High-Density Lipoprotein Cholesterol and Cardiovascular Disease

Four Prospective American Studies

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The British Regional Heart Study (BRHS) reported in 1986 that much of the inverse relation of high-density lipoprotein cholesterol (HDL-C) and incidence of coronary heart disease was eliminated by covariance adjustment. Using the proportional hazards model and adjusting for age, blood pressure, smoking, body mass index, and low-density lipoprotein cholesterol, we analyzed this relation separately in the Framingham Heart Study (FHS), Lipid Research Clinics Prevalence Mortality Follow-up Study (LRCF) and Coronary Primary Prevention Trial (CPPT), and Multiple Risk Factor Intervention Trial (MRFIT). In CPPT and MRFIT (both randomized trials in middle-aged high-risk men), only the control groups were analyzed. A 1-mg/dl (0.026 mM) increment in HDL-C was associated with a significant coronary heart disease risk decrement of 2% in men (FHS, CPPT, and MRFIT) and 3% in women (FHS). In LRCF, where only fatal outcomes were documented, a 1-mg/dl increment in HDL-C was associated with significant 3.7% (men) and 4.7% (women) decrements in cardiovascular disease mortality rates. The 95% confidence intervals for these decrements in coronary heart and cardiovascular disease risk in the four studies overlapped considerably, and all contained the range 1.9–2.9%. HDLC levels were essentially unrelated to non-cardiovascular disease mortality. When differences in analytic methodology were eliminated, a consistent inverse relation of HDLC levels and coronary heart disease event rates was apparent in BRHS as well as in the four American studies. (Circulation 1989;79:8–15)

Trends relating high plasma levels of high-density lipoprotein cholesterol (HDL-C) and decreased incidence of cardiovascular disease endpoints have been observed in prospective epidemiological studies conducted in several countries.1–12 The report from one of these studies, the British Regional Heart Study (BRHS), in which 7,415 men, aged 40–59 years, were followed for an average of 4.2 years, suggested that HDLC was not a significant risk factor for ischemic coronary heart disease (CHD) after statistical adjustment for other risk factors.9 Because comparisons of these studies are confounded by differences in their statistical methods and in the populations and cardiovascular endpoints studied, we have undertaken a systematic reexamination of two major North American population-based studies, the Framingham Heart Study (FHS) and the Lipid Research Clinics Prevalence Mortality Follow-up Study (LRCF); and of the control groups of two large North American randomized clinical trials, the Lipid Research Clin-

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ics Coronary Primary Prevention Trial (CPPT) and the Multiple Risk Factor Intervention Trial (MRFIT), using a standardized analytic approach that permits comparison with the BRHS results.

**Patients and Methods**

We have confined our consideration to white men and women between 30 and 69 years of age who were free of clinical symptoms of CHD and were neither pregnant nor taking exogenous hormones or lipid-altering drugs at baseline. Capsule descriptions of each study follow (Table 1).

**The Framingham Heart Study**

In the FHS, a prospective epidemiological study of cardiovascular diseases (CVD) initiated in 1948, 5,209 persons between 30 and 59 years of age, selected from a community of 28,000, were enrolled and followed biennially. The vital status of 97% of the original cohort is currently known. Approximately 85% of the surviving cohort participate in biennial examinations, in which interviews, physical examinations, and selected laboratory tests (including plasma cholesterol) are obtained. Fasting HDLC and triglyceride measurements were introduced in cycle 11 (1969–1971), the baseline for the present analysis. Our analysis included all FHS participants between 50 and 69 years of age at their cycle 11 examination. Endpoint diagnoses are based on a review of medical records by a committee of FHS investigators. The diagnosis of CHD includes fatal and nonfatal myocardial infarction, sudden cardiovascular death, and acute coronary insufficiency.

**The Lipid Research Clinics Prevalence Mortality Follow-up Study**

The Lipid Research Clinics Prevalence Study was an epidemiological study of the distribution and correlates of lipid and other cardiovascular risk factors, performed during 1972–1976 in 10 collaborating North American centers. More than 70,000 men and women were sampled from defined populations, and fasting plasma lipid levels and selected medical and sociodemographic data were obtained (visit 1). A 15% random sample plus all whose plasma lipid levels at visit 1 exceeded predefined cut points (or who reported using lipid-lowering drugs) were invited to return for further evaluation, including fasting lipoprotein determinations (visit 2). In 1977, a mortality follow-up study (LRCF) was begun in all participants in the Prevalence Study who were at least 30 years old at visit. The protocol includes annual mail and telephone contact with participants, but no clinical reexamination or assessment of morbidity. When a death is discovered, a copy of the death certificate is obtained, and the attending physician and next of kin are interviewed. A panel of clinical cardiologists assigns the cause of death with a standard algorithm. The vital status of 99.6% of the original cohort is currently known.

