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Low HDL₃ reduces the odds of men surviving to age 85 during 53-year follow-up

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Abstract

Objectives—To identify high-density lipoprotein (HDL) subfractions associated with longevity in men.

Design—Fifty-three-year prospective follow-up of Gofman's Livermore Cohort between 1954 and 2008.

Setting—Lawrence Livermore National Laboratory.

Participants—One thousand one hundred forty-four men who consented to the study, had analytic ultracentrifuge measurements of lipoprotein subfractions at baseline, and were old enough at baseline to have survived to age 85 during follow-up.

Measurements—Survival was determined according to participant contact, Social Security Death Index, and National Death Index.

Results—Three hundred ninety men survived to 85 years old (34.1%). Survivors were less likely than nonsurvivors to be in the lowest HDL₃ (% (standard error) 18.5% (2.0%) vs 27.3% (1.6%), $P < .001$) and HDL₂ (22.1% (2.1%) vs 27.7% (1.6%), $P = 0.04$) quartiles. Logistic regression analyses showed that the lowest HDL₃ quartile significantly predicted shorter longevity ($P = 0.002$), whereas the linear increases per mg/dL of HDL₃ did not ($P = 0.38$), suggesting a risk threshold proximal to the 25th percentile. Men who were above the 25th HDL₃ percentile had 70% greater odds of surviving until age 85 than those below this level, which persisted when adjusted for HDL₂, very low-density lipoprotein (LDL), and standard risk factors. Proportional hazard analyses of survival before age 85 showed that being in the lowest HDL₃ quartile increased age-adjusted cancer risk by 39% ($P = 0.05$) and noncancer risk by 23% ($P = 0.04$) when adjusted for other risk factors. Survivors also smoked less (mean $\pm$ SD 0.31 ± 0.48 vs 0.57 ± 0.56 packs/d, $P < .001$), had lower systolic (118.36 ± 11.08 vs 122.81 ± 13.55 mmHg, $P < .001$) and diastolic (70.61 ± 8.59 vs 73.14 ± 9.22 mmHg, $P < .001$) blood pressures and lower LDL mass (359.55 ± 80.42 vs 374.37 ± 86.10 mg/dL, $P = 0.009$) and total cholesterol concentrations (229.51 ± 43.21 vs 235.89 ± 45.40 mg/dL, $P = 0.04$) than nonsurvivors.

Conclusion—Low HDL₃ reduces the odds of extended survival in men, independent of HDL₂, other lipoproteins, and standard risk factors.

Fewer than 38% of all men will survive to their 85th birthday [1]. High plasma concentrations of high-density lipoprotein cholesterol (HDL-C) have been associated with extended longevity [2–5]. Recently, the Veteran's Affairs Normative Aging Study reported that plasma HDL-C concentrations were significantly higher in men who survived through age 85 during an average of 16.3 years of followup [6]. In part, this may be because of the well-documented inverse relationship between HDL-C concentrations and coronary heart disease (CHD) [7–9]. HDL-C is but one component of a heterogeneous class of lipoprotein particles that differ in density, size, electrophoretic mobility, and apolipoprotein composition

[10]. HDLs have been ascribed anti-inflammatory properties and anti-oxidant activities [11] and endothelial nitric oxide–promoting and anti-thrombotic effects [12] in addition to their role in reverse cholesterol transport [13]. These attributes may play a role in linking low HDL-C levels to certain health conditions (e.g., cancer, non-Hodgkin’s lymphoma, dementia [14]). HDLs may be separated into two major subfractions: larger, more-buoyant HDL₂ particles (1.063–1.125 g/mL) and smaller, less-buoyant HDL₃ particles (1.125–1.210 g/mL) [15]. Recently, using a direct measurement of total mass, it was reported that the lowest quartiles of HDL₂ and HDL₃ were associated prospectively with greater risk of CHD [16,17],

This article examines whether the mass concentrations of HDL₂, HDL₃, and other lipoproteins measured directly using analytic ultracentrifugation predict the odds of men surviving until the age of 85 in John Gofman’s prospective study of employees at Lawrence Livermore National Laboratory (formerly Livermore Radiation Laboratory) [15]. The analyses are unique in that they involve the oldest existing cohort in which HDL₂ and HDL₃ were measured directly and participants were followed prospectively [16,17]. In addition, serum concentrations of low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), and small and large very low-density lipoprotein (VLDL) mass were measured directly rather than their usual approximation from estimated LDL-C and VLDL-C [16,17]. The purpose is to confirm prior publications on the association between blood pressure, smoking, and HDL-C with longevity and to provide specificity regarding the dose-response relationship between the individual HDLs and other lipoprotein subclasses and longevity.

