

High Density Lipoprotein Cholesterol and Mortality

The Framingham Heart Study

Peter W.F. Wilson, Robert D. Abbott, and William P. Castelli

In 12 years of follow-up for 2748 Framingham Heart Study participants ages 50 to 79, low levels of high density lipoprotein cholesterol (HDL-C) were associated with increased mortality. For men, the relative risk of death in the first HDL-C quintile (<35 mg/dl) as compared to the top quintile (>54 mg/dl) was 1.9 for all causes, and 3.6 and 4.1 for death due to cardiovascular and coronary heart disease (CHD), respectively, after adjustment for standard cardiovascular risk factors. In women, corresponding relative risks, comparing the bottom HDL-C quintile (<45 mg/dl) to the top quintile (>69 mg/dl), were 1.5, 1.6, and 3.1. With HDL-C considered as a continuous variable, and after adjustment for standard cardiovascular risk factors, highly significant associations were seen with HDL-C and CHD death in both men and women. In addition, a significant HDL-C effect on total mortality and death due to cardiovascular disease was seen in men. In none of the continuous variable analyses was HDL-C associated with cancer death. We conclude that HDL-C is a potent predictor of CHD death in both sexes and has less consistent associations with other types of death. (Arteriosclerosis 8:737-741, November/December 1988)

While morbidity studies for high density lipoprotein cholesterol (HDL-C) and cardiovascular disease (CVD) are common, investigators have infrequently studied the relationship between HDL-C and mortality.¹⁻⁴ There is even less evidence available for potential relationships between HDL-C and noncardiovascular mortality. While some studies have looked into the role of HDL-C in determining mortality for myocardial infarction survivors,^{5,6,7} the results are largely confined to men, and the impact of HDL-C on mortality for individuals free of coronary heart disease (CHD) has been investigated in less detail. Recent follow-up from the Framingham Study now allows a closer look at the HDL-C to mortality relationship for healthy individuals at baseline, and enables us to determine whether this risk factor, which is so important for CVD morbidity, is equally important for mortality.

Methods

The Framingham Heart Study has followed 5209 men and women every 2 years since 1948 for the development of cardiovascular and other diseases.^{8,9} At any given examination approximately 80% of the survivors attended, and less than 1% of the population was lost to follow-up by 1970. During the 1970-1972 examination, fasting levels of HDL-C were determined among the study participants after heparin-manganese chloride precipitation of fresh plasma following a modification of the Lipid Research Clinics Program protocol.¹⁰

For this report, all subjects were followed 12 years from the time of HDL-C measurement until death due to all

causes, death from CHD, death from CVD (including coronary heart disease, stroke, cardiac failure, and pulmonary circulatory disorders), and death from cancer. None were lost to follow-up. The cause of death was determined by a panel of Framingham Heart Study physicians who reviewed all available evidence relating to death, including surgical and Heart Study records, personal physician notes, death certificates, interviews with surviving family members, and autopsy information. Further details on the definitions of fatal events are given elsewhere.⁸

Twelve-year age-adjusted incidence rates for each fatal event were calculated by approximate quintiles of HDL-C. These HDL-C quintiles were estimated from the entire sample. For men, the first through fifth quintiles consisted of the following ranges of HDL-C levels: 12 to 34, 35 to 40, 41 to 46, 47 to 54, and 55 to 159 mg/dl, with a mean of 45.2 mg/dl (standard deviation 13.3). For women, the HDL-C quintiles were 23 to 44, 45 to 51, 52 to 58, 59 to 69, and 70 to 139 mg/dl, with a mean of 57.1 mg/dl (standard deviation 15.8).

For all-cause mortality, follow-up included the entire sample of 1189 men and 1559 women ages 50 to 79 years who had HDL-C determinations. For death due to CVD, follow-up was restricted to subjects without CVD at the beginning of follow-up. Similarly, CHD death comparisons were limited to individuals free of CHD at baseline, and only subjects without cancer at baseline were considered for cancer mortality analyses.

Mean levels of additional risk factors, also measured at the beginning of follow-up, were compared across quintiles of HDL-C after adjusting for age, using analysis of covariance.¹¹ Covariates included total cholesterol, systolic blood pressure, cigarette use, and body mass index (BMI). The latter was calculated by dividing the weight in kilograms by the height in meters squared. Techniques used to measure the risk factors have been published previously.¹²

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Table 1. Number of Participants and Type of Death in 12 Years of Follow-up

Type of death	Men (Events/at risk)	Women (Events/at risk)
Coronary heart disease	84/1007	51/1418
Cardiovascular disease	107/952	84/1364
Cancer	100/1143	76/1478
All causes	402/1189	317/1559

To estimate the independent effect of HDL-C on death, proportional hazards models¹³ were used to follow subjects for the development of a fatal event over a 12-year period. Estimates of relative risk were based on the corresponding regression coefficients associated with the first through fourth quintiles of HDL-C compared to the fifth quintile by using indicator variables for the HDL-C quintiles. Comparisons were made after age adjustment and also after adjustment for age and the preceding covariates. We also considered separate analyses where HDL-C was treated as a continuous variable, along with other factors, to predict mortality.

