Association of low-grade urinary albumin excretion with left ventricular hypertrophy in the general population

The MONICA/KORA Augsburg Echocardiographic Substudy

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Abstract

Background. Even mild renal dysfunction is a predictor of cardiovascular morbidity. We investigated whether sub-threshold microalbuminuria or mildly decreased estimated glomerular filtration rate (eGFR) are related to left ventricular hypertrophy (LVH) in the general population.

Methods. Urinary albumin-to-creatinine ratio (UACR) served to determine albuminuria, eGFR was estimated using modification of diet in renal disease (MDRD) formula, and LV geometry was assessed echocardiographically in the third MONItoring of trends and determinants in CArdiovascular disease/Cooperative Health Research in the Augsburg Area (MONICA/KORA) Augsburg survey (n=1187).

Results. The prevalence of LVH increased in parallel with UACR. Compared with the first tertile of this normal population, the age, systolic blood pressure (SBP), body mass index, gender and diabetes adjusted odds ratio (OR) for LVH was elevated already in the second (4.32–8.75 mg/g in men; 4.60–9.48 mg/g in women; OR: 2.10, P=0.001) as well as in the third UACR-tertile (>8.76 mg/g in men; >9.49 mg/g in women; OR: 1.63, P=0.035). Likewise, adjusted SBP increased with UACR-tertiles [129 vs 132 (P=0.036) and 137 mmHg (P<0.001) in the first, second and third tertile, respectively], whereas diastolic blood pressure was significantly elevated only in the third UACR-tertile [79 vs 80 and 81 mmHg (P=0.002) in the tertiles, respectively]. In contrast, tertiles of eGFR or mildly impaired eGFR (<90 ml/min/1.73 m2) were not associated with the prevalence of LVH in multivariate models.

Conclusions. At the general population level, even low-grade albuminuria is associated with LVH. Thus, the conventional UACR-threshold of microalbuminuria (30 mg/g) may be too conservative given that end organ damage such as LVH is observed with increased frequency at much lower levels.

Keywords: albuminuria; epidemiology; left ventricular hypertrophy

Introduction

Left ventricular hypertrophy (LVH) is an established cardiovascular risk factor and associated with increased morbidity and mortality [1]. Microalbuminuria was originally established as a predictor of renal failure in patients with diabetes mellitus [2,3]. Subsequent studies in other patient groups as well as in the general population revealed that microalbuminuria is also associated with future cardiovascular events [4–7]. Likewise, a mildly decreased glomerular filtration rate predicts cardiovascular morbidity [8]. At present, the knowledge about the association of microalbuminuria with LVH is limited. Positive correlations between albuminuria and left ventricular mass (LVM) and LVH have been reported, but most of these studies have been conducted in selected groups, such as patients with hypertension [9,10] and diabetes mellitus [11,12], whereas the relationship of albuminuria and LVH in the general population is largely unknown. In the population-based Prevention of REnal and Vascular ENd stage Disease (PREVEND) study, Smilde et al. [13] found a positive association of mild renal dysfunction—defined as a creatinine clearance <60 ml/min/1.73 m2 or microalbuminuria [defined as an albumin excretion rate (AER)
of 30–300 mg/24 h)—with electrocardiographically determined LVH.

The association between impaired creatinine clearance and LVH has been investigated largely in patients with advanced renal disease. For example, LVH is found in up to 75% of patients starting dialysis [14]. In contrast, however, very little is known about the degree of renal impairment, at which the prevalence of LVH starts to increase.

Recently, the threshold levels defining the pathological spectrum of urinary albumin excretion have been questioned. In fact, urinary albumin excretion rates well below the currently used threshold for microalbuminuria were found to be associated with increased cardiovascular morbidity and mortality [5–7,15–17]. For example, urinary albumin excretion equal or higher than the 50th percentile has been associated with increased cardiovascular event rates in the Framingham Heart Study [16]. Furthermore, low-grade albuminuria was associated with blood-pressure progression in non-hypertensive, non-diabetic individuals [17].

