974 and 1992 showed that plasma total and HDL cholesterol levels were relatively stable, except for a decline in total cholesterol of 0.2 mmol/L in men aged 33-37 years in the early eighties and a decline of 0.1 mmol/L in 1991-1992 in men aged 20-59 years.^{3,4}

Nutritional and lifestyle factors affect plasma total and HDL cholesterol levels. Obesity, smoking and a high intake of saturated and trans fatty acids and dietary cholesterol increase plasma total cholesterol. Obesity, smoking and trans fatty acids decrease HDL cholesterol while physical activity, saturated fat and alcohol consumption increase HDL cholesterol.⁵⁻¹¹

The first aim of the present study is to describe trends in plasma total and HDL cholesterol in The Netherlands between 1993 and 1997. The second aim is to examine if the observed trend in total cholesterol could be explained by changes in body mass index, smoking, use of cholesterol lowering medication, intake of saturated fat, cholesterol and trans fatty acids.

Methods

Study population

The Monitoring Project on Risk Factors for Chronic Diseases (MORGEN-project) has been carried out in The Netherlands from 1993 to 1997. The general purpose of this project was to determine both the prevalence of risk factors for chronic diseases (e.g. plasma cholesterol, blood pressure and smoking habits) and the prevalence of some specific chronic conditions in a sample of the general population. The project was carried out at the municipal health services in three towns in The Netherlands: Amsterdam, Doetinchem, and Maastricht. Each year a new random sample of men and women aged 20-59 years was selected from the municipal registry of Amsterdam and Maastricht, stratified by age and sex. In Doetinchem, the study population consisted of individuals aged 26-59 years who had participated in the previous Monitoring Project on Cardiovascular Disease Risk Factors (1987-1991) and a new random sample of men and women aged 20-25 years from the municipal

registry of Doetinchem to cover the whole age range of 20-59 years.⁴ The overall response rate for the three towns was 48% in 1993, 51% in 1994, 44% in 1995 and 1996, and 40% in 1997. Each year the number of respondents from each town was about equal. In the analyses, respondents were excluded if they were pregnant (n=137) or if they had no measurements for the potential confounders (n=452). Data of in total 9773 men and 11 678 women were used for the analysis.

Measurements

The subjects who agreed to participate, received a general questionnaire and a semi-quantitative food frequency questionnaire, to fill in at home.

The general questionnaire asked for demographic variables, lifestyle factors, psycho-social factors, (family) history of diseases, medication use and (for women) reproductive history. Alcohol intake was measured with a standardised questionnaire as number of drinks per day and subsequently converted to grams of alcohol by multiplying each glass of beer, wine, or spirit with its alcohol content. Educational level, measured with a standardised questionnaire, was classified into three categories: low (intermediate secondary education or less), medium (intermediate vocational or higher secondary education) and high (higher vocational or university education). Information on cigarette smoking (current, former or never) was obtained by a standardised questionnaire. Physical activity was measured between 1994 and 1997 with an extended version of a validated physical activity questionnaire.¹² For the analyses, we classified physical activity in three categories: 1) less than 3.5 hours per week physical activity 2) more than 3.5 hours per week physical activity, of which less than 2 hours strenuous and 3) more than 3.5 hours per week physical activity, of which more than 2 hours strenuous.

The semi-quantitative food frequency questionnaire was designed to assess the habitual consumption of 178 food items during the previous year. In addition, this questionnaire provided information on the use of a prescribed diet. In 1991 and 1992, the reproducibility and relative validity of the nutrients were assessed in a validation study.¹³ Nutrient and energy intake were quantified for each individual using an extended version of the 1996 computerised Dutch food composition table.¹⁴ Because of the recent interest in trans fatty acids a food table was constructed with data on the amount of trans fatty acids in products.¹⁵ Chemical analyses were available for edible fats in 1990¹⁶, 1995^{17,18} and 1996¹⁷. In addition, cookies and pastries as well as dairy products and meats were analysed contributing to 95% of the total mean fat intake of the Dutch national survey of 1992.¹⁸ Trans fatty acid contents of fruit, vegetables, legumes, nuts, and game and offal were derived from the UK food table¹⁹ or based on some other analyses.^{20,21} The trans fatty acids content of the remaining foods was derived from recipes or deduced from other

foods. Trans fatty acid concentrations were corrected for measurement error due to the use of different methods of chemical analysis. To estimate the trans fatty acid concentration in 1993 and 1994, interpolation was done, assuming that the decline in trans fatty acid concentration was linear between 1990 and 1995. For 1997 the same food table was used as for 1996, because the assumption was made that there was no further decline in trans fatty acid concentration in this period.

During a physical examination weight and height were measured. Body mass index was calculated by dividing weight (kg) by the square of height (m²).

Total and HDL cholesterol determination

Non-fasting blood samples were obtained in all three towns using a standardised protocol. Venous blood samples were collected in vacutainers containing 7.5% tri potassium (K3) ethylenediaminetetraacetic acid (Safety-Monovette[®] tubes, Sarstedt, Tilburg, The Netherlands). More than 30 minutes after the blood collection, the samples were centrifuged at room temperature for 10 minutes at 3000 x g. After centrifugation the plasma was separated from blood cells, and stored at -20 °C. Once a week the blood samples were transported from the three towns to the laboratory in Rotterdam.

Total and HDL cholesterol determinations were performed in the Lipid Reference Laboratory (LRL) of the University Hospital Dijkzigt in Rotterdam using standardised enzymatic methods. Total cholesterol was measured using a CHOD-PAP method (Boehringer).²² HDL cholesterol was determined in the supernatant after precipitation of apoB-containing lipoproteins with phosphotungstic acid/MgCl₂ (Boehringer).²³ Although the specimen type was EDTA-plasma, results are standardised to a serum matrix. For lipid standardization, there is international consensus that CDC Reference Methods are solely used in combination with a serum matrix. Field methods may use an alternative matrix but standardization should be performed by means of a split sample comparison, against serum reference values. Accordingly, lipid levels in EDTA-plasma as measured in the present study, are traceable to serum values.

The LRL Rotterdam is a permanent member of the international Cholesterol Reference Method Laboratory Network²⁴, performing the Abell-Kendall cholesterol reference method exactly as it is performed at the Centres for Disease Control (CDC), Atlanta, Georgia, USA and being standardised to CDC through participation in the CDC-National Heart Lung and Blood Institute (NHLBI) Lipid Standardization Program. For HDL cholesterol the accuracy base at the LRL Rotterdam is the HDL cholesterol Designated Comparison Method.^{24,25} Performance for enzymatic total and HDL cholesterol measurements fulfilled National Cholesterol Education Program (NCEP) recommendations throughout the entire study period.^{24,26,27} Furthermore, the

internal quality control data of the LRL were analysed to detect whether, within the recommendations made by NCEP, there had been any laboratory drift over time that would influence the observed trend in plasma total cholesterol. For HDL cholesterol, adjustment was necessary for the period January 1993 to November 1994. During this period HDL cholesterol was determined manually and from November 1994 to December 1997 automatically. In total 40 samples were analysed with both methods. This crossover experiment was performed according to the NCCLS guideline EP9-A. HDL cholesterol levels ranged between 0.65 and 3.1 mmol/L -i.e. encompassing the NCEP cutpoints of 0.91 and 1.55 mmol/L- and the distribution was Gaussian. Consequently, slope and intercept of the calculated regression line of the method comparison are reliable and accurate. The following orthogonal regression equation was found: Y (automatic method, mmol/L) = 1.055 (manual method, mmol/L) + 0.029. Due to this change, HDL cholesterol was adjusted by +6.5% in the period January 1993 to November 1994.

Hypercholesterolemia was defined as a plasma total cholesterol concentration of 6.5 mmol/L or higher. For low HDL cholesterol the cut-off point of 0.9 mmol/L was used.²⁸

Statistical analyses

All data were age-standardised to the age distribution of the Dutch population aged 20-59 years in 1995. Univariate regression analysis was used to analyse trends over time with time (day) as independent variable and plasma total or HDL cholesterol as dependent variable. The multivariate regression analysis concerning total cholesterol was adjusted for age, town, body mass index, intake of saturated fat, intake of trans fatty acids, dietary cholesterol, education, smoking, cholesterol lowering medication, cholesterol or fat lowering diet, and (for women) use of oral contraceptives and estrogens. Intake of saturated fat and trans fatty acids was expressed as a percentage of total energy. Whether trends in total and HDL cholesterol differed between the three towns, the 10-year age categories, and the different educational levels was studied by including interaction terms in the regression models between town and day, age group and day, and educational level and day. All analyses were carried out for men and women separately. The SAS computer package (version 6.12) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, USA, 1989).

Results

Age-standardised yearly means and prevalence of high-risk levels of plasma total and HDL cholesterol for both men and women are given in table 1. The changes over time in plasma total and HDL cholesterol in both men and women are shown in figure 1. Between 1993 and 1997 there was a decrease in total cholesterol in both men and women, with the largest decline between 1994 and 1995. Consequently, the prevalence of hypercholesterolemia also decreased in men and women during this period. The concentration of HDL cholesterol remained almost stable from 1993 to 1997 in men and women and the prevalence of a low HDL cholesterol level (< 0.9 mmol/L) declined somewhat.

No significant differences were found in trends over time between the three towns, between 10-year age categories or between the different educational levels. Only for women aged 50-59 years the decline in plasma total cholesterol was significantly larger than in the other age categories.

In table 2 the changes in determinants of total and HDL cholesterol are shown. Between 1993 and 1997 the intake of trans fatty acids decreased significantly by 0.4 percent of energy in both men and women. The intake of saturated fat decreased significantly by 0.4 percent of energy in men and 0.5 percent of energy in women. The intake of cholesterol decreased significantly by 0.6 mg/MJ in men and 1.9 mg/MJ in women. The use of cholesterol lowering medication increased significantly by 1.5% in men and 0.4% in women. The use of oral contraceptives increased significantly by 3.0 % and prescribed estrogens increased significantly by 1.3%.

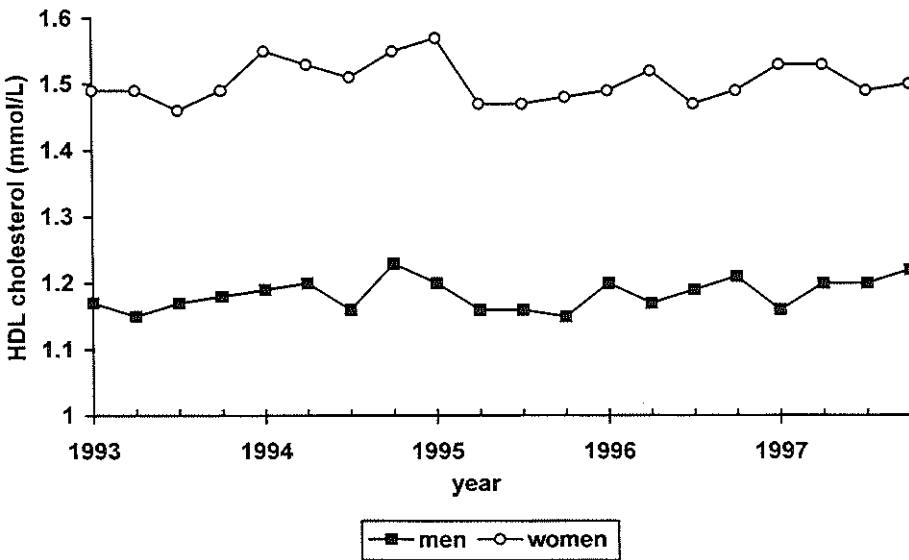
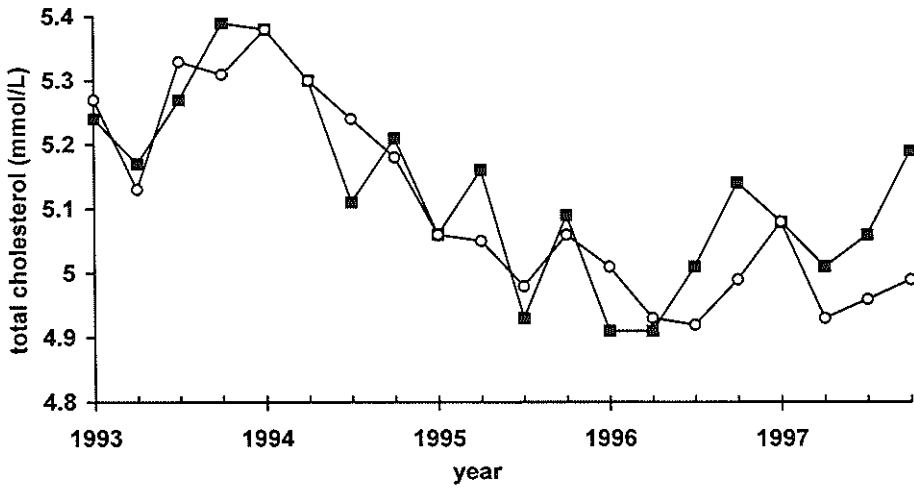


Figure 1 Mean plasma total and HDL cholesterol level per quarter in men and women, standardised for the age distribution of the Dutch population aged 20-59 years in 1995.

Table 1 Mean, standard deviation (sd) and prevalence of high-risk levels of plasma total and HDL cholesterol per year in men and women aged 20-59 years (standardised for the age distribution of the Dutch population aged 20-59 years in 1995).

	1993	1994	1995	1996	1997	p-trend
Men						
N	2,155	1,816	2,106	2,015	1,681	
total cholesterol (mmol/L)	5.27 (1.10)	5.25 (1.05)	5.06 (1.09)	4.99 (1.08)	5.08 (1.05)	< 0.001
total cholesterol \geq 6.5 mmol/L (%)	12.3	12.2	10.4	8.2	9.8	< 0.001
HDL cholesterol (mmol/L)	1.17 (0.29)	1.20 (0.30)	1.17 (0.29)	1.19 (0.29)	1.19 (0.30)	0.1
HDL < 0.9 mmol/L (%)	16.7	14.6	16.0	14.0	12.6	< 0.001
Women						
N	2,639	2,031	2,446	2,417	2,145	
total cholesterol (mmol/L)	5.26 (1.03)	5.27 (1.02)	5.04 (1.01)	4.96 (0.93)	4.99 (0.99)	< 0.001
total cholesterol \geq 6.5 mmol/L (%)	12.4	11.8	8.1	6.2	7.6	< 0.001
HDL cholesterol (mmol/L)	1.48 (0.36)	1.54 (0.37)	1.50 (0.38)	1.49 (0.35)	1.52 (0.36)	0.2
HDL < 0.9 mmol/L (%)	3.4	2.0	2.7	2.3	2.3	< 0.05

Table 2a Mean, standard deviation (sd) and prevalence of determinants per year in men aged 20-59 years (standardised for the age distribution of the Dutch population aged 20-59 years in 1995).

	1993	1994	1995	1996	1997	p-trend
N	2,155	1,816	2,106	2,015	1,681	
Classical CHD determinants:						
current smoker (%)	37.0	39.6	37.1	36.3	40.1	0.7
ex smoker (%)	28.0	27.0	28.2	27.6	26.1	
never smoker (%)	35.0	33.4	34.7	36.1	33.8	
BMI (kg/m ²)	25.0 (3.4)	25.1 (3.4)	25.0 (3.7)	25.0 (3.6)	25.1 (3.6)	0.6
alcohol intake (g/day)*	17.2 (20.0)	17.0 (20.7)	17.7 (22.6)	16.3 (18.8)	17.1 (18.8)	0.5
low activity (%)	-	43.7	43.0	42.4	43.6	0.9
medium activity (%)	-	35.8	34.9	36.2	36.6	
high activity (%)	-	20.5	22.1	21.4	19.9	
Diet:						
saturated fat (percent of energy)	15.5 (2.4)	15.3 (2.5)	15.2 (2.5)	15.1 (2.4)	15.1 (2.4)	< 0.001
trans fatty acids (percent of energy)	2.2 (0.7)	2.2 (0.7)	2.0 (0.6)	1.8 (0.5)	1.8 (0.5)	< 0.001
PUFA's (percent of energy)	7.3 (1.8)	7.2 (1.8)	7.3 (1.8)	7.2 (1.8)	7.3 (1.8)	0.4
cholesterol (mg/MJ)	25.2 (6.7)	25.4 (7.1)	25.1 (7.0)	24.8 (7.1)	24.6 (7.0)	< 0.001
cholesterol/fat lowering diet (%)	1.9	1.5	2.2	1.2	2.1	0.9
Other factors:						
low education (%)	43.9	41.8	38.6	38.3	35.1	< 0.001
medium education (%)	31.3	34.4	34.2	35.0	33.3	
high education (%)	24.8	23.8	27.2	26.7	31.7	
cholesterol medication (%)	0.7	1.0	1.0	1.3	2.2	< 0.001

* among the total population

Chapter 2

Table 2b Mean, standard deviation (sd) and prevalence of determinants per year in women aged 20-59 years (standardised for the age distribution of the Dutch population aged 20-59 years in 1995).

	1993	1994	1995	1996	1997	p-trend
N	2,639	2,031	2,446	2,417	2,145	
Classical CHD determinants:						
current smoker (%)	36.4	39.0	37.9	37.9	35.8	0.3
ex smoker (%)	24.9	25.3	23.6	24.2	24.3	
never smoker (%)	38.7	35.7	38.5	37.9	39.9	
BMI (kg/m ²)	24.4 (4.1)	24.3 (4.2)	24.1 (4.0)	24.4 (4.2)	24.4 (4.3)	0.9
alcohol intake (g/day)*	7.1 (11.2)	7.3 (10.8)	7.6 (11.3)	7.3 (10.7)	7.8 (11.0)	< 0.1
low activity (%)	-	48.1	46.1	44.5	45.0	0.07
medium activity (%)	-	39.1	40.8	42.5	41.7	
high activity (%)	-	12.8	13.1	12.9	13.3	
Diet:						
saturated fat (percent of energy)	15.5 (2.5)	15.3 (2.7)	15.1 (2.6)	15.0 (2.6)	15.0 (2.6)	< 0.001
trans fatty acids (percent of energy)	2.2 (0.7)	2.2 (0.7)	2.0 (0.6)	1.8 (0.5)	1.8 (0.5)	< 0.001
PUFA's (percent of energy)	7.1 (1.7)	7.2 (1.7)	7.2 (1.7)	7.2 (1.8)	7.3 (1.8)	< 0.01
cholesterol (mg/MJ)	26.3 (6.8)	25.9 (7.2)	25.5 (7.1)	25.1 (6.7)	24.4 (7.0)	< 0.001
cholesterol/fat lowering diet (%)	2.8	3.3	3.2	3.1	3.4	0.3
Other factors:						
low education (%)	53.4	50.6	44.6	44.8	42.1	< 0.001
medium education (%)	27.9	30.7	30.2	31.2	31.7	
high education (%)	18.7	18.7	25.2	24.0	26.3	
cholesterol medication (%)	0.4	0.5	0.5	0.8	0.8	0.02
use of oral contraceptives (%)	32.8	35.3	37.0	37.2	35.8	< 0.01
use of estrogens (%)	2.6	3.7	3.0	3.4	3.9	0.04

* among the total population

Table 3 Regression coefficients (β) and 95% confidence intervals for changes in plasma total cholesterol over time, based on age-standardised data, from univariate and multivariate^a regression models.

	men		women	
	univariate β (95% CI) (mmol/L/year)	multivariate* β (95% CI) (mmol/L/year)	univariate β (95% CI) (mmol/L/year)	multivariate* β (95% CI) (mmol/L/year)
total cholesterol	-0.062 [†] (-0.077;-0.047)	-0.060 [†] (-0.074;-0.046)	-0.084 [†] (-0.097;-0.072)	-0.075 [†] (-0.087;-0.063)

* adjusted for age, town, body mass index, intake of saturated fat, intake of trans fatty acids, dietary cholesterol, education, smoking, cholesterol lowering medication, cholesterol or fat lowering diet and (for women) use of oral contraceptives and estrogens

[†] p < 0.001

Multivariate regression models were used to examine if the changes in the determinants mentioned above could explain the trend in plasma total cholesterol (table 3). In men, the univariate and multivariate regression coefficient for the change in total cholesterol was comparable. The multivariate regression coefficient in women was somewhat lower than the univariate coefficient for the change in total cholesterol, but still significant. This means that the observed trend in total cholesterol could only for a small part be explained by changes in the determinants studied. The multivariate regression coefficients for the most important determinants of total cholesterol are given in table 4.

Discussion

The plasma total cholesterol level and the prevalence of hypercholesterolemia decreased significantly between 1993 and 1997 in men and women. The HDL cholesterol level remained stable during this period. The observed trend in total cholesterol in men and women could only for a small part be explained by changes in the determinants studied, like intake of saturated fat, trans fatty acids, dietary cholesterol, use of cholesterol lowering medication and for women use of oral contraceptives and prescribed estrogens.

Table 4 Multivariate* regression coefficients (β) and 95% confidence intervals for determinants of total cholesterol.

	men		women	
	β	95% CI	β	95% CI
age (year)	0.036	0.034;0.038	0.041	0.039;0.043
ex smoking (yes/no)	-0.00076	-0.00026;-0.0013	-0.0010	-0.00059;-0.0015
never smoking (yes/no)	-0.0012	-0.00074;-0.0017	-0.00051	-0.00090;-0.00013
BMI (kg/m ²)	0.059	0.053;0.065	0.023	0.018;0.027
saturated fat (percent of energy)	0.020	0.0097;0.030	0.019	0.010;0.027
trans fatty acids (percent of energy)	0.012	-0.025;0.049	-0.010	-0.044;0.023
cholesterol (mg/MJ)	0.0015	-0.0016;0.0046	-0.00073	-0.0034;0.0020

* adjusted for the other variables in the table and town, body mass index, education, cholesterol lowering medication, cholesterol or fat lowering diet and (for women) use of oral contraceptives and estrogens

The response rate ranged from 48% in 1993 to 40% in 1997. Each year, a small non-response survey was carried out. Plasma cholesterol levels could not be measured in non-responders, so educational level, an important determinant of non-response and associated with biological determinants like cholesterol level and blood pressure, was used to assess possible selection bias.^{29,30} From the non-response surveys it can be concluded that people with a lower level of education are possibly under-represented in the MORGEN-project. Furthermore, the number of respondents with a high level of education increased while the number of respondents with a low level of education decreased during the study period in both men and women. This change in level of education can be due to the declining response rate between 1993 and 1997 but can also be the result of the known increase in the level of education of the general Dutch population. However, we included level of education in our multivariate model so educational level cannot explain the trend in total cholesterol.

Previous monitoring projects carried out in The Netherlands between 1974 and 1992 showed almost no changes in plasma total and HDL cholesterol, except a decline in total cholesterol of 0.2 mmol/L in men aged 33-37 years in the early eighties and a decline of 0.1 mmol/L in 1991-1992 in men aged 20-59 years.^{3,4} In the present study however, plasma total cholesterol decreased significantly by 0.19 mmol/L in men and by 0.27 mmol/L in women in the relatively short period between

1993 and 1997. HDL cholesterol remained stable in both men and women. Results from the Zutphen Elderly Study showed a decline in serum total cholesterol of similar magnitude in Dutch men aged 70 years and older in the early nineties as observed in our study.³¹ Therefore, a decline in total cholesterol levels seems to be generalizable to the total Dutch population.

Saturated fat is one of the most important dietary factors that influence plasma total cholesterol.^{8,9} Between 1993 and 1997 a small, but significant, decline was observed in the intake of saturated fat in both men and women. The intake of polyunsaturated fat remained stable in men and increased in women whereas dietary cholesterol declined in both men and women. Using the equation of Keys et al.³², a decline in mean plasma total cholesterol of 0.03 mmol/L in men and 0.06 mmol/L in women from 1993 to 1997 was predicted based on the change in the intake of saturated fat, polyunsaturated fat and dietary cholesterol during this period.

Trans fatty acids from the diet also increase plasma total cholesterol.^{9,11} Since 1985, the trans fatty acid content of margarines and spreads has substantially declined in The Netherlands.^{15,33} In the present study a significant decline was observed in the intake of trans fatty acids in men and women between 1993 and 1997. Mensink and Katan¹¹ estimated that each additional percent of dietary energy as trans fatty acids results in an increase in total cholesterol of 0.026 mmol/L. Extrapolated to this study, the observed change in trans fatty acid intake would lead to a decline in mean total cholesterol of 0.01 mmol/L in both men and women between 1993 and 1997. This means that the change in the intake of the dietary determinants would result in a decline in total cholesterol of 0.04 mmol/L (20%) in men and 0.07 mmol/L (29%) in women.

The reproducibility and relative validity of the nutrients, like total fat intake, was assessed in a validation study and seemed to be adequate.¹³ This was not investigated for saturated fat and trans fatty acids. Random misclassification of dietary exposure, due to error in the quantification of saturated fat and trans fatty acids, cannot be excluded. However, using the equation of Keys, it can be calculated that a decline in the intake of saturated fat of almost 3 percent of energy in men and 4 percent of energy in women would be needed for a reduction of total cholesterol by 0.19 mmol/L in men and 0.27 mmol/L in women. This calculated decline in saturated fat is about ten times higher than the real decline observed in this study. It is therefore unlikely that misclassification of saturated fat explains the findings of this study.

In our study the use of cholesterol lowering medication, mostly statins, increased significantly by 1.5% in men and 0.4% in women. In a meta-analysis of randomised

Chapter 2

clinical trials it was estimated that persons who used statins had a 20% lower total cholesterol level compared with persons not using such cholesterol lowering medication after a mean follow-up period of 5 years.³⁴ This observed change in the use of cholesterol lowering medication would in our population lead to a decline in total cholesterol of 0.02 mmol/L in men and 0.004 mmol/L in women.

The observed trend in plasma total cholesterol could only for a small part be explained by changes in the determinants studied, like trans fatty acids, saturated fat, dietary cholesterol, use of cholesterol lowering medication and for women use of oral contraceptives and estrogens. Including these determinants and the variables age, town, body mass index, education, smoking and diet in the regression models only slightly changed the coefficients for change in total cholesterol over time. It is unclear which (other) factors are responsible for the trend.