Goodness-of-fit tests, in which the proportional hazards model regression coefficients were permitted to vary with time and with risk factor level, supported the basic proportional hazards model. All tests of significance were two-sided.

Results

Table 1 shows the number of participants in the study at risk for each event and the total who died according to various death groupings. The 402 deaths among 1189 men under study occurred an average of 6.9 years into follow-up, for a rate of 33.8 per 100 over the 12-year period. For women, there were 317 deaths among 1559 participants, occurring an average of 7.0 years into follow-up, for a rate of 20.3 per 100 over 12 years. The mean age at death was 73.0 years in men and 74.1 years in women.

Tables 2 and 3 provide estimates of age-adjusted risk factors across the quintiles of HDL-C for men and women. These analyses were undertaken because differences in the risk factors might help to explain the excess of deaths due to all causes, CVD, and CHD. Among men and women, total cholesterol tended to increase as HDL-C levels increased. The average total cholesterol in the first quintile of HDL-C (211.8 mg/dl) was significantly lower ($p < 0.01$) than the average total cholesterol in the fifth quintile (223.5 mg/dl) in men. For women, the average total cholesterol levels were significantly lower ($p < 0.05$) in the first (237.7 mg/dl), second (239.4 mg/dl), and third (239.4 mg/dl) quintiles of HDL-C compared to the average total cholesterol in the fifth quintile (247.2 mg/dl).

In men there were no apparent relationships between quintiles of HDL-C and either systolic blood pressure or use of cigarettes, but mean systolic blood pressure in

Table 2. Age-adjusted Mean Levels of Selected Risk Factors by HDL-C Quintile in Men

Risk factor	HDL-C quintile (mg/dl)				
	First (12 to 34)	Second (35 to 40)	Third (41 to 46)	Fourth (47 to 54)	Fifth (55 to 129)
Total cholesterol (mg/dl)	211.8† (41.9)	220.2 (42.5)	218.5 (39.3)	223.0 (38.5)	223.5 (37.9)
Systolic pressure (mm Hg)	140.6 (22.0)	139.6 (22.4)	138.8 (18.6)	139.6 (20.8)	142.1 (21.4)
Body mass index (kg/m ²)	27.6‡ (3.4)	27.2‡ (3.8)	26.9‡ (3.5)	26.3‡ (3.0)	24.9 (3.6)
Cigarette use (%)	52.0 (50.1)	52.7 (50.1)	47.5 (50.1)	48.0 (50.1)	55.7 (49.8)

Values in parentheses are SD.

Significantly different from the fifth quintile: † $p < 0.01$, ‡ $p < 0.001$.

Table 3. Age-adjusted Mean Levels of Selected Risk Factors by HDL-C Quintile in Women

Risk factor	HDL-C quintile (mg/dl)				
	First (23 to 44)	Second (45 to 51)	Third (52 to 58)	Fourth (59 to 69)	Fifth (70 to 139)
Total cholesterol (mg/dl)	237.7† (46.4)	239.4* (45.2)	239.4* (39.2)	243.7 (39.6)	247.2 (40.3)
Systolic pressure (mm Hg)	144.3* (24.2)	143.1 (23.2)	141.3 (22.6)	139.2 (22.6)	139.8 (22.5)
Body mass index (kg/m ²)	27.9‡ (5.2)	26.4‡ (4.4)	26.1‡ (4.3)	25.5‡ (4.1)	24.1 (3.6)
Cigarette use (%)	33.6* (46.7)	28.2 (45.2)	30.3 (45.5)	28.3 (45.3)	25.6 (45.1)

Values in parentheses are SD.

Significantly different from fifth quintile: * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$.

Table 4. 12-year Death Rates and Relative Risk of Death by HDL-C Quintile in Men

HDL-C quintile	Cause of death			
	All causes	Cardiovascular disease	Coronary heart disease	Cancer
First (12 to 34 mg/dl)	44.9 (1.92)	20.2 (3.58)	12.6 (4.09)	8.7 (1.17)
Second (35 to 40 mg/dl)	34.2 (1.28)	8.8 (1.46)	7.0 (1.99)	9.6 (1.10)
Third (41 to 46 mg/dl)	31.8 (1.27)	9.8 (1.87)	8.8 (2.76)	9.0 (1.10)
Fourth (47 to 54 mg/dl)	29.6 (1.17)	12.6 (2.37)	9.5 (2.77)	6.9 (0.80)
Fifth (55 to 129 mg/dl)	28.4 (1.00)	5.5 (1.00)	4.1 (1.00)	9.6 (1.00)
Risk reduction (%) (10 mg/dl increase in HDL-C)	12.2	13.1	18.9	9.5
<i>P</i> value	0.002	0.076	0.027	0.228

Age-adjusted 12-year death rates are given with relative risk adjusted for covariates in parentheses. A relative risk of 1.0 was assigned for the fifth HDL-C quintile for each endpoint. The HDL-C relative risk and percent reduction in risk were estimated after adjustment for total cholesterol, systolic pressure, body mass index, cigarette use, and age.

