Increased Risk of Coronary Heart Disease Death in Men With Low Total and Low-Density Lipoprotein Cholesterol in the Russian Lipid Research Clinics Prevalence Follow-up Study

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Background. A continuously increasing risk of coronary heart disease with increasing levels of cholesterol has been reported by many observational and experimental studies. However, this type of association has not been observed in studies in the Russian Lipid Research Clinics.

Methods and Results. Twelve-year coronary heart disease mortality among 40- to 59-year-old men was analyzed in the Moscow and St Petersburg examinees in the Russian Lipid Research Clinics Program. The baseline survey examined 6431 men fasting and free of prevalent coronary heart disease. Lipids and lipoproteins, blood pressure, body mass, education level, alcohol intake, and smoking history were obtained. Mortality follow-up was based on contacts with participants or their relatives or neighbors. Coronary heart disease mortality was analyzed based on risk factor levels and was further divided into rapid and nonrapid deaths. A J-shaped cholesterol–coronary heart disease risk function was present for both total and low-density lipoprotein cholesterol. Further examination showed hypocholesterolemic men to have lower low-density and higher high-density lipoprotein cholesterol, higher alcohol consumption, leaner body mass, and less education than men with normal or high cholesterol levels. When education level was considered, the J-shaped risk function was present only among men with less than a high school education. When deaths were classified into rapid (less than 24 hours after onset of symptoms) and nonrapid, the J-shaped risk function was restricted to rapid deaths.

Conclusions. The results disclose a sizeable subset of hypocholesterolemic in this population at increased risk of cardiac death associated with lifestyle characteristics. (Circulation. 1993;88:846-853.)

Key Words • coronary heart disease • cholesterol • lipoproteins • Russia

A continuously increasing risk of coronary heart disease (CHD) with increasing levels of total cholesterol is one of the fundamental tenets of cardiovascular disease epidemiology, based on the results of numerous studies, both observational and experimental. For example, the monotonically increasing nature of the total cholesterol and CHD mortality relation, extending from total cholesterol levels of 4.68 mmol/L (181 mg/dL) to levels above 6.54 mmol/L (253 mg/dL), was confirmed in the large study of 361,662 men aged 35 to 57 years screened for the Multiple Risk Factor Intervention Trial (MRFIT). It was, therefore, unexpected to observe a J- or U-shaped relation of total cholesterol and low-density lipoprotein cholesterol (LDL-C) to CHD mortality among men of similar age (40 to 59 years) in the Russian Lipid Research Clinics (LRC) Follow-up Study at 4 years and 7.5 years of follow-up. As reported herein, there is persistence of the J-shaped relation at 12 years of follow-up.

The purpose of this article is to report the 12-year follow-up experience and the results of investigation of reasons for the increased risk of CHD deaths among hypocholesterolemic men in the Russian LRC study. Our analyses of the J-shaped risk function explored four categories of possible explanations for the excess risk at low levels of total cholesterol: the effect of the LDL-C and high-density lipoprotein cholesterol (HDL-C) components of total cholesterol; the effect of nonlipid biomedical risk factors, eg, blood pressure and body mass; the effect of behavioral and social characteristics such as alcohol consumption and educational achievement; and the association of hypocholesterolemia with different modes of clinical presentation of CHD, that is, the cholesterol-CHD risk function for deaths occurring rapidly after onset of symptoms compared with nonrapid deaths.

Methods

The sampling, measurements, and quality control procedures followed the standardized methods for the US-Russian LRC collaborative program and have been described in detail previously. A brief summary of

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procedures follows: Men born between 1916 and 1935 were sampled from voter registration lists of selected residential districts in Moscow and St Petersburg from 1975 to 1977; participation rates were 77.7% in Moscow and 78.1% in St Petersburg. Of the 7815 men screened, 6431 men aged 40 to 59 years were fasting, free of prevalent CHD, and eligible for these analyses. Baseline measurements of lipids and lipoproteins were determined by standardized LRC methods. Blood pressure was measured four times, first using a standard mercury sphygmomanometer and then a random-zero device, with repeat of both. The blood pressures used for this study consisted of the average of the two random-zero blood pressures.

The body mass index (BMI), calculated as body weight (in kilograms) divided by height (in meters) squared, was used as an index of obesity. Level of education was determined by interview and classified by Russian epidemiologists into categories comparable to those used in US studies: high school graduate and more or less than that level of education. Measurements of total cholesterol, HDL-C, and triglycerides and derived LDL-C were obtained from all examinees at the first contact, as were blood pressure, height, and weight. Information regarding cigarettes smoked and alcohol intake was obtained by interview on a subsample recalled to a second clinic visit. Alcohol consumption was calculated based on 7-day recall and expressed as average daily gram intake.