In many other countries cholesterol levels have also declined during the last decades. In the WHO MONICA Project, carried out in 38 populations in 21 countries, the mean total cholesterol level declined by 0.008 mmol/L per year in men and 0.015 mmol/L per year in women between 1985 and 1995.³⁵ In the WHO MONICA Project dietary data were only collected in subsamples of some of the populations studied. The most important determinants of population changes in total cholesterol could therefore not be studied. In Finland a declining trend in serum total cholesterol is observed since 1972. Serum total cholesterol decreased by 0.9 mmol/L in men and by 1.2 mmol/L in women aged 30 to 59 years between 1972 and 1992³⁶, which seemed to be explained by dietary changes. The intake of polyunsaturated fatty acids increased by 2 percent of energy, saturated fat decreased by 5 percent of energy and dietary cholesterol decreased by about 25 mg/1000 kcal in both men and women. The expected decline in total cholesterol based on these dietary changes would be 0.6 mmol/L. A change from boiled to filtered coffee could have declined the cholesterol levels by another 0.3 mmol/L. This means that dietary changes fully explained the decline in total cholesterol in men. In women the decrease in weight was also an important determinant in addition to the dietary changes.³⁷

In the United States the mean serum total cholesterol level declined by 0.2 mmol/L and HDL cholesterol slightly increased by 0.03 mmol/L between 1976 and 1991 in men and women aged 20-74 years.³⁸ This change was fully explained by changes in the intake of polyunsaturated fatty acids, saturated fat and dietary cholesterol.³⁹

The decline in plasma total cholesterol by 4% in men and 5% in women between 1993 and 1997 in The Netherlands could only for a small part be explained by changes in trans fatty acids, saturated fat, dietary cholesterol and use of cholesterol

lowering medication. A decline in total cholesterol of this magnitude is of great public health importance because it could lead to a decline in mortality of coronary heart disease of about 8-15% in the future.²

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Chapter 2

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CHAPTER 3

Smoking and elevated blood pressure at low, medium and high serum cholesterol levels and 20-year mortality in men and women aged 30-54

Abstract

Objective. Few studies have examined the effect of smoking and/or blood pressure conditional on cholesterol levels. We investigated the additional effect of smoking and elevated blood pressure at different total cholesterol levels on mortality risk in middle-aged men and women.

Methods. Men and women aged 30-54 were examined and followed for on average 20 years. Several risk factor profiles were defined according to levels of total cholesterol, systolic blood pressure and smoking. Age-adjusted relative risks for mortality from coronary heart disease (CHD), cardiovascular diseases (CVD) and all-causes were estimated for these risk factor profiles.

Results. Given a low cholesterol level (< 5.2 mmol/L) the impact of smoking on CHD, CVD and all-cause mortality was larger than that of elevated blood pressure (systolic ≥ 140 mmHg). A low cholesterol level in combination with both elevated blood pressure and smoking was associated with relative risks for CHD, CVD and all-cause mortality of 3.0 (95% CI 1.1-8.8), 6.0 (2.4-14.9) and 4.1 (2.7-6.3) respectively in men and 2.3 (0.6-8.6), 3.6 (1.8-7.1) and 2.6 (2.0-3.5) respectively in women. An elevated cholesterol level (≥ 6.50 mmol/L) in combination with elevated blood pressure and smoking was associated with relative risks for CHD, CVD and all-cause mortality of respectively 9.7 (3.6-26.7), 13.9 (5.7-34.0) and 5.7 (3.7-8.6) respectively in men and 15.9 (5.6-44.8), 9.3 (4.8-17.8) and 4.3 (3.1-5.8) respectively in women.

Conclusion. Even at low cholesterol level smoking in combination with elevated blood pressure is associated with an increased risk of CHD, CVD and all-cause mortality. This highlights the potential power an integrated approach of risk factor reduction.

Introduction

It is well known from prospective studies that total cholesterol, blood pressure, and smoking are independent risk factors for mortality from coronary heart disease (CHD) and cardiovascular diseases (CVD) in middle-aged men and women.¹⁻⁵ Several studies have examined the effect of combinations of these risk factors on cause-specific and all-cause mortality and showed that risk increased with each additional risk factor.^{6,7} Few studies have examined the effect of smoking and/or blood pressure conditional on cholesterol levels. Stamler et al.⁸ examined the effect on long-term cause-specific and all-cause mortality of elevated risk factor levels compared to a low risk factor profile (defined as serum cholesterol < 5.17 mmol/L, blood pressure \leq 120/80 mmHg, no smoking and no history of diabetes or MI). CHD death rates were 77% to 92% lower in persons with a low risk factor profile compared to all others combined.

Since it is not realistic to expect a population in which everyone has a low risk factor profile, for public health implications it is interesting to know for example the additional effect of smoking and/or elevated blood pressure at different cholesterol levels. A prospective cohort study carried out in Korean men aged 35-59 years showed that having a low cholesterol level was not protective against the harmful effects of smoking on CHD.⁹ It has not yet been studied whether elevated blood pressure alone or in combination with smoking increases mortality risk of CHD and CVD at low cholesterol levels.

A large population-based study with a mean follow-up of 20 years carried out in about 50,000 persons aged 30 to 54 provided us with the opportunity to examine the effect of smoking and/or elevated blood pressure at different total cholesterol levels on CHD, CVD and all-cause mortality in both men and women.

Methods

Study population

The Consultation Bureau Project on Cardiovascular Diseases was carried out from 1974 to 1980 in five towns in The Netherlands: Amsterdam, Doetinchem, Maastricht, Leiden, and Tilburg. Different birth cohorts were selected in different towns. Names and addresses of the participants were obtained from the municipal registries. About 50,000 men and women were examined. The response rate ranged from 70 to 80%.¹⁰ The project was aimed primarily at the age group of around 40 years, but in some towns a wider age range was taken. The age range of the

population examined was 30 to 54 years, with about 75% aged between 35 and 44 years.

Measurements

The participants filled out a questionnaire in which information was obtained about smoking habits, use of anti-hypertensive medication, cardiovascular complaints and history of myocardial infarction, stroke, hypertension, and diabetes mellitus. Weight and height were measured and body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured once while subjects were seated with a random-zero sphygmomanometer placed on the right upper arm.¹¹ A non-fasting blood sample was taken in which total cholesterol was measured (with an accuracy of 0.1 mmol/L) at the Central Clinical Chemistry Laboratory of the University Hospital Dijkzigt in Rotterdam. This laboratory participated in the standardisation programme of the World Health Organisation (WHO). Total cholesterol was determined according to a direct Liebermann-Burchard method.^{12,13} These cholesterol values were converted to enzymatic values as described before.¹³

Mortality follow-up

The mortality follow-up lasted until January 1, 2000. Information about the vital status was obtained from the municipal population registry in the town of residence. If a person had moved with unknown destination, the date on which the person's name was removed from the municipal population register was used as censor date. For 49,153 persons mortality follow-up was successfully completed, resulting in a loss to follow-up of 3.4%. The total number of person years was almost 480,000 in men and almost 535,000 in women. The mean (sd) duration of follow-up was 20.4 (3.8) years for men and 20.8 (3.3) years for women. A total of 4,186 persons had died. For 4,065 persons, the primary cause of death was obtained from the Central Bureau of Statistics, while for 121 persons such information could not be obtained.

Causes of death were coded according to the ninth revision of the International Classification of Diseases (ICD-9) for deaths that occurred before January 1, 1996 (65%) and according to the tenth revision (ICD-10) for deaths that occurred from January 1, 1996 onwards (35%). Coronary heart disease was defined as ICD-9 codes 410-414 or ICD-10 codes I20-I25. Cardiovascular diseases were defined as ICD-9 codes 390-459 or ICD-10 codes I00-I99.

Statistical analysis

Several risk factor profiles were defined based on levels of total cholesterol, systolic blood pressure and smoking. Cholesterol levels were divided into three

Chapter 3

categories: < 5.20 mmol/L, 5.20-6.49 mmol/L and \geq 6.50 mmol/L. Systolic blood pressure was also divided into three categories: < 120 mmHg, 120-139 mmHg and \geq 140 mmHg. Smoking was dichotomised (yes/no). Absence of all major risk factors, defined as total cholesterol < 5.2 mmol/L, systolic blood pressure < 120 mmHg and no smoking, was the reference category for all analyses and will be referred to as the 'low risk factor profile'. Age-adjusted relative risks (RRs) were estimated using the Cox proportional hazards model. Subjects with diabetes (n=661) and prevalent cases of angina, stroke, and/or myocardial infarction (n=1,304) were excluded. The scope of this article was to investigate the additional effect of smoking and elevated blood pressure at different cholesterol levels. Results on six risk factor profiles are presented (see table 1). These risk factor profiles are: 1) no elevated risk factors (low risk factor profile; total cholesterol < 5.20 mmol/L, systolic blood pressure < 120 mmHg and no smoking), 2) one risk factor at low cholesterol level (< 5.20 mmol/L): elevated blood pressure (\geq 140 mmHg), 3) one risk factor at low cholesterol level: smoking, 4) two risk factors at low cholesterol level: elevated blood pressure and smoking, 5) two risk factors at medium cholesterol level (5.20-6.49 mmol/L): elevated blood pressure and smoking, 6) three risk factors (high risk factor profile; total cholesterol \geq 6.50 mmol/L, elevated blood pressure and smoking). No significant interactions were observed between the different risk factor profiles, age and use of anti-hypertensive medication.

The SAS computer package (version 6.12) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, USA, 1989).

Results

In total 3% of the men and 12% of the women had a low risk factor profile and 5% of the men and 1% of the women had a high risk factor profile (table 1). About 3% of the men and women with a low risk factor profile died during 20 years of follow-up, compared to 23% of the men and 19% of the women with a high risk factor profile.

The difference between men and women with a low risk factor profile versus men and women with a high risk factor profile was for total cholesterol almost 3.0 mmol/L, for systolic blood pressure more than 40 mmHg, for diastolic blood pressure about 20 mmHg and for body mass index more than 3 kg/m².

For the low risk factor category and the category 'low cholesterol level, elevated blood pressure and no smoking', mortality rates were comparable in men and women (table 2a and table 2b). For the other four risk factor categories CHD, CVD and all-cause mortality rates were higher in men compared to women. The mortality

Table 1 Mean, standard deviation and prevalences of risk factors in men and women aged 30-54 years according to the different risk factor profiles.

	chol < 5.2 SBP < 120 no smoking	chol < 5.2 SBP ≥ 140 no smoking	chol < 5.2 SBP < 120 smoking	chol < 5.2 SBP ≥ 140 smoking	chol 5.2-6.5 SBP ≥ 140 smoking	chol ≥ 6.5 SBP ≥ 140 smoking
Men						
N (% of the total study population)	728 (3%)	757 (3%)	1,333 (6%)	1,134 (5%)	1,793 (8%)	1,107 (5%)
number of CHD events	3	4	12	23	75	73
number of CVD events	4	8	22	57	115	133
number of events total	23	35	125	182	308	250
age (years)	37.3 (4.1)	38.7 (4.3)	38.1 (4.1)	39.4 (4.7)	40.1 (4.5)	40.4 (4.2)
total cholesterol (mmol/L)	4.43 (0.51)	4.58 (0.44)	4.45 (0.51)	4.60 (0.45)	5.80 (0.36)	7.29 (0.74)
systolic blood pressure (mmHg)	111.8 (5.8)	152.3 (10.9)	111.2 (6.0)	152.0 (11.0)	153.4 (11.7)	154.6 (12.0)
diastolic blood pressure (mmHg)	72.1 (8.3)	90.0 (10.8)	70.3 (8.0)	88.5 (11.3)	90.3 (11.1)	92.1 (10.5)
BMI (kg/m ²)	22.9 (2.5)	25.0 (3.1)	22.4 (2.5)	24.5 (3.2)	25.4 (3.2)	26.1 (3.3)
Women						
N (% of the total study population)	2,867 (12%)	1,148 (5%)	2,560 (10%)	794 (3%)	855 (4%)	355 (1%)
number of CHD events	5	6	10	4	10	14
number of CVD events	15	12	23	19	34	25
number of events total	96	72	131	86	101	68
age (years)	37.5 (3.9)	41.2 (4.6)	37.5 (3.7)	40.0 (4.0)	40.8 (4.1)	41.7 (4.5)
total cholesterol (mmol/L)	4.40 (0.51)	4.53 (0.46)	4.42 (0.51)	4.52 (0.48)	5.77 (0.36)	7.32 (0.94)
systolic blood pressure (mmHg)	109.6 (6.9)	153.1 (12.7)	109.0 (7.0)	152.6 (12.0)	152.9 (11.5)	153.7 (11.2)
diastolic blood pressure (mmHg)	70.3 (7.6)	88.9 (10.3)	68.7 (7.6)	89.4 (10.4)	90.3 (9.8)	91.8 (11.2)
BMI (kg/m ²)	22.3 (2.8)	25.6 (4.5)	22.1 (2.8)	24.6 (4.4)	25.3 (4.3)	25.9 (4.0)

Table 2 Mortality rates per 10,000 person years and relative risks* (95% confidence intervals) for mortality from coronary heart disease (CHD), cardiovascular disease (CVD) and all causes according to the different risk factor profiles in men and women aged 30-54 years.

	CHD mortality		CVD mortality		All-cause mortality	
	Mortality rate per 10,000 py	RR (95% CI)	Mortality rate per 10,000 py	RR (95% CI)	Mortality rate per 10,000 py	RR (95% CI)
Men						
chol < 5.2 / SBP < 120 / no smoking	2.0	1.00	2.7	1.00	15.3	1.00
chol < 5.2 / SBP ≥ 140 / no smoking	2.5	0.83 (0.21-3.31)	5.1	1.32 (0.43-4.03)	22.3	1.23 (0.73-2.06)
chol < 5.2 / SBP < 120 / smoking	4.4	1.57 (0.51-4.85)	8.1	2.28 (0.87-6.03)	45.9	2.75 (1.78-4.25)
chol < 5.2 / SBP ≥ 140 / smoking	10.0	3.04 (1.05-8.80)	24.8	5.96 (2.39-14.9)	79.1	4.09 (2.67-6.26)
chol 5.2-6.5 / SBP ≥ 140 / smoking	20.8	5.98 (2.18-16.4)	31.9	7.22 (2.95-17.7)	85.3	4.17 (2.75-6.33)
chol ≥ 6.5 / SBP ≥ 140 / smoking	33.5	9.73 (3.55-26.7)	61.0	13.9 (5.69-34.0)	114.7	5.65 (3.71-8.59)
Women						
chol < 5.2 / SBP < 120 / no smoking	0.8	1.00	2.5	1.00	16.2	1.00
chol < 5.2 / SBP ≥ 140 / no smoking	2.5	2.05 (0.62-6.80)	5.0	1.35 (0.63-2.90)	29.8	1.35 (0.99-1.84)
chol < 5.2 / SBP < 120 / smoking	1.9	2.31 (0.79-6.77)	4.4	1.77 (0.92-3.39)	24.8	1.54 (1.18-2.00)
chol < 5.2 / SBP ≥ 140 / smoking	2.4	2.30 (0.62-8.59)	11.4	3.61 (1.83-7.12)	51.8	2.64 (1.97-3.53)
chol 5.2-6.5 / SBP ≥ 140 / smoking	5.7	5.12 (1.74-15.1)	19.3	5.73 (3.10-10.6)	57.3	2.78 (2.10-3.69)
chol ≥ 6.5 / SBP ≥ 140 / smoking	19.3	15.9 (5.62-44.8)	34.5	9.28 (4.84-17.8)	93.9	4.25 (3.10-5.81)

* adjusted for age and use of anti-hypertensive medication and excluding prevalent CVD cases and diabetes

rates in persons with the low risk factor profile were very low, i.e. 3 per 10,000 person-years for CVD mortality in men and women. These were in sharp contrast to the CVD mortality rates in persons with the high risk factor profile, i.e. 61 per 10,000 person-years in men and 35 per 10,000 person-years in women.

Relative risks for the relation between the different risk factor profiles and CHD, CVD and all-cause mortality are shown in table 2a for men and in table 2b for women. At low cholesterol levels, in the absence of smoking, elevated blood pressure increased the relative risk of CVD and all-cause mortality by about 30% compared to the low risk factor profile. At low cholesterol levels, in the absence of elevated blood pressure, smoking increased the relative risks for CHD, CVD and all-cause mortality by approximately 100%. Men with a low cholesterol level, who smoked and had elevated blood pressure had a significantly higher risk of CHD mortality (RR=3.0), CVD mortality (RR=6.0) and all-cause mortality (RR=4.1) compared to men with a low risk factor profile. For women these relative risks were somewhat lower, 2.3 for CHD mortality, 3.6 for CVD mortality and 2.6 for all-cause mortality.

Men with intermediate cholesterol levels (total cholesterol 5.2-6.5 mmol/L), elevated blood pressure and who smoked had a six times higher risk of CHD mortality, a seven times higher risk of CVD mortality and a four times higher risk of all-cause mortality compared to men with a low risk factor profile. In women, these relative risks were also somewhat lower, i.e. 5.1 for CHD mortality, 5.7 for CVD mortality and 2.8 for all-cause mortality. The highest relative risks were found for men and women with elevated levels for all three risk factors. In men with high cholesterol levels, elevated blood pressure and who smoked the relative risk was 9.7 for CHD mortality, 13.9 for CVD mortality and 5.7 for all-cause mortality. In women, these relative risks were 15.9, 9.3 and 4.3 respectively.

Discussion

The results of the present study show that a low risk factor profile leads to very low mortality rates and, surprisingly, to similar rates in men and women. Given a low cholesterol level, the additional effect of smoking on CHD, CVD and all-cause mortality was larger compared to the additional effect of elevated blood pressure. Despite low cholesterol levels, a significantly higher risk of CHD, CVD and all-cause mortality was found in smoking men and women with elevated blood pressure. When elevated blood pressure and smoking were accompanied by intermediate cholesterol levels, these mortality risks increased further. The highest relative risks were

observed in smoking men and women with high cholesterol levels and elevated blood pressure.

We found similar mortality rates in men and women with a low risk factor profile and in non-smoking men and women with a low cholesterol level and elevated blood pressure. This is a surprising finding compared to other studies that examined the effect of different risk factor profiles on mortality.^{6,8} In these American studies, higher CHD, CVD and all-cause mortality rates were observed when men and women with a low risk factor profile were compared.^{6,8} In all those studies the number of deaths in the low risk category was small. A definite statement about differences in mortality rates between men and women with a low risk factor profile can therefore not be made.

We are not aware of other studies that focused on the additional effect of elevated blood pressure given a low cholesterol level. The present study showed that the relative risks for CHD, CVD and all-cause mortality were not significantly different from 1.00 in non-smoking men and women with a low cholesterol level and elevated blood pressure. Although not statistically significant, the risk of CVD and all-cause mortality was about 20-30% higher in both men and women compared to those with a low risk factor profile. The blood pressure values used in the present study were based on a single measurement and not on the average of two readings at one visit. This has led to an underestimation of the relative risks in the present study.

The effect of smoking was stronger than the effect of elevated blood pressure in men and women with a low cholesterol level, as shown by the differences in relative risks. The relative risks for CVD and all-cause mortality in smokers with low cholesterol and blood pressure levels were larger in men compared to women. A prospective study carried out in Korean men aged 35 to 59 years investigated smoking as an independent risk factor for cardiovascular diseases in a population with low cholesterol levels.⁹ They found that smoking men with a serum cholesterol level < 4.42 mmol/L had a relative risk of 3.3 (95% CI 1.7-6.2) for CHD and 1.6 (95% CI 1.2-2.3) for CVD. This indicates that having a low cholesterol level did not protect against the harmful effects of smoking in Korean men. The results of the present study are in line with those of the Korean study. The relative risks found in the present study were 1.8 (95% CI 0.8-4.0) for CHD mortality and 1.8 (95% CI 1.1-3.1) for CVD mortality in men and women combined. The relative risk for CHD in our study was somewhat lower than that found in the Korean study, but the relative risks for CVD were similar in both studies. These results suggest that smokers are at elevated risk for CHD and CVD, even at low cholesterol levels.

Several studies have investigated the effect of combinations of risk factors on mortality, but most studies examined the effect of the number of risk factors regardless of the combination of risk factors. Lowe et al.⁶ studied the effect on CHD and all-cause mortality of a high risk profile (consisting of total cholesterol ≥ 6.20 mmol/L; SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or use of anti-hypertensive medication; and current smoking) compared to a low risk factor profile. The relative risk for CHD mortality was 6.73 (95% CI 3.70-12.25) for men compared to 9.73 (95% CI 3.55-26.7) in the present study. For women, the relative risk was 8.92 (95% CI 3.58-22.26) compared to 15.9 (95% CI 5.62-44.8) in the present study. The most likely explanation for the higher relative risks observed in the present study is that the men and women in our study were about 10 years younger at the time of examination. It is known from several studies that the relative risk is higher the younger the age at examination.^{4,14} Besides this, the cut-off point for total cholesterol in the present study was 6.5 mmol/L compared to a cut-off point of 6.2 mmol/L in the study of Lowe et al.⁶ It is therefore not surprising that higher relative risks were found in our study, because the higher the cholesterol level, the higher the risk of coronary heart disease death

Because only a single measurement of total cholesterol and blood pressure was taken, the relative risks in the present study will be underestimated. A single baseline measurement is subject to random fluctuations, due to both measurement error and biological variation of cholesterol or blood pressure levels in individuals over time.¹⁶ Clarke et al.¹⁷ found that studies with a follow-up of about 20 years underestimate the relative risks of elevated cholesterol and systolic blood pressure separately with about 50%. If this regression dilution ratio would also apply to a combination of risk factors (in which cholesterol, systolic blood pressure and also smoking is included), correcting the regression coefficients obtained in the present study for regression dilution bias would lead to a relative risk of CHD mortality for men with a high risk factor profile of 30.4 ($9.73^{1.5}$). For women with a high risk factor profile, the corrected relative risk of CHD mortality would be 63.4 ($15.9^{1.5}$). This emphasises the impact that a favourable risk profile can have on mortality.

We can conclude that for a low cholesterol level with one additional risk factor, the effect of smoking is more harmful than the effect of elevated blood pressure. A low or intermediate cholesterol level in combination with both elevated blood pressure and smoking is associated with significantly elevated risks for CHD, CVD and all-cause mortality. When high cholesterol levels accompanied by both smoking and elevated blood pressure were adjusted for regression dilution bias, the risk of CHD mortality

Chapter 3

was 30 times higher in men and 63 times higher in women compared to those having neither of these three risk factors. This highlights the importance of combinations of the classical risk factors in CHD and CVD mortality prevention.

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Smoking and elevated blood pressure at different cholesterol levels

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CHAPTER 4

Serum cholesterol is a risk factor for myocardial infarction in elderly men and women: the Rotterdam Study

Abstract

Objective. To investigate the associations of serum total and HDL cholesterol with the risk of myocardial infarction in men and women of 55 years and over.

Methods. The Rotterdam Study is a population-based prospective cohort study. In total 2,453 men and 3,553 women of 55 years and older were included in this study. The mean duration of follow-up was 4 years. Relative risks were estimated with Cox's proportional-hazard analysis. Cholesterol was analysed as a continuous variable and in sex-specific quartiles.

Results. In subjects aged 55 years and older the relative risk of myocardial infarction was 1.9 in men (95% confidence interval 1.1-3.3) and 3.2 in women (1.5-6.4) in the highest compared to the lowest serum total cholesterol quartile (Q4 vs. Q1). In men and women of 70 years and older, total cholesterol remained an important risk factor for myocardial infarction (Q4 vs. Q1 relative risk 3.2; 1.3-7.7 and 2.9; 1.3-6.6, respectively). For HDL cholesterol, the relative risk in the highest compared to the lowest quartile (Q4 vs. Q1) was 0.5 in men (0.3-0.9) and 0.4 in women (0.2-0.9). HDL cholesterol was a weaker predictor in men after age 70 (Q4 vs. Q1 0.8; 0.3-2.1). In women of 70 years and older the relative risk was also not significant (Q4 vs. Q1 0.6; 0.3-1.3), although the trend over the quartiles was still significant.

Conclusion. Serum total cholesterol remains an important risk factor for myocardial infarction in men and women aged 70 years and older, while HDL cholesterol at older age remains important in women only.

Introduction

Several prospective studies have shown that serum total cholesterol and HDL cholesterol are important independent risk factors for coronary heart disease in middle-aged men and women.¹⁻⁵ However, the relation between cholesterol and coronary heart disease in elderly subjects is less well established. Some studies have found that serum total and HDL cholesterol are important risk factors for coronary heart disease in elderly⁶⁻¹⁰, while others have noted that the risk weakens with increasing age^{11,12}, or even disappears.¹³ For the discussion about treatment of elevated cholesterol levels in the elderly it is important to know whether the relationship between cholesterol and coronary heart disease still holds in this age group.

In the Rotterdam Study we have investigated serum total cholesterol, HDL cholesterol and the ratio of non-HDL to HDL cholesterol as risk factors for myocardial infarction in men and women of 55 years and over. In addition, separate analyses were performed in men and women of 70 years and older.

Methods

Study population

The Rotterdam Study is a population-based prospective cohort study among 7,983 men and women aged 55 years and over, living in an urban district of Rotterdam, The Netherlands. The rationale and design of the study have been described previously.¹⁴ In short, the Rotterdam Study investigates the prevalence, incidence, and determinants of cardiovascular, neurological, locomotor, and ophthalmological diseases at older age. Baseline measurements were carried out from July 1989 to July 1993. The overall response rate was 78%. The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent was obtained from all participants.

A total of 7,129 subjects visited the research centre. Cholesterol measurements were available for 2,554 men and 3,789 women. Subjects with incomplete data for the potential confounders, i.e. systolic blood pressure, body mass index and smoking (101 men and 236 women), were excluded. For 728 men and 1,307 women dietary data were not available. For alcohol, these missing values were substituted by the sex-specific median of the alcohol intake for each 5-year age group. The data of 2,453 men and 3,553 women were used in the present analyses.