Table 5. 12-year Death Rates and Relative Risk of Death by HDL-C Quintile in Women

HDL-C quintile	Cause of death			
	All causes	Cardiovascular disease	Coronary heart disease	Cancer
First (23 to 44 mg/dl)	27.0 (1.47)	8.1 (1.55)	5.8 (3.07)	6.2 (1.08)
Second (45 to 51 mg/dl)	20.3 (1.17)	7.4 (1.82)	5.2 (3.94)	5.9 (1.09)
Third (52 to 58 mg/dl)	16.7 (0.99)	5.5 (1.27)	3.6 (2.60)	2.6 (0.49)
Fourth (59 to 69 mg/dl)	21.9 (0.99)	6.5 (1.27)	2.5 (2.60)	6.1 (0.49)
Fifth (70 to 139 mg/dl)	15.4 (1.00)	3.6 (1.00)	1.2 (1.00)	4.9 (1.00)
Risk reduction (%) (10 mg/dl increase in HDL-C)	5.8	8.6	28.1	3.9
<i>P</i> value	0.162	0.285	0.006	0.661

Age-adjusted 12-year death rates are given with relative risk adjusted for covariates in parentheses. A relative risk of 1.0 was assigned for the fifth HDL-C quintile for each endpoint. The HDL-C relative risk and percent reduction in risk were estimated after adjustment for total cholesterol, systolic pressure, body mass index, cigarette use, and age.

women was higher in the lower quintiles and significantly different ($p < 0.01$) when the first quintile (mean 144.3 mm Hg) and the fifth quintile (mean 139.8 mm Hg) were compared (Table 3). Women in the first quintile of HDL-C were also more likely ($p < 0.05$) to smoke cigarettes (33.6%) as compared to those in the fifth quintile (25.6%).

The strongest risk factor relationship suggested in Tables 2 and 3 involves the association between HDL-C and BMI. In both men and women, lower BMI was associated with higher levels of HDL-C. Subjects in the fifth quintile of HDL-C were significantly leaner than those in the other four quintiles ($p < 0.001$).

As the preceding risk factors, particularly BMI, may help to explain the mortality in those with low levels of HDL-C,

age-adjusted relative risks were estimated by comparing each HDL-C quintile to the fifth HDL-C quintile (Tables 4 and 5). Risk factor-adjusted relative risks are given below in brackets; the risk factor-adjusted relative risk was set at 1.0 for the fifth HDL-C quintile within each death category. Risk factors included in the adjustments were: total cholesterol, systolic pressure, body mass index, cigarette use, and age. The percent reduction in risk associated with a 10 mg/dl increase in HDL-C and its statistical significance are given at the bottom of each table. These latter values are based on the multivariate regression coefficients for HDL-C.

For men in Table 4, death from all causes was nearly twice as frequent in the first versus the fifth quintiles of

HDL-C and suggests that the mortality effects of HDL-C cannot be explained by the other risk factors studied. Coronary death rates decreased with each successively greater quintile of HDL-C. A fourfold risk of death due to CHD occurred for the first quintile of HDL-C compared to the fifth quintile, and the risk of death due to CVD in the first quintile was more than three times the risk in the fifth quintile, although a less uniform pattern of decreasing CVD death rate with increasing HDL-C was observed.

The percent reduction in risk associated with a 10 mg/dl increase in HDL-C for various causes of death, after risk factor adjustment, are shown at the bottom of Table 4. Regression coefficients and *p* values are provided from the proportional hazards model. Inverse relationships are seen between HDL-C and all-cause mortality ($p=0.002$) and coronary mortality ($p=0.027$), while the association with cardiovascular mortality ($p=0.076$) was less strong. There were no significant associations for cancer death and HDL-C ($p=0.228$).

As shown in Table 5 for women, the excess of all-cause mortality in the first versus the fifth quintiles of HDL-C was no longer significant after control of additional risk factors, suggesting that the excess of deaths was partially attributed to higher levels of systolic blood pressure and BMI and to the more frequent use of cigarettes among those with low levels of HDL-C. A similar explanation may also hold for the reduced effect that HDL-C had on deaths due to CVD after adjustment for other risk factors.

