SERUM CHOLESTEROL IN YOUNG MEN AND SUBSEQUENT CARDIOVASCULAR DISEASE

MICHAEL J. KLAG, M.D., M.P.H., DANIEL E. FORD, M.D., M.P.H., LUCY A. MEAD, SC.M., JIANG HE, M.D., PAUL K. WHELTON, M.D., M.SC., KUNG-YEE LIANG, AND DAVID M. LEVINE, M.D., M.P.H., SC.D.

Abstract *Background.* The increased risk of cardiovascular disease associated with higher serum cholesterol levels in middle-aged persons has been clearly established, but there have been few opportunities to examine a potential link between serum cholesterol levels measured in young men and clinically evident premature cardiovascular disease later in life.

Methods. We performed a prospective study of 1017 young men (mean age, 22 years) followed for 27 to 42 years to quantify the risk of cardiovascular disease and total mortality associated with serum cholesterol levels during early adult life. The mean serum cholesterol level at entry was 192 mg per deciliter (5.0 mmol per liter).

Results. During a median follow-up of 30.5 years, there were 125 cardiovascular-disease events, 97 of which were due to coronary heart disease. The serum cholesterol level at base line was strongly associated with the incidence of events related to coronary heart disease and cardiovascular disease, as well as to total mortality and mortality due to cardiovascular disease. The risks were similar whether the events occurred before or after the age of 50. In a proportional-hazards analysis adjusted for age, body-mass index (the weight in kilograms divided by the square of the height in meters), the level of physical activity, coffee intake, change in smoking status, and the incidence of diabetes and hypertension during follow-up, a difference in the serum cholesterol level at base line of 36 mg per deciliter (0.9 mmol per liter) — the difference between the 25th and 75th percentiles of cholesterol level in the study population at base line — was associated with an increased risk of cardiovascular disease (relative risk, 1.72; 95 percent confidence interval, 1.39 to 2.14), coronary heart disease (relative risk, 2.01; 95 percent confidence interval, 1.59 to 2.53), and mortality due to cardiovascular disease (relative risk, 2.02; 95 percent confidence interval, 1.23 to 3.32). A difference in the base-line serum cholesterol level of 36 mg per deciliter was significantly associated with an increased risk of death before the age of 50 (relative risk, 1.64; 95 percent confidence interval, 1.03 to 2.61), but not with the overall risk of death (relative risk, 1.21; 95 percent confidence interval, 0.93 to 1.58).

Conclusions. These findings indicate a strong association between the serum cholesterol level measured early in adult life in men and cardiovascular disease in midlife. (N Engl J Med 1993;328:313-8.)

CARDIOVASCULAR disease is the leading cause of death in middle-aged American men.[1] In 1988, more than 41,000 U.S. residents died of cardiovascular disease before the age of 50. Atherosclerosis, however, begins at a much earlier age. Fatty streaks are common in the arterial walls of children, and a high prevalence of coronary-artery lesions has been found in young men who die accidentally or violently.[2-5] Children and adolescents with elevated serum cholesterol levels are more likely than their counterparts with normal cholesterol levels to have parents with coronary heart disease.[6] Higher serum cholesterol levels in childhood have been associated with aortic atherosclerosis at autopsy in adolescents and young adults,[7] and both aortic and coronary atherosclerosis in men ranging from 15 to 34 years of age have been correlated with postmortem cholesterol levels.[5] However, the risk of clinically evident coronary artery disease associated with serum cholesterol levels measured during childhood and early in adult life has not been determined. Most prospective studies of risk factors for clinical cardiovascular disease have examined middle-aged persons. Only a small minority of the participants in such studies were under 40 years of age at entry.[8-10]

To characterize the risk of cardiovascular disease associated with the level of serum cholesterol in young men, we analyzed data from a prospective study of white men. The unique features of this study include the measurement of cholesterol at a median age of 22 years and follow-up for up to 42 years.