Measurements

The participants were interviewed in their homes by trained research assistants. Information on current health status, medical history (including myocardial infarction), medication use, and smoking behaviour was obtained by a computerised questionnaire. A history of myocardial infarction was considered positive if the subject reported to have been hospitalised for this condition.

The home interview was followed by two visits at the research centre. During those visits several cardiovascular risk indicators were determined. Height and weight were measured, and body mass index was calculated (kg/m^2). Blood pressure was measured on the right upper arm with the participant in sitting position using a random zero sphygmomanometer. The first and fifth Korotkoff phases were recorded as systolic and diastolic blood pressure. The average of two consecutive measurements was used to calculate the diastolic and systolic blood pressure. The mean alcohol consumption (g/day) was calculated from a semi-quantitative food frequency questionnaire. Serum total cholesterol was determined by an automated enzymatic procedure in a non-fasting blood sample.¹⁵ HDL was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium. All cholesterol measurements were carried out in the laboratory of the Department of Epidemiology & Biostatistics (Erasmus University Medical School), which participates in the Dutch National Cholesterol Standardisation Program, initiated in analogy to the program of the CDC Lipid Standardisation Laboratory in Atlanta. The cholesterol ratio was defined as the concentration of non-HDL cholesterol divided by HDL cholesterol. Hypercholesterolemia was defined as a serum total cholesterol concentration of 6.5 mmol/L or higher.

Follow-up

The follow-up started at the baseline examination and lasted until April 1, 1996. The mean follow-up was 4.2 years, ranging from 3.0 to 6.5 years. With respect to the vital status of participants, information was obtained at regular intervals from the municipal registry in Rotterdam. Information on fatal and non-fatal endpoints was obtained weekly from the general practitioners working in the study district and yearly from the general practitioners working outside the study district. All the reported events were verified by research physicians from the Rotterdam Study by examining patient records of the participating general practitioners. All general practitioners working outside the study district, who had patients who participated in the Rotterdam Study, were visited to obtain information on the occurrence of non-fatal and fatal events. Cause and circumstances of death were established, shortly after deaths were reported by the municipal registry or the general practitioner. A questionnaire was sent to the general practitioner concerning the cause of death.

Overall, complete follow-up information was available for 7,054 subjects (88.4%) in the present study. Participants for whom no follow-up information was available were on average 3 years older, had a 0.1 mmol/L lower total cholesterol concentration and a 0.04 mmol/L higher HDL cholesterol concentration.

Classification of fatal and non-fatal events was based on the 10th revision of the International Classification of Diseases.¹⁶ Myocardial infarction, fatal and non-fatal, was defined as ICD-10: I21-24. All events were classified independently by two research physicians. If there was disagreement, a consensus was reached in a special session. Finally, all these events were verified by a medical expert in the field of cardiovascular diseases. In case of discrepancies, the judgment by this expert was considered definite.

Statistical analyses

Differences in risk factor levels at baseline between men and women were tested using Student's t-test. The Mann-Whitney test was used in case the risk factor distributions were skewed. For differences in levels of categorical variables (smoking) the χ^2 -test statistic was calculated.

Cox's proportional-hazard (survival) analysis was used to estimate relative risks (RRs) and their 95% confidence limits with myocardial infarction, fatal and non-fatal, as the dependent variable. Fatal and non-fatal myocardial infarction were not analysed separately because of the small number of cases in this study. Separate analyses were carried out using total cholesterol, HDL cholesterol and the non-HDL/HDL cholesterol ratio as the independent variables. Cholesterol was analysed both as a continuous variable, for 1.0 mmol/L increase in total cholesterol, 0.1 mmol/L increase in HDL cholesterol and 1 unit increase in the cholesterol ratio, and as a categorical variable calculated for each sex-specific quartile, with the lowest quartile as the reference category. Because total and HDL cholesterol were measured in one decimal, the total number of respondents in each cholesterol quartile was not completely equal. In all analyses, adjustments were made for age (years), cigarette smoking (never, former and current), systolic blood pressure (mmHg) and body mass index (kg/m^2). For HDL cholesterol and the cholesterol ratio, adjustment was also made for alcohol consumption (g/day). All the analyses were carried out separately for men and women. The analyses were repeated in men and women of 70 years and over. The cutpoint of 70 years was used to ensure enough subjects in this age group. Possible interactions between either total cholesterol, HDL cholesterol or the cholesterol ratio and age, cigarette smoking, systolic blood pressure, body mass index and alcohol consumption were tested by adding interaction terms to the model. Analyses were carried out with and without

respondents with a history of myocardial infarction (12% men and 4% women) and with and without users of cholesterol lowering medication and/or diet (3% men and 2% women). Because these results did not differ and because of the small numbers using cholesterol lowering medication and/or diet, the results reported in this article are based on all subjects.

The number of myocardial infarctions that could be prevented if the cholesterol levels of all subjects had been in the lowest, and for HDL cholesterol in the highest, cholesterol quartile were calculated as population-attributable risks (PARs). PARs were calculated using the following formula¹⁷:

$$PAR = \sum_i CF_i(RR_i - 1)/RR_i$$

where CF is the proportion of cases with myocardial infarction, RR is the relative risk and i is the quartile number. The summation ranged over all the cholesterol quartiles with the lowest quartile as the reference category.

The deviance (i.e. log likelihood) from the different survival models was compared to test whether total cholesterol, HDL cholesterol or the cholesterol ratio was the best predictor of myocardial infarction in our study. The smaller the deviance the better the prediction of the model.

Results

During 4 years of follow-up, 117 men and 76 women experienced a first or recurrent myocardial infarction of which 20 were fatal in men and 19 were fatal in women.

Baseline characteristics of the total study population are shown in table 1. The mean serum total and HDL cholesterol levels at baseline were significantly lower in men than in women. The non-HDL/HDL cholesterol ratio was significantly higher in men compared to women. The prevalence of hypercholesterolemia (total cholesterol ≥ 6.5 mmol/L) was 43% in men and 62% in women. In men aged 70 years and older the mean age was 76.7 years (range: 70.0-97.8 years) and in women aged 70 years and older the mean age was 78.0 years (range: 70.0-98.6 years).

In both men and women the relative risk of myocardial infarction increased with increasing total cholesterol concentration in both age categories (table 2). The age-adjusted relative risk of myocardial infarction in the highest compared to the lowest total cholesterol quartile was almost two times higher in men and more than three times higher in women aged 55 years and over. In men and women aged 70 years and over, the age-adjusted relative risk of myocardial infarction was about three

Table 2 Adjusted* relative risks (RR) (95% confidence intervals (CI)) of fatal and non-fatal myocardial infarction associated with total cholesterol in the total population men and women (≥ 55 years) and in the population aged ≥ 70 years in the Rotterdam Study.

		total group					
		≥ 55 years			≥ 70 years		
quartile (mmol/L)	mean	total number	number of events	RR (95% CI)	total number	number of events	RR (95% CI)
Men							
≤ 5.4	4.9	565	19	1.00	290	8	1.00
5.5 - 6.2	5.9	659	30	1.45 (0.81-2.59)	263	14	2.09 (0.87-5.01)
6.3 - 7.0	6.6	620	33	1.75 (0.98-3.10)	219	16	2.89 (1.22-6.82)
> 7.0	7.8	609	35	1.88 (1.06-3.33)	176	14	3.17 (1.31-7.67)
per 1.0 mmol/L increase		2,453	117	1.20 (1.03-1.41)	948	52	1.42 (1.13-1.79)
Women							
≤ 5.9	5.3	803	10	1.00	421	8	1.00
6.0 - 6.7	6.4	937	13	1.14 (0.50-2.61)	428	11	1.26 (0.50-3.17)
6.8 - 7.5	7.1	895	18	1.68 (0.76-3.68)	375	11	1.37 (0.54-3.50)
> 7.5	8.4	918	35	3.15 (1.54-6.42)	408	24	2.93 (1.29-6.62)
per 1.0 mmol/L increase		3,553	76	1.40 (1.20-1.65)	1,632	54	1.36 (1.12-1.65)

* adjusted for age, systolic blood pressure, body mass index and smoking

Table 3 Adjusted* relative risks (RR) (95% confidence intervals (CI)) of fatal and non-fatal myocardial infarction associated with HDL cholesterol in the total population men and women (≥ 55 years) and in the population aged ≥ 70 years in the Rotterdam Study.

quartile (mmol/L)	mean	total group					
		≥ 55 years			≥ 70 years		
		total number	number of events	RR (95% CI)	total number	number of events	RR (95% CI)
Men							
≤ 0.9	0.84	496	26	1.00	202	9	1.00
1.0 - 1.1	1.05	664	39	1.09 (0.66-1.79)	258	16	1.29 (0.56-2.93)
1.2 - 1.3	1.24	615	35	1.09 (0.65-1.83)	224	17	1.70 (0.75-3.88)
> 1.3	1.61	678	17	0.47 (0.25-0.89)	264	10	0.82 (0.32-2.09)
per 0.1 mmol/L increase		2,453	117	0.91 (0.86-0.98)	948	52	0.96 (0.87-1.05)
Women							
≤ 1.2	1.06	1,152	36	1.00	587	26	1.00
1.3 - 1.4	1.35	859	19	0.70 (0.40-1.24)	395	11	0.54 (0.26-1.13)
1.5 - 1.6	1.55	694	11	0.57 (0.29-1.13)	292	7	0.51 (0.22-1.19)
> 1.6	1.93	848	10	0.44 (0.22-0.91)	358	10	0.62 (0.29-1.32)
per 0.1 mmol/L increase		3,553	76	0.89 (0.83-0.96)	1,632	54	0.90 (0.83-0.98)

* adjusted for age, systolic blood pressure, body mass index, smoking and alcohol consumption

Table 4 Adjusted* relative risks (RR) (95% confidence intervals (CI)) of fatal and non-fatal myocardial infarction associated with the non-HDL/HDL cholesterol ratio in the total population men and women (≥ 55 years) and in the population aged ≥ 70 years in the Rotterdam Study.

quartile	mean	total group					
		≥ 55 years			≥ 70 years		
		total number	number of events	RR (95% CI)	total number	number of events	RR (95% CI)
Men							
≤ 3.3	2.7	600	13	1.00	272	7	1.00
3.4 - 4.3	3.9	666	33	2.34 (1.22-4.47)	279	16	2.25 (0.92-5.52)
4.4 - 5.3	4.8	532	30	2.80 (1.44-5.44)	188	15	3.27 (1.31-8.15)
> 5.3	6.6	655	41	3.24 (1.69-6.19)	209	14	3.06 (1.18-7.91)
per unit increase		2,453	117	1.16 (1.05-1.28)	948	52	1.16 (1.01-1.33)
Women							
≤ 2.8	2.3	811	8	1.00	359	7	1.00
2.9 - 3.8	3.4	1,021	15	1.45 (0.61-3.43)	474	12	1.29 (0.51-3.29)
3.9 - 4.8	4.3	844	14	1.43 (0.59-3.48)	376	8	0.90 (0.31-2.57)
> 4.8	6.3	877	39	4.00 (1.85-8.65)	423	27	3.24 (1.40-7.53)
per unit increase		3,553	76	1.25 (1.16-1.36)	1,632	54	1.37 (1.20-1.56)

* adjusted for age, systolic blood pressure, body mass index, smoking and alcohol consumption

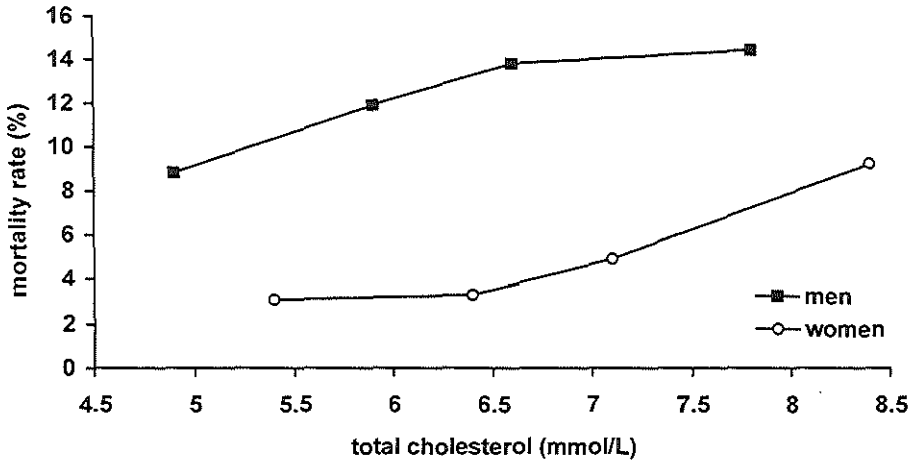


Figure 1 Mortality rates (%) of myocardial infarction in men and women aged 55 years and over per sex-specific total cholesterol quartile in the Rotterdam Study.

The mortality rates of myocardial infarction in men and women aged 55 years and over per quartile of total cholesterol are given in figure 1. In both sexes, the mortality rate increased with higher cholesterol concentrations. The mortality rates were about two times higher in men compared to women at all levels of total cholesterol, whereby the mortality rate of the highest total cholesterol concentration in women is comparable to the mortality rate of the lowest total cholesterol concentration in men.

Population-attributable risks (PARs) indicate that there would have been 34% fewer cases with myocardial infarction in men and 43% in women of 55 years and older if total cholesterol levels in the whole population were 5.4 mmol/L or lower in men and 5.9 mmol/L or lower in women (lowest quartiles) (table 5). If HDL cholesterol levels in the whole population would be 1.4 mmol/L or higher in men or 1.7 mmol/L or higher in women (highest quartiles) there would have been 48% fewer cases with myocardial infarction in men and 39% in women. The PAR for total cholesterol in subjects aged 70 years and older was higher in men (53%) and almost similar in women (39%) compared to subjects aged 55 years and over. The PAR for HDL cholesterol was lower in both men and women aged 70 years and older (31% and 12%, respectively).

Table 5 Population-attributable risk (PAR)* of myocardial infarction in the total population men and women (≥ 55 years) and in the population aged ≥ 70 years for the cholesterol parameters in the Rotterdam Study.

cholesterol parameters	men		women	
	≥ 55 years	≥ 70 years	≥ 55 years	≥ 70 years
total cholesterol	34	53	43	39
HDL cholesterol	48	31	39	12
non-HDL/HDL cholesterol ratio	57	56	50	38

* assuming that the whole population had levels similar to those of the lowest quartile for total cholesterol and the non-HDL/HDL cholesterol ratio or the highest quartile for HDL cholesterol

The deviances for the models with total cholesterol, HDL cholesterol or the non-HDL/HDL cholesterol ratio were not significantly different, meaning that no one parameter was significantly more predictive than the other in men and women aged 55 years and older.

Discussion

The results of the present study suggest that serum total cholesterol, HDL cholesterol and the ratio of non-HDL to HDL cholesterol are important risk factors for myocardial infarction in men and women aged 55 years and over. These risk factors remain important after age 70, except for HDL cholesterol in men.

Before interpreting the results of our study some methodological issues will be discussed. First, the population of the Rotterdam Study was recruited from an urban district of Rotterdam and had a somewhat higher social economic status than the general population. Our results may therefore not be completely generalizable to the general Dutch population of 55 years and over. Second, the strength of the association between the cholesterol parameters and the risk of myocardial infarction is likely to be underestimated in our study, because the cholesterol levels were measured only once. A single baseline cholesterol measurement is subject to random fluctuations, due to both laboratory measurement error and biological variation of cholesterol levels in individuals over time.¹⁸ Third, we had a relative short follow-up in this study. Because of this short follow-up period, we could not exclude events occurring during the first years of follow-up. Underlying diseases at baseline could have lowered the cholesterol levels. However, if this was the case it would

have decreased the relative risks and the true relative risks would have been even larger. Fourth, there was incomplete follow-up information in this study for 12 % of the subjects. This group mainly consisted of subjects who had a general practitioner without an automated patient registry, changed their general practitioner or moved outside the study district. These factors all contribute to a retardation in the data collection process. Based on these main reasons for incomplete follow-up information, we expect that the observed differences in baseline characteristics (subjects lost to follow-up were on average older and had a more favorable cholesterol profile) have not influenced the relation between cholesterol and myocardial infarction in this study.

Results of epidemiological studies on cholesterol and coronary heart disease in the elderly are inconsistent. Some studies that examined the relation between total cholesterol and coronary heart disease in men aged 65 years and older found a positive relation.^{7,8,10,11} However, other studies reported no association in elderly men.^{6,9,12,13} In women aged 65 years and older, two studies found a positive relationship between total cholesterol and coronary heart disease^{6,9} and two studies did not find an association.^{11,13} For HDL cholesterol, few studies observed an association with coronary heart disease in men aged 71 years and older.^{6,12} Most studies found no association in men aged 65 years and older.^{9-11,13} A relation between HDL cholesterol and coronary heart disease in women with a cut-off age ranging from 65 to 71 years was seen in three studies.^{6,9,11} Two other studies did not find an association in elderly women.^{12,13} Three out of four studies that have measured the cholesterol ratio observed a positive relation with coronary heart disease in elderly men and women with cut-off ages ranging from 65 to 71 years.^{6,9,10} The other study reported no relation in subjects older than 70 years.¹³

In our study we found a positive relation between total cholesterol and myocardial infarction in men and women aged 70 years and over. The relative risks for total cholesterol in our study are higher than those found in most studies mentioned above when comparable cut-offs were chosen. Only the Zutphen Elderly Study showed a relative risk of comparable magnitude for men aged 64 years and over.¹⁰ We found an inverse relation between HDL cholesterol as a continuous parameter and myocardial infarction in women aged 70 years and older. The relative risk in the highest HDL cholesterol quartile compared to the lowest lacked significance, probably due to small number of cases. In men aged 70 years and older the relation was not present. HDL cholesterol is apparently not as good a predictor of myocardial infarction in elderly men as total cholesterol. This is consistent with other studies

which also observed that HDL is not a strong predictor in older men^{9-11,13}, although two other studies found a clear relationship in men aged 65 years and older.^{6,12} For women, only the Framingham Study⁹ found a relative risk for HDL cholesterol in women aged 65 years and older comparable in strength to that one observed in our study. The non-HDL/HDL cholesterol ratio in our study was a good predictor of myocardial infarction in men and women aged 70 years and older. The relative risks for the cholesterol ratio observed in our study are comparable to those found in the EPESE study⁶, other studies found weaker associations.

The results of this study showed pronounced relationships for total cholesterol in men and total and HDL cholesterol in women at older age. In our study, we used fatal and non-fatal myocardial infarction as endpoint rather than coronary heart disease mortality as used in most other studies in the elderly. Possibly, the relationship between cholesterol and incidence of myocardial infarction is stronger than the relationship between cholesterol and coronary heart diseases mortality. Another explanation could be that most other studies have excluded cases with coronary heart disease at baseline. However, we have done analyses with and without respondents with myocardial infarction at baseline and these results did not differ.

We found that total cholesterol, HDL cholesterol and the cholesterol ratio were all important risk factors for myocardial infarction in men and women aged 55 years and older. In this study, the non-HDL/HDL cholesterol ratio was a slightly better predictor of myocardial infarction for both men and women compared with total cholesterol and HDL cholesterol. However, no one parameter was significantly more predictive than the others.

Population-attributable risks (PARs) are determined by relative risks and prevalences. Usually, relative risks for coronary heart disease decrease with advancing age and prevalences of coronary heart disease increase with age. A decrease in relative risk does not mean a decline in PAR. The differences in PARs in this study, in both age groups and between men and women, depended largely upon the differences in relative risks found. The PAR in women aged 55 years and older for total cholesterol is somewhat higher compared to men. However, the absolute number of myocardial infarctions that could be prevented in women would be smaller than that in men, because of the lower mortality rates in women (figure 1).

Observational studies alone are insufficient to decide whether elderly have to be treated for elevated cholesterol levels or not. An evaluation of 28 randomised clinical trials showed that a lowering of the plasma cholesterol concentrations is associated

with a reduction in incidence of coronary heart disease.¹⁹ There is little experimental data on cholesterol-lowering strategies in elderly. The Scandinavian Simvastatin Survival Study showed that also in elderly patients with coronary heart disease (aged 60-70 years) there was a significant treatment effect (RR 0.7; 95% CI 0.6-0.9).²⁰ Whether reduction of cholesterol levels in the elderly would have a beneficial effect on primary prevention should be further investigated in clinical trials. The results of our study indicate that the public health gain to be achieved in elderly men and women is potentially large.

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CHAPTER 5

Total but not HDL cholesterol is consistently associated with coronary heart disease mortality in elderly men in Finland, Italy and The Netherlands

Abstract

Objective. To study the relation between serum total and high-density-lipoprotein (HDL) cholesterol and 10-year coronary heart disease mortality in elderly men in different European countries.

Methods. The Finland, Italy and The Netherlands Elderly (FINE) Study is a prospective follow-up study in 2132 elderly men aged 65 to 84 years in Finland, The Netherlands and Italy. Relative risks using Cox's proportional-hazard analysis with time-dependent covariates.

Results. Total cholesterol was positively related to coronary heart disease mortality in all three countries. The combined relative risk for the total population of the FINE Study was 1.17 (95% CI = 1.06-1.29) for each 1.00 mmol/L increase in total cholesterol. HDL cholesterol was inversely related to coronary heart disease mortality in Finland, but not in The Netherlands and Italy. In Italy we noted an interaction between HDL cholesterol, body mass index and alcohol intake, with an inverse association for HDL cholesterol in lean men who drank < 40 g of alcohol daily and a positive association for HDL cholesterol among overweight men who drank \geq 40 g of alcohol per day.

Conclusion. Serum total cholesterol remains an important predictor of coronary heart disease mortality in elderly men in different European countries. The effect of HDL cholesterol differed between the three countries.

Introduction

It is well established that serum total and high-density-lipoprotein (HDL) cholesterol are important predictors of coronary heart disease mortality in middle-aged men.¹⁻⁴ Whether this relation holds in the elderly is not clear.⁵⁻¹¹ It is also important to know whether the relation between serum cholesterol and coronary heart disease mortality in elderly men differs between countries. After 25-years of follow-up, the Seven Countries Study showed that the strength of the relation between serum total cholesterol and coronary heart disease mortality is similar in middle-aged men across cultures.⁴ The absolute risks, however, were markedly different. Similar information on HDL cholesterol is lacking because at the beginning of the Seven Countries Study HDL cholesterol was not measured. Information on both total and HDL cholesterol was collected in the Finland, Italy and The Netherlands Elderly (FINE) Study. This study is an extension of the Seven Countries Study and carried out since 1984 in Finland, The Netherlands and Italy. The FINE Study provided the possibility to investigate the relations between serum total and HDL cholesterol and 10-year coronary heart disease mortality in elderly men, using time-dependent covariates.

Methods

Study population

The FINE Study is an extension of the Seven Countries Study.¹² The survivors of the cohorts in Finland, The Netherlands and Italy were re-examined after 25 years. This examination was the baseline of the FINE Study, a prospective study in elderly men 65 to 84 years of age. The FINE Study includes the two Finnish cohorts (both rural) known as East Finland and West Finland, the Dutch cohort from the small town of Zutphen, and the two rural cohorts in Italy from the villages of Crevalcore and Montegiorgio (in northern and central Italy, respectively).

In Finland, 716 men were re-examined in 1984 and in rural Italy, 682 men in 1985. In The Netherlands, 380 survivors were re-examined in 1985, together with a new random sample consisting of 507 men aged 65 to 84 years in Zutphen who did not participate earlier in the Zutphen Study. The response rate was 94% in Finland, 74% in The Netherlands and 76% in Italy.

Subjects with incomplete data for the main cardiovascular risk factors were excluded. The data of 668 Finnish men, 824 Dutch men and 640 Italian men were used in the present analyses.

Measurements

All men were examined according to the international protocol used in previous surveys of the Seven Countries Study.¹² Survivors were re-examined after 5 and 10 years of follow-up.

In Finland, fasting blood samples were taken and non-fasting blood samples in The Netherlands and Italy. In each country, total and HDL cholesterol determinations were carried out in lipid laboratories standardized according to the criteria of the WHO Lipid Reference Laboratories in Prague or Atlanta, Georgia.¹³ In all three laboratories, serum total cholesterol was determined enzymatically with the CHOD-PAP mono-testkit of Boehringer Mannheim (Mannheim, West Germany).^{14,15} HDL cholesterol was determined after precipitation of the apo-B containing lipoproteins with dextran-magnesium chloride in Finland, dextran-magnesium sulfate in The Netherlands, and magnesium phosphotungstate in Italy.^{16,17} Hypercholesterolemia was defined as a serum total cholesterol concentration of 6.5 mmol/L (251 mg/dl) or more. A low HDL cholesterol level was defined as HDL cholesterol less than 0.9 mmol/L (35 mg/dl).¹⁸

Height and weight were measured in light clothing without shoes and body mass index was calculated (kg/m^2). Blood pressure was measured twice on the right arm with the men in supine position using a standard sphygmomanometer in Finland and Italy and a random zero sphygmomanometer in The Netherlands. Systolic and diastolic blood pressure were recorded at the onset of the first and fifth Korotkoff phase, respectively.

Smoking was measured as never, ex, or current. Alcohol intake was measured as number of drinks per day and subsequently converted to grams of alcohol by multiplying each glass of beer, wine, or spirit with its alcohol content.¹³

Follow-up

The history of coronary heart disease was defined by the Rose questionnaire¹⁹, combined with information from reported clinical records and additional questions from the examining physician. Coronary heart disease was considered to be present when either myocardial infarction (definite) or angina pectoris (definite) was diagnosed.

Complete follow-up information after 10 years, obtained through official death certificates was available for 99.7% of the population of the FINE Study. In Finland, only information on causes of death was available. In The Netherlands and Italy, causes of death were validated through review of clinical records. Final causes of death were adjudicated by a single reviewer using the 9th revision of the WHO-ICD²⁰ adopting a hierarchical order when multiple causes were given, as follows: violent

causes, cancer, coronary heart disease, stroke and other. Coronary heart disease mortality was defined as ICD-9: 410-414 as the primary cause of death.

