Articles

Total cholesterol and risk of mortality in the oldest old

Annelies W E Weverling-Rijnsburger, Gerard J Blauw, A Margot Lagaay, Dick L Knook, A Edo Meinders, Rudi G J Westendorp

Summary

Background The impact of total serum cholesterol as a risk factor for cardiovascular disease decreases with age, which casts doubt on the necessity for cholesterol-lowering therapy in the elderly. We assessed the influence of total cholesterol concentrations on specific and all-cause mortality in people aged 85 years and over.

Methods In 724 participants (median age 89 years), total cholesterol concentrations were measured and mortality risks calculated over 10 years of follow-up. Three categories of total cholesterol concentrations were defined: <5·0 mmol/L, 5·0–6·4 mmol/L, and ⩾6·5 mmol/L. In a subgroup of 137 participants, total cholesterol was measured again after 5 years of follow-up. Mortality risks for the three categories of total cholesterol concentrations were estimated with a Cox proportional-hazards model, adjusted for age, sex, and cardiovascular risk factors. The primary causes of death were coded according to the International Classification of Diseases (ICD-9).

Findings During 10 years of follow-up from Dec 1, 1986, to Oct 1, 1996, a total of 642 participants died. Each 1 mmol/L increase in total cholesterol corresponded to a 15% decrease in mortality (risk ratio 0·85 [95% CI 0·79–0·91]). This risk estimate was similar in the subgroup of participants who had stable cholesterol concentrations over a 5-year period. The main cause of death was cardiovascular disease with a similar mortality risk in the three total cholesterol categories. Mortality from cancer and infection was significantly lower among the participants in the highest total cholesterol category than in the other categories, which largely explained the lower all-cause mortality in this category.

Interpretation In people older than 85 years, high total cholesterol concentrations are associated with longevity owing to lower mortality from cancer and infection. The effects of cholesterol-lowering therapy have yet to be assessed.

Lancet 1997; **350:** 1119–23

Department of General Internal Medicine, Section of Gerontology and Geriatrics (A W E Weverling-Rijnsburger MD, G J Blauw MD, A M Lagaay MD, D L Knook PhD, A E Meinders MD, R G J Westendorp MD)**, and Department of Clinical Epidemiology** (R G J Westendorp)**, Leiden University Medical Centre, Leiden, Netherlands**

Correspondence to: Dr Annelies W E Weverling-Rijnsburger, Leiden University Medical Centre, Department of General Internal Medicine, PO Box 9600, C1-R45, 2300 RC Leiden, Netherlands

Introduction

The importance of hypercholesterolaemia as a risk factor for cardiovascular disease in middle-aged people suggests that cholesterol-lowering therapy should be used to prevent morbidity and mortality. Above age 70 years, the significance of hypercholesterolaemia as a cardiovascular risk factor is controversial. The results of observational studies are conflicting, and data from controlled clinical trials on the effect of cholesterol lowering in the elderly are rare. Even if mechanisms of cardiovascular disease are the same for middle-aged and older people, the greater comorbidity and poorer health status in the elderly—as well as the cumulative years of risk exposure—hamper the generalisation of epidemiological results from younger to older individuals. Whether or not hypercholesterolaemia in elderly people with cardiovascular disease should be treated is therefore contested.

The finding that low cholesterol concentrations may be associated with increased mortality risk from cancer, respiratory disease, and trauma,[1] had also caused discussion. Some outcomes of clinical-intervention trials with cholesterol-lowering drugs suggest a similar increased mortality risk among the members of the actively treated group.[2,3] To explore further the relation between cholesterol as a risk factor for cardiovascular disease in the elderly, we assessed the effects of total cholesterol concentrations on specific and all-cause mortality in the Leiden 85-plus study.

Methods

Leiden 85-plus study

On Dec 1, 1986, the community of Leiden in the Netherlands had 105 000 inhabitants, of whom 1258 (1·2%) were 85 years and older. Among these oldest old, we initiated a population-based prospective follow-up study to assess the association of HLA antigens with human lifespan.[4,5] During the assessment, which lasted from Dec 1, 1986, to March 1, 1988, 221 participants died before they could be visited. A total of 1037 people were eligible for the study, of whom 977 (94%) provided informed consent and were enrolled. Blood samples were taken at their homes, according to predefined protocols under non-fasting conditions. After isolation of the leucocytes for HLA typing, which was the primary goal of the study, the remaining serum was available for laboratory measurements with a fully automated system (SMAC, Technicon, Tarrytown, NY, USA). Concentrations of total serum cholesterol were available for 724 (70%) of people. Data on HDL cholesterol and triglycerides were not gathered.

