ORIGINAL RESEARCH

Association of High-Density Lipoprotein Particles and High-Density Lipoprotein Apolipoprotein C-III Content With Cardiovascular Disease Risk According to Kidney Function: The Multi-Ethnic Study of Atherosclerosis

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***Background*—**Chronic kidney disease is associated with structural and compositional abnormalities in high-density lipoprotein particles (HDLp). We examined associations of HDLp size, particle subfractions, and apolipoprotein C-III content with incident cardiovascular disease (CVD) events across categories of estimated glomerular filtration rate (eGFR).

***Methods and Results*—**Analyses included 6699 participants in MESA (Multi-Ethnic Study of Atherosclerosis) with measurements of HDLp and 5723 participants with measurements of HDL apolipoprotein C-III. Cox-regression methods were used to evaluate associations between HDLp and apolipoproteins with CVD events. Larger HDLp size was associated with lower CVD risk in participants with lower eGFR: hazard ratio (95% CI) per SD higher mean HDL size was 1.00 (0.90–1.11) in eGFR ≥60 mL/min per 1.73 m^2, 0.65 (0.48–0.86) in eGFR 45 to 59 mL/min per 1.73 m^2, and 0.48 (0.25–0.93) in eGFR <45 mL/min per 1.73 m^2 (*P* for interaction=0.05). Associations of HDLp subfractions with CVD varied significantly by eGFR (*P* for interaction=0.04), with significant inverse associations between higher concentrations of large HDLp and CVD events across categories of kidney function, but nonsignificant results for small HDLp. Only HDLp without apolipoprotein C-III was associated with lower risk of CVD events, with seemingly (albeit not statistically significant) stronger associations among participants with lower eGFR (*P* for interaction=0.19).

***Conclusions*—**HDL particles of larger size and higher concentrations of large HDL and of HDL without apolipoprotein C-III were associated with lower CVD risk, with risk estimates seemingly stronger among participants with lower eGFR. Future larger studies are needed to corroborate these findings. **(*J Am Heart Assoc*. 2019;8:e013713. DOI: 10.1161/JAHA.119.013713.)**

Key Words: apolipoprotein • cardiovascular disease • chronic kidney disease • high-density lipoprotein particle size

High-density lipoprotein particles (HDLp) may be implicated in the high atherosclerotic cardiovascular disease (CVD) risk experienced by patients with chronic kidney disease (CKD).[1–3] Although the cholesterol content of HDL (HDLc) has traditionally been used as a marker of CVD risk, it is a poor marker of HDL function and does not reflect its complex structure.[4] This is an important consideration in patients with CKD who have profound changes in the structure and content of HDLp with potentially different vascular effects.[1,2,5]

HDL is a heterogeneous mixture of particles of different size (eg, small, medium, and large particles) that differ in their

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Accompanying Data S1, Tables S1 through S14, and Figures S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013713

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Clinical Perspective

What Is New?

- Chronic kidney disease is associated with compositional and functional abnormalities in high-density lipoprotein.
- We examined associations of high-density lipoprotein particle size, particle subfractions, and apolipoprotein C-III concentration with cardiovascular events across categories of kidney function.
- Associations between high-density lipoprotein size and particle subfractions with cardiovascular events varied significantly by kidney function.

What Are the Clinical Implications?

- Our results may inform future therapeutic trials targeting high-density lipoproteins in people with chronic kidney disease.

lipid composition and function.[6] Although small and large particles appear equally capable of reverse-cholesterol transport, small particles have potentially more potent anti-inflammatory and antioxidative vascular effect than their large counterparts.[6,7] The functionality of HDL according to particle size appears to be determined in part by the background dyslipidemic phenotype.[6] For instance, in a background of atherogenic dyslipidemia (elevated triglyceride-rich lipoproteins), small particles may not retain their protective vascular effect. These observations may be relevant to patients with CKD whose typical dyslipidemic phenotype is that of the atherogenic dyslipidemia.

In addition to HDLp size, the apolipoprotein content of HDL is an important determinant of its function. Apolipoprotein A-I is the main structural protein of HDL and a major determinant of its protective vascular effect.[4] Apolipoprotein C-III, which is present in 5% to 15% of HDLp, is an important modulator of HDL function. For instance, recent research conducted in the general population has demonstrated that the known protective vascular effect of HDL, quantified by apolipoprotein A-I, is limited to apolipoprotein A-I devoid of apolipoprotein C-III.[8] These observations may be particularly important in patients with CKD, who have a decreased fractional catabolic rate of apolipoprotein C-III and enrichment of HDL-associated apolipoprotein C-III.[9,10]

These results suggest that the association of HDLp subfractions and HDL apolipoprotein C-III content with incident CVD events may vary by kidney function. In this prospective observational study, we describe differences in HDL size, in the concentration of particle subfractions, and in HDL apolipoprotein C-III content across estimated glomerular filtration rate (eGFR) categories and examine associations with incident CVD events.

Materials and Methods

Study Population

MESA (Multi-Ethnic Study of Atherosclerosis) is a population-based prospective cohort study aimed at investigating risk factors for the onset and progression of CVD.[11] Participants in MESA were recruited between 2000 and 2002 from 6 US locations: New York, NY; Baltimore, MD; Chicago, IL; Los Angeles, CA; Twin Cities, MN; and Winston Salem, NC.

For this study, 6814 MESA participants without clinical CVD at baseline (MESA visit 1), conducted between 2000 and 2002, were included. Of these participants, those with missing cystatin-C or creatinine measurements (n=65), missing measurements of HDLc or HDLp (n=16), and missing event time data (n=30) were excluded from the analyses. For the HDLp subfraction analyses, the final study population consisted of 6699 participants (98% of the initial population) meeting the eligibility criteria. HDL apolipoprotein C-III measurements were performed in baseline plasma samples from 5795 MESA participants (1000 participants were randomly excluded by the MESA Steering Committee to preserve sample volume). For the HDL apolipoprotein C-III analyses, the final study population consisted of 5723 MESA participants (84% of the initial population) meeting the eligibility criteria and with available measurements of HDL apolipoprotein C-III.

MESA was approved by the institutional review boards of all participating institutions. All participants gave written informed consent before the start of the study. The data that support the findings of this study are available from the corresponding author on reasonable request.

Kidney Function

Kidney function was assessed by calculating the eGFR, which was calculated from serum creatinine and cystatin-C using the CKD Epidemiology Collaboration equation.[12] Serum creatinine was measured by rate reflectance spectrophotometry at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, MN). The intra-assay coefficient of variation was 2.2%. Serum cystatin C was measured with a nephelometer (BNII; Dade Behring) and was calibrated to Cleveland Clinic using internal standards supplied by the manufacturer. The intra-assay coefficient of variation ranged from 2.0% to 2.8%.

High-Density Lipoproteins

The concentration of HDLc was measured in the fasting state using standardized enzymatic methods. Nuclear magnetic spectroscopy was used to measure mean HDL size and the

concentration of HDLp.[13] Nuclear magnetic spectroscopy quantifies particle concentrations of lipoproteins of different size by measuring their distinctive signals emanated from their terminal methyl group. On the basis of this method, the concentration (in μmol/L) of the following particle subfractions was measured according to their size (values in parenthesis): small HDLp (7.3–8.1 nm), medium HDLp (8.2–9.3 nm), and large HDLp (9.4–14 nm).

HDL Apolipoproteins

Methods for the measurement of HDL apolipoprotein A-I with and without apolipoprotein C-III have been previously described in detail.[14–16] Briefly, plasma samples in MESA were frozen at −70°C. On funding of the original apolipoprotein C-III study, samples were thawed to send an aliquot on dry ice to the lipid laboratory at Harvard T.H. Chan School of Public Health. Received samples were immediately stored in liquid nitrogen freezers and thawed immediately before the apolipoprotein measurement in 2014. Whole plasma was first fractioned into lipoproteins with and without apolipoprotein C-III by immune-affinity separation with rabbit anti-human apolipoprotein C-III antibody. Standard sandwich ELISA with anti–apolipoprotein A-I polyclonal antibodies was then used in both plasma fractions to measure apolipoprotein A-I concentrations in lipoproteins with and without apolipoprotein C-III. Total apolipoprotein A-I was calculated as the sum of the 2 apolipoprotein A-I fractions. The average within-run coefficient of variation was 4% for total apolipoprotein C-III, 5% for apolipoprotein A-I without apolipoprotein C-III, and 8% for apolipoprotein A-I with apolipoprotein C-III.

Markers of Inflammation

High-sensitivity CRP (C-reactive protein) was measured by nephelometry and interleukin-6 by ultrasensitive ELISA. Nuclear magnetic spectroscopy was used to measure GlycA, a marker of systemic inflammation, reflecting the integrated concentration and glycosylation of several acute-phase proteins.[17]

Additional Baseline Assessments

Additional baseline information consisted of sociodemographic characteristics, including age, sex, and race; anthropometric measurements, including height, weight, and body mass index; self-reported medical history; current medications; and lifestyle behaviors, including history of tobacco use, defined as never, former, or current tobacco user (and, for current or former users, pack-years of exposure). Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL or use of antidiabetic medications, including insulin. Blood pressure was assessed by the systolic and diastolic blood pressure value at baseline and use of antihypertensive medications. Socioeconomic status was assessed by degree of education (college or higher) and yearly family income. Additional measurements included reported alcohol use, reported physical activity level, urinary albumin/creatinine ratio, body mass index, total cholesterol, low-density lipoprotein cholesterol, and triglycerides.