Statistical analyses

We computed age-standardized 10-year mortality rates of coronary heart disease by weighting the mortality rates for 5-year age categories to the age distribution of the total study population. We used Cox's proportional-hazard (survival) analysis, pooled after stratification by cohort, to investigate the relation between serum total and HDL cholesterol and coronary heart disease mortality during 10 years of follow-up. We included serum total and HDL cholesterol and all the covariables as time-dependent covariates. The baseline measurement and the measurement after 5 years of follow-up were both used. For those who died during the first 5 years of follow-up only the baseline measurement was used. For those who died during the second 5 years of follow-up the baseline measurement was used for the first 5-year period and the measurement after 5 years of follow-up was used for the second 5-year period. Relative risks (RR) are presented for each 1.00 mmol/L increase in total cholesterol and 0.10 mmol/L increase in HDL cholesterol, and for tertiles, the lowest tertile being the reference category. In all analyses adjustment was made for age (years), body mass index (kg/m^2), systolic blood pressure (mmHg), cigarette smoking (ex and never or current) and history of coronary heart disease. For HDL cholesterol, adjustment was also made for alcohol intake (0, 1-19, 20-39, ≥ 40 g/day). Analyses were carried out with and without respondents with a history of coronary heart disease, but because these results did not differ by much the results reported in this article are based on all respondents. We evaluated interaction by comparing the risk in the group with both an unfavorable cholesterol and covariate level with the risk expected from the additive effects of cholesterol and the covariate alone.²¹

Table 1 Baseline characteristics (mean (SD)) according to coronary heart disease (CHD) mortality in men aged 65 to 84 years in Finland, The Netherlands and Italy.

	CHD mortality					
	Finland (N=668)		The Netherlands (N=824)		Italy (N=640)	
	no (N=528)	yes (N=140)	no (N=736)	yes (N=88)	no (N=592)	yes (N=48)
age (years)	71.2 (5.0)	72.6 (5.4)	71.2 (5.2)	72.4 (5.8)	71.7 (4.4)	73.3 (4.2)
history of CHD (%)	18.6	49.3	13.0	37.5	13.2	18.8
total cholesterol (mmol/L)	6.09 (1.21)	6.39 (1.39)	6.08 (1.11)	6.36 (1.10)	5.88 (1.13)	6.09 (1.13)
HDL cholesterol (mmol/L)	1.24 (0.33)	1.15 (0.32)	1.13 (0.29)	1.11 (0.29)	1.30 (0.34)	1.35 (0.32)
% total cholesterol \geq 6.5 mmol/L	36.2	40.0	35.6	35.2	26.4	27.1
% HDL cholesterol < 0.9 mmol/L	12.3	19.3	22.8	19.3	8.3	6.3
systolic blood pressure (mmHg)	153.3 (21.9)	156.9 (25.3)	150.7 (21.3)	150.3 (20.7)	166.7 (22.0)	167.1 (25.9)
hypertension [†] (%)	57.1	70.0	41.6	39.8	75.1	87.0
BMI (kg/m ²)	25.7 (4.1)	25.8 (4.0)	25.5 (3.2)	25.4 (3.1)	25.9 (3.6)	26.2 (3.9)
overweight [‡] (%)	58.5	56.4	54.2	63.6	59.3	66.7
current smoking (%)	18.2	20.0	29.6	33.0	27.0	20.8
ex-smoking (%)	55.3	57.5	51.8	51.1	42.9	43.8
alcohol drinking (% > 0 g/day)	62.4	61.4	73.6	71.6	89.0	87.5
alcohol intake [§] (g/day)	5.3 (9.6)	4.6 (8.2)	18.3 (23.5)	16.2 (23.4)	43.3 (42.0)	47.3 (50.8)

* systolic blood pressure \geq 160 mmHg and/or diastolic blood pressure \geq 95 mmHg and/or on anti-hypertensive medication

[†] body mass index \geq 25 kg/m²

[‡] among alcohol drinkers

Results

Mean total cholesterol levels were similar in Finland and The Netherlands, but lower in Italy in both men with and without coronary heart disease mortality (table 1). The mean prevalence of hypercholesterolemia (total cholesterol ≥ 6.5 mmol/L) was 37% in Finland, 36% in The Netherlands and 26% in Italy. Mean HDL cholesterol levels were different between the three countries, with the lowest level in The Netherlands and the highest level in Italy in both men with and without coronary heart disease mortality. The mean prevalence of a HDL cholesterol level less than 0.9 mmol/L was 14% in Finland, 23% in The Netherlands and 8% in Italy.

The age-adjusted coronary heart disease mortality rates of coronary heart disease were much higher in Finland than in The Netherlands and Italy (figure 1). The number of men who died from coronary heart disease after 10 years of follow-up was 140 in Finland (21%), 88 in The Netherlands (11%) and 48 in Italy (8%). For total cholesterol, the age-adjusted coronary heart disease mortality rate in the lowest tertile in Finland was more than 1.5 times higher than that in the highest tertile in The Netherlands and Italy. For HDL cholesterol, the age-adjusted coronary heart disease mortality rate in Finland and The Netherlands decreased with respectively 12 and 3 percentage points from the lowest to the highest tertile in contrast to an increase in the coronary heart disease mortality rate in Italy with about 4 percentage points.

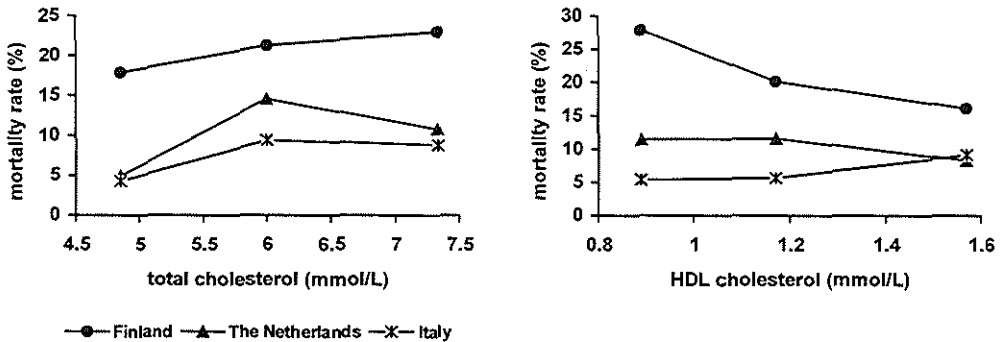


Figure 1 Age-adjusted mortality rates (%) from coronary heart disease in men aged 65 to 84 years per tertile of baseline total cholesterol and HDL cholesterol.

The risk of mortality from coronary heart disease increased with each 1.00 mmol/L increase of total cholesterol, with the highest relative risks in The Netherlands and the total population of the FINE Study (table 2). In The Netherlands, the relative risk in the highest total cholesterol tertile was about two times that in the lowest tertile

and there was a trend across the total cholesterol tertiles. In Finland and Italy there was no trend across the tertiles.

Table 2 Adjusted* relative risks (95% CIs) of coronary heart disease mortality in men aged 65 to 84 years in Finland, The Netherlands and Italy associated with total cholesterol as time-dependent covariate.

country	tertile (mmol/L)	mean (mmol/L)	total number	number of deaths	RR (95% CI)
Finland	< 5.51	4.85	216	41	1.00
	5.51 - 6.49	6.00	205	43	1.13 (0.74,1.72)
	> 6.49	7.33	247	56	1.07 (0.70,1.62)
	<i>slope of trend line</i>				<i>0.03 (-0.18,0.24)</i>
	1.00 mmol/L increase		668	140	1.10 (0.96,1.26)
The Netherlands	< 5.51	4.85	246	15	1.00
	5.51 - 6.49	6.00	285	42	1.71 (0.91,3.21)
	> 6.49	7.33	293	31	2.10 (1.12,3.92)
	<i>slope of trend line</i>				<i>0.34 (0.04,0.63)</i>
	1.00 mmol/L increase		824	88	1.29 (1.07,1.56)
Italy	< 5.51	4.85	247	11	1.00
	5.51 - 6.49	6.00	221	23	1.40 (0.69,2.83)
	> 6.49	7.33	172	14	1.92 (0.93,3.96)
	<i>slope of trend line</i>				<i>0.33(-0.04,0.69)</i>
	1.00 mmol/L increase		640	48	1.20 (0.94,1.52)
FINE	1.00 mmol/L increase		2132	276	1.17 (1.06,1.29)

* adjusted for age, body mass index, systolic blood pressure, smoking and history of CHD and stratified by cohort

Table 3 Adjusted* relative risks (95% CIs) of coronary heart disease mortality in men aged 65 to 84 years in Finland, The Netherlands and Italy associated with HDL cholesterol as time-dependent variable.

country	tertile (mmol/L)	mean (mmol/L)	total number	number of deaths	RR (95% CI)
Finland	< 1.04	0.89	204	57	1.00
	1.04 - 1.31	1.17	224	45	0.96 (0.93,1.00)
	> 1.31	1.57	240	38	0.95 (0.91,0.99)
	<i>slope of trend line</i>				<i>-0.04(-0.05, -0.005)</i>
	0.10 mmol/L increase			668	140
The Netherlands	< 1.04	0.89	367	42	1.00
	1.04 - 1.31	1.17	265	31	0.99 (0.95,1.04)
	> 1.31	1.57	192	15	0.96 (0.90,1.02)
	<i>slope of trend line</i>				<i>-0.02(-0.05,0.01)</i>
	0.10 mmol/L increase			824	88
Italy	< 1.04	0.89	142	8	1.00
	1.04 - 1.31	1.17	210	12	0.97 (0.89,1.06)
	> 1.31	1.57	288	28	1.01 (0.94,1.09)
	<i>slope of trend line</i>				<i>0.01(-0.03,0.05)</i>
	0.10 mmol/L increase			640	48

* adjusted for age, body mass index, systolic blood pressure, smoking, alcohol intake and history of CHD and stratified by cohort.

In Finland, the risk of mortality from coronary heart disease decreased with an increase in HDL cholesterol and there was a trend (table 3). In The Netherlands and Italy, HDL cholesterol was not associated with mortality from coronary heart disease.

In Italy, the risk for coronary heart disease mortality in men with both a low HDL cholesterol level and a high BMI was lower than expected from the additive effects, which turned out to be dependent on the level of alcohol intake: there was an inverse association between HDL cholesterol and coronary heart disease mortality in lean men (body mass index < 25 kg/m²) with no or moderate alcohol intake (< 40 g/day) (RR 0.76; 95% CI = 0.59-0.97) and a positive association in overweight men (body mass index ≥ 25 kg/m²) with a high alcohol intake (≥ 40 g/day) (RR 1.25; 95% CI =

1.07-1.46). The HDL concentration was 1.29 mmol/L in both subgroups. The total cholesterol concentrations were 5.88 mmol/L in lean men with no or moderate alcohol intake and 6.01 mmol/L in overweight men with a high alcohol intake. In the other two subgroups, lean men with a high alcohol intake and overweight men with no or moderate alcohol intake, a weak association was found with coronary heart disease mortality (RR 0.90; 95% CI = 0.72-1.13 and RR 0.96; 95% CI = 0.81-1.14, respectively). Also in Finland and The Netherlands there was an inverse, but less strong, relation between HDL cholesterol and coronary heart disease mortality (RR 0.93; 95% CI = 0.85-1.02 and RR 0.99; 95% CI = 0.85-1.15, respectively) in lean men with no or moderate alcohol intake. In the total population of the FINE Study the relative risk in lean men with no or moderate alcohol intake was 0.92 (95% CI = 0.86-0.99).

Discussion

The results of the present study show that serum total cholesterol is positively associated with 10-year coronary heart disease mortality in elderly men in Finland, The Netherlands and Italy. HDL cholesterol is inversely associated with 10-year coronary heart disease mortality in Finnish men only.

Non-response could have influenced the results of our study, especially in The Netherlands and Italy. In Zutphen (The Netherlands), however, there was no difference in average serum total cholesterol level in 1960 between respondents of the 25-year follow-up survey and non-respondents, men who did not participate in the 25-year follow-up survey. Similar results were found in Montegiorgio (Italy). In Crevalcore (Italy), the respondents had in 1960 a lower total cholesterol level (0.16 mmol/l) compared with the non-respondents. The difference in average serum total cholesterol level in 1960 between the respondents in the three countries together and the non-respondents was 0.08 mmol/L. It is therefore unlikely that our results are strongly influenced by non-response.

Estimation of absolute risks is important, because decisions to treat high risk persons are based on absolute risks, which increase with age. For total cholesterol, the mortality rates for coronary heart disease showed large differences between the countries, with the highest rates in Finland, intermediate rates in The Netherlands and the lowest rates in Italy. In the middle total cholesterol tertile for example, the absolute risk in Finland is almost 1.5 times higher than that in The Netherlands and

2.5 times that in Italy. This finding is in accordance with previous reports from the same countries in middle-aged men.^{4,22}

We found a positive association in this study between serum total cholesterol and coronary heart disease mortality. The results using time-dependent covariates did not differ much from those using only the baseline cholesterol measurement for each respondent (results not shown). Usually the relation found using time-dependent covariates is stronger than that using the baseline measurement only, because with longer follow-up a risk factor loses its predictive value.²³ The more or less similar relative risks found in the present study for the two methods could be explained by the relatively short follow-up period of 10 years.

Other epidemiologic studies among elderly men have so far given equivocal results concerning the relation between serum total cholesterol and coronary heart disease mortality.⁵⁻¹¹ A possible explanation for this result could be the age at which the cholesterol level of the respondents was measured. Our hypothesis is that in the studies that did not find a relation between total cholesterol and coronary heart disease mortality the respondents were older at the time of the measurements (> 70 years) compared with the studies that did find a positive relation (> 60 or 65 years). Also the present study provides some evidence for this hypothesis. Our data showed that the association between total cholesterol and coronary heart disease mortality in the total FINE population in the first 5 years of follow-up (men aged 65-84 years) was stronger (RR 1.21; 95% CI = 1.06-1.38, per 1.00 mmol/L increase) than in the second 5 years of follow-up (men aged 70-89 years) (RR 1.13; 95% CI = 0.94-1.36, per 1.00 mmol/L increase). The Whitehall study also observed a weaker association between total cholesterol and coronary heart disease mortality for men whose cholesterol concentration was measured at older age.²⁴ In the Seven Countries Study, the overall estimate of the predictive power of serum total cholesterol decreased from 1.25 (95% CI = 1.19-1.35, per 1.00 mmol/L increase) in middle-aged men to 1.17 (95% CI = 1.06-1.29) in the elderly in the present analyses.⁴ The results of the present study, however, indicate that serum total cholesterol remains a predictor of coronary heart disease mortality in men aged 65 to 84 years in different countries.

For HDL cholesterol, we found a different relation with coronary heart disease mortality between the three countries. In Finland we found an inverse association and in The Netherlands and Italy no association. For HDL cholesterol we found somewhat lower relative risks using time-dependent covariates compared with using only the baseline measurement (results not shown). Also in other studies

inconsistent results were noted for the association between HDL cholesterol and coronary heart disease mortality.^{7,9,11}

Overall, we found little relation between HDL cholesterol and coronary heart disease mortality in Italy. Exploring these differences we found that there was an inverse association in Italy in lean men (body mass index < 25 kg/m²) with no or moderate alcohol intake (< 40 g/day), but a positive association in overweight men (≥ 25 kg/m²) with a high alcohol intake (≥ 40 g/day). These findings could be a chance result owing to the small numbers in the subgroups.

A biological explanation for the interaction between HDL cholesterol, body mass index and alcohol might be that a potentially favorable effect of high HDL cholesterol on coronary heart disease mortality may be counterbalanced by a high body mass index in combination with a high alcohol intake. Being overweight reduces HDL cholesterol through a high concentration of triglycerides and an increased catabolism of HDL by an excess of adipose tissue.²⁵ This effect could counterbalance the HDL cholesterol increasing effect of alcohol. This hypothesis is supported by our data. The HDL cholesterol concentration in overweight men with a high alcohol intake (1.29 mmol/L) was comparable with that in lean men with no or moderate alcohol intake (1.29 mmol/L). Nevertheless, the total cholesterol concentrations were different between both groups. This finding indicates a disturbance of the lipid metabolism in overweight men with a high alcohol intake.

Using the combined data of Finland, The Netherlands and Italy we observed an inverse relation between HDL cholesterol and coronary heart disease mortality in lean men with no or moderate alcohol intake. Thus, in a particular subgroup of the elderly population there may be an inverse association between HDL cholesterol and coronary heart disease mortality. We could not investigate this association in overweight men with a high alcohol intake in Finland and The Netherlands, because in both Finland and The Netherlands high alcohol intake (≥ 40 g/day) is rare. We know of no other study that has reported on this interaction. A prospective follow-up study in middle-aged Russian men also found no relation between HDL cholesterol and coronary heart disease mortality, a result that could be due to the high intake of alcohol in these men.²⁶

In conclusion, this study indicates that serum total cholesterol remains an important predictor of coronary heart disease mortality in men aged 65 to 84 years in the countries studied. The effect of HDL cholesterol on coronary heart disease mortality differed among the three countries.

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CHAPTER 6

Predicting cardiovascular risk in the elderly in different European countries

Abstract

Objective. The objective of this study was to develop risk functions for coronary heart disease (CHD) and cardiovascular diseases (CVD) mortality for elderly men in different European countries.

Methods. The FINE Study is a prospective follow-up study in 2,170 elderly men aged 65-84 years in Finland, The Netherlands and Italy. During 10-years of follow-up 289 men died from CHD and 545 men from CVD. Risk functions were estimated using logistic regression analysis, in order to take competing causes of death into account.

Results. Total cholesterol and smoking were the most important predictors for CHD mortality and HDL cholesterol, systolic blood pressure and smoking for CVD mortality. Left ventricular hypertrophy, being a prevalent case of CHD or CVD in Finland and The Netherlands and use of anti-hypertensive medication in Italy were also important risk factors. For estimating the absolute risk of CHD and CVD mortality in these elderly it was necessary to take country into account.

Conclusion. Total and HDL cholesterol, systolic blood pressure and smoking remain important predictors of CHD and/or CVD mortality in elderly men but also left ventricular hypertrophy, being a prevalent case, use of anti-hypertensive medication and country are predictive of CHD and CVD risk.

Introduction

Guidelines for prevention of coronary heart disease (CHD) or cardiovascular diseases (CVD) are nowadays based on the absolute level of risk of CHD or CVD, taking the total risk profile of an individual into account. Absolute risks for CHD and CVD in the elderly are high and the number of elderly people in Europe will increase in the years to come. Therefore even a small decrease in risk causes a substantial reduction in the number of CHD and CVD events. Estimation of absolute risk of CHD and CVD in the elderly is needed for targeted preventive activities.

In middle-aged men and women, the Framingham risk function¹ is widely used to estimate absolute risks of CHD and CVD and has proven to be reasonably valid also for northern European populations.² Menotti et al.³ showed that in middle-aged men the Framingham risk function overestimates absolute coronary risk in Italy due to a lower incidence of coronary events. In the elderly it is not known whether the Framingham risk function is a valid tool for risk prediction. Due to weaker associations between risk factors and CHD and CVD mortality in the elderly compared with middle-aged men⁴⁻⁶ it is necessary to develop separate risk functions for CHD and CVD mortality in the elderly.

The aim of the present study is to develop risk functions for CHD and CVD mortality for elderly men based on data collected in Finland, Italy and The Netherlands.

Methods

Study population

The FINE Study is an extension of the Seven Countries Study. Between 1958 and 1964, 16 cohorts of middle-aged men were examined according to a standardized protocol in seven countries.⁷ The survivors of the cohorts in Finland, The Netherlands and Italy were re-examined after 25 years. This examination was the baseline of the FINE Study, a prospective study in elderly men aged 65 to 84 years. The FINE Study includes the two Finnish cohorts (both rural) known as East Finland and West Finland, the Dutch cohort from the small town of Zutphen, and the two rural cohorts in Italy from the villages of Crevalcore and Montegiorgio (in northern and central Italy, respectively).

In Finland, 716 men were re-examined in 1984 and in rural Italy, 682 men in 1985. In The Netherlands, 380 survivors were re-examined in 1985, together with a new random sample consisting of 507 men aged 65 to 84 years in Zutphen who did not

participate earlier in the Zutphen Study. The response rate was 94% in Finland, 74% in The Netherlands and 76% in Italy.

Subjects with incomplete data for the risk factors included in the risk function (age, total and HDL cholesterol, systolic blood pressure, smoking, diabetes, ECG-left ventricular hypertrophy, use of anti-hypertensive medication and being a prevalent case of CHD or CVD) were excluded (n=115).

Measurements

All men were examined according to the international protocol used in previous surveys of the Seven Countries Study.⁷ In Finland, fasting blood samples were taken and non-fasting blood samples in The Netherlands and Italy. In each country, total and HDL cholesterol determinations were carried out enzymatically in lipid laboratories standardized according to the criteria of the WHO Lipid Reference Laboratories in Prague, Czech Republic, or Atlanta, Georgia, USA.⁸ Blood pressure was measured twice on the right arm with the men in supine position using a standard sphygmomanometer in Finland and Italy and a random zero sphygmomanometer in The Netherlands. Systolic blood pressure was recorded at the first Korotkoff phase. Smoking was measured as current or non-smoking. Clinical diabetes mellitus was established by means of a standardised questionnaire. A 12-lead resting ECG was recorded. ECG-left ventricular hypertrophy was defined according to the Minnesota Code (codes 3.1 or 3.3, plus any code 4.1 to 4.3 or 5.1 to 5.3).⁹ Use of anti-hypertensive medication was assessed with a standardised questionnaire.

Information on the history of CHD and CVD was obtained from the Rose questionnaire⁹, combined with information from reported clinical records and additional questions from the examining physician. CHD was considered to be present when either myocardial infarction (definite) or angina pectoris (definite) was diagnosed. CVD was considered to be present when either myocardial infarction (definite), angina pectoris (definite), intermittent claudication (definite), stroke (definite), TIA (definite) or heart failure (definite) was diagnosed.

Follow-up

Complete follow-up information after 10 years, obtained through official death certificates, was available for 99.7% of the population of the FINE Study. In Finland, only information on causes of death was available. In The Netherlands and Italy, causes of death were in part validated through review of clinical records. Final causes of death were adjudicated by a single reviewer using the 9th revision of the WHO-ICD¹⁰ adopting a hierarchical order when multiple causes were given, as

follows: violent causes, cancer, CHD, stroke and other. CHD mortality was defined as ICD-9: 410-414 and CVD mortality as ICD-9: 390-459.

Statistical analyses

Logistic regression analysis was used to calculate the 10-year probability of CHD and CVD mortality. We did not use the Cox proportional hazards regression model or an accelerated failure time model like the Framingham Study did^{1,11} because these models calculate the risk of CHD or CVD mortality in the absence of competing causes of death. As death by other causes becomes more important with increasing age, calculating the risk of CHD or CVD mortality in the presence of competing causes of death, as is done by logistic regression, yields different results. As these equations are meant to be used by clinicians in order to predict the risk of individual patients, and such patients are subject to competing causes of death, equations should give risk in the presence of competing causes of death, and thus logistic regression is better suited for the elderly. A disadvantage of logistic regression is that results apply only to the fixed follow-up time chosen for the analysis.

Risk factors included in the risk functions were: age, total and HDL cholesterol, systolic blood pressure, smoking, diabetes mellitus, ECG-left ventricular hypertrophy, use of anti-hypertensive medication and being a prevalent case of CHD or CVD. Dummy variables for country were added to the logistic regression models to take into account the differences in absolute risk between the countries. The maximum likelihood method was used to test if quadratic terms, log transformations of the continuous variables or interaction terms had to be added to the risk functions. A statistically significant interaction between the use of anti-hypertensive medication and Italy was included in the risk function for CHD and CVD mortality and a statistically significant interaction between being a prevalent case of CHD or CVD and Italy was also included in the risk functions.

The SAS computer package (version 6.12) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, USA, 1989).

Results

The mean levels of the risk factors included in the risk functions for CHD and CVD mortality are given in table 1. Total cholesterol ranged from 5.9 mmol/L in Italy to 6.2 mmol/L in Finland. HDL cholesterol ranged from 1.1 mmol/L in The Netherlands to 1.3 mmol/L in Italy. Systolic blood pressure was lowest in The Netherlands (151 mmHg) and highest in Italy (167 mmHg). The percentage of smokers was 19% in Finland, 26% in Italy and 30% in The Netherlands. The prevalence of diabetes was

highest in Italy and Finland (9%) and lowest in The Netherlands (6%). The prevalence of left ventricular hypertrophy was highest in Finland (10%) and lowest in Italy (3%). The use of anti-hypertensive medication varied from 13% in The Netherlands to 34% in Italy. A history of CHD (25%) and a history of CVD (39%) were both most prevalent in Finland. During the 10 years of follow-up, 289 CHD events (13%) and 545 CVD events (25%) occurred in 2,170 men.

Table 1 Mean, standard deviation and prevalence of risk factors included in the risk functions for CHD and CVD mortality in men aged 65-84 years in the total population of the FINE Study, Finland, The Netherlands and Italy.

	FINE	Finland	The Netherlands	Italy
total number	2,170	679	879	612
number of CHD events	289	142	100	47
number of CVD events	545	204	198	143
age (years)	71.6 (5.1)	71.5 (5.2)	71.5 (5.3)	72.0 (4.5)
total cholesterol (mmol/L)	6.05 (1.18)	6.17 (1.26)	6.10 (1.11)	5.85 (1.15)
HDL cholesterol (mmol/L)	1.20 (0.33)	1.23 (0.33)	1.12 (0.29)	1.29 (0.34)
systolic blood pressure (mmHg)	156.5 (23.1)	153.9 (22.6)	151.1 (21.5)	167.1 (22.4)
smoking (%)	25.5	18.6	30.4	26.3
diabetes (%)	7.6	8.8	5.7	9.0
left ventricular hypertrophy (%)	6.7	9.9	6.7	3.1
anti-hypertensive medication (%)	21.2	20.8	12.9	33.5
history of CHD (%)	18.0	24.6	15.9	13.6
history of CVD (%)	31.0	39.3	24.9	30.4

Table 2 shows the risk functions for CHD and CVD mortality fitted on the FINE data. The table presents the regression coefficients and the corresponding odds ratios (with 95% CI) for the risk factors. In appendix A the calculation of absolute risks for those coefficients is described. In the risk function for CHD mortality, total cholesterol was a statistically significant predictor (OR=1.24; 95% Confidence Interval 1.11-1.38), but this was not the case in the risk function for CVD mortality (OR=1.06; 95% CI 0.97-1.16). HDL cholesterol was statistically significantly associated with CVD mortality (OR=0.69; 95% CI 0.49-0.96), but not with CHD mortality. Systolic blood pressure was only statistically significantly associated with CVD mortality (OR=1.05; 95% CI 1.01-1.11). The effect of smoking on CHD and CVD

mortality was comparable, but was only statistically significant for CVD mortality (OR=1.28; 95% CI 1.01-1.63).

