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THE LOW CHOLESTEROL–MORTALITY ASSOCIATION IN A NATIONAL COHORT

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Abstract—The relationship of low serum cholesterol and mortality was examined in data from the NHANES I Epidemiologic Followup Study (NHEFS) for 10,295 persons aged 35–74, 5833 women with 1281 deaths and 4462 men with 1748 deaths (mean followup = 14.1 years). Serum cholesterol below 4.1 mmol/l was associated with increased risk of death in comparison with serum cholesterol of 4.1–5.1 mmol/l (relative risk (RR) for women = 1.7, 95% confidence interval (CI) = (1.2, 2.3); for men RR = 1.4, CI = (1.1, 1.7)).

However, the low serum cholesterol–mortality relationship was modified by time, age, and among older persons, activity level. The low serum cholesterol–mortality association was strongest in the first 10 years of followup. Moreover, this relationship occurred primarily among older persons (RR for low serum cholesterol for women 35–59 = 1.0 (0.6, 1.8), for women 70–74, RR = 2.1 (1.2, 3.7); RR for low serum cholesterol for men 35–59 = 1.2 (0.8, 2.0), for men 70–74, RR = 1.9 (1.3, 2.7)). Among older persons, however, the low serum cholesterol–mortality association was confined only to those with low activity at baseline.

Factors related to underlying health status, rather than a mortality-enhancing effect of low cholesterol, likely accounts for the excess risk of death among persons with low cholesterol. The observed low cholesterol–mortality association therefore should not discourage public health programs directed at lowering serum cholesterol.

Cholesterol Mortality Aged Epidemiology Geriatrics

INTRODUCTION

An important role for serum cholesterol in the etiology of atherosclerosis and coronary heart disease is well-established [1–5], particularly for middle-aged males. However, the relationship of total mortality to serum cholesterol is less clear, especially for non-coronary mortality. Both clinical trials and longitudinal cohort studies have found a significant risk of non-coronary mortality associated with low serum cholesterol levels, including deaths from infectious disease [6], cancer [7–9], hemorrhagic stroke [10], and accidental death [11]. Based on these findings, questions have been raised regarding the overall benefit of serum cholesterol-lowering as a public health program [11]. In response, alternative hypotheses regarding the association of low serum cholesterol and poor health outcomes have been investigated, including depression of serum cholesterol by preclinical disease [12–14] and the potential role of

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nutritional confounders [15]. Moreover, these results regarding low cholesterol need additional study in populations including women and older persons.

Mortality data on men and women aged 35–74 from the National Health and Nutrition Examination Survey I Epidemiologic Followup Study (NHEFS) were analyzed to address two questions: first, what is the association of serum cholesterol, and specifically low serum cholesterol, to all-cause and cause-specific mortality; and second, is there evidence of modification of this association by factors indicative of underlying health status?

METHODS

The National Health and Nutrition Examination Survey I (NHANES I) took place in 1971–75 [16]. The population was a nationally representative sample of those aged 1–74 years old, with oversampling of women, the poor and older persons. The NHANES I assessed risk factors and diseases of public health importance including cardiovascular disease, diabetes, arthritis and pulmonary disease, as well as information on nutrition. A longitudinal followup, the NHANES I Epidemiologic Followup Study (NHEFS), of the 14,407 persons aged 25–74 who participated in NHANES I was initiated in the early 1980s [17]. There have been three waves of followup: 1982–84, 1986 and 1987 [18]. The followup has consisted primarily of questionnaire material, although blood pressure and weight were measured in 1982–84. Death certificates were obtained and coded for 97% of decedents through 1987 and hospital records have been obtained and compiled.

Study population

The study population for this paper included the 5833 women age 35–74 at baseline, for whom there was a serum cholesterol measurement available and for whom menopausal status was known, and the 4462 men for whom there was a serum cholesterol measurement. As the paper is focused primarily on all-cause mortality, there were no exclusions for diseases prevalent at baseline. Mean follow-up time for survivors through the 1987 followup was 14.1 years. Cause-specific mortality was determined from the underlying cause of death on death certificates coded according to ICD 9 for cancer (ICD 9 coded 140–208), cardiovascular death (ICD 9 coded 390–459, with ICD 410–414 for coronary heart disease) and all other deaths.

