Published in final edited form as:

Atherosclerosis. 2008 March ; 197(1): 407–414.

Mild elevations of urine albumin excretion are associated with atherogenic lipoprotein abnormalities in the Multi-Ethnic Study of Atherosclerosis

Ian H. de Boer, MD, MS,

Division of Nephrology, University of Washington

Brad C. Astor, PhD, MPH,

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Holly Kramer, MD, MPH,

Department of Preventive Medicine, Loyola University

Walter Palmas, MD, MS,

Department of Medicine, Columbia University

Kyle Rudser, MS,

Department of Biostatistics, University of Washington

Stephen L. Seliger, MD, MS,

Division of Nephrology, University of Maryland

Michael G. Shlipak, MD, MPH,

Department of Medicine, University of California, San Francisco

David S. Siscovick, MD, MPH,

Cardiovascular Health Research Unit, University of Washington

Michael Y. Tsai, PhD, and

Laboratory Medical Pathology, University of Minnesota

Bryan Kestenbaum, MD, MS

Division of Nephrology, University of Washington

Abstract

Objective—Elevated urine albumin excretion is an established risk factor for cardiovascular disease. Increased cardiovascular risk may be partly mediated by abnormalities in lipoprotein metabolism. We examined cross-sectional associations of urine albumin-creatinine ratio (ACR) with standard lipid measurements and with lipoprotein particle concentrations measured by Nuclear Magnetic Resonance (NMR) in the Multi-Ethnic Study of Atherosclerosis.

Methods and Results—Among 5633 participants who were not using lipid-lowering medications, greater ACR was associated with greater triglyceride concentration and lesser high density lipoprotein cholesterol concentration (women only), but not with low density lipoprotein

Address correspondence to: Ian H. de Boer, MD MS, University of Washington, Division of Nephrology, Box 356521, BB-1265 Health Sciences Building, 1959 NE Pacific, Seattle, WA 98195. PHONE (206) 543-3792; FAX (206) 685-6881; EMAIL deboer@u.washington.edu.

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(LDL) cholesterol calculated using conventional methods. In contrast, unadjusted mean small LDL particle concentrations measured by NMR were 770, 827, and 935 nmol/L for women ($p<0.001$) and 996, 1030, and 1040 nmol/L for men ($p=0.037$) among participants with normal, high normal, and elevated ACR. Adjusting for age, race/ethnicity, diabetes, impaired fasting glucose, hypertension, smoking, medications, body mass index, and serum creatinine, each two-fold greater ACR was associated with an increase in small LDL particle concentration of 27 nmol/L for women ($p<0.001$) and 14 nmol/L for men ($p=0.008$). Greater ACR was also associated with greater intermediate density lipoprotein particle concentration and smaller mean LDL particle size.

Conclusions—Mild elevations of urine ACR are associated with atherogenic lipoprotein abnormalities that are not directly observed with a standard lipid panel.

Keywords

Albuminuria; kidney; lipids; lipoproteins; epidemiology

Elevated urine albumin excretion (UAE) is an established risk factor for cardiovascular (CV) disease.^{1–5} Greater levels of UAE have been associated with increased risk for cardiovascular events and an increased prevalence of subclinical CV disease even within the proposed normal range of UAE.^{6–9}

The increased CV risk associated with elevated UAE may be mediated, in part, by abnormalities in lipoprotein metabolism. Conventional lipid measurements have been reported to be altered in the setting of microalbuminuria.^{10, 11} However, important lipoprotein abnormalities may not be detected using conventional methods. In particular, differences in the distribution of low density lipoprotein (LDL) are not reflected by standard measurements of LDL cholesterol (LDL-c).¹² Small, dense LDL particles have been associated with incident CV events independent of standard measurements of LDL-c.^{13, 14} Similarly, greater levels of intermediate density lipoprotein (IDL) particles, also measured as a component of LDL-c using conventional methods, have been independently associated with coronary artery disease progression.¹⁵ It is not known whether LDL distribution is altered in the setting of elevated UAE without the nephrotic syndrome (characterized by very high levels of UAE) or diabetes, and detailed lipoprotein measurements have not been described in relation to UAE in the general population.

