Abstract—The strong relationship between urinary albumin excretion (UAE) and pulse pressure (PP) in cross-sectional studies suggests that pressure pulsatility may contribute to renal microvascular injury. The longitudinal relationships between UAE and the various indices of blood pressure (BP) are not well studied. We compared the associations of UAE with the longitudinal exposure to PP and systolic, diastolic, and mean BPs. UAE was measured from 24-hour urine collections in 450 community-dwelling subjects (age: 57±15 years, 53% women, all with UAE <200 μg/min). For each subject, longitudinal indices of BP were estimated by dividing the area under the curve of serial measurements of BP (median: 5) during 1 to 22 years preceding UAE measurement by the number of follow-up years. Median (interquartile range) UAE was 4.7 μg/min (3.3 to 7.8 μg/min) in women and 5.2 μg/min (3.7 to 9.8 μg/min) in men. In women, UAE was not related to longitudinal indices of BP. In men, in multivariable-adjusted models that included either longitudinal systolic and diastolic BPs or longitudinal PP and mean BP, UAE was independently associated with systolic (standardized regression coefficient [β]=0.227; \( P=0.03 \)) but not with diastolic (β = −0.049; \( P=0.59 \)) BP and with PP (β = 0.216; \( P=0.01 \)) but not with mean BP (β = 0.032; \( P=0.72 \)). Comparisons of these 2 models and stepwise regression analyses both indicated that, of the 4 longitudinal indices of BP, PP was the strongest predictor of UAE in men. The pulsatile component of BP confers the highest risk for BP-induced renal microvascular injury. Future studies should examine whether PP reduction provides additional renoprotection beyond that attained by conventional BP goals alone. (Hypertension. 2010;55:00-00.)

Key Words: pulse pressure  ■ albuminuria  ■ microvascular  ■ renal function  ■ longitudinal studies

Urinary albumin excretion (UAE) is an early marker of glomerular injury and a well-established risk factor for cardiovascular morbidity and mortality in diverse populations,1 even within the conventional “normal” range.2 Although increased UAE is a sign of glomerular injury, it has long been considered a marker of generalized vascular dysfunction,3 partially explaining the significant risk associated with increased UAE.1,2

Although the pathophysiologic factors that influence UAE have not been fully elucidated, a link between blood pressure (BP) and renal dysfunction in general,4 as well as UAE in particular,5 has long been recognized. Previous studies have uncovered significant associations between UAE and the 4 indices of BP, namely, systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), and mean BP (MBP). Although some studies, especially earlier works, emphasized associations between UAE and DBP or MBP,6–8 more recent studies found stronger associations between UAE and SBP or PP.9–16

It is hypothesized that the high-flow, low-resistance arterial system of the kidneys and the unique arterial structure of the glomeruli contribute to BP-induced renal microvascular injury.17,18 In most systemic arterial territories, the precapillary resistance arterioles absorb the bulk of the pulsatile energy of the blood, thus shielding the microvasculature from excessively pulsatile pressure and flow. In contrast, in the kidneys, to maintain filtration pressure in the glomerulus, vascular resistance in the afferent arteriole is constantly maintained below that in the efferent arteriole, exposing the glomeruli to high levels of pressure and flow pulsatility. The bulk of the pulsatile energy that is transmitted through the afferent arteriole is dissipated in the glomerulus19 and is thought to contribute to renal microvascular injury.17–19 Notably, the myogenic response of the glomerular afferent arteriole, the mechanism that protects the kidneys from elevated BP, seems to primarily respond to changes in SBP and is insensitive to changes in other indices of BP, including PP.20 Therefore, it may be hypothesized that, when BP is within the autoregulatory range, the pulsatile component of BP can still penetrate the glomeruli and cause renal microvascular injury. Thus, as a marker of glomerular injury, UAE would be expected to be

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more strongly associated with PP than with other indices of BP, including SBP.

