Articles

Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study

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Summary

Background A generally held belief is that cholesterol concentrations should be kept low to lessen the risk of cardiovascular disease. However, studies of the relation between serum cholesterol and all-cause mortality in elderly people have shown contrasting results. To investigate these discrepancies, we did a longitudinal assessment of changes in both lipid and serum cholesterol concentrations over 20 years, and compared them with mortality.

Methods Lipid and serum cholesterol concentrations were measured in 3572 Japanese/American men (aged 71–93 years) as part of the Honolulu Heart Program. We compared changes in these concentrations over 20 years with all-cause mortality using three different Cox proportional hazards models.

Findings Mean cholesterol fell significantly with increasing age. Age-adjusted mortality rates were 68·3, 48·9, 41·1, and 43·3 for the first to fourth quartiles of cholesterol concentrations, respectively. Relative risks for mortality were 0·72 (95% CI 0·60–0·87), 0·60 (0·49–0·74), and 0·65 (0·53–0·80), in the second, third, and fourth quartiles, respectively, with quartile 1 as reference. A Cox proportional hazard model assessed changes in cholesterol concentrations between examinations three and four. Only the group with low cholesterol concentration at both examinations had a significant association with mortality (risk ratio 1·64, 95% CI 1·13–2·36).

Interpretation We have been unable to explain our results. These data cast doubt on the scientific justification for lowering cholesterol to very low concentrations (<4·65 mmol/L) in elderly people.

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Introduction

High concentration of total serum cholesterol is known to be directly related to mortality in individuals aged younger than 65 years. Previous clinical trials have not had large numbers of patients aged older than 70 years, and researchers have been unable to conclusively show this relation in elderly people.[1,2] Results of several studies have shown an inverse relation, or no relation, between total cholesterol concentration and risk of death in elderly people.[3–6] A U-shaped distribution has also been recorded, in which low concentrations of serum cholesterol in elderly people predict increased mortality.[7] These findings suggest that cholesterol metabolism and homoeostatic mechanisms might differ between older and younger populations.

Corti and colleagues[8] however, suggested that frailty (or disease) in elderly people is more likely to contribute to decreased survival than low cholesterol alone. They took data from the Established Populations for Epidemiologic Studies in the Elderly, in which 4066 patients had serum lipids measured and were followed up for 4 years, and adjusted the analysis for frailty measures (concentrations of albumin and iron in serum). The modified analysis showed that the relation between total cholesterol and coronary heart disease mortality in elderly people was the same as it was for younger and middle-aged individuals. The researchers therefore concluded that the usual statistical adjustments for traditional coronary heart disease risk factors (ie, excluding older persons from cholesterol screening) do not account for possible changes associated with frailty, and are therefore inappropriate.[8]

By contrast, Manolio and colleagues[9] pooled data from several studies and showed that total cholesterol concentration was significantly correlated with fatal coronary heart disease in both men and women across a broad age range and well into older populations (ages 65–100 years). The relative risk of mortality nonetheless lessened with increasing age. Such reductions in risk of mortality in elderly people could be because elderly people generally have a higher attributable risk.[10] Clearly, whether the total concentration of cholesterol in serum has the same relation to mortality in older people as it does in younger people is not conclusive. These differing opinions have direct clinical relevance, since a judgment about total cholesterol and mortality in the elderly age-group should precede screening and attempts to lower serum cholesterol concentrations.

We have therefore assessed changes in various lipid concentrations over about 20 years from 1972 to 1992 and correlated them with all-cause mortality in a large cohort of Japanese/American men who were followed up in the Honolulu Heart Program. Such longitudinal data for serum cholesterol concentration are not available from cross-sectional studies or from shorter follow-up times.

Methods

Study population

The Honolulu Heart Program is a longitudinal epidemiological study of cardiovascular disease which began with 8006 Japanese/American men, living on the island of Oahu, Hawaii in 1965. The men were born between 1900 and 1919 (age 45–68 years at the time of the first examination in 1965–68). Details of the selection process for the cohort have been published.[11] The entire cohort has undergone six examinations so far. This report is based on the fourth examination of the cohort which was done in 1991–93, and the ascertainment of mortality which was done between the fourth examination and Dec 31, 1996. At the fourth examination, 3741 men aged 71–93 years were assessed (80% of survivors). The study was approved by the institutional review board of Kuakini Medical Center. Procedures were done in accordance with institutional guidelines, and written informed consent was obtained from all participants.

