High-Density Lipoprotein Particle Subclass Heterogeneity and Incident Coronary Heart Disease

Akintunde O. Akinkuolie, MBBS, MPH; Nina P. Paynter, PhD; Latha Padmanabhan, MA, MSc; Samia Mora, MD, MHS

Background—Raising the cholesterol of high-density lipoprotein (HDL) particles is targeted as a cardiovascular disease prevention strategy. However, HDL particles are heterogeneous in composition and structure, which may relate to differences in antatherogenic potential. We prospectively evaluated the association of HDL subclasses, defined by a recently proposed nomenclature, with incident coronary heart disease (CHD).

Methods and Results—Baseline HDL particle concentrations were measured by nuclear magnetic resonance spectroscopy and categorized into 5 subclasses (very large, large, medium, small, and very small) among 26,332 initially healthy women. During a median follow-up of 17 years, 969 cases of incident CHD (myocardial infarction, revascularization, and CHD death) were ascertained. In Cox models that adjusted for age, race/ethnicity, blood pressure, smoking, postmenopausal status, and hormone therapy, associations with incident CHD were inverse (P trend<0.0001) for concentrations of very large (hazard ratio for top versus bottom quartile, 0.49; 95% confidence interval, 0.41–0.60), large (0.54; 0.45–0.64), and medium (0.69; 0.58–0.83) HDL subclasses. Conversely, hazard ratios (95% confidence intervals) for small and very small HDL were 1.22 (1.01–1.46; P trend=0.08) and 1.67 (1.39–2.02; P trend<0.0001), respectively. However, after additionally adjusting for metabolic and lipoprotein variables, associations for the spectrum of large, medium, and small HDL subclasses were inverse (P trend<0.05 for large and small and 0.07 for medium), whereas subclasses at either end of the spectrum were not associated with CHD (P trend=0.97 for very large and 0.21 for very small HDL).

Conclusions—In this prospective study, associations with incident CHD differed by HDL particle subclass, which may be relevant for developing HDL-modulating therapies.

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Key Words: coronary disease □ epidemiology □ lipids □ lipoproteins

Robust epidemiological evidence of an inverse association between high-density lipoprotein-cholesterol (HDL-C) and coronary heart disease (CHD)1 has failed to translate into clinical benefit.2–4 However, HDL represents a spectrum of heterogeneous particles,5 which may have important implications for capturing HDL-attributable CHD risk and developing HDL-modulating therapies. In particular, certain HDL particle subclasses may differ in their biological functions, including their role in reverse cholesterol transport, as well as anti-inflammatory, antioxidant, and vasodilatory functions.5 It is unclear whether specific subclasses of HDL are more cardioprotective or useful in assessing the benefits of HDL-related therapeutic interventions.6,7 Hence, identification of specific HDL subclasses that maximize information on CHD risk may also enhance the development of more targeted therapies.

Various HDL subfractionation methods exist, which also differ in their nomenclature,5,6 making comparisons across these methods challenging. A recent consensus statement by Rosenson et al8 proposed a new nomenclature for HDL particle subclasses based on their physiochemical properties.8 This nomenclature groups HDL particles based on their density and size into 5 distinct subclasses (very large, large, medium, small, and very small).8 Better characterization of HDL into these 5 subclasses may allow for more specific CHD risk information although the clinical use of this classification scheme in relation to incident CHD is uncertain.

Furthermore, the association of HDL-C with CHD risk is influenced by metabolic and lipoprotein variables, in particular triglycerides and atherogenic lipoproteins, making it important to assess HDL-related risk by accounting for such correlations.9,10 Nuclear magnetic resonance (NMR) spectroscopy is a method that detects HDL subclass particle concentrations (reported in μmol/L) based on their unique subclass lipid methyl signal amplitudes.11 Because NMR simultaneously quantifies the particle concentrations of the HDL subclasses, it may be particularly useful for examining correlations among...
WHAT IS KNOWN

• High-density lipoprotein (HDL)-cholesterol is protective against coronary heart disease (CHD), but the physical and biological properties of HDL particles are heterogeneous, particularly with regard to their cholesterol efflux capacity and anti-inflammatory function.
• Studies reporting associations between HDL particle subclass and CHD risk have been conflicting.

WHAT THE STUDY ADDS

• A recently proposed nomenclature that classifies HDL particles into 5 subclasses may offer new insight.
• We found differential associations with incident CHD events for baseline concentrations of 5 HDL subclasses measured by nuclear magnetic resonance spectroscopy, and these associations further differed after adjusting for lipoprotein and metabolic variables.
• After adjusting for lipoprotein and metabolic variables, no associations with CHD were noted for subclasses at the extremes of the HDL spectrum, that is, very small HDL subclasses, which may include nascent HDL particles, and very large HDL particles, which may represent more mature particles. HDL particles in the middle of the spectrum (i.e., small, medium, and large subclasses) were inversely associated with CHD.

these particles, as well as with other lipoproteins, in relation to CHD risk.