In these elderly men, diabetes was not statistically significantly associated with CHD and CVD mortality. Elderly men with left ventricular hypertrophy had a two times higher risk of CHD and CVD mortality compared to men without left ventricular hypertrophy. In Finland and The Netherlands, use of anti-hypertensive medication was not associated with CHD mortality. However, in Italy the odds ratio for the use of anti-hypertensive medication in the risk function for CHD mortality was 3.4 (0.95*3.58). Use of anti-hypertensive medication was not statistically significantly associated with CVD mortality. Being a prevalent case of CHD or CVD was associated with both CHD and CVD mortality, especially in Finland and The Netherlands. In Italy, the effect of being a prevalent case on CHD and CVD mortality was much lower, as shown by the lower ORs (OR=1.34 (0.32*4.18) for CHD mortality and 1.30 (0.51*2.55) for CVD mortality).

Table 2 Regression coefficients and odds ratios (95% Confidence Intervals) for the risk factors and 10-year CHD and CVD mortality in men aged 65-84 years.

	CHD mortality		CVD mortality	
	coefficient	OR (95% CI)	coefficient	OR (95% CI)
intercept	-7.9578	-	-9.0941	-
age (years)	0.0682	1.07 (1.04-1.10)	0.0963	1.10 (1.08-1.12)
total cholesterol (1 mmol/L)	0.2146	1.24 (1.11-1.38)	0.0584	1.06 (0.97-1.16)
HDL cholesterol (1 mmol/L)	-0.1842	0.83 (0.54-1.27)	-0.3773	0.69 (0.49-0.96)
systolic blood pressure (10 mmHg)	0.0014	1.01 (0.94-1.07)	0.0523	1.05 (1.01-1.11)
smoking (no/yes)	0.2140	1.24 (0.91-1.69)	0.2471	1.28 (1.01-1.63)
diabetes (no/yes)	0.0765	1.08 (0.67-1.74)	0.2230	1.25 (0.87-1.80)
left ventricular hypertrophy (no/yes)	0.6842	1.98 (1.30-3.02)	0.7042	2.02 (1.40-2.93)
anti-hypertensive medication	-0.0515	0.95 (0.63-1.42)	0.2306	1.26 (0.91-1.75)
anti-hypertensive medication * Italy	1.2741	3.58 (1.72-7.43)	0.4605	1.59 (0.96-2.62)
prevalent case	1.4291	4.18 (3.05-5.71)	0.9378	2.55 (1.98-3.29)
prevalent case * Italy	-1.1495	0.32 (0.13-0.77)	-0.6775	0.51 (0.31-0.82)
dummy The Netherlands (no/yes)	-0.6264	0.53 (0.40-0.72)	-0.2858	0.75 (0.59-0.97)
dummy Italy (no/yes)	-1.2469	0.29 (0.16-0.50)	-0.2846	0.75 (0.52-1.09)

The coefficients in the estimated risk functions for the dummy variables of country showed that the risk of CHD mortality was significantly lower in both The Netherlands and Italy, with the lowest risk in Italy. The risk of CVD mortality was highest in

Finland. The Netherlands and Italy had comparable absolute risks of CVD mortality, as shown by the comparable coefficients for the dummy variables of these countries.

Discussion

The results of the present study show that most classical risk factors for CHD and CVD mortality remain predictive in the elderly, of which total cholesterol and smoking were the most important ones for CHD mortality and HDL cholesterol, systolic blood pressure and smoking for CVD mortality. Left ventricular hypertrophy was also an important risk factor for CHD and CVD mortality in these elderly men. Being a prevalent case of CHD or CVD was an important risk factor in Finland and The Netherlands, while in Italy the use of anti-hypertensive medication was a risk factor for CHD mortality. For estimating the absolute risk of CHD and CVD mortality in the elderly it is necessary to take into account the European country in which they live.

In this study separate risk functions for CHD and CVD mortality in the elderly were developed. Several reasons could be given for the fact that it is important to have separate risk functions for the elderly to predict absolute risks instead of using the Framingham risk function in this age group. First, the Framingham risk function is developed to estimate absolute risks in persons aged 30-74 years.¹ The number of elderly (> 70 years) used to calculate the risk function in the Framingham Study is only 111 (4%) men and 163 (5%) women leading to unreliable estimates for the elderly.

Second, the Framingham risk function is calculated with an accelerated time failure model in which the presence of competing causes of death is not taken into account. Especially in the elderly in whom dying of causes other than CHD and CVD is frequent, it is important that absolute risks are calculated in the presence of competing causes of death. This is so because overall health in a population does not benefit from preventive action against CVD in persons who will die from other causes. Therefore in the present study, logistic regression analysis was used in which absolute risks of CHD or CVD mortality are calculated in the presence of competing causes of death.

Third, the relation between cardiovascular disease risk factors and CHD or CVD mortality is weaker in elderly men compared to middle-aged men.⁴⁻⁶ In general, relative risks decrease with increasing age, but absolute risks increase. The relative risk found in the Seven Countries Study for the relation between total cholesterol and CHD mortality in middle-aged men using Cox proportional hazards regression was 1.25 (95% CI 1.19-1.35, per 1.00 mmol/L increase).¹² In a recent analysis carried out

in the elderly men in the FINE Study, we found a relative risk of 1.17 (95% CI 1.06-1.29) using Cox proportional hazard analysis¹³ showing that also in this study population the predictive power of total cholesterol was lower in the elderly compared to that in middle-aged men.

In the present study, a non-significant odds ratio was found for the relation between total cholesterol and CVD mortality. This could be due to the assumption that serum total cholesterol is not associated with stroke.¹⁴ Therefore, the effect of total cholesterol on CVD mortality is diluted compared to the effect on CHD mortality. HDL cholesterol was not significantly associated with CHD mortality in the present study. It is unclear whether HDL cholesterol is an important risk factor for CHD mortality in the elderly.¹³ However, there was a statistically significant inverse association between HDL cholesterol and CVD mortality in the present study. This could be explained by the fact that several studies have found that a low HDL cholesterol level is a risk factor for stroke, even in the elderly.¹⁵⁻¹⁷

Systolic blood pressure was statistically significantly associated with CVD mortality but not with CHD mortality in these elderly men. Van den Hoogen et al.¹⁸ found a significant relation between systolic blood pressure and CHD mortality in middle-aged men in the Seven Countries Study (RR=1.17; 95% CI 1.14-1.20 per 10 mmHg increase). It was not estimated what the effect was of systolic blood pressure on CVD mortality in these middle-aged men. Systolic blood pressure is a risk factor for both CHD and CVD in Norwegian men until age 80, although the relative risks decrease with age.⁶ However, a relation between systolic blood pressure and CHD mortality in the elderly was not supported by our results.

There was an effect of smoking in both CHD and CVD risk functions, but only for CVD mortality the odds ratio was statistically significant. The effect of smoking in the elderly is attenuated compared to the effect in middle-aged men. Shopland et al.⁵ reported a relative risk for the relation between smoking and CHD mortality in men aged < 65 years of 2.8 and a relative risk in men aged ≥ 65 years of 1.6.

There was a positive, non-significant, effect of diabetes on both CHD and CVD mortality in this elderly population. The reason for the somewhat lower odds ratios for diabetes found in the present study compared with those found in other studies^{19,20} could be that we have adjusted for several variables associated with diabetes. If we calculate the crude odds ratio for diabetes in this study, it is indeed higher for both CHD and CVD mortality (OR=1.30; 95% CI 0.85-2.01 and OR=1.59; 95% CI 1.13-2.23, respectively).

Left ventricular hypertrophy was positively associated with CHD and CVD mortality. From the literature it is known that left ventricular hypertrophy is an independent risk factor for CHD and CVD mortality in the elderly.^{21,22} The odds ratio

found in the present study was comparable with that found in the Framingham Study in men aged 65 years and older (OR=2.1; 95% CI 1.3-3.5).

In Italy, men using anti-hypertensive medication had a higher risk of CHD mortality compared to those not using this type of medication. In Finland and The Netherlands, prevalent cases had a statistically significant higher risk of dying of CHD and CVD. These findings are difficult to explain with the data available. An explanation could be that using anti-hypertensive medication in Italy and being a prevalent case in Finland and The Netherlands are both proxies for being at a high risk for dying of CHD or CVD in the future. To examine this hypothesis a combined 'disease variable' was included in the risk functions for men using anti-hypertensive medication and/or being a prevalent case. The odds ratio for this 'disease variable' in the risk function for CHD mortality was 2.83 (95% CI 2.16-3.72) and in the risk function for CVD mortality 2.25 (1.82-2.78). These odds ratios were not significantly different between the countries. This means that elderly men using anti-hypertensive medication and/or being a prevalent case have a higher risk of dying of CHD and CVD, irrespective of the country in which they live.

The present study showed that, except for the intercept, the same risk functions for CHD and CVD mortality could be used in Finland, The Netherlands and Italy. Earlier results of the FINE Study showed indeed comparable relative risks for the relation between cholesterol levels and CHD mortality in the different European countries, but different absolute risks at the same the same cholesterol level in the elderly.¹³ Different absolute risks between the countries for men with the same risk factor profile were also found in the present study (see Appendix A). Therefore, dummy variables for country were added to the risk functions to take into account the differences in absolute risk between the countries. This means that a person in Italy with the same risk profile as a person in Finland would have a lower absolute risk due to a negative coefficient in the risk function for the dummy variable in Italy. Appendix A gives two examples demonstrating the effect of this difference between the countries. This may be due to differences in e.g. dietary patterns between the countries. The Mediterranean diet consumed by the Italian men is healthier than the Northern European diet consumed by the Finnish and Dutch men. This may explain the lower absolute risk for CHD at the same risk blood pressure and cholesterol levels in Italy.^{12,18} The effect of the dummy variables for country on the prediction of the absolute risks is larger for the risk function for CHD compared to that for CVD mortality. This is probably due to the fact that diet has a larger impact on the absolute risks of CHD compared to CVD.

Chapter 6

We can conclude that there is still an association between the risk factors total and HDL cholesterol, systolic blood pressure and smoking and CHD and/or CVD mortality in elderly men although the associations are weaker than in middle-aged men. Therefore, specific risk functions are needed for the elderly. Left ventricular hypertrophy, being a prevalent case of CHD or CVD in Finland and The Netherlands and using anti-hypertensive medication in Italy are also important risk factors. Besides this, it is necessary to take the European country into account when the absolute risk of CHD and CVD mortality in elderly men is calculated. The results of the present study have important implications for prevention in the elderly. A reduction in the absolute risk of dying from CHD or CVD through lifestyle and dietary changes in combination with proper clinical treatment is necessary and will probably increase the quantity and quality of life of elderly men.

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Appendix A

In this appendix the method of calculating absolute risks is presented, using the regression coefficients given in table 2. The 10-year probability of dying from a coronary heart disease (CHD) event is computed using the following equation:

$$\text{10-year probability} = \frac{1}{1 + \exp(-L)}$$

,where $L = -7.9578 + 0.0682 \cdot \text{age} + 0.2146 \cdot \text{total cholesterol} - 0.1842 \cdot \text{HDL cholesterol} + 0.0014 \cdot \text{systolic blood pressure} + 0.2140 \cdot \text{smoking} + 0.0765 \cdot \text{diabetes} + 0.6842 \cdot \text{left ventricular hypertrophy} - 0.0515 \cdot \text{use of anti-hypertensive medication} + 1.2741 \cdot (\text{anti-hypertensive medication} \cdot \text{Italy}) + 1.4291 \cdot \text{prevalent case} - 1.1495 \cdot (\text{prevalent case} \cdot \text{Italy}) - 0.6264 \cdot \text{dummy The Netherlands} - 1.2469 \cdot \text{dummy Italy}$.

Using the above mentioned equation, the 10-year probabilities of dying from a CHD event is estimated for four fictive persons. An *Italian man* aged 70 years without diabetes, who smokes, has no ventricular hypertrophy, no history of CHD, doesn't use anti-hypertensive medication, has a total cholesterol level of 6.0 mmol/L, HDL

cholesterol level of 1.3 mmol/L, and systolic blood pressure of 145 mmHg, has an L of $-7.9578 + 0.0682*70 + 0.2146*6.0 - 0.1842*1.3 + 0.0014*145 + 0.2140*1 - 1.2469*1 = -2.9656$ and thus a 10-year probability of dying from a CHD event of $\frac{1}{1 + \exp(2.9656)} = 0.05$. A *Finnish man* of the same age and with a similar risk profile

has a 10-year probability of dying from a CHD event of 0.15.

An *Italian man* aged 80 years with diabetes, who smokes, has ventricular hypertrophy, a history of CHD, use anti-hypertensive medication, has a total cholesterol level of 6.5 mmol/L, HDL cholesterol level of 1.2 mmol/L, and systolic blood pressure of 150 mmHg, has a 10-year probability of dying from a coronary heart disease event of 0.47. A *Finnish man* of the same age and with a similar risk profile has a 10-year probability of dying from a CHD event of 0.74.

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Chapter 6

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CHAPTER 7

Primary prevention of coronary heart disease through serum cholesterol lowering: quantifying the impact of different population strategies and a high-risk strategy

Abstract

Objective. Modeling the impact of different population prevention strategies and a high-risk strategy on the primary prevention of coronary heart disease (CHD).

Methods. Recent data on prevalence of risk factors from two Dutch population-based studies, including men and women aged 35-74 years, were used. We used the Framingham risk function to estimate absolute risks of CHD. Several population strategies were simulated: lowering the intake of saturated and trans fatty acids and smoking cessation. In the high-risk strategy, all persons with a high absolute risk for CHD were treated with cholesterol lowering medication.

Results. In total 13% of the CHD events can be prevented through lowering the intake of saturated fat from on average 15 percent of energy to 12 percent of energy, trans fatty acids from on average 1.9 percent of energy to 0.5 percent of energy and reducing the number of smokers by 15% in the The Netherlands. Almost 2% of the CHD events can be prevented using the high-risk strategy.

Conclusion. Of the population interventions, lowering the intake of trans fatty acids, attainable through advances in food technology, had the largest impact on the number of CHD events.

Introduction

Observational studies and clinical trials have indicated that a reduction in serum cholesterol is associated with a reduction of coronary heart disease and total mortality.¹⁻⁴ The serum cholesterol level can be lowered through different preventive strategies aimed at the total population or at high risk groups only. In the population strategy, focused on the reduction of risk factors in the general population, changes in lifestyle such as lowering the intake of saturated fat⁵ and trans fatty acids⁶, and smoking cessation⁷ could be induced. In the high-risk strategy, focused on individuals with a high absolute risk of coronary heart disease due to an unfavorable risk factor profile, serum cholesterol could be lowered by cholesterol lowering medication, like statins.

In 1998, a revised version of the Dutch consensus guidelines for cholesterol lowering therapy was published.⁸ According to this consensus, treatment with cholesterol lowering medication in primary prevention is based on the absolute level of risk of coronary heart disease, taking the total risk profile of an individual into account, including gender, age, serum total and HDL cholesterol, hypertension, diabetes mellitus, smoking and family history of premature coronary heart disease (< 60 years). Cholesterol lowering therapy is indicated in persons with an absolute risk for developing coronary heart disease above a given age- and gender specific cut-off point.

The purpose of this article is to calculate the impact of different preventive population strategies and a high-risk strategy on the primary prevention of coronary heart disease, using the new Dutch consensus guidelines for cholesterol lowering therapy based on absolute risks. Outcome parameters that are modeled are 10-year absolute risk of coronary heart disease, the number of coronary heart disease events, life expectancy and the number of people needing cholesterol lowering medication in The Netherlands.

Methods

Study population

We used data of two population-based studies carried out in The Netherlands. The first study, the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN-project), is a cross-sectional study carried out from 1993 to 1997 in more than 21,000 men and women aged 20-64 years. The general purpose of this project was to determine both the level of risk factors for chronic diseases, e.g. cholesterol, blood pressure, smoking, and the prevalence of several chronic conditions in a

random sample of the general population. The project was carried out at the municipal health services in three towns in The Netherlands: Amsterdam, Doetinchem, and Maastricht.

The second study, the Rotterdam Study, is a population-based prospective study carried out in almost 8,000 men and women aged 55 years and over, living in an urban district of Rotterdam. The Rotterdam Study investigates the prevalence, incidence, and determinants of cardiovascular, neurological, locomotor, and ophthalmologic diseases.⁹ Baseline measurements were carried out from 1990 to 1993.

In the analyses, respondents with prevalent cardiovascular disease (n=463 in MORGEN and n=440 in the Rotterdam Study) or missing values for the risk factors (n=355 and n=254 respectively) were excluded. Respondents with prevalent cardiovascular disease were excluded because we studied only primary prevention. In total data of 8,019 men and 9,674 women aged 35 to 74 years were used for the modeling approach.

Dutch consensus guidelines for cholesterol lowering therapy

In the new Dutch consensus guidelines for cholesterol lowering therapy, medication treatment in primary prevention is recommended in persons with a combination of risk factors for coronary heart disease leading to a high absolute risk for developing coronary heart disease based on the Framingham risk function.^{8,10} The factors included in the risk function are gender, age, total to HDL cholesterol ratio, hypertension, diabetes mellitus and smoking.

Cholesterol lowering medication in primary prevention is indicated if the absolute risk of coronary heart disease over the next 10 years (based on a combination of the above mentioned risk factors) is > 25% at ages < 60 years and > 30% at age 60-69 years. In persons aged 70 years and over, cholesterol lowering medication is indicated if the absolute risk exceeds 40% in men and 35% in women. For persons with a family history of premature coronary heart disease and for patients with diabetes mellitus the cut-off point was lowered with 5%, because of their increased risk of coronary heart disease due to factors that are not taken into account in the Framingham risk function.

Measurements

Nonfasting serum total cholesterol was determined in both studies using a CHOD-PAP method (Boehringer).^{11,12} HDL cholesterol was determined in the supernatant after precipitation of apoB-containing lipoproteins with magnesium phosphotungstate.¹³ All cholesterol measurements were performed in two laboratories that are permanent members of the international Cholesterol Reference

Method Laboratory Network. The cholesterol ratio was defined as the concentration of total cholesterol divided by HDL cholesterol. The levels for the cholesterol ratio were somewhat higher in the Rotterdam Study compared with those in the MORGEN-project, mostly due to time trends. Cholesterol levels in all age groups have declined in The Netherlands since 1993 and data from the Rotterdam Study were collected earlier (1990-1993) than those from the MORGEN-project (1993-1997). To make the levels of the cholesterol ratio consistent over the entire age range we corrected these levels in the Rotterdam Study in both men and women assuming a uniform decrease of 0.05 in men and 0.09 in women over the time period between both studies.

Blood pressure was measured twice on the upper arm with the participant in sitting position using a random zero sphygmomanometer. Systolic and diastolic blood pressure were recorded as the first and fifth Korotkoff phase, respectively. Hypertension was defined as a systolic blood pressure ≥ 160 mmHg and/or a diastolic blood pressure ≥ 95 mmHg and/or the use of anti-hypertensive medication.¹⁴ Information on smoking habits was obtained from a standardized questionnaire in both studies. Two categories were defined: current smokers and non-smokers. In the MORGEN-project, diabetes mellitus was defined as self-reported diabetes or a random nonfasting serum glucose level ≥ 11.1 mmol/L. In the Rotterdam Study, diabetes mellitus was defined as use of antidiabetic medication or a random or post-load serum glucose level ≥ 11.1 mmol/L. Family history of premature coronary heart disease in first degree relatives was measured in the MORGEN-project for premature (<60 years) myocardial infarction in parents only and in the Rotterdam Study for premature (< 65 years) myocardial infarction in parents, siblings and children. Prevalence of cardiovascular disease was defined as a self-reported history of myocardial infarction, stroke or claudicatio intermittens in the MORGEN-project and as a self-reported history of myocardial infarction, stroke, claudicatio intermittens or angina pectoris in the Rotterdam Study.

In the MORGEN-project dietary intake was measured with a 178-item semi-quantitative food frequency questionnaire.¹⁵ In the Rotterdam Study dietary intake was assessed with a 170-item semi-quantitative food frequency questionnaire adapted for use in the elderly.¹⁶ Nutrient and energy intake were quantified for each individual using the 1996 automated version of the Dutch food composition table for the MORGEN-project and that from 1993 for the Rotterdam Study.^{17,18} Separate food tables were constructed with data on the amount of trans fatty acids in products.¹⁹

Strategies of intervention

We simulated different intervention strategies: three population strategies and a high-risk strategy, and compared them with a reference scenario of no intervention.

In the reference scenario, the current age- and gender specific prevalence of the risk factors from the MORGEN-project and the Rotterdam Study were used.

Three different population strategies were simulated: intervention on saturated fat, trans fatty acids and smoking. For the intervention on saturated fat and smoking we defined an optimistic and a realistic scenario, based on what is known from the literature. We also estimated the combined effect of the three different population strategies. In the optimistic intervention scenario on saturated fat, the saturated fat intake of each individual was reduced to 10 percent of energy (the Dutch national target, the current average intake in The Netherlands is 15 percent of energy) and in the realistic scenario, it was reduced to 12 percent of energy. For each individual, the equation of Keys et al.²⁰ was used to transform the reduction in saturated fat intake into a reduction in serum total cholesterol. For the intervention on trans fatty acids we simulated one feasible scenario in which the intake of trans fatty acids of each individual was reduced to 0.5 percent of energy (the current average intake in The Netherlands is 1.9 percent of energy). This intake level could be achieved if all trans fatty acids are removed from predominantly vegetable oils, through food technology, leaving an intake level of 0.5 percent of energy from natural sources (meat and dairy products).²¹ In the Rotterdam Study, there were no data available about the intake of trans fatty acids and therefore we have assumed a mean intake of trans fatty acids of 1.9 percent of energy in both men and women (mean intake in the MORGEN-project), which was reduced to 0.5 percent of energy. To transform the reduction in the intake of trans fatty acids into a change in serum cholesterol, we assumed a decline in total cholesterol by 0.026 mmol/L and an increase in HDL cholesterol by 0.017 mmol/L for each 1 percent of energy decline in trans fatty acids.⁶ In the optimistic intervention scenario on smoking, the number of smokers was reduced by 25% (e.g. from 40% to 30%) and in the realistic scenario, it was reduced by 15% (e.g. from 40% to 34%). These percentages were chosen based on the results of a Dutch media campaign to encourage smokers to quit smoking, that found that about 14% of the smokers had stopped smoking after one year.²²

In the high-risk strategy we assumed that all persons with an absolute risk for developing coronary heart disease above their age- and gender specific cut-off point were treated with cholesterol lowering medication according to the primary prevention guidelines of the Dutch cholesterol consensus. We assumed that the absolute risk of coronary heart disease of those using cholesterol lowering medication was lowered by 33%.¹

Calculation method of outcome parameters

To estimate the 10-year absolute risk of coronary heart disease, the number of coronary heart disease events in the next ten years and the number of people needing cholesterol lowering medication for the different strategies, we used the Framingham risk function,¹⁰ the age- and gender specific prevalence of the risk factors from the MORGEN-project for the 35-64 year olds and from the Rotterdam Study for the 65-74 year olds and demographic data from Statistics Netherlands [<http://statline.cbs.nl/statweb/>].

To estimate the gain in life expectancy for the different strategies we used the life table method. Total mortality rates were derived from Statistics Netherlands for 1994. For each strategy, all cause mortality rates were calculated for each 5-year age group, using the age and gender-specific prevalence of the risk factors and relative risks from literature. For the interventions on saturated fat and trans fatty acids, the decrease in total mortality was calculated using a relative risk of 0.94 per 1 mmol/L decrease in total cholesterol for men and women²³ and relative risks of 0.95 and 0.98 per 0.1 mmol/L increase in HDL cholesterol in men and women, respectively.²⁴ For the interventions on smoking, we used a relative risk of 2.34 for current smoking versus non-smoking men and a relative risk of 1.90 for current smoking versus non-smoking women.²⁵ For the high-risk strategy, new total mortality rates were calculated by subtracting the reduction in coronary heart disease mortality (33%)¹, assuming that the mortality reduction was proportional to the reduction of event risks.

Results

Baseline characteristics of both populations studied are shown in table 1. The mean total to HDL cholesterol ratio was 5.0 in men and 3.9 in women aged 35-64 years and 5.5 in men and 5.1 in women aged 65-74 years. Almost 95% of the men and women aged 35-74 years consumed more than 10 percent of energy saturated fat and more than 80% consumed more than 12 percent of energy saturated fat. The prevalence of diabetes and hypertension was higher and the prevalence of smoking was lower in men and women in the older age group compared with the younger age group.