**The Lipid Research Clinics Coronary Primary Prevention Trial**

The CPPT was a multicenter, randomized, double-blinded trial of the efficacy of lowering low-density lipoprotein cholesterol (LDLC) levels in reducing CHD risk in 3,806 asymptomatic middle-aged men with primary hypercholesterolemia (plasma cholesterol ≥265 mg/dl [6.87 mM]). The treatment group received a moderate cholesterol-lowering diet plus cholestyramine; the control group received the identical diet plus placebo. The therapeutic diet (daily cholesterol intake of about 400 mg and a polyunsaturated fat/saturated fat ratio of 0.8) low-

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**Table 1. Description of Studies**

<table>
<thead>
<tr>
<th>Study feature</th>
<th>FHS</th>
<th>LRCF</th>
<th>CPPT</th>
<th>MRFIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Residents of Framingham, Massachusetts</td>
<td>High lipid range over-sampled</td>
<td>Volunteers with high LDLC levels</td>
<td>Volunteers with high CHD risk index</td>
</tr>
<tr>
<td>Number of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>704</td>
<td>3,937</td>
<td>1,808</td>
<td>5,792</td>
</tr>
<tr>
<td>Women</td>
<td>714</td>
<td>2,297</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age range (yr)</td>
<td>50–69</td>
<td>30–69</td>
<td>35–59</td>
<td>35–57</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interval</td>
<td>2 yr</td>
<td>1 yr</td>
<td>2 mo</td>
<td>1 yr</td>
</tr>
<tr>
<td>Baseline</td>
<td>Cycle 11</td>
<td>Visit 2</td>
<td>Randomization</td>
<td>Randomization</td>
</tr>
<tr>
<td>Mean years</td>
<td>10.3</td>
<td>8.5</td>
<td>7.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Contact</td>
<td>Examination</td>
<td>Mail/telephone</td>
<td>Examination</td>
<td>Usual care</td>
</tr>
<tr>
<td>Treatment</td>
<td>None</td>
<td>None</td>
<td>Diet + placebo</td>
<td></td>
</tr>
<tr>
<td>HDLC methodology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Plasma</td>
<td>Plasma</td>
<td>Plasma</td>
<td>Plasma</td>
</tr>
<tr>
<td>Fasting</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Precipitant</td>
<td>Manganese-heparin</td>
<td>Manganese-heparin</td>
<td>Manganese-heparin</td>
<td>Manganese-heparin</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Abell-Kendall</td>
<td>AutoAnalyzer</td>
<td>AutoAnalyzer</td>
<td>AutoAnalyzer</td>
</tr>
</tbody>
</table>

FHS, Framingham Heart Study; LRCF, Lipid Research Clinics Prevalence Mortality Follow-up Study; CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; MRFIT, Multiple Risk Factor Intervention Trial; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; CHD, coronary heart disease.
ered plasma cholesterol levels by an average 4–6%, with a trivial effect on HDLC levels.\textsuperscript{17} The present analysis is confined to the placebo group.

Participants were examined bimonthly for an average of 7.4 years; none was lost to follow-up. The diagnosis of CHD included fatal and nonfatal myocardial infarction and sudden cardiovascular death, based on review of hospital records, electrocardiograms, and death certificates by a committee of clinical cardiologists, who used a standard algorithm.\textsuperscript{16,17} The average of four prerandomization HDLC determinations was used as a baseline.\textsuperscript{12}

**The Multiple Risk Factor Intervention Trial**

MRFIT was a randomized multicenter clinical trial conducted in men without clinical CHD manifestations but who were at high CHD risk (upper 10–15%) because of a combination of hypertension, cigarette smoking, and elevated plasma cholesterol.\textsuperscript{18,19} Eligible male volunteers (12,866), aged 35–57 years, were randomized into two groups. The “special intervention” group received stepped-care therapy for the control of elevated blood pressure, a dietary program for lowering plasma cholesterol, and a counseling program to encourage cessation of cigarette smoking. The control group continued with their usual source of medical care (e.g., personal physician). The present analysis is confined to the “usual care” group.

Participants were examined annually for determination of risk factors and disease occurrence for an average of 6.7 years. Vital status was ascertained in 99.7% of the cohort. The definitions and mechanisms for endpoint diagnosis were similar to those in the CPPT.