The aim of the present cross-sectional study was to assess the relationship between the urine albumin-to-creatinine ratio (UACR) and the prevalence of LVH in the general population and to evaluate, whether albuminuria below the current threshold for microalbuminuria is associated with an increased prevalence of LVH. For comparison, the association of mildly or moderately reduced estimated glomerular filtration rate (eGFR) with LVH was investigated.

**Subjects and methods**

**Study population**

The subjects of this study participated in the echocardiographic substudy (total n = 1678) of the third MONICA (MONItoring of trends and determinants in Cardiovascular disease) Augsburg survey [18], which is now continued in the framework of KORA (Cooperative Health Research in the Augsburg Area). Of the 2376 invited individuals, 1678 agreed to participate in the echocardiographic substudy (response rate: 70.6%) [19]. The survey represents a gender- and age-stratified random sample of all German residents of the Augsburg area and consists of individuals 25–74 years of age, with about 300 subjects for each 10-year increment. The population was studied by physical examination, blood testing and a standardized interview including medical history, physical activity, medication and personal habits.

Resting blood pressure was taken according to MONICA guidelines using the random zero sphygmomanometer after subjects had been resting in a sitting position. The mean of the second and third recording was calculated and employed to define hypertension as a blood pressure ≥140/90 mmHg or the intake of antihypertensive medication. Body weight in kilograms and height in meters were determined with subjects wearing light clothing. Diabetes mellitus was defined by self-report or intake of antidiabetic medication. Fat-free mass (FFM) and body fat were obtained by bioelectric impedance measurements (BIA) with a Body Composition Analyzer TVI-10 (Danzinger Medical Technology, Heidelberg, Germany). Written informed consent was obtained from all subjects, and a local ethical committee approved the study protocol. The investigation conforms with the principles outlined in the Declaration of Helsinki.

**Echocardiographic measurements**

Two-dimensional guided M-mode echocardiograms were obtained by two expert sonographers using the Sonos 1500 (Hewlett Packard Inc. Bühlberg, Germany). M-mode tracings were recorded on strip-chart paper at 50 mm/s. To reduce interobserver variability, all M-mode tracings were analysed by a single cardiologist who was blinded from obtaining and noticing the data.

Measurements for M-mode guided calculation of the LVM were taken just below the tip of the mitral valve. Only high-quality tracings that demonstrated optimal visualizations of endocardial and epicardial surfaces throughout the cardiac cycle were used. This resulted in exclusion of 16% of potential subjects.

Left ventricular end-diastolic diameter (LVEDD), septal wall (SWT) and posterior wall (PWT) thickness were measured according to the Penn convention and LVM was calculated using the formula 

\[
LVM = \frac{1}{2} \left[ (LVEDD + SWT + PWT)^2 - (LVEDD)^2 \right] - 13.6
\]

as described by Devereux et al. [20]. The rank correlation of 144 duplicate measurements by the two sonographers was 0.91 for the determination of LVM.

LVM was indexed to FFM (LVMI = LVM/FFM), thereby eliminating sex-specific LVH-criteria [18]. LVH was defined as LVMI >4.1 g/kg in men and women [18]. These partition values represent 2 SD above the mean of healthy subjects in the present population [18]. Relative wall thickness (RWT) was calculated as 

\[
RWT = \frac{2 \times PWT}{LVEDD} - 1
\]

**Biochemical analyses**

Blood was drawn for biochemical analyses from non-fasting subjects. Spot urine was collected, cooled and transported to the laboratory at the end of each day and analysed the following work day. Albumin was measured quantitatively with an immunoturbidimetric test (Tina-quant® Albumin in urine, Boehringer Mannheim, Germany) and creatinine was assessed quantitatively with an enzymatic colorimetric test (Hitachi 717, Boehringer Mannheim, Germany). The sensitivity limits for albumin were 3–3000 mg/l.