Data collection

The fourth examination included gathering of demographic information, medical and psychosocial questionnaires, cognitive function testing, fasting blood tests, a 2-h glucose tolerance test, blood pressure, anthropometry, spirometry, and an electrocardiogram. All these variables were assessed with standard methods, as used in previous examinations.[12,13] We measured fasting cholesterol and high-density lipoprotein (HDL) cholesterol in 3572 patients. Morbidity and mortality has been assessed since the beginning of the study by monitoring hospital discharge records and death certificates. Data collection is believed to be complete for all-cause mortality. Attrition in this cohort is very small—at the fourth examination only five men were lost to follow-up.

Measurement of variables

At both the third and fourth examinations, procedures for taking and preparing blood specimens for laboratory analysis were standardised by guidelines of the lipid standardisation laboratory of the US Centers for Disease Control and Prevention. Lipid concentrations were measured in San Francisco as part of the Cooperative Lipoprotein Phenotyping Study in the third examination, and at the University of Vermont in the fourth. Comparability of these two examinations was not assessed.

For all examinations, blood specimens were taken by venepuncture after an overnight fast of at least 12 h. Specimens were then put in edetic acid vacutainer tubes and placed in an ice bath. Plasma was separated in a refrigerated centrifuge at 4°C within 1–2 h after collection. Separated plasma was thoroughly mixed, transferred into cryovials, and frozen for later measurement of total cholesterol concentration.[14]

Covariates were selected because of their potential relation with either serum cholesterol or mortality. Body-mass index was defined as weight (kg) divided by height (m) squared. Physical activity index was calculated by multiplication of the approximate oxygen consumption of five different levels of activity with the reported usual numbers of hours a day engaged in that activity.[15,16] Hypertension was defined as systolic blood pressure 140 mm Hg or greater, or diastolic blood pressure 90 mm Hg or greater, or if the patient was taking antihypertensive drugs. Diabetes mellitus was defined by history (as diagnosed by doctor), taking medications (insulin or oral hypoglycaemics), fasting glucose of 7·0 mmol/L or greater, or 2-h post-load glucose of 11·1 mmol/L or greater.

Since low concentrations of cholesterol might be associated with physical frailty, some frailty measures were used as covariates. Details on measurement of forced expiratory volume and hand-grip strength have been published.[17,18] Physical function was measured by self-report of ability to undertake 17 activities of daily living.[19] If participants had difficulty with even one activity of daily living, their physical function was judged poor.

The third Honolulu Heart Program examination was held in 1971–74, about 20 years before the fourth examination. Longitudinal data for serum cholesterol and weight were available for 3398 participants from both the third and the fourth examinations. Weight change was defined as weight loss of 10% or greater.

Data analysis

Participants were divided into quartiles of serum cholesterol concentration (2·09–4·32, 4·33–4·86, 4·87–5·43, 5·44–9·88 mmol/L). Means of variables were compared with linear regression. Age-adjusted mortality rates were calculated, according to quartiles of cholesterol. Mortality rates were also calculated excluding deaths from the first year of follow-up, since patients who are very ill and close to death might have a very low cholesterol concentration because of chronic disease.

We assessed the association between concentrations of cholesterol in serum and mortality with three separate Cox proportional hazards models, using the first quartile as the reference group. The first model adjusted for age and cardiovascular risk factors (body-mass index, physical activity index, pack-years smoking, alcohol intake, HDL cholesterol, chronic hypertension and diabetes, and serum fibrinogen). The second model added frailty measures (haemoglobin, forced expiratory volume, hand-grip strength, weight loss 10% or greater between the third and fourth examinations, and poor physical function). A third model included the above variables and cirrhosis, coronary heart disease, stroke, and cancer at the fourth examination.

We assessed the effect of change in cholesterol between the third and fourth examinations on mortality after the fourth examination. On the basis of tertiles of cholesterol at each of these examinations, we created nine groups: low/low, low/intermediate, low/high, intermediate/low, intermediate/intermediate, intermediate/high, high/low, high/intermediate, and high/high. The third Cox proportional hazards model was repeated with these nine groups entered in the same model, and the

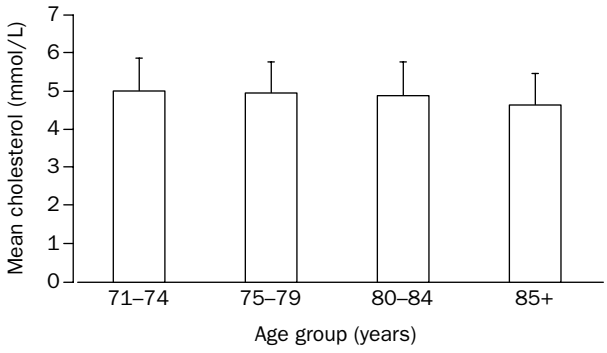


Figure 1: **Mean concentrations of serum cholesterol**
Serum cholesterol concentrations by 5-year age groups (n=3572). Test for trend p<0·0001.

