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Change in High-Density Lipoprotein Cholesterol and Incident Coronary Heart Disease in Apparently Healthy Male Physicians

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Abstract

The association between change in high-density lipoprotein cholesterol (HDL-C) and risk of subsequent coronary heart disease (CHD) remains unclear. We calculated the change in HDL-C in a prospective cohort of 4501 male physicians enrolled in the Physician's Health Study I (PHS I) who had HDL-C levels measured in 1982-1983 and again approximately 14 years later. Subjects were divided into categories: those with a decrease (of ≥ 2.5 mg/dL or more), those with no change in HDL-C (change between -2.5 mg/dL and 2.5 mg/dL), those with a small increase in HDL-C of 2.5 to 12.5 mg/dL, and those with a large increase in HDL-C of ≥ 12.5 mg/dL. We used Cox proportional hazards to examine the association between change in HDL-C and incident CHD (confirmed acute myocardial infarction or cardiac death). Hazard ratios were adjusted for age, initial HDL-C level, diabetes mellitus, hypertension, non-HDL cholesterol, and history of cholesterol medication. Compared to subjects with a decrease in HDL-C, multivariable-adjusted hazard ratios (HR, 95% confidence interval, CI) for CHD were 0.66(0.40-1.09) in subjects with no change in HDL-C, 0.56 (0.35-0.89) for subjects with an increase in HDL-C between 2.5 mg/dL and 12.5 mg/dL, and 0.43 (0.23-0.83) for subjects with HDL-C increase of ≥ 12.5 mg/dL. In conclusion, our findings are consistent with an inverse, graded relation between 14-year increase in HDL-C and risk of subsequent CHD.

Keywords

epidemiology; lipoproteins; coronary disease; prevention

Introduction

In a prospective cohort of men aged between 40 and 84 years enrolled in the Physician's Health Study I (PHS I), we determined whether change in high-density lipoprotein cholesterol (HDL-C) over a 14-year period was associated with subsequent risk of coronary heart disease (CHD). In secondary analyses, we explored whether this association varied in subgroups of age, body mass index (BMI), and alcohol consumption.

Methods

The PHS I is a prospective cohort of U.S. male physicians who have been followed using annual follow-up questionnaires since enrollment between August, 1982 and August, 1983. The cohort consists of 22,071 apparently healthy men aged 40 to 84 years who were randomized in a clinical trial of aspirin and beta-carotene. Baseline information was collected on self-reported demographic, lifestyle, and clinical factors including height, weight, blood pressure, and comorbidities. Updated information on new diagnoses and medications were collected at 6 months and annually thereafter. Detailed description of the methods of PHS have been published elsewhere.¹⁻³

Of the 22,071 PHS I participants, 15,120 returned blood samples in kits provided between August 1982 and August 1983 ("initial" blood sample). Of these men, 9,436 returned a second blood sample between December 1995 and January 1998 ("follow-up" blood sample). Of these sets of samples, 4593 were available for testing for HDL-C and total cholesterol levels. From these 4593 subjects, we excluded 92 men because they developed incident CHD between the two blood sample collections. Our cohort therefore consisted of 4501 men with 2 blood samples collected approximately 14 years apart, who were free of CHD through the date of their follow-up blood collection.

The PHS has been approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, Massachusetts. All subjects in the PHS I gave written informed consent to participate in the study.

The blood collection method used in PHS I has been described elsewhere.¹⁻³ HDL-C was determined using standard laboratory techniques on initial and final blood samples for each subject. We calculated the change in HDL-C by subtracting the initial HDL-C level from the final HDL-C level. Incident CHD included confirmed acute myocardial infarction and cardiac death. When a relevant outcome was reported during annual follow-up questionnaires, permission was requested to review the medical records. Details of the event were then obtained from hospitals and treating physicians. An outcome was confirmed only after review of all available information pertaining to the event by an Endpoints Committee consisting of two internists, a cardiologist, and a neurologist.¹⁻³ All deaths were reported by family members. After obtaining permission to review pertinent medical records relating to a subject's death, cause-specific mortality including cardiac death was determined by nosologists using the *Ninth International Classification of Diseases* (ICD-9) and the *Automated Classification of Medical Entities Decision Tables*. "Cardiac death" was defined as death from ICD-9 codes 410-414.