Incident CVD

The primary end point was a composite cardiovascular end point of the first occurrence of myocardial infarction, resuscitated cardiac arrest, nonfatal stroke, or coronary heart disease or stroke death, according to MESA recommended analyses of adjudicated end points (Data S1). In MESA, identification of clinical events is done through active surveillance by trained staff. MESA staff document possible events through review and abstraction of medical records and death certificates, interviews, questionnaires, and other procedures. At least 2 physicians reviewed each possible event case, and its data were analyzed by standardized criteria to assign a final classification.

Statistical Analysis

Baseline demographic and clinical characteristics were compared using the χ^2 statistic for categorical variables and the Kruskal-Wallis statistic for continuous variables. Multiple linear regression was used to examine the associations between categories of kidney function and concentrations of HDLc, HDLp, and HDL particle subfractions, adjusting for age, sex, and ethnicity. These coefficients were then used to calculate mean concentrations of HDL particles across eGFR categories. These models were also used to obtain adjusted concentrations of apolipoprotein C-III, total apolipoprotein A-I, and apolipoprotein A-I with or without apolipoprotein C-III, with a robust variance estimation specification. Residual diagnostics were used to test distributional assumptions.

To calculate the proportion of HDL particles with apolipoprotein C-III, the concentration of HDL apolipoprotein A-I with apolipoprotein C-III was divided by the total HDL apolipoprotein A-I concentration. Two strategies were then used when modeling these proportions as a function of eGFR. We used tobit regression with modeling of HDL apolipoprotein C-III proportions as a function of eGFR, with specification of an upper censoring limit (maximum observed proportion), adjusting for age, sex, and ethnicity. In addition, we created a binary variable with high or low HDL apolipoprotein C-III proportions based on a 75th percentile threshold. We then used Poisson regression with robust variance estimation to

obtain probabilities, adjusting for age, sex, and ethnicity by eGFR.

In survival analyses, participants were followed up from the time of the first MESA visit to the development of a CVD event or to the end of follow-up. Cox-regression methods were used to examine the association of HDLc, HDLp, HDLp subfractions, apolipoprotein C-III, and apolipoprotein A-I with or without apolipoprotein C-III (per 1-SD higher biomarker concentration) with incident CVD, with models sequentially adjusting for possible confounders (Table S1). The proportional hazard assumption was tested through examination of the time dependency of the Schoenfeld partial residuals. Final models adjusted for age, sex, ethnicity, socioeconomic status, reported physical activity, reported alcohol use, presence of diabetes mellitus, systolic blood pressure, diastolic blood pressure, use of an antihypertensive medication, cigarette smoking status, including current, former, or never user (or, in case of current or former user, pack-year history of tobacco use), current use of any lipid-lowering therapy, including statins and fibrates, urinary albumin/creatinine ratio, and body mass index. Likelihood ratio tests were used to evaluate for the presence of multiplicative interactions in the associations of HDL particles and HDL apolipoprotein C-III content with CVD events by eGFR categories.

Given the strong correlation among HDL particle subfractions (Figure S1), analyses of HDL particles with CVD also adjust for other fractions. For example, multivariable models of the concentrations of large HDLp adjust for concentrations of small and medium HDLp. This approach follows previously published methods for the analysis of small and large low-density lipoprotein particles.[18] Similarly, multivariable models of HDL apolipoproteins and CVD events adjust for the complementary fraction (eg, adjustment for the concentration of HDL without apolipoprotein C-III when we investigate the association of the concentration of HDL with apolipoprotein C-III and CVD events), following previously published methods.[8]

Results

Of the total study population (n=6699), 572 participants (9%) had an eGFR <60 mL/min per 1.73 m^2 at baseline. Participants with lower eGFR were, on average, older and had a markedly higher proportion of diabetes mellitus, hypertension, and use of any lipid-lowering therapy, including statins (Table 1). The concentrations of inflammatory markers, including CRP, interleukin-6, and GlycA were all significantly higher with lower eGFR. Although no substantial differences were encountered for the concentration of total and low-density lipoprotein cholesterol, participants with CKD had significantly higher triglyceride concentrations.

HDL Lipoprotein Particles and HDL Apolipoproteins

Concentrations of HDLc and total HDLp were significantly lower in patients with lower eGFR (Table 2). Although concentrations of small HDLp were not significantly different across eGFR categories, participants with eGFR <45 mL/min per 1.73 m^2 had a significantly lower mean HDL size and concentration of medium HDLp and large HDLp compared with participants with eGFR ≥60 mL/min per 1.73 m^2 (Table 2).

Total concentrations of total plasma apolipoprotein C-III were higher and HDL apolipoprotein A-I lower in patients with lower eGFR (Table 2). Concentrations of HDL apolipoprotein A-I with apolipoprotein C-III were higher and those of apolipoprotein A-I without apolipoprotein C-III were lower in participants with eGFR <45 mL/min per 1.73 m^2 compared with those with eGFR ≥60 mL/min per 1.73 m^2 (Table 2).

A minority of HDL apolipoprotein A-I contained apolipoprotein C-III: median (interquartile range)=6% (5%–7%). Lower eGFR was associated with a higher proportion of HDL containing apolipoprotein C-III. Each 17 mL/min per 1.73 m^2 lower estimated eGFR (1 SD) was associated with a 0.1% (P=0.020) higher HDL with apolipoprotein C-III. Consistent with these findings, the probability of HDL apolipoprotein A-I having a high apolipoprotein C-III (proportion >75th percentile=7%) was 10% higher in participants with eGFR <60 mL/min per 1.73 m^2 compared with those without eGFR ≥60 mL/min per 1.73 m^2 (P<0.001) (Figure S2).

High-Density Lipoproteins and Apolipoproteins and Incident CVD

During a median follow-up time of 11 years, incident CVD developed in 552 participants (9%) with eGFR ≥60 mL/min per 1.73 m^2, 87 participants (20%) with eGFR 45 to 59 mL/min per 1.73 m^2, and in 33 participants (25%) with eGFR <45 mL/min per 1.73 m^2. Crude incident CVD rates were 7.3 events per 1000 person-years in participants with eGFR ≥60 mL/min per 1.73 m^2, 19 events per 1000 person-years in participants with eGFR 45 to 59 mL/min per 1.73 m^2, and 28 events per 1000 person-years in those with eGFR <45 mL/min per 1.73 m^2 (P for difference in event rates <0.001).

HDLc was strongly and positively correlated with large HDLp (r=0.9) and negatively correlated with small HDLp (r=−0.28) (Figure S1). Mean HDL size was significantly associated with CVD in participants with eGFR <60 mL/min per 1.73 m^2 with evidence of significant heterogeneity by eGFR category. Similarly, eGFR significantly modified the association between HDL particle subfractions and CVD (P for interaction by presence of CKD=0.04) (Table 3). Although

Table 1. Demographic and Clinical Characteristics Across eGFR Categories

Characteristics	eGFR, mL/min per 1.73 m^2		
	≥60 (n=6127)	45–59 (n=440)	<45 (n=132)
Demographics			
Age, y	61 (53–69)	74 (68–79)	75 (67–79)
Women	3200 (52)	263 (59)	72 (55)
Race			
Black	1705 (28)	101 (23)	39 (29)
White	2317 (38)	223 (51)	45 (34)
Chinese	737 (12)	42 (10)	16 (12)
Hispanic	1368 (22)	74 (17)	32 (24)
Medical history			
Diabetes mellitus	725 (12)	67 (15)	42 (32)
Hypertension	2587 (42)	316 (72)	112 (84)
SBP, mm Hg	122 (110–138)	135 (117–148)	140 (118–156)
DBP, mm Hg	72 (65–79)	70 (63–77)	72 (63–79)
Smoking			
Former	2237 (37)	163 (37)	47 (36)
Current	814 (13)	41 (9)	14 (11)
Pack-years, mean (SD)	11 (21)	12 (36)	12 (21)
BMI, kg/m^2	28 (24–31)	28 (25–32)	28 (25–33)
Lipid-lowering therapy	947 (15)	100 (22)	40 (30)
Statins	875 (14)	89 (21)	35 (26)
Fibrates	60 (1)	13 (2)	5 (3)
Alcohol use (current)	3430 (69)	215 (63)	50 (54)
Physical activity, h/wk	12 (9–15)	10 (7–14)	10 (7–15)
Social history			
Education (college or higher)	2226 (36)	107 (24)	27 (20)
Family income (>50 000/y)	2419 (91)	104 (80)	30 (73)
Markers of inflammation			
CRP, mg/L	1.85 (0.81–4.18)	2.42 (1.13–5.42)	2.49 (1.20–5.66)
Interleukin-6, pg/mL	1.16 (0.75–1.83)	1.55 (1.10–2.41)	1.74 (1.20–2.68)
GlycA, μmol/L	373 (335–417)	395 (350–444)	414 (380–454)
Lipids			
Total cholesterol, mg/dL	192 (170–215)	194 (175–216)	184 (165–215)
LDLc, mg/dL	116 (96–136)	115 (96–135)	109 (89–134)
Triglycerides, mg/dL	110 (77–159)	128 (91–175)	131 (92–197)
Markers of kidney function			
eGFR, mL/min per 1.73 m^2	87 (77–99)	55 (51–36)	38 (30–43)
UACR, mg/g	5 (3–10)	8 (4–21)	25 (7–187)

Data are given as number (percentage) or median (interquartile range), unless otherwise specified. All comparisons are statistically significant ($P<0.05$), except for concentrations of total cholesterol ($P=0.8$) and LDL cholesterol ($P=0.4$). BMI indicates body mass index; CRP, high-sensitivity C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDLc, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

higher concentrations of small HDLp were not associated with lower risk of CVD in patients with eGFR <60 mL/min per 1.73 m^2, higher concentrations of large HDLp were strongly associated with lower CVD risk in participants with lower kidney function (Table 3).