**Laboratory Methods**

Lipid and lipoprotein determinations were performed on fresh plasma samples collected after at least 12 hours of fasting.\textsuperscript{20} Cholesterol levels were determined by the Abell-Kendall method\textsuperscript{21} in FHS and by the Technicon AutoAnalyzer (standardized to the Abell-Kendall method)\textsuperscript{20} in LRCF, CPPT, and MRFIT. Manganese-heparin precipitation was used in measuring HDLC in all four studies.\textsuperscript{20} Plasma LDL cholesterol levels were determined by ultracentrifugation\textsuperscript{20} and plasma very-low-density lipoprotein cholesterol (VLDLC) levels were estimated as one fifth the plasma triglyceride level.\textsuperscript{22}

**Statistical Methods**

CHD incidence and CHD, CVD, and all-cause mortality rates (events per 1,000 person-years) were calculated for subgroups of each cohort defined by HDLC levels as “high” (≥50 mg/dl or 1.30 mM), “medium” (40–50 mg/dl), or “low” (<40 mg/dl or 1.04 mM). In FHS and LRCF, men and women were analyzed as separate cohorts.

Cox’s proportional hazards model\textsuperscript{23} was used to quantify the relation of HDLC levels to event rates and to adjust for other baseline risk factor levels. The regression coefficient (a) for HDLC was converted to a percent increment in risk corresponding to a 1 mg/dl (0.026 mM) increment in HDLC as follows:

\[
a' = 100 \cdot (e^a - 1)
\]

when the value of a is much less than 1, \(a' = 100 \cdot a\).

The logistic regression coefficients relating HDL and non-HDL (NHDL) cholesterol levels to CHD incidence in BRH\textsuperscript{9} were used to calculate the logistic coefficients of the algebraically equivalent alternative model containing HDL and total (TOT) cholesterol. Because \(\text{NHDL} = \text{TOT} - \text{HDL}\) by definition,

\[
a \cdot \text{HDL} + b \cdot \text{NHDL} = (a - b) \cdot \text{HDL} + b \cdot \text{TOT}
\]

Thus, the total cholesterol–adjusted coefficient for HDL cholesterol can be calculated by subtracting the published coefficient for NHDL cholesterol (b) from the published coefficient for HDL cholesterol (a). Each logistic coefficient was then converted to a percent increment in risk for each 1 mg/dl (0.026 mM) increment in HDLC as described above.

**Results**

The mean values of HDLC and several other CHD risk factors in each study are provided in

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HFS</th>
<th>LRCF</th>
<th>CPPT</th>
<th>MRFIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.7</td>
<td>60.2</td>
<td>44.6</td>
<td>46.2</td>
</tr>
<tr>
<td>% Smokers</td>
<td>30.5</td>
<td>33.3</td>
<td>39.2</td>
<td>34.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>138.8</td>
<td>138.4</td>
<td>126.1</td>
<td>121.7</td>
</tr>
<tr>
<td>Body mass index (kg/m)</td>
<td>26.4</td>
<td>25.9</td>
<td>26.8</td>
<td>25.2</td>
</tr>
<tr>
<td>Cholesterol (mg/dl*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>221.1</td>
<td>239.2</td>
<td>222.2</td>
<td>221.7</td>
</tr>
<tr>
<td>LDL</td>
<td>143.5</td>
<td>154.8</td>
<td>146.5</td>
<td>146.2</td>
</tr>
<tr>
<td>HDL</td>
<td>45.8</td>
<td>57.3</td>
<td>44.2</td>
<td>56.4</td>
</tr>
</tbody>
</table>

FHS, Framingham Heart Study; LRCF, Lipid Research Clinics Prevalence Mortality Follow-up Study; CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; MRFIT, Multiple Risk Factor Intervention Trial; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

*38.7 mg/dl = 1 mM.
“high” HDLC (≥50 mg/dl [1.30 mM]). This inverse trend was most striking in FHS women, where incidence rates were 2.6 times higher in the former than latter HDLC stratum. Note that event rates within a given HDLC category should not be compared across studies without taking into account their differing CHD risk factor profiles (Table 2) as well as the absence of data on nonfatal myocardial infarction in LRCF.

Although CHD, CVD, and all-cause mortality rates (Figure 1B) also tended to be lowest among subjects with the highest HDLC levels, the numbers of fatal cardiovascular events were relatively small, and their relation to HDLC levels appeared more irregular. However, in both FHS and LRCF, CVD mortality rates were at least four times higher in low HDLC than in high HDLC women. When CVD mortality rates in FHS and CRCF women were compared with those of their male counterparts, their survival advantage was confined to the middle and high HDLC categories. No trend relating HDLC levels to non-CVD mortality rates was evident in men or women in FHS (not shown), LRCF, CPPT, and MRFIT (Figure 1B).

