Total cholesterol and risk of mortality in the oldest old


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.

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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 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.5 Smoking habits were recorded by self-reports, and participants were classified as current smokers (including former smokers who had stopped <10 years ago) or...
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).1 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 various infectious diseases among middle-aged men in the town of Zutphen in the Netherlands. Longitudinal, population-based study of risk factors for chronic diseases among middle-aged men in the town of Zutphen in the Netherlands.

**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.

**Results**

724 participants aged 85 years and older for whom total cholesterol concentrations were available 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 1, 1996, mortality risks 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.10 Finally, we restricted the analysis to a subgroup of participants who had stable cholesterol concentrations over time.

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

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Number (%) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>200/524</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>89 (85–103)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total cholesterol concentration (mmol/L)†</th>
<th>Number of participants</th>
<th>Unadjusted</th>
<th>Adjusted for age and sex</th>
<th>Adjusted for age, sex, and cardiovascular risk factors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6·5</td>
<td>171</td>
<td>0·55 (0·42–0·73)</td>
<td>0·42 (0·23–0·78)</td>
<td>0·50 (0·22–1·16)</td>
</tr>
<tr>
<td>5·0–6·4</td>
<td>350</td>
<td>0·69 (0·56–0·86)</td>
<td>0·57 (0·35–0·95)</td>
<td>0·65 (0·32–1·33)</td>
</tr>
<tr>
<td>&lt;5·0</td>
<td>203</td>
<td>1·00</td>
<td>1·00</td>
<td>1·00</td>
</tr>
</tbody>
</table>

*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. Finally, we restricted the analysis to a subgroup of participants who had stable cholesterol concentrations over time.

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

<table>
<thead>
<tr>
<th>Total cholesterol concentration (mmol/L)*</th>
<th>Mortality risk (adjusted for age and sex)</th>
<th>Equal cholesterol concentrations in 1987 and 1991 (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured in 1987 (n=724)</td>
<td>Measured in 1991 (n=137)</td>
<td></td>
</tr>
<tr>
<td>&gt;6·5</td>
<td>0·55 (0·42–0·73)</td>
<td>0·50 (0·22–1·16)</td>
</tr>
<tr>
<td>5·0–6·4</td>
<td>0·69 (0·56–0·86)</td>
<td>0·65 (0·32–1·33)</td>
</tr>
<tr>
<td>&lt;5·0</td>
<td>1·00</td>
<td>1·00</td>
</tr>
</tbody>
</table>

*Reference category.
1,996, 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 estimate was 0·75 (0·65–0·86) for men and 0·85 (0·79–0·92) for women.

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 the difference between the two cholesterol measurements. Mortality was
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. 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. 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. In the Honolulu and Framingham studies, 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 of life. 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.
before cancer death. The Paris Prospective Study I, 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. In an experimental study, Netea and colleagues showed that mice deficient in receptors for low-density lipoprotein with endogenous hypercholesterolemia, 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, 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, two meta-analyses have shown that treatment with inhibitors of hydroxymethylglutaryl-coA reductase reduces stroke risk by 30%. 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 J Weverling-Rinsburger 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 manuscript. G J Blauw formulated the hypothesis for the study and follow-up, carried out data analysis, interpreted results, and wrote the manuscript. All authors contributed to the writing of the manuscript. R G J Westendorp formulated the hypothesis for the study, overall conduct of the Leiden 85-plus study, and advised 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 manuscript. G J Blauw formulated the hypothesis for the study and helped interpret results. All authors contributed to the writing of the manuscript. R G J Westendorp formulated the hypothesis for the study, overall conduct of the Leiden 85-plus study, and advised on the follow-up, carried out data analysis, interpreted results, and wrote the manuscript.

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References