Table 2. Baseline Concentrations of HDL and HDL Apolipoproteins Across eGFR Categories

Variables	eGFR, mL/min per 1.73 m^2			*P* Value*
	≥60 (n=6127)	45–59 (n=440)	<45 (n=132)	
HDLc, mg/dL	51.34 (51.00–51.68)	48.31 (47.00–49.63)	44.91 (42.56–47.25)	<0.001
HDLp, μmol/L	34.24 (34.09–34.39)	32.51 (31.93–33.08)	30.48 (29.45–31.51)	<0.001
Mean HDL size, nm	9.26 (9.25–9.27)	9.21 (9.17–9.25)	9.19 (9.11–9.26)	0.02
HDLp subfraction, μmol/L				
Small HDLp	14.76 (14.62–14.90)	14.34 (13.79–14.89)	15.17 (14.19–16.14)	0.23
Medium HDLp	13.38 (13.22–13.54)	12.78 (12.15–13.41)	10.49 (9.37–11.61)	<0.001
Large HDLp	6.09 (6.01–6.17)	5.38 (5.08–5.69)	4.83 (4.28–5.37)	<0.001
Total apolipoprotein C-III, mg/dL	9.26 (9.15–9.37)	10.27 (9.85–10.68)	11.07 (10.35–11.80)	<0.001
Total HDL apolipoprotein A-I, mg/dL	131 (130–132)	124 (121–128)	118 (112–125)	<0.001
HDL apolipoprotein A-I without apolipoprotein C-III	123 (122–124)	116 (113–119)	111 (106–116)	<0.001
HDL apolipoprotein A-I with apolipoprotein C-III	8.45 (8.38–8.53)	8.82 (8.54–9.09)	9.06 (8.57–9.54)	<0.001

Data are given as mean concentrations (95% CIs), adjusted for age, sex, and ethnicity. eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein; HDLc, HDL cholesterol; HDLp, HDL particles.
**P* value calculated on the basis of global test for equality in means across eGFR categories.

Higher total HDL apolipoprotein A-I concentrations were inversely associated with lower CVD risk across categories of kidney function, with numerically (albeit not statistically significant) stronger associations among participants with lower eGFR (*P* for interaction=0.20) (Table 4). Overall, the inverse associations between HDL apolipoprotein A-I were confined to HDL apolipoprotein A-I without apolipoprotein C-III (hazard ratio per 1-SD higher HDL apolipoprotein A-I, 0.84; 95% CI, 0.75–0.95). Although estimates for the association between HDL apolipoprotein A-I without apolipoprotein C-III and CVD appeared stronger among participants with lower kidney function, tests for interaction were not significant (*P* for interaction=0.19). Similar results were obtained in categorical analyses (by tertiles of predictors) of HDL lipoproteins and HDL apolipoproteins (Table S2).

Sensitivity Analyses

Results were consistent when further stratifying the sample by eGFR and albuminuria (urinary albumin/creatinine ratio >30 mg/g) (Tables S3 and S4). We also excluded 1087 participants on any lipid-lowering therapy, including statins and fibrates, with largely unchanged results (Table S5).

To evaluate whether the results observed in the analyses of HDL particle subfractions and apolipoproteins with CVD were

Table 3. Associations Between HDL Cholesterol and Particles With Cardiovascular Events Across eGFR Categories

Variables	eGFR, mL/min per 1.73 m^2			*P* for Interaction*
	≥60 (n=6127)	45–59 (n=440)	<45 (n=132)	
HDLc	0.91 (0.81–1.02)	0.61 (0.44–0.84)	0.56 (0.30–1.05)	0.31
HDLp	0.86 (0.77–0.95)	0.84 (0.63–1.12)	0.84 (0.53–1.33)	0.67
Mean HDL size	1.00 (0.90–1.11)	0.65 (0.48–0.86)	0.48 (0.25–0.93)	0.05
HDLp subfractions				0.04†
Small HDLp	0.81 (0.70–0.94)	1.10 (0.76–1.59)	1.78 (0.81–3.91)	0.06
Medium HDLp	0.81 (0.70–0.94)	1.07 (0.72–1.58)	1.13 (0.48–2.64)	0.84
Large HDLp	0.96 (0.85–1.08)	0.52 (0.35–0.78)	0.42 (0.17–1.01)	0.09

Data are given as hazard ratios per 1-SD higher concentration in predictor (95% CIs). SD in HDL lipoproteins: HDLc (14 mg/dL), mean HDL size (0.45 nm), HDLp (6 μmol/L), large HDLp (3.5 μmol/L), medium HDLp (7 μmol/L), and small HDLp (6 μmol/L). Hazard ratios adjusted for age, sex, ethnicity, diabetes mellitus, socioeconomic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin/creatinine ratio, body mass index, cigarette smoking, and reported alcohol use. Additional simultaneous adjustment for complementary subfractions on HDLp subfraction models. eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein; HDLc, HDL cholesterol; HDLp, HDL particles.
*Multiplicative interactions evaluated with likelihood ratio tests.
†*P* value for significance of global interaction between eGFR and each HDLp subfraction.

Table 4. Associations Between HDL Apolipoproteins With Cardiovascular Events Across eGFR Categories

Variables	All Participants (n=5723)	eGFR, mL/min per 1.73 m^2			*P* for Interaction*
		≥60 (n=5215)	45–59 (n=387)	<45 (n=121)	
Total apolipoprotein C-III	1.14 (1.05–1.23)	1.11 (1.00–1.21)	1.24 (0.94–1.65)	1.65 (1.04–2.60)	0.78
Total HDL apolipoprotein A-I	0.89 (0.80–0.99)	0.95 (0.85–1.07)	0.74 (0.55–0.98)	0.53 (0.28–1.00)	0.20
HDL apolipoprotein A-I without apolipoprotein C-III	0.84 (0.75–0.95)	0.90 (0.78–1.02)	0.73 (0.52–1.02)	0.55 (0.25–1.25)	0.19
HDL apolipoprotein A-I with apolipoprotein C-III	1.09 (0.99–1.19)	1.10 (0.99–1.22)	1.01 (0.73–1.39)	0.94 (0.45–1.95)	0.36

Data are given as hazard ratios per 1-SD higher concentration in predictor (95% CIs). SD in HDL apolipoproteins: total HDL apolipoprotein A-1 (37 mg/dL), HDL apolipoprotein A-1 without apolipoprotein C-III (35 mg/dL), and HDL apolipoprotein A-I with apolipoprotein C-III (3 mg/dL). Hazard ratios adjusted for age, sex, ethnicity, diabetes mellitus, socioeconomic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin/creatinine ratio, body mass index, cigarette smoking, and reported alcohol use. eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein.
*Multiplicative interactions evaluated with likelihood ratio tests.

confounded by triglycerides (as a marker of atherogenic dyslipidemia), we first assessed the association of triglycerides with HDLp and apolipoproteins (Figures S3 and S4). These results indicated a negative correlation between triglycerides and large HDLp, minimal correlation between triglycerides and medium HDLp, and a positive correlation between triglycerides and small HDLp. Similarly, higher triglyceride concentrations were correlated with higher total apolipoprotein C-III, lower total apolipoprotein A-I, and higher apolipoprotein A-I with apolipoprotein C-III. Analyses of HDL lipoprotein particles and apolipoproteins with CVD were then conducted with further adjustment for triglycerides (Tables S6 and S7). Although there was a small attenuation in the strength of the association between all HDL lipoproteins and CVD, the strong association between large HDLp with CVD in CKD remained statistically significant and different from that in participants without CKD. Similar results were obtained with adjustment for markers of inflammation (Tables S8 and S9).

To further evaluate the heterogeneity in the association of HDLp with CVD in patients with CKD, we tested for possible modification in the association by levels of inflammatory markers. We categorized each inflammatory marker into high or normal using a 75th percentile threshold. This corresponded to concentrations in interleukin-6 of 1.88 pg/mL, in GlycA of 420 μmol/L, and in CRP of 4.23 mg/L (Tables S10 through S12). Results were consistent with those in the main analyses, suggesting possible (albeit not statistically significant) stronger associations in participants with CKD and high levels of inflammatory markers.

Finally, the results presented in the main analyses were robust to the use of a more specific atherosclerotic CVD end point, including a composite coronary heart disease end point (Table S13) and myocardial infarction (Table S14).

Discussion

In this population-based cohort study, we found that associations between HDL size and HDL particle subfractions and CVD events varied significantly by kidney function. With lower eGFR, higher concentrations of large HDL particles were more strongly associated with CVD risk, but higher concentrations of small HDL particles (which were associated with CVD in participants with eGFR >60 mL/min per 1.73 m^2) were not associated with CVD risk. Across eGFR categories, only HDL without apolipoprotein C-III was associated with the risk of CVD events.