Methods

The cohort consisted of male employees of the Livermore Radiation Laboratory who participated in the original follow-up study by Gofman and colleagues [15]. All of the men were free of prior ischemic heart disease at baseline as determined according to self-report and physical examination. Qualification presumably corresponded to the criteria adopted by the Cooperative Study [18], i.e., disqualified for more than trace amounts of urine protein or sugar; diabetes mellitus; nephritis (except past history of pyelonephritis, nephrolithiasis, or loss of kidney); treatment with adrenocorticotrophic hormone, cortisone, or related hormones; history of rheumatic heart disease; known congenital heart disease; syphilis; or Buerger’s disease.

Height, weight, and blood pressure measurements and casual (potentially nonfasting) blood draws were obtained during employees’ annual physical examination. Cigarette consumption was determined according to self-report. Serum total cholesterol was assayed using a modification of the Abell method [19]. Corrected lipoprotein subfraction concentrations were obtained using analytic ultracentrifugation [15]. The committee for the protection of human subjects, University of California at Berkeley, approved follow-up of this cohort.

Vital status was determined according to participant contact, the National Death Index [20], and the Social Security Administration Death Index (<http://www.rootweb.com>). Cause of death through 2008 was determined from the National Death Index between 1979 and 2008 and according to physician review of death certificates and hospital records before 1979 [16]. Statistical analyses were performed using JMP version 5.1 (SAS Institute, Inc., Cary, NC). Stochastic imputation was used for missing covariates. Including the missing values did not result in noticeably different coefficients for lipoprotein mass concentrations from deleting the missing values. Logistic regression analyses were used to test whether HDL₂ and HDL₃ predicted total mortality through age 85 as of December 31, 2008. The analyses were repeated excluding various endpoints to assess whether lipoproteins affected the risks

of specific diseases in extending longevity. Survival to age 85 was chosen to correspond to another recent report [6] rather than being results driven.

RESULTS

One thousand one hundred forty-four men out of the original cohort of 1,905 were old enough at baseline to have potentially survived to their 85th birthday during the 53.2 years of follow-up. These included 390 men who did survive to 85 years old (34.1%). Those who died before reaching 85 died mostly from circulatory diseases ($n = 325$, 43.1% of all deaths, including 185 coronary heart disease deaths), neoplasm ($n = 193$, 25.6%), respiratory conditions ($n = 71$, 9.4%), accidents, injury or suicide ($n = 46$, 6.1%), and other conditions or unknown causes ($n = 119$, 15.8%, including 24 foreign or lost death certificates).

Table 1 shows that those who survived were slightly younger, smoked less, and had lower blood pressure and lower serum LDL mass and total cholesterol concentration at baseline. Although average serum HDL₃ mass and HDL₂ mass concentrations were not significantly higher in survivors than nonsurvivors (Table 2), there were fewer survivors in the lowest HDL₃ quartile (survivors vs nonsurvivors % ($\pm$ standard error): $18.5\% \pm 2.0\%$ vs $27.3\% \pm 1.6\%$, $P < .001$) and HDL₂ quartile ($22.1\% \pm 2.1\%$ vs $27.7\% \pm 1.6\%$), $P = 0.04$) than of nonsurvivors. Survival status did not significantly affect the proportion of men in the highest quartiles of small VLDL ($27.4\% \pm 2.3\%$ vs $32.8\% \pm 1.7\%$, $P = 0.07$), large VLDL ($29.2\% \pm 2.3\%$ vs $30.4\% \pm 1.7\%$, $P = 0.62$), or total VLDL ($28.0\% \pm 2.3\%$ vs $31.0\% \pm 1.7\%$, $P = 0.28$). Survivors were less likely to fall within the highest LDL mass quartile than nonsurvivors ($25.4\% \pm 2.2\%$ vs $34.9\% \pm 1.7\%$, $P = 0.001$), whereas the proportion of men within the highest total cholesterol quartile was similar in survivors and nonsurvivors ($29.5\% \pm 2.3\%$ vs $33.2\% \pm 1.7\%$, $P = 0.21$). In the preceding examples, the quartiles for survivors and nonsurvivors combined did not equal 25% because they were based on the complete sample of 1,905 men, which included 761 men who were too young at baseline to have reached the age of 85 during follow-up.