A medical history was taken by a physician during a home visit with special emphasis on cardiovascular disease, diabetes mellitus, and other chronic disorders. The method of history taking seemed to be closely consistent with the medical records of the general practitioner.[6] Smoking habits were recorded by self-reports, and participants were classified as current smokers (including former smokers who had stopped <10 years ago) or

	Number (%) or median (range)
Demographic data	
Male/female	200/524
Median age in years (range)	89 (85–103)*
Total cholesterol concentration (mmol/L)†	
⩾6·5	171 (24%)
5·0–6·4	350 (48%)
<5·0	203 (28%)
Cardiovascular risk factors‡	
Diastolic hypertension (>90 mm Hg)	204 (32%)
Systolic hypertension (>160 mm Hg)	285 (44%)
Diabetes mellitus	89 (12%)
Present smoking	117 (17%)
Previous myocardial infarction	58 (9%)
Previous cerebrovascular accident	19 (3%)

*Year of birth 1883–1901. †For 38·7 mg/dL=1 mmol/L. ‡Data on hypertension available for 645 participants. Previous history known for 682 participants.

Table 1: **Baseline characteristics of study population**

non-smokers. Diastolic and systolic blood pressure were measured once during the home visit. Individuals with glucosuria or blood glucose higher than 11 mmol/L were classified as having diabetes mellitus. No participant was using cholesterol-lowering drugs. In 1991, a representative sample of the participants was visited a second time. Of the 315 survivors, a series of 137 elderly people were recruited, irrespective of their total serum cholesterol at baseline. The measurements described earlier were repeated at this second visit.

All participants were followed up for mortality until Oct 1, 1996. We assessed the primary and secondary causes of death by linking the death-certificate numbers, obtained from the civic registries, to the causes of death recoded by a physician of the Dutch Central Bureau of Statistics. Causes of death were classified according to the ninth version of the International Classification of Diseases (ICD-9).[7] Death certificates from 1996, coded according to the tenth version of the International Classification of Diseases, were recoded according to the ninth. We reviewed the ICD-9 codes and categorised each code for cardiovascular disease (390–459), malignant neoplasms (140–239), respiratory diseases (460–519), senility without mention of psychosis (ie, a specific cause of death was not known; code 797), external causes (E800–E999), and all causes (000–999). Death from infection was coded according to Pinner and colleagues' study.[8] The selected infectious-disease groups were tuberculosis (ICD-9 010–018·9, 137–137·4), septicaemia (038–038·9), selected respiratory-tract infections (460–466·1, 475, 480–487·8, 510·0–510·9, 513·0–513·1), and infections of kidney and urinary tract (590–590·9, 599). Bacterial meningitis, HIV-1/AIDS, hepatobiliary disease, selected perinatal infections, mycoses and infections of the heart, and selected gastrointestinal-tract infections were not recorded in our study.

Zutphen study

To obtain information on total cholesterol distribution from a comparable birth cohort at a younger age (born 1900–10), we used data on total cholesterol from the Zutphen Study—a longitudinal, population-based study of risk factors for chronic diseases among middle-aged men in the town of Zutphen in the Netherlands.[9,10] In 1960, a random sample of 1088 men was drawn from a total population of 2450 men, born 1900–19. 878 men aged 40–59 years were examined, and their serum samples stored at −20°C. We restricted the sample to the 442 Zutphen men who were born 1900–10. The total serum cholesterol concentrations for these men were assessed in 1990 with a fully automated system (SMAC).[11] For the purpose of comparison, this birth cohort of 442 men represents the total cholesterol values of the male participants from Leiden at age 60 years.

Statistical analysis

Data are presented as mean (SD) unless otherwise stated. We compared groups by means of the Student's *t* test. Survival was estimated with the Kaplan-Meier product-limit method, compared with the log-rank test, and stratified for age and sex.

