Clinical Investigations

# Lifestyle Change and High-Density Lipoprotein Change: The US Department of Veterans Affairs Normative Aging Study

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ABSTRACT

*Background:* We sought to determine whether lifestyle modifications are associated with high-density lipoprotein cholesterol (HDL-C) change in a cohort with long-term follow-up.

*Hypothesis:* Changes in alcohol consumption, smoking, or body mass index (BMI) are associated with within-individual changes in HDL-C.

*Methods:* We selected 1420 men with ≥2 HDL-C measurements from the US Department of Veterans Affairs Normative Aging Study (NAS). Changes in HDL-C (in milligrams/deciliter) over a 3-year period were calculated for each pair of exams. For each interval of HDL-C change, lifestyle exposures were categorized: participants maintained a stable BMI >25 kg/m² (reference) or ≤25 kg/m² since the previous exam, or increased or decreased BMI; participants were actively smoking at both exams (reference), nonsmokers at both exams, quit, or initiated smoking between exams; and participants maintained alcohol intake of <2 (reference) or ≥2 drinks daily since the previous exam, or increased or decreased alcohol intake. Longitudinal analysis was used to examine the relationship between the lifestyle change categories and 3-year change in HDL-C for each interval, adjusting for comorbidities, lipids, and cholesterol medication.

*Results:* Participants were followed for approximately 14.3 years. Increases in HDL-C were associated with maintaining alcohol intake of ≥2 drinks daily (mean HDL-C increase, 0.86; $P = 0.02$), increasing alcohol intake from <2 to ≥2 drinks daily (mean, 2.53; $P = 0.0003$), and with maintaining a BMI of ≤25 kg/m² (mean, 0.71; $P = 0.04$).

*Conclusions:* Increases in alcohol consumption, maintaining moderate alcohol intake, and maintaining BMI ≤25 kg/m² were associated with significant 3-year increases in HDL-C.

## Introduction

High-density lipoprotein cholesterol (HDL-C) has been associated in an inverse fashion with risk for cardiovascular disease (CVD) in multiple cross-sectional observational cohorts.[1–8] Clinical trials have demonstrated that HDL-C increases are associated with a reduction in risk for adverse cardiovascular events,[9–11] as have cohort studies in which HDL-C levels have been modified by a combination of medication and lifestyle changes.[12] The evidence that higher HDL-C levels are protective against CVD has prompted dialogue regarding whether this lipid parameter should be a therapeutic target in patients with or at risk for CVD.[13]

While previous studies have evaluated the association between lifestyle factors and HDL-C levels in a cross-sectional manner, fewer studies have examined the impact that changes in lifestyle have on HDL-C levels within individuals.[14–17] We sought to examine the relationship between changes in lifestyle habits known to be associated with HDL-C, including alcohol consumption, body mass index (BMI), and smoking, and HDL-C change in a

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community sample of men in whom such factors and HDL-C measurements were repeatedly documented over an average 14.3-year period.

## Methods

### Population

The US Department of Veterans Affairs (VA) Normative Aging Study (NAS) is an ongoing longitudinal study that enrolled a community sample of 2280 men living in the Boston area, age 21 to 81 years, between 1961 and 1970. Men with a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, diabetes mellitus, coronary heart disease (CHD), or cancer were excluded from enrollment. Participants were evaluated every 3 to 5 years, depending on their age, until 1984, after which all surviving participants were evaluated every 3 years. The institutional review board of VA Boston Healthcare approved this study. At each follow-up exam, NAS enrollees provided written informed consent. Further details of the methods of the NAS have been described previously.[18]

Starting in 1981, HDL-C, total cholesterol, and triglycerides were measured at each study exam on surviving members of the cohort. From these, men were selected with at least 2 HDL-C measurements during follow-up. For each participant included, all observations with available data on HDL-C and the exposures of interest were incorporated into the analysis.

