High-Density Lipoprotein and Mortality Before Age 90 in Male Physicians

Catherine Rahilly-Tierney, MD, MPH; Howard D. Sesso, ScD, MPH; J. Michael Gaziano, MD, MPH; Luc Djoussé, MD, ScD

Background—In cross-sectional and some cohort studies with shorter follow-up, high-density lipoprotein cholesterol (HDL-C) has been associated with longer life. We sought to examine the relationship between HDL-C and death before age 90 in the Physicians’ Health Study (PHS).

Methods and Results—Of PHS enrollees who had blood collected at PHS II baseline (approximately 1997), we selected 1351 men old enough to reach age 90 by March 4, 2009, and with complete data on HDL-C and total cholesterol, lifestyle factors, and comorbidities. We used Cox proportional hazards to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, cardiovascular disease (CVD), and non-CVD mortality before age 90, adjusting for potential confounders.

After a mean (SD) follow-up of 6.8 (3.2) years, 44.1% of men in the lowest baseline HDL-C quartile (<32.8 mg/dL) compared with 32.9% (11.2% absolute risk reduction) in the highest HDL-C quartile (≥54.1 mg/dL) died before age 90. In multivariable adjusted analyses, men in the highest HDL-C quartile had a 28% lower risk (HR, 0.72; 95% CI, 0.55 to 0.94) of death before age 90 compared with men in the lowest HDL-C quartile. In age-adjusted analyses, increasing baseline HDL-C was significantly associated with a lower risk of CVD death. No association was found between HDL-C and non-CVD mortality.

Conclusion—In male physicians, higher baseline HDL-C levels were associated with a lower risk of all-cause and CVD mortality before age 90. (Circ Cardiovasc Qual Outcomes. 2012;5:00-00.)

Key Words: aging ■ lipoproteins ■ epidemiology ■ prevention

E levated high-density lipoprotein cholesterol (HDL-C) levels have been associated with a lower risk of cardiovascular disease (CVD) events in numerous prospective studies.1–14 Cross-sectional studies have identified high HDL-C levels as a characteristic of individuals who survive to exceptionally old age.15–20 Only a few studies have prospectively examined the relation between baseline HDL-C levels and survival to exceptionally old ages.21–23 Though these studies have had short follow-up, they still demonstrated an inverse association between higher HDL-C levels and dying before reaching age 85 or 90. Thus, few studies have examined the relation between baseline HDL-C levels and survival to exceptionally old age in a prospective cohort with long-term follow-up. Therefore, we sought to examine the relation between baseline HDL-C levels and death before age 90 in a subgroup of Physicians’ Health Study (PHS) participants old enough at the time of blood sample collection to reach age 90 by the end of follow-up.

Design and Methods

Study Setting
A detailed description of the methods of PHS have been previously published.24–26 PHS I began in 1982 as a clinical trial of aspirin and β-carotene in 22 071 male physicians aged 40 to 84 years at enrollment. In 1997, the PHS I concluded and enrollment into the PHS II (a controlled trial of β-carotene, vitamin C, vitamin E, and a multivitamin) randomized 7641 PHS I participants plus 7000 new physicians. All 29 071 PHS participants have been followed prospectively, using annual mailed health questionnaires to collect self-reported data, including demographics; anthropometric measures; lifestyle factors including smoking status, physical activity, and alcohol consumption; and new diagnoses. From 1995 to 2001, participants in PHS I (n=11 718) and new enrollees in PHS II (n=5535) provided blood samples, from which total and HDL-C cholesterol were measured.

Participants
From all PHS I and PHS II participants who provided blood samples between 1995 and 2001 (n=17 253), we selected 1511 men who were old enough on the date of that blood collection to potentially reach age 90 by March 4, 2009. We then excluded 126 men with
missing data on lipid levels, lifestyle factors, or comorbidities. Finally, 34 men who were heavy alcohol consumers (≥4 drinks daily) were excluded for a baseline sample of 1351 participants. All participants in PHS I and PHS II provided written informed consent to participate in the study. PHS has been approved by the Institutional Review Board of Brigham and Women’s Hospital.