Therefore, in a prospective study of 26,332 initially healthy women followed up prospectively for 17 years, we evaluated the association of baseline concentrations of HDL particle subclasses grouped by the newly proposed nomenclature described above3 and the risk of incident CHD events, before and after accounting for metabolic and lipoprotein variables.

Methods

Study participants were recruited from the Women’s Health Study (WHS), a completed randomized, double-blinded, placebo-controlled trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer.12 Participants were apparently healthy women followed up prospectively for 17 years; we evaluated the association of baseline concentrations of HDL particle subclasses grouped by the newly proposed nomenclature described above3 and the risk of incident CHD events, before and after accounting for metabolic and lipoprotein variables.

Laboratory Measurements

Blood samples obtained at enrollment were collected in EDTA tubes and stored in vapor phase liquid nitrogen (−170°C) until the time for laboratory analysis. Samples for lipoprotein particle analysis were thawed, separated into 200 μL aliquots, refrozen and shipped on dry ice to LipoScience, Inc (Raleigh, NC) where NMR spectroscopy was used to analyze plasma lipoprotein particles according to the Lipoprofile-3 algorithm. Concentrations of HDL particle subclasses were calculated from the measured amplitudes of the spectroscopically distinct lipid methyl group NMR signals of the HDL subclasses that constitute the spectrum of total HDL particles (HDL-P) by NMR.11 Using the range of size for each HDL subclass, we reclassified HDL subclasses according to the classification scheme proposed by Rosenson et al8 into 5 distinct HDL subclasses (very large, 10.3–13.5 nm; large, 8.6–10.2 nm; medium, 8.3–8.5 nm; small, 8.0–8.2 nm; and very small, 7.4–7.9 nm). Thus, the concentration of particles for each HDL subclass was determined for every participant. Total low-density lipoprotein particle concentration was also measured at LipoScience, Inc, by NMR spectroscopy.13

Additional plasma lipid measurements were analyzed in a core laboratory facility certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization Program.13,14 Standard lipids were measured directly with a Hitachi 917 analyzer using reagents from Roche Diagnostics (Indianapolis, IN); specifically, HDL-C was measured with a direct homogenous polyethylene-glycol assay.13 Apolipoprotein AI and apolipoprotein B_100 (ApoB) were measured with immunoturbidometric assays (DiaSorin, Stillwater, MN).

Assessment of Other Variables

Covariates of interest were self-reported on the questionnaire administered at study entry and included age, race/ethnicity, smoking, menopausal status, use of hormone replacement therapy (HRT), history of diabetes mellitus, and hypertension (defined as physician diagnosis of hypertension, antihypertensive treatment, or self-reported systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg). Body mass index was calculated as the weight in kilograms divided by the square of the height in meters.

Ascertainment of CHD Events

We selected CHD as our prespecified primary outcome based on a previous analysis suggesting that HDL-C and apolipoprotein AI were not associated with ischemic stroke.16 Incident CHD was a composite of nonfatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and CHD death. Information on the occurrence of these events was ascertained via annual follow-up questionnaire, letters, and telephone calls. After written informed consent, medical records were obtained and reviewed by a blinded End points Committee for the adjudication of all reported events based on predefined criteria.17 Myocardial infarction was confirmed if symptoms met World Health Organization criteria and the event was associated with diagnostic ECG changes and abnormal levels of cardiac enzymes. Revascularization procedures were confirmed on review of hospital records. CHD deaths were confirmed by review of autopsy reports, death certificates, information obtained from family members or postal authorities, or through the National Death Index.

Statistical Analyses

Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC). Wilcoxon rank-sum tests and χ2 tests were used to analyze the differences between women who did or did not develop CHD during follow-up. Using guidelines from the Department of Health and Human Services,17 each of the 5 HDL particle subclasses was divided into quartiles based on the distribution of women who were not on HRT at baseline. Variables that were not normally distributed were transformed using the natural logarithm. Person-years contributed by each participant were calculated from baseline to the date of CHD diagnosis, death, or the end of follow-up (March...
Independent censoring was assumed and subjects lost to follow-up were considered censored at the time of last contact. Cox proportional hazard regression models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for incident CHD according to quartiles and per 1 SD of HDL variables using separate models for each HDL particle subclass. The proportionality hazard assumption was tested for and satisfied for all 5 HDL subclasses by including an interaction term between the follow-up time (log) and each HDL subclass ($P > 0.05$ for all). Cox models were initially adjusted for age, race/ethnicity, systolic blood pressure, smoking, menopausal status, HRT, and randomization treatment assignment (model 1). To account for lipoprotein correlations with each other and with other related metabolic variables, model 1 was then additionally adjusted for body mass index, diabetes mellitus, low-density lipoprotein-cholesterol and particle concentration, and triglycerides (natural logarithm transformed); this model was also mutually adjusted for the other HDL particle subclasses entered as continuous variables (model 2). Further adjustment for high-sensitivity C-reactive protein or antihypertensive medication use resulted in no change in the results.

