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

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The associations of serum total and high density lipoprotein (HDL) cholesterol with coronary heart disease were investigated in men aged 64-84 years from the Dutch town of Zutphen during 5 years of follow-up. In 1985, 885 randomly selected men, 710 of whom did not have a history of clinical coronary heart disease, participated in the study. Associations were adjusted for age, body mass index, systolic blood pressure, cigarette smoking, and alcohol consumption. Total cholesterol was not significantly associated with the incidence of coronary heart disease, but for mortality the relative risk corresponding to a 1.00 mmol/liter increase was 1.40 (95 percent confidence interval (CI) 1.07-1.83). HDL cholesterol was not associated with mortality from coronary heart disease. The relative risk for the incidence of the disease, corresponding to a 0.26 mmol/liter increase, was 0.80 (95 percent CI 0.60-1.08). For the ratio of HDL cholesterol to total cholesterol, the relative risk for coronary heart disease incidence corresponding to a 0.05 increase amounted to 0.70 (95 percent CI 0.51-0.95). These results show that in elderly men followed for 5 years, both total and HDL cholesterol are important in predicting coronary heart disease. Total cholesterol seems to be a stronger risk factor for mortality from the disease, whereas HDL cholesterol is more strongly associated with the incidence of a first coronary heart disease event. Am J Epidemiol 1996;143:151-8.

The associations of serum total and high density lipoprotein cholesterol (HDL cholesterol) levels with the risk of coronary heart disease among middle-aged men are currently well established (1, 2). It is not clear whether these associations pertain to elderly people (3–10). Several issues should be considered when follow-up studies are conducted among elderly people, which could explain part of this controversy.

When quality of life is considered, it seems more meaningful to investigate the incidence of a first coronary heart disease event rather than death due to this disease. However, most studies among elderly people have focused on mortality from coronary heart disease, and potential risk factors have often been measured in populations that included individuals with the disease at baseline (4–8). Possible confounding and effect modification of observed associations due to the prevalence of coronary heart disease at baseline may be larger among older persons than among those who are younger because of the higher prevalence of coronary heart disease in the elderly (11). In addition, due to possible increasing comorbidity and comortality with age, true associations between risk factors and incidence or mortality may be difficult to establish (12). These problems can possibly be circumvented by conducting prospective studies among apparently disease-free older people during a relatively short follow-up period.

Besides these methodological issues, controversy concerning the predictive value of total cholesterol for coronary heart disease among the elderly may exist because HDL cholesterol has rarely been investigated in this age group. It has been suggested that with increasing age low HDL cholesterol levels may be a more important predictor of coronary heart disease than elevated total cholesterol levels (13).

We therefore investigated serum total cholesterol and HDL cholesterol as risk factors for the incidence of and mortality from coronary heart disease among elderly men during 5 years of follow-up.
MATERIALS AND METHODS

Population

The Zutphen Study is a longitudinal investigation of chronic disease risk factors initiated in 1960 among middle-aged men as the Dutch contribution to the Seven Countries Study (14). In 1985, 555 men from the 1960 cohort were still alive and were invited for new examinations. In addition, a random sample (two of three) of all men of the same age living in Zutphen who were not part of the 1960 cohort were invited to take part in the study. From then on, the study was continued as the Zutphen Elderly Study. Of the 1,266 men contacted, 939 (74 percent) agreed to participate. A total of 109 men (9 percent) could not be examined because of serious illness or death, 62 men (5 percent) had moved, and 156 men (12 percent) refused to participate or could not be reached. Complete information on risk factors was available for 885 men aged 64–84 years. The two groups of men, those who participated since 1960 and those who did so since 1985, did not differ significantly with regard to coronary heart disease risk factors such as age, body mass index, total and HDL cholesterol, and blood pressure levels.

