Orthostatic Hypotension and Incident Chronic Kidney Disease

The Atherosclerosis Risk in Communities Study

Nora Franceschini, Kathryn M. Rose, Brad C. Astor, David Couper, Suma Vupputuri

See Editorial Commentary, pp 1042–1044

Abstract—Orthostatic hypotension is associated with cardiovascular disease and mortality, but little is known of its association with incident chronic kidney disease. We evaluated this association in the Atherosclerosis Risk in Communities study. Orthostatic hypotension was defined as a decrease in systolic blood pressure of ≥20 mm Hg or a decrease in diastolic blood pressure of ≥10 mm Hg within 2 minutes of standing. Incident chronic kidney disease was defined using an estimated glomerular filtration rate <60 mL/min/1.73 m², or a coded hospitalization (discharge) or death for chronic kidney disease through 2005, after exclusion of chronic kidney disease at baseline. The associations between orthostatic hypotension and chronic kidney disease were modeled using Cox proportional hazard while adjusting for confounders including resting blood pressure and medications. Among 12,593 participants, 1326 developed chronic kidney disease (6.3 cases per 1000 person-years; median follow-up of 16 years), with higher rates in blacks than whites. An increased risk of chronic kidney disease was observed among persons with orthostatic hypotension compared with those without it (blacks hazard ratio 2.0, 95% CI, 1.5 to 2.8; whites hazard ratio 1.2, 95% CI, 1.0 to 1.6; P for race interaction=0.02). An alternative chronic kidney disease classification, based on an increase in serum creatinine at the 3- or 9-year follow-up visits, showed significant associations with orthostatic hypotension in both whites and blacks. These findings suggest that orthostatic hypotension increases the risk of chronic kidney disease in middle-aged persons, but race effects vary by choice of chronic kidney disease definition. (Hypertension. 2010;56:1054-1059.)

Key Words: orthostatic hypotension • kidney disease

Multiple physiological mechanisms are activated in response to gravitational pooling of blood, reduced venous return, and reduced cardiac output that occurs when one changes from the supine to the standing position. The autonomic nervous system, particularly the sympathetic nervous system, has an important role in the short-term regulation of blood pressure (BP). In population studies, the BP response to a change in posture is approximately normally distributed with a mean close to 0 mm Hg, but the range includes BP increases and decreases of considerable magnitude, and some persons meet criteria for orthostatic hypotension (OH). In these middle-aged persons, OH is associated with incident hypertension, coronary heart disease, stroke, and all-cause mortality.

To date, the association between OH and chronic kidney disease (CKD) has not been systematically investigated, although a recent cross-sectional analysis reported that those with OH had a modestly lower estimated glomerular filtration rate (eGFR) than did those without OH. Several mechanisms may increase the risk of CKD in persons with OH. OH is associated with elevated BP and hypertension, and elevated BP is a strong independent risk factor for end-stage renal disease (ESRD), development of CKD, and albuminuria. Recent research has also shown associations of visit-to-visit BP variability and episodic hypertension with cardiovascular disease (CVD) outcomes. However, the role of large, episodic changes in BP, such as those that occur in persons with OH, on end-organ damage in kidneys is unknown.

The purpose of the current analysis is to examine the association between OH and CKD in the population-based and prospective study of black and white participants of the Atherosclerosis Risk in Communities (ARIC) study. We hypothesize that OH is associated with the development of incident CKD, and that this association differs by race and the co-occurrence of hypertension and type 2 diabetes.
Methods

Study Population

The ARIC study is a multicenter prospective study of atherosclerosis in a biracial population. Persons 45 to 64 years of age were recruited from 4 communities: Forsyth County, NC; Jackson, Miss (blacks only); suburban areas of Minneapolis, Minn; and Washington County, Md. A total of 15,792 persons participated in the baseline examination in 1987 to 1989, with triennial follow-up examinations in 1990 to 1992 (visit 2), 1993 to 1995 (visit 3), and 1996 to 1998 (visit 4). This study was approved by the institutional review board at each participating institution. All subjects provided written informed consent to participate in the main study. This study complied with the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Study Variables and Outcome Definitions