Study variables and statistical methods

The variable of interest was serum cholesterol which was measured at the CDC Laboratory by a semiautomated method based on that of Abell *et al.* [19]; comparison of the CDC method with that of Abell led to an adjustment of 4.5% for the bloods processed in 1971–74 [20]. No lipoprotein fraction data were available. For this paper, serum cholesterol values were grouped into four categories: <4.1 mmol/l, 4.1–5.1, 5.2–6.1 and 6.2 or more, the upper levels selected to match the guidelines of the National Cholesterol Education Program [21]. The 4.1 mmol/l represented approximately the lowest 5% of values for the NHANES. Those with serum cholesterol levels between 4.1 and 5.1 mmol/l were used as the reference group for all analyses.

Potential confounders included in multivariate models were sociodemographic variables (age, race [white vs others], education level [0 through 8 years, 9–12 years, and more than 12 years], poverty index [less than 1 vs 1 or more]) and cardiovascular risk factors (systolic blood pressure [less than 120 mmHg, 120–139, 140–159, 160 or more], told by a physician of diabetes, alcohol intake [never, daily or less than daily], cigarette smoking [current, former, never [22]], body mass index [in sex-specific quartiles], activity level [low, moderate, and high based on usual and recreational activity], and menopausal status). Indicators of illness or nutritional status were also considered as potential confounders. These variables include reported weight loss from maximum (less than 5% loss, or 5% or more), serum vitamin A, albumin, hemoglobin, and sedimentation rate, all expressed as quartiles. Among the older persons, we tested for multiplicative interaction by physical activity and weight loss as these variables have been shown to modify risk of heart disease secondary to cholesterol in older persons [23, 24].

Cox proportional hazard models were used for all statistical modelling to account for the variable follow-up time [25]. Ninety-five percent confidence intervals were calculated for all estimates. All univariate models were age-adjusted, and for women, adjusted for menopausal status as well.

RESULTS

About 5% of the study population had serum cholesterol values of less than 4.1 mmol/l, while

Table 1. Association of cholesterol and mortality in persons aged 35–74 years

Cholesterol level (mmol/l)	Number	Deaths	Rate ratios and 95% CI*
Women			
<4.1	317	55	1.7 (1.2, 2.3)
4.1–5.1	1222	175	1.0
5.2–6.1	1919	392	0.9 (0.8, 1.1)
6.2 or greater	2375	659	0.9 (0.7, 1.1)
Men			
<4.1	235	109	1.4 (1.1, 1.7)
4.1–5.1	1030	400	1.0
5.2–6.1	1664	600	0.9 (0.8, 1.0)
6.2 or greater	1533	639	1.0 (0.9, 1.2)

*Adjusted for age in men and women, model for women adjusted for menopausal status as well.

41% of the women and 34% of the men had serum cholesterol values of 6.2 mmol/l or more. About 22% of deaths were due to cancer and 50% to cardiovascular disease in either sex. Of the 1281 deaths in women, 737 occurred in the first 10 years; for men 1170 of the 1748 deaths occurred in the first 10 years.

Serum cholesterol level of less than 4.1 mmol/l was associated with an increased risk of mortality in both men and women (Table 1), while risks for higher levels of serum cholesterol were not elevated.

Is the low serum cholesterol–mortality association modified by followup time period?

Attenuation of the low cholesterol–mortality association was assessed by comparison of results for three separate followup time periods: less than 5 years, 5–10 years, and more than 10 years. For both women and men, risk of mortality associated with serum cholesterol of less than 4.1 mmol/l persisted up to 10 years (Table 2), although women experienced the greatest risk of mortality associated with low serum cholesterol in the first 5 years of followup. After 10 years, this increased risk of mortality associated with low serum cholesterol was no longer present.

The relationship of low serum cholesterol to cause-specific mortality was evaluated in similar fashion. For the first 10 years of followup, risk of death associated with low cholesterol was increased for each cause-specific mortality for women, whereas after 10 years, risks were attenuated (Table 3). For men, mortality risk associated with low serum cholesterol was elevated only for cancer and all other mortality. Both risks attenuated over time but that for cancer remained positive.