Figure 1 displays the relationship between HDL₃ and longevity according to quartiles of HDL₃. The odds for surviving to age 85 increased from the first to the second quartile of HDL₃, with no evidence of additional improvement thereafter. Age-adjusted logistic regression analysis of surviving until 85 (not displayed) showed that, when the linear effect of HDL₃ mass (per mg/dL) and the lowest quartile of HDL₃ were included simultaneously in the same analyses, the coefficient for the lowest HDL₃ quartile was significantly different from zero ($P = 0.002$), whereas the linear effect was not ($P = 0.38$). These analyses showed that there was not a linear increase in the log odds of longevity with increasing concentrations of HDL₃ and suggest instead a threshold in risk specifically associated with low HDL₃. Figure 1 also shows that the age-adjusted greater odds of longevity for the second through fourth quartiles of HDL₃ remained significant when adjusted for HDL₂ mass, VLDL mass, and the set of standard risk factors. Other analyses (not displayed) showed that the survival advantage of the second through fourth HDL₃ quartiles persisted when adjusted for the lowest HDL₂ quartile ($P = 0.002$ when adjusted) or when adjusted for the highest quartiles of small ($P < 0.001$), large ($P < 0.001$), and total VLDL mass ($P < 0.001$).

Figure 2 (top and middle panels), which shows the relationships between blood pressure and longevity according to hypertension status, shows that the age-adjusted odds of extended longevity decreased progressively with higher blood pressure. When linear effects per mmHg of blood pressure and hypertensive status were included simultaneously in a logistic regression analysis (not shown), the linear declines in the log odds for extended survival were significant (systolic, $P < 0.001$; diastolic, $P = 0.006$), whereas hypertension status was

not (systolic, $P = 0.44$; diastolic, $P = 0.18$), suggesting that the log-odds of surviving to age 85 decreases linearly with increasing blood pressure. Figure 2 also shows that the relationships persist when adjusted for other standard risk factors (BMI, cigarette use, and total cholesterol). Figure 2 (bottom panel) shows that the odds of extended longevity were more than 50% lower for smoking less than one pack per day than for not smoking. When included simultaneously in the logistic regression analyses (not displayed), cigarette packs smoked per day was significant ($P = 0.04$), and smoker status was not significant ($P = 0.08$), suggesting a somewhat nonlinear relationship between cigarettes smoked per day and log odds of extended longevity, with a somewhat greater decrease in the odds of longevity due to smoking at all and further decreases with the packs of cigarettes smoked per day.

The simultaneous effects of multiple risk factors on the odds of living to age 85 are presented in Table 3. The strongest effect was attributed to cigarette use. Higher systolic blood pressure resulted in lower odds of long-term survival. The lowest HDL₃ quartile had 38% lower odds of extended longevity when adjusted for the standard risk factors (age, smoking, blood pressure, and cholesterol) and when adjusted for standard risk factors plus other lipoprotein mass concentrations.

The modest sample size limited the ability to identify the specific disease risks associated with the lowest HDL₃ quartile. Figure 1 shows that men with HDL₃ greater than its 25th percentile still had greater odds of surviving to age 85 when fatal CHD ($P = 0.002$) or all diseases of the circulatory system ($P = 0.005$) were eliminated from the analyses. In addition, improved survival to age 85 continued to be significant with the elimination of all fatal infectious diseases ($P < 0.001$); neoplasms ($P = 0.003$); endocrine, nutritional, and metabolic diseases ($P < 0.001$); diseases of the blood and blood-forming organs ($P < 0.001$); mental disorders ($P < 0.001$); diseases of the nervous system ($P < 0.001$), respiratory system ($P = 0.002$), digestive system ($P < 0.001$), and genitourinary system ($P = 0.001$); or injuries and poisoning ($P < 0.001$, analyses not displayed). Proportional hazards analyses of survival through age 85 showed that being in the lowest HDL₃ quartile had a 41% greater age-adjusted cancer risk ($P = 0.04$) that persisted when adjusted for standard risk factors (39% greater risk, $P = 0.05$, when adjusted for smoking, blood pressure, BMI, and cholesterol). There was also a 25% greater age-adjusted risk for noncancer mortality ($P = 0.02$), which was still statistically significant after standard risk factor adjustment (23% greater increase, $P = 0.04$). The lowest HDL₃ quartile was also associated with a nonsignificant 42% greater risk for respiratory disease ($P = 0.19$), 21% greater risk for CHD ($P = 0.25$), and 21% greater risk for all circulatory diseases ($P = 0.14$, analyses not displayed).

