Urine Albumin Excretion and Subclinical Cardiovascular Disease

The Multi-Ethnic Study of Atherosclerosis

Holly Kramer, David R. Jacobs, Jr, Diane Bild, Wendy Post, Mohammed F. Saad, Robert Detrano, Russell Tracy, Richard Cooper, Kiang Liu

Abstract—We examined the association between urine albumin excretion (UAE) and common and internal carotid artery intima-media thickness (IMT), end-diastolic left ventricular (LV) mass, and coronary artery calcification (CAC) scores using data from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based study of 6814 adults aged 45 to 85 years without clinical cardiovascular disease (CVD). The mean age of the MESA participants was 62.7 years, 47% were male, and 15% had diabetes mellitus (DM). Sex-specific spot urine albumin/creatinine ratios were used to define 4 UAE categories: normal, high normal, microalbuminuria, and macroalbuminuria. CAC scores were log-transformed after adding 1 to all scores. Mean values of subclinical CVD measures were computed by level of UAE after adjustment for blood pressure, DM, and other covariates. After adjustment for all covariates, geometric mean CAC scores were higher among participants with high normal UAE (8.8; \( P = 0.07 \)), microalbuminuria (9.9; \( P = 0.002 \)), and macroalbuminuria (13.1; \( P = 0.02 \)) compared with normal UAE (7.4), but only microalbuminuria reached statistical significance. Mean LV mass (g/m\(^2.7\)) was significantly higher in participants with high normal UAE (37.0; \( P = 0.001 \)), microalbuminuria (38.3; \( P = 0.0001 \)), and macroalbuminuria (42.3; \( P = 0.0001 \)) compared with normal UAE (36.0) after adjustment for all covariates. No significant difference in mean carotid IMT was found after adjustment for all covariates. Similar results were noted in MESA participants with and without DM.

In conclusion, higher UAE, including levels below microalbuminuria, may reflect the presence of subclinical CVD among adults without established CVD. \( \text{(Hypertension. 2005;46:38-43.)} \)

Key Words: cardiovascular diseases ■ urine

Microalbuminuria, increased urine albumin excretion (UAE) below the detection of urinary dipstick measurement, strongly predicts cardiovascular disease (CVD) mortality in nondiabetic patients with established CVD.\(^1\) Moreover, the association between UAE and increased CVD mortality in high-risk groups begins at levels of UAE below clinically defined thresholds for microalbuminuria.\(^1\) Subclinical CVD, such as left ventricular (LV) hypertrophy\(^2–6\) and increased carotid artery intima-media thickness (IMT),\(^7–12\) has been associated with microalbuminuria among individuals at high risk for CVD. Whether the presence of increased UAE provides any additional predictive value for the presence of subclinical CVD in groups not at high risk aside from established, independent CVD risk factors remains unestablished. Coronary artery calcification (CAC) is highly correlated with the presence of coronary atherosclerotic plaque.\(^13–15\) However, information on the association between CAC scores and UAE is currently limited.

This study examined the association between UAE and several measures of subclinical CVD, including CAC scores, in a large multi-ethnic population without clinical CVD. We hypothesized that increased UAE is associated with subclinical CVD reflecting kidney damage caused by exposure to CVD risk factors, particularly diabetes mellitus (DM) and hypertension, and that these associations exist at UAE cutpoints below thresholds currently used to define microalbuminuria. An association between increased UAE and subclinical CVD in adults without clinical CVD may give further credence to using UAE to identify individuals who may benefit from aggressive risk factor intervention for the primary prevention of CV events.

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Methods

Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based study of 6814 men and women aged 45 to 85 years, without clinical CVD, recruited from 6 US communities (Baltimore, Md; Chicago, Ill; Forsyth County, NC; Los Angeles County, Calif; northern Manhattan, NY; and St. Paul, Minn). The main objective of the MESA Study is to determine the characteristics of subclinical CVD and its progression, and adults with symptoms or history of medical or surgical treatment for CVD were excluded. Information on the sampling frame and study design have been previously reported.16 Participants who self-reported their race/ethnicity group as Caucasian or white, African-American or black, Asian, or Spanish/Hispanic/Latino were asked to participate and were enrolled between July 2000 and August 2002. Adults weighing >300 pounds were not eligible for participation. Institutional review board approval was obtained at all MESA sites. This study was limited to the 6775 MESA participants who completed the first MESA examination and provided a spot urine sample.