	Quartiles of serum cholesterol				
	1 (n=904)	2 (n=858)	3 (n=902)	4 (n=908)	p-value*
Cholesterol concentration (mean [SE], mmol/L)	3·85 (0·01)	4·61 (0·01)	5·15 (0·01)	5·99 (0·01)	
Age (mean [SD], years)	78·6 (5·0)	77·9 (4·7)	77·4 (4·4)	76·9 (4·1)	<0·0001
Body-mass index (mean [SE], kg/m^2)	23·4 (0·11)	23·3 (0·11)	23·6 (0·10)	23·6 (0·10)	0·034
HDL (mean [SE], mmol/L)	1·21 (0·01)	1·32 (0·01)	1·35 (0·01)	1·39 (0·01)	<0·0001
Hypertension	624 (69%)	618 (72%)	677 (75%)	708 (78%)	<0·0001
Fibrinogen (mean [SE], mg/L)	303·2 (2·13)	300·4 (2·17)	306·0 (2·12)	317·3 (2·12)	<0·0001
Haemoglobin (mean [SE], g/dL)	14·5 (0·05)	14·8 (0·05)	15·0 (0·05)	15·1 (0·05)	<0·0001
Grip strength (mean [SE], kg)	29·3 (0·20)	30·4 (0·21)	30·7 (0·20)	30·6 (0·20)	<0·0001
Weight loss ⩾10%†	248 (30%)	160 (20%)	173 (20%)	149 (17%)	<0·0001
Poor physical function†	430 (48%)	309 (36%)	352 (39%)	336 (37%)	<0·0001
Examination 3 cholesterol (mean [SE], mmol/L)	5·11 (0·03)	5·45 (0·03)	5·74 (0·03)	6·11 (0·03)	<0·0001

All means are adjusted for age. *Test for trend. †Data not available for all patients.

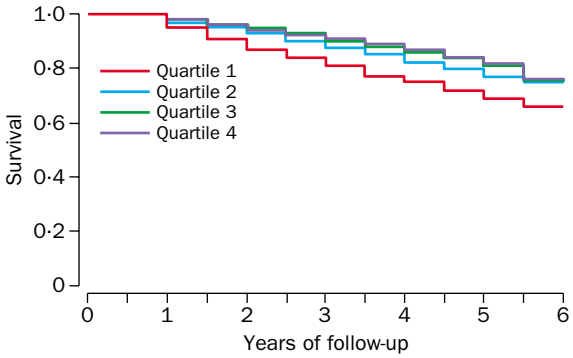
Table 1: **Population characteristics based on quartiles of cholesterol concentrations**

intermediate/intermediate group as reference. All statistical analyses were done with SAS software, version 8.0.

Results

Mean cholesterol concentration fell significantly with increasing age—from 5·00 mmol/L in those aged 71–74, to 4·93 mmol/L in those aged 75–79, to 4·85 mmol/L in those aged 80–84, and 4·61 mmol/L in those aged older than 85 years (test for trend p<0·0001) (figure 1). Mortality rates were significantly higher in the 20% non-respondents than in those who participated in the fourth examination. The rates for non-respondents were high even when compared with those in the lowest quartile of cholesterol, suggesting that non-respondents had more serious illness, and therefore did not participate in the examination.

For increasing quartiles of cholesterol concentration, there were significant positive associations with body mass index, HDL cholesterol, hypertension, fibrinogen, haemoglobin, hand-grip strength, and cholesterol concentration at the third examination (table 1). There were significant negative relations with age, weight loss of 10% or greater between the third and fourth examinations, and poor physical function. There were no significant associations with physical activity index, smoking, alcohol intake, diabetes, forced expiratory volume after 1 s (FEV_1), cirrhosis, congestive heart disease, stroke, and cancer.