We examined the association of UAE with lipid and lipoprotein concentrations in the Multi-Ethnic Study of Atherosclerosis (MESA), a community-based cardiovascular cohort study.¹⁶ Lipoproteins were measured using nuclear magnetic resonance (NMR), which accurately categorizes lipoprotein particles by size.¹⁷ We hypothesized that greater UAE is associated with atherogenic changes in lipoprotein distribution that are not detected using conventional measurements.

STUDY DESIGN AND METHODS

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) was designed to investigate the prevalence, correlates, and progression of subclinical CVD. As described in detail elsewhere, 6814 community-dwelling residents aged 45–84 were first sampled between 2000 and 2002 at six centers across the United States.¹⁶ Individuals with known coronary heart disease were excluded. At enrollment, detailed data describing demographics, comorbidities, and medications were collected, and each participant gave baseline blood and urine samples. Informed consent was granted by all MESA participants, and the University of Washington Institutional Review Board approved the study described here.

The current analyses evaluate the association of UAE with lipid and lipoprotein concentrations in cross-section at the baseline MESA examination. Measurements of UAE and NMR lipoproteins were available for 6765 MESA participants (99%). Because lipid-lowering therapy strongly affects lipid and lipoprotein concentrations, we excluded participants who reported use of any lipid-lowering agent (HMG-CoA reductase inhibitors, fibrates, niacin, and/or bile acid sequestrants, $n=1094$) or those for whom data on lipid-lowering therapy was not available ($n=3$). In addition, we excluded MESA participants with a urine albumin-creatinine ratio $\geq 3000 \text{ mg/g}$ ($n=4$), since lipoprotein abnormalities have been described in the setting of the nephrotic syndrome, and those for whom any of the covariates described below were not documented ($n=31$).

Urine albumin excretion

Urine was collected from single voided specimens. At the Clinical Chemistry Laboratory at Fletcher Allen Health Care (Burlington, VT), urine albumin concentration was measured by nephelometry and urine creatinine concentration was measured using the Jaffe reaction. Albumin-creatinine ratio (ACR) was expressed in units of mg/g . Sex-specific thresholds have been recommended for the categorization of urine ACR.^{18–20} These thresholds account for differences in the normal distribution of ACR by sex caused by a greater average muscle mass and daily urine creatinine excretion for men compared with women. We applied the recommended sex-specific upper limits of normal to the MESA population to define “elevated ACR” ($\geq 25 \text{ mg/g}$ for women, $\geq 17 \text{ mg/g}$ for men). Because relatively few participants had macroalbuminuria (ACR $\geq 355 \text{ mg/g}$ for women, $\geq 250 \text{ mg/g}$ for men), these participants were grouped with those who had microalbuminuria (ACR $25\text{--}354 \text{ mg/g}$ for women, $17\text{--}249 \text{ mg/g}$ for men) for categorical analyses. The recommended normal range was further subdivided into “high normal ACR” ($13\text{--}25 \text{ mg/g}$ for women, $9\text{--}17 \text{ mg/g}$ for men) and “normal ACR” ($<13 \text{ mg/g}$ for women, $<9 \text{ mg/g}$ for men), as in previous reports.⁹ Because urine ACR is a naturally continuous variable with strong rightward skew, we also evaluated urine ACR as a log-transformed continuous exposure.

Lipids and lipoproteins

Lipid concentrations were measured using standard enzymatic methods, with LDL cholesterol (LDL-c) calculated using the Friedewald formula.²¹ Lipoprotein concentrations were measured using nuclear magnetic resonance (NMR) spectroscopy, as described in detail elsewhere.^{17, 22, 23} This method uses the characteristic signals broadcast by lipoprotein subclasses of different size as the basis for their quantification. Each subclass signal emanates from the total number of terminal methyl groups on the lipids contained within the particle core and in the surface shell. Lipoprotein particles were classified as HDL ($7.3\text{--}13.0 \text{ nm}$), LDL ($18.0\text{--}27.0 \text{ nm}$), or VLDL ($> 27 \text{ nm}$), with LDL subclassified as small LDL ($18.0\text{--}21.2 \text{ nm}$), large LDL ($21.2\text{--}23.0 \text{ nm}$), or IDL ($23.0\text{--}27.0 \text{ nm}$), consistent with prior studies.^{22, 23} Average lipoprotein particle sizes were calculated from the concentrations of lipoprotein subclasses and the diameters assigned to each subclass.