Examinations

Physical examinations and dietary surveys took place between March and June 1985. Physical examinations were carried out by five trained physicians according to a standardized protocol. Height was measured to the nearest 0.1 cm, and body weight was measured to the nearest 0.5 kg with the men wearing underwear. Body mass index (weight (kg)/height (m)$^2$) was calculated. Systolic and diastolic (fifth Korotkoff phase) blood pressures were measured in duplicate with a random zero sphygmomanometer on the right arm while subjects were in the supine position. These measurements were taken at the end of the physical examination. The mean of the two blood pressure values was used in the analyses. Hypertension was defined as a systolic pressure greater than or equal to 160 mmHg or a diastolic pressure greater than or equal to 95 mmHg or the use of antihypertensive medication regardless of the blood pressure levels (15). Information on medication use, prescribed diets, and smoking habits was assessed with a standardized questionnaire. In our study, smoking was defined as never, former, or current cigarette smoking. Amount of cigarette-years (amount (cigarettes/day) × duration (years)) was also computed to investigate its correlation with other baseline variables. Information on alcohol consumption was assessed by trained dietitians with a cross-check dietary history (16), adapted to the Dutch situation (17). Dietary information was available for 825 men.

Nonfasting venous blood samples were taken for the analysis of serum total and HDL cholesterol. The analyses were carried out in the standardized lipid laboratory of the Department of Human Nutrition, Agricultural University, Wageningen, the Netherlands. High density lipoprotein was isolated after precipitation of apo B-containing particles by dextran sulfate-Mg$^{2+}$ (18). Total and HDL cholesterol were determined enzymatically with the CHOD-PAP monostestkit from Boehringer Mannheim GmbH, Mannheim, Germany (19, 20). Standardization was realized by using calibration sera from the Foundation of Chemical Analysis Quality Control (the Netherlands) for total cholesterol, and calibration sera were prepared according to the method of van der Haar et al. (21) for HDL cholesterol. Control sera were obtained from the Centers for Disease Control and Prevention, Atlanta, Georgia.

Information on the presence of diabetes mellitus was obtained through a standardized medical questionnaire during the physical examination. Patients with insulin-dependent or non-insulin-dependent diabetes mellitus were considered in this study.

Follow-up

Information on the prevalence of coronary heart disease was obtained during the physical examination in 1985 and a similar examination between March and June 1990 with the use of the Dutch translation of a questionnaire developed at the London School of Hygiene and Tropical Medicine (22). For men who did not participate in the 1990 examination, information on major chronic diseases was obtained from a questionnaire for nonparticipants. Coronary heart disease was considered to be present when either myocardial infarction or angina pectoris was diagnosed. For myocardial infarction, the final diagnosis was based on whether two of the following three criteria were met: a specific medical history, i.e., severe chest pain lasting for more than 20 minutes that did not disappear at rest; characteristic electrocardiogram changes; and specific enzyme elevations. The diagnosis of angina pectoris was based on information obtained from the Rose questionnaire (22). The diagnoses were additionally verified with hospital discharge data and written information from the subjects’ general practitioners. All information was eventually coded by a single physician, and the year of first diagnosis was recorded.

Information on the vital status of the participants was obtained until July 1990. One person had moved abroad and was lost to follow-up. The date on which he moved was used as his (censored) endpoint date.

Information on the causes of death was obtained from the Dutch Central Bureau of Statistics after verification with hospital discharge data and information from the general practitioners of the deceased. The causes of death were coded according to the *International Classification of Diseases*, Ninth Revision (23). Because of the frequency of possible comorbidity and comorbidity in elderly people, the underlying cause of death is often difficult to determine. Death due to coronary heart disease was therefore defined by *International Classification of Diseases*, Ninth Revision, codes 410-414 recorded for either the primary or secondary cause of death.

The endpoints investigated were the incidence of a first fatal or nonfatal coronary heart disease event (i.e., incidence of coronary heart disease) and mortality from coronary heart disease, from causes other than coronary heart disease, and from all causes.

### Statistical methods

Statistical analyses were carried out using the SAS program (SAS Institute, Inc., Cary, North Carolina, 1989, version 6.07). All tests were two sided, and *p* values smaller than 5 percent were considered statistically significant. Spearman correlation coefficients (*r*) were calculated between total and HDL cholesterol levels and levels of other risk factors for coronary heart disease. Differences in risk factor levels between levels of categorical variables were evaluated using Student’s *t* tests and Mann-Whitney *U* tests in case the risk factor distributions were skewed. For differences in levels of categorical variables, the chi-square test statistic was used. Incidence and mortality rates were computed for tertiles of total and HDL cholesterol.