Adjustment of the models for confounders did not alter the coefficient for low serum cholesterol (Table 4). Similarly, addition of indicators of nutritional status or inflammatory illness (compare simple model 2 with multivariate model 2), did not alter the coefficient for low serum cholesterol.

Is the low serum cholesterol–mortality association modified by age?

Age also acted as a modifier of the low cholesterol–mortality association. In women age 35–59, the relative risk for serum cholesterol

Table 2. Cholesterol and all-cause mortality in persons age 35–74: modification by followup time

	Years of followup*		
Cholesterol level (mmol/l)	<5 yr	5–10 yr	>10 yr
Women			
<4.1	2.7 (1.6, 4.5)	1.6 (0.9, 2.7)	1.0 (0.5, 1.7)
4.1–5.1	1.0	1.0	1.0
5.2–6.1	1.0 (0.7, 1.4)	0.8 (0.6, 1.1)	1.0 (0.7, 1.3)
6.2 or greater	0.7 (0.5, 1.0)	0.9 (0.7, 1.2)	1.0 (0.8, 1.3)
Men			
<4.1	1.4 (1.0, 2.0)	1.7 (1.2, 2.3)	1.0 (0.6, 1.5)
4.1–5.1	1.0	1.0	1.0
5.2–6.1	0.9 (0.7, 1.1)	0.9 (0.8, 1.2)	0.8 (0.7, 1.1)
6.2 or greater	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	1.1 (0.9, 1.4)

*Adjusted for age in men and women, model for women adjusted for menopausal status as well.

Table 3. Cholesterol and cause-specific mortality in persons age 35–74: modification by followup time. Results for cholesterol of 4.1 mmol/l compared with cholesterol of 4.1–5.1 mmol/l

Cause of death	Years of followup*	
	First 10 yr	>10 yr
Women		
Cancer	3.3 (1.9, 5.9)	0.6 (0.2, 2.1)
Coronary heart disease	2.7 (1.5, 5.0)	1.1 (0.4, 2.9)
Other cardiovascular	1.4 (0.7, 2.7)	0.8 (0.2, 2.3)
All other	1.7 (0.7, 4.0)	1.0 (0.4, 2.9)
Men		
Cancer	2.6 (1.6, 4.0)	1.5 (0.7, 3.4)
Coronary heart disease	1.0 (0.6, 1.5)	0.5 (0.2, 1.3)
Other cardiovascular	1.0 (0.5, 1.8)	0.8 (0.2, 2.6)
All other	2.1 (1.3, 3.2)	1.2 (0.6, 2.5)

*Adjusted for age in men and women, model for women adjusted for menopausal status as well.

of less than 4.1 was 1.0 (0.6, 1.8), while that for women age 60–69 or 70–74, was 2.2 (1.2, 3.7) (Table 5) (interaction term for age level and serum cholesterol level, $p = 0.001$). For men, the low serum cholesterol effect was concentrated primarily in the oldest age group of persons age 70–74, where the relative risk was 1.9 (1.3, 2.7) (interaction term, $p = 0.04$).

Among older persons, is the low serum cholesterol–mortality association modified by other health-related factors?

For persons age 65–74 at baseline, analyses were conducted stratified for physical activity and weight loss from age 50. Among those of high activity, the relative risk for mortality in the low serum cholesterol group was 0.9 in women and 1.1 in men (Table 6), whereas both the moderate and low activity groups showed elevated relative risks for low serum cholesterol (interaction term for activity level and serum cholesterol level, $p = 0.17$ for men and $p = 0.002$ for women). Stratification by weight loss showed an increased risk of mortality in those with larger weight loss for both men and women; however, only the interaction term for men was marginally significant ($p = 0.11$ for men and $p = 0.36$ for women).