Follow-up, which averaged 12.1 years at the time of the analyses, began in January 1979, based on contacts with participants or their relatives or neighbors. Address bureaus were used for those who moved recently. For participants who had died, death certificates were obtained; when cardiovascular disease was listed as a direct cause of death or as a related disease, information from the hospital, physician, relative, neighbor, or witness was collected. Final event information was evaluated by a classification panel. A sample of 58 Russian decedent cause of death classifications was independently classified by two US cardiologists experienced in similar activities for the US LRC studies; comparison indicated good agreement between the two classifications. All deaths classified as due to CHD were further identified as rapid if death occurred within 24 hours of onset of the final clinical episode and as nonrapid if survival exceeded 24 hours of onset. The experiences of the Moscow and St Petersburg cohorts were aggregated for this report.

From the original cohort of 7815 men, we have excluded 244 who were fasting less than 10 hours at the time of blood drawing, 148 who were either younger than 40 years or older than 59, and 992 who had either clinically manifest CHD or a history of CHD at the time of the screening. This leaves a total of 6431 men aged 40 to 59 years who were fasting and free of CHD for this report.

### Statistical Methods

As a first step, the distribution of each important potential risk factor was stratified by quintiles, and age-adjusted death rates were computed for each quintile. The age adjustment was accomplished by direct standardization using the World Health Organization standard population. Further analyses centered on the association of CHD mortality with total cholesterol, LDL-C, and HDL-C.

For multivariable analyses, the proportional hazards model was used. In the proportional hazards model, all deaths from causes other than CHD are treated as losses in the analysis. A restricted cubic spline of LDL-C was fit to test for nonlinearity of the risk ratio function. If this cubic spline model indicated statistically significant departures from linearity, a model was fit using a quadratic term for the risk factors. The risk ratios recorded are computed from the proportional hazards model adjusted for other covariates, and the multivariable models were repeated separately for rapid and nonrapid CHD deaths. Variables included in these models were restricted to those measurements obtained on the first clinic visit; data on cigarettes smoked and alcohol consumed (obtained on the subsample that was called to the second visit) were analyzed only in aggregate comparisons of the quintiles of lipids or lipoprotein estimates.
Results

Table 1 sets out the number of deaths and death rates per 1000 person-years for the participants in the study. A total of 1266 participants died during the 12 years of follow-up, and 334 of the deaths were attributed to CHD. Death rates for CHD and most other major causes of death were similar for participants residing in St Petersburg and Moscow, and the aggregate of participants residing in both cities was used for all subsequent analyses. Fig 1 displays the age-adjusted CHD mortality by quintiles of candidate risk factors, for which cutpoints shown in Table 2. It is noticeable that the death rate in the lowest quintile for both total cholesterol and LDL-C is higher than the death rates in the second quintile, with the death rate highest in the fifth quintile, leading to a J-shaped curve. This result previously has been reported for shorter follow-up periods of these sampled populations. There is a negative association between HDL-C and CHD mortality, although the gradient is of lesser magnitude and less consistent than for total cholesterol and LDL-C. There is a shallow U-shaped relation between BMI and CHD mortality. In contrast, there is a strong positive association between systolic blood pressure and CHD mortality and a strong inverse relation between level of attained education and CHD mortality.

Age-adjusted death rates by quintiles of total cholesterol, LDL-C, and HDL-C within the three educational achievement strata are presented in Fig 2. For total cholesterol and LDL-C, the mortality rate varies in a
J-shaped manner among individuals with less than a high school education. In contrast, among those who had a high school education or more, a positive association between CHD mortality and quintiles of the cholesterol levels is observed. It is to be noted, however, that despite the apparent difference of the shape of the risk function by educational achievement, there is a stepwise increase in the mortality rate within each quintile level of total cholesterol and LDL-C extending from those men with greater than a high school education to high school education only to those men with less than a high school education.

The relative risk of CHD mortality among men with less than a high school education compared with men with more than a high school education is greatest in the lowest total cholesterol quintile (2.9) and decreases to 1.9 and 1.6 in the two highest quintiles, respectively.

The relation of CHD mortality to HDL-C quintiles also varies among educational strata. There is a suggestive U-shaped relation among those with less than a high school education (although these differences are not statistically significant); in contrast, the relation appears negative or inverse among individuals with more than a high school education. At each level of HDL-C, the mortality is greatest among those with less than a high school education, intermediate among those with a high school education, and lowest among those with more than a high school education. The mortality rate ratio increases with increasing HDL levels, from 1.8 at the lowest HDL-C level to 3.1 at the highest HDL-C level.