Cox proportional hazard (survival) analysis was carried out to investigate the associations between lipid variables and the endpoints of interest during 5 years of follow-up (24). Relative risks for the incidence or mortality endpoints are presented according to 1.00 of follow-up (24). Relative risks for the incidence or mortality endpoints are presented according to 1.00 years). During the follow-up period, 212 men died from total population died (52.1 per 1,000 person-years), 53 from coronary heart disease (13.0 per 1,000 person-years). Four of these men had coronary heart disease coded as a secondary cause of death.

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### RESULTS

In 1985, 885 men aged 64–84 years (mean age, 71.5 years) were examined. The mean baseline serum total cholesterol level was 6.10 mmol/liter (± 1.11 standard deviation (SD)), and the mean baseline HDL cholesterol level was 1.12 mmol/liter (±0.29 SD). Thirty-five percent of the men were hypercholesterolemic (total cholesterol ≥ 6.5 mmol/liter) (27), and 23 percent of the men had HDL cholesterol levels lower than 0.9 mmol/liter.

Serum total and HDL cholesterol levels were significantly correlated with each other (*r* = 0.13). Total cholesterol was inversely associated with age (*r* = -0.21) and positively associated with body mass index (*r* = 0.18), alcohol intake (*r* = 0.08), and amount of cigarette smoking years (*r* = 0.11). HDL cholesterol was inversely associated with body mass index (*r* = -0.27) and positively associated with alcohol intake (*r* = 0.31), but did not vary significantly with age. All of these correlation coefficients are statistically significant at the 5 percent level.

At the initial examination, the prevalence of coronary heart disease was 19.8 percent. Men with coronary heart disease at baseline were significantly older, had lower levels of HDL cholesterol, and had a lower mean HDL/total cholesterol level than did men without the disease (table 1). Baseline serum total cholesterol levels were higher among men with coronary heart disease at baseline than among men without the disease, although this difference was not statistically significant (*p* = 0.15). Among men with coronary heart disease in 1985, there were fewer alcohol drinkers, more former smokers, and fewer current smokers than among men without the disease (table 1).

Among the 710 men free of coronary heart disease at baseline, a first fatal or nonfatal coronary heart disease event occurred in 56 men during 5 years of follow-up. The incidence rate was 17.2 per 1,000 person-years. During the follow-up period, 212 men from the total population died (52.1 per 1,000 person-years), 53 from coronary heart disease (13.0 per 1,000 person-years). Four of these men had coronary heart disease coded as a secondary cause of death.
TABLE 1. Baseline values of selected risk factors according to prevalence of coronary heart disease in 1985, in 885 men aged 64–84 years from the Zutphen Elderly Study, 1985

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 710)</td>
<td>(n = 175)</td>
</tr>
<tr>
<td><strong>Mean (standard deviation)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.3 (5.4)</td>
<td>72.2 (5.3)*</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.5 (3.2)</td>
<td>25.5 (3.0)</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/liter)</td>
<td>6.06 (1.10)</td>
<td>6.24 (1.11)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/liter)</td>
<td>1.14 (0.30)</td>
<td>1.06 (0.28)**</td>
</tr>
<tr>
<td>HDL cholesterol/total cholesterol</td>
<td>0.19 (0.06)</td>
<td>0.17 (0.05)**</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>151.2 (21.1)</td>
<td>150.6 (22.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.6 (11.4)</td>
<td>84.7 (11.7)</td>
</tr>
<tr>
<td><strong>Percentage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>43.2</td>
<td>37.7</td>
</tr>
<tr>
<td>Prevalence of diabetes mellitus</td>
<td>6.2</td>
<td>8.0</td>
</tr>
<tr>
<td>Alcohol use (&gt;0 g/day)</td>
<td>75.0</td>
<td>64.0**</td>
</tr>
<tr>
<td>Former cigarette smoker in 1985</td>
<td>48.9</td>
<td>61.1*</td>
</tr>
<tr>
<td>Current cigarette smoker in 1985</td>
<td>32.0</td>
<td>22.9*</td>
</tr>
</tbody>
</table>

*p < 0.05; ** p < 0.01; *** p < 0.001.
† Prevalence of myocardial infarction and/or angina pectoris.
‡ HDL cholesterol, high density lipoprotein cholesterol.