DISCUSSION

These analyses suggest that serum HDL₃ mass concentration substantially affects the odds of men surviving to their 85th birthday. Specifically, the odds of surviving to age 85 were 70% greater for the second through fourth quartiles of HDL₃ (or conversely, 38% lower for the lowest quartile). This effect is more substantial than the 28% lower risk of dying before 85 for the 50-mg/dL or greater vs the less than 40-mg/dL difference in HDL-C that the Veterans Affairs (VA) Normative Aging Study reported [6]. The current results suggest that having a HDL₃ concentration greater than the 25th percentile could increase the odds of survival to age 85 by reducing the risk of cancer mortality by 39% and noncancer mortality by 23%. These associations may reflect the pleiotropic effects of HDL in mitigating disease risk extending well beyond its anti-atherogenic function [11–14].

Increasing levels of HDL-C are purported to reduce CHD risk linearly [7]. The Framingham Heart Study, the Lipid Research Clinics Primary Prevention Trial and Prevalence Mortality Follow-up Study, and the Multiple Risk Factor Intervention Trial reveal that each 1-mg/dL

increment in HDL-C reduces CHD risk by 2% in men and 3% in women [21]. Figure 1 shows that the greater odds of living until 85 were attributable entirely to greater odds of survival in moving from the first to the second quartiles of HDL₃ mass concentrations. The linearity hypothesis was strongly rejected ($P = 0.002$) in favor of a threshold increase in risk below the HDL₃ 25th percentile. This finding is consistent with the Framingham data that showed that high HDL-C levels were not overrepresented in healthy octogenarians, whereas low HDL levels were exceedingly uncommon [22].

HDL₃ is defined according to analytical ultracentrifugation as the entire F_{1,20} 0–3.5 flotation interval [15]. This interval contains a heterogeneous mixture of HDL particles of differing sizes and protein compositions, which may also differ in their association with disease risk. Flotation intervals between 0 and 1.5 appear to contain the HDL_{3c} and HDL_{3b} subclasses, whereas those between 2.0 and 3.5 include the majority of HDL_{3a} [23]. HDL_{3b} and HDL_{3a} have different associations with sex [24], puberty [24], type 2 diabetes mellitus [25], adiposity [24], alcohol use [24], physical activity [26], resting heart rate [25], fasting insulin and glucose concentrations [25], and other lipoproteins [23], suggesting divergent metabolism and health implications. HDL₃ includes particles that contain apolipoproteins (apo) A-I and A-II that are concentrated in HDL_{3b} and HDL_{3a} and particles that contain apo A-I but no A-II concentrated within HDL_{3c} and HDL_{3a} [27,28]. It remains to be determined which HDL₃ component is responsible for enhanced longevity or whether low HDL₃ is associated with other factors predisposing men to earlier mortality. Heterogeneity within HDL₃ may account for the contrasting HDL differences reported previously [5]. That study compared the lipoprotein profiles of Ashkenazi Jews of exceptional longevity to age-matched Ashkenazi controls and participants from the Framingham Offspring Study and found that longevity was associated with significantly larger-diameter HDL and significantly lower apo A-I, without any difference in HDL-C or VLDL-C levels. Although a shift to larger-diameter HDL could arise as a relative increase in larger HDL (HDL₂), this should produce an increase in HDL-C and apo A-I and a decrease in VLDL [27], which was not observed. Alternatively, the shift toward larger HDL could involve a redistribution of mass within HDL₃, in which the predominant HDL peaks and the HDL mass shifts from the HDL_{3b} subclass to the HDL_{3a} subclass [23]. Such a shift would be expected to correspond to an increase in HDL₃ mass concentrations and a shift toward larger-diameter LDL particles, consistent with that report [23].

The results of the current study, based on analytical ultracentrifuge measurements of lipoprotein mass concentration, may not necessarily apply to the lowest HDL-C or HDL₃-C quartile because of their lack of specificity (i.e., HDL-C and HDL₃-C concentrations exhibit broadly overlapping associations with the analytical ultracentrifuge measurements of HDL₂ mass and HDL₃ mass) [23]. Unpublished analyses of data from 337 middle-aged men showed that plasma concentrations of HDL₃ mass were correlated only moderately with HDL-C (correlation coefficient (r) = 0.53) and HDL₃-C (r = 0.56) and that 44% and 45% of men in the lowest quartile of HDL₃ mass were not in the lowest quartile of HDL-C or HDL₃-C, respectively. These results also do not negate the possible role of high HDL₂ in promoting longevity [29].