Based on the prior literature, we prespecified potential interactions by ApoB concentrations that were assessed by stratified analyses and interaction terms. A cut point of 90 mg/dL was used to discriminate between low and high concentrations of ApoB based on a previous analysis in the WHS where we found that HDL-C was not associated with cardiovascular events among women with ApoB <90 mg/L (corresponding to the lowest tertile of ApoB in this population). We also examined potential interaction by HRT use.

Linear tests for trend ($P$ trend) were performed using the median value within each quartile as an ordinal variable. All reported $P$ values were 2-sided, with values <0.05 considered statistically significant.

### Results

#### Baseline Characteristics and Correlations

Baseline characteristics of the 26,332 women according to whether they did or did not develop a first CHD event during follow-up are shown in Table 1. Compared with participants who remained event-free during follow-up, those who developed CHD had higher risk profiles at baseline, including older age, higher blood pressure, and body mass index and increased prevalence of diabetes mellitus, smoking, and dyslipidemia. Participants who developed CHD had lower HDL-C concentrations, which resulted from having lower concentrations of the very large, large, and medium HDL subclasses along with higher concentrations of the small and very small HDL subclasses.

Table 2 shows Spearman correlation coefficients for the various HDL measures (including the 5 subclasses) and other lipid and lipoprotein measures.
Table 2. Spearman Correlation Coefficients

<table>
<thead>
<tr>
<th>variable</th>
<th>HDL-C</th>
<th>ApoAI</th>
<th>LDL-C</th>
<th>LDL-P</th>
<th>ApoB</th>
<th>TG</th>
<th>HDL-P</th>
<th>HDL-VL</th>
<th>HDL-L</th>
<th>HDL-M</th>
<th>HDL-S</th>
<th>HDL-VS</th>
<th>BMI</th>
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<tbody>
<tr>
<td>ApoAI</td>
<td>0.79</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LDL-C</td>
<td>-0.05</td>
<td>-0.07</td>
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<tr>
<td>LDL-P</td>
<td>-0.40</td>
<td>-0.20</td>
<td>0.70</td>
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<tr>
<td>ApoB</td>
<td>-0.32</td>
<td>-0.10</td>
<td>0.79</td>
<td>0.85</td>
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<td></td>
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<td></td>
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<tr>
<td>TG</td>
<td>-0.40</td>
<td>-0.09</td>
<td>0.28</td>
<td>0.52</td>
<td>0.52</td>
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<tr>
<td>HDL-P</td>
<td>0.47</td>
<td>0.74</td>
<td>-0.08</td>
<td>0.01</td>
<td>0.01</td>
<td>0.22</td>
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<td></td>
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<tr>
<td>HDL-VL</td>
<td>0.73</td>
<td>0.65</td>
<td>-0.34</td>
<td>-0.53</td>
<td>-0.43</td>
<td>-0.37</td>
<td>0.36</td>
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<tr>
<td>HDL-L</td>
<td>0.48</td>
<td>0.50</td>
<td>-0.12</td>
<td>-0.19</td>
<td>-0.16</td>
<td>-0.07</td>
<td>0.50</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HDL-M</td>
<td>0.27</td>
<td>0.40</td>
<td>-0.15</td>
<td>-0.10</td>
<td>-0.09</td>
<td>0.13</td>
<td>0.65</td>
<td>0.24</td>
<td>0.38</td>
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<tr>
<td>HDL-S</td>
<td>-0.05</td>
<td>0.11</td>
<td>-0.001</td>
<td>0.12</td>
<td>0.09</td>
<td>0.20</td>
<td>0.33</td>
<td>-0.04</td>
<td>-0.11</td>
<td>-0.05</td>
<td></td>
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<tr>
<td>HDL-VS</td>
<td>-0.26</td>
<td>-0.15</td>
<td>0.30</td>
<td>0.40</td>
<td>0.35</td>
<td>0.23</td>
<td>-0.06</td>
<td>-0.37</td>
<td>-0.28</td>
<td>-0.35</td>
<td>-0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.26</td>
<td>-0.26</td>
<td>0.15</td>
<td>0.30</td>
<td>0.26</td>
<td>0.33</td>
<td>-0.08</td>
<td>0.38</td>
<td>-0.14</td>
<td>-0.08</td>
<td>0.06</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

ApoAI indicates apolipoprotein AI; ApoB, apolipoprotein B100; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; HDL-L, large high-density lipoprotein; HDL-M, medium high-density lipoprotein; HDL-P, total high-density lipoprotein particle concentration; HDL-S, small high-density lipoprotein; HDL-VL, very large high-density lipoprotein; HDL-VS, very small high-density lipoprotein; LDL-C, low-density lipoprotein-cholesterol; LDL-P, total low-density lipoprotein particles; and TG, triglycerides.

All P-values <0.0001 except, *P<0.03 and †P= not significant.

HDL-C with each of the 5 subclasses ranged from 0.73 (for the very large HDL subclass; P<0.0001) to –0.26 (for the very small HDL subclass; P<0.0001). In comparison, total HDL-P (the sum of the HDL subclasses) had the strongest correlation with the medium and large HDL subclasses (r=0.65 and 0.50) and minimal correlation with the very small particle subclass (r=0.06), P for all <0.0001. The correlation coefficients for the 5 HDL particle subclasses with each other ranged from 0.38 to –0.37, P for all <0.0001. The HDL subclasses also differed in the direction and magnitude of correlation with low-density lipoprotein cholesterol and particle concentration, ApoB, triglycerides, and body mass index, going from negative (r=−0.5) to positive (r=0.4) as HDL particles became progressively smaller in size.