Covariates

Race/ethnicity was self-classified by participants as Caucasian, Chinese-American, African-American, or Hispanic. Diabetes was defined as a fasting blood glucose ≥ 126 or use of diabetic medications (insulin, sulfonylureas, biguanides, thiazolidinediones, or alpha-glucosidase inhibitors).²⁴ Impaired fasting glucose was defined as a fasting blood glucose ≥ 110 in the absence of diabetes.²⁴ Hypertension was defined as use of antihypertensive agents, systolic blood pressure (SBP) ≥ 140 , or diastolic blood pressure (DBP) ≥ 90 .²⁵ Estimated glomerular filtration rate (GFR), used to assess for effect modification by kidney function, was calculated using the Modification of Diet in Renal Disease formula.²⁶

Statistical analysis

Participant characteristics were summarized by category of urine ACR. Because both urine ACR and lipid/lipoprotein levels differ strongly by sex, all analyses assessing their associations were stratified by sex. First, lipid and lipoprotein levels were summarized by category of urine ACR, with significance of trend tested by linear regression. Next, the associations of lipid/lipoprotein concentrations with log-transformed urine ACR (logACR), each described continuously, were evaluated using linear regression. Graphical analyses (scatter plots, lowess curves, and spline models) demonstrated linear relationships between log(ACR) and lipids/lipoproteins. Addition of polynomial terms for ACR and log(ACR) did not significantly improve the fit of linear models, and analysis of residuals did not suggest that the assumption of linearity was violated. Models were adjusted for potential confounders, which included age, race/ethnicity, diabetes, impaired fasting glucose, hypertension, smoking status, medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, diuretics, hydrochlorothiazide, dihydropyridine calcium channels blockers, nondihydropyridine calcium channels blockers, estrogens [excluding topical preparations], and progestones), and the reciprocal of serum creatinine concentration. Each component of estimated GFR (age, sex, race/ethnicity, and serum creatinine) was included individually, rather than including calculated estimated GFR. Differences in lipid/lipoprotein concentrations associated with a two-fold greater ACR were calculated by multiplying the beta coefficient (and 95% confidence interval) obtained for log(ACR) by log(2). Finally, the association of log(ACR) with small LDL particle concentration was compared among relevant covariate subgroups using models which included log(ACR)*covariate interaction terms, in order to evaluate for evidence of effect modification. To determine the statistical significance of each potential interaction, the Wald test was used to test the joint probability that interaction term coefficients for each level of the covariate were equal to zero. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Six hundred nineteen of the 5633 participants included in analyses (11%) had high normal urine ACR and 715 (13%) had elevated urine ACR (Table 1). Of those with elevated urine ACR, 646 (90%) had microalbuminuria, and 69 (10%) had macroalbuminuria. Compared with subjects who were included in the analyses, MESA participants excluded for use of lipid-lowering therapy (n=1094) were more likely to have elevated urine ACR (n=189, 17%) or high normal urine ACR (n=160, 15%). Sex distribution did not differ between included and excluded participants (47% men in each group).

Greater urine ACR was associated with greater age, male sex, non-Caucasian race/ethnicity, diabetes, impaired fasting glucose, and hypertension (Table 1). Participants with greater urine ACR reported greater use of antihypertensive medications and less frequent use of estrogens and progestones (among women). Mean levels of estimated GFR did not vary by category of urine ACR, but the proportion of participants with an estimated GFR $<60\text{mL/min/1.73m}^2$ was greater among those with greater urine ACR.

Assessing conventional lipid measurements, greater urine ACR was associated with greater triglyceride concentration and lesser HDL-c concentration (clinically relevant HDL-c differences for women only), but not with concentrations of LDL-c or total cholesterol (Table 2). In contrast, urine ACR was associated with significant differences in the distribution of LDL, measured using NMR. Specifically, greater urine ACR was associated with a greater number of small LDL and IDL particles, fewer large LDL particles; and a smaller mean LDL particle size. Greater urine ACR was also associated with greater VLDL particle concentration and, among women only, with lesser HDL particle concentration and smaller mean HDL

particle size. For lipid and lipoproteins associated with urine ACR, a graded relationship was evident, with differences observed between the normal and high normal categories of ACR.