Total cholesterol concentration (mmol/L)*	Number of participants	Mortality risk		
		Unadjusted	Adjusted for age and sex	Adjusted for age, sex, and risk factors*
⩾6·5	171	0·56 (0·45–0·69)	0·62 (0·49–0·77)	0·64 (0·50–0·82)
5·0–6·4	350	0·72 (0·60–0·86)	0·78 (0·65–0·94)	0·81 (0·66–1·01)
<5·0†	203	1·00	1·00	1·00

*Risk factors also adjusted for: diastolic and systolic hypertension, diabetes mellitus, smoking, previous myocardial infarction, and previous cerebrovascular accident. †Reference category.

Table 2: **10-year mortality risks**

Survival time for participants was defined as the period from the date of the home visit to the date of one of the following events: death from a specific cause, death from any cause, and Oct 1, 1996. Mortality risks and 95% CIs for the three categories of total cholesterol concentrations were estimated with a Cox proportional-hazards model. According to the guidelines of the Dutch Cholesterol Consensus, we defined a low total cholesterol concentration as below 5·0 mmol/L; a moderately high total cholesterol concentration as 5·0–6·4 mmol/L; and a high total cholesterol concentration as equal to or above 6·5 mmol/L. Mortality risks were adjusted for age, sex, and cardiovascular risk factors (ie, a history of diabetes mellitus, myocardial infarction, cerebrovascular accident, smoking, and hypertension) with a multivariate Cox proportional-hazards model.

In an attempt to assess whether the observations were distorted by underlying disease—known or unknown—that might cause both low values of total serum cholesterol and increased mortality, we did several additional analyses. First, we left out the events that occurred during year 1 of follow-up, thus excluding participants with comorbidity whose decrease in total serum cholesterol concentration was a marker of imminent death. Second, on the assumption that serum albumin is a biochemical marker of health, we adjusted for underlying disease by entering the albumin values as a continuous covariate in the regression model. Third, we modelled the baseline value as well as the change in cholesterol over time; to correct for regression towards the mean, the average of the two measurements was entered in the model.[12] Finally, we restricted the analysis to a subgroup of participants who had stable cholesterol concentrations over time.

Results

724 participants aged 85 years and older for whom total cholesterol concentrations were available are included in this analysis. Their baseline characteristics (table 1) did not differ from those of participants whose total cholesterol concentrations were unavailable (data not shown). The 724 participants are from a cohort of 1037 people in an impact study of the HLA system and survival (Leiden 85-plus study). Compared with the 1037 people eligible for the study, the cumulative 10-year mortality risk for the 724 participants was 0·97 (95% CI 0·87–1·07). The mean total cholesterol concentration was 5·2 (SD 1·1) mmol/L in men and 5·9 (1·3) mmol/L in women ($p<0·001$); it was 5·8 (1·3) mmol/L in participants aged under 90 years and 5·5 (1·2) mmol/L in those aged 90 years or older ($p<0·0005$).

During the 10-year follow-up from Dec 1, 1986, to Oct

Total cholesterol concentration (mmol/L)*	Mortality risk (adjusted for age and sex)		
	Measured in 1987 (n=724)	Measured in 1991 (n=137)	Equal cholesterol concentrations in 1987 and 1991 (n=86)
⩾6·5	0·55 (0·42–0·73)	0·42 (0·23–0·78)	0·50 (0·22–1·16)
5·0–6·4	0·69 (0·56–0·86)	0·57 (0·35–0·95)	0·65 (0·32–1·33)
<5·0*	1·00	1·00	1·00

*Reference category.

Table 3: **5-year mortality risks for three groups of participants**

Cause of death	ICD-9 code	Number (%) with total cholesterol concentration (mmol/L)*		
		≥6·5	5·0–6·4	<5·0
Cardiovascular disorders				
All	390–459	72 (52%)	135 (43%)	66 (34%)
Ischaemic heart disease	410–414	22 (16%)	33 (11%)	13 (7%)
Cerebrovascular disease	430–438	26 (19%)	45 (15%)	24 (13%)
Malignant neoplasms	140–239	20 (14%)	45 (15%)	40 (21%)
Respiratory diseases	460–519	10 (7%)	39 (13%)	28 (21%)
All infections		8 (6%)	41 (13%)	20 (10%)
Septicaemia	038–038·9	1	4	1
Tuberculosis	010–018·9, 137–137·4	0	1	0
Respiratory-tract infections	460–466·1, 480–487·8, 510–510·9, 513–513·1	5	27	17
Infections of kidney and urinary tract	590–590·9, 599·0	2	9	2
Senility without mention of psychosis	797	8 (6%)	27 (9%)	21 (11%)
External causes	E800–E999	4 (3%)	12 (4%)	7 (4%)
All causes	000–999	139 (100%)	311 (100%)	192 (100%)

Percentages may add up to >100 since some causes of death are classified twice.
*Not known for 3 participants.