In the analyses described below, we used several covariates. Subjects reported whether or not they had diabetes mellitus or hypertension, the latter defined as having either systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg. History of cholesterol medication was defined as having a history of ever taking cholesterol medication. Non-HDL cholesterol was determined by subtracting each subject's follow-up HDL-C level from their follow-up total cholesterol level. Non-HDL cholesterol served as a marker of low-density lipoprotein cholesterol (LDL-C), which was not available in the PHS database. All of these variables were determined as close as possible to the date of the final blood collection, when follow-up began. We assessed lifestyle factors using information collected as close as possible to each subject's final blood collection, including body mass index (BMI), alcohol consumption (rarely/never, 1-3 drinks monthly, 1-6 drinks weekly, or 1 or more drinks daily); smoking status (never, past, current); or physical activity as determined in the 1991 questionnaire (exercising to sweat once or more week).

Because few previous studies have examined the association between change in HDL-C and CHD, we did not assume linearity of HDL-C change as a predictor. Instead, we categorized

men into the following groups based on change in HDL-C to reflect the spectrum of change and to provide clinically meaningful increments: a decrease in HDL-C (change ≥ -2.5 mg/dL or more) no change in HDL-C (a change of -2.5 mg/dL to $+2.5$ mg/dL), small increase in HDL-C (an increase between $+2.5$ mg/dL and $+12.5$ mg/dL), or large increase in HDL-C (an increase of $\geq +12.5$ mg/dL). Without intervention, HDL-C has been demonstrated to drift downward over time as a person ages; thus we chose subjects who experienced a decrease in HDL-C between the 2 measurements as the reference group and compared subjects with stable or increasing HDL-C to this reference.⁴⁻⁷ Follow-up began on the date of receipt of each subject's final blood sample. We calculated person-years by summing the follow-up times of all subjects for each HDL-C change category. We determined unadjusted incidence rates by dividing the number of events (acute myocardial infarction or cardiac death) in each category of HDL-C change by the total number of person-years in that category. Unadjusted incidence is expressed as rate of events per 10,000 person-years. Rate of long-term follow-up in the PHS I is very high.⁸

We used Cox proportional hazards to estimate the hazard ratios (95% confidence intervals) for CHD for each category of change in HDL-C (no change, small increase in HDL-C, or large increase in HDL-C), compared to the reference group (subjects with a decrease in HDL-C of at least 2.5 mg/dL). Subjects were censored on the date of acute myocardial infarction or cardiac death, or on the date of their last returned questionnaire, whichever came first. First, we examined changes in HDL-C and risk of CHD adjusting for age at the start of follow-up. We then adjusted for initial HDL-C, diabetes mellitus, hypertension, non-HDL cholesterol, and history of ever using cholesterol medication. Finally, we conducted analyses to determine whether selected lifestyle factors were modifiers of the association between change in HDL-C and CHD risk. Lifestyle intermediaries added into the model included BMI, smoking status, alcohol consumption, and physical activity. P-values for trend were calculated by assigning median change in HDL-C within each HDL-C change category to all men in that category and testing for association between these median values and CHD, adjusting for age, initial HDL-C, diabetes mellitus, hypertension, non-HDL cholesterol, and cholesterol medication. A test for the existence of proportional hazards revealed that the effect of none of the 3 exposure categories (no change in HDL-C, small increase in HDL-C, or large increase in HDL-C) varied over time during the follow-up period. Thus, the assumption of proportional hazards for the HDL-C change categories was valid.

In secondary analyses, we examined the association between change in HDL-C and CHD in subgroups stratified by median age at the start of follow-up (62.0 years), median BMI at the start of follow-up (25.0 kg/m²), and alcohol consumption (either 1 or more drinks daily or less than 1 drink daily).