METHODS

Study Population and Measurements

The Johns Hopkins Precursors Study was started in 1947.[11] A total of 1337 students at Johns Hopkins Medical School who were members of the graduating classes of 1948 through 1964 were enrolled; 1271 (95 percent) received a standardized medical examination and completed a questionnaire during medical school. Physical activity in medical school was defined as any "physical training" occurring within the previous month, a measure shown to be protective against cardiovascular disease in this cohort.[12] Information about smoking habits, coffee intake, body weight, and drug treatment for hyperlipidemia was gathered at base line and over the course of follow-up by means of annual questionnaires. It was not customary to obtain informed consent during the period in which the base-line data were collected. After the establishment of the Joint Committee on Clinical Investigation at our institution, the protocol for follow-up was reviewed and approved.

Starting with the class of 1949, serum cholesterol was measured in the non-fasting state on multiple occasions during medical school with use of the Bloor method.[13] (Therefore, the 79 members of the class of 1948 were not included in the analysis.) The coefficient of variation for the assay used in this study was 5 percent. The number of measurements per subject ranged from 1 to 11 (median, 3). For this analysis, the average of all cholesterol measurements obtained during medical school was used, and values were adjusted to correspond to the Abell–Kendall method.[14,15] In pre-

From the Departments of Medicine (M.J.K., D.E.F., L.A.M., P.K.W., D.M.L.), Epidemiology (M.J.K., D.E.F., J.H., P.K.W.), Health Policy and Management (M.J.K., D.E.F., D.M.L.), and Biostatistics (K.-Y.L.), Johns Hopkins University School of Medicine and School of Hygiene and Public Health, Baltimore, and Peking Union Medical College and Chinese Academy of Medical Sciences, People's Republic of China (J.H.). Address reprint requests to Dr. Klag at the Johns Hopkins Precursors Study, 550 N. Broadway, Rm. 503, Baltimore, MD 21205.

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vious work from the Precursors Study, serum cholesterol values measured on a single occasion were used.[16-18] The use of the average of multiple determinations over time yields a more precise estimate of a person's true cholesterol value.[19]

A total of 1017 white men (90 percent of the white men in the study) had their serum cholesterol levels determined while in medical school. These men form the basis of the present analysis.

Follow-up Procedures

The development of cardiovascular disease after graduation was assessed by means of annual questionnaires. The present analysis was based on events reported through December 31, 1991, representing 27 to 42 years of follow-up. The yearly response rates ranged from 68 to 78 percent. Between 87 and 94 percent of the cohort responded at least once over any five-year period. The vital status of nonrespondents was ascertained by contacting family members, scanning obituaries, and searching the National Death Index through 1989. The vital status of more than 99 percent of the cohort was known. An end-points committee of five internists who were also trained in epidemiology confirmed all reports of morbidity and mortality due to cardiovascular disease. After a review of associated medical records, autopsy reports, and death certificates, a diagnosis was assigned with use of a modification of the Lipid Research Clinics criteria classified according to the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD).[20,21] Self-reports of the occurrence of disease were very accurate. For example, medical records were obtained for 90 percent of the patients with myocardial infarction, and the self-reported diagnosis was verified in every instance.

Cardiovascular disease was categorized as follows. The most specific category, myocardial infarction, included myocardial infarction (ICD 410 and 412) and sudden death (ICD 427.5 and 798.2). Coronary heart disease included all events in the myocardial-infarction codes as well as angina pectoris (ICD 413), chronic ischemic heart disease (ICD 411), and other types of symptomatic coronary disease that did not meet these criteria but required coronary-artery bypass surgery or percutaneous transluminal coronary angioplasty (ICD 414). The broadest category, cardiovascular disease, included events due to coronary heart disease as well as hypertensive heart and renal diseases (ICD 402 to 404), congestive heart failure (ICD 428), and cerebrovascular disease (ICD 430 to 438).