UAE

Urine albumin and creatinine were measured at the Clinical Chemistry Laboratory at Fletcher Allen Health Care (Burlington, Vt). Urine albumin and creatinine were measured by nephelometry and the rate Jaffe reaction, respectively. Spot urine albumin (\(\mu g/mL\))-to-creatinine (mg/mL) ratios (ACRs) were calculated for all participants except those with missing urine data (\(n=39\)). Sex-specific ACR cut-points were used to define microalbuminuria (\(\geq 17\) and \(\geq 25\) mg/g for men and women, respectively) and macroalbuminuria (\(\geq 250\) to \(\geq 355\) mg/g in men and \(\geq 355\) mg/g in women).17,18 Normal and high normal UAE was defined as an ACR <9 mg/g and <13 mg/g in men and women, respectively, and 9 to 16.9 mg/g and 13 to 24.9 mg/g, in men and women, respectively. These ACR cut points represent the mid-point of distribution of UAE below the threshold for microalbuminuria.18,19

Measures of Subclinical CVD

CAC was measured using 2 scans obtained on the same occasion in all participants during the baseline visit using electron beam computed tomography or multi-detector computed tomography.20 Increased CAC scores were defined as CAC scores >0, >100, and >400. Internal and common carotid artery maximum IMT was assessed with B-mode ultrasound (Logiq 700 ultrasound machine; General Electric Medical Systems). Carotid artery stenosis was defined as \(\geq 25\%\) stenosis in the common or internal carotid artery. End-diastolic LV mass was determined by cardiac MRI using a 1.5-T magnet.21 LV mass was indexed to participant’s height (m) raised to the 2.7th power (g/m\(^{2.7}\)).22 LV hypertrophy was defined as LV mass/H927317 and H1135025

Covariates

All MESA participants completed self-administered questionnaires, provided fasting blood samples, and were interviewed and examined by trained research staff.23 Blood pressure was measured 3 times at 1-minute intervals using a Dinamap PRO 100 automated oscillometric device. The average of the second and third measurements was used for this analysis. DM was defined as self-reported physician diagnosis, use of insulin or oral hypoglycemic agents, or fasting glucose \(\geq 126\) mg/dL. Hypertension was defined as self-reported treatment or systolic blood pressure \(\geq 140\) mm Hg or diastolic blood pressure \(\geq 90\) mm Hg.

Statistical Analysis

Continuous variables across the 4 UAE categories were compared using ANOVA, and categorical variables were compared using the \(\chi^2\) statistic. If these tests were statistically significant, then the high normal UAE, microalbuminuria, and macroalbuminuria groups were compared with the normal UAE group. When comparing participants with increased UAE categories (high normal, microalbuminuria, and macroalbuminuria) to participants with normal UAE, we set the level of statistical significance at \(P<0.017\) (0.05/3) to account for multiple comparisons (normal UAE versus high normal UAE, microalbuminuria, and macroalbuminuria groups). The Cochran-Armitage trend test was used to assess linear trends of subclinical CVD measures across the 4 UAE categories.

Generalized linear models (SAS software v. 8.0) were used to calculate adjusted mean common and internal carotid intima-media thickness (IMT), LV mass, and CAC scores by categories of UAE (with normal UAE as the reference group). CAC scores, which have a skewed distribution, were first transformed: ln (CAC score + 1). We reported the adjusted geometric mean CAC scores: [exp(mean-\((ln\text{CAC score} + 1))-1]. Several regression models were created to examine the mediating effects of covariates, especially DM and hypertension. Model 1 adjusted for age, sex, and race/ethnicity to establish the group-specific UAE values. Model 2 adjusted for blood pressure and DM, 2 factors strongly associated with increased UAE, by adding systolic blood pressure, use of antihypertensive medications, and DM to model 1. In model 3, body mass index (BMI), current smoking status, use of lipid-lowering medications, and serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were added to determine whether these remaining risk factors explained any residual differences in subclinical CVD measures between increased and normal UAE categories. In all models, age, BMI, systolic blood pressure, and serum HDL and LDL levels were fitted as continuous variables, whereas current smoking and use of antihypertensive medication and lipid-lowering medication were included as binary variables (yes/no). If the overall test for significance among the four UAE groups (F-test) was significant for a given model, then each increased UAE group was compared with normal UAE with statistical significance set at \(P<0.017\) to account for multiple comparisons. All analyses were repeated after stratifying MESA participants by presence of DM. Effect modification by racial/ethnicity group was examined using interaction terms in the model, which adjusted for all covariates when a significant association was noted between UAE categories and a subclinical CVD measure. Because certain thresholds of CAC scores have been associated with clinical outcomes, CAC scores were also analyzed as ordinal categories. Non-zero CAC scores were divided into 3 categories (1 to 100, 101 to 400, and >400). The odds of having each non-zero CAC category compared with CAC scores of 0 by presence of increased UAE (with normal UAE as the reference group) was examined using ordinal logistic regression while simultaneously adjusting for covariates. The same covariates included in the generalized linear models were used for the ordinal logistic regression analyses. All analyses were repeated after stratifying participants by presence of DM.