The incidence rate of coronary heart disease did not vary with tertiles of total cholesterol and decreased gradually with increasing tertiles of HDL cholesterol (table 2). The mortality rate from coronary heart disease more than doubled between the first and second tertiles of total cholesterol. For HDL cholesterol, the mortality rates did not differ between tertiles of HDL cholesterol.

Survival analysis revealed that HDL cholesterol appeared to be associated with a reduced incidence of coronary heart disease (table 3). The unadjusted association was borderline significant (p for trend = 0.08), and the adjusted relative risk was of the same magnitude, but was not significantly different from unity. The relative risk was lower among men without diabetes mellitus at baseline (adjusted relative risk (RR) = 0.74, 95 percent confidence interval (CI) 0.53–1.02, p interaction = 0.14). HDL cholesterol/total cholesterol ratio was independently associated with a decreased incidence of coronary heart disease (adjusted RR for an 0.05 increase = 0.70, 95 percent CI 0.51–0.95). HDL cholesterol was not significantly associated with mortality from coronary heart disease. Serum total cholesterol was not significantly associated with the incidence of coronary heart disease (table 3). No association was observed among men

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TABLE 2. Incidence and mortality rates for coronary heart disease among elderly men aged 64–84 years according to tertiles of total and HDL cholesterol*, the Zutphen Elderly Study, 1985

<table>
<thead>
<tr>
<th>Tertiles</th>
<th>Incidence of coronary heart disease†</th>
<th>Mortality from coronary heart disease‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range§</td>
<td>No.</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2.78–5.55</td>
<td>237</td>
</tr>
<tr>
<td>Medium</td>
<td>5.57–6.52</td>
<td>236</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.56–0.97</td>
<td>234</td>
</tr>
<tr>
<td>Medium</td>
<td>0.98–1.22</td>
<td>239</td>
</tr>
<tr>
<td>High</td>
<td>1.23–3.34</td>
<td>237</td>
</tr>
</tbody>
</table>

* HDL cholesterol, high density lipoprotein cholesterol.
† Based on 710 men free of coronary heart disease at baseline.
‡ Based on 885 men.
§ Range in mmol/liter for total cholesterol and HDL cholesterol.
|| Rate per 1,000 person-years.

TABLE 3. Relative risks for the incidence of and mortality from coronary heart disease in men aged 64–84 years associated with total cholesterol and HDL cholesterol*, the Zutphen Elderly Study, 1985

<table>
<thead>
<tr>
<th></th>
<th>Incidence of coronary heart disease†</th>
<th>Mortality from coronary heart disease‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR*</td>
<td>95% CI*</td>
</tr>
<tr>
<td>Total cholesterol (for 1.00 mmol/liter increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.03</td>
<td>0.81–1.32</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.11</td>
<td>0.86–1.43</td>
</tr>
<tr>
<td>Adjusted for risk factors§</td>
<td>1.17</td>
<td>0.90–1.52</td>
</tr>
<tr>
<td>HDL cholesterol (for 0.26 mmol/liter increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.78</td>
<td>0.59–1.03</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>0.80</td>
<td>0.61–1.05</td>
</tr>
<tr>
<td>Adjusted for risk factors§</td>
<td>0.80</td>
<td>0.60–1.08</td>
</tr>
</tbody>
</table>

* HDL cholesterol, high density lipoprotein cholesterol; RR, relative risk; Cl, confidence interval.
† Based on 710 men free of coronary heart disease at baseline with 56 new events during follow-up.
‡ Based on 885 men with 53 mortality cases during follow-up.
§ Adjusted for age, body mass index, systolic blood pressure, cigarette smoking, and alcohol consumption.

free of diabetes mellitus at baseline ($p$ for trend = 0.79, $p$ interaction = 0.01). Total cholesterol was positively and independently associated with mortality from coronary heart disease in the total population. The risk factor-adjusted relative risk was 1.40 and was reduced to 1.29 (95 percent CI 0.99–1.69) after additional adjustment for the prevalence of coronary heart disease and diabetes mellitus at baseline. In the association with mortality from coronary heart disease, there was a significant interaction between total cholesterol and body mass index ($p$ = 0.005). Total cholesterol was independently associated with increased mortality from coronary heart disease in overweight men (body mass index $\geq$ 25 kg/m²) (adjusted RR = 1.70, 95 percent CI 1.22–2.38), but not in lean men (adjusted RR = 1.06, 95 percent CI 0.67–1.66).