Table 4: **Comparison of primary causes of death according to total cholesterol concentration at baseline**

1, 1996, 642 participants died. The all-cause mortality risks for the three categories of total cholesterol concentrations are shown in table 2. Adjustment for age, sex, and cardiovascular risk factors and disease did not substantially influence these risk estimates. Each 1 mmol/L increase of total cholesterol corresponded to a 15% decrease in mortality (risk ratio 0·85 [95% CI 0·79–0·91]) after adjustment for differences in age and sex. When age was entered into the model as a quadratic term to adjust for residual confounding—because cholesterol decreases with age—the mortality-risk estimates remained similar. The mortality-risk estimate was 0·75 (0·65–0·86) for men and 0·85 (0·79–0·92) for women.

In an attempt to adjust the mortality risk for underlying disease—known or unknown—we excluded the events during year 1 of follow-up (n=119), thereby excluding participants with a concentration of total serum cholesterol as a marker of imminent death. In the remaining 605 participants, the mortality risk associated with a 1 mmol/L increase in total serum cholesterol was 0·85 (0·79–0·92). When serum albumin concentrations were entered into the model as a biochemical marker of health, the mortality risk associated with total serum cholesterol was 0·91 (0·84–0·97). In this final model, the risk estimate for a 1 g/L decrease in serum albumin was 0·93 (0·90–0·95); for an increase of 1 year of age it was 1·07 (1·04–1·10); and for men compared with women, 1·01 (0·83–1·25).

In 1991, after 5 years of follow-up, 137 participants of the original cohort were re-examined. On average, the total cholesterol concentration had decreased by 0·4 (SD 1·0) mmol/L (p<0·0001). Mortality-risk estimates based on the second measurement of cholesterol for these 137 participants were almost the same as those for the whole group (table 3). To adjust for differences in the total cholesterol concentrations over time, a multivariate analysis was done, including both the average of the two cholesterol measurements and as the difference between the two cholesterol measurements. Mortality was

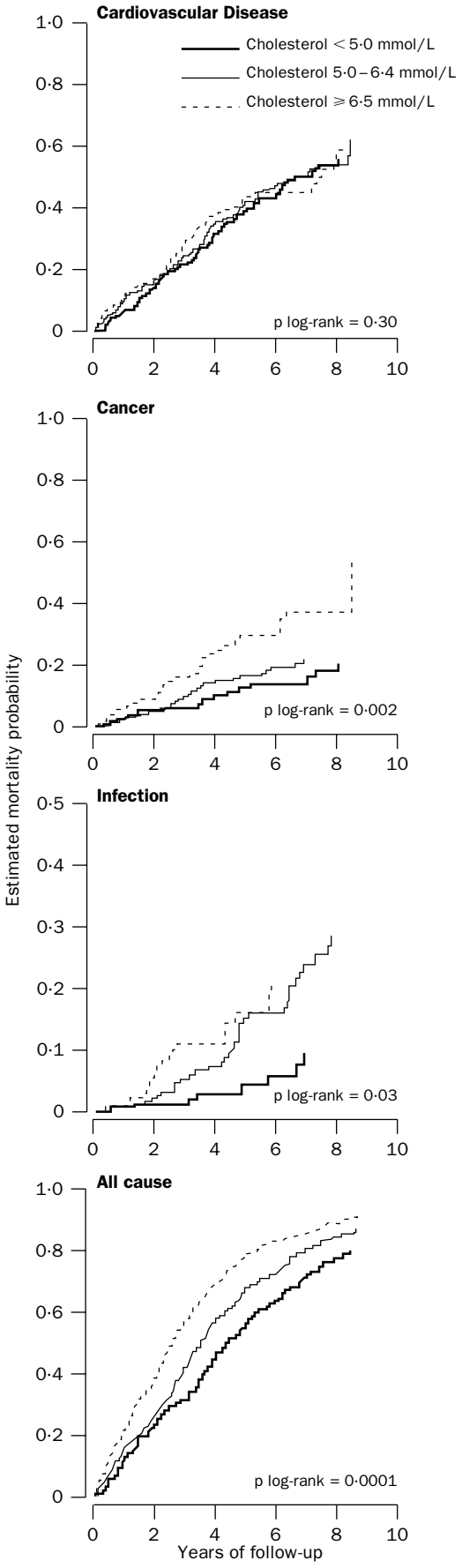

Figure 1: Cumulative mortality for various causes of death
Patients who died from other causes censored at times of death, assuming that causes of death were independent.