Results

The mean age of the 6775 MESA participants was 62.7 years, 47% were male, 45% had hypertension, and 15% had DM (n=1010). Race was reported as white in 38%, black in 28%, Chinese in 12%, and Hispanic in 22%. Normal and high normal UAE were noted in 75% (n=5073) and 11% (n=748), respectively, whereas microalbuminuria and macroalbuminuria were noted in 13% (n=854) and 1% (n=100), respectively. Table 1 shows the characteristics of the MESA participants by level of UAE. Compared with participants with normal UAE, BMI, systolic blood pressure, and diastolic blood pressure were all significantly higher in participants with high normal UAE, microalbuminuria, and macroalbuminuria compared with normal UAE. Maximum common and internal carotid IMT and LV mass increased steadily across the 4 UAE categories, with significantly higher values noted.
among MESA participants with high normal UAE, microalbuminuria, and macroalbuminuria compared with participants with normal UAE. The distribution of urine albumin excretion categories differed among the race/ethnicity groups with the nonwhite racial/ethnicity groups having significantly lower frequency of normal UAE and higher frequency of hypertension and DM compared with whites (Table I).

Detailed information on racial/ethnicity differences in hypertension and blood pressure in the MESA cohort have been previously published.24

The Figure shows the prevalence of categorical measures of subclinical CVD by UAE categories. The frequency of CAC scores >400 was 13%, 17%, and 28% among participants with high normal UAE, microalbuminuria, and macroalbuminuria, respectively, compared with 8% with normal UAE (P<0.0001 for all comparisons). Higher frequency of common or internal carotid artery stenosis was noted among participants with high normal (17%), microalbuminuria (19%), and macroalbuminuria (23%) compared with participants with normal UAE (11%) (P<0.0001 for all comparisons). LV hypertrophy was also significantly more prevalent among participants with high normal UAE (9%), microalbuminuria (13%), and macroalbuminuria (29%) compared with participants with normal UAE (3%) (P<0.0001 for all comparisons). Test for linear trend for each of the subclinical CVD measures across UAE categories was significant at P<0.0001.

Geometric mean CAC scores remained significantly higher among those with microalbuminuria compared with normal UAE (9.9 versus 7.4; P=0.002) after adjustment for all covariates (Table 2). Differences between participants with high normal UAE and macroalbuminuria and normal UAE