### Exposure

The exposures of interest were changes in alcohol consumption, BMI, and smoking status. Change in alcohol consumption was categorized as: maintaining <2-beverage consumption daily (reference), maintaining ≥2 drinks daily, increasing from <2 to ≥2 drinks daily, or decreasing from ≥2 to <2 drinks daily. BMI change between study visits was categorized as: maintaining a BMI of >25 kg/m$^2$ (reference), maintaining a BMI of ≤25 kg/m$^2$, increasing from ≤25 kg/m$^2$ to >25 kg/m$^2$, or decreasing from >25 kg/m$^2$ to ≤25 kg/m$^2$. Change in smoking status was categorized as follows: currently smoking at both exams (reference), quitting between exams, initiating between exams, or remaining abstinent at both exams. If data were missing on any of these exposures (6.5% or less in all cases), values from that participant's previous visit, if available, were used to impute the current visit's values.

### Outcome

Change in HDL-C was calculated by subtracting the previous exam's HDL-C level from that of the current exam. To adjust for difference in time between HDL-C measurements, change in HDL-C was divided by the time (in increments of 3 years) between the 2 measurements.

### Covariates

Low-density lipoprotein cholesterol (LDL-C) (calculated using fasting triglycerides, total cholesterol, and HDL-C) and baseline HDL-C were included in the models. Comorbidities including diabetes mellitus, hypertension, cerebrovascular disease, CHD, statin use, nonstatin HDL-C–modifying medication use (including fenofibrate, clofibrate, gemfibrozil, and niacin use), and other cholesterol medication use (including acarbose, cholestyramine, ezetimibe, and colestipol) were also incorporated. For each covariate, updated data documented at the time of each repeated determination of change in HDL-C were used.

### Statistical Analysis

First, we examined characteristics of the cohort as documented at the time of first HDL-C measurement (starting in 1981, the baseline for this analysis) and at the time of the last HDL-C for each participant. Baseline and final characteristics were compared using *t* tests to compare continuous variables, and Cochran-Mantel-Haenszel tests to compare categorical characteristics. Longitudinal analysis was then used to determine the age-adjusted parameter estimates and *P* values for association with HDL-C as a repeated outcome for each of the categorized lifestyle change factors and other covariates. In multivariate modeling, the association between categorized lifestyle factors and repeated change in HDL-C were determined, adjusting for other lifestyle change factors, comorbidities, baseline HDL-C, calculated LDL-C, and cholesterol medications. Triglycerides were not included in multivariate-adjusted models because this parameter would be expected to be collinear with other predictors of interest, including change in lifestyle factors and baseline HDL-C.[19] In all analyses, we accounted for clustering at the level of the individual, most of whom provided several outcome (HDL-C change) observations. To further examine whether variability in time between 2 HDL-C measurements affected our results, we reran the main analysis after excluding observations with particularly long (4.5 years or more) or short (1.5 years or less) intervals between visits. To examine whether age at the time of HDL-C change determination was an effect modifier of any associations between lifestyle change and HDL-C change, we executed analyses in subgroups above and below the median age of 68 years at each visit. In a sensitivity analysis, we excluded observations in which a participant was documented as using any cholesterol-modifying therapy to isolate the effects of lifestyle factor changes on 3-year change in HDL-C.

All analyses were executed using Statistical Analysis Software version 9.2, (SAS Institute Inc., Cary, NC). The funding source for the NAS had no role in the design, execution, or reporting of the study.

## Results

From this community sample recruited through the VA, 1420 men were selected who had a minimum of 2 HDL-C measurements documented during follow-up. Each participant contributed between 1 and 9 (mean, 4) outcome measurements to the analysis, for a total of 5895 observations. On average, men provided repeated HDL-C measurements over a 14.3-year (standard deviation, 6.4 years) period. Table 1 displays characteristics of the 1420 included participants at the time of their baseline and final HDL-C measurements. Although men with hypertension, diabetes, or other conditions were excluded at NAS entry (between 1961 and