LDL mass concentrations only weakly affected survival until 85, in contrast to the strong association reported previously between LDL and total and premature CHD [16,17]. In the current study, the significant inverse relationship between LDL mass and the odds of surviving until 85 became nonsignificant when adjusted for other risk factors, notably cigarettes/day smoked (adjusted $P = 0.15$), systolic blood pressure (adjusted $P = 0.06$), and total cholesterol (adjusted $P = 0.14$), the last having strong colinearity with LDL mass concentrations (correlated $r = 0.75$ at baseline). The VA Normative Aging Study also reported a lack of an association between LDL-C and survival through age [85,6] and others

have reported that total cholesterol and LDL-C were not different between octogenarians with and without CHD [2,22]. The importance of LDL as a risk factor diminishes with age [7]. For example, there was no significant association between lipid levels and incidence of myocardial infarctions in adults aged 65 and older as reported by the Cardiovascular Health Study [30]. In the current study, 72% of CVD deaths in the men who did not survive until age 85 occurred between the ages of 65 and 85.

It was also observed that smoking and hypertension significantly reduced the odds of surviving until 85, which is consistent with previous reports [31]. The lack of a significant effect of BMI on surviving until 85 in age-adjusted (Table 2) and fully adjusted (Table 3) analyses is consistent with the VA Normative Aging Study results [6]. An important strength of this study is its prospective design. Centenarians are reported to have HDL-C levels that are 20% lower than those of individuals 35 years younger [32], while at the same time lacking very low HDL [33]. This has been interpreted as the consequence of two effects [34]: selection against individuals with low HDL and declining HDL-C as an element of aging. In older individuals, the aging effect can be substantial (i.e., longitudinal observations in the Rancho Bernardo Study suggest that HDL-C levels decline 1% annually in individuals aged 50 and older) [35]. Half of the participants in the current analyses were younger than 39 when they had their HDL measured, and 90% were younger than 52. Moreover, HDL₂ and HDL₃ were unrelated to baseline age, and little mortality selection occurs before 51 years of age. Thus, it is likely that the young age of this cohort ensured against age-related declines in HDL affecting the associations between HDL and mortality reported here.

Currently, low HDL₃ concentrations are not targeted for intervention. Niacin effectively increases HDL-C, but this does not appear to involve HDL₃. Specifically, niacin increases HDL_{2b} and reduces HDL_{3c} and HDL_{3b} without significantly affecting HDL_{2a} or HDL_{3a} [36]. Fenofibrate is reported to increase HDL₃-C and apo A-II while decreasing HDL₂-C [37], which may not be the change desired. Lifestyle approaches to raising HDL, such as physical activity and weight loss, primarily raise HDL₂ mass concentrations and not HDL₃ mass concentrations [26]. It has been reported that higher HDL₃ mass concentrations are associated with greater alcohol intake and lower carbohydrate intake [38] and subsequently shown that, in moderate drinkers randomized to an abstinence group or a control drinking group (n = 12), HDL-C and HDL₃-mass decreased significantly in abstainers but not in drinkers and that resumption of drinking increased HDL-C levels and HDL₃ mass without affecting HDL₂ mass [39]. Another study confirmed that replacing dietary carbohydrates with fat significantly increased HDL₃ mass concentrations [40]. In conclusion, components within HDL₃, or factors associated with the metabolic state characterized by HDL₃ mass greater than the 25th percentile, may promote longevity in men.

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Glossary

HDL	high-density lipoprotein
LDL	low-density lipoprotein
IDL	intermediate-density lipoprotein