Microalbuminuria was defined as, a UACR between 30 and 300 mg/g [21], proteinuria as UACR above 300 mg/g. Glomerular filtration rate was estimated using the abbreviated modification of diet in renal disease (MDRD) equation [22].

**Statistical analyses**

Two-dimensional echocardiograms of optimal quality were obtained in 1404 of the 1678 participants. We excluded 166 individuals with missing urine albumin or serum samples, seven individuals with proteinuria, 16 individuals missing serum creatinine values, one individual with an implausible eGFR value (323 ml/min/1.73 m²) and 27 individuals missing other anthropometrical data, leaving a total of 1187 subjects for the final analyses.
To assess the shape of the association of UACR and eGFR with LVH and hypertension we computed logistic regression models with LVH or hypertension as dependent variable and UACR-tertiles or tertiles of eGFR as independent variables. We present odds ratios (ORs) and respective 95% confidence intervals (CIs) that were obtained after adjusting for relevant covariates: the models for LVH were adjusted for age, BMI, systolic blood pressure, gender and diabetes. The logistic model for hypertension was adjusted for age, gender, BMI and diabetes. We used gender-specific UACR-tertiles and eGFR-tertiles to account for gender-related differences in urine creatinine excretion [23]. As only few individuals had diabetes (n = 40), diabetes was not a significant covariate in the logistic regression models. Therefore, we repeated the logistic regression models after exclusion of diabetics and obtained similar results.

Multiple linear regression analyses were performed with left ventricular mass indexed to fat-free mass (LVMI), SWT, PWT, LVEDD and RWT as dependent and with ln(UACR + 1) as independent variable, including age, BMI, SBP, gender and diabetes as covariates. UACR was transformed by taking the natural logarithm for better symmetry of the distribution and the transformation ln(UACR + 1) was used to avoid indeterminable values for UACR values zero.

Least square means adjusted for age, BMI, gender, and diabetes were calculated for SBP, diastolic blood pressure (DBP), and eGFR according to UACR-tertiles. In a similar way, echocardiographic parameters of LVM and blood pressure were compared between individuals with and without mildly impaired eGFR, as well as in those with and without microalbuminuria. LVMI, SWT, PWT and LVEDD were adjusted for age, BMI, SBP, diabetes and gender. SBP and DBP were adjusted for age, BMI, gender and diabetes. UACR values of individuals with and without LVH were compared using Mann–Whitney U-test. Statistical analyses were carried out with statistical product and services solution (SPSS). P-values of a two-tailed t-test for independent groups were obtained for continuous variables while prevalences of LVH were compared using chi-square test. Statistical significance was accepted at P-values below the 5% level.

Results

Anthropometrical data of the study population are shown in Table 1. The distribution of UACR in this sample of the general population is shown in Figure 1. The prevalence of microalbuminuria and LVH were 6.2 and 17.9%, respectively. Mildly or moderately impaired eGFR, as well as in those with and without microalbuminuria, was associated independently with LVMI and PWT in multivariate models (Table 3). Likewise, individuals with microalbuminuria (30–300 mg/g UACR; prevalence 6.2%) displayed higher values for LVMI, SWT and PWT as well as higher blood pressure levels and a higher prevalence of LVH, although the P-values for LVMI, SWT, PWT and LVH did not reach statistical significance in multivariate models (Table 4). These associations remained consistent after exclusion of diabetics and obtained similar results.

Association of UACR with LVM measurements

With increasing tertiles of UACR, the OR for LVH increased (Table 2). After adjustment for age, BMI, SBP, gender and diabetes, the prevalence of LVH was significantly higher even in the second as well as in the third tertile as compared with the first tertile of this population sample. Analyses stratified by gender revealed similar trends in men and women, although the association in men was somewhat stronger than in women (data not shown). Furthermore, ln(UACR) was associated independently with LVMI and PWT in multivariate models (Table 3). Likewise, individuals with microalbuminuria (30–300 mg/g UACR; prevalence 6.2%) displayed higher values for LVMI, SWT and PWT as well as higher blood pressure levels and a higher prevalence of LVH, although the P-values for LVMI, SWT, PWT and LVH did not reach statistical significance in multivariate models (Table 4). These associations remained consistent after exclusion of diabetics and obtained similar results.
Table 2. OR and 95% CI for LVH according to tertiles of UACR and tertiles eGFR