Associations With CHD Events

A total of 969 incident CHD events (365 myocardial infarctions, 600 revascularization procedures, and 4 CHD deaths) occurred during a median follow-up of 17 years. HDL-C was inversely associated with incident CHD: model 1 HR (95% CI) for top versus bottom quartile, 0.34 (0.28–0.41), and model 2 HR (95% CI), 0.59 (0.43–0.88), P trend<0.0001 for both models. Table 3 shows the association for total HDL-P (the sum of the subclasses) and each of the 5 HDL subclasses with incident CHD. In the minimally adjusted model 1, there were inverse associations with CHD for increasing quartiles of total HDL-P and each of very large, large, and medium HDL subclasses; respective HRs (95% CIs) for top versus bottom quartiles were 0.77 (0.64–0.92), 0.49 (0.41–0.60), 0.54 (0.45–0.64), and 0.69 (0.58–0.83), all P trend≤0.008. By contrast, small and very small HDL subclasses were associated with increased risk of CHD, respective HRs (95% CIs) for top versus bottom quartiles were 1.22 (1.01–1.46), P trend=0.08, and 1.67 (1.39–2.02), P trend<0.0001.

After additionally adjusting for the metabolic and lipoprotein variables, including mutual adjustment for the other HDL particle subclasses (model 2; Table 3), higher concentrations of the large and small HDL subclasses showed a statistically significant trend for lower CHD, respective HRs (95% CIs) for top versus bottom quartiles were 0.71 (0.58–0.86; P trend=0.003) and 0.84 (0.68–1.03; P trend =0.03), with a borderline significant trend for medium HDL: 0.84 (0.68–1.03), P trend=0.07. Total HDL-P also was associated with a reduced risk of incident CHD (P trend=0.0003). Similar results were obtained when the HDL subclasses were examined per 1 SD increments.

Stratified Analyses

Event rates differed in participants with ApoB <90 versus ≥90 mg/dL (1.4% and 4.9%, respectively). The associations of HDL subclasses with incident CHD were significant only among participants with ApoB ≥90 mg/dL (Tables 4 and 5), with statistically significant interactions by ApoB for the association of total HDL-P and the large HDL subclass with incident CHD (P for interaction=0.01 and 0.003, respectively). CHD event rates were similar in baseline users and nonusers of HRT (3.7%). Somewhat attenuated associations were seen among HRT users, with only the large HDL subclass having statistically significant interaction by HRT use (P for interaction=0.02, data not shown).

Discussion

In this prospective study of 26,332 initially healthy women followed up for a median duration of 17 years, differential associations with incident CHD events were found for baseline concentrations of 5 HDL subclasses measured by NMR spectroscopy and grouped according to a newly proposed classification scheme. Before accounting for the correlations of the HDL subclasses with each other and with metabolic and lipoprotein variables, the very large, large, and medium HDL subclasses had inverse association with CHD, whereas small and very small HDL subclasses had positive association. Once the correlations were accounted for, associations for the spectrum of large, medium, and small HDL subclasses showed...
a tendency toward a reduced risk of CHD (P trend<0.05 for large and small, 0.07 for medium), whereas the subclasses at either end of the spectrum were not associated with CHD (P trend=0.97 and 0.21 for very large and very small HDL, respectively). These findings underscore the heterogeneity of HDL particle subclasses in conveying clinical CHD risk information.

This is the first study to examine incident CHD associations in relation to NMR-measured HDL particle subclasses grouped according to the 5 subclasses that were recently recommended.4 Related studies that have assessed the association between HDL subclasses and CHD risk by NMR spectroscopy have previously grouped HDL particles into 3 subclasses (large, medium, and small).8,13,19–22 The previously designated NMR-derived large HDL subclass corresponds to the very large HDL subclass assessed in the present study, whereas the previously designated small HDL particle subclass is a combination of both the very small and small HDL subclasses assessed in the present study.3 Using the new classification scheme additionally identified a very small HDL subclass, which was not associated with CHD in our study, and refined the range of medium to large HDL subclasses. Hence, this new HDL subclass distribution may provide better assessment of CHD risk attributable to specific HDL particle subclasses.

In a previous case–control study of high-risk men with established CHD and low HDL-C, all 3 subclasses tended toward a reduced risk of CHD although only small and medium HDL were statistically significant after accounting for lipoprotein correlations.20 Similar results were obtained in a secondary prevention study, with only small and medium HDL subclasses having significant inverse association with CHD after adjustment for lipoprotein correlations, whereas the association of large HDL was attenuated after adjustment.21 Taken together, our results in a low-risk primary prevention population of women are in agreement with these prior studies.