Accordingly, the present longitudinal study was conducted in a community-dwelling sample of clinically healthy, normotensive, and untreated hypertensive individuals with up to 22 years of follow-up. We hypothesized that a cumulative index of longitudinal exposure to PP would be a stronger predictor of UAE than other longitudinal indices of BP, namely, SBP, DBP, and MBP.

### Methods

#### Study Population

The study population was drawn from participants in the Baltimore Longitudinal Study of Aging, an ongoing, prospective, observational study of normative aging in community-dwelling volunteers. The Baltimore Longitudinal Study of Aging was established in 1958 and has been described in detail elsewhere. Briefly, subjects, who are healthy at study entry, undergo ~2.5 days of medical examinations at the clinical research unit of the National Institute on Aging in Baltimore at preset intervals.

Twenty-four–hour urine collections were performed in participants who visited the study site between 1996 and 1999. The present analyses involved all of the Baltimore Longitudinal Study of Aging volunteers who underwent UAE measurement, were free from macroalbuminuria (UAE >200 μg/min), had no clinical evidence of cardiovascular disease other than hypertension (defined as BP ≥140/90 mm Hg), and were not receiving medications for hypertension or diabetes mellitus.

#### Definition of Variables

UAE was measured with nephelometry (Beckman Array System) in 24-hour urine samples collected onsite. Brachial BP was measured with conventional sphygmomanometry using an appropriately sized cuff and standard methods after ≥5 minutes of rest in the seated position. PP was calculated as (SBP–DBP) and MBP as [DBP+(PP/3)]. Blood glucose and circulating lipid concentrations were determined in samples drawn after an overnight fast using commercially available methods. Serum creatinine was not measured concurrent with UAE measurement. Therefore, in a subset of subjects in whom serum creatinine was measured during the visits immediately before and after the UAE measurement, serum creatinine at the time of UAE measurement was imputed with linear mixed-effects models and an interpolation technique, as described previously. Glomerular filtration rate was estimated using the imputed creatinine values and the 4-element Modification of Diet in Renal Disease equation. White blood cell count was used as a crude measure of inflammation.

#### Longitudinal Variables

Cumulative exposure to all of the variables except age and height was estimated as described by Li et al. Briefly, serial measurements of each variable during the 1 to 22 years preceding UAE measurement (median number of visits: 5) were analyzed with linear mixed-effects models to derive the trajectory of each variable for each subject, as described previously. The random effects included in the mixed-effects models allowed the initial value of each variable (intercept) and its trajectory (slope) for each subject to vary from the corresponding population mean values. For each subject, cumulative exposure to each variable was estimated by integrating the area under the curve of the trajectory of that variable using a simple trapezoidal integration method. This was then divided by the number of follow-up years for each subject to estimate the average cumulative exposure (the “longitudinal index”) for that variable.

#### Statistical Analysis

Variables with a skewed distribution (UAE and triglycerides) were natural log-transformed (ln[UAE] and ln[triglycerides]). Correlations between variables were assessed with a Pearson correlation coefficient (r). Independent correlates of UAE were assessed with linear regression analyses. Variance inflation factors were monitored and were <4 in all of the models, ensuring lack of multicollinearity among the independent variables. Selection of covariates for inclusion in regression analyses was on the basis of their significant associations with UAE in the present study or previous studies. When smoking was included in the models, it was not associated with UAE in any of the models. Therefore, smoking was removed from all of the models.

We used 2 different approaches to compare the strength of the associations between UAE and the longitudinal indices of BP. First, we used a linear regression model with a stepwise entry method that allowed all of the longitudinal indices of BP and other covariates to compete for entry into the model. Next, we constructed 2 models, which were adjusted for the same set of covariates and differed only in that 1 included longitudinal SBP and DBP and the other included longitudinal PP and MBP (nonnested models). The combinations of SBP and DBP or PP and MBP were used so that the steady and pulsatile components of BP are both represented in each model. Model predictions were then compared with statistical methods appropriate for the comparison of nonnested models, namely, J-test, Cox test, and Encompassing test. Additional confirmatory analyses included comparisons of the 2 nonnested models with the fast double bootstrap test and the Akaiké Information Criterion (a measure of goodness of fit).