<table>
<thead>
<tr>
<th>UACR-tertiles</th>
<th>OR (95% CI) a</th>
<th>P-value</th>
<th>OR (95% CI) b</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.29 (1.52–3.44) &lt;0.001</td>
<td></td>
<td>2.10 (1.34–3.30) <strong>0.001</strong></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.66 (1.78–3.98) &lt;0.001</td>
<td></td>
<td>1.63 (1.04–2.57) <strong>0.035</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR-tertiles</th>
<th>OR (95% CI) a</th>
<th>P-value</th>
<th>OR (95% CI) b</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.53 (1.71–3.73) &lt;0.001</td>
<td></td>
<td>0.99 (0.63–1.57) 0.96</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.82 (1.21–2.72) <strong>0.004</strong></td>
<td></td>
<td>1.17 (0.74–1.86) 0.51</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
<td></td>
</tr>
</tbody>
</table>

Data are P-values and ORs from logistic regression analyses.

*unadjusted.

badjusted for age, BMI, systolic blood pressure, gender and diabetes.

Terile ranges for UACR were as follows: in men, 0.00–4.31, 4.32–8.75 and 8.76–207.5 mg/g; in women, 0.00–4.59, 4.60–9.48, 9.49–182.8 mg/g.

Terile ranges for eGFR were as follows: in men, 51.7–98.2, 98.3–114.9, 115.0–186.1 ml/min/1.73 m^2; in women, 31.2–94.8, 94.9–111.7, 111.8–192.0 ml/min/1.73 m^2.

UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy. 

P < 0.05 are bold.

Table 3. Multiple linear regression analyses with LVMI, SWT, PWT, LVEDD and RWT as dependent and with ln (UACR) as independent variable

<table>
<thead>
<tr>
<th>Factors in model</th>
<th>LVMI (g/kg)</th>
<th>SWT (mm)</th>
<th>PWT (mm)</th>
<th>LVEDD (mm)</th>
<th>RWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.33</td>
<td>0.26</td>
<td>0.21</td>
<td>–0.11</td>
<td>–0.25</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>0.21</td>
<td>0.29</td>
<td>0.28</td>
<td>0.20</td>
<td>0.16</td>
</tr>
<tr>
<td>Gender (M vs F)</td>
<td>0.001</td>
<td>0.096</td>
<td>0.23</td>
<td>0.24</td>
<td>0.45</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.19</td>
<td>0.18</td>
<td>0.18</td>
<td>0.02</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes (yes vs no)</td>
<td>-0.05</td>
<td>0.055</td>
<td>-0.06</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Ln UACR (mg/g)</td>
<td>0.05</td>
<td>0.035</td>
<td>0.04</td>
<td>0.06</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Data are β-coefficients and P-values. UACR, urinary albumin-to-creatinine ratio; BMI, body mass index; SBP, systolic blood pressure; LVMI, left ventricular mass indexed to fat-free mass; SWT, septal wall thickness; PWT, posterior wall thickness; LVEDD, left ventricular end-diastolic diameter; RWT, relative wall thickness. 

P < 0.05 are bold.