The relation of CHD death rates to lipid and lipoprotein estimates for those deaths occurring rapidly and contrasted with nonrapid deaths is shown in Fig 3. For both total cholesterol and LDL-C, the mortality rate for rapid deaths presented a U-shaped relation with highest rates in the lowest and highest quintiles; in sharp contrast, there was a generally positive increasing death rate for nonrapid CHD deaths in relation to increasing total cholesterol and LDL-C. The relative risk, contrasting the highest with the minimum death rates, was approximately 2.1 for the U-shaped rapid deaths and approximately 3 to 1 for the linearly increasing nonrapid deaths.

The relation of HDL-C quintiles was different for rapid and nonrapid deaths. Among rapid deaths, a U-shaped relation was present; in contrast, there was an inverse association of nonrapid CHD death rates with increasing levels of HDL-C. For the rapid deaths, the relative risk contrasting the maximum with the minimum was 1.2; for the nonrapid deaths, the mortality rate was 1.5 times higher in the lowest than in the highest HDL-C quintile.

The relation of rapid and nonrapid CHD death rates to education level is also presented in Fig 3. The major difference was in a markedly higher death rate for rapid CHD deaths among men with less than a high school education.

We next set out the relation of rapid and nonrapid CHD death rates to lipid and lipoprotein levels within educational strata. As shown in Fig 4, there is a general preservation of the educational level gradient at all quintile levels of total cholesterol, LDL-C, and HDL-C, inverse in nature such that rapid and nonrapid death rates at each lipid and lipoprotein level were higher, the lower the educational achievement. Furthermore, there is an emergent pattern of a U-shaped relation for both total cholesterol and LDL-C and rapid deaths, the lower the education stratum, in sharp contrast to the generally positive increasing level of nonrapid death rates with increasing levels of both total cholesterol and LDL-C for all educational strata.

The risk function also was different for rapid and nonrapid deaths in relation to education level and HDL-C level. For rapid deaths there was no association in the lowest education stratum and a slight U-shaped relation otherwise; in marked contrast, for nonrapid deaths there was generally an inverse relation with decreasing nonrapid death rates with increasing levels of HDL-C.

Statistical tests of significance were performed to evaluate the shapes of the risk functions derived from the stratified analyses. The J- or U-shaped relation of CHD death rates modeled by quadratic lipid terms was statistically significant for rapid deaths among men with less than a high school education: for LDL-C, \(P < .05\), with minimum risk at LDL-C, of 143 mg/dL. For rapid deaths among men with a high school education there was no significant association with LDL-C, and for rapid deaths among men with more than a high school education, the quadratic term was not statistically significant, whereas the linear term was at \(P < .05\).

In contrast to the risk functions for rapid deaths, the quadratic term for LDL-C in relation to nonrapid deaths was not statistically significant within any of the education strata. However, the linear term for LDL-C in relation to nonrapid deaths was statistically significant \((P < .05)\) for each education achievement group. Thus, the nature of the risk function for LDL-C in relation to nonrapid CHD deaths was similar to the positive, monotonically increasing risk observed in most other settings.

There was neither a significant linear nor quadratic relation of HDL-C to rapid deaths. In contrast, among men with less than a high school education there was a statistically significant inverse association of HDL-C.
with nonrapid CHD deaths ($P < .05$). For each of the other two education strata, i.e., men with a high school education and those with more than a high school education, the linear term coefficient for HDL-C in relation to nonrapid CHD deaths was negative but did not reach statistical significance.

We next fit multivariable models adjusting for age, BMI, systolic blood pressure, HDL-C, and education, categorizing the CHD deaths into rapid and nonrapid deaths (not shown). The U-shaped relation between LDL-C and CHD mortality remained strong when restricted to deaths occurring within 24 hours after the onset of symptoms. However, for deaths occurring more than 24 hours after the onset of symptoms, the U-shaped relation disappeared.

Finally, we fit multivariable models within education categories for rapid CHD deaths and nonrapid CHD deaths separately. An inverse relation between LDL-C and CHD death was present only for rapid deaths of men with less than a high school education. The U-shaped relation initially observed for the total cohort is primarily a result of the strong inverse association between LDL-C and rapid CHD deaths among the less-educated participants.

Table 3 lists characteristics of the men in the lowest LDL-C quintile compared with those in the third and fifth quintiles. Since the categorization is based on LDL-C, it is not surprising that there is a sizeable difference in total cholesterol between the groups. However, men in the lowest quintile of LDL-C also have lower BMI, higher HDL-C, and higher alcohol intake; in this quintile there is a larger proportion of smokers and a larger proportion with education less than high school than in the four higher LDL-C quintiles. The age distribution and blood pressure means for the groups are essentially the same.

**Discussion**

The total cholesterol–CHD mortality risk function observed in the Russian LRC study differs markedly from that observed in numerous other epidemiological studies. The incremental risk of deaths from CHD observed among men with the lowest levels of total cholesterol now has been observed to persist through 12 years of follow-up. Methodological errors in measurement of total cholesterol and certification of cause of death differences between the Russian and the US LRC programs have been virtually eliminated as possible causes.5,6,10,11 The association with mortality is similar for LDL-C as for total cholesterol. The increased risk among hypocholesterolemic men cannot be attributed to low levels of HDL-C; in fact, in this population, men with lowest total cholesterol and LDL-C levels had the highest HDL-C levels.