Besides NMR spectroscopy, HDL particle subclass concentrations can also be measured with ion mobility, but the 2 methods have not been directly compared.4 Ion mobility currently subfractionates HDL particles into 2 subclasses (large and small); both subclasses were inversely associated with coronary heart disease. The association of women are in agreement with these prior studies.

### Table 3. Association of the 5 HDL Particle Subclasses With Incident CHD

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P Trend</th>
<th>Per 1 SD*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total HDL-P (7.4–13.5 nm)</td>
<td></td>
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<tr>
<td>Range, μmol/L</td>
<td>≤31.39</td>
<td>31.40–34.66</td>
<td>34.67–38.25</td>
<td>≥38.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>0.85 (0.69–1.04)</td>
<td>0.81 (0.66–0.98)</td>
<td>0.77 (0.64–0.92)</td>
<td>0.008</td>
<td>0.91 (0.86–0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>0.87 (0.71–1.07)</td>
<td>0.78 (0.63–0.95)</td>
<td>0.70 (0.58–0.85)</td>
<td>0.0003</td>
<td>0.88 (0.83–0.93)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Very large (10.3–13.5 nm) | | | | | | | |
| Range, μmol/L | ≤1.53 | 1.54–2.69 | 2.70–4.32 | ≥4.33 | | | |
| Model 1, HR (95% CI) | 1 | 0.81 (0.68–0.95) | 0.60 (0.50–0.72) | 0.49 (0.41–0.60) | <0.0001 | 0.77 (0.72–0.81) | <0.0001 |
| Model 2, HR (95% CI) | 1 | 0.93 (0.78–1.11) | 0.85 (0.69–1.04) | 1.00 (0.80–1.25) | 0.97 | 0.95 (0.88–1.03) | 0.18 |

Large (8.6–10.2 nm) | | | | | | | |
| Range, μmol/L | ≤3.51 | 3.52–4.92 | 4.93–6.55 | ≥6.56 | | | |
| Model 1, HR (95% CI) | 1 | 0.69 (0.57–0.82) | 0.68 (0.57–0.82) | 0.54 (0.45–0.64) | <0.0001 | 0.82 (0.77–0.86) | <0.0001 |
| Model 2, HR (95% CI) | 1 | 0.74 (0.61–0.89) | 0.81 (0.67–0.97) | 0.71 (0.58–0.86) | 0.003 | 0.89 (0.83–0.94) | 0.0002 |

Medium (8.3–8.5 nm) | | | | | | | |
| Range, μmol/L | ≤5.52 | 5.53–8.02 | 8.03–10.80 | ≥10.81 | | | |
| Model 1, HR (95% CI) | 1 | 0.82 (0.68–0.98) | 0.68 (0.56–0.82) | 0.69 (0.58–0.83) | <0.0001 | 0.89 (0.84–0.94) | 0.005 |
| Model 2, HR (95% CI) | 1 | 0.96 (0.79–1.16) | 0.85 (0.70–1.05) | 0.84 (0.68–1.03) | 0.07 | 0.94 (0.87–1.00) | 0.06 |

Small (8.0–8.2 nm) | | | | | | | |
| Model 1, HR (95% CI) | 1 | 1.17 (0.97–1.42) | 1.11 (0.91–1.34) | 1.22 (1.01–1.46) | 0.08 | 1.07 (1.01–1.13) | 0.03 |
| Model 2, HR (95% CI) | 1 | 1.08 (0.88–1.32) | 0.95 (0.78–1.16) | 0.84 (0.69–1.03) | 0.03 | 0.93 (0.87–0.99) | 0.02 |

Very small (7.4–7.9 nm) | | | | | | | |
| Range, μmol/L | ≤3.30 | 3.31–11 | 11.01–13.69 | ≥13.70 | | | |
| Model 1, HR (95% CI) | 1 | 1.20 (0.98–1.48) | 1.57 (1.30–1.91) | 1.67 (1.39–2.02) | <0.0001 | 1.22 (1.14–1.30) | <0.0001 |
| Model 2, HR (95% CI) | 1 | 1.05 (0.85–1.30) | 1.12 (0.91–1.39) | 0.88 (0.70–1.11) | 0.21 | 0.95 (0.88–1.02) | 0.16 |

Model 1 included age, race/ethnicity, blood pressure, smoking, postmenopausal status, hormone replacement therapy, and treatment assignment. Model 2 included model 1 covariates plus body mass index, diabetes mellitus, low-density lipoprotein-cholesterol and particle concentration, triglycerides, and the other 4 HDL subclasses. Total HDL particle concentration was not adjusted for the HDL subclasses as it is the sum of the subclasses. Because of participants with missing information on adjusted covariates, model 1 included a total of 25,706 participants (847 events) and model 2 included a total of 25,232 participants (911 events). CHD indicates coronary heart disease; CI, confidence interval; HDL-P, total high-density lipoprotein particle concentration; and HR, hazard ratio.