Our results suggest that lower eGFR is associated with higher concentrations of HDL particles that may not have protective cardiovascular effects. These observations support the concept of "dysfunctional HDL" that has been used to refer to the marked compositional and structural changes of HDL in CKD, and that may impair the protective vascular effects of HDL.[1,4] In our study, the possible dysfunctionality of HDL in CKD was supported by the differential expression of smaller HDL particles and of higher concentrations of HDL with higher apolipoprotein C-III concentrations with lower eGFR. Higher concentrations of these particles were not associated with lower CVD risk. These novel results extend previous reports of altered HDL structure and composition in CKD to evaluate associations with clinical cardiovascular events.

On the other hand, lower eGFR was associated with lower concentrations of large HDL particles. Higher concentrations of these particles were associated with lower CVD risk with lower eGFR. These results suggest that with worsening kidney function, there is underexpression of the type of HDL that may have protective vascular effects.

These results may be explained, in part, by the predominance of the atherogenic dyslipidemia that is typical of patients with CKD and caused by a reduced catabolic rate of triglyceride-rich lipoproteins.[19] With the atherogenic dyslipidemia, triglyceride enrichment of HDL enhances its metabolic clearance, leading to lower concentrations of large cholesterol-buoyant HDL and to differential production of smaller HDL particles enriched with triglycerides and devoid of cholesterol.[20,21] The observed reductions in HDL size and in the concentrations of large HDL particles (but not of smaller

and denser particles) in participants with lower eGFR are consistent with these observations.

In addition to the atherogenic dyslipidemia, it has been suggested that the high inflammatory and oxidative burden typically observed in patients with CKD may impair normal HDL maturation and function and be partly responsible for the profound enzymatic dysregulation of HDL metabolism in patients with CKD.[2–4] Although stratified results by level of inflammatory markers appear to strengthen our primary observations of heterogeneity in HDL particles with CVD in participants with eGFR <60 mL/min per 1.73 m^2, the small sample size in these analyses precludes drawing any definitive conclusions. Future larger studies are needed to establish whether the presence of inflammation modifies the association between HDL particle subfractions and CVD in patients with CKD.

We found evidence for enrichment of HDL with apolipoprotein C-III with lower eGFR. These findings are consistent with prior research that has shown decreased clearance of apolipoprotein C-III in patients with moderate CKD and with HDL proteomic analyses showing higher HDL apolipoprotein C-III concentrations with declining kidney function.[9,10] Furthermore, although HDL without apolipoprotein C-III was inversely associated with CVD, no significant associations were found for HDL with apolipoprotein C-III. These results suggest that the protective vascular effect of HDL is confined to HDL lacking apolipoprotein C-III and are consistent with observations from research done in the general population showing qualitative differences in HDL function according to the presence or absence of apolipoprotein C-III.[8] A proposed mechanism for the reduced protective activity of apolipoprotein A-I with apolipoprotein C-III includes reduced anti-inflammatory activity by enhancing monocytic cell adhesions to endothelial cells and by a diminished capacity to inhibit endothelial cell apoptosis.[22,23] More research is, however, needed to understand the mechanisms by which lipoprotein-bound apolipoprotein C-III modulates atherosclerosis. Beyond apolipoprotein C-III, proteomic analyses in people with CKD suggest independent associations between CKD and HDL retinol-binding protein 4, apolipoproetein L1, and vitronectin. The clinical significance of these and other compositional HDL changes remains unknown and should be the focus of further research.

Prior observational studies have shown inconsistent results in the association between HDLc and CVD in CKD. Although studies conducted in MESA and the ARIC (Atherosclerosis Risk in Communities) study have shown strong, independent, inverse associations between HDLc and CVD,[24,25] Bowe et al reported U-shaped associations between HDLc and all-cause mortality and Zewinger et al reported a lack of a protective association between higher HDLc and cardiovascular mortality in patients with CKD.[26,27] Although our results cannot explain the discrepancy in the association between HDLc and CVD between the studies, they add to a large body of evidence that shows that the sole focus on the cholesterol content of HDL lipoproteins may not capture the significant heterogeneity in function between HDL lipoproteins of different structure and composition.[1]

A significant limitation of this study is the small sample of participants with severe reductions in kidney function. These findings should, therefore, be interpreted as preliminary and should be corroborated in larger studies, including people with severe kidney dysfunction. Similarly, the presented tests for interaction should be interpreted in the context of a relatively small sample size of participants with severely reduced kidney function. This limitation is particularly relevant for the HDL apolipoprotein C-III analyses because most of HDL (94% of HDL in our cohort) is devoid of apolipoprotein C-III. Testing for statistically significant interactions would require a substantially larger population with low eGFR. Finally, only a minority of MESA participants had macroalbuminuria or nephrotic range proteinuria. Because significant excretions of protein in the urine may be associated with different patterns of dyslipidemia than those observed in this study, extrapolation of these results to patients with significant proteinuria cannot be made.

Another important limitation of this study is that HDL particles and HDL apolipoproteins were not measured concurrently. Therefore, we cannot directly assess the apolipoprotein content of HDL particles of different size. Our observations lead to additional questions about whether the discrepant associations observed between HDL particles of different size and CVD are related to different content in HDL apolipoproteins or in HDL function. Future studies should, therefore, focus on directly evaluating the association between HDL particles, HDL composition, and HDL function with cardiovascular end points. Finally, we assume that a 1-time measurement of HDL particles and apolipoprotein C-III content is a good proxy for usual long-term concentrations.

In conclusion, our results suggest that HDL particle size, HDL particle subfractions, and HDL apolipoprotein C-III content may be important determinants of the vascular effects of HDL in people with low eGFR. These results offer new mechanistic insights into the strong association between kidney function and CVD and may inform future therapeutic trials targeting HDL lipoproteins in people with CKD.

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Disclosures

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Supplemental Material

Data S1.

MESA adjudication of clinical cardiovascular events.

Trained personnel abstracted any hospital records suggesting possible cardiovascular events. They recorded symptoms, history and biomarkers; scanned ECGs, echocardiograms, catheterization reports, outpatient records, and other relevant diagnostic and procedure reports; and transmitted these to the coordinating center. The coordinating center collated the abstracted or original endpoint records and sent them to two paired physicians for independent endpoint classification and assignment of incidence dates. Cardiologists or cardiovascular physician epidemiologists reviewed non-neurovascular endpoints; neurologists reviewed all neurovascular endpoints. If the reviewing pair disagreed on the classification, they adjudicated differences. If disagreements persisted, the full review committee made the final classification.

MYOCARDIAL INFARCTION. Reviewers classified MI as definite, probable, or absent, based primarily on combinations of symptoms, ECG, and cardiac biomarker levels. In most cases, definite or probable MI required either abnormal cardiac biomarkers (2 times upper limits of normal) regardless of pain or ECG findings; evolving Q waves regardless of pain or biomarker findings; or a combination of chest pain, and ST-T evolution or new LBBB, and biomarker levels 1-2 times upper limits of normal.

RESUSCITATED CARDIAC ARREST. Reviewers classified resuscitated cardiac arrest when a patient successfully recovered from a full cardiac arrest through cardiopulmonary resuscitation (including cardioversion).

CHD DEATH was classified as definite, possible, or absent. Definite fatal CHD required a documented MI within the previous 28 days, chest pain within the 72 hours before death, or a history of CHD, and required the absence of a known non-atherosclerotic or non-cardiac cause of death. If the definite fatal CHD criteria were not met, possible fatal CHD could be assigned with an underlying cause of death consistent with fatal CHD and required the absence of a known non-atherosclerotic or non-cardiac cause of death.

STROKE was classified as present or absent and consisted of rapid onset of a documented focal neurologic deficit lasting 24 hours or until death, or if < 24 hours, there was a clinically relevant lesion on brain imaging. Patients with focal neurologic deficits secondary to brain trauma, tumor, infection, or other non-vascular cause were excluded. Strokes were subclassified on the basis of neuroimaging or other tests into subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, brain infarction, or other stroke. Infarcts were also subtyped.

Combination	Criteria (any of the following)
CHD	MI
	Resuscitated Cardiac Arrest
	CHD Death
CVD	MI
	Resuscitated Cardiac Arrest
	Stroke (not TIA)
	CHD Death
	Stroke Death

Table S1. Association between HDL particles and apolipoproteins with cardiovascular events in eGFR<60 with sequential adjustment for confounders.

	Model 1	Model 2	Model 3
HDLc	0.66 (0.52, 0.82)	0.65 (0.52, 0.81)	0.59 (0.45, 0.77)
HDLp	0.79 (0.66, 0.96)	0.80 (0.65, 0.97)	0.81 (0.64, 1.03)
Mean HDL size	0.69 (0.57, 0.85)	0.68 (0.55, 0.83)	0.63 (0.49, 0.81)
HDLp sub-fraction			
Small HDLp	1.01 (0.79, 1.29)	1.02 (0.79, 1.31)	1.15 (0.84, 1.57)
Medium HDLp	0.92 (0.70, 1.22)	0.94 (0.71, 1.25)	1.03 (0.73, 1.45)
Large HDLp	0.62 (0.47, 0.80)	0.60 (0.45, 0.78)	0.52 (0.36, 0.74)
Total HDL Apo A-I	0.70 (0.56, 0.86)	0.70 (0.56, 0.86)	0.69 (0.53, 0.88)
HDL Apo A-I without Apo C-III	0.70 (0.54, 0.90)	0.70 (0.54, 0.91)	0.69 (0.51, 0.93)
HDL Apo A-I with Apo C-III	0.99 (0.79, 1.24)	0.99 (0.79, 1.23)	0.99 (0.75, 1.31)

Model 1: Adjustment for age, sex, and ethnicity

Model 2: Adjustment for model 1 plus body mass index, and tobacco use

Model 3: Adjustment for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking, reported alcohol use. Additional simultaneous adjustment for complementary subfractions on HDLp subfraction models.