Quartile 1	1	0·95	0·91	0·87	0·84	0·81	0·77	0·75	0·72	0·69	0·66	0·66
Quartile 2	1	0·97	0·95	0·93	0·90	0·88	0·85	0·82	0·80	0·77	0·76	0·76
Quartile 3	1	0·98	0·96	0·95	0·93	0·90	0·88	0·86	0·84	0·81	0·75	0·75
Quartile 4	1	0·98	0·96	0·94	0·92	0·91	0·89	0·87	0·84	0·82	0·76	0·76

Figure 2: **Probability of mortality by quartiles of serum cholesterol**

Kaplan-Meier survival curves for 5-year all-cause mortality in association with quartiles of serum cholesterol at examination 4 (1991–93). Wilcoxon Log-Rank test p<0·0001.

	Quartiles of serum cholesterol			
	1	2	3	4
All deaths				
Participants	904	858	902	908
Deaths	259	173	147	148
Mortality rate*				
Unadjusted	72·3	48·2	37·9	37·9
Age-adjusted	68·3	48·9	41·1	43·4
Age-adjusted relative risk for mortality (95% CI)	1	0·72† (0·60–0·87)	0·60† (0·49–0·74)	0·65† (0·53–0·80)
Deaths excluding first year				
Deaths	215	147	127	132
Age-adjusted Mortality rate*	56·8	41·3	35·2	38·4
Age-adjusted relative risk ratio for mortality (95% CI)	1	0·73‡ (0·59–0·90)	0·62† (0·50–0·77)	0·69§ (0·55–0·86)

*p<0·0001 people per year. †p=0·0012. ‡p=0·0010. §p=<0·0010.

Table 2: **Mortality rates by quartiles of cholesterol**

Follow-up was defined as the time between measurement of cholesterol in serum at the fourth examination (1991–93), and Dec 31, 1996. There were 727 deaths in the group over this time period (table 2). Table 2 shows age-adjusted mortality rates and relative risk for mortality. The results did not change significantly when deaths from the first year of follow-up were excluded (table 2). Kaplan-Meier survival curves showed lowest survival rates for those with the lowest serum cholesterol concentrations (Wilcoxon Log-Rank test p<0·0001) (figure 2).

Three separate Cox proportional hazards models were analysed with total mortality as the endpoint, and the first quartile of serum cholesterol as reference (table 3). In the first model (adjusted for age and cardiovascular risk factors) significant associations with mortality were seen in the third and fourth quartiles of cholesterol, compared with the first quartile. These relations were not apparent in the second model, in which frailty measures were added as covariates. No significant associations were seen between serum cholesterol and mortality in model 3, in which chronic diseases were added to the model. We

Cox model	n	Quartiles of serum cholesterol			
		1	2	3	4
1	3163	1	0·82 (0·65–1·03)	0·65 (0·51–0·83)*	0·73 (0·57–0·93)†
2	2864	1	0·90 (0·70–1·17)	0·77 (0·59–1·00)	0·86 (0·66–1·12)
3	2853	1	0·93 (0·71–1·20)	0·77 (0·59–1·01)	0·88 (0·67–1·15)

*p=0·0005; †p=0·0103.

Table 3: **Cox proportional hazard models for association between quartiles of serum cholesterol and all-cause mortality**

	Examination 4		
	Low (2·40–4·50 mmol/L)	Intermediate (4·51–5·25 mmol/L)	High (5·26–9·88 mmol/L)
Examination 3			
Low (2·04–5·12 mmol/L)	1·64* (1·13–2·36)	1·39 (0·91–2·12)	1·05 (0·61–1·81)
Intermediate (5·13–5·95 mmol/L)	1·22 (0·80–1·87)	1	1·25 (0·81–1·93)
High (5·96–10·34 mmol/L)	1·58 (0·93–2·69)	1·33 (0·87–2·03)	1·38 (0·94–2·02)

The nine groups were based on tertiles of cholesterol at examinations three and four (low/low, n=609; low/intermediate 364; low/high, 173; intermediate/low, 337; intermediate/intermediate, 415; intermediate/high, 373; high/low, 174; high/intermediate, 362; high/high, 591). Cox proportional hazards analysis was done with the intermediate/intermediate group as reference.*p=0·0089.

Table 4: **Relative risk for mortality based on change in cholesterol between examinations three and four**

repeated model 2 several times, with each frailty measured individually. Each of these frailty measures by themselves did not change the significant association between cholesterol and mortality. However, when all were put into the model at the same time, the significance of the association between cholesterol and mortality was lost.