DISCUSSION

The consistency of the low serum cholesterol–mortality association in multiple studies [6–11] suggests it is not a chance phenomenon. Our data, from a national cohort with over 14 years of followup supports an association of low serum cholesterol and mortality as well. However, it remains unclear whether low serum cholesterol is causally related to poor health outcomes, or whether the poor outcomes and the low serum cholesterol reflect other factors associated with underlying health status. Our observations would appear to support the latter conclusion as the low serum cholesterol–mortality association was present primarily among the oldest, least active persons in the data set.

In our study, those with low serum cholesterol apparently constitute two distinct populations. In one group, low serum cholesterol is not associated with adverse outcomes. In the other group, low serum cholesterol is an indicator for increased risk of death. While these low serum cholesterol groups can be differentiated indirectly by health-related variables such

Table 4. Adjustment of the cholesterol–mortality association by covariates

Cholesterol level (mmol/l)	First 10 years of follow-up			
	Simple model*	Multivariate†	Simple model‡	Multivariable§
Women	$n = 5833$	$n = 5766$	$n = 3648$	$n = 3648$
<4.1	2.1 (1.5, 3.0)	2.1 (1.5, 3.1)	1.8 (1.2, 2.8)	1.7 (1.1, 2.7)
4.1–5.1	1.0	1.0	1.0	1.0
5.2–6.1	0.8 (0.7, 1.1)	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	0.9 (0.7, 1.2)
6.2 or greater	0.8 (0.6, 1.0)	0.9 (0.7, 1.1)	0.8 (0.6, 1.0)	0.9 (0.6, 1.1)
Men	$n = 4462$	$n = 4399$	$n = 2677$	$n = 2677$
<4.1	1.5 (1.2, 2.0)	1.5 (1.2, 1.9)	1.4 (1.0, 1.9)	1.3 (0.9, 1.7)
4.1–5.1	1.0	1.0	1.0	1.0
5.2–6.1	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)
6.2 or greater	1.0 (0.9, 1.2)	1.1 (0.9, 1.2)	1.0 (0.8, 1.2)	1.1 (0.9, 1.3)

*Controlling for age, and for women, menopausal status.

†Also controlling for race, systolic blood pressure, diabetes, alcohol intake, cigarette smoking, education level, body mass index, and activity level.

‡Controlling for age, and for women, menopausal status; all missing values for covariates deleted so n is the same for last two models.

§Also controlling for race, systolic blood pressure, diabetes, alcohol intake, cigarette smoking, education level, body mass index, activity level, weight loss, serum vitamin A, poverty index, serum albumin, hemoglobin and sedimentation rate.

Table 5. Cholesterol and all-cause mortality: modification by age

Cholesterol level (mmol/l)	Age at baseline in NHANES I*		
	35–59	60–69	70–74
Women			
<4.1	1.0 (0.6, 1.8)	2.2 (1.4, 3.5)	2.2 (1.2, 3.7)
4.1–5.1	1.0	1.0	1.0
5.2–6.1	1.0 (0.7, 1.4)	1.0 (0.8, 1.3)	0.7 (0.5, 1.0)
6.2 or greater	1.5 (1.0, 2.0)	0.9 (0.7, 1.1)	0.7 (0.5, 0.9)
Men			
<4.1	1.2 (0.8, 2.0)	1.2 (0.9, 1.6)	1.9 (1.3, 2.7)
4.1–5.1	1.0	1.0	1.0
5.2–6.1	0.9 (0.7, 1.1)	0.7 (0.6, 0.9)	1.2 (0.9, 1.5)
6.2 or greater	1.2 (0.9, 1.5)	0.9 (0.8, 1.1)	1.1 (0.9, 1.4)

*Model for women adjusted for menopausal status.

as age and activity level, serial measurements of serum cholesterol would be a preferable method to evaluate these different groups as those with declines in serum cholesterol secondary to illness could be differentiated from those whose cholesterol is stable and remains low. Spontaneous decline in serum cholesterol has been associated with poor health outcomes [26–28]. It is likely that the low serum cholesterol in the group at high risk of mortality may represent a change in values from usual level; however, our data, in which only one serum cholesterol measurement was available cannot address this question.