Linear regression models revealed similar relationships of urine ACR, examined continuously on a log scale, with lipid and lipoprotein concentrations (Table 3). After adjustment, each two-fold increase in urine ACR was associated with significantly greater concentrations of small LDL particles, IDL particles, and LDL particles of all sizes, as well as with smaller mean LDL particle size, but not with LDL-c measured using conventional methods (Table 3 and Online Supplement Figure). Associations were similar when urine albumin concentration, unadjusted for urine creatinine concentration, was examined as the predictor variable, and when analyses were restricted to participants without elevated urine ACR.

The absolute unadjusted mean concentration of small LDL particles varied by covariate subgroup, with greater levels observed among participants who were male, young, and Hispanic (Table 4). In addition, absolute small LDL particle concentration increased in a graded fashion among categories of worsening glucose tolerance. However, the association of urine ACR with small LDL particle concentration did not differ by age, race/ethnicity, category of glucose tolerance, or presence of hypertension or impaired kidney function. Compared with men, women did appear to have a somewhat stronger association of urine ACR with small LDL particle concentration (p for interaction = 0.073), an interaction also observed with HDL-c concentration (standard lipid panel), large LDL particle concentration, HDL particle concentration, LDL particle size, and HDL particle size (p for interactions < 0.05).

DISCUSSION

Atherogenic lipoprotein abnormalities, including greater concentrations of small LDL and IDL particles, were observed to be present with mild elevations of urine ACR in an ethnically diverse, community based population. These lipoprotein abnormalities were not appreciated using conventional lipid measurements, were observed within the normal range of urine ACR, and were associated with urine ACR independent of potential confounding factors. Urine ACR was also associated with levels of lipids and lipoproteins (triglyceride, VLDL, and, in women, HDL-c and HDL particles) that correlate with small LDL particle concentration. Associations were consistent across subgroups defined by age, race/ethnicity, glucose tolerance, blood pressure, and kidney function.

These results indicate that lipoprotein abnormalities are more extensive and are present at lower levels of UAE than has been previously reported. In a population-based Korean study, microalbuminuria was associated with greater triglyceride concentration and lower HDL concentration, but not with LDL or total cholesterol levels measured using conventional methods.¹⁰ In comparison, the current study confirms these findings in an ethnically diverse population, demonstrates using detailed NMR measurements that relevant changes in LDL distribution are also present, and shows that lipoprotein abnormalities occur even within the proposed normal range of urine ACR. In the Third National Health and Nutrition Examination Survey (NHANES III), microalbuminuria was associated with an increased risk for elevated total and LDL cholesterol, but not for diminished HDL cholesterol.¹¹ Differing results may be influenced by inclusion in the NHANES III study of participants taking lipid-lowering medications. Associations of elevated urine albumin excretion with detailed measurements of lipoprotein distribution have been described among people with diabetes; changes are consistent with those reported here for people with and without diabetes.^{27, 28}

The associations of urine ACR with most lipids and lipoproteins measured in the current study appeared to be stronger among women than men, and greater urine ACR was associated with unfavorable HDL abnormalities (diminished HDL particle number and smaller mean HDL

particle size) among women only. Sex differences persisted when we evaluated urine ACR as a continuous variable, eliminating as an explanation sex-specific differences in sensitivity or specificity of ACR thresholds. Differential exclusion for use of lipid-lowering therapy is also unlikely to bias results, since the distribution of sex did not differ between excluded and included participants. Compared with men, women are well known to have a favorable lipoprotein profile, including lesser concentrations of small LDL particles, greater concentrations of HDL particles, and larger mean LDL and HDL particle sizes.^{23, 29} Elevated UAE may account for a larger portion of lipoprotein abnormalities among women because other factors (for example androgen levels or visceral obesity) are less dominant, relative to men.

Elevated UAE may lead to abnormalities in lipoprotein metabolism. In patients with the nephrotic syndrome, in which renal injury is clearly the primary pathologic process, both quantitative elevations in LDL cholesterol concentration and qualitative changes in LDL distribution are present.^{30, 31} Qualitative changes, which are similar to those observed in the current study, are mediated by greater activity of cholesterol ester transfer protein in combination with increased concentrations of triglyceride-rich VLDL.^{32, 33} A similar mechanism may apply in the setting of mildly elevated urine albumin excretion, even if elevated LDL cholesterol concentration is not present.