The relation of HDLC to each endpoint was quantified and adjusted for age, cigarette smoking, systolic blood pressure, body mass index, and LDL-C levels by proportional hazards regression (Table 3). Consistent with the univariate results (Figure 1A), significant inverse associations of HDLC and CHD incidence were observed in both men (FHS, CPPT, and MRFIT) and women (FHS). A hypothetical 1-mg/dl (0.026 mM) increment in HDL-C was associated with a CHD risk decrement of 1.9–2.3% in men and 3.2% in women.

The regression models for mortality (Table 3) were also consistent with the corresponding univariate analyses (Figure 1B). In men, the regression coefficients relating HDLC levels to CHD and total CVD mortality in FHS, CPPT, and MRFIT were generally smaller than those for CHD incidence; none was statistically significant. However, in LRCF men, these two coefficients were highly significant (p<0.001) and were more than twice as large as those in the other three male cohorts. In both female cohorts, as in LRCF men, a 1-mg/dl (0.026 mM) increment in HDL-C was associated with a 3.7–4.7% decrement in CHD and total CVD mortality rates. The number of FHS and LRCF women dying of CHD was small (17 in both cohorts combined), and only the coefficients for total CVD mortality attained statistical significance. The coefficients relating HDLC to all-cause mortality were generally weak, reflecting the dilution of cardiovascular with unrelated causes of death; only those for LRCF men and women remained statistically significant.

The 95% confidence intervals for the regression coefficients relating HDLC levels to CHD incidence and CVD mortality in the four male and two female cohorts are compared in Figure 2. Although these coefficients vary among studies, the corresponding

![Figure 1](image_url)
confidence intervals overlap considerably, and all include the range 1.9–2.9% as the estimated decrement in risk associated with a 1 mg/dl (0.026 mM) increment in HDLC level.

The relation of HDLC to CHD incidence in 7,415 men, aged 40–59, followed for 4.2 years in the BRHS was reported using a logistic regression model with age, smoking, systolic blood pressure, and NHDLG included as covariates. We have used these published data to calculate the percent increment in CHD risk for a 1-mg/dl increment in HDLC in this model and in a model with TOTC rather than NHDLG as a covariate (see "Patients and Methods"). We have then compared these results with the corresponding results among men in FHS, LRCF, CPPT, and MRFIT with the same covariates (Table 4). Table 4 also includes the unadjusted proportional hazards regression coefficients for HDLC, as well as coefficients adjusted for LDLC and for both LDLC and VLDLC, in the four American studies.

In each of the five studies, the inverse relation of HDLC and CHD incidence was weaker for the model containing NHDLG than for any of the other models. However, except in FHS (p=0.06) and BRHS (p=0.21), the coefficient remained statistically significant. In FHS and MRFIT, adjustment for TOTC, LDLC, or both LDLC and VLDLC did not change the regression coefficient for HDLC from its unadjusted value. In LRCF, these covariance adjustments actually increased the magnitude of this coefficient. This coefficient decreased substantially after covariance adjustment only in the CPPT. Although LDLC and VLDLC levels were not obtained in BRHS and the unadjusted regression coefficient for HDLC was not reported, the values of the coefficients for HDLC in BRHS for models containing NHDLG or TOTC as covariates.
TABLE 4. Alternative Estimates of Regression Coefficients Relating High-Density Lipoprotein Cholesterol Levels and Coronary Heart Disease Incidence in Men*

<table>
<thead>
<tr>
<th>Study</th>
<th>None</th>
<th>NHDLC</th>
<th>Total</th>
<th>LDL</th>
<th>LDL, VLDLt</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHS</td>
<td>-1.9</td>
<td>-1.6</td>
<td>-2.0</td>
<td>-1.9</td>
<td>-1.9</td>
</tr>
<tr>
<td>LRCF†</td>
<td>-2.7</td>
<td>-2.7</td>
<td>-3.3</td>
<td>-3.6</td>
<td>-3.4</td>
</tr>
<tr>
<td>CPPT</td>
<td>-3.0</td>
<td>-1.8</td>
<td>-2.8</td>
<td>-2.3</td>
<td>-2.1</td>
</tr>
<tr>
<td>MRFIT</td>
<td>-1.7</td>
<td>-1.1</td>
<td>-2.0</td>
<td>-2.0</td>
<td>-1.6</td>
</tr>
<tr>
<td>BRHS</td>
<td></td>
<td>-1.0</td>
<td>-2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NHDLC, non–high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; FHS, Framingham Heart Study; LRCF, Lipid Research Clinics Prevalence Mortality Follow-up Study; CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; MRFIT, Multiple Risk Factor Intervention Trial; BRHS, British Regional Heart Study.