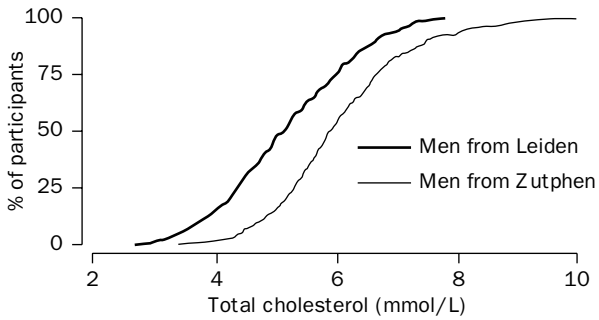

Figure 2: **Cumulative distribution of total cholesterol concentrations**

associated with the average value of the total cholesterol concentration (risk ratio 0·71 [0·59–0·87]), but not with the change in cholesterol concentrations over time (1·07 [0·89–1·29]).

To explore further the effects of underlying disease, which cause both low total cholesterol and mortality, we restricted the analysis to participants who had similar cholesterol concentrations over time. Compared with their total cholesterol concentration at baseline, 86 (63%) of the 137 participants remained in the same total cholesterol category, 37 (27%) participants changed to a lower category, and 14 (10%) changed to a higher category. Among the 86 participants who remained stable in their total cholesterol category, the mortality estimates did not substantially differ from those for the whole group (table 3).

For 639 (99·5%) of the 642 patients who died, the cause of death could be determined (table 4). In all three cholesterol categories the main cause of death was cardiovascular disease. The second and third leading causes of death were cancer and infection. External causes contributed little to mortality in patients older than 85 years. Suicide was not reported. 46 (7%) participants died from senility.

To adjust for the different mortality rates in the three total cholesterol categories, we calculated separately the cumulative mortality risk of cardiovascular disease, cancer, infection, and all causes (figure 1). Mortality risk from cardiovascular disease was divided equally over the three categories of total cholesterol (p log-rank=0·30). The mortality risk from cancer and infection was significantly lower among the participants in the high-cholesterol category, which largely explained the lower all-cause mortality in this category. Median survival of the participants was 2·5 years in the lowest cholesterol category, 3·4 years in the middle category, and 4·3 years in the highest category; this trend was significant (p log-rank <0·0001).

Total cholesterol concentrations in the elderly men from Leiden were compared with those of a comparable birth cohort from Zutphen at age 60 years (figure 2). The mean total cholesterol concentrations in the male population of Leiden was 5·2 (SD 1·1) mmol/L and in that of Zutphen, 6·1 (1·2) mmol/L.

Discussion

The results of our study show that for both men and women of 85 years and older, high total serum cholesterol concentrations are inversely correlated with mortality—ie, high cholesterol is associated with increased survival. Compared with participants who had low total cholesterol concentrations, those with moderately high and high concentrations have a lower mortality risk of of 22% and 38%, respectively.

The total cholesterol concentration of the participants aged 85 years and over might not reflect their life-time cholesterol concentration, and thus not effectively stratify their risk. This might be true especially for elderly people with comorbidity, causing increased mortality and low total serum cholesterol concentrations when close to death. This factor may explain, hypothetically, the inverse association between cholesterol and mortality in the oldest old. This association was confirmed, however, in a subgroup with equal cholesterol concentrations over a follow-up period of 5 years; such a distorting mechanism is thus unlikely.