Statistical Analysis

After the frequency distribution of all variables was examined, the association of the serum cholesterol level, categorized by quartiles, with possible confounders was assessed by chi-square analysis and analysis of variance. The relation of the serum cholesterol level at base line with the subsequent incidence of disease was examined with Kaplan–Meier analysis.[22] The log-rank test was used to assess whether the incidence of disease varied significantly according to the quartile of cholesterol level.[23] Follow-up began with the subjects' graduation from medical school. The interval between the beginning of follow-up and the occurrence of an event was used as the time variable in all analyses of survival. For categories in which a subject may have had more than one type of event, only the first event to occur was used in the analysis. To investigate whether the relation between the serum cholesterol level measured in young adulthood and the end points differed for events that occurred earlier as opposed to later in life, the analysis was repeated after the end points were stratified as occurring before the age of 50 or as occurring at the age of 50 or later. To determine whether the associations of the serum cholesterol level with cardiovascular disease were independent of other risk factors, Cox proportional-hazards analysis was used.[24] Multivariate analyses were performed in which serum cholesterol was used as both a continuous and a categorical (by quartile) variable. To account for possible secular trends in the serum cholesterol level and the incidence of coronary heart disease, the Cox models were stratified according to calendar time: 1948 through 1957 and 1958 through 1964. The intake of coffee, which has been associated with the incidence of coronary heart disease in this cohort[16,18]; the level of physical activity; body-mass index (the weight in kilograms divided by the square of the height in meters); and the age at graduation were also included in the multivariate models. In addition, the effects of a change in cigarette-smoking status and the development of hypertension and diabetes during the course of follow-up were assessed by including time-dependent covariates for these variables in the Cox models. The results of the proportional-hazards analysis are presented for a difference in the serum cholesterol level at base line of 36 mg per deciliter (0.9 mmol per liter), the difference between the 25th and the 75th percentiles (interquartile range) of serum cholesterol level in this study population at base line. This difference in serum cholesterol levels is clinically important, and a reduction of this magnitude in the cholesterol level could reasonably be expected from a combined dietary and pharmacologic intervention. Hazard ratios are reported as relative risks with 95 percent confidence intervals. All P values of ≤ 0.05 were considered to indicate statistical significance (by a two-tailed test).

Results

The characteristics of the men in this analysis at base line are presented in Table 1. In general, the participants were young, healthy, and at low risk for cardiovascular disease. Their average age at entry into medical school was 22 years, and their average age at graduation was 26 years. The mean systolic and diastolic blood pressures and body-mass index were well within the normal range. Only 36 (3.5 percent) of the men had elevated blood pressures, as defined by a systolic pressure of 160 mm Hg or more, a diastolic pressure of 95 mm Hg or more, or both. Forty-eight (5 percent) of the men were overweight, as defined by a body-mass index of 27.8 or more. The average serum cholesterol level was 192 mg per deciliter (5.0 mmol per liter). The difference in the mean cholesterol levels was greatest between the third and the fourth quartile: 32 mg per deciliter (0.8 mmol per liter). Almost half the men smoked during medical school, and 19 percent had engaged in physical training during the month before the base-line examination.

Men whose serum cholesterol levels were in the highest quartile were slightly older at admission than their counterparts in the other three quartiles (Table 1). Body-mass index, although well within the normal range, was higher for each successive quartile of cholesterol. Coffee intake, blood pressure, degree of physical activity, and prevalence of smoking were not associated with the serum cholesterol level.