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Table 1. Characteristics of 1420 Men at the Time of Baseline and Final High-Density Lipoprotein Cholesterol Measurements

| Characteristic | Baseline | Final Follow-up | *P* Value |
|---|---|---|---|
| Age, mean (SD) | 59.4 (7.6) | 73.7 (7.6) | <0.0001 |
| HDL-C, mean (SD) | 48.8 (13.6) | 47.6 (13.1) | 0.01 |
| LDL-C, mean (SD) | 166.1 (39.8) | 125.1 (38.8) | <0.0001 |
| BMI, mean (SD) | 27.0 (3.5) | 27.6 (4.1) | <0.0001 |
| Current smoker, no. (%) | 216 (15.2) | 98 (6.9) | <0.0001 |
| Consumes ≥alcoholic drinks daily, no. (%) | 360 (25.4) | 284 (20.0) | 0.0007 |
| Diabetes mellitus, no. (%) | 27 (1.9) | 89 (6.3) | <0.0001 |
| Hypertension, no. (%) | 176 (12.4) | 373 (26.3) | <0.0001 |
| Cerebrovascular disease, no. (%) | 11 (0.8) | 59 (4.2) | <0.0001 |
| Coronary artery disease, no. (%) | 190 (13.4) | 510 (35.9) | <0.0001 |
| Statin use, no. (%) | 7 (0.5) | 343 (24.2) | <0.0001 |
| HDL-C–related nonstatin cholesterol-modifying therapy, no. (%) | 0 | 5 (0.4) | 0.03 |
| Other nonstatin cholesterol-modifying therapy, no. (%) | 10 (0.7) | 27 (1.9) | 0.005 |

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

1970), many participants had developed comorbidities prior to their first HDL-C measurement (1981 or later), which are reflected in Table 1.

Table 2 displays the age-adjusted and multivariate-adjusted parameter estimates and *P* values for each predictor of 3-year change in HDL-C. In both age-adjusted and multivariate-adjusted analyses, higher baseline HDL-C was associated with significant 3-year decreases in HDL-C. In multivariate-adjusted models, maintaining a BMI of ≤25 kg/m$^2$, maintaining alcohol intake of ≥2 drinks daily, and increasing from <2 to ≥2 drinks daily were all associated with 3-year increases in HDL-C. In age- and multivariate-adjusted analyses, higher baseline LDL-C levels were associated with a 3-year decrease in HDL-C. In a sensitivity analysis, we excluded observations that consisted of HDL-C measurements that were >4.5 years or <1.5 years apart. Multivariate-adjusted results were materially the same as those described.

Table 3 displays results of analyses stratified by age at the time of the study visit. As in the overall analysis, higher baseline HDL-C levels were associated with 3-year decreases in men of all ages. Quitting smoking, increasing alcohol intake, and maintaining moderate alcohol intake of ≥2 drinks daily all had larger effect on HDL-C levels at ages less than the median observation age of 68 years. Statin use in ages ≥68 years was associated with significant 3-year increases in HDL-C. In a subgroup of 1386 men not taking cholesterol-modifying therapy, quitting smoking between exams, maintaining alcohol intake of ≥2 drinks daily, and increasing from <2 to ≥2 drinks daily were all associated with 3-year HDL-C increases.

## Discussion

In 1420 men enrolled in the VA NAS, each providing a mean of 4 outcome measurements over about 14 years of follow-up, we found that maintaining a BMI of <25 kg/m$^2$, maintaining alcohol intake of >2 drinks daily, and increasing alcohol intake from <2 to ≥2 drinks daily were all associated with significant 3-year increases in HDL-C. In analyses stratified by the median age at time of HDL-C change determination, these lifestyle changes were significantly associated with 3-year HDL-C change only in participants younger than age 68 years. Other factors associated with significant 3-year changes in HDL-C included baseline HDL-C in all analyses and statin use in observations of HDL-C change determined when participants were ≥68 years.