Statistical analyses were performed using R 2.8.1 (R Foundation for Statistical Computing), SPSS 14.0 (SPSS Inc), and SAS 9.1 (SAS Institute). Unless otherwise specified, descriptive statistics are expressed as mean±SD for continuous variables and as N (%) for discrete variables. Statistical significance was inferred for P<0.05.

All of the participants provided written informed consent and the study protocol was approved by the institutional review board of the National Institute on Aging.

#### Results

##### Characteristics of the Study Population

Characteristics of the 450 study subjects at the time of UAE measurement are summarized in Table 1. Women composed nearly half of the study cohort, which predominantly included middle-aged, white subjects with a median follow-up of 4 years (range: 1 to 22 years) and a body mass index in the overweight range. Notably, UAE (median [interquartile range]) was well within the “normal” range in both men (5.2 μg/min [3.7 to 9.8 μg/min]) and women (4.7 μg/min [3.3 to 7.8 μg/min]), and only 9% of the men and 3% of the women in the study cohort had microalbuminuria (UAE: 20 to 200 μg/min). When subjects were stratified according to cross-sectional BP, lnUAE was higher in hypertensive men than in normotensive men (2.15±0.96 versus 1.68±0.65 μg/min; P<0.001), whereas in women lnUAE did not significantly differ between hypertensive and normotensive subjects (1.62±0.55 versus 1.70±0.64 μg/min, respectively; P=0.40). When subjects were stratified according to longitudinal BP, there were no significant differences between hypertensive and normotensive subjects in either men (2.09±0.87 versus 1.86±0.82 μg/min, respectively; P=0.27) or women (1.66±0.65 versus 1.67±0.62 μg/min, respectively; P=0.93).

##### Association of UAE With Cross-Sectional Indices of BP

In cross-sectional analyses with UAE as the dependent variable, the interactions of sex with both SBP and PP were
highly significant (both \( P<0.001 \)). Therefore, all of the analyses were performed separately in men and women.

In women, UAE did not correlate with any of the cross-sectional indices of BP (\( r = -0.02, 0.01, -0.04, \) and \( -0.01 \) for SBP, DBP, PP, and MBP, respectively; all \( P\geq 0.57 \)). Therefore, no further analyses were pursued in women. Conversely, in men, UAE correlated significantly and positively with all of the cross-sectional indices of SBP (\( r = 0.33, 0.15, 0.29, \) and \( 0.27 \) for SBP, DBP, PP, and MBP, respectively; all \( P\leq 0.03 \)). Cross-sectional data from men were analyzed in 2 separate models that were adjusted for the same set of covariates and included either SBP and DBP or PP and MBP, with UAE as the dependent variable. In the model with SBP and DBP (\( R^2=0.204 \)), UAE was significantly associated with SBP (standardized regression coefficient [\( \beta = 0.355; P<0.001 \]) but not with DBP (\( \beta = -0.077; P=0.33 \)). In the model with PP and MBP (\( R^2=0.204 \)), UAE was significantly associated with PP (\( \beta = 0.246; P=0.003 \)) but not with MBP (\( \beta = 0.127; P=0.09 \)).

### Association of UAE With Longitudinal Indices of BP

In longitudinal analyses with UAE as the dependent variable, the interactions of sex with both SBP and PP were significant (both \( P=0.01 \)). Therefore, all of the analyses were performed separately in men and women.

In women, UAE was not related to any of the longitudinal indices of BP (Table 2). Therefore, no further analyses were pursued in women. Conversely, in men, UAE correlated significantly and positively with all of the longitudinal indices of BP, as well as with weight, heart rate, and fasting blood glucose (Table 2).