Table 4. Prevalence of LVH, adjusted OR and 95% CI for LVH, and echocardiographic as well as blood pressure measurements, by presence or absence of microalbuminuria (30–300 mg/g UACR)

<table>
<thead>
<tr>
<th></th>
<th>No microalbuminuria (n = 1113)</th>
<th>Microalbuminuria (n = 74)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH, n (%)</td>
<td>188 (16.9)</td>
<td>24 (32.4)</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Adj. OR (95% CI) for LVH</td>
<td>Ref.</td>
<td>1.23 (0.68–2.24)</td>
<td>0.491</td>
</tr>
<tr>
<td>LVMI (g/kg)</td>
<td>3.29 ± 0.03</td>
<td>3.47 ± 0.10</td>
<td>0.081</td>
</tr>
<tr>
<td>Septal wall (mm)</td>
<td>9.3 ± 0.05</td>
<td>9.7 ± 0.20</td>
<td>0.061</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>7.6 ± 0.04</td>
<td>7.9 ± 0.14</td>
<td>0.058</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>49.5 ± 0.13</td>
<td>49.1 ± 0.51</td>
<td>0.432</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>132 ± 0.51</td>
<td>140 ± 1.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80 ± 0.32</td>
<td>83 ± 1.24</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Prevalence of LVH given as number of individuals (%); OR for LVH by logistic regression and least square means ± SE for continuous variables adjusted for age, BMI, SBP, gender and diabetes. SBP and DBP not adjusted for SBP.

*P-values from t-test for independent groups for individuals vs. without microalbuminuria, except for comparison of prevalence of LVH where chi-square test was used and for calculation of OR for LVH where logistic regression analysis was used.

LVH, left ventricular hypertrophy; LVMI, left ventricular mass indexed to fat-free mass; LVEDD, left-ventricular end-diastolic diameter; SBP, systolic blood pressure; DBP, diastolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

P < 0.05 are bold.
of individuals with diabetes mellitus (n=40; data not shown). Furthermore, individuals with LVH displayed higher UACR-values (men: median, 7.03 mg/g, interquartile range (IQR), 5.10–17.17; women: median, 8.50 mg/g, IQR, 4.64–20.24) than individuals without LVH (men: median, 5.61 mg/g, IQR, 3.33–10.94; women: median, 6.31 mg/g, IQR, 3.77–10.79; P < 0.001 for men and P = 0.001 for women).

Association of eGFR with LV and blood pressure measurements

Stratification of the entire sample in tertiles of eGFR revealed elevated unadjusted ORs for LVH in the first and second as compared with the third eGFR-tertile (Table 2). However, after adjustment for age, BMI, SBP, gender and diabetes no significant association with LVH was found (Table 2). Likewise, individuals with an eGFR <90 ml/min/1.73 m² did not reveal significant elevations of LVMi, SWT, PWT, LVEDD, SBP or DBP in multivariate models (Table 5).

Association of UACR with blood pressure measurements and eGFR

To elucidate possible mechanisms responsible for the increased OR for LVH with increasing urinary albumin excretion we analysed SBP, DBP, the prevalence of hypertension and eGFR across UACR-tertiles (Table 6). In the second tertile, only SBP was significantly higher than in the first tertile. In the third tertile, SBP and DBP, and eGFR displayed higher values as compared with the first tertile (Table 6). The prevalence of hypertension was not elevated in the second [OR: 1.07 (95% CI 0.77–1.49), P = 0.69] but significantly higher in the third UACR-tertile [OR: 2.13 (95% CI 1.53–2.96), P < 0.001] in a multivariate model adjusting for age, BMI, gender and diabetes.

Discussion

The present study provides evidence, that low-grade urinary albumin excretion may be associated with LVH. Thus, important end organ damage may be observed with increased prevalence at albumin excretion rates much lower than those currently considered to be at a pathological level. Moreover, in our multivariate analyses, UACR displayed a stronger association with LVH in apparently healthy individuals than a mildly impaired eGFR.