Our findings are qualitatively consistent with cross-sectional studies that have examined the associations between lifestyle and HDL-C. Increases in alcohol consumption were associated with approximately a 5% increase in HDL-C. This is consistent with previous studies, in which changes in alcohol consumption have been associated with increasing HDL-C levels of 5% to 15%.[13,16] Other researchers have found that each 1-kg decrease or increase in weight is associated with a 0.35-mg/dL increase or decrease in HDL-C.[13] In our cohort, each 1-kg increase in weight was associated with a 3-year decrease in HDL-C of −0.53 mg/dL. The majority of visit-to-visit evaluations (>90%) documented that a subject was nonsmoking at both visits. Our findings related to changes in smoking habits, therefore, describe only 9% of our observations, which was too small a number to identify associations between changes in smoking habits and changes in HDL-C. Although our findings corroborate those of cross-sectional and trial data, they expand this foundation by adding to the understanding of which factors are associated with HDL-C change within, rather than between, individuals.

There are advantages to using the NAS database to conduct this kind of longitudinal analysis. Because HDL-C


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Table 2. Parameter Estimates and *P* Values for Lifestyle Changes and Covariates on Change in High-Density Lipoprotein Cholesterol in 1420 Men

| | Age Adjusted | | Multivariate Adjusted | |
|---|---|---|---|---|
| Characteristic | Parameter Estimate | *P* Value | Parameter Estimate | *P* Value |
| Age | −0.0006 | 0.96 | −0.02 | 0.31 |
| Baseline HDL-C | −0.08 | <0.0001 | −0.13 | <0.0001 |
| Categorized change in BMI | | | | |
| Maintenance of BMI >25 kg/m² | Reference | | Reference | |
| Increasing from ≤25 kg/m² to BMI >25 kg/m² | −1.03 | 0.10 | −0.76 | 0.22 |
| Decreasing from >25 kg/m² to BMI ≤25 kg/m² | −0.23 | 0.73 | 0.18 | 0.78 |
| Maintenance of BMI <25 kg/m² | 0.12 | 0.73 | 0.71 | 0.04 |
| Categorized change in smoking status | | | | |
| Maintenance of smoking habit | Reference | | Reference | |
| Initiating smoking | 0.46 | 0.77 | 0.79 | 0.62 |
| Quitting smoking | 1.00 | 0.31 | 1.57 | 0.11 |
| Abstaining from smoking | −0.08 | 0.89 | 0.50 | 0.39 |
| Categorized change in alcohol consumption | | | | |
| Consuming <2 drinks daily | Reference | | Reference | |
| Decreasing from ≥2 drinks to <2 drinks daily | −1.01 | 0.10 | −0.54 | 0.38 |
| Increasing from <2 drinks to ≥2 drinks daily | 2.08 | 0.003 | 2.53 | 0.0003 |
| Consuming ≥2 drinks daily | 0.03 | 0.95 | 0.86 | 0.02 |
| LDL-C | −0.006 | 0.02 | −0.009 | 0.01 |
| Diabetes mellitus | −0.43 | 0.33 | −0.51 | 0.47 |
| Hypertension | 0.17 | 0.41 | −0.15 | 0.65 |
| Cerebrovascular disease | −0.20 | 0.74 | −0.82 | 0.34 |
| Coronary heart disease | −0.10 | 0.62 | −0.59 | 0.07 |
| Statin use | 0.45 | 0.12 | 0.68 | 0.11 |
| HDL-C–related nonstatin cholesterol-modifying therapy | −2.74 | 0.42 | −0.81 | 0.84 |
| Other nonstatin cholesterol-modifying therapy | 0.42 | 0.68 | −0.09 | 0.94 |

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

levels were documented repeatedly in the NAS cohort over a long follow-up period (average of 14.3 years), each participant contributed multiple outcome measures (change in HDL-C between study exams) to the longitudinal analysis we performed. Therefore, unmeasured factors within an individual that impact HDL-C change in response to environment could be accounted for in a way that cross-sectional studies cannot. There were some limitations to using this particular database to answer our study question. Due to large amounts of missing data on exercise, we were unable to account for the impact of physical activity on HDL-C change. Additionally, because of the binary nature of the alcohol consumption variable in NAS (<2 vs >2 drinks daily, as opposed to a more refined categorical variable), we were unable to specify further how much alcohol intake was associated with the 3-year increases or decreases in HDL-C that we observed. We began our analysis starting at the time of first HDL-C determination for each participant, not at VA NAS entry, therefore many participants who were smokers at entry had quit by the time of inclusion into our cohort. Our cohort consisted of men, and our results may not be generalized to women. Further studies examining the relation between long-term changes in lifestyle factors and changes in HDL-C in cohorts including women are warranted. There may be residual confounders, such as dietary factors, for which we did not account, that may have biased our results. Dietary changes or other unobserved lifestyle changes in men >68 years old may be