Longitudinal data from men were analyzed in 2 separate models similar to those described in the cross-sectional analyses above (Table 3, models A and B). In the model with SBP and DBP (\( R^2=0.151 \)), UAE was significantly associated with SBP (\( \beta = 0.227; P=0.03 \)) but not with DBP (\( \beta = -0.049; P=0.59 \)). In the model with PP and MBP (\( R^2=0.164 \)), UAE was significantly associated with PP (\( \beta = 0.216; P=0.01 \)) but not with MBP (\( \beta = 0.032; P=0.72 \)). Longitudinal PP alone accounted for 3% of the overall variance in UAE, which was higher than that for longitudinal MBP (0.1%), SBP (2.0%), or DBP (0.1%). When the analyses were repeated with further adjustments for estimated glomerular filtration rate in the subset of men for whom serum creatinine was available (\( N=178 \)), similar results were obtained (data not shown).

### Table 1. Characteristics of the Study Population at the Time of UAE Measurement

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (N=213)</th>
<th>Women (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of follow-up, y</td>
<td>8.0±5.6</td>
<td>4.2±2.8</td>
</tr>
<tr>
<td>Demographics and anthropometric data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>60±16</td>
<td>55±14</td>
</tr>
<tr>
<td>Height, cm</td>
<td>176±7</td>
<td>163±7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85±14</td>
<td>69±14</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±4</td>
<td>26±5</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>181 (85)</td>
<td>195 (82)</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>133 (62)</td>
<td>99 (42)</td>
</tr>
<tr>
<td>Comorbidities and medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>89 (42)</td>
<td>65 (27)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)*</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lip-levitering drug use, n (%)</td>
<td>15 (7)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Hemodynamic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>67±12</td>
<td>70±12</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>131±20</td>
<td>125±21</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82±11</td>
<td>77±11</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>50±17</td>
<td>48±16</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>98±12</td>
<td>93±13</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria, n (%)†</td>
<td>19 (9)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>ln(UAE), μg/min</td>
<td>1.88±0.83</td>
<td>1.67±0.62</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>95±14</td>
<td>89±7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>200±29</td>
<td>204±34</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>111±61</td>
<td>96±51</td>
</tr>
<tr>
<td>White blood count, mL⁻¹</td>
<td>5937±1513</td>
<td>5778±1358</td>
</tr>
<tr>
<td>Serum creatinine‡</td>
<td>1.0±0.2</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>eGFR‡</td>
<td>89±50</td>
<td>80±23</td>
</tr>
</tbody>
</table>

*Diabetes mellitus was diet controlled.
†Microalbuminuria was defined as UAE = 20 to 200 μg/min.
‡Concurrent serum creatinine was imputed for 178 (84%) of the men and 184 (78%) of the women in the study cohort.
§eGFR denoted estimated glomerular filtration rate at the time of UAE measurement, calculated with the 4-element Modification of Diet in Renal Disease equation.
Comparisons of the Longitudinal Indices of BP as Predictors of UAE

First, we used a regression model with a stepwise entry method, which allowed all of the indices of BP and other covariates to compete for entry into the model. Longitudinal PP was the only index of BP that entered the model ($P = 0.232; P = 0.001$), suggesting that UAE was more strongly associated with longitudinal PP than with other longitudinal indices of BP.

Next, we used the J-test, the Cox test, and the Encompassing test to directly compare the contributions of longitudinal SBP and DBP with those of longitudinal PP and MBP as predictors of UAE. Specifically, these tests compared models A and B in Table 3 in 2 distinct ways. First, they tested whether model A can improve on the predictions of UAE yielded by model B. Next, they tested whether model B can improve on the predictions of UAE that were provided by the model with longitudinal SBP and DBP ($P = 0.007$). Consistently, the model with longitudinal PP and MBP had a smaller Akaike Information Criterion than the model with longitudinal SBP and DBP ($1124$ versus $1126$), indicating that the former provided a better fit for the data.

