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

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Abstract. Houterman S, Verschuren WMM, Hofman A, Witteman JCM (Erasmus University Medical School, Rotterdam; National Institute of Public Health and the Environment, Bilthoven, The Netherlands). Serum cholesterol is a risk factor for myocardial infarction in elderly men and women: the Rotterdam Study (Review). *J Intern Med* 1999 **246**: 25–33.

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.
Design. The Rotterdam Study is a population-based prospective cohort study. In total 2453 men and 3553 women of 55 years and older were included in this study. The mean duration of follow-up was 4 years.
Main outcome measures. 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 the age of 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, whilst HDL cholesterol at older age remains important in women only.

Keywords: cholesterol, myocardial infarction, elderly, prospective study, risk.

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 relationship 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 the elderly [6–10],

whilst 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 amongst 7983 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 7129 subjects visited the research centre. Cholesterol measurements were available for 2554 men and 3789 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 1307 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 2453 men and 3553 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 computerized questionnaire. A history of myocardial infarction was considered positive if the subject reported to have been hospitalized 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 a 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^{-1}) was calculated from a semiquantitative food frequency questionnaire. Serum total cholesterol was determined by an automated enzymatic procedure in a nonfasting 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 Standardization Program, initiated in analogy to the program of the CDC Lipid Standardization 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^{-1} or higher.

Follow-up

The follow-up started at the baseline examination and lasted until 1 April 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 nonfatal 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 nonfatal 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 7054 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^{-1} lower total cholesterol concentration and a 0.04 mmol L^{-1} higher HDL cholesterol concentration.

Classification of fatal and nonfatal events was based on the 10th revision of the International Classification of Diseases [16]. Myocardial infarction, fatal and nonfatal, 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 judgement 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 nonfatal, as the dependent variable. Fatal and nonfatal 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^{-1} increase in total cholesterol, 0.1 mmol L^{-1} 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^{-1}). 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 cut-off point 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 formula [17]:

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

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

Table 1 Baseline characteristics (mean (SD)) of men and women aged 55 years and over in the Rotterdam Study

	Men (n = 2453)	Women (n = 3553)
Age (years)	68.3 (8.1)	69.7 (9.1)*
Total cholesterol (mmol L^{-1})	6.32 (1.16)	6.85 (1.21)*
HDL cholesterol (mmol L^{-1})	1.21 (0.32)	1.43 (0.36)*
Non-HDL/HDL cholesterol ratio	4.52 (1.62)	4.08 (1.61)*
Systolic blood pressure (mmHg)	139 (22)	140 (22)
BMI (kg m^{-2})	25.7 (3.0)	26.8 (4.1)*
Alcohol drinking (% >0 g day^{-1})	87.4	73.6*
Alcohol consumption (g day^{-1})[a]	15.7 (18.1)	5.5 (9.7)*
Smoking (%)		
current	25.3	18.2*
former	58.5	28.3
Hypercholesterolemia (%)[b]	42.5	61.8*
History of myocardial infarction (%)	12.4	3.9*
Cholesterol lowering medication (%)[c]	2.9	2.3

[a] Amongst alcohol drinkers. [b] Serum total cholesterol $\geq$ 6.5 mmol L^{-1}. [c] Information available for 2379 men and 2463 women. *$P < 0.001$, significantly different between men and women.

hypercholesterolemia (total cholesterol $\geq$6.5 mmol L^{-1}) 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 cate-gories (Table 2). The age-adjusted relative risk of myocardial infarction in the highest compared to the lowest total cholesterol quartile was almost twice as high 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 times higher in the highest compared to the lowest total cholesterol quartile. Further adjustment for systolic

Table 2 Adjusted[a] relative risks (RR) (95% confidence intervals (CI)) of fatal and nonfatal myocardial infarction associated with total cholesterol in the total population of men and women ($\geq$55 years) and in the population aged $\geq$70 years in the Rotterdam Study

		Total group					
		$\geq$55 years			$\geq$70 years		
Quartile (mmol L^{-1})	Mean	Total number	Number of events	RR (95% CI)	Total number	Number of events	RR (95% CI)
Men							
$\leq$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^{-1} increase		2453	117	1.20 (1.03–1.41)	948	52	1.42 (1.13–1.79)
Women							
$\leq$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^{-1} increase		3553	76	1.40 (1.20–1.65)	1632	54	1.36 (1.12–1.65)

[a] Adjusted for age, systolic blood pressure, body mass index and smoking.