*Natural log transformation was used to compute values for very large and large HDL subclasses.
HDL size using these other subfractionation methods have found mostly inverse association for large HDL size with CHD but equivocal results for smaller HDL size.36-34

HDL metabolism is a dynamic process during which HDL particles are constantly being remodeled in a lipidation–delipidation cycle, and effective metabolism depends on a system of recycling between larger and smaller HDL particles.5,35 Individual HDL subclasses differ in their ability to promote cholesteryl efflux.35,36 This, along with relative differences in other nontransport related functions of HDL,5 may explain the lack of uniform CHD risk across the spectrum of HDL subclasses in our study. The pattern of association that we observed suggests that metabolic processes involved in the maturation and delipidation of HDL may be coupled to CHD risk. The lack of an association between either very large HDL or very small HDL after adjusting for metabolic and lipoprotein variables may thus be unrelated to the cholesteryl content of these particles and may be relevant for understanding HDL-attributable CHD risk. By contrast, in the middle of the spectrum, increasing concentrations of progressively larger HDL particles (small, medium, and large HDL) had inverse associations with CHD.

The metabolic fate of very large HDL is predominantly the regeneration of small HDL either through transporting cholesterol to the liver for excretion or through the concerted action of lipid transfer proteins and lipases.35 In particular, very large HDL particles may be limited in their cholesterol efflux capacity as noted by their inability to interact with ATP binding cassette transporter A1, a potent pathway for cholesterol efflux.35 Very large HDL may also have other diminished atheroprotective functions.37,38 For instance, accumulation of very large HDL at the expense of small HDL particles after intervention with cholesteryl ester transfer protein inhibitors is debated as a possible reason for their inability to reduce cardiovascular events.37,39 Events involved in the maturation and recycling of HDL particles may thus underlie the observations in our study.

However, HDL metabolism may also be altered in dyslipidemic conditions such as diabetes mellitus and insulin resistance states, with a redistribution of HDL particles toward atherogenic dyslipidemia may reflect enhanced enzymatic...

Table 4. Association of HDL Particle Subclasses With Incident CHD in Participants With Apolipoprotein B ≥90 mg/dL (n=17227, CHD Events=838)

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P Trend</th>
<th>Per 1 SD*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total HDL-P (7.4–13.5 nm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, μmol/L</td>
<td>≤31.39</td>
<td>31.40–34.66</td>
<td>34.67–38.25</td>
<td>≥38.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>0.84 (0.68–1.04)</td>
<td>0.76 (0.61–0.94)</td>
<td>0.73 (0.60–0.89)</td>
<td>0.003</td>
<td>0.90 (0.85–0.96)</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>0.85 (0.68–1.05)</td>
<td>0.72 (0.58–0.89)</td>
<td>0.65 (0.53–0.80)</td>
<td>&lt;0.0001</td>
<td>0.86 (0.81–0.92)</td>
</tr>
<tr>
<td>Very large (10.3–13.5 nm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, μmol/L</td>
<td>≤1.53</td>
<td>1.54–2.69</td>
<td>2.70–4.32</td>
<td>≥4.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>0.84 (0.71–1.01)</td>
<td>0.67 (0.55–0.81)</td>
<td>0.62 (0.50–0.77)</td>
<td>&lt;0.0001</td>
<td>0.82 (0.77–0.88)</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>0.93 (0.78–1.12)</td>
<td>0.84 (0.68–1.04)</td>
<td>1.08 (0.85–1.38)</td>
<td>0.70</td>
<td>0.96 (0.88–1.04)</td>
</tr>
<tr>
<td>Large (8.6–10.2 nm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, μmol/L</td>
<td>≤3.51</td>
<td>3.52–4.92</td>
<td>4.93–6.55</td>
<td>≥6.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>0.71 (0.59–0.86)</td>
<td>0.71 (0.59–0.86)</td>
<td>0.54 (0.44–0.65)</td>
<td>&lt;0.0001</td>
<td>0.82 (0.77–0.87)</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>0.75 (0.62–0.91)</td>
<td>0.80 (0.66–0.98)</td>
<td>0.65 (0.52–0.80)</td>
<td>0.0003</td>
<td>0.87 (0.82–0.93)</td>
</tr>
<tr>
<td>Medium (8.3–8.5 nm)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Range, μmol/L</td>
<td>≤5.52</td>
<td>5.53–8.02</td>
<td>8.03–10.80</td>
<td>≥10.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>0.82 (0.68–1.00)</td>
<td>0.69 (0.56–0.84)</td>
<td>0.69 (0.58–0.84)</td>
<td>0.0001</td>
<td>0.89 (0.83–0.95)</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>0.93 (0.76–1.14)</td>
<td>0.82 (0.66–1.02)</td>
<td>0.80 (0.64–1.00)</td>
<td>0.04</td>
<td>0.93 (0.86–1.00)</td>
</tr>
<tr>
<td>Small (8.0–8.2 nm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>1.16 (0.94–1.43)</td>
<td>1.09 (0.88–1.35)</td>
<td>1.14 (0.94–1.39)</td>
<td>0.35</td>
<td>1.04 (0.98–1.11)</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>1.08 (0.87–1.33)</td>
<td>0.94 (0.76–1.17)</td>
<td>0.81 (0.65–1.01)</td>
<td>0.01</td>
<td>0.91 (0.85–0.98)</td>
</tr>
<tr>
<td>Very small (7.4–7.9 nm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, μmol/L</td>
<td>≤8.30</td>
<td>8.31–11</td>
<td>10.13–13.69</td>
<td>≥13.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>1.24 (0.98–1.57)</td>
<td>1.45 (1.16–1.82)</td>
<td>1.52 (1.23–1.89)</td>
<td>&lt;0.0001</td>
<td>1.16 (1.08–1.24)</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>1.17 (0.91–1.49)</td>
<td>1.14 (0.90–1.48)</td>
<td>0.93 (0.72–1.20)</td>
<td>0.22</td>
<td>0.94 (0.87–1.02)</td>
</tr>
</tbody>
</table>