Table 1 Mean, standard deviation and prevalence of risk factors in men and women aged 35-64 years in the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN-project) and in men and women aged 65-74 years in the Rotterdam Study.

	men (N=8,019)		women (N=9,674)	
	MORGEN-project (N=7,289)	Rotterdam Study (N=730)	MORGEN-project (N=8,593)	Rotterdam Study (N=1,081)
age (years)	47.6 (7.4)	69.4 (2.9)	47.5 (7.4)	69.9 (2.8)
total cholesterol (mmol/L)	5.52 (1.02)	6.29 (1.14)	5.46 (1.05)	6.98 (1.21)
HDL cholesterol (mmol/L)	1.19 (0.31)	1.23 (0.33)	1.51 (0.38)	1.45 (0.39)
total/HDL cholesterol	4.96 (1.69)	5.45 (1.67) [‡]	3.85 (1.25)	5.11 (1.56) [‡]
saturated fat intake (percent of energy) [*]	14.8 (2.6)	14.4 (3.0)	15.0 (2.7)	14.7 (3.3)
trans fatty acids (percent of energy) [†]	1.9 (0.6)	-	1.9 (0.6)	-
current smoker (%)	34.8	23.7	35.3	18.4
non-smoker (%)	65.2	76.3	64.7	81.6
hypertension (%) [§]	13.8	30.3	11.7	36.1
diabetes (%) [§]	2.3	10.5	1.7	10.2
cholesterol lowering medication (%)	1.7	1.4	1.5	2.2

* information available for 7,253 men and 8,565 women from the MORGEN-project and 559 men and 774 women from the Rotterdam Study

† information available for 7,253 men and 8,565 women from the MORGEN-project and no information about the intake of trans fatty acids available from the Rotterdam Study

‡ not corrected

§ for definition see methods

Table 2 10-year absolute risk (%) of coronary heart disease for the reference scenario, the different population strategies and the high-risk strategy and baseline values of the risk factors in men and women aged 35-74 years in 10-year age groups.

	men (N=8,019)				women (N=9,674)			
	35-44 yrs (N=2,731)	45-54 yrs (N=2,974)	55-64 yrs (N=1,584)	65-74 yrs (N=730)	35-44 yrs (N=3,331)	45-54 yrs (N=3,415)	55-64 yrs (N=1,847)	65-74 yrs (N=1,081)
Baseline values of the risk factors								
saturated fat (percent of energy)	14.6	14.8	14.9	14.2	14.9	15.1	15.2	14.1
trans fatty acids (percent of energy)	1.9	1.9	1.8	-	2.0	1.9	1.9	-
smoking (%)	39	34	30	29	39	36	28	26
Reference scenario	5.1	10.8	17.2	23.4	1.4	4.8	9.0	11.5
Population strategies								
saturated fat to 12 percent of energy	4.7	10.1	16.4	22.5	1.2	4.3	8.4	10.8
saturated fat to 10 percent of energy	4.6	9.9	16.1	22.1	1.1	4.2	8.2	10.5
trans fatty acids to 0.5 percent of energy	4.5	9.7	15.9	21.9	1.2	4.3	8.2	10.5
15% quit smoking	4.9	10.4	16.9	23.1	1.3	4.6	8.8	11.4
25% quit smoking	4.8	10.3	16.7	22.9	1.3	4.5	8.7	11.3
High-risk strategy	5.1	10.6	16.6	22.8	1.4	4.8	8.9	11.4

The 10-year absolute risks of coronary heart disease for the different strategies in men and women in 10-year age groups are given in table 2. In the reference scenario, the average 10-year absolute risk of coronary heart disease was 5.1% in men and 1.4% in women aged 35-44 years and increased to 23.4% in men and 11.5% in women aged 65-74 years. The decline in absolute risk of coronary heart disease was highest for the intervention on trans fatty acids (1.5% in men and 1.0% in women aged 65-74 years), followed by the intervention on saturated fat and smoking. The interventions on smoking showed the same decline in absolute risk of coronary heart disease in every age category between 45 and 75 years in both men and women, while the interventions on diet showed a greater decline in absolute risk with increasing age.

Table 3 Number of events of coronary heart disease in the next 10 years for the reference scenario, the different population strategies and the high-risk strategy in men and women aged 35-74 years in the total population of The Netherlands (N=6,933,000 in 1994).

	men	women
Total number of events of coronary heart disease	394,037	186,408
reference scenario		
Number of events of coronary heart disease prevented*:		
population strategies		
saturated fat to 12 percent of energy	19,993 (5%)	15,220 (8%)
saturated fat to 10 percent of energy	28,743 (7%)	19,641 (11%)
trans fatty acids to 0.5 percent of energy	32,859 (8%)	18,635 (10%)
15% quit smoking	8,375 (2%)	4,539 (2%)
25% quit smoking	13,960 (4%)	7,566 (4%)
combination of population strategies		
saturated fat to 12 percent of energy, trans fatty acids to 0.5 percent of energy and 15% quit smoking	49,967 (13%)	22,629 (12%)
saturated fat to 10 percent of energy, trans fatty acids to 0.5 percent of energy and 25% quit smoking	62,133 (16%)	28,104 (15%)
high-risk strategy	8,252 (2%)	1,751 (1%)

* number of events in reference scenario – number of events in population or high-risk strategy

The total number of events of coronary heart disease in the next ten years for the reference scenario and the population and high-risk strategies in men and women in The Netherlands are given in table 3. In the combination of the realistic population intervention strategies (reducing saturated fat from on average 15 percent of energy to 12 percent of energy, trans fatty acids from on average 1.9 percent of energy to 0.5 percent of energy and the number of smokers with 15%) 49,967 (13%) events in men and 22,629 (12%) events in women would be prevented. For the high-risk strategy, 8,252 (2%) and 1,751 (1%) events in men and women respectively would be prevented.

The gain in life expectancy for the population and high-risk strategies in men and women is given in figure 1. The gain in life expectancy was highest for the optimistic intervention on smoking in both men (mean gain 7.3 months) and women (mean gain 2.6 months) aged 35-74 years. The gain in life expectancy for the optimistic intervention on saturated fat was 1.7 months in both men and women aged 35-74 years. For the intervention on trans fatty acids the mean gain in life expectancy was 1.3 months for men and 0.7 month for women aged 35-74 years. For the combination of the realistic population interventions (reducing saturated fat from on average 15 percent of energy to 12 percent of energy, trans fatty acids from on average 1.9 percent of energy to 0.5 percent of energy and the number of smokers by 15%) the gain in life expectancy varied from 7.7 months in men and 3.8 months in women aged 35-44 years to 4.8 months in men and 2.3 months in women aged 65-74 years. The gain in life expectancy for the high-risk strategy was 0.3 month in men aged 65-74 years and 0.08 month in women of the same age. In those aged 35-64 years the gain in life expectancy for the high-risk strategy was almost zero.

The number of people needing cholesterol lowering medication, according to the Dutch consensus guidelines for cholesterol lowering therapy, for the reference scenario and the different population strategies in men and women is given in figure 2. The number of people needing cholesterol lowering medication was about four times higher in men compared to women. For the population strategies, the number of people needing cholesterol lowering medication was lowest after the intervention on trans fatty acids, followed by the interventions on smoking and saturated fat. In men aged 55-64 years for example, the total number of people needing treatment was around 55 per 1000 for the reference scenario and 37 per 1000 for the intervention on trans fatty acids. In women, these figures were only 11 per 1000 and 8 per 1000 respectively.

Table 4 Gain in life expectancy (in months) for the population strategies and the high-risk strategy compared with the reference scenario in men and women aged 35-74 years in 10-year age groups.

	men				women			
	35-44 yrs	45-54 yrs	55-64 yrs	65-74 yrs	35-44 yrs	45-54 yrs	55-64 yrs	65-74 yrs
Population strategies								
saturated fat to 12 percent of energy	0.98	0.92	0.81	0.64	0.97	0.91	0.83	0.70
saturated fat to 10 percent of energy	1.96	1.83	1.62	1.28	1.94	1.83	1.65	1.41
trans fatty acids to 0.5 percent of energy	1.50	1.40	1.23	0.98	0.82	0.78	0.70	0.60
15% quit smoking	5.21	4.80	4.10	3.14	2.02	1.76	1.39	0.97
25% quit smoking	8.83	8.15	6.96	5.34	3.39	2.94	2.33	1.62
High-risk strategy	0	0	0.064	0.27	0	0	0.0094	0.076

Table 5 Total number of people needing cholesterol lowering medication (per 1,000) for the reference scenario and the population strategies in men and women aged 35-74 years in 10-year age groups.

	men				women			
	35-44 yrs	45-54 yrs	55-64 yrs	65-74 yrs	35-44 yrs	45-54 yrs	55-64 yrs	65-74 yrs
Reference scenario	0.3	18.5	54.9	42.6	0	2.1	10.6	15.1
Population strategies								
saturated fat to 12 percent of energy	0	14.1	43.2	31.9	0	1.6	9.5	10.6
saturated fat to 10 percent of energy	0.2	16.1	45.3	36.0	0	1.7	10.2	12.1
trans fatty acids to 0.5 percent of energy	0.2	10.8	36.6	27.2	0	1.2	7.5	11.4
15% quit smoking	0.3	14.7	44.9	36.1	0	1.8	9.4	12.8
25% quit smoking	0.3	16.2	48.9	38.7	0	1.9	9.9	13.7

Discussion

The results of the present study indicate that in both men and women the population strategies showed a larger effect on the primary prevention of coronary heart disease than the high-risk strategy. Of the population strategies, the trans fatty acids strategy had the largest effect on the decline in 10-year absolute risk of coronary heart disease, the number of events of coronary heart disease in the next ten years and the number of people needing cholesterol lowering medication across all age groups. The smoking strategies had the largest effect on the gain in life expectancy in both men and women.

We modeled two different kind of diet interventions, of which the intervention on trans fatty acids showed a slightly stronger effect on most parameters studied. The reason for this is that a decline in trans fatty acids has not only an effect on total cholesterol but also on HDL cholesterol while saturated fat has only an impact on total cholesterol. It can be estimated, using the equation of Keys et al.²⁰ what change in serum cholesterol can be expected for both strategies of intervention. The mean intake of saturated fat in this study was 15 percent of energy. A decline in the saturated fat intake by 5 percent of energy (optimistic saturated fat scenario) results in a decline in serum total cholesterol by about 0.30 mmol/L. The mean intake of trans fatty acids in this study was 1.9 percent of energy. A decline in the intake of trans fatty acids by 1.4 percent of energy (trans fatty acids scenario) results in a decline in serum total cholesterol by 0.04 mmol/L and an increase in HDL cholesterol by 0.02 mmol/L.⁶

Changes in the intake of trans fatty acids and saturated fat do not only have an impact on the serum cholesterol level, but also on other factors which are important in atherogenesis, like LDL-oxidation, coagulation factors, lipoprotein(a) and the quality of the vessel wall.²⁶ This means that the impact of the diet interventions could be larger than expected on the basis of the cholesterol level only, and therefore possibly underestimated.

The intervention on trans fatty acids in the population could be achieved through advances in food technology, needing no behavioral change from the public.²⁷ Artificial trans fatty acids in food products, derived from the partial hydrogenation of oils, can be eliminated, leaving an intake level of approximately 0.5 percent of energy from natural sources (meat and dairy products).²² In contrast, a decline in the intake of saturated fat can only be achieved through changes in dietary habits of the population. Dietary intervention trials have shown that serum total cholesterol was reduced with 3.0% (95% CI 1.8% to 4.1%) after a diet with 8-10% saturated fat (step 1 diet of the American Heart Association).²⁸

The impact of the different intervention strategies depends on the prevalence of the risk factor in the population studied and the relative risk associated with it. The effect of the different strategies of intervention on the decline in absolute risk of coronary heart disease seems to be larger in the older age groups, due to their higher absolute risk. However, the effect of the interventions in the older age groups could be overestimated because the relative risks tend to decrease with increasing age. For the smoking strategies there was no larger decline in absolute risk in the older age groups due to the lower prevalence of smoking at older age. The effect of the population strategies on the gain in life expectancy was different across the age groups. The gain in life expectancy decreased with increasing age in especially the smoking strategies. This was also due to declining prevalence of smoking with age. For the diet strategies there was no large decline in the gain in life expectancy with increasing age. However, especially in the older age groups the life expectancy could be overestimated. We have used the same relative risks across all age groups for the calculation of the life expectancy, whereas there is evidence that relative risks tend to decrease with age. The gain in life expectancy was higher in men after the smoking strategy, because of the higher relative risk used for men and the higher smoking prevalence in men compared to women. The effect of the high-risk strategy on the decline in absolute risk of coronary heart disease and the gain in life expectancy in the whole population was low, due to the relatively small number of people eligible for drug treatment. However, the effect of the high-risk strategy on the individual level would be large and still 10,000 coronary heart disease events could be prevented in the next ten years in both men and women aged 35-74 years. The number of people needing cholesterol lowering medication was higher in those aged 55-64 years compared with men and women aged 65-74 years, because the cut-off point of the absolute risk of coronary heart disease indicating medication use is higher in men and women aged 65-74 years. The number of events of coronary heart disease and the number of people needing treatment was higher in men compared with women for all strategies because of the higher absolute risks in men.

There are several limitations of this study that should be mentioned. First, the estimation of the 10-year absolute risk of coronary heart disease in this study was based on the Framingham risk function. The question is whether this risk function can be generalized to the Dutch population. A recent study showed that the Framingham risk function is accurate for northern European populations.²⁹ Second, ECG-left ventricular hypertrophy, a variable included in the Framingham risk function for 10-year coronary heart disease risk, was not used in this study because of lack of Dutch prevalence data. We assumed that nobody had ECG-left ventricular hypertrophy in the study population. This means that especially in the elderly (> 60

years) the risk of coronary heart disease could be underestimated, because ECG-left ventricular hypertrophy is more common in this age group. Third, two different datasets were used in this study, data from the MORGEN-project and the Rotterdam Study. The measurement protocols of most variables were comparable, but diabetes was measured differently. In the MORGEN-project the use of antidiabetic medication was not known and therefore not included in the definition of diabetes. Therefore, the prevalence of diabetes could be somewhat underestimated in the MORGEN-project (persons aged 35-64 years). Fourth, we have not included the effect of lag-time in our model. However, we expect that the effect of lag-time on the coronary heart disease mortality would be approximately the same for the different interventions.

A decline in serum total cholesterol has a significant impact on coronary heart disease mortality. We estimated that in total 10,003 (2%) coronary heart disease cases in Dutch men and women aged 35-74 years would be prevented in the next 10 years if persons were treated according to the Dutch consensus guidelines for cholesterol lowering therapy. However, if all people aged 35-74 years in The Netherlands reduce their saturated fat intake to 12 percent of energy or less (instead of an average of 15 percent of energy), their trans fatty acid intake to 0.5 percent of energy or less (instead of an average of 1.9 percent of energy) and if 15% of the smokers stop smoking, in total 72,596 (13%) cases of coronary heart disease would be prevented in the next 10 years. This means that a combination of the three population strategies would have a larger impact on the primary prevention of coronary heart disease compared to the high-risk strategy.

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CHAPTER 8

General discussion

The aim of this thesis was to study the public health impact of serum total and HDL cholesterol levels in The Netherlands. In this chapter the results of the studies described in this thesis are integrated and discussed. After a summary of the main findings, the impact of the long-term trends in cholesterol levels on public health in The Netherlands is described. Subsequently, the question whether serum total and HDL cholesterol are still risk factors in the elderly is discussed. Therefore, the studies described in this thesis on the relation between total and HDL cholesterol and coronary heart disease carried out in the elderly are compared and some methodological aspects of studies in the elderly are considered. Also the public health effect of cholesterol treatment in the elderly is described. Risk functions developed for the elderly are described and discussed. Prevention of coronary heart disease through cholesterol lowering can be achieved by several types of interventions, of which the effect of dietary interventions and the use of cholesterol lowering medication is described in the third part of this chapter. Finally, the main conclusions are formulated.

Main findings

Recent levels and trends in total and HDL cholesterol levels in The Netherlands were studied (chapter 2). The total cholesterol level decreased significantly by 0.19 mmol/L in men and by 0.27 mmol/L in women between 1993 and 1997, while the level of HDL cholesterol remained stable in both men and women. The observed trend in total cholesterol could only for a small part be explained by changes in the intake of saturated fatty acids, trans fatty acids, dietary cholesterol, use of cholesterol lowering medication and for women oral contraceptives and estrogen replacement.

Results from a large 20-year follow-up study in middle-aged men and women showed that, given a low cholesterol level (< 5.2 mmol/L), the additional effect of smoking on coronary heart disease, cardiovascular diseases and all-cause mortality was larger compared to that of elevated blood pressure (systolic ≥ 140 mmHg) (chapter 3). Despite low cholesterol levels, a significantly higher risk of coronary heart disease, cardiovascular diseases and all-cause mortality was found in smoking men and women with elevated blood pressure. These mortality risks increased further in persons with intermediate cholesterol levels (5.2-6.5 mmol/L). When the

total cholesterol level in smoking men and women with elevated blood pressure was elevated to ≥ 6.5 mmol/L, the risk of coronary heart disease mortality was almost 10 times higher in men and 16 times higher in women compared to those with a low risk factor profile.

Because it is still unclear whether the relation between serum cholesterol and coronary heart disease still holds in the elderly, more evidence on the impact of total and HDL cholesterol on coronary heart disease in the elderly is needed (chapter 4 and 5). Results from two large prospective studies showed that serum total cholesterol remains an important predictor of coronary heart disease in elderly men and women. The effect of HDL cholesterol was less consistent in the elderly. HDL cholesterol was related to coronary heart disease in men and women aged 55 years and older, but lost its predictive power in men at older age (> 70 years). In women aged 70 years and older, HDL cholesterol was still a risk factor.

Furthermore, a 10-year follow-up study carried out in the elderly in different European countries showed that it is essential to have separate risk functions developed in the elderly to predict their absolute risk for coronary heart disease and cardiovascular diseases mortality (chapter 6). Most classical risk factors for coronary heart disease and cardiovascular diseases mortality remain predictive in the elderly, of which total cholesterol and smoking were the most important ones for coronary heart disease mortality and HDL cholesterol, systolic blood pressure and smoking for cardiovascular diseases mortality. Left ventricular hypertrophy, being a prevalent case of coronary heart disease or cardiovascular diseases in Finland and The Netherlands and use of anti-hypertensive medication in Italy were also important risk factors. For estimating absolute risks in the elderly, it was necessary to take country into account.

Finally, the impact of different preventive population strategies and a high-risk strategy on the primary prevention of coronary heart disease was statistically modelled (chapter 7). The results showed that in total 13% of the coronary heart disease events can be prevented in the next ten years in men and women aged 35-74 years through lowering the intake of saturated fatty acids from on average 15 percent of energy to 12 percent of energy, trans fatty acids from on average 1.9 percent of energy to 0.5 percent of energy and reducing the number of smokers by 15%. Of the population interventions separately, lowering the intake of trans fatty acids had the largest effect on the number of coronary heart disease events that could be prevented.

Trends in total and HDL cholesterol

From a public health point of view it is important to study trends in total and HDL cholesterol. A decline in total cholesterol could have a large impact on incidence of and mortality from coronary heart disease. Besides this, monitoring studies can be used for evaluation of public health campaigns that are focused on reducing cholesterol levels in the general population. The long-term trend in total and HDL cholesterol in The Netherlands could be studied using data from two large monitoring studies carried out between 1987 and 1997 in men and women aged 20-59 years. The results of both studies can be analysed together because the same study protocol was used and the same standardised measurements of cholesterol were carried out in the same reference laboratory.

The trend in total and HDL cholesterol between 1987 and 1992 has previously been described by Verschuren et al.¹ In men, a decline in total cholesterol of 0.1 mmol/L and a decline in HDL cholesterol of 0.07 mmol/L was observed between 1987 and 1992. In women, no statistically significant changes in total and HDL cholesterol levels were observed.

The trend in total and HDL cholesterol between 1993 and 1997 was described in chapter 2. In figure 1, the age-standardised long-term trends in total and HDL cholesterol levels are given. Between 1987 and 1997, total cholesterol declined significantly by 6.1% in men from 5.41 mmol/L to 5.08 mmol/L and by 6.6% in women from 5.34 mmol/L to 4.99 mmol/L. In both men and women, the largest decline was observed between 1994 and 1995. HDL cholesterol declined from 1.22 mmol/L in 1987 to 1.19 mmol/L in 1997 in men and increased from 1.47 mmol/L in 1987 to 1.52 mmol/L in 1997 in women. This means that between 1987 and 1997 a substantial decline in the level of total cholesterol has taken place in The Netherlands in men and women aged 20-59 years. Small, non-significant, changes in HDL cholesterol levels were observed. Results from the Zutphen Elderly Study showed also a decline in total cholesterol of similar magnitude in Dutch men aged 70 years and older in the early nineteen nineties. Also in these elderly men, no change in HDL cholesterol levels was observed.² Therefore, it can be concluded that a decline in total cholesterol has taken place in the total Dutch population.

The decline in total cholesterol levels observed between 1987 and 1997 in The Netherlands is of great public health importance. Most cases of coronary heart disease occur in persons aged 60 years and older. It is known from a meta-analysis of longitudinal studies that on average a total cholesterol reduction of 1% results in a decrease of coronary heart disease mortality by 2-3% in men and women aged 60 years and older.⁸ Because the observed decline in total cholesterol by 6.1% in men

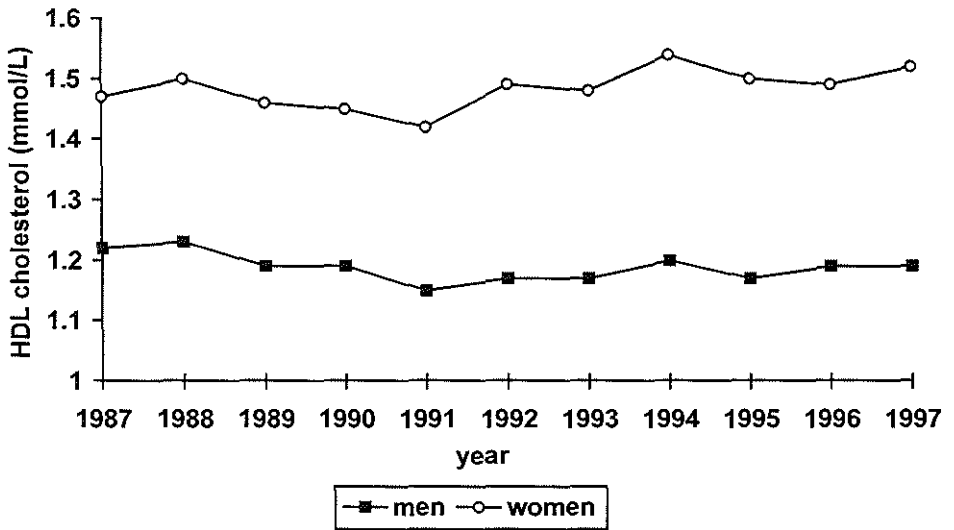
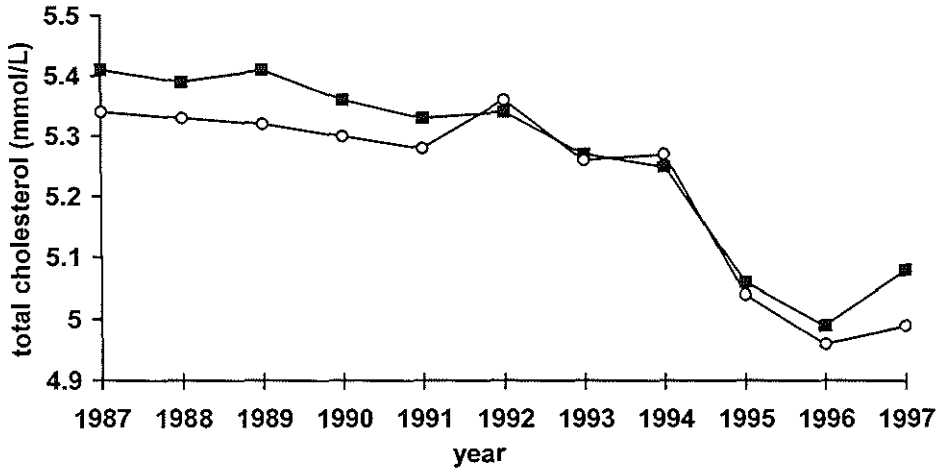


Figure 1: Mean total and HDL cholesterol level per year in men and women, standardised to the age distribution of the Dutch population aged 20-59 years in 1995. (Note: HDL cholesterol levels measured in the period January 1987 to November 1994 were corrected for laboratory drift as described in chapter 3 of this thesis)

and by 6.6% in women was generalizable to the elderly, this would lead to a decline in mortality from coronary heart disease in the future by at least 12%. Applying these figures to a yearly mortality of coronary heart disease of 20,000 persons in The Netherlands aged mainly 60 years and older, this corresponds to a decline in the absolute number of coronary heart disease deaths per year of 2,400.

It is interesting to relate the recent trend in total cholesterol levels to mortality from coronary heart disease. In Finland, it was estimated to what extent changes in total cholesterol levels explained the decline in coronary heart disease mortality.⁹ In men, the observed 13% decline in total cholesterol level was associated with a 26% decline in coronary heart disease mortality. In women, the observed 18% decline in total cholesterol level was associated with a 35% decline in coronary heart disease mortality. This means that a 1% decrease in cholesterol concentration leads to an approximately 2% decline in coronary heart disease risk in Finland.

In The Netherlands, it took until the early nineteen nineties before the total cholesterol level started to decline. This is in contrast with for example Finland where total cholesterol levels have decreased substantially since the nineteen seventies.³ Mean total cholesterol declined by about 1.2 mmol/L in both men and women aged 30-59 years between 1972 and 1997.³ In 1997, the mean cholesterol level for men was 5.61 mmol/L and 5.45 mmol/L for women. Despite the large decline in cholesterol levels over the last decades in Finland, total cholesterol levels are still higher compared to those in The Netherlands.

The large decline in cholesterol levels in Finland can mainly be attributed to intensive nutritional education and health promotion activities for preventing cardiovascular diseases. In Finland the North Karelia Project, a community-based cardiovascular prevention programme, was started in the early 1970s. The aim of this project was to give health education to the public on lifestyle, diet and coronary heart disease. Based on the provided health information people started to change their dietary habits and food and agricultural industries developed new low-fat products, like soft margarines and low-fat milk. The use of butter on bread declined for example from almost 90% to 10%. As a result, the intake of polyunsaturated fatty acids increased by 3 percent of energy, the intake of saturated fatty acids decreased by 6 percent of energy and dietary cholesterol decreased by about 25 mg/1000 kcal in Finland between 1972 and 1997.³ Based on these dietary changes, the expected decline in total cholesterol would be more than 0.6 mmol/L. A change from boiled to filtered coffee could have lowered the cholesterol levels by another 0.3 mmol/L.⁴ Since 1995 margarine fortified with plant stanols was introduced in Finland. It was estimated that using three servings of plant stanol ester margarine a day could

reduce serum total cholesterol with 10%. Approximately 140,000 (3%) individuals in Finland use this margarine daily.⁵ In Finland, changes in dietary and other life-style factors could explain the decline in serum cholesterol.