Serum total cholesterol and HDL cholesterol were not significantly associated with all-cause mortality (adjusted RR = 1.05, 95 percent CI 0.92–1.21 for total cholesterol, and RR = 0.99, 95 percent CI 0.86–1.14 for HDL cholesterol). There were no significant associations between the different lipid variables and mortality from causes other than coronary heart disease. For total cholesterol, the adjusted relative risk was 0.96 (95 percent CI 0.81–1.13).

DISCUSSION

The main results of this study show that in elderly men followed for 5 years total cholesterol is an independent risk factor for mortality from coronary heart disease, whereas HDL cholesterol seems to be a stronger risk factor for the incidence of coronary heart disease.

We did not find a convincing relation between total cholesterol and the incidence of coronary heart disease. In a previous investigation among men from the Zutphen Study followed from 1960 until 1985, an inverted U-shaped relation between quartiles of serum total cholesterol and the incidence of myocardial infarction was observed. This was a result of a selective loss of men with serum total cholesterol levels in the highest quartile due to early incidence of or death from myocardial infarction (28). In five studies that were part of a recent National Heart, Lung, and Blood Institute workshop on cholesterol and heart disease in older people and women, the association between cholesterol and the incidence of coronary heart disease was also investigated (29–33). Three of the studies (30–32) found serum total cholesterol to be an independent risk factor for the incidence of coronary heart disease among healthy men aged 65 years or older. In the Framingham Study, the association was borderline significant in men aged 65 years or older ($p$ value for trend = 0.07) (29). In the Italian cohorts of elderly men from the Seven Countries Study, total cholesterol was not an independent risk factor for the incidence of coronary heart disease (33). A possible explanation for these discrepancies may be the duration of follow-up. A positive and significant, or borderline significant, association was indeed observed among elderly men who were followed for at least 14 years (29–32). The association was lacking in the Italian studies (33), in a recent study by Krumholz et al. (9), and in our study, in which the durations of follow-up were only 5 years or less. Thus, a longer follow-up period may be necessary to reveal an association, whether inverted U-shaped or not, between total cholesterol and the incidence of coronary heart disease in elderly men.

HDL cholesterol was measured in only two of the studies presented during the National Heart, Lung, and Blood Institute workshop in which the incidence of coronary heart disease was investigated (29, 30). Al-
though HDL cholesterol was inversely associated with the incidence of coronary heart disease in both studies, the associations did not reach statistical significance. This is in accordance with our findings. The ratio of HDL cholesterol to total cholesterol was independently associated with a decreased incidence of coronary heart disease. HDL cholesterol is probably the underlying factor driving this association since there is no evidence from this study for an independent association between total cholesterol and the incidence of coronary heart disease. The inverse association with HDL cholesterol was especially pronounced among men initially free of diabetes mellitus. In the Bronx Aging Study (34), a consistently low HDL cholesterol level (≤0.8 mmol/liter at two separate assessments) was significantly independently associated with the incidence of cardiovascular disease among men aged 75–85 years. In the general male population, serum total cholesterol increases with age until 60 years and decreases after 70 years, whereas HDL cholesterol does not change with age (35). It has been suggested that HDL cholesterol is more important in predicting coronary heart disease with increasing age than is total cholesterol (13). In the Framingham Study, for example, HDL cholesterol was found to be inversely associated with the incidence of coronary heart disease regardless of the total cholesterol level in men and women aged 49–82 years (36). Our study confirms the importance of HDL cholesterol in predicting the incidence of coronary heart disease in elderly men followed for only 5 years.