Results

The mean (standard deviation, SD) age at the start of follow-up of the 4501 men in the study cohort was 63.0 (6.8) years. The mean (SD) time between the 2 HDL-C measurements was 14.2 (0.29) years. The mean (SD) initial HDL-C was 42.1 (14.7) mg/dL and the mean (SD) final HDL-C was 43.0 (15.0) mg/dL. The mean (SD) change in HDL-C was an increase of 0.88 (11.5) mg/dL. As expected, a large number of participants experienced a decline in HDL-C between the 2 measurements. The number of participants in each of the HDL-C change categories is displayed at the top of each column in Table 1.

Baseline characteristics of the study cohort by category of HDL-C change are also displayed in Table 1. Larger magnitudes of increase in HDL-C were associated with lower initial HDL-C levels, older age at the start of follow-up, lower non-HDL cholesterol, diabetes mellitus, hypertension, history of CMT use higher levels of alcohol consumption, and lower BMI.

Subjects were followed for a mean of 7.9 years following their final blood collection, during which there were 123 incident cases of CHD, including 103 confirmed myocardial infarctions and 29 cardiac deaths. The unadjusted incidence of CHD per 10,000 person-years was 42 in subjects whose HDL-C decreased, 31 in subjects who had no change in HDL-C, 32 in subjects who had small increase in HDL-C, and 28 in subjects who had a large increase in HDL-C.

In age-adjusted analyses, change in HDL-C was not significantly associated with risk of CHD (see Table 2). In analyses adjusting for age, initial HDL-C, diabetes mellitus, hypertension, non-HDL cholesterol and history of cholesterol medication, increase in HDL-C was inversely associated with the risk of CHD, with the largest increases in HDL-C associated with the lowest risk of CHD. As expected, adding lifestyle covariates into the model including BMI, smoking, physical activity, and alcohol consumption (along with age, initial HDL-C, diabetes mellitus, hypertension, non-HDL cholesterol and history of cholesterol medication) modestly attenuated the association between increases in HDL-C and CHD. As displayed in Table 3, the magnitude of the association between change in HDL-C and risk of CHD varied among subgroups based on age, BMI, and alcohol consumption.

Discussion

In this prospective cohort study of apparently healthy male physicians, increases in HDL-C over approximately 14 years were associated with a lower risk of subsequent CHD. Previous studies have demonstrated a linear association between change in LDL-C and risk of cardiovascular disease.⁹⁻¹¹ The results of our study reveal that a graded relationship may also exist between long-term increases in HDL-C and risk of CHD. Our observational data therefore lend support to HDL-C as a potential therapeutic target in the primary prevention of CHD.

Previous studies examining the association between a single measurement of HDL-C and CHD have consistently demonstrated that HDL-C is inversely associated with the risk of CHD.¹²⁻²⁴ The linearity of the relationship in these studies suggests that change in HDL-C would be associated with a graded decrease in cardiovascular risk, with larger increases in HDL-C associated with lower risks of CHD. Some large, randomized clinical trials of HDL-C-modifying therapies have reported that a HDL-C increases were associated with reductions in adverse cardiovascular events.²⁵ In the Bezafibrate Infarction Prevention trial, each 5 mg/dL increase in HDL-C was associated with a 27% reduction in risk of cardiac mortality.²⁶ This is consistent with our finding that larger HDL-C increases of 12.5 mg/dL or greater were associated with a 57% lower risk of CHD.