Table 3 Adjusted[a] relative risks (RR) (95% confidence intervals (CI)) of fatal and nonfatal 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

| | | Total group | | | | | |
| | | ≥55 years | | | ≥70 years | | |
Quartile (mmol L^{-1})	Mean	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^{-1} increase		2453	117	0.91 (0.86–0.98)	948	52	0.96 (0.87–1.05)
Women							
≤1.2	1.06	1152	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^{-1} increase		3553	76	0.89 (0.83–0.96)	1632	54	0.90 (0.83–0.98)

[a]Adjusted for age, systolic blood pressure, body mass index, smoking and alcohol consumption.

blood pressure, body mass index and smoking did not change the risk estimates.

The relative risk of myocardial infarction decreased with increasing HDL cholesterol concentration in both age categories in women and in men aged 55 years and over (Table 3). The age-adjusted relative risk of myocardial infarction in the highest quartile was less than half that of the lowest quartile in both men and women aged 55 years and over. In subjects aged 70 years and older the age-adjusted relative risk of myocardial infarction was more than 15% lower in men and almost 40% lower in women in the highest compared to the lowest HDL cholesterol quartile. The risk estimates did not change after further adjustment for systolic blood pressure, body mass index, smoking and alcohol consumption.

There was a positive trend in relative risk of myocardial infarction with increase of the non-HDL/HDL cholesterol ratio in both age categories (Table 4). The age-adjusted relative risk in the highest compared to the lowest quartile, was more than three times higher in both men and women of 55 years and older and in men and women aged 70 years and over.

The mortality rates of myocardial infarction in men and women aged 55 years and over per quartile of total cholesterol are given in Fig. 1. In both sexes, the mortality rate increased with higher cholesterol concentrations. The mortality rates were about twice as high 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^{-1} or lower in men and 5.9 mmol L^{-1} or lower in women (lowest quartiles) (Table 5). If HDL cholesterol levels in the whole population were 1.4 mmol L^{-1} or higher in men or 1.7 mmol L^{-1} 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).

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.

Table 4 Adjusted[a] relative risks (RR) (95% confidence intervals (CI)) of fatal and nonfatal 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 (mmol L^{-1})	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		2453	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	1021	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		3553	76	1.25 (1.16–1.36)	1632	54	1.37 (1.20–1.56)

[a]Adjusted for age, systolic blood pressure, body mass index, smoking and alcohol consumption.

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
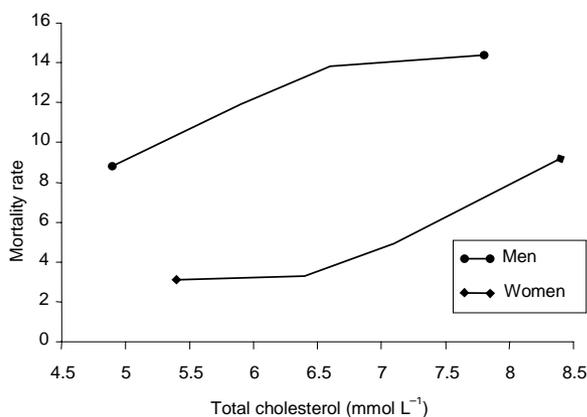
Fig. 1 Mortality rates (per 1000 person-years) of myocardial infarction in men and women aged 55 years and over per sex-specific total cholesterol quartile in the Rotterdam Study.

from an urban district of Rotterdam and had a somewhat higher social economic status than the general population. We therefore may not be able to completely generalize to the general Dutch population of 55 years and over. Secondly, 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]. Thirdly, we had a relatively 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. Fourthly, 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, or who had 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

Table 5 Population-attributable risk (PAR)[a] 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

	Men		Women	
Cholesterol parameters	≥ 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

[a]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.

baseline characteristics (subjects lost to follow-up were on average older and had a more favourable cholesterol profile) have not influenced the relationship 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 relationship between total cholesterol and coronary heart disease in men aged 65 years and older found a positive relationship [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 relationship 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 relationship 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 relationship in subjects older than 70 years [13].