Model 1 included age, race/ethnicity, blood pressure, smoking, postmenopausal status, hormone replacement therapy, and treatment assignment. Model 2 included model 1 covariates plus body mass index, diabetes mellitus, low-density lipoprotein cholesterol and particle concentration, triglycerides, and the other 4 HDL subclasses. Because of participants with missing information on adjusted covariates, model 1 included a total of 16 800 participants (817 events) and model 2 included a total of 16 459 participants (786 events). CHD indicates coronary heart disease; CI, confidence interval; HDL-P, total high-density lipoprotein particle concentration; and HR, hazard ratio.

*Natural log transformation was used to compute values for very large and large HDL subclasses.
remodeling of large HDL into small HDL particles. It is also possible that very small HDL may accumulate as a consequence of impaired HDL maturation. The result of this study and others do not support the notion that small HDL particles are atherogenic per se, but instead suggest that the apparent increased CHD risk for small HDL particles may be because of their co-occurrence with other metabolic and lipoprotein derangements. Analysis and interpretation of data relating to HDL and CHD risk should therefore account for the correlation between different HDL particle subclasses and atherogenic lipids/lipoproteins. From a therapeutic standpoint, conversion of large lipid-rich HDL particles into small lipid-poor HDL particles by autologous delipidation of selective HDL may diminish atheroma volume, but whether this improves clinical outcomes has not been determined. The WHS is a lower risk population of women. Notably, we found evidence of interaction by atherogenic lipoprotein burden (as quantified by ApoB≥90 mg/dL), with a stronger inverse association of total HDL-P and CHD among WHS participants with high ApoB, consistent with our prior findings. This may be, in part, because of the different study populations, in that the WHS is a lower risk population of women. Notably, we found evidence of interaction by atherogenic lipoprotein burden (as quantified by ApoB≥90 mg/dL), with a stronger inverse association of total HDL-P and CHD among WHS participants with high ApoB, consistent with our prior finding for HDL-C. Other differences in the studies include the method of HDL-C measurement, sample collection and storage, and timing of the NMR measurements.

Strengths of this study include the long prospective follow-up (median, 17 years), large sample size, and the well-characterized information on cardiovascular health and outcomes. Limitations of our study include that HDL particle concentrations were only measured at baseline. It is possible that processing and storage duration of the blood samples may introduce measurement error; however, this would not be expected to differentially affect the HDL subclasses. HDL particle subclasses were obtained by NMR spectroscopy, and others do not support the notion that small HDL particles are atherogenic per se, but instead suggest that the apparent increased CHD risk for small HDL particles may be because of their co-occurrence with other metabolic and lipoprotein derangements. Analysis and interpretation of data relating to HDL and CHD risk should therefore account for the correlation between different HDL particle subclasses and atherogenic lipids/lipoproteins. From a therapeutic standpoint, conversion of large lipid-rich HDL particles into small lipid-poor HDL particles by autologous delipidation of selective HDL may diminish atheroma volume, but whether this improves clinical outcomes has not been determined. The WHS is a lower risk population of women. Notably, we found evidence of interaction by atherogenic lipoprotein burden (as quantified by ApoB≥90 mg/dL), with a stronger inverse association of total HDL-P and CHD among WHS participants with high ApoB, consistent with our prior finding for HDL-C. Other differences in the studies include the method of HDL-C measurement, sample collection and storage, and timing of the NMR measurements.

Strengths of this study include the long prospective follow-up (median, 17 years), large sample size, and the well-characterized information on cardiovascular health and outcomes. Limitations of our study include that HDL particle concentrations were only measured at baseline. It is possible that processing and storage duration of the blood samples may introduce measurement error; however, this would not be expected to differentially affect the HDL subclasses. HDL particle subclasses were obtained by NMR spectroscopy.