In this cohort, subjects with initially low HDL-C levels at baseline tended to achieve the largest increases in HDL-C. We speculate that subjects with initially lower HDL-C levels were more likely to undergo favorable lifestyle modification in an effort to manage their cardiac risk factor profile. Therefore, as expected, these subjects tended to have more favorable lifestyle profiles when ascertained near the date of their follow-up HDL-C, including lower BMI, higher prevalence of moderate alcohol consumption, and higher prevalence of regular physical activity (see Table 1). Adjustment for these lifestyle factors modestly attenuated the association between change in HDL-C and CHD risk, which suggests that favorable lifestyle factors likely contributed to increases in HDL-C over the 14-year period between measurements. In other observational cohorts and some randomized controlled trials, alcohol consumption, BMI, and physical activity were also associated with increases in HDL-C.²⁷⁻³⁰

Regression to the mean may have contributed to some of the change between the baseline and follow-up measurements of HDL-C. To evaluate whether regression to the mean impacted our findings, we re-ran our analysis after re-defining categories of HDL-C change by dividing the change by the average of the 2 HDL-C measurements for each subject. Categories of HDL-C

change were defined as $<-5\%$ (reference), between -5% and 5% change (no change), between 5% and 30% (small change), and $\geq 30\%$ (large change). The results were identical. We conclude that while regression to the mean may be responsible for some change in HDL-C, lifestyle factors likely explain much of the change in HDL-C we observed in this cohort, as discussed above.

There are limitations to our study. As with any observational study, residual confounding may exist due to unmeasured differences across the exposure categories, such as differences in diet or differences in type and dose of medications. In addition, the PHS I is a relatively homogenous cohort of mostly white males of similar socioeconomic status. Selection bias might have affected our results, as not all sets of blood samples returned were tested for HDL-C and total cholesterol levels. We did not account for unmeasured HDL-C fluctuations that occurred between the initial and final HDL-C measurements which might have affected risk of CHD. Finally, we did not have data available on LDL-C or triglyceride levels. However, when we used non-HDL cholesterol as a surrogate for non-HDL lipid parameters, the HRs were minimally altered. Thus we would expect that adjusting for LDL-C, triglycerides, and other lipid parameters would not have materially altered our results.

In secondary analyses, we found that the association between change in HDL and CHD risk may be stronger among men of younger age and normal BMI. Stratified analyses in men with different alcohol consumption patterns did not reveal the graded relationship seen in the overall analyses. Some of the inconsistencies in the association between change in HDL-C and risk of CHD in these subgroup analyses may reflect the limited number of CHD endpoints in our cohort. The findings of these secondary analyses highlight the need for further studies exploring which subjects might benefit the most from increase in HDL-C.

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TABLE 1

Characteristics of n=4501 subjects with high-density lipoprotein cholesterol (HDL-C) measured in 1982 and 1997, by category of change in HDL-C.

Characteristic at baseline	HDL-C Change (mg/dL)			
HDL-C change category	Reference <-2.5 mg/dL (n=1633) [36%]	None -2.5 to +2.5 mg/ dL (n=937) [21%]	Increase 2.5< to <12.5 mg/dL (n=1339) [30%]	Increase ≥12.5 mg/dL (n=592) [13%]
Change in HDL-C, median (IQR)	-8.5 (-12.7 to -5.4)	0 (-1.2 to 1.2)	6.6 (4.6 to 8.9)	17.4 (14.3 to 22.4)
Age, mean (SD) (years)	62.8 (6.8)	62.8 (6.7)	62.9 (6.7)	64.1 (7.3)
Non-HDL cholesterol, mean (SD)	164.9 (35.7)	165.3 (35.4)	162.6 (35.2)	157.4 (39.3)
HDL-C, 1982, mean (SD)	48.2 (14.8)	40.6 (12.8)	37.3 (13.2)	38.5 (14.7)
Active	1037 (63.6%)	595 (63.7%)	818 (61.1%)	387 (65.5%)
Body mass index, mean (SD)(kg/ m ²)	25.9 (3.3)	25.7 (3.2)	25.5 (3.3)	24.7 (2.7)
Alcohol consumption				
Rarely or never	278 (17.1%)	159 (17.1%)	216 (16.2%)	71 (12.0%)
1-3 drinks per month	65 (4.0%)	36 (3.9%)	55 (4.1%)	22 (3.7%)
1 to 6 drinks per week	586 (36.1%)	332(35.7%)	476 (35.8%)	191 (32.4%)
1 or more drinks per day	696 (42.8%)	402 (43.3%)	584 (43.9%)	306 (51.9%)
Smoking				
Never	870 (53.3%)	538 (57.4%)	784 (58.6%)	296 (50.0%)
Past	735 (45.0%)	372 (39.7%)	518 (38.7%)	283 (47.8%)
Current	28 (1.7%)	27 (2.9%)	37 (2.8%)	13 (2.2%)
Cholesterol medication	323 (19.8%)	184 (19.7%)	318 (23.8%)	156 (26.4%)
Diabetes mellitus	53 (3.3%)	27 (2.9%)	69 (5.2%)	27 (4.6%)
Hypertension	382 (23.4%)	209 (22.3%)	327 (24.4%)	167 (28.2%)
Incident cancer	217 (13.5%)	121 (12.9%)	180 (13.4%)	95 (16.1%)