For deaths due to CHD, however, the rate of deaths in the first and second quintiles of HDL-C was three to four times the rate in the fifth quintile. As in men, there was no association between HDL-C and cancer death, after age and risk factor adjustments. The percent reductions in risk associated with a 10 mg/dl increase in HDL-C for mortality are shown at the bottom of Table 5 for women, and only the inverse association between HDL-C as a continuous variable with coronary mortality ($p=0.0006$) was significant.

Discussion

An elevated blood cholesterol is well-recognized as a risk factor for early death. An increased cholesterol level is a strong predictor of CHD in the young. While associations between cholesterol level and CVD weaken as age advances, recent evidence suggests that significant associations are still obtained between cholesterol and cardiovascular events at older ages.^{14,15} Conversely, low total cholesterol values in Western societies are associated with chronic illness, debility, and cancer.^{16,17}

Less is known about the association between HDL-C and mortality. This prospective report of men and women over 50 who were healthy at baseline clearly links low HDL-C levels with coronary mortality. Similar trends were observed in men for cardiovascular death and all-cause mortality, while no associations between HDL-C and cancer mortality were manifest (Tables 4 and 5).

It is noteworthy that large prospective studies from Israel and Framingham investigating HDL-C and mortality show HDL-C to be inversely associated with all-cause and coronary mortality, but not with cancer death. Previous prospective studies from Finland, the USSR, and Minne-

sota have failed to show such a salutary effect of elevated HDL-C.^{3,4,18} The USSR study even showed that HDL-C was lowest in survivors, intermediate in those dying of CVD, and highest in those dying of cancer.⁴ These studies often had few events and did not include analyses using life-table techniques. For instance, the Finnish study included 518 men, of whom 155 died over the 24 years of follow-up; the Soviet report examined 6614 men and reported 273 deaths over 4 years of follow-up; and the Minnesota cohort of 260 experienced 135 deaths over 25 years of follow-up.

The Israeli Heart Study investigated the potential associations between HDL-C and various causes of death. A recent article by Goldbourt et al.² showed an association between cholesterol or HDL-C and mortality. A 15-year follow-up of more than 10 000 Israeli male civil servants (1664 of whom died) revealed a continuous relationship between the HDL-C/total cholesterol ratio and death, with no evidence of a threshold.

Different methodologies for HDL-C measurement and analyses help to explain how the Israeli results vary from those in Framingham. Their group used the 'dosage rapide' method to determine HDL-C after precipitation of very low density lipoproteins and low density lipoproteins according to the method of Burstein and Samaille¹⁹; the estimated mean HDL-C for their participants was 36.5 mg/dl. Framingham used a modified Lipid Research Clinics Program technique, and the mean HDL-C was 45 mg/dl in men.

Our data for men also demonstrate a significant relationship between HDL-C, either as a continuous variable or in quintiles, and mortality from coronary disease. Similarly, recent data from an autopsy series of 471 Oslo Study participants also suggest a strong HDL-C link to coronary lesions and coronary death, even after controlling for covariates by multivariate analyses.¹⁷ Coronary disease death and all-cause mortality were less frequent in women with elevated HDL-C levels, and a similarly strong association between HDL-C levels and coronary mortality was observed.

Whereas low HDL-C levels are associated with greater mortality from coronary, cardiovascular, and all other causes among men, the relationship is particularly strong for the lowest HDL-C levels. A weaker relationship is seen for women, where only the lowest quintiles of HDL-C are associated with coronary mortality.

Cross-sectional studies with clinical, angiographic, or pathological techniques have elucidated strong relationships between HDL-C and coronary disease,²⁰⁻²³ and prospective studies have shown important relationships between HDL-C and clinical coronary disease.^{14,24,25,26} However, morbidity data should not be extrapolated to studies with mortality as an endpoint. Risk factors such as cigarette use, blood cholesterol level, and blood pressure may be strongly associated with initial manifestations of coronary disease, while long-term survival of coronary patients may be predicated on different factors. Traditionally, ventricular function and arrhythmic status²⁷ were thought to be important, but there is convincing evidence from the follow-up of male participants in the Coronary Drug Project, the Malmo, Sweden Study, and the Israeli Study that HDL-C levels help to predict survival.^{5,6,7}

The current study points up that prospective studies may need large cohorts with long-term follow-up to show certain relationships, such as a significant relationship between HDL-C and mortality. Excess risk for coronary death may cluster among individuals with the lowest HDL-C levels. Performing analyses that look at HDL-C levels as a continuous variable were statistically significant for some of the death endpoints studied, but it should be noted that similar analyses might yield different results in populations where the average total cholesterol and HDL-C levels differ from those in Framingham.

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