Cell contents are hazard ratios (HR) per one standard deviation increase in predictor and 95% confidence intervals.

Standard deviation in HDL lipoproteins: HDLc (14 mg/dl), mean HDL size (0.45 nm), HDLp (6 μmol/L), large HDLp (3.5 μmol/L), medium HDLp (7 μmol/L), small HDLp (6 μmol/L).

Table S2. Categorical associations between HDL cholesterol and particles, and HDL apolipoproteins with cardiovascular events by eGFR.

Lipid category	eGFR≥60 (n=6,127)		eGFR<60 (n=572)	
	N at risk (N events)	HR (95%CI)	N at risk (N events)	HR (95%CI)
HDLc; mg/dl				
≤43	2115 (244)	Ref	225 (55)	Ref
44-55	2056 (173)	0.88 (0.70, 1.11)	165 (39)	0.86 (0.52, 1.43)
>55	1956 (135)	0.76 (0.57, 1.00)	182 (26)	0.36 (0.19, 0.67)
HDLp; µmol/L				
≤30	1743 (195)	Ref	201 (50)	Ref
30-36	2230 (211)	0.91 (0.72, 1.14)	182 (37)	0.65 (0.37,1.14)
>36	2154 (146)	0.72 (0.55, 0.94)	189 (33)	0.57 (0.31, 1.04)
Mean HDL size, nmol				
≤9	2311 (241)	Ref	192 (49)	Ref
9-9.4	1813 (142)	0.77(0.59, 0.99)	177 (43)	0.91 (0.55, 1.50)
>9.4	2003 (169)	1.00 (0.78, 1.28)	203 (28)	0.39 (0.21, 0.73)
Small HDLp; µmol/L				
≤9	2038 (170)	Ref	179 (28)	Ref
9-9.4	2103 (182)	0.77 (0.59, 1.00)	194 (40)	1.16 (0.59, 2.24)
>9.4	1986 (200)	0.69 (0.51, 0.95)	199 (52)	1.53 (0.74, 3.14)
Medium HDLp; µmol/L				
≤9.8	1995 (224)	Ref	227 (58)	Ref
9.8-15.2	2029 (184)	0.69 (0.54, 0.89)	178 (31)	0.80 (0.45, 1.43)
>15.2	2103 (144)	0.63 (0.47, 0.86)	167 (23)	0.87 (0.44, 1.70)
Large HDLp; µmol/L				
≤3.9	2036 (216)	Ref	188 (50)	Ref
3.9-6.8	2043 (183)	0.97 (0.73, 1.27)	202 (47)	0.87 (0.51, 1.49)
>6.8	2048 (153)	0.91 (0.55, 1.51)	182 (23)	0.29 (0.14, 0.60)
Total HDL Apo A-I; mg/dl				
≤113	1663 (189)	Ref	176 (47)	Ref
113-139	1753 (152)	0.82 (0.63, 1.06)	176 (40)	0.63 (0.35, 1.11)
>139	1799 (141)	0.93 (0.70, 1.23)	156 (24)	0.48 (0.25, 0.96)

HDL Apo A-I without Apo C-III ≤106 106-129 >129	1672 (191) 1700 (142) 1843 (149)	Ref 0.75 (0.58, 0.98) 0.86 (0.63, 1.16)	183 (49) 163 (38) 162 (24)	Ref 0.67 (0.36, 1.22) 0.47 (0.21, 1.04)
HDL Apo A-I with Apo C-III ≤6.82 6.82-9.09 >9.09	1749 (176) 1702 (154) 1764 (152)	Ref 0.98 (0.76, 1.28) 1.24 (0.91, 1.68)	136 (36) 180 (38) 192 (37)	Ref 0.72 (0.38, 1.38) 0.97 (0.43, 1.74)

N without ≥60=6127 for HDL lipoproteins, and 5,215 for HDL apolipoproteins

[†]N with <60=572 for HDL lipoproteins, and 508 for HDL apolipoproteins

CVD (cardiovascular disease), HDLc (high-density lipoprotein cholesterol), HDLp (high density lipoprotein particles), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate).

Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking and reported alcohol use. Additional simultaneous adjustment for complementary subfractions on HDLp subfraction models.

Table S3. Associations between HDL cholesterol and particles with cardiovascular events by eGFR and albuminuria strata.

	eGFR≥60 without albuminuria (n=5622)	eGFR≥60 with albuminuria (n=505)	eGFR<60 without albuminuria (n=418)	eGFR<60 with albuminuria (n=154)	P-interaction*
HDLc	0.88 (0.77, 0.99)	1.08 (0.82, 1.41)	0.67 (0.48, 0.92)	0.51 (0.28, 0.91)	0.06
HDLp	0.86 (0.76, 0.96)	0.83 (0.63, 1.09)	0.94 (0.70, 1.26)	0.68 (0.42, 1.09)	0.51
Mean HDL size	1.03 (0.91, 1.15)	0.82 (0.63, 1.07)	0.70 (0.52, 0.95)	0.59 (0.36, 0.97)	0.05
HDLp sub-fractions					0.02
Small HDLp	0.83 (0.71, 0.97)	0.66 (0.45, 0.96)	1.26 (0.86, 1.85)	1.07 (0.57, 2.02)	0.24
Medium HDLp	0.80 (0.68, 0.94)	0.92 (0.66, 1.29)	1.15 (0.77, 1.70)	0.87 (0.41, 1.86)	0.62
Large HDLp	0.97 (0.86, 1.11)	0.79 (0.56, 1.10)	0.62 (0.41, 0.94)	0.41 (0.19, 0.88)	0.06

CVD events. eGFR ≥60 without albuminuria=467 **eGFR** ≥60 with albuminuria=85 **eGFR<**60 without albuminuria=82 **eGFR<**60 with albuminuria=38

CVD (cardiovascular disease), HDLc (high-density lipoprotein cholesterol), HDLp (high density lipoprotein particles), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate).

Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.

Standard deviation in HDL lipoproteins: HDLc (14 mg/dl), mean HDL size (0.45 nm), HDLp (6 μmol/L), large HDLp (3.5 μmol/L), medium HDLp (7 μmol/L), small HDLp (6 μmol/L).

Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking and reported alcohol use. Additional simultaneous adjustment for complementary subfractions on HDLp subfraction models.

*Multiplicative interactions evaluated with likelihood ratio tests.

†P-value for significance of global interaction between CKD and each HDLp size.

Table S4. Associations between HDL apolipoproteins with cardiovascular events by eGFR and albuminuria strata.

	eGFR≥60 without albuminuria (n=4765)	eGFR≥60 with albuminuria (n=450)	eGFR<60 without albuminuria (n=369)	eGFR<60 with albuminuria (n=139)	P-interaction*
Total Apo C-III	1.11 (1.00, 1.23)	1.07 (0.89, 1.30)	1.26 (0.92, 1.71)	1.15 (0.84, 1.58)	0.82
Total HDL Apo A-I	0.95 (0.84, 1.07)	0.92 (0.66, 1.29)	0.77 (0.57, 1.01)	0.51 (0.28, 0.95)	0.09
HDL Apo A-I without Apo C-III	0.89 (0.77, 1.02)	0.93 (0.62, 1.36)	0.82 (0.56, 1.19)	0.42 (0.21, 0.85)	0.08
HDL Apo A-I with Apo C-III	1.10 (0.99, 1.23)	1.00 (0.69, 1.44)	0.91 (0.64, 1.30)	1.32 (0.78, 2.24)	0.73

CVD events. eGFR ≥60 without albuminuria=410 eGFR ≥60 with albuminuria=72 eGFR<60 without albuminuria=74 eGFR<60 with albuminuria=37

HDL (high density lipoprotein), Apo A-1 (apolipoprotein A-I), Apo C-III (apolipoprotein C-III), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate).

Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.

Standard deviation in HDL apolipoproteins: Total HDL Apo A-1 (37 mg/dl), HDL Apo A-1 without Apo C-III (35 mg/dl), HDL Apo A-I with Apo C-III (3 mg/dl).

Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking and reported alcohol use.

*Multiplicative interactions evaluated with likelihood ratio tests.