HDL-C=high density lipoprotein cholesterol

TABLE 2
Age-adjusted and multivariable-adjusted hazard ratios (95% confidence intervals) for incident coronary heart disease in each category of change in high-density lipoprotein cholesterol (HDL-C).

Change in HDL-C (mg/dL)	N	Incident CHD	Person-years	Age-adjusted	Model 1*	Model 2†
≤-2.5	1633	53 (3.3%)	12,713	Reference	Reference	Reference
-2.5 to +2.5	937	23 (2.5%)	7,376	0.74 (0.45-1.21)	0.66 (0.40-1.09)	0.70 (0.42-1.18)
+2.5 to +12.5	1339	34 (2.5%)	10,511	0.76 (0.50-1.17)	0.56 (0.35-0.89)	0.64 (0.40-1.04)
≥12.5	592	13 (2.2%)	4,587	0.64 (0.40-1.04)	0.43 (0.23-0.83)	0.52 (0.26-1.01)
P-value for trend				0.08	0.003	0.03

* **Model 1:** Adjusted for age, initial HDL-C, diabetes mellitus, hypertension, history of cholesterol medication, and non-HDL cholesterol.
† **Model 2:** Adjusted for age, initial HDL-C, diabetes mellitus, hypertension, history of cholesterol medication, non-HDL cholesterol, body mass index, smoking, alcohol consumption, and exercise.
HDL-C=high density lipoprotein cholesterol

TABLE 3

Multivariable-adjusted hazard ratios (95% confidence intervals) for incident coronary heart disease in each category of high-density lipoprotein (HDL-C) change, stratified by age, body mass index (BMI), and alcohol consumption.

	HDL-C Change (mg/dL)				p-value trend
	Change ≤-2.5	Change -2.5 to +2.5	Change 2.5 to 12.5	Change ≥12.5	
Above median age (≥62.0 years), 75 events					
Multivariable-adjusted*	Reference	0.81 (0.43-1.54)	0.74 (0.41-1.34)	0.60 (0.28-1.27)	0.06
Below median age (<62.0 years), 43 events					
Multivariable-adjusted*	Reference	0.47 (0.21-1.08)	0.34 (0.15-0.77)	0.19 (0.04-0.83)	0.003
Above median BMI (≥25.0), 74 events					
Multivariable-adjusted*	Reference	0.66 (0.33-1.31)	0.95 (0.53-1.70)	0.68 (0.30-1.58)	0.14
Below median BMI (<25.0), 44 events					
Multivariable-adjusted*	Reference	0.71 (0.34-1.50)	0.24 (0.10-0.56)	0.23 (0.08-0.64)	0.003
≥1 alcohol beverages daily, 43 events					
Multivariable-adjusted*	Reference	0.35 (0.13-0.96)	0.72 (0.35-1.48)	0.24 (0.07-0.86)	0.02
<1 alcohol beverage daily, 75 events					
Multivariable-adjusted*	Reference	0.91 (0.50-1.65)	0.48 (0.25-0.90)	0.60 (0.28-1.31)	0.03

BMI=body mass index

HDL-C=high density lipoprotein cholesterol