We came to the same conclusion when we analysed the data after excluding the events that occurred during year 1 of follow-up; the patients with a decrease in total cholesterol just before death were not included. The data were also analysed with the use of the plasma concentrations of albumin as a biochemical marker of health. The inverse association between total cholesterol and mortality was confirmed, although the association was weaker. However, whether the latter is the most appropriate analysis to correct for underlying disease—known or unknown—is questionable. If, for instance, malnutrition or hepatic disease is causally related to increased mortality (eg, infection) by means of low concentrations of plasma total cholesterol, adjustment for albumin might weaken the association. Taken together, the results probably cannot be explained by disease, known or unknown, that causes both low total cholesterol concentrations and increased all-cause mortality.[13]

Among these oldest old, cardiovascular disease was, as in middle-aged and younger elderly people, the most important cause of death, albeit independent of total cholesterol concentration. Total cholesterol concentrations in the elderly men from Leiden were lower than in a comparable birth cohort from Zutphen at age 60 years, which suggests that high total cholesterol concentrations in middle age were associated with mortality in our birth cohort. As a result of selective survival, hypercholesterolaemic individuals who remain in the cohort may be resistant to the effects of high cholesterol, which corroborates the findings of other studies.[14,15] Another possible explanation for the observation that cholesterol is not a risk factor for cardiovascular disease in the very old is that changes in the vessel wall may lower susceptibility to cholesterol.

We found in this study an inverse association between serum total cholesterol concentration and 10-year cancer mortality. Reports suggest that cancer rates are higher among people with low total serum cholesterol concentrations simply because cardiovascular-disease rates are low. However, in our cohort, death from cardiovascular disease was independent of the total serum cholesterol concentration.

Many epidemiological studies have examined the relation between low concentrations of total serum cholesterol and cancer risk, but their results are inconsistent.[15–18] In the Honolulu and Framingham studies,[15,16] there was an inverse association, which is unlikely to be explained by a preclinical cancer effect because the first years of follow-up were excluded from analysis. This year, a study suggested that the decline in serum total cholesterol occurred only in the final 4 years

before cancer death.[19] In the Paris Prospective Study I,[20] a decline in total cholesterol over time was associated with a higher risk of cancer mortality; but there was also an association between low baseline total cholesterol concentration and cancer mortality.

In our study, death from infectious disease was scored as a primary cause of death, and no other terminal diseases entered into this group. The association between infectious-disease mortality and a low total cholesterol concentration is surprising. The inverse association between total cholesterol and the risk of nosocomial infection in surgical patients supports our findings.[21] In an experimental study, Netea and colleagues[22] showed that mice deficient in receptors for low-density lipoprotein with endogenous hypercholesterolaemia, were protected against infections with gram-negative micro-organisms. Rejection of organ transplants is clearly less likely when patients are treated with cholesterol-lowering drugs,[23,24] which suggests that such drugs may have an immunomodulatory effect.

Our study shows that a high total serum cholesterol concentration is not a risk factor for cardiovascular disease in people aged 85 years and over—on the contrary, it is associated with longevity. On the evidence of our data, cholesterol-lowering therapy in the elderly is questionable. However, stroke is still one of the most prevalent and disabling disorders in old people. Physicians must remember that although total cholesterol is not a risk factor for cerebrovascular disease,[25] two meta-analyses have shown that treatment with inhibitors of hydroxymethylglutaryl-coA reductase reduces stroke risk by 30%.[26,27] A conclusion about the balance between the benefit and the risk of cholesterol-lowering therapy in the oldest has yet to be reached.

Contributors

A W E Weverling-Rijnsburger reviewed the literature, collated data on the follow-up, carried out data analysis, interpreted results, and wrote the manuscript. G J Blauw formulated the hypothesis for the study and helped interpret results. A M Lagaay was primarily responsible for the population survey, collected cross-sectional data, and formulated the hypothesis for the study. D L Knook and A E Meinders supervised the overall conduct of the Leiden 85-plus study, and advised on the manuscript. R G J Westendorp formulated the hypothesis for the study, supervised the analysis of data and the writing of the manuscript, and helped interpret results. All authors contributed to the writing of the manuscript.

Acknowledgments

We thank Edith J M Feskens (National Institute of Public Health and the Environment, Bilthoven), for providing the cholesterol data of the Zutphen Study; the Central Bureau of Statistics, Voorburg, Netherlands, for death-certificate information; Edmond J Remarque for technical assistance with the Leiden 85-plus database; and Gerrit J Weverling (Academic Medical Centre, Amsterdam) for helpful discussion and statistical analysis.

References

1 Jacobs D, Blackburn H, Higgins M, et al. Report of the conference on low blood cholesterol: mortality associations. *Circulation* 1992; **86:** 1046–60.

2 Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantative review of primary prevention trials. *BMJ* 1990; **301:** 309–14.

3 Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; **335:** 1001–09.