Orthostatic Hypotension

Orthostatic BP measurements were taken during the baseline ARIC visit (1987 to 1989) using a Dinamap 1846 SX oscillometric device, which has high within-subject reliability and is comparable to Doppler ultrasound BP measurement. After 20 minutes of supine rest, participants were instructed on how to change positions. As participants stood up, a standing BP measurement was taken. Measurements were repeated approximately every 30 seconds during the first 2 minutes after standing (range of 2 to 5 measurements; 91% had ≥4 measurements). BP change was defined as the difference between the average of the standing and the supine BP measurements, excluding the first standing measurement. OH was defined as a decrease in systolic BP (SBP) ≥20 mm Hg or a decrease in diastolic BP (DBP) ≥10 mm Hg on standing.8

Kidney Function and Albuminuria

Serum (collected at baseline and visit 2) and plasma (collected at visit 4) creatinine were measured by a modified kinetic Jaffe reaction. Creatinine concentrations were corrected for interlaboratory differences and calibrated using Cleveland Clinic measurement standards (subtracting 0.24 mg/dL from baseline and visit 2 measurements and by adding 0.18 mg/dL to visit 4 measurements), as described previously.25-26 An unimpaired urine sample was collected during the visit 4 clinical examination. Urinary albumin was measured by a nephelometric method either on the Dade Behring BN100 (assay sensitivity; 2.0 mg/L) or on the Beckman IMMAGE nephelometer, and urinary creatinine levels were measured using the Jaffe method. The urinary albumin to creatinine ratio (ACR; mg/g) was used in the analyses. eGFR was calculated using the simplified Modification of Diet in Renal Disease equation:27 eGFR=186.3×(serum creatinine)−1.154×age−0.203×(0.742 if female)×(1.212 if black).

CKD cases were classified using 2 criteria: an eGFR <60 mL/min/1.73 m² at visit 2 or visit 4, or a CKD International Classification of Diseases, 9th Revision (ICD-9) hospitalization discharge or death coded for CKD through 2005 (including cases of ESRD).25,26 We excluded persons with eGFR <60 mL/min/1.73 m² at baseline visit (visit 1) and CKD cases at visit 2 that had an eGFR ≥60 mL/min/1.73 m² at follow-up visit 4 (n=134). ESRD was defined by renal replacement by dialysis or a kidney transplant and obtained from hospital discharge ICD-9 codes. Noncases were censored at the date of last contact (or date of non-CKD death) or December 31, 2005. Giving some reported inconsistency in CKD findings based on CKD definition,26 we used an alternative classification of incident CKD based on either an increase in serum creatinine levels of ≥0.4 mg/dL above baseline (twice the minimum within-person detectable difference in serum creatinine)23 or ICD-9 discharge codes for CKD at follow-up for persons without baseline CKD. Microalbuminuria was defined as an ACR of 30 to 299 mg/g, and macroalbuminuria was defined as an ACR ≥300 mg/g.

Assessment of Covariates

Resting and seated BPs and heart rate were measured using a random-zero sphygmomanometer, and the average of the second and third BP measurements was used in analyses. Hypertension was defined as an SBP/DBP ≥140/90 mm Hg or reported use of antihypertensive medications during the previous 2 weeks. Type 2 diabetes was defined by a fasting plasma glucose level of ≥7.0 mmol/L, nonfasting glucose levels of ≥11.1 mmol/L, current use of medications prescribed to treat diabetes, or a positive response to the question: “Has a doctor ever told you that you have diabetes?” Self-reported current cigarette smoking and alcohol intake were used in analysis. Anthropometric measures were obtained during each clinic visit. A list of medications was verified by bottle inspection.