*All regression coefficients are expressed as percent risk increment for each 1 mg/dl (0.026 mM) increment in high-density lipoprotein cholesterol level. All except those in the “None” column have been adjusted for age, cigarette smoking, systolic blood pressure, and body mass index. A logistic model was used in BRHS, and a proportional hazards model was used elsewhere.

†VLDL cholesterol was estimated as one fifth the plasma triglyceride level. Subjects with triglyceride levels above 500 mg/dl were excluded.

‡Models for cardiovascular disease mortality are presented because nonfatal coronary heart disease cases were not ascertained.

Discussion

When the BRHS results are viewed with the results from the four American studies (Table 4), there is no real disagreement except in the choice of other cholesterol fractions to include in the statistical model. When LDLC (with or without VLDLC) or TOTC is included as a covariate, the HDLC coefficient does not deviate systematically from its adjusted value; when NHDLC is included as a covariate, the HDLC coefficient is systematically suppressed. Table 4 provides no evidence to support a systematic difference between British and American men in the nature of the relation between HDLC and CHD.

The question remains of why NHDLC (which is, after all, simply the sum of LDLC and VLDLC) acts as a confounder of the HDLC-CHD relation, whereas its individual components, included as separate terms, do not. To act as a confounder, a variable must be associated with both the presumptive risk factor (HDLC) and the outcome (CHD incidence). In these data, LDLC meets only the latter criterion, whereas VLDLC meets only the former; thus, even when both terms are included separately as covariates, there is no confounding, and the HDLC coefficient is essentially unchanged. However, the composite variable NHDLC is associated both with CHD and (inversely) with HDLC, and its inclusion in the model weakens the inverse association of HDLC and CHD. Although this model is not “wrong” in an absolute sense, it gives a result that differs from models in which each lipoprotein species is represented by a separate term. If the latter type of model were used as the standard but (as in the BRHS, where blood specimens were not drawn in the fasting state) separate LDLC and VLDLC levels are unavailable, then the model containing HDLC and TOTC or HDLC alone will usually provide a “better” estimate of the relation between HDLC and CHD incidence than does the model containing HDLC and NHDLC.

We also considered the possible implications of another methodological difference—the use of the logistic model in BRHS and of the proportional hazards model in the current analysis. In general, these two models differ only when a substantial proportion of a cohort has had the event of interest, has died, or has been lost to follow-up. This was not true in any of the cohorts discussed here. Logistic models that we computed for LRCF and CPPT gave essentially the same results as the proportional hazards models.

Although the data relating HDLC and CVD mortality are relatively sparse and are not statistically compelling, they are generally consistent with the data for CHD incidence (Figure 2). A 1-mg/dl increment in HDLC is associated with a 2–3% decrement in risk. Our analysis yielded no trends relating HDLC to increased non-CVD mortality rates as have been reported elsewhere. In the Minneapolis study, in which 260 men were followed for 25 years with a 52% cumulative mortality rate, the trend in non-CVD mortality may be attributed (at least in part) to the opposing trend in CVD mortality; that is, men with low HDLC tend to die most often from CVD, and those with high HDLC tend to die most often from other causes. Life-table analyses that include the duration of survival, as well as the cause of death, are needed to determine whether there was any real benefit (or detriment) associated with a high HDLC level in this study. However, in the USSR study, the trend relating...
high HDLC levels to high non-CVD mortality was not offset by a trend toward fewer CVD deaths. Although such a result may be explained by patterns of alcohol consumption, it persisted after adjustment for self-reported habitual alcohol intake and other potential confounding variables.

In conclusion, the epidemiological data generally support an independent inverse association of HDLC levels and CHD event rates, in which CHD risk decreases by 2−3% for a 1-mg/dl (0.026 mM) increment in HDLC levels. Several hypothesized underlying mechanisms for this association have been advanced, most notably “reverse transport” of cholesterol by the HDL particle, but as yet, none has been clearly established.27 Although clinical trials of cholesterol lowering in hypercholesterolemic men indicate that increases in HDLC may enhance the benefit of decreasing LDL-C,12,28−30 the value of therapy aimed specifically at increasing HDLC levels remains unproven. However, the adoption of certain hygienic measures, such as exercise, weight loss, and smoking cessation, which are beneficial in their own right and may also raise HDLC levels,31,32 appear prudent.

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