Table S5. **Associations between HDL particles and apolipoproteins with cardiovascular events by eGFR excluding 1087 participants on lipid lowering therapy.**

	All participants (n=5612)	eGFR≥60 (n=5180)	eGFR<60 (n=432)	P-value for Interaction*
HDLc	0.81 (0.72, 0.92)	0.88 (0.78, 1.00)	0.56 (0.41, 0.75)	0.22
HDLp	0.77 (0.69,0.86)	0.79 (0.70,0.89)	0.72 (0.55, 0.94)	0.47
Mean HDLp size	0.95 (0.85,1.05)	1.04 (0.92, 1.16)	0.58 (0.44, 0.78)	0.01
HDLp subfraction				0.02 †
Small HDLp	0.79 (0.68, 0.91)	0.76 (0.64, 0.89)	1.08 (0.75, 1.55)	0.04
Medium HDLp	0.72 (0.62, 0.84)	0.72 (0.61,0.84)	0.91 (0.62, 1.35)	0.96
Large HDLp	0.88 (0.77,0.99)	0.97 (0.85,1.09)	0.47 (0.31, 0.72)	0.03
Total Apo C-III	1.12 (1.02, 1.24)	1.08 (0.97, 1.20)	1.31 (1.01, 1.68)	0.12
Total HDL Apo A-I	0.86 (0.76, 0.96)	0.92 (0.81, 1.05)	0.66 (0.49, 0.88)	0.17
HDL Apo A-I without Apo C-III	0.81 (0.71, 0.91)	0.87 (0.75, 1.00)	0.67 (0.47, 0.95)	0.14
HDL Apo A-I with Apo C-III	1.09 (0.98, 1.21)	1.09 (0.99, 1.23)	0.98 (0.71, 1.33)	0.37

N with eGFR ≥60=4382 for HDL apolipoproteins, and 378 with eGFR<60

HDL (high density lipoprotein), Apo A-1 (apolipoprotein A-I), Apo C-III (apolipoprotein C-III), eGFR (estimated glomerular filtration rate).

Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.

Standard deviation in HDL apolipoproteins: Total HDL Apo A-1 (37 mg/dl), HDL Apo A-1 without Apo C-III (35 mg/dl), HDL Apo A-I with Apo C-III (3 mg/dl).

Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking and reported alcohol use.

*Multiplicative interactions evaluated with likelihood ratio tests

Table S6. Associations between HDL with CVD events by eGFR conditioning on triglycerides.

	All participants (n=6,699)	eGFR≥60 (n=6,127)	eGFR<60 (n=572)	P-value for Interaction*
HDLc	0.88 (0.78, 0.99)	0.92 (0.81, 1.04)	0.74 (0.54, 1.02)	0.16
HDLp	0.85 (0.77, 0.94)	0.86 (0.77, 0.96)	0.87 (0.69, 1.11)	0.33
Mean HDL size	0.96 (0.86, 1.06)	1.02 (0.91, 1.14)	0.74 (0.56, 0.96)	0.02
HDLp sub-fractions				0.01 †
Small HDLp	0.82 (0.72, 0.94)	0.79 (0.68, 0.92)	1.07 (0.77, 1.46)	0.04
Medium HDLp	0.82 (0.71, 0.93)	0.80 (0.69, 0.93)	1.00 (0.71, 1.40)	0.87
Large HDLp	0.94 (0.83, 1.06)	1.00 (0.88, 1.13)	0.63 (0.43, 0.93)	0.04

CVD (cardiovascular disease), HDLc (high-density lipoprotein cholesterol), HDLp (high density lipoprotein particles), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate).
Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.
Standard deviation in HDL lipoproteins: HDLc (14 mg/dl), mean HDL size (0.45 nm), HDLp (6 μmol/L), large HDLp (3.5 μmol/L), medium HDLp (7 μmol/L), small HDLp (6 μmol/L).
Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking, reported alcohol use, and triglycerides. Additional simultaneous adjustment for complementary subfractions on HDLp subfraction models. *Multiplicative interactions evaluated with likelihood ratio tests.
†P-value for significance of global interaction between CKD and each HDLp size.

Table S7. Associations between HDL apolipoproteins with CVD events by eGFR conditioning on triglycerides.

	All participants (n=5,723)	eGFR≥60 (n=5,215)	eGFR<60 (n=508)	P-value for Interaction
Total Apo C-III	1.11 (0.99, 1.23)	1.14 (1.01, 1.28)	0.92 (0.68, 1.22)	0.47
Total HDL Apo A-I	0.90 (0.81, 1.00)	0.96 (0.85, 1.07)	0.71 (0.54, 0.94)	0.15
HDL Apo A-I without Apo C-III	0.86 (0.76, 0.97)	0.89 (0.78, 1.02)	0.72 (0.52, 0.99)	0.12
HDL Apo A-I with Apo C-III	1.07 (0.97, 1.18)	1.10 (0.78, 1.02)	0.98 (0.74, 1.29)	0.28

HDL (high density lipoprotein), Apo A-1 (apolipoprotein A-I), Apo C-III (apolipoprotein C-III), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate).
Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.
Standard deviation in HDL apolipoproteins: Total HDL Apo A-1 (37 mg/dl), HDL Apo A-1 without Apo C-III (35 mg/dl), HDL Apo A-I with Apo C-III (3 mg/dl).
Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking, reported alcohol use, and triglycerides.
*Multiplicative interactions evaluated with likelihood ratio tests.

Table S8. Associations between HDL with CVD events by eGFR conditioning on markers of inflammation.

	All participants (n=6,699)	eGFR≥60 (n=6,127)	eGFR<60 (n=572)	P-value for Interaction*
HDLc	0.86 (0.77, 0.96)	0.92 (0.82, 1.03)	0.59 (0.43, 0.78)	0.09
HDLp	0.86 (0.77, 0.94)	0.87 (0.78, 0.97)	0.79 (0.60, 1.02)	0.54
Mean HDL size	0.93 (0.83, 1.02)	0.99 (0.89, 1.11)	0.65 (0.50, 0.84)	0.02
HDLp sub-fractions				0.01 †
Small HDLp	0.87 (0.76, 0.99)	0.84 (0.72, 0.98)	1.15 (0.82, 1.61)	0.03
Medium HDLp	0.82 (0.71, 0.95)	0.81 (0.70, 0.95)	0.95 (0.65, 1.36)	0.88
Large HDLp	0.92 (0.82, 1.03)	0.99 (0.88, 1.12)	0.56 (0.38, 0.81)	0.02

CVD (cardiovascular disease), HDLc (high-density lipoprotein cholesterol), HDLp (high density lipoprotein particles), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate).
Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.
Standard deviation in HDL lipoproteins: HDLc (14 mg/dl), mean HDL size (0.45 nm), HDLp (6 μmol/L), large HDLp (3.5 μmol/L), medium HDLp (7 μmol/L), small HDLp (6 μmol/L).
Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking, reported alcohol use, CRP, IL-6 and Glyc-A. Additional simultaneous adjustment for complementary subfractions on HDLp subfraction models.
*Multiplicative interactions evaluated with likelihood ratio tests.
†P-value for significance of global interaction between CKD and each HDLp size.

Table S9. Associations between HDL apolipoproteins with CVD events by eGFR conditioning on markers of inflammation.

	All participants (n=5,723)	eGFR≥60 (n=5,215)	eGFR<60 (n=508)	P-value for Interaction
Total Apo C-III	1.15 (1.05, 1.24)	1.12 (1.02, 1.23)	1.27 (1.01, 1.59)	0.53
Total HDL Apo A-I	0.91 (0.82, 1.01)	0.97 (0.87, 1.09)	0.70 (0.54, 0.91)	0.12
HDL Apo A-I without Apo C-III	0.86 (0.76, 0.97)	0.91 (0.79, 1.03)	0.69 (0.50, 0.95)	0.10
HDL Apo A-I with Apo C-III	1.09 (0.99, 1.20)	1.11 (1.00, 1.23)	1.02 (0.77, 1.36)	0.31

HDL (high density lipoprotein), Apo A-1 (apolipoprotein A-I), Apo C-III (apolipoprotein C-III), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate).
Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.
Standard deviation in HDL apolipoproteins: Total HDL Apo A-1 (37 mg/dl), HDL Apo A-1 without Apo C-III (35 mg/dl), HDL Apo A-I with Apo C-III (3 mg/dl).
Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking, reported alcohol use, and triglycerides.
*Multiplicative interactions evaluated with likelihood ratio tests.

Table s10. Hazard Ratio for CVD (95% CI) per 1 SD higher HDL concentration in participants eGFR<60 stratified by inflammatory biomarker concentration - Interleukin-6.

	eGFR<60 N=572		
	IL6<1.88 pg/ml (n=327)	IL6≥1.88 pg/ml (n=245)	P-value for interaction*
HDLc	0.62 (0.43, 0.89)	0.53 (0.34, 0.83)	0.96
HDLp	0.99 (0.70, 1.41)	0.80 (0.58, 1.10)	0.39
Large HDLp	0.51 (0.31, 0.83)	0.47 (0.24, 0.90)	0.80
Medium HDLp	1.20 (0.82, 1.79)	0.88 (0.48, 1.17)	0.07
Small HDLp	1.27 (0.82, 1.97)	1.55 (0.96, 2.50)	0.28

Table S11. Hazard Ratio for CVD (95% CI) per 1 SD higher HDL concentration in participants eGFR<60 stratified by inflammatory biomarker concentration - Glyc-A.

	eGFR<60 N=572		
	GlycA<420 N=347	GlycA≥420 N=225	P-value for interaction*
HDLc	0.71 (0.49, 1.00)	0.47 (0.29, 0.76)	0.12
HDLp	0.75 (0.51, 1.09)	0.82 (0.57, 1.18)	0.95
Large HDLp	0.59 (0.38, 0.93)	0.41 (0.19, 0.88)	0.12
Medium HDLp	0.96 (0.57, 1.60)	1,01 (0.56, 1.81)	0.10
Small HDLp	0.84 (0.50, 1.39)	1.39 (0.87, 2.20)	0.03

Table S12. Hazard Ratio for CVD (95% CI) per 1 SD higher HDL concentration in participants eGFR<60 stratified by inflammatory biomarker concentration - C-reactive protein.

	eGFR<60 N=572		
	CRP<4.23 N=396	CRP≥4.23 N=176	P-value for interaction*
HDLc	0.64 (0.45, 0.89)	0.45 (0.25, 0.81)	0.17
HDLp	0.93 (0.67, 1.26)	0.70 (0.46, 1.07)	0.64
Large HDLp	0.52 (0.34, 0.81)	0.47 (0.21, 1.05)	0.54
Medium HDLp	1.11 (0.74, 1.60)	0.81 (0.42, 1.54)	0.07
Small HDLp	1.24 (0.82, 1.87)	1.44 (0.78, 2.63)	0.39

CVD (cardiovascular disease), HDLc (high-density lipoprotein cholesterol), HDLp (high density lipoprotein particles), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate).
Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.
Standard deviation in HDL lipoproteins: HDLc (14 mg/dl), mean HDL size (0.45 nm), HDLp (6 μmol/L), large HDLp (3.5 μmol/L), medium HDLp (7 μmol/L), small HDLp (6 μmol/L).
Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking and reported alcohol use. Additional simultaneous adjustment for complementary subfractions on HDLp subfraction models.
*Multiplicative interactions evaluated with likelihood ratio tests.