WHAT IS KNOWN
- Elevated high-density lipoprotein cholesterol (HDL-C) levels have been associated with a lower risk of cardiovascular disease (CVD) in cross-sectional and prospective studies.
- HDL-C has been associated with increased longevity in some cohorts.
- Factors including smoking abstinence, weight management, blood pressure control, regular exercise, and lower body mass index are associated with exceptional longevity in the Physicians’ Health Study (PHS).

WHAT THE STUDY ADDS
- After adjusting for other factors previously associated with longevity, higher HDL-C levels were significantly associated with survival to age 90 in the PHS.
- HDL-C likely increases survival to exceptionally old age by protecting against CVD death, the most prevalent cause of death.

HDL-C Assessment
PHS participants were mailed blood kits that included Vacutainer tubes containing EDTA, instructions for blood draws, and cold packs. Blood samples were returned via overnight carrier, were processed, and have been stored since their receipt at −80°C. Total cholesterol and HDL-C were measured in the Lipid Research Laboratory of Brigham and Women’s Hospital, using a Hitachi 911 analyzer and reagents manufactured by Roche Diagnostics and Genzyme. Further details regarding lipid measurements in PHS have been previously described.

Outcome
The main outcome for the analysis described below was death from any cause before the date of each participant’s 90th birthday. No participant who was alive at the end of follow-up (March 4, 2009) for this study was <90 years. Cause-specific mortality was determined by an End Point Committee using International Classification of Diseases, Ninth Revision and the Automated Classification of Medical Entities Decision Tables, after obtaining permission to review medical records. Members of the End Point Committee were blinded to treatment status and to data collected as part of the PHS study protocol.

Covariates
We examined several potential confounders of the relation between HDL-C levels and death before age 90. Baseline lifestyle factors (near the date of the HDL-C measurement) included body mass index (BMI), alcohol consumption, smoking status, and physical activity. BMI was calculated using self-reported height and weight. Alcohol consumption was categorized as rarely or never consumed alcohol, consumed 1 to 3 drinks per month, consumed 1 to 6 drinks per week, or consumed ≥1 drink daily. Smoking status was characterized as never, past, or current. Exercise was categorized by number of days of vigorous physical activity weekly.

Baseline comorbidities included diabetes mellitus, hypertension, angina, coronary heart disease (CHD) [including history of coronary revascularization or myocardial infarction, stroke, congestive heart failure (CHF)], and cancer, diagnosed before the date of HDL-C measurement. Non-HDL cholesterol was calculated by subtracting baseline HDL-C from total cholesterol.

Statistical Analysis
We examined the characteristics of survivors and nonsurvivors to age 90 and used t-tests to compare continuous variables and Cochran-Mantel-Haenszel tests to compare binary or categorical variables. We determined causes of death, including cardiovascular deaths, cancer deaths, gastrointestinal bleeds, pulmonary causes, renal or urogenital causes, violent causes or suicide, or other causes. We expected that most men who died before age 90 would die from cardiovascular causes.

For the main analysis, we categorized baseline HDL-C into quartiles, treating the lowest quartile as reference. We determined the hazard ratio (HR) and 95% confidence interval (CI) for total and cause-specific mortality before age 90 for each category of HDL-C, compared with reference. Modeling the relationship between subject characteristics and mortality before exceptionally old age in the PHS in this way has been previously reported. Models were adjusted for age, non-HDL cholesterol, and comorbidities, including hypertension, diabetes mellitus, congestive heart failure, stroke, and cancer. We further adjusted for lifestyle factors known to be associated with HDL-C levels, including categorized alcohol use, BMI, categorized smoking status, and exercise; categorized into vigorous physical activity ≥ or <1× weekly. To test for linear trend, we assigned all participants in each baseline HDL-C quartile the median HDL value in that quartile and ran the main analysis using “median HDL-C” as a continuous variable. We additionally tested for trend by examining the relationship between increments of baseline HDL-C (in increments of the standard deviation of HDL-C), quadratic baseline HDL-C, and cubic HDL-C, and the outcome. In secondary analyses, we examined the relation between quartiles of baseline HDL-C and cause-specific mortality before age 90, including CVD death and non-CVD death, adjusting for age and then for comorbidities and non-HDL cholesterol.