Carotid artery intima media thickness (IMT), an index of generalized atherosclerosis, was determined by high-resolution B-mode ultrasound as described previously at baseline.30,31 The reliability coefficient for mean carotid IMT (cIMT) was 0.67, estimated from repeat measurements at 3 visits, 7 to 14 days apart in 36 volunteers from each of the 4 ARIC field centers.32 We excluded persons with ethnicity other than black or white, blacks from Minneapolis (n=12) and Washington County (n=26), and persons without creatinine measures at baseline (n=149), as well as those with CKD (eGFR <60 mL/min/1.73 m²) at baseline (n=459). In addition, we excluded those with missing data on orthostatic measures and covariates including hypertension and diabetes status. Therefore, a total of 12,593 persons contributed to this analysis.

Statistical Analysis

For descriptive analyses, means, SD, and frequencies were measured as appropriate. We used t tests or the Pearson χ² to compare persons with and without OH. Overall and race-specific incidence rates of CKD and ESRD per 1000 person-years were estimated relying on the Poisson distribution by dividing the number of events by person-time at risk. The association between OH and incident CKD was modeled using Cox proportional hazards models. The proportional hazards assumptions were tested by comparing estimated -ln(-ln) survivor curves of those with and without OH. We report hazard ratio (HR) and 95% CI. Multivariate models adjusted for age (centered at 54 years), sex, race, type 2 diabetes, resting SBP, current smoking and alcohol intake, body mass index (BMI), resting heart rate, and use of hypertensive medications (model 1). We also performed sensitivity analyses excluding participants using medications known to be associated with OH (tricyclic antidepressants, benzodiazepines, and phenothiazines; n=965; model 2).

We tested the a priori hypothesis of effect measure modification by race/ethnicity, baseline hypertension, and diabetes using interaction terms and the likelihood ratio test. The likelihood estimate from the model with interaction terms was compared with the model without interaction terms using an α=0.10. In addition, we performed analyses excluding participants with baseline hypertension (n=4227) while adjusting for age, sex, race, resting SBP, resting heart rate, type 2 diabetes, BMI, and current smoking (model 3). Finally, we performed analysis adjusting for measures of generalized atherosclerosis (cIMT; model 4).

Using available urinalysis data from visit 4 (approximately 9 years after the baseline examination), we studied the association of OH with microalbuminuria and macroalbuminuria using logistic regression while adjusting for age, sex, center, race, type 2 diabetes, resting SBP, current smoking and alcohol intake, BMI, resting heart rate, and use of hypertensive medications. We also tested for interactions with hypertension and race as described above.

Results

The participant characteristics, overall and by OH status, are displayed in Table 1. The mean age of participants was 54 years, 45% were male, and 26% were blacks. Thirty-four percent had hypertension (of whom 73% used medication to control BP), 11% had type 2 diabetes, and 9%
reported using other medications associated with OH. OH was present in 604 (5%) of participants. As reported previously, persons with OH were more likely to be older, black, smokers, and have comorbidities (hypertension and type 2 diabetes) than those without OH but less likely to report drinking alcohol (Table 1).

Table 2 shows the incidence rates of CKD, overall and by OH status, defined on the basis of eGFR as well as serum creatinine levels over a median follow-up of 16 years. Using the eGFR definition, 1326 (10.7%) persons developed CKD (6.3 cases per 1000 person-years), of whom 116 (0.9%) developed ESRD (0.23 per 1000 person-years; 95% CI, 0.16, 0.33). The incidence of CKD was markedly higher ($P < 0.0001$) among those with OH (14.8 per 1000 person-years) than among those without OH (6.0 per 1000 person-years). The overall and OH-stratified incident rates of CKD were higher in blacks compared with whites. When CKD was alternatively defined using the creatinine-based criteria, increased incidence rates of CKD persisted among those with OH.