Over the 27 to 42 years of follow-up, members of the cohort contributed 27,871 person-years of observation, with a median follow-up of 30.5 years. At the end of follow-up in 1991, the mean age of the cohort was 60 years (range, 50 to 89). A total of 125 cardiovascular-disease events and 97 coronary-heart-disease events were reported during follow-up (Table 2). Among the 95 participants who died, death was attributed to cardiovascular disease in 21, and 18 of these 21 subjects had coronary heart disease (Table 2). The average age at the time of the diagnosis of coronary disease was 53 years. In 1985, only 10 men reported being treated with drugs that lowered lipid levels; their mean cholesterol level at base line was 225 mg

Table 1. Base-Line Characteristics of 1017 White Men, According to the Serum Cholesterol Level.*

VARIABLE	ALL SUBJECTS	QUARTILE OF CHOLESTEROL LEVEL				P VALUE†
		118–172 mg/dl	173–189 mg/dl	190–208 mg/dl	209–315 mg/dl	
No. of subjects	1017	250	258	254	255	
Age (yr)	22.0±2.3	21.6±1.9	21.8±2.0	21.8±2.0	22.7±3.1	0.001
Coffee intake (cups/day)‡	2.3±1.8	3.1±1.9	2.2±1.8	2.3±1.7	2.4±1.9	0.2
Body-mass index	23.2±2.6	22.5±2.4	22.8±2.2	23.4±2.6	24.0±2.9	0.001
Systolic blood pressure (mm Hg)	125±14	124±14	126±15	125±14	126±14	0.3
Diastolic blood pressure (mm Hg)	75±9	74±9	75±10	75±9	76±10	0.2
Serum cholesterol (mg/dl)	192±29	158±11	181±5	199±6	231±20	—
No. of current cigarette smokers§	443 (48)	108 (48)	105 (44)	109 (47)	121 (53)	0.4
No. physically active¶	175 (19)	42 (19)	46 (19)	52 (22)	35 (15)	0.3

*Plus–minus values are means ±SD. Values in parentheses are percentages. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

†By analysis of variance or chi-square analysis.

‡Data were available for 939 men.

§Data were available for 921 men.

¶Data were available for 923 men.

per deciliter (5.8 mmol per liter), which was significantly higher than that of the other members of the cohort ($P<0.001$). The cumulative incidence of hypertension over the course of follow-up was 38.4 percent; the cumulative incidence of diabetes mellitus was 6.0 percent. The prevalence of smoking decreased from 48.1 percent at base line to 10.5 percent in 1986.

Univariate Analysis

The serum cholesterol level at base line was strongly associated with the subsequent incidence of coronary heart disease (Table 2 and Fig. 1), with a marked stepwise increase in the cumulative incidence for successively higher quartiles of serum cholesterol. The same graded pattern of increasing risk with increasing levels of serum cholesterol was seen for myocardial infarction, angina, and total cardiovascular disease. The risk associated with the base-line serum cholesterol level was highest for myocardial infarction and lowest for angina.

There was also a graded relation between the base-line serum cholesterol level and total mortality (Table 2). Despite the relatively small number of deaths ascribed to cardiovascular disease, participants with serum cholesterol levels in the highest quartile at base line had a markedly higher risk of death during follow-up than those with cholesterol levels in the lowest quartile ($P<0.001$).

The relative risks of disease associated with a difference in the base-line serum cholesterol level of 36 mg per deciliter, derived by univariate Cox proportional-hazards analysis, are shown in Table 3. The risk associated with the serum cholesterol level during young adulthood was essentially the same whether the cardiovascular events occurred before or after the age of 50. For all the end points, including total mortality, there was no evidence of a J-shaped relation with the serum cholesterol level; the risk of disease was lowest in the men whose serum cholesterol levels were in the lowest eighth of the distribution. Moreover, the addition of quadratic terms (the square of the cholesterol level) did not improve the fit of the models.