Results
At baseline, mean (standard deviation [SD]) age was 81.9 (2.9) years. Mean (SD) HDL-C was 44.8 (16.5) mg/dL, and mean (SD) non-HDL cholesterol was 155.5 (37.2) mg/dL. Most men (60.7%) were hypertensive, and almost 20% had angina; however, a more modest proportion of men had been diagnosed with CHD (15.0%), stroke (5.4%), or CHF (5.2%) before the date of HDL-C measurement. The mean (SD) BMI was 24.6 (3.1), and 9.2% of men had diabetes mellitus on the date of HDL-C measurement. At baseline, 21.7% of men had been diagnosed with cancer. The majority of men (97.8%) were not currently smoking at baseline, with 53% having been past smokers. Consumption of ≥1 alcoholic drink daily was the most prevalent alcohol intake pattern (37.8%). Most men exercised to sweat 1× or more weekly (57.7%). Table 1 presents the characteristics of the 1351 PHS participants eligible for this study, by quartile of baseline HDL-C. Men with higher baseline HDL-C levels had significantly lower BMI; lower non-HDL-C; lower prevalence of hypertension, diabetes mellitus, angina, and CHD; and were more likely to exercise regularly and consume moderate amounts of alcohol.

During a mean (SD) follow-up of 6.8 (3.2) years (maximum 12.5 years), 501 (37.1%) of 1351 men died before age
The most prevalent cause of death was CVD, including CHD and cerebrovascular events (159 men, 31.7% of all deaths before age 90). The second most prevalent cause of death was cancer (123 men, 24.6% of deaths). Table 2 compares characteristics of men who did and those who did not survive until age 90. Survivors were older at baseline and had significantly higher HDL-C levels. They were less likely to have diabetes mellitus, angina, CHD, CHF, cancer, or stroke at baseline. They were more likely to have never smoked and more likely to have exercised regularly than men who did not survive until age 90.

The unadjusted incidence of death before age 90 in each quartile of baseline HDL-C was 44.1% in the first quartile, 37.0% in the second, 34.4% in the third, and 32.9% in the highest (probability value 0.003). Table 3 presents the age and multivariable adjusted HRs (95% CIs) for each quartile of baseline HDL-C, compared with the lowest quartile, for all-cause mortality. Adjusting for age, baseline HDL-C in increasing quartiles was associated with significantly lower risk of death before age 90 \((P = 0.006)\). After adjusting for non-HDL cholesterol, comorbidities, and lifestyle factors, the association between highest versus the lowest baseline HDL-C quartiles and all-cause mortality remained robust, with a 28% lower risk \((HR, 0.72; 95\% CI, 0.55 \text{ to } 0.94)\). The \(P\) for trend across the quartiles was 0.006.

In secondary analyses (see Table 3), there was an inverse age-adjusted association between increasing quartiles of HDL-C and decreasing risk of CVD death before age 90 \((P \text{ for trend} = 0.004)\). After additional adjustment for non-HDL cholesterol, comorbidities, and lifestyle factors, the association between baseline HDL-C and CVD mortality before age 90 was attenuated \((P \text{ for trend of median HDL-C levels across quartiles} = 0.07)\). The age-adjusted HR (95% CI) for the association between baseline HDL-C and CVD mortality was 0.78 (0.65 to 0.93). As in the main analysis, model fit was not improved when quadratic or cubic HDL-C was added to the models. In analyses examining the

### Table 1. Characteristics of 1351 Physicians’ Health Study Participants, by Quartile of Baseline High-Density Lipoprotein Cholesterol