The apparent U-shaped total cholesterol–CHD mortality rate relation observed in men from this population-based study has been found to be restricted to a subset of the examinees characterized by educational achievement level. It was only among men with the lowest educational achievement, identified in this study as equivalent to less than a high school education, that the U-shaped relation was manifest. In contrast, among men with the highest educational achievement (those with more than a high school education), the more usually observed positive association between total cholesterol and LDL-C and CHD mortality was present. Not only was there modification of the risk function by educational achievement level but in addition, there was a major association of education level per se with CHD mortality levels. In this sample of middle-aged male residents of neighborhoods in Moscow and St Petersburg, there was a two- to threefold gradient of increasing CHD mortality with decreasing educational achievement level at all levels of total cholesterol and LDL-C.

The finding of an inverse association of educational level with CHD in the Russian cohort study is not unique. A similar strong inverse relation of CHD with educational level has emerged in the United States, transforming a previously positive or nonexistent asso-
The lack of alcohol intake and cigarette smoking data on a large portion of the sampled populations is a weakness of the study. Were such measures available on all participants, the statistical models could assess directly the joint effects of smoking, alcohol, and LDL-C. Lacking this direct assessment, it can only be inferred indirectly that excess alcohol intake and smoking may be contributing to the excess CHD mortality in men with low LDL-C, particularly in the lower-educated men.

Selenium was not measured in this study, but it is possible that a low dietary intake of selenium and fat-soluble vitamins could be associated with low cholesterol levels. Low selenium levels have been associated with increased risk of coronary disease in Finland.

The men in this study were free of clinically diagnosed prevalent CHD at time of entry into the study. However, this does not rule out the possibility of preexistent underlying coronary atherosclerosis in a subset of men vulnerable to sudden arrhythmic deaths.

It is noteworthy in the US and British studies that the composite effect of the major risk factors of smoking, elevated blood pressure, and total cholesterol statistically explained only a relatively small fraction of the excess CHD mortality associated with low social status and/or educational achievement. The remainder of the excess may be attributable to random measurement errors and intraindividual variation of risk factors with resultant regression bias, to other biological risk factors not measured in these studies such as hemostatic factors, or to psychosocial and behavioral risk factors associated with lower socioeconomic status. Further
in the Russian LRC Study are in progress.

This study of CHD mortality cannot distinguish between determinants of disease incidence and case-fatality rates. The strong association of excess mortality from noncardiovascular causes with hypocholesterolemia and low educational achievement points to the need for study of processes of host susceptibility more general than that assessed by cardiovascular risk factors.24

In summary, the U-shaped relation of total cholesterol and LDL-C with all-cause mortality and the J-shaped relation with CHD mortality observed in the Russian LRC Follow-up Study was present only among the men in the lowest educational achievement stratum. Behavioral (alcohol consumption and smoking), anthropometric (BMI), and other lipid and lipoprotein characteristics (HDL-C) further characterized the J-shaped phenomenon for deaths occurring within 24 hours of onset of the final episode. In contrast, a positive association of total cholesterol and LDL-C to CHD was observed among middle-aged men with high educational achievement in the Russian LRC Study; these were men who drank less, had lower levels of HDL-C and higher BMI, smoked less, and whose risk of dying of CHD during 12 years of follow-up was one third to one half lower than that of men with the lowest educational achievement.

The Russian LRC Follow-up Study was carried out during a period of increasing CHD mortality rates in the Soviet Union.25 The results of the study reported herein suggest the potential for CHD prevention by combined high-risk subgroup and community intervention strategies.
TABLE 3. Characteristics of Russian Men by LDL-C Quintiles

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LDL-C quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1438</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48.4 (5.1)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>93.8 (16.3)</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>175.7 (23.6)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>62.4 (22.8)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>135.9 (21.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 (3.6)</td>
</tr>
<tr>
<td>Alcohol* (g/d)</td>
<td>18.9 (25.0)</td>
</tr>
<tr>
<td>Current smoker* (%)</td>
<td>66.3 (1.2)†</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>&lt;High school (%)</td>
<td>53.8 (1.3)†</td>
</tr>
<tr>
<td>High school (%)</td>
<td>22.2 (1.1)†</td>
</tr>
<tr>
<td>&gt;High school (%)</td>
<td>24.0 (1.1)†</td>
</tr>
</tbody>
</table>

LDL-C indicates low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; and BMI, body mass index.

Values are mean (standard deviation in parentheses). *Estimates based on second visit subsample. †Standard error.

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