Multivariate Analysis

The risk estimates associated with the serum cholesterol level after adjustment for covariates were remarkably similar to those from the univariate analysis (Table 3). Higher serum cholesterol levels were associated with a greater risk of cardiovascular disease and coronary heart disease that was independent of the other risk factors. As in the univariate analysis, the relative risk was greatest for the development of myocardial infarction and somewhat lower for angina pectoris. Each difference in the base-line serum cholesterol level of 36 mg per deciliter was associated with a 72 percent increase in the risk of total cardiovascular disease, a doubling of the risk of coronary heart disease and myocardial infarction, and a 54 percent increase in the risk of angina. The risk of death from cardiovascular disease was also increased for higher base-line serum cholesterol levels. After an adjustment for the covariates listed above, the se-

Table 2. Cumulative Incidence of Cardiovascular Disease and Total Mortality in 1017 White Men after 40 Years of Follow-up, According to the Base-Line Serum Cholesterol Level.

VARIABLE	NO. OF EVENTS*	QUARTILE OF CHOLESTEROL LEVEL†				P VALUE‡
		118–172 mg/dl	173–189 mg/dl	190–208 mg/dl	209–315 mg/dl	
Cardiovascular disease	125	9.7	18.5	22.4	37.7	<0.001
Coronary heart disease	97	6.9	11.5	17.5	35.2	<0.001
Myocardial infarction	62	3.4	5.1	7.2	29.2	<0.001
Angina pectoris	49	5.7	4.2	13.4	9.2	<0.08
Cardiovascular-disease mortality	21	1.2	5.0	2.7	14.0	<0.001
Total mortality	95	10.8	14.9	16.8	29.2	0.01

*For men who had more than one type of event, the first event to occur was used for analysis.

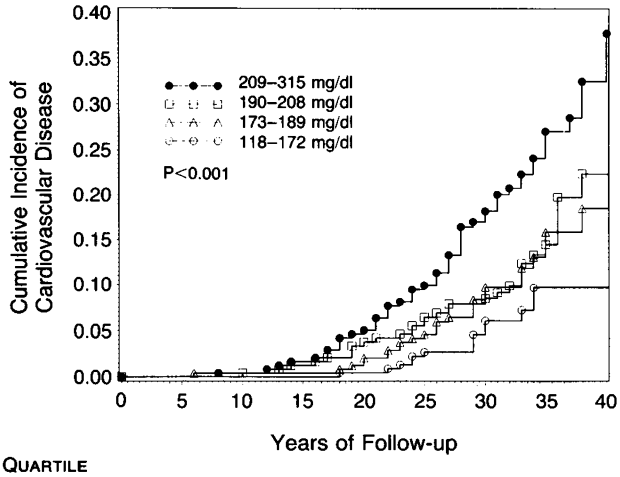
†To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

‡By the log-rank test.

rum cholesterol level at base line was not associated with total mortality, but was significantly associated with mortality from all causes before the age of 50.

When the multivariate analysis was repeated with serum cholesterol level as a categorical variable, similar results were obtained. The adjusted relative risk for the highest quartile as compared with the lowest quartile of serum cholesterol was 3.56 (95 percent confidence interval, 1.78 to 7.11) for total cardiovascular disease, 5.26 (95 percent confidence interval, 2.21 to 12.53) for coronary heart disease, 6.02 (95 percent confidence interval, 2.10 to 17.22) for myocardial infarction, 2.25 (95 percent confidence interval, 0.80 to 6.32) for angina, 9.63 (95 percent confidence interval, 1.20 to 77.15) for mortality due to cardiovascular disease, and 1.26 (95 percent confidence interval, 0.68 to 2.31) for mortality from all causes.

When the analyses were repeated with a single measurement of serum cholesterol rather than the average of multiple measurements, the estimates of risk were somewhat lower. After adjustment for the covariates listed in Table 3, multivariate analyses showed that the relative risk associated with a difference of 36 mg per deciliter in the base-line serum cholesterol level was 1.50 (95 percent confidence interval, 1.22 to 1.84) for cardiovascular disease, 1.77 (95 percent confidence interval, 1.41 to 2.21) for coronary heart disease, 2.01 (95 percent confidence interval, 1.23 to 3.27) for death from cardiovascular disease, and 1.22 (95 percent confidence interval, 0.95 to 1.56) for total mortality.