For mortality from coronary heart disease, the results of this study are in accordance with those from the review of the National Heart, Lung, and Blood Institute workshop in which the associations between total cholesterol and mortality from coronary heart disease were reinvestigated in 25 initially middle-aged populations that had aged (5). Caution is warranted in interpreting the results of this review because the relative risks were not adjusted for potential confounders. In our study, age and the prevalence of coronary heart disease at baseline were the main confounding factors in the associations between lipid variables and mortality endpoints. Adjustment for the prevalence of coronary heart disease and diabetes mellitus at baseline attenuated the association of total cholesterol with mortality from coronary heart disease. The presence of coronary heart disease at baseline may be considered as a confounder because the disease is associated with these mortality endpoints and because of acute effects of myocardial infarction on cholesterol levels or the use of cholesterol-lowering medication after the diagnosis of coronary heart disease. However, the actual event among men with the disease at baseline may have occurred a long time before baseline cholesterol measurement, and treatment for high cholesterol levels was very limited in our cohort. The prevalence of the disease at baseline is, therefore, probably not a confounder but, rather, is an intermediate step in the causal pathway. Thus, additional adjustment for the prevalence of coronary heart disease may have resulted in an overadjustment of the relative risks. Additional survival analysis among men initially free of coronary heart disease revealed a relative risk (adjusted RR = 1.3) similar to that of the entire population, indicating that the baseline prevalence of disease could not explain our findings.

It should be noted that we observed an interaction of total cholesterol with body mass index. Harris et al. (31) found that considerable weight loss in elderly people modified the association between total cholesterol and the incidence of coronary heart disease, and a significant association was observed only when people who had lost weight were excluded from the analysis. The association between total cholesterol and mortality from coronary heart disease in our cohort was absent among lean men. The mean total cholesterol level of these men was lower than that of overweight men (5.87 mmol/liter (±1.09 SD) versus 6.28 mmol/liter (±1.09 SD). A low body mass index and a low total cholesterol level could be a sign of poor health and possible subclinical disease (37, 38). Therefore, this older group of lean men could form a heterogeneous group including both healthy people who are at a decreased risk of morbidity and mortality and people with clinical or subclinical disease who are thereby at an increased risk of morbidity and mortality (38). This may explain the lack of association between total cholesterol and coronary heart disease mortality among lean men in our study.

No clear association between HDL cholesterol and mortality from coronary heart disease was seen, in contrast to the result for the incidence of the disease. In the Rancho Bernardo Study, which was presented at the National Heart, Lung, and Blood Institute workshop, low HDL cholesterol levels were also not associated with mortality from coronary heart disease among elderly men followed for 3 years (39). Our results suggest that in elderly men and during a relatively short period of time, HDL cholesterol is important in predicting less severe coronary heart disease (i.e., not leading to death), whereas total cholesterol predicts fatal coronary heart disease. Additional analyses showed that this is especially the case for acute myocardial infarction (adjusted RR = 1.8). This is supported by the fact that angina pectoris constituted a larger portion of the incidence (39 of 56) than of mortality from coronary heart disease (three of 53). It
is also supported by the baseline data: HDL cholesterol was significantly lower in men with coronary heart disease, and for total cholesterol, the difference between men with and those without coronary heart disease did not reach statistical significance. The latter finding could be due to earlier death of men with elevated total cholesterol levels (28) and survival of men with low HDL cholesterol levels. Moreover, a low HDL cholesterol level in itself is not known to be atherogenic (40). Possibly, the protective effect of HDL cholesterol is strongest in less-advanced atherogenesis and thus in men without preexisting coronary heart disease.

Neither total nor HDL cholesterol appeared to be predictive for all-cause mortality. This would suggest an inverse association between total cholesterol and mortality from noncoronary heart disease (41). However, such an association was not observed, and neither was an inverse association between total cholesterol and all-cause cancer, as suggested by others (42). The effect of total cholesterol on mortality from coronary heart disease has probably been diluted using all-cause mortality as endpoint. Indeed, coronary heart disease constituted 25 percent of deaths in this study.

The use of a ratio including both total and HDL cholesterol may not be correct since it remains unknown which component of the ratio is important for the effect under study. However, such a ratio has been strongly suggested for routine use in screening to identify patients with hyperlipidemia (43) and has been identified as most efficiently predicting coronary heart disease at all ages (44). The Framingham Study was the only one presented at the National, Heart, Lung, and Blood Institute workshop in which such a ratio was investigated, and it was the only lipid predictor independently related to the incidence of coronary heart disease in elderly men (29). This is in accordance with our results.

In summary, evidence from this study indicates that total cholesterol remains an independent predictor of mortality from coronary heart disease in elderly men and that HDL cholesterol appears to be protective of a first coronary heart disease event. Moreover, the associations were observed during a relatively short follow-up time, stressing the short-term predictive importance of total and HDL cholesterol for coronary heart disease in older men.

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REFERENCES