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartiles of Baseline HDL-C (mg/dL)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;32.8 mg/dL, n = 324 (24.0%)</td>
<td>32.8 - but &lt;42.9 mg/dL, n = 365 (27.0%)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>81.8 (2.9)</td>
<td>81.8 (2.8)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>25.7 (3.3)</td>
<td>24.9 (3.0)</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL, mean (SD)</td>
<td>163.1 (37.8)</td>
<td>160.3 (36.5)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL, mean (SD)</td>
<td>26.2 (5.0)</td>
<td>38.0 (3.1)</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>225 (69.4)</td>
<td>213 (58.4)</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>58 (17.9)</td>
<td>31 (8.5)</td>
</tr>
<tr>
<td>Angina, No. (%)</td>
<td>82 (25.3)</td>
<td>75 (20.6)</td>
</tr>
<tr>
<td>Coronary heart disease, No. (%)</td>
<td>24 (7.4)</td>
<td>24 (6.6)</td>
</tr>
<tr>
<td>Congestive heart failure, No. (%)</td>
<td>15 (4.6)</td>
<td>25 (6.9)</td>
</tr>
<tr>
<td>Cancer, No. (%)</td>
<td>66 (20.4)</td>
<td>80 (21.9)</td>
</tr>
<tr>
<td>Stroke, No. (%)</td>
<td>27 (8.3)</td>
<td>15 (4.1)</td>
</tr>
<tr>
<td>Smoking status, No. (%)</td>
<td>104 (32.1)</td>
<td>83 (22.7)</td>
</tr>
<tr>
<td>Alcohol use, No. (%)</td>
<td>17 (5.3)</td>
<td>23 (6.3)</td>
</tr>
<tr>
<td>Rare/never</td>
<td>118 (36.4)</td>
<td>142 (38.9)</td>
</tr>
<tr>
<td>1 to 6 drinks per week</td>
<td>85 (26.2)</td>
<td>117 (32.1)</td>
</tr>
</tbody>
</table>

\(*\) HDL-C indicates high-density lipoprotein cholesterol; mg/dL, milligrams/deciliter; SD, standard deviation; BMI, body mass index; kg/m², kilograms/meters².
were each significantly associated with a higher risk for death before age 90, suggesting that the protective effect of HDL-C on CVD, the most common cause of death among older persons, is driving the overall effect of HDL-C on longevity.

There are some limitations to our study. Neither triglycerides nor low-density lipoprotein cholesterol levels were available; however, previous authors have argued that triglycerides and HDL-C are entities within the same physiological pathway, and including both in statistical models obscures the relation of 1 or the other with the outcome of interest.31 Non-HDL cholesterol served as a marker for other non-HDL lipid parameters in our analyses.32 Our study included a relatively homogeneous cohort of white males of higher-than-average socioeconomic status, with an average age of 82 years at baseline. Studies examining the relation between HDL-C and longevity in other prospective cohorts that include women, persons of other racial or ethnic backgrounds, and younger participants are warranted. Not all PHS participants provided blood samples at baseline, so there may be some selection bias inherent in limiting our study cohort to men with information on the exposure of interest (HDL-C). Ideally, we might have examined whether there was effect modification by baseline participant characteristics, such as CVD or diabetes mellitus; however, sample sizes were too limited to reliably examine subgroups until additional follow-up accrues. Finally, as in any observational study, there may be unmeasured confounders of the association between baseline HDL-C and longevity.

In a previous analysis among PHS I participants, examining modifiable risk factors for all-cause death before age 90, hypertension, diabetes mellitus, smoking, and lack of exercise were each significantly associated with a higher risk for death before age 90; however, lipid parameters were not included in that analysis.28 In our study using PHS I and PHS II participants with available lipid parameters, we included these prior predictors and added HDL-C. Because HDL-C was significantly associated with mortality before age 90, our findings suggest that HDL-C is an important predictor of longevity after adjustment for predictors previously associated with mortality before age 90 in this cohort. Our results are consistent with cross-sectional studies of lipid levels in exceptionally old cohorts, in which higher HDL-C levels are a marker of longevity.15–20 The few shorter-term prospective studies examining the relation between a baseline HDL-C measurement and survival to old age have similarly found that higher HDL-C levels are associated with survival to ≥age 80.21–23 In the VA Normative Aging Study, higher HDL-C levels were associated with lower risk of death before age 85 in a cohort, with an average of 65 years at baseline.22 Our findings expand on that study in that our findings demonstrate an association between HDL-C and survival into the 10th decade.

We evaluated whether HDL-C was related to CVD and non-CVD mortality and found that, in age-adjusted analyses, the highest HDL-C levels versus the lowest were associated with almost 50% reduced risk of CVD death before age 90 (see Table 3). After adjustment for non-HDL cholesterol, comorbidities, and lifestyle factors, this effect was attenuated slightly (P for trend = 0.06), likely owing to colinearity between some covariates (such as diabetes mellitus and alcohol consumption) and HDL-C. We found no significant association between baseline HDL-C and non-CVD causes of mortality before age 90, suggesting that the protective effect of HDL-C on CVD, the most common cause of death among older persons, is driving the overall effect of HDL-C on longevity.