QUARTILE (mg/dl)									
118–172	250	248	245	240	234	217	128	61	7
173–189	258	256	254	250	243	216	131	62	15
190–208	254	251	248	240	228	208	155	75	12
209–315	255	251	243	235	222	196	140	78	13
Total	1017	1006	990	965	927	837	554	276	47

Figure 1. Cumulative Incidence of Cardiovascular Disease in 1017 White Men, According to the Serum Cholesterol Level at a Median Age of 22 Years.

To convert values for cholesterol to millimoles per liter, multiply by 0.02586. The numbers below the figure are the numbers of men included in the analysis at each time point.

Discussion

This study demonstrated a strong, graded relation between the serum cholesterol level measured early in adult life in men and the subsequent incidence of coronary heart disease, cardiovascular disease, and death from cardiovascular disease in midlife, which was independent of other risk factors. The average serum cholesterol level of this group was well within the desirable level specified by current national guidelines and was lower than corresponding values in U.S. white men of similar age and with similar levels of education in the period from 1960 through 1962.[25,26] However, the risk of cardiovascular disease was increased even among men with serum cholesterol levels in the "normal" range. In keeping with previous studies in older adults, this relation was stronger for coronary heart disease than for overall cardiovascular disease.[27] Almost all the events in this analysis were premature in the sense that over 95 percent occurred before the age of 65. However, the risk associated with the base-line serum cholesterol level did not differ markedly for events occurring before the age of 50 as compared with those that occurred later in life. Similar trends were noted for total mortality, without evidence of an increased risk for those with the lowest levels of serum cholesterol at base line.

The measurement of serum cholesterol at a young age, the long duration of follow-up, and the availability of data on other cardiovascular risk factors at base line and during follow-up are the strengths of the present study. The high follow-up rate of the cohort and the accuracy of physicians' self-reports are also major advantages. Few other studies have examined the risk of cardiovascular disease associated with characteristics assessed before midlife. Because the incidence of coronary artery disease before the age of 40 is relatively low, studies of risk factors in youth require very large samples or decades of follow-up in order to detect associations with cardiovascular disease. For example, although the present study was begun in 1947, only within the past several years have enough events occurred to allow us to study risk factors for cardiovascular disease. Previous studies of students entering college (average age, 18 years) and young aviators (average ages, 24 and 31) did not collect data on serum cholesterol.[28-30]

Two possible biases could have contributed to the marked excess risk of coronary heart disease in men with higher levels of serum cholesterol at base line. Men with higher serum cholesterol levels may have been subjected to increased surveillance for coronary disease. Thus, it is possible that mild, minimally symptomatic coronary disease could have been more readily detected in this group. In addition, the misdiagnosis of noncoronary symptoms as coronary heart

Table 3. Relative Risk of Cardiovascular Disease Associated with a Difference in the Serum Cholesterol Level of 36 mg per Deciliter during Medical School in 1017 White Men as a Group and According to the Age of the Men at the Time of the Event.*