We divided patients into two groups—those with coronary heart disease risk factors (smoking, hypertension, diabetes mellitus, or coronary heart disease) and those without. Cox model 1 was repeated for these two groups separately. Mortality was lower in the higher cholesterol quartiles for both subgroups. Compared with patients in the first quartile, those in the fourth quartile had a relative risk of 0·75 (p=0·038) in those with risk factors, and of 0·56 (p=0·023) in those that did not.

The third Cox proportional hazards model was repeated with the nine groups detailed in the methods section entered in the same model as dummy variables, with the intermediate/intermediate group as reference (table 4). Only the low/low group had a significant association with mortality.

Discussion

Our data accord with previous findings of increased mortality in elderly people with low serum cholesterol, and show that long-term persistence of low cholesterol concentration actually increases risk of death. Thus, the earlier that patients start to have lower cholesterol concentrations, the greater the risk of death. Cholesterol metabolism and homoeostatic mechanisms might differ in the very old (>75 years), and little information is available about cholesterol-mortality relations in this age group.

The reasons for these results are not clear. Perhaps they indicate a selective mortality; those individuals who are susceptible to biological effects of high serum cholesterol die before they reach age 75 years. The individuals who are left would be a select group with lower cholesterol and whose genetic makeup or other factors protect them from the effects of higher cholesterol concentrations. To some degree Honolulu Heart Program data support this hypothesis—there are few individuals with truly high concentrations of cholesterol remaining in this population. Previous data on concentration of cholesterol from this population show that the distribution of cholesterol has shifted towards the left as the cohort ages.

Is frailty a mortality trait? Frailty measures correlated with low serum cholesterol at the fourth examination, but are unlikely to explain the adverse effects of cholesterol in the low/low group (table 4). Since we have no data correlating frailty measures from the third examination, it seems implausible to posit that there was a group of patients in examination 3 with low cholesterol who also had increased frailty measures over this 20-year period. Nonetheless we cannot rule out this possibility.

The most striking findings were related to changes in cholesterol between examination three (1971–74) and examination four (1991–93). There are few studies that have cholesterol concentrations from the same patients at both middle age and old age. Although our results lend support to previous findings that low serum cholesterol imparts a poor outlook when compared with higher concentrations of cholesterol in elderly people, our data also suggest that those individuals with a low serum cholesterol maintained over a 20-year period will have the worst outlook for all-cause mortality. Iribarren and colleagues[20] suggested that a decline in serum cholesterol might occur over a decade before diagnosis of disease, and such long-term morbidity could be attributable to chronic subclinical infections with hepatitis B, or to chronic respiratory disease resulting in repeated respiratory infections. These disorders could increase concentration of proinflammatory cytokines that cause hypocholesterolaemia.[21] Our present analysis suggests that this hypothesis is implausible and is unlikely to account for the adverse effects of low cholesterol over 20 years.

Is this low/low effect unique to individuals of Japanese ethnic extraction? There is no evidence to support such a contention. Risk factors for atherosclerosis in Japanese are much the same as those for whites.[12] Did these individuals follow a very atypical, very low-fat, low–cholesterol diet, or were they taking powerful lipid-lowering agents? In a separate analysis of the small group of patients who took lipid-lowering drugs, there was no evidence of significant mortality differences and therefore no need to exclude these patients from the analysis. Although there are several prospective clinical trials showing that reduction of serum cholesterol is beneficial, their relevance to elderly people is not straightforward.[1,2] Patients in such studies are self-selected for their interest in participating and there are insufficient numbers aged older than 70 years to allow meaningful conclusions. The absence of comparability studies of laboratory analyses for 20 years might restrict interpretation of variations in cholesterol concentrations. However, this seems unlikely.

Clinically, two issues emerge. First, is there a difference in biological effect from a permanent, untreated, intrinsically low concentration of cholesterol when compared with the effect in those who have a dietary or pharmacologically induced reduction of cholesterol? As far as we are aware, this issue has not been addressed scientifically. Second, in view of our data, and those of others, is there scientific justification for attempts to lower cholesterol to concentrations below 4·65 mmol/L in elderly people? We believe that until more information about these complex relations is available, prudence dictates a more conservative approach in this age group.

Contributors

Irwin Schatz, Kamal Masaki, and J David Curb designed this study. Irwin Schatz and Kamal Masaki wrote the paper and all authors contributed to the final version. Katsuhiko Yano and Beatriz Rodriguez did data analysis, and Randi Chen did biostatistical analyses.

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