Table S13. Associations between HDL particles and apolipoproteins with risk of coronary heart disease events by eGFR.

	All participants (n=6,699)	eGFR≥60 (n=6,127)	eGFR<60 (n=572)	P-value for Interaction*
HDLc	0.89 (0.78, 1.01)	0.97 (0.84, 1.12)	0.61 (0.44, 0.86)	0.15
HDLp	0.87 (0.77,0.98)	0.88 (0.77,1.01)	0.85 (0.63, 1.14)	0.49
Mean HDLp size	0.97 (0.86,1.10)	1.07 (0.93, 1.22)	0.67 (0.50, 0.91)	0.05
HDLp subfraction				0.03 †
Small HDLp	0.86 (0.73, 1.02)	0.84 (0.70, 1.01)	1.07 (0.72, 1.57)	0.08
Medium HDLp	0.84 (0.71, 0.99)	0.80 (0.66,0.97)	1.16 (0.77, 1.79)	0.31
Large HDLp	0.93 (0.80, 1.07)	1.04 (0.90,1.21)	0.51 (0.33, 0.79)	0.05
Total Apo C-III	1.08 (0.97, 1.20)	1.02 (0.90, 1.16)	1.26 (0.97, 1.62)	0.39
Total HDL Apo A-I	0.91 (0.79 1.03)	0.99 (0.86, 1.15)	0.66 (0.49, 0.89)	0.05
HDL Apo A-I without Apo C-III	0.87 (0.74, 1.00)	0.94 (0.79, 1.11)	0.68 (0.49, 0.94)	0.06
HDL Apo A-I with Apo C-III	1.07 (0.94, 1.21)	1.09 (0.95, 1.25)	0.97 (0.69, 1.36)	0.18

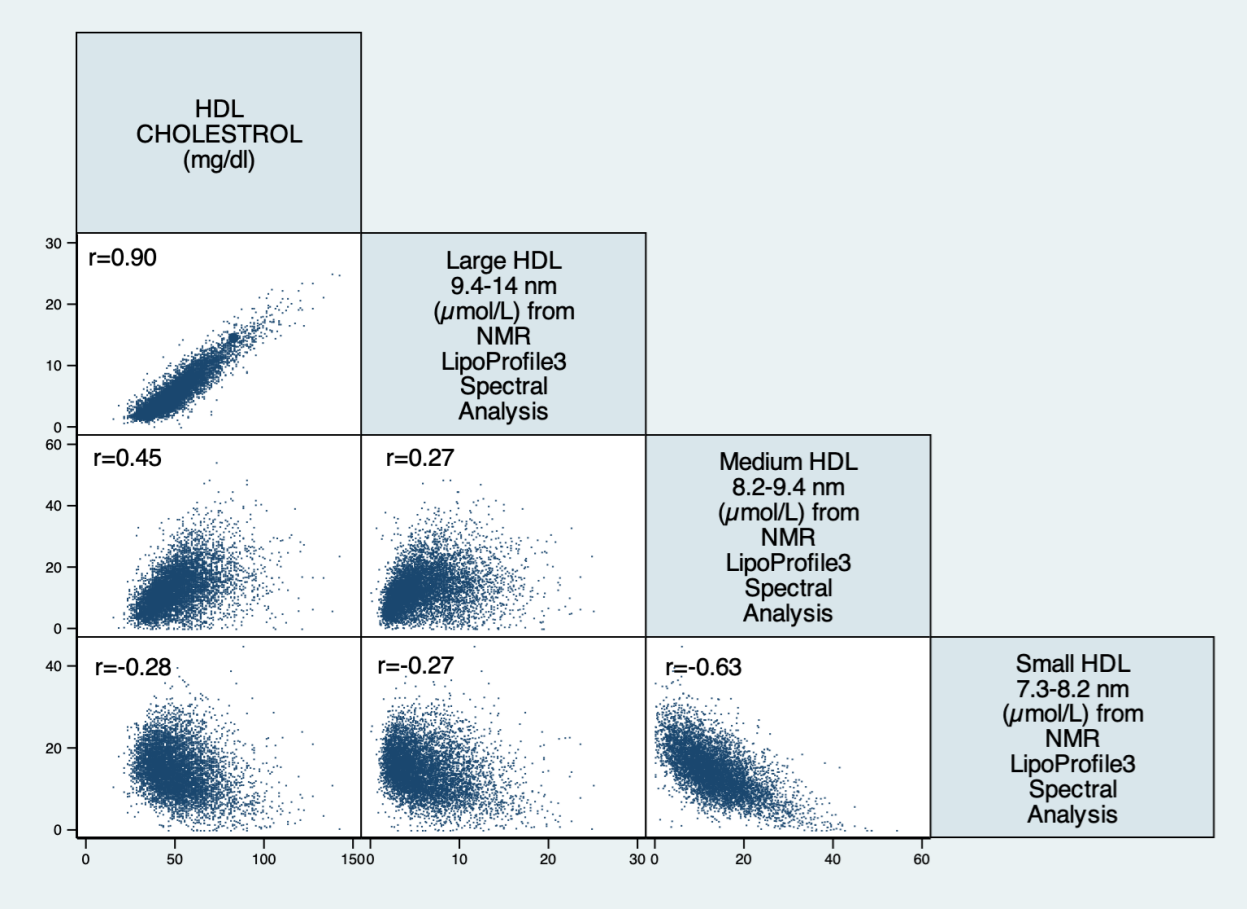
Lipoprotein particles: eGFR (n events) eGFR≥60 (347) eGFR<60 (81)
Apolipoprotein particles: eGFR (n events) eGFR≥60 (298) eGFR<60 (74)
CVD (cardiovascular disease), HDLc (high-density lipoprotein cholesterol), HDLp (high density lipoprotein particles), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate). Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.
Standard deviation in HDL lipoproteins: HDLc (14 mg/dl), mean HDL size (0.45 nm), HDLp (6 μmol/L), large HDLp (3.5 μmol/L), medium HDLp (7 μmol/L), small HDLp (6 μmol/L).
Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking and reported alcohol use. Additional simultaneous adjustment for complementary subfractions on HDLp subfraction models.
*Multiplicative interactions evaluated with likelihood ratio tests.
†P-value for significance of global interaction between CKD and each HDLp size.

Table S14. Associations between HDL particles and apolipoproteins with risk of myocardial infarction by eGFR.

	All participants (n=6,699)	eGFR≥60 (n=6,127)	eGFR<60 (n=572)	P-value for Interaction*
HDLc	0.88 (0.76, 1.03)	0.96 (0.81, 1.13)	0.67 (0.46, 0.97)	0.41
HDLp	0.87 (0.75,0.99)	0.89 (0.75,1.03)	0.89 (0.63, 1.24)	0.44
Mean HDLp size	0.98 (0.85,1.13)	1.06 (0.91, 1.24)	0.72 (0.51, 1.00)	0.19
HDLp subfraction				0.05 †
Small HDLp	0.85 (0.70, 1.03)	0.86 (0.69, 1.06)	0.97 (0.61, 1.50)	0.78
Medium HDLp	0.82 (0.67, 1.00)	0.77 (0.62,0.96)	1.26 (0.79, 2.00)	0.08
Large HDLp	0.95 (0.81, 1.12)	1.08 (0.91,1.28)	0.53 (0.32, 0.87)	0.18
Total Apo C-III	1.11 (0.99, 1.25)	1.07 (0.93, 1.23)	1.32 (0.98, 1.78)	0.71
Total HDL Apo A-I	0.91 (0.78, 1.07)	1.01 (0.86, 1.21)	0.66 (0.45, 0.95)	0.06
HDL Apo A-I without Apo C-III	0.88 (0.74, 1.05)	0.96 (0.79, 1.17)	0.68 (0.44, 1.02)	0.07
HDL Apo A-I with Apo C-III	1.06 (0.92, 1.22)	1.09 (0.93, 1.29)	0.95 (0.62, 1.45)	0.15