Table 5. Association of HDL Particle Subclasses With Incident CHD in Participants With Apolipoprotein B <90 mg/dL (n=9100, CHD events=131)

<table>
<thead>
<tr>
<th>Range, μmol/L</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P Trend</th>
<th>Per 1 SD*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total HDL-P (7.4–13.5 nm)</td>
<td>≤31.39</td>
<td>31.40–34.66</td>
<td>34.67–38.25</td>
<td>≥38.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>1.26 (0.65–2.45)</td>
<td>1.47 (0.78–2.75)</td>
<td>1.37 (0.76–2.47)</td>
<td>0.40</td>
<td>1.04 (0.90–1.20)</td>
<td>0.61</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>1.23 (0.63–2.40)</td>
<td>1.41 (0.75–2.65)</td>
<td>1.32 (0.72–2.43)</td>
<td>0.46</td>
<td>1.02 (0.87–1.19)</td>
<td>0.85</td>
</tr>
<tr>
<td>Very large (10.3–13.5 nm)</td>
<td>≤1.53</td>
<td>1.54–2.69</td>
<td>2.70–4.32</td>
<td>≥4.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>0.96 (0.48–1.89)</td>
<td>0.80 (0.42–1.51)</td>
<td>0.70 (0.38–1.29)</td>
<td>0.14</td>
<td>0.85 (0.69–1.06)</td>
<td>0.14</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>0.94 (0.46–1.90)</td>
<td>0.89 (0.45–1.75)</td>
<td>0.82 (0.41–1.65)</td>
<td>0.54</td>
<td>0.93 (0.72–1.20)</td>
<td>0.58</td>
</tr>
<tr>
<td>Large (8.6–10.2 nm)</td>
<td>≤3.51</td>
<td>3.52–4.92</td>
<td>4.93–6.55</td>
<td>≥6.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>0.78 (0.41–1.48)</td>
<td>0.93 (0.52–1.69)</td>
<td>1.06 (0.62–1.81)</td>
<td>0.43</td>
<td>1.01 (0.98–1.04)</td>
<td>0.57</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>0.83 (0.43–1.61)</td>
<td>1.10 (0.60–2.05)</td>
<td>1.36 (0.76–2.43)</td>
<td>0.11</td>
<td>1.08 (0.88–1.32)</td>
<td>0.48</td>
</tr>
<tr>
<td>Medium (8.3–8.5 nm)</td>
<td>≤5.52</td>
<td>5.53–8.02</td>
<td>8.03–10.80</td>
<td>≥10.81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>1.30 (0.69–2.45)</td>
<td>1.22 (0.66–2.24)</td>
<td>1.29 (0.72–2.30)</td>
<td>0.53</td>
<td>1.03 (0.88–1.20)</td>
<td>0.72</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>1.31 (0.69–2.48)</td>
<td>1.17 (0.62–2.19)</td>
<td>1.13 (0.60–2.14)</td>
<td>0.96</td>
<td>0.96 (0.80–1.17)</td>
<td>0.71</td>
</tr>
<tr>
<td>Small (8.0–8.2 nm)</td>
<td>≤4.12</td>
<td>4.13–6.33</td>
<td>6.33–9.17</td>
<td>≥9.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>1.16 (0.69–1.96)</td>
<td>1.16 (0.69–1.94)</td>
<td>1.36 (0.83–2.24)</td>
<td>0.23</td>
<td>1.10 (0.94–1.28)</td>
<td>0.22</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>1.10 (0.64–1.87)</td>
<td>1.03 (0.61–1.75)</td>
<td>1.10 (0.65–1.86)</td>
<td>0.78</td>
<td>1.03 (0.86–1.22)</td>
<td>0.77</td>
</tr>
<tr>
<td>Very small (7.4–7.9 nm)</td>
<td>≤3.98</td>
<td>3.98–5.2</td>
<td>5.2–6.5</td>
<td>≥6.55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1</td>
<td>0.78 (0.50–1.21)</td>
<td>1.21 (0.78–1.88)</td>
<td>0.72 (0.38–1.35)</td>
<td>0.69</td>
<td>0.98 (0.81–1.18)</td>
<td>0.84</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>1</td>
<td>0.71 (0.44–1.15)</td>
<td>1.21 (0.74–1.97)</td>
<td>0.59 (0.29–1.20)</td>
<td>0.43</td>
<td>0.93 (0.74–1.16)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Natural log transformation was used to compute values for very large and large HDL subclasses.
hence we were not able to make comparison based on sub-
classes obtained from other techniques or in relation to HDL
function. The study population of low-risk female health
professionals who were middle-aged and older at baseline
can have different health behaviors from men or women in
the general population which may limit the generalizability
of these results to other populations. Residual confounding
or chance cannot be ruled out because of the observational
nature of this study. Finally, as the current study did not set out
to assess risk stratification, we note that the data presented do
not suggest a recommendation for the measurement of HDL
subclasses as a clinical tool to assess CHD risk.

In conclusion, we provide evidence that concentrations of
HDL particle subclasses are differentially related to incident
CHD. This heterogeneity in HDL particle subclasses and their
attributable CHD risk may have important implications for the
development of HDL-modulating therapies.

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served as a consultant to Pfizer, Genzyme, and Quest Diagnostics; re-
served as a consultant to Pfizer, Genzyme, and Quest Diagnostics; re-
served as a consultant to Pfizer, Genzyme, and Quest Diagnostics; re-
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served as a consultant to Pfizer, Genzyme, and Quest Diagnostics; re-

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changed by gemfibrozil therapy in the Veterans Affairs High-Density
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Akintunde O. Akinkuolie, Nina P. Paynter, Latha Padmanabhan and Samia Mora

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