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Table 3. Parameter Estimates and *P* Values for Lifestyle Changes and Covariates on Change in High-Density Lipoprotein Cholesterol by Strata of Age.

| | Age <68 Years | | Age ≥68 Years | |
|---|---|---|---|---|
| Characteristic | Parameter Estimate | *P* Value | Parameter Estimate | *P* Value |
| Age | −0.02 | 0.68 | 0.03 | 0.44 |
| Baseline HDL-C | −0.19 | <0.0001 | 0.07 | <0.0001 |
| Categorized change in BMI | | | | |
| Maintenance of BMI >25 kg/m² | Reference | | Reference | |
| Increasing from ≤25 kg/m² to BMI >25 kg/m² | −0.51 | 0.55 | 1.29 | 0.16 |
| Decreasing from >25 kg/m² to BMI ≤25 kg/m² | 0.49 | 0.66 | 0.15 | 0.85 |
| Maintenance of BMI <25 kg/m² | 0.93 | 0.09 | 0.58 | 0.19 |
| Categorized change in smoking status | | | | |
| Maintenance of smoking habit | Reference | | Reference | |
| Initiating smoking | 0.67 | 0.72 | 0.93 | 0.76 |
| Quitting smoking | 2.69 | 0.02 | 1.13 | 0.47 |
| Abstaining from smoking | 0.29 | 0.69 | 1.02 | 0.33 |
| Categorized change in alcohol consumption | | | | |
| Consuming <2 drinks daily | Reference | | Reference | |
| Decreasing from ≥2 drinks to <2 drinks daily | −0.83 | 0.36 | 0.12 | 0.88 |
| Increasing from <2 drinks to >2 drinks daily | 3.74 | 0.0002 | 1.43 | 0.14 |
| Consuming ≥2 drinks daily | 1.48 | 0.008 | 0.17 | 0.75 |
| LDL-C | −0.02 | 0.004 | 0.002 | 0.75 |
| Diabetes mellitus | −0.25 | 0.85 | 0.66 | 0.42 |
| Hypertension | −0.78 | 0.16 | 0.26 | 0.53 |
| Cerebrovascular disease | −2.03 | 0.28 | −0.36 | 0.71 |
| Coronary artery disease | −0.60 | 0.27 | −0.60 | 0.13 |
| Statin use | −0.15 | 0.86 | 1.23 | 0.01 |
| HDL-C–related nonstatin cholesterol-modifying therapy | 0 | 0 | −0.55 | 0.88 |
| Other nonstatin cholesterol-modifying therapy | 0.12 | 0.86 | −0.51 | 0.74 |

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

an explanation as to why statin use, which minimally impacts HDL-C levels, was associated with small but statistically significant increases in HDL-C. HDL-C measurement error introduced by changing laboratory assays during the course of the VA NAS follow-up would impact the data in a uniform fashion and would thus bias our results toward the null. Therefore, the HDL-C-lifestyle factors associations we found are likely to be underestimated.

## Conclusion

Interim results from the recently stopped trial, Atherosclerosis Intervention in Metabolic Syndrome with low HDL/high triglycerides: Impact on Global Health Outcomes (AIM-HIGH), suggest that using some medications to increase HDL-C levels may not be safe, especially in subjects taking statins for LDL-C reduction.[20] Our study suggests that specific lifestyle recommendations could safely raise HDL-C levels, especially in younger patients (those <68 years old). Although the risks of advising against weight gain and for weight loss are few, the benefit of advising patients to maintain moderate alcohol consumption must be weighed against the risks of alcohol before this strategy can be safely accepted in the clinical setting. Future research might address this benefit-risk balance


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by examining CVD risk and competing cancer or dependence risk in prospective cohorts in which alcohol intake is variable.

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