Table 1. Characteristics of ARIC Participants at Baseline Examination (1987–1989), Overall, and by OH Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (n=12 593)</th>
<th>Mean (SD) or %</th>
<th>OH Present (n=604)</th>
<th>Mean (SD) or %</th>
<th>OH Absent (n=11 989)</th>
<th>Mean (SD) or %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.0 (5.7)</td>
<td></td>
<td>57.0 (5.2)</td>
<td></td>
<td>53.8 (5.6)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>45.3</td>
<td></td>
<td>46.5</td>
<td></td>
<td>45.3</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Black</td>
<td>26.3</td>
<td></td>
<td>32.3</td>
<td></td>
<td>26.0</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current drinking</td>
<td>56.8</td>
<td></td>
<td>46.1</td>
<td></td>
<td>57.3</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>26.3</td>
<td></td>
<td>33.3</td>
<td></td>
<td>25.9</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.6 (5.3)</td>
<td></td>
<td>27.7 (6.0)</td>
<td></td>
<td>27.6 (5.3)</td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>136.9 (38.9)</td>
<td></td>
<td>145.9 (39.9)</td>
<td></td>
<td>136.8 (38.8)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>51.7 (17.3)</td>
<td></td>
<td>50.5 (16.6)</td>
<td></td>
<td>51.7 (17.3)</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>11.3</td>
<td></td>
<td>19.9</td>
<td></td>
<td>10.9</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33.6</td>
<td></td>
<td>57.0</td>
<td></td>
<td>32.4</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resting SBP, mm Hg</td>
<td>121.0 (18.7)</td>
<td></td>
<td>130.1 (22.0)</td>
<td></td>
<td>120.5 (18.4)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resting DBP, mm Hg</td>
<td>73.5 (11.2)</td>
<td></td>
<td>76.1 (12.7)</td>
<td></td>
<td>73.4 (11.1)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg*</td>
<td>47.5 (13.7)</td>
<td></td>
<td>54.0 (16.3)</td>
<td></td>
<td>47.1 (13.5)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>66.6 (10.2)</td>
<td></td>
<td>68.7 (12.6)</td>
<td></td>
<td>66.5 (10.0)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>cIMT, mm</td>
<td>0.72 (0.18)</td>
<td></td>
<td>0.82 (0.23)</td>
<td></td>
<td>0.72 (0.18)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives†</td>
<td>73.0</td>
<td></td>
<td>72.6</td>
<td></td>
<td>76.7</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>2.0</td>
<td></td>
<td>&lt;1%</td>
<td></td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>6.0</td>
<td></td>
<td>&lt;1%</td>
<td></td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>&lt;1.0</td>
<td></td>
<td>&lt;1%</td>
<td></td>
<td>&lt;1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other‡</td>
<td>&lt;1.0</td>
<td></td>
<td>&lt;1%</td>
<td></td>
<td>&lt;1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*SBP = DBP; †among hypertensive individuals; ‡includes thioxanthenes, butyrophenones, anti-Parkinsonian anticholinergic drugs, anti-Parkinsonian dopaminergic drugs, monoamine-oxidase inhibitors. Some individuals were taking >1 medication.

Table 2. Overall and Race-Specific Incidence Rates (per 1000 Person-Years) of CKD by OH (ARIC Cohort, 1987–2005)

<table>
<thead>
<tr>
<th>CKD Definition</th>
<th>Overall</th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/Total No.</td>
<td>Incident Rate‡ (95% CI)</td>
<td>Events/Total No.</td>
<td>Incident Rate‡ (95% CI)</td>
</tr>
<tr>
<td>eGFR-based*</td>
<td>1326/12 398</td>
<td>6.3 (5.8, 6.8)</td>
<td>925/9119</td>
</tr>
<tr>
<td>OH present</td>
<td>120/594</td>
<td>14.8 (11.3, 19.4)</td>
<td>74/404</td>
</tr>
<tr>
<td>OH absent</td>
<td>1206/11 795</td>
<td>6.0 (5.5, 6.5)</td>
<td>851/8715</td>
</tr>
<tr>
<td>Creatinine-based†</td>
<td>1009/12 593</td>
<td>3.1 (2.7, 3.4)</td>
<td>601/9241</td>
</tr>
<tr>
<td>OH present</td>
<td>103/600</td>
<td>8.1 (5.6, 11.8)</td>
<td>58/408</td>
</tr>
<tr>
<td>OH absent</td>
<td>906/11 923</td>
<td>2.9 (2.5, 3.2)</td>
<td>543/8833</td>
</tr>
</tbody>
</table>