UAE was not independently associated with longitudinal MBP ($0.135; P = 0.09$) or with longitudinal DBP ($0.68; P = 0.35$) when they were individually entered in the multivariate-adjusted models. In contrast, UAE was independently associated with longitudinal PP ($0.231; P = 0.003$) and longitudinal SBP ($0.194; P = 0.02$) when they were individually entered in the multivariate-adjusted models. The model with longitudinal PP provided better predictions of UAE than the model with longitudinal SBP, as indicated by both $R^2$ ($0.164$ versus $0.150$, respectively) and Akaike Information Criterion ($1122$ versus $1124$, respectively) values.

Discussion

In the present study, we examined the associations between UAE and 4 longitudinal indices of BP in a community-dwelling sample of clinically healthy, normotensive, and untreated hypertensive individuals. In women, UAE was not associated with any of the cross-sectional or longitudinal indices of BP. Conversely, in men, longitudinal SBP and PP were independent predictors of UAE, whereas longitudinal DBP and MBP were not. Comparative analyses indicated that, among the 4 longitudinal indices of BP, PP was the strongest predictor of UAE in men.

Previous Comparisons of the Indices of BP as Predictors of Renal Injury

The association of UAE with the various indices of BP has been the subject of many previous studies. However, to date, only 1 study has compared the associations of UAE with the various indices of BP. In a cross-sectional study that only included men, Pedrinelli et al. found that, among the 4 indices of BP, PP was the best predictor of microalbuminuria (defined as UAE ≥15 μg/min). In another study, Tsakiris et al. found that, after adjusting for age, spot urinary albumin concentration measured in a morning urine sample was significantly associated with concurrent SBP and PP but not with concurrent DBP or MBP. Although urinary albumin concentration had a stronger association with concurrent PP ($0.199; P = 0.00001$) than with concurrent SBP ($0.164; P = 0.005$), these associations were not directly compared in that study. In addition, there was considerable variability in the associations of urinary albumin concentration with the 4 BP indices measured 3 and 12 years before urinary albumin measurement.

Two other studies have compared the associations of worsening renal function with the various indices of BP. In a post hoc analysis of data from the Reduction of Endpoints in Noninsulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Study, Bakris et al. found that, in subjects with hypertension and established diabetic nephropathy, baseline PP was a better predictor of the primary composite outcome of doubling of serum creatinine than the model with longitudinal SBP and DBP ($P = 0.002$). Consistently, the model with longitudinal PP and MBP had a smaller Akaike Information Criterion than the model with longitudinal SBP and DBP ($1124$ versus $1126$), indicating that the former provided a better fit for the data.

Table 3. Longitudinal Determinants of UAE Among Men in the Study Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>A: Model With SBP and DBP</th>
<th>B: Model With PP and MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>White race</td>
<td>0.041 ± 0.167</td>
<td>0.030 ± 0.165</td>
</tr>
<tr>
<td>Age, y*</td>
<td>−0.029 ± 0.005</td>
<td>−0.029 ± 0.004</td>
</tr>
<tr>
<td>Height, cm*</td>
<td>0.092 ± 0.009</td>
<td>0.099 ± 0.009</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>0.065 ± 0.006</td>
<td>0.078 ± 0.006</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>0.070 ± 0.002</td>
<td>0.054 ± 0.002</td>
</tr>
<tr>
<td>I(triglycerides)</td>
<td>−0.055 ± 0.158</td>
<td>−0.057 ± 0.157</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>0.208 ± 0.011</td>
<td>0.202 ± 0.011</td>
</tr>
<tr>
<td>White blood cell count, mL⁻¹</td>
<td>0.045 ± 0.000</td>
<td>0.054 ± 0.000</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>0.115 ± 0.010</td>
<td>0.128 ± 0.010</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>0.227 ± 0.008</td>
<td>...</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>−0.049 ± 0.013</td>
<td>...</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>...</td>
<td>0.216 ± 0.004</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.151 ± 0.164</td>
<td></td>
</tr>
</tbody>
</table>

$\beta$ denotes standardized regression coefficient.