In The Netherlands however, the decline in total cholesterol levels between 1993 and 1997 could only for a small part be explained by changes in dietary and life-style factors (chapter 2). The changes in these factors in The Netherlands were too small to explain the trend. The change in the intake of saturated fatty acids, polyunsaturated fatty acids, dietary cholesterol and trans fatty acids between 1993 and 1997 in The Netherlands could only explain 20% of the observed decline in total cholesterol in men and about 30% of the observed decline in women. In the United States, mean total cholesterol declined by 0.2 mmol/L between 1976 and 1991 in men and women aged 20-74 years.⁶ This decline is comparable with that observed in The Netherlands. However, in the United States the decline in serum cholesterol could be fully explained by changes in dietary factors.⁷

The decline in mean total cholesterol level in The Netherlands resulted in a decline of the prevalence of hypercholesterolemia (total cholesterol \geq 6.5 mmol/L). The prevalence of hypercholesterolemia declined by 8 percentage points in men (from 18% to 10%) and by 6 percentage points in women (from 14% to 8%) aged 20-59 years between 1987 and 1997. This means that the decline of mean levels by about 6% led to a decrease in the number of people with hypercholesterolemia by more than 40% during this period. For public health it is important that the cholesterol distribution in a population moves to a lower level, because every person in the population would then have a lower risk of coronary heart disease. The impact of a population approach is larger than that of a high risk approach in which only persons with very high cholesterol levels are treated. This is illustrated by the results of chapter 7 in which the impact of different population prevention strategies and a high-risk strategy on primary prevention of coronary heart disease was statistically modelled. It could be calculated that for example lowering the intake of trans fatty acids from on average 1.9 percent of energy to 0.5 percent of energy (resulting in a decline in total cholesterol by 0.04 mmol/L and an increase in HDL cholesterol by 0.02 mmol/L) will lead to a reduction in the number of coronary heart disease events in men and women aged 35-74 years in the next 10 years of 32,878. If all persons with a high absolute risk for coronary heart disease were treated with cholesterol lowering medication about 10,000 coronary heart disease events would be prevented in the next 10 years. These results suggest that a substantial number of coronary heart disease events in The Netherlands can be prevented through a combination of a population and a high-risk approach.

The health effects of a low risk factor profile (cholesterol < 5.2 mmol/L, systolic blood pressure < 120 mmHg and no smoking) in the general population are rarely studied because very large prospective studies are needed to study the health effects of a low risk factor profile. Since it is not realistic to expect a population in which everyone has a low risk factor profile, it is for public health action interesting to know for example the additional effect of smoking and elevated blood pressure at different cholesterol levels. The results in chapter 3 indicate that, given a low cholesterol level, the additional effect of smoking on coronary heart disease, cardiovascular diseases and all-cause mortality is more harmful than the effect of elevated blood pressure. However, having a low cholesterol level in combination with elevated blood pressure and smoking showed higher relative risks. This means that having low cholesterol levels only, in the presence of elevated blood pressure and smoking, is not a sufficient condition to prevent coronary heart disease, cardiovascular diseases and all-cause mortality. Extra health gain can therefore be achieved in smoking men and women with low cholesterol levels and elevated blood pressure through smoking cessation and treatment of elevated blood pressure. As expected, the highest relative risks were found in men and women with elevated cholesterol levels, elevated blood pressure and who smoked. Adjusted for regression dilution bias, the risk of coronary heart disease mortality was 30 times higher in men and 63 times higher in women with high risk factor levels compared to those with low risk factor levels. This clearly indicates that substantial health gain can be achieved in a population through a combined approach to lower cholesterol levels, blood pressure and smoking cessation.

Although it is more effective to shift the population distribution of serum cholesterol to a lower level, adequate cholesterol lowering treatment for individuals with a high absolute risk for coronary heart disease remains required. Results from the large statin trials showed that using cholesterol lowering medication reduces not only coronary heart disease and total mortality, but also other manifestations of cardiovascular diseases.¹⁰ These results prompted to revise the Dutch consensus guidelines for cholesterol lowering therapy. Nowadays, treatment with cholesterol lowering medication is recommended for cardiac patients and for persons with an increased risk of developing coronary heart disease taking the total risk profile of a person into account.¹⁰ Risk factors included in this risk profile are gender, age, serum total and HDL cholesterol, hypertension, diabetes mellitus, smoking and family history of premature coronary heart disease (< 60 years).

In The Netherlands, cholesterol lowering medication in secondary prevention is indicated in men aged younger than 70 years and women aged younger than 75

years with a serum cholesterol level > 5.0 mmol/L. Cholesterol lowering in primary prevention is indicated if the absolute risk of coronary heart disease over the next 10 years is > 25% at ages < 60 years and > 30% at age 60-69 years. In persons aged 70 years and over, cholesterol lowering medication is indicated if the absolute risk exceeds 40% in men and 35% in women. For persons with a family history of premature coronary heart disease and for patients with diabetes mellitus the cut-off point was lowered with 5%, because of their increased risk of coronary heart disease due to factors that are not taken into account in the risk function.¹⁰

Cholesterol and coronary heart disease in the elderly

When serum cholesterol is still a risk factor for coronary heart disease in the elderly, substantial health gain can be achieved in this age group because the number of elderly people will increase in the years to come and most cases of coronary heart disease occur in this age group. Relative risks for coronary heart disease decrease with increasing age, but the absolute risk increases. This means that a decline in cholesterol level could also in the elderly lead to a decline in the number of coronary heart disease events.

The evidence that serum total cholesterol is positively associated and HDL cholesterol inversely associated with coronary heart disease mortality in middle-aged men and women is very strong. Whether these relations hold in the elderly is less clear. Results of epidemiological studies on serum total and HDL cholesterol and coronary heart disease in the elderly are inconsistent. Most studies have found that serum total cholesterol is still an important risk factor for coronary heart disease in the elderly, but the results for HDL cholesterol differed between the studies.¹¹⁻¹⁷

In both the Rotterdam Study and the FINE Study a statistically significant association was found between serum total cholesterol and coronary heart disease in the elderly (chapter 4 and 5). This is consistent with the results found in other studies. However, comparing the Rotterdam Study and the FINE Study, differences in population characteristics and endpoints studied have to be taken into account. In the Rotterdam Study, both men and women were included in contrast to the FINE study in which only men were included. For elderly men, the relative risks for coronary heart disease found in both studies were comparable, namely a relative risk of 1.20 (95% CI 1.03-1.41) per 1.00 mmol/L increase in total cholesterol in the Rotterdam Study and a relative risk of 1.29 (95% CI 1.07-1.56) per 1.00 mmol/L increase in total cholesterol in the Dutch cohort of the FINE Study. Also in women that participated in the Rotterdam Study, a statistically significant association was found between total cholesterol and coronary heart disease (RR 1.40; 95% CI 1.20-

1.65). Besides this, the age range of the elderly in both studies was different. In the Rotterdam Study, the age of the men and women included varied from 55 years to over 95 years with a mean age of 69 years and in the FINE Study the age range was 65-84 years, with a mean age of the elderly men of 72 years. It is well known that the relative risk for coronary heart disease declines with increasing age. However, in subgroup analyses carried out in the Rotterdam Study, the relative risk for coronary heart disease in men aged 70 years and older was higher compared to that in the total group of men aged 55 years and older. In women these relative risks were comparable between both age groups. It can be concluded that serum total cholesterol is still an important risk factor for coronary heart disease in the elderly.

Declining relative risks with increasing age were observed for the relation between HDL cholesterol and coronary heart disease. The relation between HDL cholesterol and coronary heart disease was less consistent in both studies, as was seen in other studies. In the Rotterdam Study, there was a significant inverse association between HDL cholesterol and coronary heart disease in men and women aged 55 years and older. However, in elderly men aged 70 years and older (mean age 76.7 years) the risk weakened and was no longer statistically significant. Also in the Dutch cohort of the FINE Study, no significant inverse association between HDL cholesterol and coronary heart disease was found in elderly men. Women aged 70 years and older included in the Rotterdam Study still showed a significant relation between HDL cholesterol and coronary heart disease. It can be concluded that HDL cholesterol is a risk factor for coronary heart disease in both men and women aged 55-70 years, but after the age of 70 HDL cholesterol remained a risk factor in women only.

When interpreting the results of epidemiological studies in the elderly, some methodological aspects have to be taken into account. First, co-morbidity and co-mortality are highly prevalent in older people. The presence of more than one underlying disease or cause of death can modify the association between cholesterol and coronary heart disease. It is difficult to allow for co-morbidity in the analysis, because exclusion of all people with underlying diseases at baseline would lead to a select elderly population. This group would no longer be representative of the general elderly population. Therefore, prevalent cases of coronary heart disease were included, but adjusted for, in the analyses of the studies described in chapter 4 and 5, although excluding prevalent cases of coronary heart disease did not alter the results. Cox's proportional hazards analysis was used for estimating relative risks in the elderly in chapter 4 and 5 because this method partly takes co-mortality into account. In this method individuals remain at risk for coronary heart disease until they die of other causes than coronary heart disease.^{18,19} However, using logistic

regression also showed that total cholesterol is still a risk factor for coronary heart disease in the elderly (chapter 6).

Second, the cholesterol level of a person at older age may not represent the lifetime exposure of that person. Due to underlying diseases and/or increased medication use in the elderly, cholesterol levels could be lower compared to the prior exposure level. Misclassification of elderly according to their cholesterol level could lead to an attenuation of the relation between cholesterol and coronary heart disease at older age.¹⁸

Third, at older age selective survival has taken place. Persons with high cholesterol levels, especially those who also smoke or who are susceptible for coronary heart disease because of e.g. family history, are more likely to die with increasing age. Those with high cholesterol levels who are still alive at older age are possibly less susceptible to coronary heart disease.^{18,19} This can partly explain the lower relative risks generally found in the elderly for the relation between cholesterol and coronary heart disease.

To estimate the absolute risk of coronary heart disease in middle-aged men and women the Framingham risk function is widely used.²⁰ Because this risk function does not apply to the elderly, a separate risk function for elderly men was presented in chapter 6. This risk function can be used in men aged 65 years and older to estimate absolute risks for coronary heart disease and cardiovascular diseases mortality. The risk functions developed for the elderly in the FINE Study showed that most classical risk factors for coronary heart disease and cardiovascular diseases mortality remain predictive in the elderly. Total cholesterol and smoking were the most important ones for coronary heart disease mortality and HDL cholesterol, systolic blood pressure and smoking for cardiovascular diseases mortality. Comparing the risks estimated from the coefficients of the classical risk factors included in the risk function for the elderly with the risks observed in middle-aged men, indeed lower, but for most risk factors still significant risks, were observed in the elderly. Left ventricular hypertrophy, being a prevalent case of coronary heart disease or cardiovascular diseases in Finland and The Netherlands and use of anti-hypertensive medication in Italy were also important risk factors for coronary heart disease and cardiovascular diseases mortality included in the risk functions for elderly men. This means that not only risk factors related to diet and lifestyle (like cholesterol, blood pressure and smoking) are important in the elderly, but also variables related to disease (like left ventricular hypertrophy and being a prevalent case) have an important predictive value in the elderly.

These findings have major implications for prevention and treatment of coronary heart disease in the elderly. Lowering cholesterol levels and blood pressure through dietary and lifestyle changes, smoking cessation and proper treatment of risk factors and diseases will also in the elderly lead to a substantial reduction of the absolute risk.

When calculating absolute risks for coronary heart disease in the elderly it is necessary to take country into account (chapter 6). Absolute risks in southern European populations are lower than absolute risks in northern European populations (chapter 5). This is probably due to differences in dietary habits, lifestyle factors and unknown genetic factors between the different populations. In the European Atherosclerosis Research Study, designed to assess the influence of genetic and environmental factors on predisposition for coronary heart disease, differences in distributions of apoE4 were found between different European countries.²¹ There was a clear decreasing gradient in apoE4 from the northern to the southern regions of Europe that followed the gradient of coronary heart disease mortality rates. Therefore, both genetic and environmental factors are important in influencing the level of absolute risk.

To take into account the differences in absolute risk between countries, a variable for country was added to the risk functions for the elderly. Also for middle-aged persons it is important to develop a European risk function in which a variable for country is included, because absolute risks for coronary heart disease estimated at the same cholesterol and blood pressure level in middle-aged men were also different between countries.^{22,23} In the European guidelines for prevention of coronary heart disease, based on absolute risks estimated with the Framingham risk function²⁴, a variable for country was not included. However, this is necessary because it was estimated that the Framingham risk function overestimates the absolute risk of coronary heart disease in Italy.²⁵ Using the European coronary risk chart in Italy will consequently lead to overtreatment. Therefore, the SCORE (Systematic Coronary Risk Evaluation) project was started to develop and compare risk functions derived from prospective population-based studies carried out in different European countries. The goal of the project is to create a uniform coronary risk chart that can be used in all European countries.²⁶ Based on the results presented in chapter 6 it is very important to include a variable for country in this European risk function to take into account the differences in absolute risks between different European countries.

The fact that there is still an association between total cholesterol and coronary heart disease in the elderly and the high absolute risks of coronary heart disease in the elderly means that modifying cholesterol levels in this age group could have a large impact on public health. However, observational studies alone are insufficient to decide whether elderly have to be treated for elevated cholesterol levels or not. It is therefore important to perform randomised controlled clinical trials to establish if cholesterol lowering treatment is efficacious in preventing coronary heart disease in the elderly. A meta-analysis of the most important statin trials showed that reduction of coronary events was similar above (32%; 95% CI 23%-39%) and below the age of 65 years (31%; 95% CI 23%-39%).²⁷ However, there are insufficient data yet to conclude definitively that treatment with cholesterol lowering medication is as effective in middle-aged persons as it is in the 'oldest elderly'. Persons older than 75 years were not included in the statin trials used in the meta-analysis. Therefore, several ongoing trials investigate the effect of cholesterol lowering by statins in the elderly.

Both secondary and primary prevention in the elderly are important, because the prevalence of coronary heart disease in the elderly is high and most coronary events occur in people aged 65 years and over. The question in the elderly is: who should be treated? It is important to take the overall health status and life expectancy into account. In the Dutch cholesterol consensus, starting cholesterol lowering medication is indicated in men and women with a life expectancy of at least about 5 years in order to be able to profit from the benefit of statin treatment. This means that it is recommended that most newly diagnosed patients are not treated with cholesterol lowering medication if they are older than 70 years (men) or older than 75 years (women). This cut-off point was chosen since there are no specific data available on the effect of treatment in elderly aged 75 years and older.

Prevention through cholesterol lowering

Primary and secondary prevention of coronary heart disease through cholesterol lowering can be achieved by means of several types of interventions, of which dietary interventions such as reducing the intake of saturated and trans fatty acids, and use of cholesterol lowering medication, mainly statins, are the most important ones.

Dietary interventions can lower serum cholesterol concentrations, which would subsequently lead to a decline in coronary heart disease mortality and morbidity. The extent to which cholesterol declines depends on the intensity of the dietary change. Reducing saturated and trans fatty acids, increasing polyunsaturated fatty acids and

reducing dietary cholesterol can have a substantial effect on serum total cholesterol lowering. In a review of 17 randomised controlled dietary intervention studies Truswell²⁸ showed that a 10% reduction in total cholesterol levels resulted in a significantly lower number of coronary events in the intervention group compared to the control group (OR=0.87; 95% CI 0.83-0.91). Besides this, the pooled odds ratio for total mortality was also significantly lower in the intervention group compared to the control group (OR=0.94; 95% CI 0.89-0.99). But in the seven trials with most effective cholesterol lowering (about 13%) the number of coronary events decreased with 30% and the number of total deaths with 11%. This suggests a dose-response relation between degree of cholesterol lowering in relation to coronary events and all-cause mortality.

The effect of different dietary interventions on cholesterol lowering has been extensively studied in different settings. A meta-analysis of metabolic ward studies showed that replacement of 60% of saturated fatty acids by unsaturated fatty acids and a reduction of the intake of dietary cholesterol by 60%, reduces serum total cholesterol by 10-15% (about 0.8 mmol/L).²⁹ Metabolic ward studies, in which the adherence to diets is likely to be high, showed what could be achieved with dietary interventions under ideal conditions. It is also important to look at the more realistic effects of dietary interventions that can be achieved in free living subjects. The effects of a lipid lowering diet in the general population would be smaller than that in volunteers living in a metabolic ward, due to the lower compliance with the prescribed diet. Dietary advice given to free living subjects reduce serum total cholesterol by 3-6% depending on the type and intensity of the diet.³⁰ In people going on a step 1 diet of the American Heart Association (< 30% of total energy intake as fat, with 8-10% as saturated fatty acids and cholesterol intake < 300 mg/day) for at least six months, total cholesterol levels were reduced by 3%. These results are in line with other reviews that found a decline in serum total cholesterol of about 4-5% in free living persons receiving different types of dietary advice.^{31,32}

The effect of dietary advice on coronary heart disease and all-cause mortality is not only effective through lowering cholesterol levels. Changes in the intake of saturated fatty acids can also have an impact on other factors that are important in the atherogenesis, like LDL-oxidation, coagulation factors, lipoprotein(a) and the quality of the vessel wall.³³ Besides this, the DART trial showed a reduction in coronary heart disease mortality and all-cause mortality by about 30% due to the use of fatty fish at least twice a week.³⁴ An even larger reduction in coronary heart disease and all-cause mortality of respectively 65% and 56% was observed in the Lyon Diet Heart Study after 46 months of follow-up.³⁵ The intervention in this study consisted of an α -linolenic acid enriched Mediterranean type of diet. These trials

showed that changes in the diet are an important tool for reducing coronary heart disease and all-cause mortality risk.

The number of coronary heart disease events that can be prevented in The Netherlands through dietary and lifestyle interventions was statistically modelled in chapter 7. Lowering the intake of trans fatty acids from on average 1.9 percent of energy to 0.5 percent of energy had the largest impact, preventing more than 50,000 (9%) coronary heart disease events in the next ten years in men and women aged 35-74 years. The effect of a decline in trans fatty acids was modelled through a decline in serum cholesterol levels. However, the effect of a change in trans fatty acids on coronary heart disease seems to be larger than the effect on cholesterol levels alone³⁶, so our estimate probably even underestimates the effect. The intervention on trans fatty acids could be achieved through advances in food technology.³⁷ Since 1985, the amount of trans fatty acids in fats for use in households has decreased substantially through changes in the production process. In commonly used products like hard margarines the trans fatty acid content decreased from a maximum of 50% in the nineteen eighties to on average 1-2% nowadays.³⁸ Further elimination of manufactured trans fatty acids that are nowadays mainly present in bakery products and fast foods, may reduce the intake to approximately 0.5 percent of energy from natural sources (meat and dairy products). It was estimated that lowering the intake of trans fatty acids from on average 1.9 to 0.5 percent of energy would lead to a reduction in the number of coronary events by 8% (almost 33,000) in men and by 10% (almost 19,000) in women aged 35-74 years in the next ten years. Lowering the intake of saturated fatty acids from on average 15 to 12 percent of energy, almost 20,000 (5%) coronary heart disease events in men and more than 15,000 (8%) coronary heart disease events in women aged 35-74 years could be prevented in the next ten years. This means that the number of coronary heart disease events prevented was 30% lower for the saturated fatty acid intervention compared to the trans fatty acid intervention. However, reducing the saturated fatty acid intake from on average 15 to 10 percent of energy reduced the number of coronary events by 7% in men and by 11% in women aged 35-74 years in the next ten years. This means that the magnitude of the reduction in coronary events depends on the target of the intervention. However, as shown in chapter 7 the number of coronary events prevented was largest for a combination of the dietary interventions.

Larger reductions in cholesterol levels through 'manufactured' dietary interventions can be obtained by using margarines with added plant sterols or

stanols. Plant sterols and stanols lower serum cholesterol levels through reducing the absorption of cholesterol from the gut. The daily intake of plant sterols occurring naturally in the diet, is about 0.25 grams. Adding 2 grams of plant sterols or stanols to the daily diet, which corresponds to putting sterol or stanol enriched margarine on 4 slices of bread, reduces the level of LDL cholesterol by 0.33-0.54 mmol/L, depending on age. The reduction in LDL cholesterol was significantly higher in older persons compared to younger persons. A daily dose of more than 2 grams of plant sterols or stanols per day does not further reduce LDL cholesterol levels. However, the use of margarines fortified with plant sterols or stanols may be limited due to the high costs of approximately 115 euros per person per year.³⁹

Changes in diet, like lowering the intake of saturated and trans fatty acids, can substantially change the serum cholesterol levels. It can be estimated that if the saturated fatty acid intake of a person is lowered from 15 to 10 percent of energy, the trans fatty acid intake from 1.9 to 0.5 percent of energy and margarine enriched with plant sterols or stanols was put on 4 slices of bread, LDL cholesterol levels would be reduced by about 0.8 mmol/L (=20% decline in a person with an average LDL cholesterol level of 4.0 mmol/L). This means that the decline in cholesterol that can be achieved with these dietary interventions is somewhat lower than that obtained by using statins, but if there are also changes in other dietary and lifestyle factors like an increase in the intake of soluble fibre, a decrease in body weight, stop smoking and an increase in physical activity, the effects could be comparable. Besides this, dietary interventions are much cheaper compared to statin treatment and can be advised to the whole population while statin treatment is restricted to persons with high absolute risks.

For cholesterol lowering by drugs nowadays mostly statins (HMG-CoA reductase inhibitors) are used because of their efficacy in reducing LDL cholesterol and their tolerability and safety. Statins also raise HDL cholesterol and lower triglyceride levels.⁴⁰ Five large statin trials have been carried out during the past years, of which three secondary prevention trials (4S, CARE and LIPID) and two primary prevention trials (WOSCOPS and AFCAPS/TexCAPS). Recently, a meta-analysis of these trials was published.²⁷ Pooling the results of the five trials, statin treatment was associated with a 20% reduction in total cholesterol, 28% reduction in LDL cholesterol and 13% reduction in triglycerides and 5% increase in HDL cholesterol. Overall, statin treatment reduced the number of coronary events by 31% (95% CI 26%-36%), the number of fatal coronary events by 29% (95% CI 20%-36%) and total mortality by 21% (95% CI 14%-28%). These trials showed that non-cardiovascular mortality was not increased. This was an important finding, because the first-generation trials

found an increase in non-cardiovascular mortality and no effect on all-cause mortality. Besides this, the reduction in cholesterol levels was comparable between primary and secondary prevention trials. Therefore it now seems effective to use statins in both primary and secondary prevention of coronary heart disease.

Statin do not only have an effect on coronary heart disease mortality and all-cause mortality. Despite the fact that there is no clear relationship between serum cholesterol levels and the risk of stroke in observational studies, two meta-analyses found that using statins lowered the risk of stroke.^{41,42} Patients assigned to statins had a 24-29% lower risk of stroke. This suggests that the effect of statins on cerebrovascular diseases is probably independent of cholesterol. A recently published case-control study found a substantially lowered risk of dementia in persons aged 50 years and older using statins.⁴³ This effect was independent of the presence or absence of untreated hyperlipidemia, or the use of other lipid lowering drugs. This means that statins can be used also for reducing the risk of other diseases than coronary heart disease.

The relative effect of statin treatment is large, preventing 31% of the coronary events and 21% of the total mortality, but the absolute effects are rather small especially in middle-aged persons. The absolute risk reduction in coronary events was 32 per 1000 treated patients younger than 65 years and 44 per 1000 patients aged 65 years and older after about 5 years of treatment.²⁷ This means that a large number of persons has to be treated with statins to prevent a few cases of coronary heart disease. Because the costs of statins are high, about 500 euros per treated person per year, it is important to consider these costs when treatment decisions are made. The annual costs of statins in The Netherlands went up from more than 50 million euros in 1994 to almost 160 million euros in 1998. This means an average increase in costs of statins of 32% yearly.⁴⁴ The Dutch consensus guidelines for cholesterol lowering therapy in primary prevention takes into account the cost-effectiveness. Statin treatment is indicated if the cost-effectiveness ratio is 18,180 euros per life year gained. This corresponds to a 10-year absolute risk of coronary heart disease ranging from 25% at 40 years of age to 35-40% at 70 years of age.

Recently, a report about cholesterol-lowering therapy was published by the Cholesterol Committee of the Health Council in The Netherlands.⁴⁵ The committee recommended to use cholesterol lowering therapy in: 1) patients with familial hyperlipidemia, 2) patients with manifest cardiovascular disease and a total cholesterol level above 5 mmol/L, and 3) patients with diabetes mellitus and a total cholesterol level above 5 mmol/L and one of the following criteria: CHD risk score of at least 8, microalbuminuria or left ventricular hypertrophy. The CHD risk score is

defined as: $n + \text{total/HDL cholesterol ratio}$, where n equals the number of risk factors (diabetes mellitus, hypertension, smoking and the occurrence of coronary heart disease before the age of 60 in first-degree relatives). The committee could not reach agreement about the indications for cholesterol lowering therapy in primary prevention. The majority of the committee advises to use cholesterol lowering therapy when it is medically worthwhile, without considering the costs of statins. They recommend to use cholesterol lowering therapy in persons aged 40 years and over with a total cholesterol level above 5 mmol/L and when there is either a CHD risk score of at least 8, or left ventricular hypertrophy. The minority of the committee takes the costs of statins into account in advising on the use of cholesterol lowering therapy. They stated that persons free of cardiovascular diseases, diabetes or severe lipid disorders, with the exception of a small group of middle-aged male smokers with multiple risk factors, have a high absolute risk for coronary heart disease comparable with patients who have to be treated with cholesterol lowering therapy. In those patients to stop smoking is much more cost-effective in relation to health gain than prescription of statins. This point of view of the minority of the committee was recently (February 2001) supported by the Dutch Minister of Health, Welfare and Sport. Applying the recommendations of the majority of the committee would have a large impact on the costs of health care in The Netherlands, due to the high costs of statins. Because of the high prevalence of people at high risk in The Netherlands, especially at older ages, an integrated approach of lifestyle changes and treatment with cholesterol lowering medication is important to limit the costs of health care.