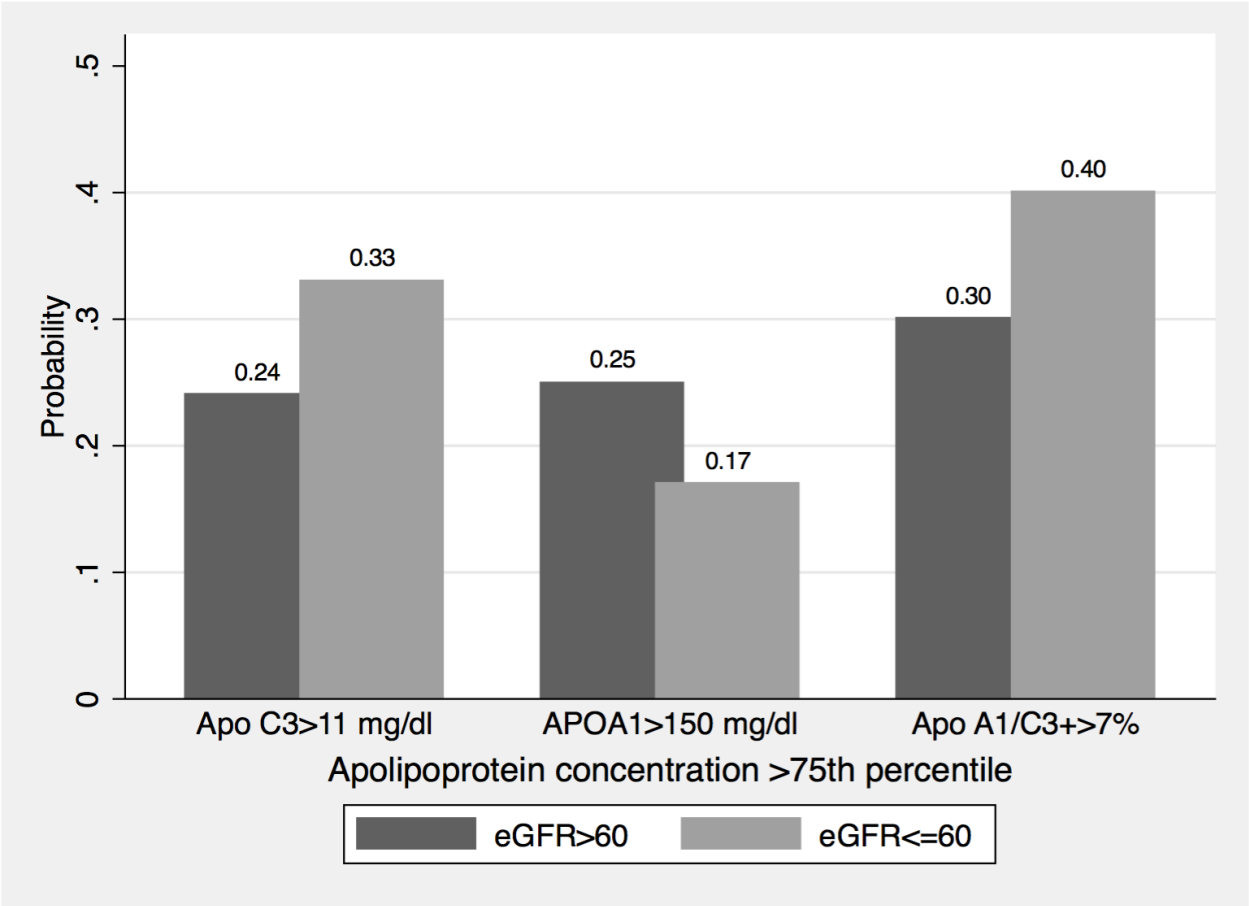
Lipoprotein particles: eGFR (n events) eGFR≥60 (244) eGFR<60 (56)
Apolipoprotein particles: eGFR (n events) eGFR≥60 (209) eGFR<60 (50)
CVD (cardiovascular disease), HDLc (high-density lipoprotein cholesterol), HDLp (high density lipoprotein particles), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate). Cell contents are hazard ratios (HR) per one standard deviation higher concentration in predictor and 95% confidence intervals.
Standard deviation in HDL lipoproteins: HDLc (14 mg/dl), mean HDL size (0.45 nm), HDLp (6 μmol/L), large HDLp (3.5 μmol/L), medium HDLp (7 μmol/L), small HDLp (6 μmol/L).
Hazard ratios adjusted for age, sex, ethnicity, diabetes, socio-economic status, physical activity, systolic and diastolic blood pressure, antihypertensive medication use, lipid-lowering therapy use, urinary albumin to creatinine ratio, body mass index, cigarette smoking and reported alcohol use. Additional simultaneous adjustment for complementary subfractions on HDLp subfraction models.
*Multiplicative interactions evaluated with likelihood ratio tests.
†P-value for significance of global interaction between CKD and each HDLp size.

Figure S1. Correlation* between HDL lipoproteins.



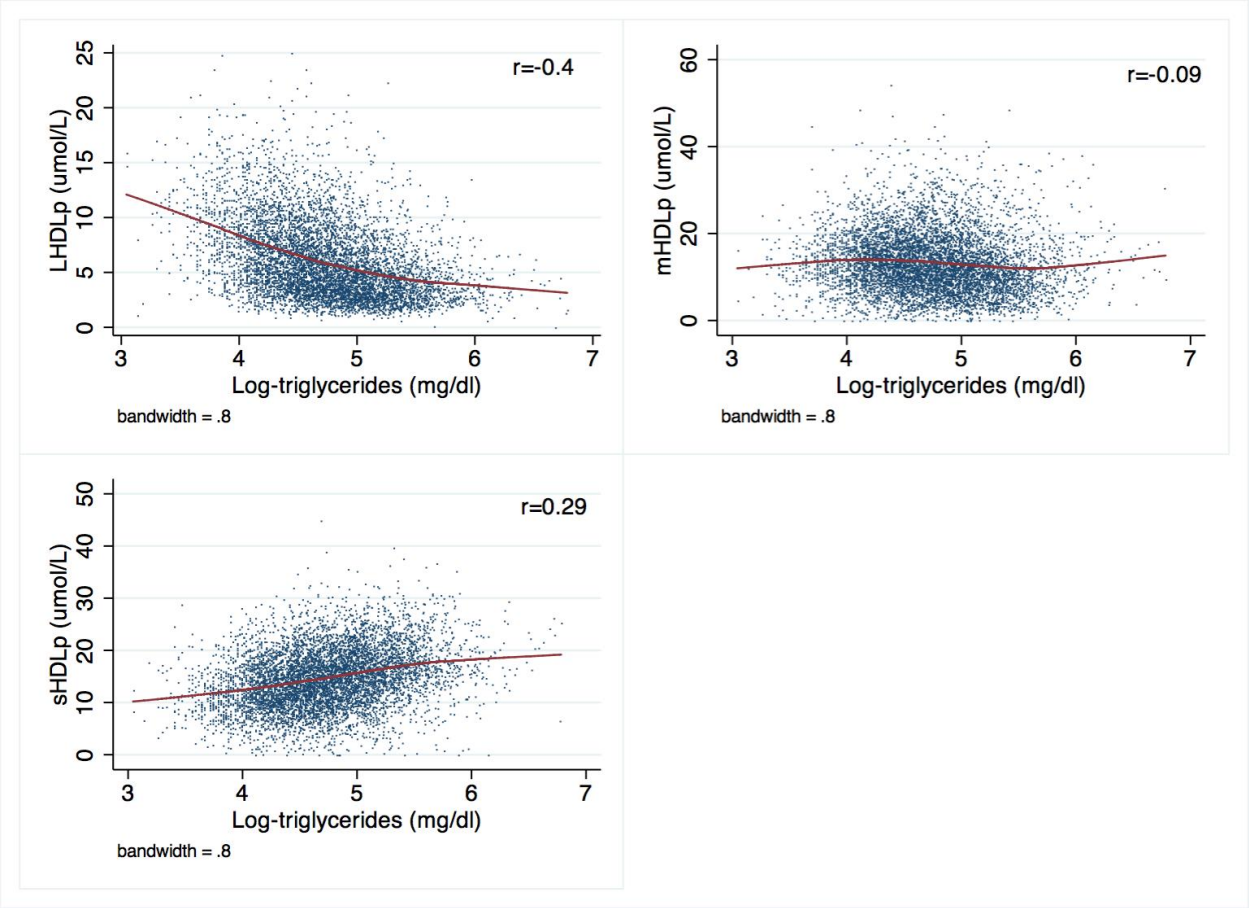
*This scatterplot matrix represents pairwise graphical scatterplots of the relationship among different HDL lipoproteins. For example, the scatterplot in the second row represents the relationship of HDL cholesterol (in the x-axis) with large HDL particles (in the Y-axis). In turn, the first scatterplot in row 3 (from left to right) represents the relationship between HDL cholesterol (in the x-axis) and medium HDL particles (in the Y-axis).

Figure S2. Predicted probabilities of apolipoproteins by eGFR.



Threshold at 75th percentile in each marker: high total Apo CIII (11 mg/dl), high total Apo A-1 (150 mg/dl), high proportion Apo A-1 with Apo C-III (7%).
Predicted probabilities adjusted for age, sex and ethnicity.

Figure S3. Correlation between HDL lipoproteins and triglycerides.



LHDLp (large HDL particles), mHDLp (medium HDL particles), sHDLp (small HDL particles)

Figure S4. Correlation between HDL apolipoproteins and triglycerides.