These data are in line with other studies providing evidence of an increased cardiovascular morbidity and mortality at urinary albumin excretion rates below the...
Low-grade albuminuria and left ventricular hypertrophy

Recently, data from the Framingham Heart Study indicated for low-grade urinary albumin excretion in otherwise healthy subjects a more rapid progression towards hypertensive blood pressure levels [17] and, in the long term, an increased incidence of cardiovascular disease events [16]. In that study by Årnlov et al. [16], the cut-off for an elevated cardiovascular event rate was the 50th percentile, of 3.9 mg/g UACR for men and 7.5 mg/g UACR for women. These levels are similar to those observed in our study in which the OR for LVH was elevated at women. These levels are similar to those observed in cardiovascular event rate was the 50th percentile, of a lack of statistical power. Nevertheless, these data eGFR in this population sample may account in part [25] and small numbers of individuals with impaired microalbuminuria or a creatinine clearance <60 ml/min/1.73 m², was associated with increased LV mass or LVH [13,26]. In the population-based PREVEND study, microalbuminuria was determined based on the mean of two 24-h urine collections. An albumin excretion rate of 30 to 300 mg/24 h as well as a creatinine clearance <60 ml/min/1.73 m² were associated with an electrocardiographically determined LVH [13]. In the present study, only very few individuals (n = 18) had a moderately reduced eGFR <60 ml/min/1.73 m². Consistent with our other results, these individuals did not display any significant differences with respect to LVMI, SWT, PWT or LVEDD in multivariate models, when compared with individuals with a eGFR ≥60 ml/min/1.73 m² (data not shown).

The pathophysiological link between urinary albumin excretion and increased LVMI might therefore also be a marker for slightly elevated blood pressure levels. In a recent investigation, microalbuminuria was significantly associated with high-normal blood pressure in non-diabetic, non-hypertensive individuals [27]. High–normal blood pressure is associated with an increased cardiovascular risk [28] and LVH might be one reason for the increased cardiovascular morbidity in these individuals. In our analyses, the association of UACR with LVH persisted even after adjustment for systolic blood pressure, suggesting that additional mechanisms may be involved. In fact, recent studies provide evidence that microalbuminuria indicates, to some extent, altered haemodynamics including renal hyperperfusion and systemic endothelial dysfunction [29].

Limitations of the study

There are different ways to measure urinary albumin excretion rate (AER). Originally, timed (e.g. 24-h or overnight) urine collections were used to measure AER. In the present study, albuminuria was measured using the albumin-to-creatinine ratio from a spot urine sample (UACR) and not by obtaining 24-h urine collections. In addition, there was no testing of possible bacteriuria. Likewise, the glomerular filtration rate was not measured in a 24-h urine collection but estimated with the MDRD formula. However, 24-h and overnight urine collections are time consuming and often inaccurate in population-based studies, particularly because incomplete collections are frequent. Good correlations between the UACR and albuminuria measured in overnight and 24-h urine collection are reported [30,31] and UACR measured in a single urine sample...
is established as a good predictor for overt nephropathy in prospective studies [32]. The MDRD formula is recommended for estimation of GFR in adults by the National Kidney Foundation [33].

Another limitation is, that only a single urine sample was available from each individual. As urine albumin excretion shows a significant intra-individual variability [34,35], this may have led to some misclassifications, reducing the probability to find a positive association. For individual risk stratification multiple urine samples of the same individual may give better risk estimates.

In the present study, the models used to evaluate the association of eGFR with LVMI and LVH included age as a covariate while age was concurrently a component of the MDRD estimation formula. This may have resulted in a certain amount of ‘statistical overadjustment’ for age in these models. As a consequence, the association between eGFR and LVH may appear somewhat weaker than it actually is. However, as age is such a strong confounder in the association under study, the alternative approach, that is, complete omission of age from the statistical models, seemed even more inappropriate to us.

Finally, it will be important to confirm our findings in independent populations with different cultural and ethnic background. In addition, prospective studies are needed to investigate the predictive value of low-grade albuminuria for the incidence of LVH in the general population.

Clinical implications

The association between renal damage and related cardiovascular risk is well documented. Here, we demonstrate that even low-grade albuminuria, which is found in a large proportion of the overall population, may represent some of this risk as it is associated with LVH. In fact, in the setting of a white population-based sample, low-grade albuminuria is more strongly associated with LVH than mildly impaired eGFR in multivariate models. Thus, the data add to the growing notion that sub-threshold albuminuria may be indicative in a more complex fashion as suggested previously [5–7,15–17].

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