It is also possible that lipoprotein abnormalities cause elevated UAE. Cohort studies have demonstrated that lipid levels, predominantly elevated triglyceride and low HDL-c, predict subsequent progression of kidney disease.^{34–36} Since elevated triglyceride and low HDL-c levels are correlated with greater small LDL particle concentration, it is possible that an unmeasured greater quantity of small LDL particles is pathogenically responsible for these associations. Compared with larger LDL particles, small LDL particles penetrate the arterial wall more easily, bind more avidly to extracellular matrix proteoglycans, and are more susceptible to oxidation and more resistant to clearing from the plasma.^{37–40} Whether these particles lead to increased damage in the renal endothelium or mesangium, relative to larger LDL particles, has not been described. Similarly, whether small LDL particles *per se* are associated with progression of kidney disease has not been reported.

A third factor could cause both elevated UAE and lipoprotein abnormalities. However, detailed information on relevant covariates was collected for the MESA cohort and used in these analyses, reducing the potential impact of known confounders on the relationships observed. Further, the MESA cohort is characterized by the absence of clinically apparent CV disease, reducing potential confounding by CV health status.

Greater concentrations of small LDL particles, measured using NMR, have been associated with an increased risk for CV events in the Cardiovascular Health Study, the Women's Health Study, the Epidemiology of Diabetes Complications Study, and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT).^{14, 41–43} Thus, the greater concentrations of small LDL particles associated with elevated UAE in MESA may identify or contribute to excess CV risk. Once outcome data become available for the MESA cohort, we will be able to evaluate the risk for CV events associated with elevated UAE in this population, and the portion of increased risk explained by lipoprotein abnormalities.

Results from this study suggest that LDL-c, measured from a standard lipid panel, may not adequately quantify CV risk among patients with mild elevation of UAE. Rather, measures of LDL particle number and/or size, such as apolipoprotein B concentration or NMR small LDL particle number, may better reflect CV risk in this population, and may possibly better inform decisions regarding initiation or titration of lipid-lowering therapy.

The major limitation of this study is its cross-sectional nature. Temporal and causal relationships of elevated UAE with lipoprotein abnormalities cannot be defined, nor can associations with clinical events be evaluated at this time. An additional limitation is lack of repeat measurements of UAE, which are recommended to increase specificity. However, measurement error in ascertainment of lipoprotein concentrations or urine ACR is likely to be nonselective, resulting in attenuated estimates of association between urine ACR and lipoproteins.

In summary, mild elevations of urine ACR were associated with atherogenic lipoprotein abnormalities among a multi-ethnic cohort of community-dwelling adults. Differences in LDL detected using NMR were not appreciated with a standard lipid panel. The association of urine ACR with small LDL particle concentration was observed in all subgroups defined by age, race/ethnicity, and glucose tolerance, and appeared to be somewhat stronger among women than men. Lipoprotein abnormalities may partially explain the increased cardiovascular risk associated with elevated UAE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

FUNDING SOURCES

Supported by grant number K12 HD049100 from the NIH Roadmap/National Institute of Child Health and Human Development; NIH grant DK007247; and contracts N01-HC-95159 through N01-HC-95166 from the National Heart, Lung, and Blood Institute.

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Table 1
Participant characteristics by category of urine Albumin Creatinine Ratio.