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Chapter 8

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Chapter 8

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Summary

Despite the declining trend in age-adjusted coronary heart disease mortality since 1972, it is still the most important cause of death in The Netherlands. Due to better treatment and the increasing number of elderly in the Dutch population in the future, the prevalence of coronary heart disease will increase. This means that coronary heart disease remains one of the largest public health problems in The Netherlands. Serum cholesterol is a major risk factor for coronary heart disease. To quantify the amount of health gain that can be achieved through cholesterol lowering, it is important to have information on recent levels and trends in total and HDL cholesterol levels in the general population. Also more evidence on the impact of total and HDL cholesterol on coronary heart disease in the elderly is needed. Furthermore, for treatment purposes it is necessary to develop risk functions for the elderly to predict their absolute risk of coronary heart disease. Finally information on the effect of different cholesterol lowering interventions on incidence of coronary heart disease in The Netherlands is needed.

Trends in plasma total and HDL cholesterol in The Netherlands between 1993 and 1997 were studied using data from the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN-project). It was also examined whether the observed trend in total cholesterol could be explained by changes in body mass index (weight/height²), smoking, use of cholesterol lowering medication, intake of saturated fatty acids, cholesterol and trans fatty acids (chapter 2). The MORGEN-project was carried out in three towns: Amsterdam, Doetinchem and Maastricht. In total more than 21,000 men and women aged 20-59 years were examined. The total cholesterol level decreased significantly by 0.19 mmol/L in men and 0.27 mmol/L in women between 1993 and 1997. The prevalence of hypercholesterolemia (total cholesterol \geq 6.5 mmol/L) decreased in men from 12.3% in 1993 to 9.8% in 1997 and in women from 12.4% in 1993 to 7.6% in 1997. The level of HDL cholesterol remained stable between 1993 and 1997 in both men and women.

Between 1993 and 1997 the intake of trans fatty acids decreased significantly by 0.4 percent of energy in both men and women. The intake of saturated fatty acids decreased significantly by 0.4 percent of energy in men and 0.5 percent of energy in women. The intake of cholesterol decreased significantly by 0.6 mg/MJ in men and 1.9 mg/MJ in women. The use of cholesterol lowering medication increased significantly by 1.5% in men and 0.4% in women. The use of oral contraceptives increased significantly by 3.0% and the prescription of estrogens increased

Summary

significantly by 1.3%. However, changes in these determinants could only for a small part explain the observed trend in total cholesterol.

The effect of low, medium and high serum cholesterol levels in combination with elevated blood pressure and smoking on cause-specific and all-cause mortality in middle-aged men and women was studied in the CB Heart project (chapter 3). The CB Heart Project is a large population based cohort study carried out in The Netherlands between 1974 and 1980 in about 49,000 men and women aged 30-54 years. The mean follow-up period was 20 years. Several risk factor profiles were defined according to levels of total cholesterol, systolic blood pressure and smoking. Having a low risk factor profile was associated with low mortality rates and, surprisingly, to similar mortality rates in men and women. Given a low cholesterol level (< 5.2 mmol/L), the impact of smoking on coronary heart disease, cardiovascular diseases and all-cause mortality was larger than that of elevated blood pressure (systolic ≥ 140 mmHg). A low cholesterol level in combination with both elevated blood pressure and smoking was associated with relative risks for CHD, CVD and all-cause mortality of 3.0 (95% CI 1.1-8.8), 6.0 (95% CI 2.4-14.9) and 4.1 (95% CI 2.7-6.3) respectively in men and 2.3 (95% CI 0.6-8.6), 3.6 (95% CI 1.8-7.1) and 2.6 (95% CI 2.0-3.5) respectively in women. When elevated blood pressure and smoking were accompanied by intermediate cholesterol levels (5.2-6.5 mmol/L), these relative risks increased further. An elevated cholesterol level (≥ 6.50 mmol/L) in combination with elevated blood pressure and smoking was associated with relative risks for CHD, CVD and all-cause mortality of respectively 9.7 (95% CI 3.6-26.7), 13.9 (95% CI 5.7-34.0) and 5.7 (95% CI 3.7-8.6) respectively in men and 15.9 (95% CI 5.6-44.8), 9.3 (95% CI 4.8-17.8) and 4.3 (95% CI 3.1-5.8) respectively in women.

The association between serum total and HDL cholesterol and the risk of myocardial infarction in men and women aged 55 years and over was studied in the Rotterdam Study (chapter 4). The relation between serum total and HDL cholesterol and coronary heart disease mortality in elderly men in different European countries was studied in the Finland, Italy and The Netherlands Elderly (FINE) Study (chapter 5). The Rotterdam Study is a population-based prospective cohort study carried out in 2,453 men and 3,553 women aged 55 years and older. During 4 years of follow-up, 117 men and 76 women had a first or recurrent myocardial infarction. The FINE Study is a prospective follow-up study carried out in 2,132 men aged 65-84 years in Finland, The Netherlands and Italy. During 10 years of follow-up, 140 Finnish men, 88 Dutch men and 48 Italian men died from coronary heart disease.

In the Rotterdam Study, the relative risk of myocardial infarction in subjects aged 55 years and older was 1.9 (95% CI 1.1-3.3) in men and 3.2 (95% CI 1.5-6.4) in women in the highest compared to the lowest serum total cholesterol quartile. In a subcohort of men and women aged 70 years and older, total cholesterol remained an important risk factor for myocardial infarction, the relative risk was about three times higher in the highest compared to the lowest total cholesterol quartile. In men aged 65-84 years living in The Netherlands and Italy, the relative risk of coronary heart disease mortality in the highest total cholesterol tertile was about two times that in the lowest tertile. In Finland, there was a small but not significantly higher risk in the highest tertile. The combined relative risk for the total population of the FINE Study was 1.17 (95% CI 1.06-1.29) for each 1.00 mmol/L increase in total cholesterol.

For HDL cholesterol, the relative risk of myocardial infarction in the highest compared to the lowest quartile was 0.5 (95% CI 0.3-0.9) in men and 0.4 (95% CI 0.2-0.9) in women aged 55 years and older participating in the Rotterdam Study. Subgroup analyses in men and women aged 70 years and older showed that HDL cholesterol was a weaker predictor of myocardial infarction in the elderly men but not in women. In the FINE Study, HDL cholesterol was inversely related to coronary heart disease mortality in Finland, but not in The Netherlands and Italy. In Italy, an interaction between HDL cholesterol, body mass index and alcohol intake was found. There was an inverse association between HDL cholesterol and coronary heart disease mortality in lean men (body mass index < 25 kg/m²) with no or moderate alcohol intake (< 40 g/day) (RR=0.76; 95% CI 0.59-0.97) and a positive association in overweight men (body mass index ≥ 25 kg/m²) with a high alcohol intake (≥ 40 g/day) (RR=1.25; 95% CI 1.07-1.46).

The non-HDL/HDL cholesterol ratio is also an important predictor of myocardial infarction in men and women aged 55 years and older. The relative risk of myocardial infarction observed in the Rotterdam Study in the highest compared to the lowest quartile was more than three times higher in both men and women.

Data of the FINE Study were used to develop risk functions for coronary heart disease and cardiovascular diseases mortality for elderly men in different European countries (chapter 6). Of the 2,170 elderly men 289 died from coronary heart disease and 545 from cardiovascular diseases during 10 years of follow-up. Most classical risk factors for coronary heart disease and cardiovascular diseases mortality remain predictive in the elderly, of which total cholesterol (OR=1.24; 95% CI 1.11-1.38) and smoking (OR=1.24; 95% CI 0.91-1.69) were the most important ones for coronary heart disease mortality and HDL cholesterol (OR=0.69; 95% CI 0.49-0.96), systolic

Summary

blood pressure (OR=1.05; 95% CI 1.01-1.11 per 10 mmHg increase) and smoking (OR=1.28; 95% CI 1.01-1.63) for cardiovascular diseases mortality. Left ventricular hypertrophy, being a prevalent case of coronary heart disease or cardiovascular diseases in Finland and The Netherlands and use of anti-hypertensive medication in Italy were also important risk factors. For estimating the absolute risk of coronary heart disease and cardiovascular diseases mortality in the elderly it is necessary to take country into account. The absolute risk of coronary heart disease and cardiovascular diseases was higher in Northern Europe compared with Southern Europe at similar levels of the risk factors.

The impact of different population prevention strategies and a high-risk strategy on the primary prevention of coronary heart disease was modelled in men and women aged 35-74 years (chapter 7). Several population strategies were simulated: lowering the intake of saturated and trans fatty acids and smoking cessation. In the high-risk strategy, all persons with a high absolute risk of coronary heart disease were treated with cholesterol lowering medication. Through lowering the intake of saturated fatty acids from on average 15 percent of energy to 12 percent of energy, trans fatty acids from on average 1.9 percent of energy to 0.5 percent of energy and reducing the number of smokers by 15%, 49,967 (13%) coronary heart disease events can be prevented in men and 22,629 (12%) events in women aged 35-74 years in the next 10 years. Using the high-risk strategy, 8,252 (2%) and 1,751 (1%) events in men and women respectively would be prevented. The gain in life expectancy for the combination of the population interventions varied from 7.7 months in men and 3.8 months in women aged 35-44 years to 4.8 months in men and 2.3 months in women aged 65-74 years. The gain in life expectancy for the high-risk strategy was 0.3 month in men and 0.08 month in women aged 65-74 years. In those aged 35-64 years the gain in life expectancy for the high-risk strategy was almost nil. Of the population interventions simulated, lowering the intake of trans fatty acids, attainable through advances in food technology, had the largest effect on the number of events of coronary heart disease that could be prevented in the years to come.

In conclusion, total cholesterol levels declined in The Netherlands between 1987 and 1997. This decline is of great public health importance because it could lead to a decline in mortality from coronary heart disease in the future. For public health purposes it is important to know that the cholesterol distribution in a population moves to a lower level. A population approach together with a high risk approach is the best way to prevent coronary heart disease. Because it was shown that serum

total cholesterol is also an important risk factor for coronary heart disease in the elderly, modifying cholesterol levels in the elderly could have a major impact on the health of this age group. Cholesterol reduction in the whole population can be achieved by dietary interventions. Apart from lowering the intake of saturated fatty acids, a further elimination of trans fatty acids and the use of margarines enriched with plant sterols or stanols can lower the total cholesterol levels. Besides this, adequate cholesterol lowering treatment of persons with high absolute risks is necessary.

Samenvatting

De sterfte aan coronaire hartziekten is nog steeds de belangrijkste doodsoorzaak in Nederland, ondanks een daling hierin sinds 1972. Door verbeteringen van de medische technologie en de vergrijzing van de Nederlandse bevolking zal de prevalentie van coronaire hartziekten de komende jaren toenemen. Dit betekent dat het voorkomen van coronaire hartziekten een van de belangrijkste volksgezondheidsproblemen blijft in Nederland. Het cholesterolgehalte in het bloed is een belangrijke risicofactor voor coronaire hartziekten. Voor het kwantificeren van de gezondheidswinst, die behaald kan worden door het cholesterolgehalte te verlagen, is het van belang om over gegevens te beschikken over het totaal en HDL cholesterolgehalte in de algemene bevolking en veranderingen die daarin plaatsvinden. Ook kennis over de relatie tussen totaal en HDL cholesterol en de sterfte aan coronaire hartziekten bij ouderen is in dit kader van belang. Daarnaast is het met het oog op behandeling van de ouderen belangrijk om risicofuncties te ontwikkelen voor deze groep om hun absolute risico op coronaire hartziekten te voorspellen. Tenslotte is het noodzakelijk om te weten wat het effect is van verschillende cholesterolverlagende interventies op de incidentie van coronaire hartziekten in Nederland.

Veranderingen in het totaal en HDL cholesterolgehalte in Nederland tussen 1993 en 1997 zijn bestudeerd door gebruik te maken van gegevens uit het project Monitoring van Risicofactoren en Gezondheid in Nederland (MORGEN). Daarnaast is onderzocht of veranderingen in Quetelet index (gewicht/lengte²), roken, gebruik van cholesterolverlagende medicatie, inname van verzadigde vetzuren, cholesterol en transvetzuren de gevonden verandering in het totaal cholesterolgehalte konden verklaren (hoofdstuk 2). Het MORGEN-project werd uitgevoerd in drie steden: Amsterdam, Doetinchem en Maastricht. Ruim 21.000 mannen en vrouwen in de leeftijd van 20 to 59 jaar werden onderzocht. Tussen 1993 en 1997 werd een significante daling in het totaal cholesterolgehalte gevonden van 0,19 mmol/l bij mannen en 0,27 mmol/l bij vrouwen. De prevalentie van hypercholesterolemie (totaal cholesterol \geq 6,5 mmol/l) daalde van 12,3% in 1993 tot 9,8% in 1997 bij mannen en van 12,4% in 1993 naar 7,6% in 1997 bij vrouwen. Het HDL cholesterolgehalte veranderde niet tussen 1993 en 1997 bij de mannen en de vrouwen.

Tussen 1993 en 1997 was er bij zowel mannen als vrouwen een significante daling in de inname van transvetzuren met 0,4 energieprocent. De inname van verzadigde vetzuren daalde significant met 0,4 energieprocent bij mannen en 0,5 energieprocent bij vrouwen. De inname van cholesterol daalde significant met 0,6

Samenvatting

mg/MJ bij mannen en 1,9 mg/MJ bij vrouwen. Het gebruik van cholesterolverlagende medicatie steeg significant met 1,5% bij mannen en 0,4% bij vrouwen. Het gebruik van de anti-conceptiepil steeg significant met 3,0% en het gebruik van postmenopauzale oestrogenen steeg significant met 1,3%. Veranderingen in bovengenoemde determinanten konden echter maar een klein deel van de gevonden verandering in het totaal cholesterolgehalte verklaren.

In het CB-project is het effect onderzocht van een laag, middelmatig en hoog cholesterolgehalte in combinatie met een verhoogde bloeddruk en roken op de oorzaak-specifieke en totale sterfte bij mannen en vrouwen van middelbare leeftijd (hoofdstuk 3). Het CB-project is een groot bevolkingsonderzoek dat uitgevoerd is in Nederland tussen 1974 en 1980 bij ruim 49.000 mannen en vrouwen in de leeftijd van 30 to 54 jaar. De gemiddelde follow-up periode bedroeg 20 jaar. Aan de hand van verschillende categorieën voor totaal cholesterol, systolische bloeddruk en roken zijn verschillende risicofactor profielen gedefinieerd. Mannen en vrouwen met een laag risicoprofiel hadden verrassend genoeg gelijke, zeer lage sterftcijfers. Bij mannen en vrouwen met een laag cholesterolgehalte (< 5,2 mmol/l) was het effect van roken op de totale sterfte en de sterfte aan coronaire hartziekten en cardiovasculaire ziekten groter dan het effect van een verhoogde bloeddruk (systole ≥ 140 mmHg). De relatieve risico's voor de relatie tussen een laag cholesterolgehalte in combinatie met een verhoogde bloeddruk en roken en de sterfte aan coronaire hartziekten, cardiovasculaire ziekten en de totale sterfte waren respectievelijk 3,0 (95% BI 1,1-8,8), 6,0 (95% BI 2,4-14,9) en 4,1 (95% BI 2,7-6,3) voor mannen en 2,3 (95% BI 0,6-8,6), 3,6 (95% BI 1,8-7,1) en 2,6 (95% BI 2,0-3,5) voor vrouwen. Deze relatieve risico's waren hoger bij personen met een matig verhoogd cholesterolgehalte (5,2-6,5 mmol/l), een verhoogde bloeddruk en die rookten. De relatieve risico's voor de relatie tussen een verhoogd cholesterolgehalte ($\geq 6,5$ mmol/l) in combinatie met een verhoogde bloeddruk en roken en de sterfte aan coronaire hartziekten en cardiovasculaire ziekten en de totale sterfte waren respectievelijk 9,7 (95% BI 3,6-26,7), 13,9 (95% BI 5,7-34,0) en 5,7 (95% BI 3,7-8,6) voor mannen en 15,9 (95% BI 5,6-44,8), 9,3 (95% BI 4,8-17,8) en 4,3 (95% BI 3,1-5,8) voor vrouwen.

De relatie tussen het totaal en HDL cholesterolgehalte en het risico op een myocardi infarct bij mannen en vrouwen van 55 jaar en ouder werd onderzocht in het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek (hoofdstuk 4). Het verband tussen het totaal en HDL cholesterolgehalte en de sterfte aan coronaire hartziekten bij oudere mannen is onderzocht in een studie uitgevoerd in Finland,

Nederland en Italië (FINE studie) (hoofdstuk 5). Het ERGO onderzoek is een prospectief bevolkingsonderzoek uitgevoerd bij 2.453 mannen en 3.553 vrouwen van 55 jaar en ouder. Na gemiddeld 4 jaar follow-up kregen 117 mannen en 76 vrouwen een myocard infarct. De FINE studie is een prospectieve follow-up studie uitgevoerd bij 2.132 mannen van 65-84 jaar wonend in Finland, Nederland en Italië. Gedurende een follow-up periode van 10 jaar stierven 140 Finse mannen, 88 Nederlandse mannen en 48 Italiaanse mannen aan een coronaire hartziekten.

In het ERGO onderzoek was het risico op een myocard infarct bij personen van 55 jaar en ouder 1,9 (95% BI 1,1-3,3) voor mannen en 3,2 (95% BI 1,5-6,4) voor vrouwen in het hoogste totaal cholesterol kwartiel vergeleken met het laagste kwartiel. Voor mannen en vrouwen van 70 jaar en ouder was het totaal cholesterolgehalte nog steeds een belangrijke risicofactor voor het ontstaan van een myocard infarct. Het relatieve risico was ongeveer drie keer hoger in het hoogste totaal cholesterol kwartiel vergeleken met het laagste kwartiel. Het relatieve risico voor sterfte aan coronaire hartziekten voor Nederlandse en Italiaanse mannen van 65-84 jaar was twee keer hoger in het hoogste totaal cholesterol tertiel vergeleken met het laagste tertiel. Voor de Finse mannen was er een klein, niet-significant, hoger risico in het hoogste tertiel. Het gecombineerde relatieve risico voor de gehele populatie in de FINE studie was 1,17 (95% BI 1,06-1,29) voor elke toename in totaal cholesterol met 1,00 mmol/l.

Voor het HDL cholesterolgehalte was het risico op een myocard infarct bij deelnemers aan het ERGO onderzoek van 55 jaar en ouder 0,5 (95% BI 0,3-0,9) voor mannen en 0,4 (95% BI 0,2-0,9) voor vrouwen in het hoogste vergeleken met het laagste kwartiel. Voor mannen van 70 jaar en ouder was HDL cholesterol een slechtere voorpeller van het risico op een myocard infarct, maar dat was niet het geval voor vrouwen van 70 jaar en ouder. HDL cholesterol was invers gerelateerd aan sterfte aan coronaire hartziekten in Finland, maar niet in Nederland en Italië. In Italië was er een interactie tussen HDL cholesterol, Quetelet index en alcohol consumptie. Er was een invers verband tussen HDL cholesterol en sterfte aan coronaire hartziekten in slanke mannen (Quetelet index < 25 kg/m²) die niet of matig alcohol dronken (< 40 g/dag) (RR=0,76; 95% BI 0,59-0,97) en een positief verband in dikke mannen (Quetelet index ≥ 25 kg/m²) die veel alcohol dronken (≥ 40 g/dag) (RR=1,25; 95% BI 1,07-1,46).

De non-HDL/HDL cholesterol ratio is een belangrijke voorspeller van het risico op een myocard infarct voor mannen en vrouwen van 55 jaar en ouder. In het ERGO onderzoek was het risico op een myocard infarct bij zowel mannen als vrouwen ruim drie keer hoger in het hoogste vergeleken met het laagste kwartiel.

Samenvatting

Voor het ontwikkelen van risicofuncties voor sterfte aan coronaire hartziekten en cardiovasculaire ziekten voor oudere mannen in verschillende Europese landen is gebruik gemaakt van gegevens uit de FINE studie (hoofdstuk 6). Van de in totaal 2.170 oudere mannen waren na 10 jaar follow-up 289 mannen overleden aan coronaire hartziekten en 545 aan cardiovasculaire ziekten. De meeste klassieke risicofactoren voor sterfte aan coronaire hartziekten en cardiovasculaire ziekten behielden hun voorspellende waarde bij de ouderen, waarbij totaal cholesterol (OR=1,24; 95% BI 1,11-1,38) en roken (OR=1,24; 95% BI 0,91-1,69) de belangrijkste risicofactoren waren voor sterfte aan coronaire hartziekten en HDL cholesterol (OR=0,69; 95% BI 0,49-0,96), systolische bloeddruk (OR=1,05; 95% BI 1,01-1,11 per 10 mmHg toename) en roken (OR=1,28; 95% BI 1,01-1,63) de belangrijkste risicofactoren waren voor sterfte aan cardiovasculaire ziekten. Daarnaast waren in Finland en Nederland ook linker ventrikel hypertrofie en het eerder hebben doorgemaakt van een coronaire hartziekte of cardiovasculaire ziekte en in Italië het gebruik van anti-hypertensiva belangrijke risicofactoren. Voor het berekenen van het absolute risico voor sterfte aan coronaire hartziekten en cardiovasculaire ziekten bij ouderen is het eveneens belangrijk om rekening te houden met het land waarin de personen leven. Bij vergelijkbare niveau's van risicofactoren is het absolute risico op coronaire hartziekten en cardiovasculaire ziekten hoger in Noord-Europa vergeleken met Zuid-Europa.

Het effect van verschillende preventie strategieën gericht op de totale populatie en een hoog-risico strategie in het kader van primaire preventie van coronaire hartziekten is bestudeerd bij mannen en vrouwen van 35-74 jaar (hoofdstuk 7). Er werd gebruik gemaakt van verschillende populatie strategieën, te weten het verlagen van de inname van verzadigde- en transvetzuren en stoppen met roken. In de hoog-risico strategie werd verondersteld dat alle personen met een hoog absoluut risico voor coronaire hartziekten werden behandeld met cholesterolverlagende medicatie. Op grond van de populatie strategieën zouden in de komende 10 jaar 49.967 (13%) gevallen van coronaire hartziekten bij mannen en 22.629 (12%) gevallen van coronaire hartziekten bij vrouwen van 35-74 jaar voorkomen kunnen worden als de inname van verzadigde vetzuren verlaagd wordt van gemiddeld 15 naar 12 energieprocenten, de inname van transvetzuren verlaagd wordt van gemiddeld 1,9 naar 0,5 energieprocenten en het aantal rokers wordt verlaagd met 15%. In de hoog-risico strategie zouden bij mannen 8.252 (2%) en bij vrouwen 1.751 (1%) gevallen van coronaire hartziekten voorkomen kunnen worden. De winst in levensverwachting voor de combinatie van de populatie interventies varieerde van 7,7 maanden voor mannen en 3,8 maanden voor vrouwen van 35-44 jaar tot 4,8 maanden voor

mannen en 2,3 maanden voor vrouwen van 65-74 jaar. De winst in levensverwachting voor de hoog-risico strategie was 0,3 maanden voor mannen en 0,08 maand voor vrouwen van 65-74 jaar. De winst in levensverwachting voor de hoog-risico strategie voor personen van 35-64 jaar was nihil. Van de onderzochte scenario's resulteert de verlaging van de inname van transvetzuren, die bereikt kan worden door technologische verbeteringen in de samenstelling van voedingsmiddelen, in het grootste effect op het aantal gevallen van coronaire hartziekten die voorkomen zouden kunnen worden in de komende jaren.

Geconcludeerd werd dat het totaal cholesterolgehalte in Nederland is gedaald tussen 1987 en 1997. Deze daling is van groot belang voor de volksgezondheid, omdat die in de toekomst kan leiden tot een daling in de sterfte aan coronaire hartziekten. Voor de volksgezondheid is het van groot belang dat de cholesterolverdeling van de bevolking opschuift naar een lager niveau. Deze populatie benadering, samen met een hoog-risico benadering, is de beste manier om coronaire hartziekten te voorkomen. Omdat aangetoond is dat het totaal cholesterolgehalte ook een belangrijke risicofactor is voor coronaire hartziekten bij ouderen, kan een verlaging van het cholesterolgehalte bij ouderen een behoorlijk effect hebben op de gezondheid in deze leeftijdsgroep. Een verlaging van het cholesterolgehalte in de gehele bevolking kan bereikt worden door voedingsinterventies. Naast de verlaging van de inname van verzadigde vetzuren zouden een verdere eliminatie van transvetzuren en het gebruik van margarines verrijkt met planten sterolen of stanolen verder kunnen bijdragen aan een verlaging van het cholesterolgehalte. Daarnaast is adequate behandeling van personen met een hoog absoluut risico met cholesterolverlagende medicatie noodzakelijk.

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About the author

Saskia Houterman was born on April 30th, 1973 in Vleuten-De Meern, the Netherlands. In 1991 she completed secondary school (VWO) at the 'Thijcollege' in Oldenzaal. From 1991 to 1996 she studied Biological Health Sciences with majors in nutrition and epidemiology at the Maastricht University. In November 1996 she started the work described in this thesis at the Department of Chronic Diseases Epidemiology of the National Institute of Public Health and the Environment in Bilthoven and at the Department of Epidemiology & Biostatistics of the Erasmus University Medical School in Rotterdam. In 1999 she obtained a Master of Science in Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam. In February 2001 she started to work on a project of the Dutch Cancer Society named 'Co-morbidity in cancer patients: prevalence and prognostic implications' at the Comprehensive Cancer Centre South in Eindhoven.