*Definition based on eGFR < 60 mL/min/1.73 m² or a CKD ICD-9 hospitalization discharge or death coded for CKD; 134 cases with eGFR ≥ 60 mL/min/1.73 m² at follow-up visit were excluded.
†Definition based on an increase in serum creatinine levels of ≥ 0.4 mg/dL above baseline or a CKD ICD-9 hospitalization discharge or death coded for CKD; ‡adjusted for a mean age of 54 years, sex and race; †‡adjusted for a mean age of 54 years and sex.
compared with those without OH. Among blacks, overall and within OH strata, the incidence rates of CKD were similar when using the eGFR-based and creatinine-based definitions. In contrast, rates of CKD were consistently lower among whites when the creatinine-based definition was used (Table 2).

Table 3 shows the multivariable analysis HRs for the association between OH and CKD using both the eGFR-based and the creatinine-based definitions. Using the eGFR-based definition, we identified significant OH–race interactions ($P=0.02$) but no OH–hypertension ($P=0.31$) or OH–type 2 diabetes ($P=0.21$) interactions. Thus, race-specific models are presented. Blacks with OH had a 2-fold increased HR of CKD compared with those without OH (model 1; Table 3), whereas whites had a modest (22%) but not significant increase in CKD risk. When specific classes of antihypertensive medications (angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, and beta blockers) were included in models instead of a covariate for any hypertensive medication, estimates did not substantially change (data not shown). OH was associated with ESRD (HR, 2.6; 95% CI, 1.5; 4.4), but the number of events was small (3% for OH and 0.8% for non-OH).

After excluding 978 whites and blacks using drugs that could affect OH other than antihypertensive agents (model 2; Table 3), the risk of CKD among blacks with OH was still elevated. In repeated analyses in the subset of participants without hypertension at baseline (and thus, not using antihypertensive agents; $n=4188$ excluded), the magnitude of the OH–CKD association in blacks became stronger (model 3; Table 3). Additional adjustment for baseline cIMT did not substantially change the HR (model 4; Table 3).

When we examined the associations of OH with CKD defined as an increase in serum creatinine levels of $\geq 0.4$ mg/dL above baseline or coded CKD deaths and hospitalizations (Table 3), the OH–race interaction was not statistically significant ($P=0.48$). However, we stratified this analysis by race for comparability with the eGFR-based definition. Among blacks, the HRs for the OH–CKD association did not appreciably differ from those estimated using the eGFR-based definition of CKD, whereas among whites, the HRs were modestly higher compared with results from the eGFR definition.

We also examined the association of OH with urine ACR measured approximately 9 years after the baseline examination (visit 4). Among 9210 participants with ACR measures and complete risk factor data, 577 had microalbuminuria and 148 had macroalbuminuria. OH was associated with increased odds of albuminuria (microalbuminuria and macroalbuminuria; odds ratio, 1.7; 95% CI, 1.2, 2.3; $n=9210$) after adjustment for age, sex, race, resting SBP, and heart rate, type 2 diabetes, BMI, current smoking and drinking, and use of antihypertensive medications; model 2, same as model 1, excluding individuals taking medications that can lower BP (tricyclic antidepressants, benzodiazepines, phenothiazine, and others); model 3, same as model 1, excluding prevalent hypertension; model 4, same as model 1, adjusting for carotid artery IMT at baseline visit.

**Discussion**

In our study, the incidence of CKD was higher in blacks than whites. Among blacks with OH, we observed a consistent 2- to 3-fold increased risk of CKD across classifications used to define CKD. In contrast, among whites, the magnitude of associations was weaker and only significant when the alternative, serum creatinine level–based algorithm was used to define CKD.