	Urine Albumin Creatinine Ratio		
	Normal N (%)	High normal N (%)	Elevated N (%)
Urine ACR (median and IQR, mg/g)	4299 (76%)	619 (11%)	715 (13%)
Age (mean $\pm$ SD, years)	4 (3, 6)	14 (12, 17)	46 (28, 111)
Sex (n, % male)	60 $\pm$ 10	65 $\pm$ 10	66 $\pm$ 10
Race/ethnicity (n, %)	1921 (45)	318 (51)	417 (58)
Caucasian	1730 (40)	199 (32)	194 (27)
Chinese	495 (11)	84 (14)	104 (15)
Black	1143 (27)	173 (28)	227 (32)
Hispanic	931 (22)	163 (26)	190 (27)
Diabetes (n, %)	342 (8)	121 (20)	235 (33)
Impaired fasting glucose (n, %)	1104 (26)	203 (33)	220 (31)
Hypertension (n, %)	1457 (34)	364 (59)	501 (70)
Smoking status (n,%)			
Never	2206 (51)	288 (47)	348 (49)
Former	1512 (35)	240 (39)	273 (38)
Current	581 (14)	91 (15)	94 (13)
Medications (n, %)			
ACE inhibitor/ARB	522 (12)	128 (21)	205 (29)
Beta-blocker	293 (7)	62 (10)	100 (14)
Any diuretic	469 (11)	78 (13)	123 (17)
Hydrochlorothiazide	396 (9)	67 (11)	100 (14)
Dihydropyridine CCBs	205 (5)	70 (11)	121 (17)
Nondihydropyridine CCBs	108 (3)	35 (6)	37 (5)
Estrogens*	689 (29)	58 (19)	56 (19)
Progesterones*	304 (13)	26 (9)	21 (7)
Body mass index (mean $\pm$ SD, kg/m ²)	28 $\pm$ 5	29 $\pm$ 6	29 $\pm$ 6
MDRD eGFR (mean $\pm$ SD, mL/min/1.73m ²)	82 $\pm$ 18	83 $\pm$ 19	82 $\pm$ 23
MDRD eGFR <60mL/min/1.73m ² (n, %)	289 (7)	57 (9)	113 (16)

Normal ACR <13mg/g for women or <9mg/g for men, High Normal ACR 13–25mg/g for women or 9–17mg/g for men, Elevated ACR $\geq$ 25mg/g for women or $\geq$ 17mg/g for men. SD = standard deviation, IQR = intraquartile range, ACR = albumin-creatinine ratio, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, MDRD eGFR = Modification of Diet in Renal Disease estimated glomerular filtration rate. *Frequencies of estrogen and progesterone use are calculated among women only.

Table 2
Lipid and lipoprotein measurements by category of urine albumin creatinine ratio

	Normal	Urine ACR, Women		p (trend)	Normal	Urine ACR, Men		p (trend)
		High normal	Elevated			High normal	Elevated	
N (%)	2378 (80%)	301 (10%)	298 (10%)		1921 (72%)	318 (12%)	417 (16%)	
Standard lipids								
Total cholesterol (mg/dL)	202±35	203±38	199±38	0.442	190±33	192±33	191±41	0.618
Triglycerides (mg/dL)	121±79	128±69	152±99	<0.001	129±78	144±89	155±156	<0.001
LDL-c (mg/dL)	120±31	122±33	118±34	0.594	120±30	119±29	117±33	0.140
HDL-c (mg/dL)	57±16	55±15	51±13	<0.001	45±12	45±11	44±12	0.048
NMR particle number								
VLDL (nmol/mL)	68±39	73±40	80±43	<0.001	78±37	79±38	85±48	0.002
LDL (nmol/mL)	1279±371	1313±387	1359±412	<0.001	1354±370	1382±337	1369±397	0.296
IDL (nmol/mL)	18±24	21±25	29±29	<0.001	20±22	23±23	25±30	<0.001
Large LDL (nmol/mL)	490±205	465±213	395±210	<0.001	338±180	329±189	304±181	0.001
Small LDL (nmol/mL)	770±440	827±466	935±485	<0.001	996±430	1030±403	1040±451	0.037
HDL (μmol/mL)	33.1±5.9	32.8±5.3	31.7±5.9	<0.001	28.7±4.7	29.2±5.3	28.5±5.3	0.790
NMR particle size								
VLDL (nm)	51.2±9.3	51.3±7.9	52.1±8.7	0.090	50.6±8.7	51.5±9.4	51.7±9.2	0.008
LDL (nm)	21.1±0.8	21.0±0.8	20.8±0.8	<0.001	20.6±0.7	20.5±0.7	20.5±0.7	0.001
HDL (nm)	9.31±0.4	9.25±0.4	9.19±0.4	<0.001	9.01±0.4	9.01±0.4	9.01±0.4	0.907

Values are mean ± standard deviation.

Table 3

Expected differences in lipid/lipoprotein measurements associated with twofold greater urine albumin-creatinine ratio, adjusted for age, race/ethnicity, diabetes, impaired fasting glucose, hypertension, smoking status, medications, body mass index, and serum creatinine.