*The reported statistics for age and height were computed for their values at the time of UAE measurement.
ine, end-stage renal disease, or death than baseline SBP or DBP and that SBP and PP were equivalent as predictors of incident end-stage renal disease. In contrast, in a subgroup of subjects from the placebo arm of the Systolic Hypertension in the Elderly Program, Young et al. found that baseline SBP was better than baseline PP in predicting a decline in kidney function, defined as a 0.4-mg/dL increase in serum creatinine, during 5 years of follow-up. It is noteworthy that both of these studies only used the baseline BP variables to predict the study outcomes. This is important because all of the subjects in the Reduction of Endpoints in Noninsulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Study and 44% of the subjects in the placebo arm of Systolic Hypertension in the Elderly Program received antihypertensive medications, which would affect their BP during the course of the study.

The present study is the first to compare the relationships of UAE, a measure of renal microvascular injury, and the 4 longitudinal indices of BP. Our findings underscore the importance of the pulsatile component of BP as a risk factor for increased UAE and support the hypothesis that implicates pressure pulsatility in renal microvascular injury. It should be noted that the present study examined the relationships of the longitudinal indices of BP with UAE, and not with glomerular filtration rate, which is a measure of overall renal function.

It is also noteworthy that, compared with longitudinal models, cross-sectional models accounted for a larger proportion of the overall variance in UAE, suggesting a stronger association of UAE with concurrent indices of BP than with longitudinal indices of BP. This observation may suggest that the renal microvasculature is more susceptible to short-term, rather than to long-term, exposure to BP, or that concurrent BP may be influenced by the same pathophysiological processes that mediate higher UAE levels and, thus, may demonstrate a stronger association with UAE. Future studies of the longitudinal changes in both BP and UAE are required to further elucidate the interrelationship between BP and UAE.

Mechanistic Hypotheses That Link UAE With the Pulsatile Component of BP

Contemporary views suggest that the high-flow, low-resistance arterial system of the kidneys and the unique arterial structure of the glomeruli may play a major role in the pathogenesis of renal microvascular injury in hypertension. Specifically, to maintain glomerular filtration pressure, vascular resistance in the afferent arteriole is constantly maintained below that in the efferent arteriole. Thus, unlike most systemic arterial territories, where the precapillary resistance arterioles shield the microcirculation from excessive pressure pulsatility, the glomeruli are exposed to high levels of pulsatile pressure. In addition, PP decay across the glomerulus is drastic, indicating that the bulk of the pulsatile energy that is transmitted through the afferent arteriole is absorbed in the glomerulus. Additional evidence for the vulnerability of glomeruli to pulsatile pressure comes from experimental studies of the myogenic response of the afferent arteriole, which is thought to be the primary mechanism that protects the glomeruli from BP-induced injury.

Loutzenhiser et al. found that this mechanism primarily responded to changes in SBP, whereas, when SBP was held constant, this renoprotective mechanism was insensitive to changes in the other indices of BP, including PP. Thus, it may be concluded that, although the myogenic response can protect the glomeruli from SBP-induced barotrauma within the autoregulatory range of BP, it is not equipped to protect the glomeruli from the detrimental effects of PP.

Additional support for the role of PP in the pathogenesis of increased UAE comes from studies of the effects of PP on small artery structure and function. There is good evidence that, among the various indices of BP, PP is most strongly correlated with small artery remodeling (eg, increased medial: lumen ratio). Interestingly, among the currently available classes of medications, angiotensin-converting enzyme inhibitors, which are the standard treatment for the reduction of UAE, also appear to be the most effective in reversing these small-artery structural abnormalities. Importantly, such structural changes are often accompanied by significant abnormalities in small-artery function, including endothelial dysfunction, which is strongly linked to UAE.