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**TABLE 1. Characteristics of the Total MESA Population by Level of Urine Albumin Excretion**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal UAE (n=5073)</th>
<th>High Normal UAE (n=748)</th>
<th>Microalbuminuria (n=854)</th>
<th>Macroalbuminuria (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.5 (0.14)</td>
<td>65.9 (0.37)†</td>
<td>66.7 (0.34)†</td>
<td>66.8 (1.0)†</td>
</tr>
<tr>
<td>Male, %</td>
<td>45</td>
<td>48</td>
<td>58†</td>
<td>65†</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>41</td>
<td>33†</td>
<td>28†</td>
<td>14†</td>
</tr>
<tr>
<td>Black</td>
<td>27</td>
<td>29</td>
<td>32‡</td>
<td>37‡</td>
</tr>
<tr>
<td>Chinese</td>
<td>11</td>
<td>13</td>
<td>15‡</td>
<td>13‡</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21</td>
<td>24</td>
<td>25†</td>
<td>36‡</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1 (0.08)</td>
<td>28.8 (0.20)‡</td>
<td>29.2 (0.19)†</td>
<td>30.3 (0.55)‡</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122.9 (0.29)</td>
<td>134.9 (0.75)†</td>
<td>136.9 (0.70)†</td>
<td>147.3 (2.0)†</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>70.8 (0.14)</td>
<td>74.6 (0.37)†</td>
<td>75.3 (0.34)†</td>
<td>78.0 (1.0)†</td>
</tr>
<tr>
<td>Htn, %</td>
<td>37</td>
<td>62†</td>
<td>71†</td>
<td>88†</td>
</tr>
<tr>
<td>DM, %</td>
<td>10</td>
<td>21†</td>
<td>35†</td>
<td>62†</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>+HDL, mmol/L</td>
<td>1.34 (0.01)</td>
<td>1.29 (0.01)‡</td>
<td>1.22 (0.01)†</td>
<td>1.19 (0.04)†</td>
</tr>
<tr>
<td>+LDL, mmol/L</td>
<td>3.05 (0.01)</td>
<td>3.03 (0.03)</td>
<td>2.97 (0.03)‡</td>
<td>3.04 (0.08)‡</td>
</tr>
<tr>
<td>Common carotid IMT, mm</td>
<td>0.85 (0.003)</td>
<td>0.90 (0.01)‡</td>
<td>0.94 (0.01)‡</td>
<td>0.93 (0.02)‡</td>
</tr>
<tr>
<td>Geometric mean CAC score*</td>
<td>5.9</td>
<td>14.4†</td>
<td>20.8‡</td>
<td>32.2†</td>
</tr>
<tr>
<td>Internal carotid IMT, mm</td>
<td>1.03 (0.01)</td>
<td>1.18 (0.02)‡</td>
<td>1.24 (0.02)‡</td>
<td>1.26 (0.06)‡</td>
</tr>
<tr>
<td>LV mass, g/m²²</td>
<td>35.4 (0.13)</td>
<td>38.3 (0.34)†</td>
<td>40.6 (0.33)‡</td>
<td>46.2 (1.0)†</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; Htn, hypertension; IMT, intima-media thickness; LDL, low-density lipoprotein; LV, left ventricle.

Values are shown as mean (standard error) or percentage (%).

Normal UAE=ACR <13 mg/g in women and <9 mg/g in men; high normal UAE=ACR 13 to 24.9 mg/g in women and 9 to 16.9 mg/g in men; microalbuminuria=ACR 25 to 354.9 mg/g in women and 17 to 249.9 mg/g in men; and macroalbuminuria=ACR ≥355 mg/g in women and ≥250 mg/g in men.

*Geometric least square mean CAC scores: {exp[mean(ln(CAC score−1))−1].

†P<0.0001; ‡P<0.001; and §P<0.017 compared to normal UAE.
associations were explained by presence of CVD risk factors, particularly DM and increased blood pressure. We noted higher internal carotid artery IMT and LV mass in addition to a higher frequency of increased CAC scores in the MESA participants with high normal UAE compared with those with normal UAE. Even after adjustment for all covariates, including DM and blood pressure, LV mass remained significantly higher among MESA participants with higher urine albumin excretion, including levels below the threshold for microalbuminuria. Thus, levels of urine albumin excretion below clinical thresholds used to define microalbuminuria may prove useful as an early marker of target organ damage from increased blood pressure and other CVD risk factors and potentially help identify adults who need more intensive medical interventions to prevent cardiovascular events.

The finding of significantly higher LV mass among participants with higher UAE compared with normal UAE is consistent with previous reports.4–6 The Losartan Interven-

**TABLE 2. Adjusted Geometric Mean CAC Scores* by Level of Urine Albumin Excretion, Compared to Normal Albuminuria, in the Total MESA Population**

<table>
<thead>
<tr>
<th>Level of UAE</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(P)</td>
<td>(P)</td>
<td>(P)</td>
</tr>
<tr>
<td>Normal UAE</td>
<td>7.0 (Referent)</td>
<td>7.4 (Referent)</td>
<td>7.4 (Referent)</td>
</tr>
<tr>
<td>High normal UAE</td>
<td>&lt;0.0001</td>
<td>0.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>&lt;0.0001</td>
<td>1.00</td>
<td>0.002</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&lt;0.0001</td>
<td>12.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Geometric mean CAC scores: \(\exp\{\text{mean}(\ln(\text{CAC score}+1))\}-1\).