VARIABLE	OVERALL		<50 YEARS OF AGE		≥50 YEARS OF AGE	
	NO. OF EVENTS	RELATIVE RISK (95% CI)	NO. OF EVENTS	RELATIVE RISK (95% CI)	NO. OF EVENTS	RELATIVE RISK (95% CI)
Cardiovascular disease						
Crude	125	1.76 (1.46–2.12)†	37	1.93 (1.40–2.68)†	88	1.67 (1.33–2.10)†
Adjusted‡		1.72 (1.39–2.14)†		2.05 (1.36–3.08)†		1.60 (1.24–2.06)†
Coronary heart disease						
Crude	97	2.04 (1.66–2.50)†	30	2.18 (1.54–3.08)†	67	1.97 (1.53–2.52)†
Adjusted‡		2.01 (1.59–2.53)†		2.25 (1.47–3.45)†		1.92 (1.44–2.55)†
Myocardial infarction						
Crude	62	2.42 (1.90–3.08)†	20	2.44 (1.62–3.68)†	42	2.40 (1.78–3.23)†
Adjusted‡		2.22 (1.67–2.94)†		2.09 (1.25–3.47)§		2.31 (1.63–3.25)†
Angina pectoris						
Crude	49	1.56 (1.15–2.11)§	16	1.75 (1.05–2.92)¶	33	1.47 (1.02–2.14)¶
Adjusted‡		1.54 (1.10–2.17)¶		2.09 (1.15–3.80)¶		1.34 (0.88–2.04)
Cardiovascular-disease mortality						
Crude	21	2.03 (1.37–3.00)†	5	3.29 (1.53–7.06)§	16	1.74 (1.10–2.77)¶
Adjusted‡		2.02 (1.23–3.32)‖		5.63 (1.63–19.48)§		1.70 (0.97–2.98)
Total mortality						
Crude	95	1.33 (1.06–1.66)¶	32	1.49 (1.02–2.19)¶	63	1.25 (0.95–1.65)
Adjusted‡		1.21 (0.93–1.58)		1.64 (1.03–2.61)¶		1.06 (0.77–1.47)

*Cox proportional-hazards analysis was used. A total of 874 men were included in the multivariate analyses. Serum cholesterol was analyzed as a continuous variable. Relative risks are presented for a difference in the cholesterol level between the 25th and 75th percentiles of cholesterol in this study population at base line. CI denotes confidence interval.

†P<0.001.

‡The multivariate Cox model was adjusted for the calendar year, age at graduation, body-mass index, coffee intake, degree of physical activity, and three time-dependent covariates: a change in cigarette-smoking status during follow-up, the development of hypertension, and the development of diabetes mellitus during follow-up.

§P<0.01. ¶P<0.05. ‖P = 0.005.

disease may have been more likely in this group because of their elevated cholesterol levels. Similar associations with the base-line serum cholesterol level were observed for death from cardiovascular disease and total mortality, however, making it very unlikely that such biases accounted for the associations. The lack of information on dietary intake of fat and cholesterol is a limitation of the present study. Although much of the risk associated with such intake would probably be mediated through the serum cholesterol level, there may be additional mechanisms not accounted for in the present study.[31] No information was available on lipoprotein or apolipoprotein levels, because lipoprotein fractionation was not yet being performed when this study was initiated. On the basis of studies of middle-aged men, lipoprotein fractions or apolipoprotein levels would be expected to have an even stronger relation with cardiovascular disease than with the total cholesterol level.[27] Another potential limitation of this and most cohort studies is that serum cholesterol levels were not assessed during follow-up. Considering the length of the follow-up and the limitations in the measurement of the exposure variable, the strong relation of serum cholesterol measured at base line to future events, especially after the age of 50, is even more remarkable.

The homogeneous high socioeconomic status in this cohort permits an estimation of the risk associated with the serum cholesterol level at base line that is relatively unconfounded by socioeconomic status. These data are strictly applicable only to advantaged white men who have a lower absolute incidence of disease than the general population. But the similarity of the estimates of the relative risk of cardiovascular disease in the present study to those in community-based studies, in which serum cholesterol was measured later in life, supports the idea that these findings can be applied to men of other social classes.[9,32] If deaths due to cardiovascular disease make up a greater proportion of total deaths in this group of white professionals than in the general population, however, this study might overestimate the relative risk of total mortality associated with the base-line serum cholesterol level, as compared with that in the general population.

In healthy young adults, the serum total cholesterol level is a strong predictor of clinically evident cardiovascular disease occurring 25 or more years later. This relation was present even though this group had a favorable risk-factor profile for cardiovascular disease, and it persisted after an adjustment for changes in the risk factors during follow-up. It remains for future studies to demonstrate that interventions designed to lower the cholesterol level in young adulthood are effective in the primary prevention of coronary heart disease and other types of cardiovascular disease.

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