In our study we found a positive relationship 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 relationship 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 the small number of cases. In men aged 70 years and older the relationship 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 Study [9] found a relative risk for HDL cholesterol in women aged 65 years and older comparable in strength to that 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 study [6]; 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 nonfatal 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 carried out 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 (Fig. 1).

Observational studies alone are insufficient to decide whether the elderly have to be treated for elevated cholesterol levels or not. An evaluation of 28 randomized 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 the elderly. The Scandinavian Simvastatin Survival Study also showed that 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.

Acknowledgements

References

1 Verschuren WMM, Jacobs DR, Bloemberg BPM, Kromhout D, Menotti A, Aravanis C, *et al.* Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the Seven Countries Study. *JAMA* 1995; **274**: 131–6.

2 Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, *et al.* Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial *Arch Intern Med* 1992; **152**: 1490–500.

3 Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. *JAMA* 1987; **257**: 2176–80.

4 Kromhout D, Bosschieter EB, Drijver M, de Lezenne Coulander C. Serum cholesterol and 25-year incidence of and mortality from myocardial infarction and cancer. The Zutphen Study. *Arch Intern Med* 1988; **148**: 1051–5.

5 Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, *et al.* High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies *Circulation* 1989; **79**: 8–15.

6 Corti MC, Guralnik JM, Salive ME, Harris T, Field TS, Wallace RB, *et al.* HDL cholesterol predicts coronary heart disease mortality in older persons. *JAMA* 1995; **274**: 539–44.

7 Benfante R, Reed D. Is elevated serum cholesterol level a risk factor for coronary heart disease in the elderly? *JAMA* 1990; **263**: 393–6.

8 Rubin SM, Sidney S, Black DM, Browner WS, Hulley SB, Cummings SR. High blood cholesterol in elderly men and the excess risk for coronary heart disease. *Ann Intern Med* 1990; **113**: 916–20.

9 Castelli WP, Anderson K, Wilson PWF, Levy D. Lipids and risk of coronary heart disease. The Framingham study. *Ann Epidemiol* 1992; **2**: 23–8.

10 Weijenberg MP, Feskens EJM, Kromhout D. Total and high density lipoprotein cholesterol as risk factors for coronary heart disease in elderly men during 5 years of follow-up. The Zutphen Elderly Study. *Am J Epidemiol* 1996; **143**: 151–8.

11 Manolio TA, Pearson TA, Wenger NK, Barrett-Connor E, Payne GH, Harlan WR. Cholesterol and heart disease in older persons and women. Review of an NHLBI workshop. *Ann Epidemiol* 1992; **2**: 161–76.

12 Zimetbaum P, Frishman WH, Ooi WL, Derman MP, Aronson M, Gidez LI, Eder HA. Plasma lipids and lipoproteins and the incidence of cardiovascular disease in the very elderly. The Bronx Aging Study. *Arterioscler Thromb* 1992; **12**: 416–23.

13 Krumholz HM, Seeman TE, Merrill SS, de Mendes Leon CF, Vaccarino V, Silverman DI, *et al.* Lack of association between cholesterol and coronary heart disease mortality and

morbidity and all-cause mortality in persons older than 70 years. *JAMA* 1994; **272**: 1335–40.

14 Hofman A, Grobbee DE, de Jong PTVM, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991; **7**: 403–22.

15 Gent CM, van der Voort HA, de Bruijn AM, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. *Clin Chim Acta* 1977; **75**: 243–51.

16 Who. *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. Geneva: World Health Organization, 1992.

17 Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. *Am J Epidemiol* 1974; **99**: 325–32.

18 MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, *et al.* Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias *Lancet* 1990; **335**: 765–74.

19 Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994; **308**: 367–73.

20 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–9.

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