Model 1 includes age, sex and race; model 2 includes model 1 and use of antihypertensive medications, SBP, and DM; model 3 includes model 2 and BMI, current smoking status, use of lipid-lowering medication, and serum HDL and LDL levels.

UAE indicates urine albumin excretion.

only reached borderline significance after accounting for multiple comparisons. Similar results were noted among participants without DM. Among participants with DM, the overall test for significance among the 4 UAE groups was not significant in model 3 (F test=0.2) (data not shown).

Associations between UAE categories and increased CAC scores were markedly attenuated after adjustment for presence of DM, antihypertensive medication use, and systolic blood pressure, and results did not change substantially after additional adjustment for other covariates (Table II). Only macroalbuminuria remained significantly associated with CAC scores >400 after adjustment for all covariates. After stratifying participants by presence of DM, and nondiabetic participants, no significant association was noted between UAE categories and CAC scores in models 2 or 3 among the diabetic or nondiabetic participants (data not shown).

The results of the analyses of adjusted mean common and internal carotid IMT by UAE categories are shown in Table III. Adjustment for presence of DM, antihypertensive medication use, and systolic blood pressure showed no significant difference in mean common carotid artery IMT among the increased UAE categories compared with normal UAE. Similar results were noted for internal carotid artery IMT. After stratification by DM, no significant difference was noted in mean common or internal carotid artery IMT among the increased UAE categories compared with normal UAE after adjustment for antihypertensive medication use and systolic blood pressure among the nondiabetic or diabetic MESA participants (data not shown).

Significantly higher adjusted mean LV mass was noted among participants with increased UAE compared with those with normal UAE (Table 3). Mean LV mass remained significantly higher among participants with high normal UAE, microalbuminuria, and macroalbuminuria compared with participants with normal UAE after adjustment for all covariates. No effect modification was noted between racial/ethnicity group and UAE category on LV mass. Among the MESA participants with DM, high normal UAE (40.4; \(P=0.05\)), microalbuminuria (40.5 g/m\(^2\); \(P=0.01\)), and macroalbuminuria (46.0 g/m\(^2\); \(P=0.0001\)) were all associated with higher mean LV mass compared with normal UAE (38.7 g/m\(^2\)) in model 3, but only microalbuminuria and macroalbuminuria reached statistical significance after accounting for multiple comparisons. Among the nondiabetic participants, significantly higher mean LV mass was noted among participants with high normal UAE (36.5; \(P=0.008\)), microalbuminuria (38.1; \(P=0.0001\)), and macroalbuminuria (40.2; \(P=0.0005\)) compared with participants with normal UAE (35.6 g/m\(^2\)) after adjustment for all covariates. Again, no effect modification was noted by racial/ethnicity group.

**TABLE 3. Adjusted Left Ventricular Mass (g/m\(^2\)) by Level of UAE Compared to Normal Albuminuria in the Total MESA Population**

<table>
<thead>
<tr>
<th>Level of UAE</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(P)</td>
<td>(P)</td>
<td>(P)</td>
</tr>
<tr>
<td>Normal UAE</td>
<td>35.5 (Referent)</td>
<td>35.9 (Referent)</td>
<td>36.0 (Referent)</td>
</tr>
<tr>
<td>High normal UAE</td>
<td>&lt;0.0001</td>
<td>37.3</td>
<td>37.0</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>&lt;0.0001</td>
<td>38.8</td>
<td>38.3</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&lt;0.0001</td>
<td>41.9</td>
<td>42.5</td>
</tr>
</tbody>
</table>

Model 1 includes age, sex and race; model 2 includes model 1 and use of antihypertensive medications, SBP, and DM; model 3 includes model 2 and BMI, current smoking status, use of lipid-lowering medication, and serum HDL and LDL levels.

**Discussion**

In this large multi-ethnic population of men and women without established CVD, UAE was strongly associated with several measures of subclinical CVD. Many, but not all, of these associations were explained by presence of CVD risk factors, particularly DM and increased blood pressure. We noted higher internal carotid artery IMT and LV mass in addition to a higher frequency of increased CAC scores in the MESA participants with high normal UAE compared with those with normal UAE. Even after adjustment for all covariates, including DM and blood pressure, LV mass remained significantly higher among MESA participants with higher urine albumin excretion, including levels below the threshold for microalbuminuria. Thus, levels of urine albumin excretion below clinical thresholds used to define microalbuminuria may prove useful as an early marker of target organ damage from increased blood pressure and other CVD risk factors and potentially help identify adults who need more intensive medical interventions to prevent cardiovascular events.