There is currently no consensus on how to best define incident CKD. Previous studies have shown differences in risk factor profiles for CKD depending on the definition used. Both of our definitions of CKD include cases that were identified via ICD-9 hospital discharge or death codes, as well as cases identified using a threshold ($eGFR < 60$ mg/dL or a change in serum creatinine levels of $\geq 0.4$ mg/dL above baseline) in longitudinal data. For the eGFR-based definition, 63% of the cases in whites and 43% of the blacks meet the criteria based on the eGFR threshold, compared with 34% in white and 42% in black cases meeting criteria based on serum creatinine increases for the alternative classification. Misclassification of some events may explain the discrepant findings in whites, particularly when using the eGFR-based definition, because the mean
eGFR at baseline was lower in whites (90.3 mL/min/1.73 m²) compared with blacks (104.4 mL/min/1.73 m²). As noted above, the number of cases in the threshold definition (eGFR) was greatly increased in whites and unchanged in blacks.

OH is associated with incident hypertension, one of the most common causes of CKD, and CVD events in population studies. In our study, OH was independently associated with an increased risk of incident CKD and presence of increased albuminuria at follow-up. Participants with OH more often had baseline hypertension, but the associations of OH with CKD were independent of BP and remained strong after excluding participants with baseline hypertension. Hypertension is a risk factor for CKD, but BP also increases as a consequence of developing CKD. Because OH precedes both development of CKD and hypertension in the ARIC study, our findings suggest that both outcomes may be secondary to the same disease process. Therefore, autonomic dysfunction may be causally related to development of hypertension and to target organ damage to the kidneys.

Conditions affecting autonomic nervous system response to hemodynamic changes may contribute to CKD in susceptible persons. They may affect the autonomic innervation in large vessels and in renal microcirculation and consequently may affect kidney perfusion or the compensatory pathways triggered by changes in kidney perfusion during orthostasis. Decreased kidney perfusion and intraglomerular pressure attributable to impaired glomerular autoregulation may be causally linked to the development of CKD.

Atherosclerosis and CVD risk factors could play a role in the increased risk of CKD attributable to OH in middle-aged persons through, for example, stiff arterial vasculature leading to impaired renal perfusion and autoregulation. However, the analysis adjusting for CVD risk factors including diabete,s, hyperlipidemia, BP, smoking, and measures of atherosclerosis (ie, baseline cIMT) did not change the strength of the association of OH and incident CKD.

To our knowledge, the association among OH and increased albuminuria has not been reported previously. Similar to findings of analysis of eGFR decline, increased albuminuria associated with OH was independent of baseline hypertension and CVD risk factors. These findings in middle-aged adults of the ARIC study (mostly asymptomatic for OH) support the hypothesis of causal mechanisms related to postural homeostasis contributing to kidney damage.

Our study has several strengths, including the availability of a large population-based cohort of middle-aged adults with standardized measures of orthostasis at baseline and incident data on kidney function at follow-up. Some limitations are related to the definition of CKD events, which relies only on measures of kidney function and not kidney damage/albuminuria (because ACR was only measured at follow-up), which could have underestimated the strength of the associations. In addition, albuminuria was obtained from urine samples taken approximately 9 years after the baseline OH measures, and therefore, we cannot ascertain the temporal relationship of OH with the development of increased albuminuria. Events related to kidney markers were obtained at clinical visits, and therefore, the precise time to the events is unknown. Finally, direct measures of autonomic function were not evaluated in the ARIC study.

**Perspectives**

In this large prospective study, OH was associated with development of kidney dysfunction and prevalent increased albuminuria at follow-up among middle-aged persons. This association is consistent in blacks, but OH effects in whites varied by definition of CKD. Because OH also precedes hypertension in this population, autonomic dysfunction may be causally related to development of both hypertension and damage in kidneys.

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**Disclosures**

None.

**References**


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