	Expected difference in lipid/lipoprotein measurement (95% confidence interval)	
	Women	Men
Standard lipids		
cholesterol (mg/dL)	−0.5 (−1.4, 0.5)	1.2 (0.4, 2.1)
Triglycerides (mg/dL)	3.7 (1.6, 5.7)	5.8 (3.4, 8.1)
LDL-c (mg/dL)	−0.4 (−1.2, 0.5)	0.6 (−0.2, 1.4)
HDL-c (mg/dL)	−0.9 (−1.3, −0.6)	−0.2 (−0.5, 0.1)
NMR particle number		
VLDL (nmol/mL)	2.1 (1.2, 3.2)	2.3 (1.4, 3.3)
LDL (nmol/mL)	12 (2, 22)	10 (1, 19)
IDL (nmol/mL)	1.2 (0.6, 1.9)	1.0 (0.4, 1.6)
Large LDL (nmol/mL)	−16 (−21, −11)	−4.7 (−9.1, −0.2)
Small LDL (nmol/mL)	27 (16, 39)	14 (4, 24)
HDL (μmol/mL)	−0.3 (−0.4, −0.2)	−0.1 (−0.2, 0.01)
NMR particle size		
VLDL (nm)	−0.05 (−0.30, 0.19)	0.10 (−0.12, 0.32)
LDL (nm)	−0.06 (−0.08, −0.04)	−0.02 (−0.04, −0.01)
HDL (nm)	−0.02 (−0.02, −0.01)	0 (−0.01, 0.01)

Table 4

Subgroup small LDL particle concentrations (NMR): mean values and expected differences associated with a two-fold greater urine albumin excretion rate.

	Women			Men		
	Mean $\pm$ SD	Expected difference (95% CI) associated with two-fold greater ACR*	P (interaction)	Mean $\pm$ SD	Expected difference (95% CI) associated with two-fold greater ACR*	P (interaction)
All	793 $\pm$ 450	27 (16, 39)		1007 $\pm$ 431	14 (4, 24)	***
Age						
45–54 years	794 $\pm$ 436	33 (12, 54)		1069 $\pm$ 433	13 (–8, 35)	
55–64 years	818 $\pm$ 456	36 (14, 59)		1038 $\pm$ 422	14 (–4, 32)	
65–74 years	784 $\pm$ 445	8 (–12, 28)		979 $\pm$ 429	13 (–4, 31)	
75–84 years	753 $\pm$ 480	38 (13, 63)	0.145	868 $\pm$ 410	8 (–15, 30)	0.974
Race/ethnicity						
Caucasian	745 $\pm$ 441	29 (7, 50)		988 $\pm$ 405	18 (1, 36)	
Asian	879 $\pm$ 442	20 (–9, 49)		988 $\pm$ 435	9 (–17, 35)	
African American	742 $\pm$ 411	27 (8, 45)		941 $\pm$ 461	15 (–2, 32)	
Hispanic	893 $\pm$ 493	30 (8, 52)	0.953	1123 $\pm$ 411	10 (–8, 29)	0.908
Diabetes status						
None	730 $\pm$ 425	25 (9, 40)		972 $\pm$ 432	16 (0, 32)	
Impaired fasting glucose	900 $\pm$ 469	32 (9, 54)		1040 $\pm$ 427	11 (–6, 29)	
Diabetes	949 $\pm$ 479	28 (4, 52)	0.883	1068 $\pm$ 420	15 (–4, 34)	0.856
Hypertension status						
No hypertension	773 $\pm$ 438	26 (8, 43)		1007 $\pm$ 431	15 (–10, 41)	
Hypertension	819 $\pm$ 465	28 (14, 43)	0.816	990 $\pm$ 417	28 (–2, 58)	0.517
Estimated GFR						
> 60mL/min/1.73m ²	789 $\pm$ 444	27 (14, 39)		1011 $\pm$ 432	16 (5, 27)	
< 60mL/min/1.73m ²	824 $\pm$ 504	25 (–1, 52)	0.914	958 $\pm$ 410	7 (–17, 32)	0.518

* Adjusted for age, race/ethnicity, diabetes, impaired fasting glucose, hypertension, smoking status, medications, body mass index, and serum creatinine; CI = confidence interval.

** Tests hypothesis that association between ACR and small LDL particle concentration does not vary by subgroup of covariate (interaction)

*** p=0.073 for interaction, all men *versus* all women