The strong association between UAE and generalized endothelial dysfunction suggests that glomerular endothelial dysfunction may play a causative role in the pathogenesis of increased UAE. Indeed, in an experimental study, endothelial dysfunction antedated the rise in UAE in hypertensive rats. Importantly, clinical studies indicate that endothelial dysfunction is more strongly associated with PP than with SBP, suggesting that endothelial cells may be more susceptible to oscillatory than to peak shear stress. Collectively, these findings support our results and suggest that the stronger association of UAE with longitudinal PP rather than with longitudinal SBP in the present study may be a manifestation of the stronger deleterious effects of chronic exposure to PP on endothelial function.

Sex-Related Differences: Potential Explanations

Although the reasons for the lack of association between UAE and BP among the women in our cohort are not entirely clear, several observations may help to explain the sex-related discordance in our results. Compared with men, women in our cohort had a shorter duration of follow-up (P<0.001), significantly lower UAE (P=0.003), less microalbuminuria (P=0.009), and a lower global vascular risk burden (Table 1). Notably, sex-related differences in the incidence and severity of renal disease are not uncommon. Multiple studies have found higher levels of UAE in men than in women, which may be because of sex-related differences in endothelial function or glomerular hemodynamics.

Clinical Implications

Previous studies have demonstrated that the association between UAE and the risk of adverse outcomes is linear, without any specific thresholds. Thus, identification of modifiable risk factors for low-grade UAE is important, especially vis-à-vis the rising prevalence of albuminuria. Our results suggest that, at least in men, chronic exposure to high PP can lead to higher UAE. This finding suggests that therapies that reduce central arterial stiffness may have
superior renoprotective effects compared with therapies that reduce BP but have a lesser impact on central arterial stiffness. Interestingly, the vasopeptidase inhibitor, omapatrilat, which was more effective than enalapril in reducing proximal aortic stiffness in humans,45 also produced a larger reduction in glomerular pressure and proteinuria and conferred superior renoprotection compared with enalapril in an animal model of glomerulosclerosis.46

**Strengths and Limitations**

The strengths of our study include using the gold standard measure of UAE and using longitudinal data derived from repeated measurements of BP performed over long time periods. In addition, we confined the analyses to clinically healthy, community-dwelling individuals who were not using antihypertensive medications to minimize the confounding effects of comorbidities and antihypertensive medications. Moreover, we used statistical methods26–28 that allowed us to avoid multicollinearity while comparing the interrelated BP indices and did not rely solely on stepwise regression analysis, in which minor differences between predictor variables can potentially determine which variable(s) would enter the final model.47

One factor that potentially limits the generalizability of our results is that the participants in the Baltimore Longitudinal Study of Aging are predominantly white, well-educated, and health-conscious individuals. Another important limitation is that UAE was measured at a single time point. Therefore, the effect of BP on longitudinal changes in UAE cannot be determined from the present study. In addition, because of PP amplification across the arterial tree, the operational PP at the level of the kidneys likely differs from brachial PP and may be closer to central aortic PP. However, as in previous studies that compared the relationships of renal outcomes with the 4 indices of BP, longitudinal measurements of central aortic BP were not available in our cohort. Whether the use of central aortic BP would yield uniform associations with UAE in men and women remains to be examined in future studies. Finally, the longitudinal index for each variable was computed by dividing the cumulative exposure to that variable by the number of follow-up years for each subject. This approach, which was necessary to ensure the comparability of longitudinal indices among subjects with differing durations of follow-up, may dilute the effect of the duration of exposure to each variable. However, this would not be expected to affect our findings, because the duration of exposure to each of the 4 indices of BP was similar within each subject (ie, equal to the duration of follow-up).

**Perspectives**

This longitudinal study provides robust evidence that the pulsatile component of BP confers the highest risk for BP-induced renal microvascular injury, as evidenced by UAE. Although our findings were restricted to men, our results do not rule out the possibility of similar associations in women with a higher vascular risk burden or a longer duration of exposure to elevated PP. Future studies should examine whether PP reduction with interventions that reduce central arterial stiffness48 can enhance the renoprotective benefits of BP reduction beyond that conferred by achieving the conventional BP goals alone.

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**Disclosures**

None.

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