VLDL	very-low-density lipoprotein
CHD	coronary heart disease

References

1. Arias E. United States life tables, 2006. *Natl Vital Stat Rep.* 2010; 58:1–40.
2. Campbell AJ, Busby WJ, Roberson MC. Over 80 years and no evidence of coronary heart disease: Characteristics of a survivor group. *J Am Geriatr Soc.* 1993; 41:1333–1338. [PubMed: 8227916]
3. Nikkilä M, Pitkälä T, Koivula T, et al. Elevated high density-lipoprotein cholesterol and normal triglycerides as markers of longevity. *Klin Wochenschr.* 1991; 69:780–785. [PubMed: 1762383]
4. Nikkilä M, Heikkinen J. High-density lipoprotein cholesterol and longevity. *Age Ageing.* 1990; 19:119–124. [PubMed: 2337007]
5. Barzilai N, Atzmon G, Schechter C, et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. *JAMA.* 2003; 290:2030–2040. [PubMed: 14559957]
6. Rahilly-Tierney CR, Spiro A III, Vokonas P, et al. Relation between high-density lipoprotein cholesterol and survival to age 85 years in men (from the VA Normative Aging Study). *Am J Cardiol.* 2011; 107:1173–1177. [PubMed: 21296318]
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA.* 2001; 285:2486–2497. [PubMed: 11368702]
8. Wilson PW, Garrison RJ, Castelli WP, et al. Prevalence of coronary heart disease in the Framingham Offspring Study: Role of lipoprotein cholesterol. *Am J Cardiol.* 1980; 46:649–654. [PubMed: 7416024]
9. Assmann G, Schulte H, von Eckardstein A, et al. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk: The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis.* 1996; 124(suppl 6):S11–S20. [PubMed: 8831911]
10. Nichols AV, Krauss RM, Musliner TA. Nondenaturing polyacrylamide gradient gel electrophoresis. *Methods Enzymol.* 1986; 128:417–431. [PubMed: 3724517]
11. Barter PJ, Nicholls S, Rye KA, et al. Antiinflammatory properties of HDL. *Circ Res.* 2004; 95:764–772. [PubMed: 15486323]
12. Mineo C, Deguchi H, Griffin JH, et al. Endothelial and antithrombotic actions of HDL. *Circ Res.* 2006; 98:1352–1364. [PubMed: 16763172]
13. Tall AR. An overview of reverse cholesterol transport. *Eur Heart J.* 1998; 19(suppl A):A31–A35. [PubMed: 9519340]
14. McGrowder D, Riley C, Morrison EY, et al. The role of high-density lipoproteins in reducing the risk of vascular diseases, neurodegenerative disorders, and cancer. *Cholesterol.* 2011; 2011:496925. [PubMed: 21490772]
15. Gofman JW, Young W, Tandy R. Ischemic heart disease, atherosclerosis, and longevity. *Circulation.* 1966; 34:679–697. [PubMed: 5921763]
16. Williams PT, Feldman DE. Prospective study of coronary heart disease vs HDL2, HDL3, and other lipoproteins in Gofman's Livermore Cohort. *Atherosclerosis.* 2011; 214:196–202. [PubMed: 21109246]
17. Williams PT. Fifty-three year follow-up of coronary heart disease vs HDL2 and other lipoproteins in Gofman's Livermore cohort. *J Lipid Res.* 2011; 53 Epub ahead of print.
18. Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis: Report of a cooperative study of lipoproteins and atherosclerosis. *Circulation.* 1956; 14:691–742. [PubMed: 13374848]
19. Colman DM, McPhee AF. An improved method for determination of total serum cholesterol. *Am J Clin Pathol.* 1956; 26:181–186. [PubMed: 13292411]