One strategy to differentiate these low cholesterol subgroups was stratification on followup time. The low cholesterol–mortality relationship was present through as long as 10 years of followup. While a causal role for the low cholesterol with mortality risk is possible with this long a duration, an alternative explanation may involve multiple etiologic factors. For instance, over the first few years of followup, the direct effects of poor health on both serum cholesterol and mortality may be primary, with lower cholesterol levels reflecting weight loss [29] or humoral factors [26, 30]. Over longer followup, other factors, including alcohol-related disease may be important, as those who are heavier drinkers may have lower serum cholesterol levels and yet may be at increased risk of mortality due to the alcohol intake [31]. Similar

Table 6. Cholesterol and all-cause mortality in older persons: modification by activity level and weight loss

Cholesterol level (mmol/l)	Activity level*		
	High	Moderate	Low
Women			
<4.1	0.9 (0.3, 3.2)	2.0 (1.2, 3.3)	3.5 (1.8, 6.8)
4.1–5.1	1.0	1.0	1.0
5.2–6.1	1.2 (0.7, 2.0)	1.0 (0.7, 1.3)	0.7 (0.5, 1.1)
6.2 or greater	1.3 (0.8, 2.0)	0.8 (0.6, 1.1)	0.8 (0.5, 1.2)
Men			
<4.1	1.1 (0.7, 1.8)	1.5 (1.0, 2.1)	1.9 (1.1, 3.2)
4.1–5.1	1.0	1.0	1.0
5.2–6.1	1.0 (0.7, 1.3)	0.9 (0.7, 1.2)	0.8 (0.5, 1.1)
6.2 or greater	1.1 (0.8, 1.4)	1.0 (0.8, 1.3)	1.1 (0.7, 1.6)
	Weight loss		
	<5%	⩾5%	
Women			
<4.1	1.2 (0.4, 4.1)	1.9 (1.3, 2.7)	
4.1–5.1	1.0	1.0	
5.2–6.1	0.9 (0.6, 1.6)	1.0 (0.8, 1.2)	
6.2 or greater	1.0 (0.6, 1.6)	1.1 (0.8, 1.4)	
Men			
<4.1	1.0 (0.4, 2.2)	2.3 (1.3, 4.1)	
4.1–5.1	1.0	1.0	
5.2–6.1	0.9 (0.6, 1.3)	1.0 (0.8, 1.5)	
6.2 or greater	1.2 (0.8, 1.6)	1.0 (0.7, 1.5)	

*Models for men and women adjusted for age.

issues may arise for smoking [32]. Studies of populations with systematically lower serum cholesterol values may be useful to address these biological hypotheses as those with very low serum cholesterol values remain rare in the U.S. population, and without serial measurements of serum cholesterol and good health status data, disentangling cause and effect may prove difficult.

It is noteworthy that the differences in the interpretation of the data which would have followed from simply controlling for confounding and omitting the stratified models. Few studies of low serum cholesterol have included models of interaction, particularly for health status variables. This may be an important consideration for estimation of risk associated with low serum cholesterol, as has been true for studies of health outcomes and body weight [33, 34].

In these data, we can also consider the effect of higher levels of serum cholesterol on mortality, although that is not the focus of this paper. Using those with serum cholesterol between 4.1 and 5.1 as a reference group, our results suggest that serum cholesterol level is neutral with regard to mortality, except for women aged 35–59 who showed a 50% increased risk of mortality. As we have discussed above, our methods to separate out those with "lowered" cholesterol secondary to adverse health status are relatively crude and may account for the observed lack of association between higher levels of cholesterol and mortality. However, even if the serum cholesterol data were neutral with regard to overall mortality, these results would be supportive of public health initiatives directed to prevention of cardiovascular disease, due to the major disability and morbidity which accompanies this diagnosis.

In this paper, we have demonstrated that the increased relative risk of mortality for those with very low serum cholesterol was modified by time, age, and other factors, such as activity level. These modifications suggest the biologic meaning of low serum cholesterol is different in different groups of individuals, particularly among the elderly in whom the prevalence of poor health increases. As the biological factors responsible for cholesterol lowering are elucidated, it may be possible to analyze serum cholesterol–disease–mortality relations taking into account these factors. In the meantime, these data support current efforts directed to reduction of serum cholesterol levels.

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