In this cohort of PHS I and PHS II participants, men who survived to age 90 had significantly higher HDL-C levels at baseline than those who died before age 90. We found a significant age-adjusted association between increasing HDL-C levels and decreasing risk for all-cause mortality before age 90. After adjustment for additional potential confounders, the association between the highest baseline HDL-C levels versus the lowest levels and lower risk for all-cause mortality before age 90 remained robust (HR, 0.72; CI, 0.55 to 0.94).

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### Table 2. Characteristics of 1351 Physicians’ Health Study Participants, by Survival to Age ≥90 y

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors n=850</th>
<th>Nonsurvivors n=501</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)*</td>
<td>82.4 (3.1)</td>
<td>81.1 (2.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>24.7 (3.2)</td>
<td>24.5 (3.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL, mean (SD)*</td>
<td>155.2 (36.9)</td>
<td>155.9 (37.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL, mean (SD)*</td>
<td>45.6 (16.3)</td>
<td>43.5 (16.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>503 (59.2)</td>
<td>317 (63.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>65 (7.7)</td>
<td>59 (11.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Angina, No. (%)</td>
<td>143 (16.8)</td>
<td>126 (25.2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Coronary heart disease, No. (%)</td>
<td>100 (11.8)</td>
<td>103 (20.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Congestive heart failure, No. (%)</td>
<td>33 (3.9)</td>
<td>37 (7.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Cancer, No. (%)</td>
<td>167 (19.7)</td>
<td>126 (25.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke, No. (%)</td>
<td>30 (3.5)</td>
<td>43 (8.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Smoking status, No. (%)</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Never</td>
<td>404 (47.5)</td>
<td>201 (40.1)</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>428 (50.4)</td>
<td>288 (57.5)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>18 (2.1)</td>
<td>12 (2.4)</td>
<td></td>
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<tr>
<td>Alcohol use, No. (%)</td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Rare/never</td>
<td>173 (20.4)</td>
<td>121 (24.2)</td>
<td></td>
</tr>
<tr>
<td>1 to 3 drinks per month</td>
<td>46 (5.4)</td>
<td>28 (5.6)</td>
<td></td>
</tr>
<tr>
<td>1 to 6 drinks per week</td>
<td>310 (36.5)</td>
<td>162 (32.3)</td>
<td></td>
</tr>
<tr>
<td>1+ drinks per day</td>
<td>321 (37.8)</td>
<td>190 (37.9)</td>
<td></td>
</tr>
<tr>
<td>Exercise≥once per week, No. (%)</td>
<td>513 (60.4)</td>
<td>267 (53.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*HDL-C indicates high-density lipoprotein cholesterol; mg/dL, milligrams/deciliter; SD, standard deviation; BMI, body mass index; km/m², kilograms/meters².

relation between quartiles of baseline HDL-C and non-CVD death before age 90, there was no association found.

### Discussion

In this cohort of PHS I and PHS II participants, men who survived to age 90 had significantly higher HDL-C levels at baseline than those who died before age 90. We found a significant age-adjusted association between increasing HDL-C levels and decreasing risk for all-cause mortality before age 90. After adjustment for additional potential confounders, the association between the highest baseline HDL-C levels versus the lowest levels and lower risk for all-cause mortality before age 90 remained robust (HR, 0.72; CI, 0.55 to 0.94).
years) with extended follow-up (12.5 years). In this group of 1351 men, we found that baseline HDL-C was significantly associated with a lower risk of death before the exceptional age of 90. Secondary analyses, examining the relation between HDL-C and CVD versus non-CVD death, confirmed that the HDL-C and longevity association was likely owing to the cardioprotective effect of higher HDL-C levels. Our results support identifying low HDL-C levels as an important predictor of CVD death in older persons and suggest that considering modification of HDL-C levels may be warranted in older persons who could tolerate lifestyle or medication strategies targeted to HDL-C.

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References


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