The finding of significantly higher LV mass among participants with higher UAE compared with normal UAE is consistent with previous reports.4–6
tion for Endpoint Reduction compared 833 hypertensive patients with and without LV hypertrophy and noted a significantly higher prevalence of microalbuminuria in the group with LV hypertrophy (26% versus 9%; \( P<0.001 \)).

These results support the hypothesis that increased UAE is an independent marker of increased LV mass, which suggests that these 2 entities share the same pathophysiological mediators, including both environmental and genetic factors and, in particular, hypertension.

No significant differences in mean common or internal carotid artery IMT were noted between increased and normal UAE categories after adjustment for DM and blood pressure. These results differ from several previous studies such as the Insulin Resistance and Atherosclerosis Study (IRAS), which noted significantly higher common carotid artery IMT in participants with microalbuminuria, based on a single spot urine sample, compared with those without microalbuminuria (0.86 mm versus 0.83; \( P=0.02 \)) after adjustment for covariates including DM and presence of hypertension. Although significantly higher common and internal carotid artery IMT were noted in the MESA population with microalbuminuria compared with normal UAE after adjustment for age, sex, and race/ethnicity, the differences were not significant after further adjustment for DM, antihypertensive medication use, and SBP. Moreover, no association was noted between UAE and common or internal IMT after controlling for antihypertensive medication use and SBP among the nondiabetic or hypertensive medication use and SBP of the nondiabetic or diabetic MESA participants. Thus, in IRAS, the association between UAE and IMT may be explained by a residual association between UAE and blood pressure. Agewall et al also reported no significant association between microalbuminuria and common carotid artery IMT in clinically healthy men after adjustment for SBP.

MESA participants with higher UAE had a higher frequency of increased CAC scores compared with participants with normal UAE. This association between UAE and increased CAC scores also appears to be strongly mediated by several CVD risk factors, particularly DM and hypertension, as reflected by the substantial reduction in the odds ratios after the addition of these factors to the regression models. Geometric mean CAC scores were higher among participants with increased UAE compared with normal UAE after adjustment for all covariates, but differences in geometric mean CAC scores between UAE categories were small and not necessarily clinically meaningful. Our findings suggest that increased UAE in adults without clinical CVD reflects the presence of atherosclerosis (increased CAC scores and/or carotid artery IMT) but this association is mediated by CVD risk factors, especially DM and hypertension.

The limitations of this study include the one-time measurement of UAE. Up to one-third of adults in the general population with increased UAE in the first urine sample may not have increased UAE in a subsequent urine sample. The possible misclassification of albuminuria could have biased the results toward the null. In addition, urine creatinine excretion differs by race/ethnicity, but race-specific ACR cut-points were not used because ACR cut-points have not been validated in Chinese or Hispanic adults. We did use sex-specific ACR cut-points that account for differences in urine creatinine excretion between men and women. The small number of MESA participants with very high levels of UAE also limited the power to detect associations between macroalbuminuria and measures of subclinical CVD. The strengths of the study include the representation of several race/ethnicity groups. Moreover, MESA participants were free of all clinical CVD at enrollment and therefore represent those patients who would be targeted for the primary prevention of CVD.

**Perspectives**

Higher UAE, even at levels below the clinical threshold for microalbuminuria, is generally associated with several measures of subclinical CVD in adults without established CVD. These subclinical CVD measures appear to have a common risk factor source, particularly DM and hypertension, but may represent different pathways with relatively small commonalities beyond their associations with risk factors. Associations between UAE and other subclinical markers that persist after risk factor adjustment may indicate a somewhat more advanced state of subclinical disease, wherein several pathologic pathways begin to converge. Future studies should determine whether the measurement of UAE can help identify adults who should be targeted for the primary prevention of CVD.

**Acknowledgments**

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**References**


15. Kramer et al. Albumin Excretion and Subclinical Disease. 43


Urine Albumin Excretion and Subclinical Cardiovascular Disease
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