20. National Death Index User's Manual. Hyattsville, MD: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Health Statistics; 1990.
21. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*. 1989; 79:8–15. [PubMed: 2642759]
22. Schaefer EJ, Moussa PB, Wilson PW. Plasma lipoproteins in healthy octogenarians: Lack of reduced high density lipoprotein cholesterol levels: Results from the Framingham Heart Study. *Metabolism*. 1989; 38:293–296. [PubMed: 2725273]
23. Williams PT, Krauss RM, Vranizan KM, et al. Associations of lipoproteins and apolipoproteins with gradient gel electrophoresis estimates of high density lipoprotein subfractions in men and women. *Arterioscler Thromb*. 1992; 12:332–340. [PubMed: 1547192]
24. Williams PT, Vranizan KM, Austin MA, et al. Associations of age, adiposity, alcohol intake, menstrual status, and estrogen therapy with high-density lipoprotein subclasses. *Arterioscler Thromb*. 1993; 13:1654–1661. [PubMed: 8218107]
25. Williams PT, Haskell WL, Vranizan KM, et al. The associations of highdensity lipoprotein subclasses with insulin and glucose levels, physical activity, resting heart rate, and regional adiposity in men with coronary artery disease: The Stanford Coronary Risk Intervention Project baseline survey. *Metabolism*. 1995; 44:106–614. [PubMed: 7854154]
26. Williams PT, Krauss RM, Vranizan KM, et al. Effects of weight-loss by exercise and by diet on apolipoproteins A-I and A-II and the particle-size distribution of high-density lipoproteins in men. *Metabolism*. 1992; 41:441–449. [PubMed: 1556953]
27. Cheung MC, Albers JJ. Distribution of cholesterol and apolipoprotein A-I and A-II in human high density lipoprotein subfractions separated by CsCl equilibrium gradient centrifugation: Evidence for HDL subpopulations with differing A-I/A-II molar ratios. *J Lipid Res*. 1979; 20:200–207. [PubMed: 220358]
28. Cheung MC, Albers JJ. Characterization of lipoprotein particles isolated by immunoaffinity chromatography. Particles containing A-I and A-II and particles containing A-I but no A-II. *J Biol Chem*. 1984; 259:12201–12209. [PubMed: 6434538]
29. Ettinger WH Jr, Verdery RB, Wahl PW, et al. High density lipoprotein cholesterol subfractions in older people. *J Gerontol*. 1994; 49:M116–M122. [PubMed: 8169333]
30. Psaty BM, Furberg CD, Kuller LH, et al. Traditional risk factors and subclinical disease measures as predictors of first myocardial infarction in older adults: The Cardiovascular Health Study. *Arch Intern Med*. 1999; 159:1339–1347. [PubMed: 10386510]
31. Yates LB, Djoussé L, Kurth T, et al. Exceptional longevity in men: Modifiable factors associated with survival and function to age 90 years. *Arch Intern Med*. 2008; 168:284–290. [PubMed: 18268169]
32. Baggio G, Donazzan S, Monti D, et al. Lipoprotein (a) and lipoprotein profile in healthy centenarians: A reappraisal of vascular risk factors. *FASEB J*. 1998; 12:433–437. [PubMed: 9535215]
33. Barter P. HDL: A recipe for longevity. *Atherosclerosis*. 2004; 5:25–31. [PubMed: 15121032]
34. Walter M. Interrelationships among HDL metabolism, aging, and atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2009; 29:1244–1250. [PubMed: 19667114]
35. Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and HDL cholesterol decrease with age in older men and women The Rancho Bernardo Study 1984–1994. *Circulation*. 1997; 96:37–43. [PubMed: 9236414]
36. Johansson J, Carlson LA. The effects of nicotinic acid treatment on high density lipoprotein particle size subclass levels in hyperlipidaemic subjects. *Atherosclerosis*. 1990; 83:207–216. [PubMed: 2242098]
37. Hiukka A, Leinonen E, Jauhiainen M, et al. Long-term effects of fenofibrate on VLDL and HDL subspecies in participants with type 2 diabetes mellitus. *Diabetologia*. 2007; 50:2067–2075. [PubMed: 17653691]
38. Williams PT, Krauss RM, Wood PD, et al. Associations of diet and alcohol intake with high-density lipoprotein subclasses. *Metabolism*. 1985; 34:524–530. [PubMed: 3999973]

39. Haskell WL, Camargo C Jr, Williams PT, et al. The effect of cessation and resumption of moderate alcohol intake on serum high-density-lipoprotein subfractions. A controlled study. *N Engl J Med.* 1984; 310:805–810. [PubMed: 6366553]
40. Krauss RM, Dreon DM. Low-density-lipoprotein subclasses and response to a low-fat diet in healthy men. *Am J Clin Nutr.* 1995; 62:478S–487S. [PubMed: 7625363]

Figure 1.

Age-adjusted logistic regression analyses of the odds of men surviving to their 85th birthday according to quartile of high-density lipoprotein (HDL)₃ mass concentrations: 1st quartile < 190 mg/dL, 2nd quartile 190 to 217 mg/dL, 3rd quartile 218 to 245 mg/dL, 4th quartile 246 mg/dL. Top panel: with and without adjustment for standard risk factors (cigarettes smoked, body mass index, and blood pressure). Middle panel: adjusted for HDL₂ and very low-density lipoprotein (VLDL) mass concentrations in addition to age. Bottom panel: excluding coronary heart disease (CHD) and circulatory disease deaths from nonsurvivors. There were 390 survivors in 1,144 men. * P=0.05, † P=0.01, ‡ P=0.001.

Figure 2.

Age-adjusted logistic regression analyses of the odds of men surviving to their 85th birthday according to systolic and diastolic blood pressure (top and middle panels), and cigarettes smoked per day (bottom panel). Normal blood pressure: systolic < 120 mmHg, diastolic < 80 mmHg; low prehypertensive: systolic 120–129 mmHg, diastolic 80–84 mmHg; high prehypertensive: systolic 130–139 mmHg, diastolic 85–89 mmHg; hypertensive: systolic 140 mmHg, diastolic 90 mmHg. * $P=0.05$, † $P=0.01$, ‡ $P=0.001$.