4 Lagaay AM, Asperen van IA, Hijmans W. The prevalence of morbidity in the oldest old, age 85 and over: a population-based survey in Leiden, the Netherlands. *Arch Gerontol Geriatr* 1992; **15:** 115–31.

5 Izaks GJ, Houwelingen Van HC, Schreuder GMT, Ligthart GJ. The association between human leucocyte antigens (HLA) and mortality in community residents aged 85 and over. *J Am Geriatr Soc* 1997; **45:** 56–60.

6 Lagaay AM, Meij van der JC, Hijmans W. Validation of medical history taking as part of a population based survey in subjects aged 85 and over. *BMJ* 1992; **304:** 1091–92.

7 WHO. International classification of diseases: manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland: WHO, 1977.

8 Pinner RW, Teutsch SM, Simonsen L, et al. Trends in infectious diseases mortality in the United States. *JAMA* 1996; **275:** 189–93.

9 Kromhout D, Bosschieter EB, Drijver M, Lezenne Coulander de C. Serum cholesterol and 25-year incidence of and mortality from infarction and cancer. *Arch Intern Med* 1988; **148:** 1051–55.

10 Vries de CL, Feskens EJM, Lezenne Coulander de C, Kromhout D. Repeated measurements of serum cholesterol and blood pressure in relation to long-term incidence of myocardial infarction. *Cardiology* 1993; **82:** 89–99.

11 Geriatric clinical chemistry reference values. Washington: American Association for Clinical Chemistry Inc, 1994: 312/467.

12 Oldham PD. A note on the analysis of repeated measurements of the same subjects. *J Chron Dis* 1962; **15:** 969–77.

13 Corti MC, Guralnik JM, Salive ME, et al. Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. *Ann Intern Med* 1997; **126:** 753–60.

14 Krumholz HM, Seeman TE, Merrill SS, 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.

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

16 Stemmerman GN, Chyou P, Kagan A. Serum cholesterol and mortality among Japanese-American men: the Honolulu (Hawaii) heart program. *Arch Intern Med* 1991; **151:** 969–72.

17 Schuit AJ, Dijk Van CEMJ, Dekker JM, Schouten EG, Kok FJ. Inverse association between serum cholesterol and cancer mortality in Dutch civil servants. *Am J Epidemiol* 1993; **137:** 966–76.

18 Schatzkin A, Hoover NR, Taylor PR, et al. Site-specific analysis of total serum cholesterol and incident cancer in the National Health and Nutrition Examination Survey I: Epidemiological Follow-up Study. *Cancer Res* 1988; **48:** 452–58.

19 Sharp SJ, Pocock SJ. Time trends in serum cholesterol before cancer death. *Epidemiology* 1997; **8:** 132–36.

20 Zureik M, Courbon D, Ducimetière P. Decline in serum total cholesterol and the risk of death from cancer. *Epidemiology* 1997; **8:** 137–43.

21 Delgado-Rodriguez M, Medina-Caudros M, Martinez-Gallego G, Sillero-Arenas M. Total cholesterol, HDL-cholesterol, and the risk of nosocomial infection: a prospective study in surgical patients. *Infect Control Hosp Epidemiol* 1997; **18:** 9–18.

22 Netea MG, Demacker PNM, Kullberg BJ, et al. Low-density lipoprotein receptor-deficient mice are protected against lethal endotoxemia and severe gram-negative infections. *J Clin Invest* 1996; **97:** 1366–72.

23 Katznelson S, Wilkinson AH, Kobashigawa JA, et al. The effect of pravastin on acute rejection after kidney transplantation: a pilot study. *Transplantation* 1996; **61:** 1469–74.

24 Kobashigawa JA, Katnelson S, Laks H, et al. Effect of pravastin on outcomes after cardiac transplantation. *N Engl J Med* 1995; **333:** 621–27.

25 Prospective studies collaboration. Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. *Lancet* 1995; **333:** 1301–07.

26 Blauw GJ, Lagaay AM, Smelt AHM, Westendorp RGJ. Stroke, statins, and cholesterol: a meta-analysis of randomized placebo controlled blind trials with HMG-Co-A-reductase inhibitors. *Stroke* 1997; **28:** 946–50.

27 Crouse III JR, Byington RP, Hoen HM, Furberg CD. Reductase inhibitor monotherapy and stroke prevention. *Arch Intern Med* 1997; **157:** 1305–10.