Table 1

Characteristics of men who survived or died prior to age 85.

	Survivors	Non-survivors	Significance of Difference (P)
Sample	390	754	
Baseline Age (years)	39.42±6.63	41.25±7.22	0.0001
BMI (kg/m ²)	24.27±2.95	24.55±3.28	0.16
Cigarette (packs/day)	0.31±0.48	0.57±0.56	10 ⁻¹³
Systolic blood pressure (mm Hg)	118.36±11.08	122.81±13.55	10 ⁻⁷
Diastolic blood pressure (mm Hg)	70.61±8.59	73.14±9.22	10 ⁻⁵
Cholesterol (mg/dL)	229.51±43.21	235.89±45.40	0.04
HDL2-mass (mg/dL)	38.61±27.36	36.19±28.79	0.15
HDL3-mass (mg/dL)	224.78±39.43	221.05±48.19	0.12
LDL-mass (mg/dL)	359.55±80.42	374.37±86.10	0.009
IDL-mass (mg/dL)	52.25±22.51	54.86±24.10	0.14
Small VLDL (mg/dL)	93.82±54.48	100.97±61.62	0.07
Large VLDL (mg/dL)	55.61±79.88	59.22±73.25	0.47

Two-sample t-test. Mean ±SD. BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; IDL: intermediate density lipoprotein; VLDL: very low density lipoprotein.

Table 2

Age-adjusted odds of surviving to age 85 for the individual risk factors.

	Estimate	95% Confidence	Significance of odds
BMI (kg/m ²)	0.978	(0.940, 1.018)	0.28
Cigarettes (packs/day)	0.376	(0.284, 0.497)	<10 ⁻¹¹
Systolic blood pressure (10 mm Hg)	0.763	(0.682, 0.853)	<10 ⁻⁵
Diastolic blood pressure (10 mm Hg)	0.764	(0.662, 0.882)	0.0002
Cholesterol (10 mg/dL)	0.976	(0.949, 1.004)	0.10
HDL2-mass (10 mg/dL)	1.038	(0.995, 1.084)	0.09
HDL3-mass (10 mg/dL)	1.023	(0.995, 1.051)	0.10
LDL-mass (10 mg/dL)	0.983	(0.969, 0.998)	0.02
IDL-mass (10 mg/dL)	0.965	(0.915, 1.018)	0.19
Small VLDL (10 mg/dL)	0.984	(0.962, 1.006)	0.14
Large VLDL (10 mg/dL)	0.996	(0.979, 1.013)	0.61

There were 1144 men, of whom 390 survived to age 85. Logistic regression analyses adjusted for baseline age (age and age²). BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; IDL: intermediate density lipoprotein; VLDL: very low density lipoprotein.

Table 3

Logistic regression analyses for the odds of surviving until age 85 when multiple risk factors are included in the model.

	Standard risk factors	Standard risk factors & lipoproteins
Cigarettes (packs/day)	0.411 (0.313, 0.540) P<10 ⁻⁹	0.413 (0.313, 0.546) P<10 ⁻⁹
BMI (kg/m ²)	0.988 (0.948, 1.030) P=0.58	0.989 (0.947, 1.033) P=0.62
Systolic blood pressure (10 mm Hg)	0.848 (0.737, 0.975) P=0.02	0.847 (0.736, 0.976) P=0.02
Diastolic blood pressure (10 mm Hg)	0.870 (0.723, 1.046) P=0.14	0.870 (0.722, 1.047) P=0.14
Cholesterol (10 mg/dL)	0.981 (0.952, 1.011) P=0.22	0.981 (0.920, 1.047) P=0.57
Lowest HDL3 quartile	0.617 (0.449, 0.848) P=0.003	0.622 (0.447, 0.867) P=0.005
HDL2 (10 mg/dL)		1.007 (0.954, 1.063) P=0.80
LDL (10 mg/dL)		0.999 (0.968, 1.032) P=0.97
IDL (10 mg/dL)		1.004 (0.918, 1.099) P=0.93
Small VLDL (10 mg/dL)		0.994 (0.948, 1.043) P=0.81
Large VLDL (10 mg/dL)		1.005 (0.976, 1.036) P=0.72

There were 1144 men, of whom 390 survived to age 85. 95% confidence intervals are presented in the parentheses. Baseline age and age² were also included as covariates. BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; IDL: intermediate density lipoprotein; VLDL: very low density lipoprotein.