Arterial Stiffness in Mild-to-Moderate CKD

Ashish Upadhyay,* Shih-Jen Hwang,† Gary F. Mitchell,‡ Ramachandran S. Vasan,†§
Joseph A. Vita,§ Plamen I. Stantchev,† James B. Meigs,‖ Martin G. Larson,†¶ Daniel Levy,†
Emelia J. Benjamin,†§** and Caroline S. Fox†††

*Renal Section, Boston Medical Center and Boston University School of Medicine, Boston, Massachusetts; †National Heart, Lung and Blood Institute's Framingham Heart Study and the Center for Population Studies, Framingham, Massachusetts; ‡Cardiovascular Engineering Inc., Norwood, Massachusetts; §Cardiology Section and Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, Massachusetts; ‖Division of General Internal Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; ¶Department of Mathematics and Statistics, Boston University, Boston, Massachusetts; **Boston University School of Public Health, Boston, Massachusetts; ††Division of Endocrinology, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts

ABSTRACT

Whether arterial stiffness correlates with mild-to-moderate CKD and albuminuria in the community is unclear. We studied the association between arterial stiffness and mild-to-moderate CKD and albuminuria in the Framingham Heart Study. CKD was present in 6.7% (181 of 2682) of participants and microalbuminuria was present in 8.2% (479 of 5818). The measures of arterial stiffness were the carotid femoral pulse wave velocity, forward pressure wave amplitude, central pulse pressure, augmentation pressure, augmentation index, and mean arterial pressure. In cross-sectional analyses, arterial stiffness did not associate with CKD (defined by estimated GFR < 60 ml/min/1.73 m²) in either age- and gender-adjusted or multivariable-adjusted linear regression models. Carotid femoral pulse wave velocity associated with both urinary albumin-to-creatinine ratio and microalbuminuria (P < 0.0001 after multivariable adjustment). In longitudinal analyses, we used logistic regression models to examine the associations between baseline arterial stiffness measures (exposure variables) and incident CKD or microalbuminuria (n = 1675 for CKD analyses and n = 1252 for microalbuminuria analyses). Baseline arterial measures did not associate with incident CKD or incident microalbuminuria. In summary, arterial stiffness correlates with albuminuria but not with mild-to-moderate CKD.


Chronic kidney disease (CKD) is a global public health problem affecting >26 million adults in the United States. Mild-to-moderate CKD and the presence of microalbuminuria are associated with an increased risk for cardiovascular diseases (CVD). The mechanisms linking CKD and CVD are not fully elucidated and likely involve both traditional and nontraditional CVD risk factors. Increased arterial stiffness may be one of the nontraditional mechanisms responsible for disproportionate CVD burden in the CKD population. Arterial stiffness is higher in patients on dialysis and in those with advanced CKD compared with the general population. Arterial stiffness is also associated with CVD risk factors including advancing age, hypertension, diabetes, dyslipidemia, and smoking. The role of arterial stiffness in mild-to-moderate kidney disease beyond these...
traditional CVD risk factors is unclear. Some community-based\textsuperscript{15–18} and hospital-based\textsuperscript{19–21} reports have observed increased arterial stiffness in association with mild-to-moderate CKD. These studies, however, have been limited by small samples of CKD subjects\textsuperscript{16,17,19–21} or the lack of data for carotid femoral pulse wave velocity (CFPWV), a gold standard measure of central arterial stiffness.\textsuperscript{15,20} Therefore, the association of arterial stiffness and mild-to-moderate CKD warrants further examination.

We hypothesized that arterial stiffness is higher in community-dwelling individuals with primarily stage 3 CKD and among individuals with microalbuminuria. To test these hypotheses, we cross-sectionally looked at measures of arterial stiffness and wave reflection in relation to CKD and urinary albumin excretion in the Framingham Heart Study cohorts. We also assessed the longitudinal associations between baseline arterial stiffness measures and incident CKD and incident microalbuminuria over a 7- to 10-yr period in the Framingham Offspring cohort.

### RESULTS

#### Participant Characteristics

Table 1 shows participant characteristics by CKD and microalbuminuria status. Among participants included for estimated GFR (eGFR)-based cross-sectional analyses, 6.7% (n = 181 of 2682) had CKD by creatinine-based eGFR (eGFRcrea). The mean eGFRcrea for these participants was 51 ml/min/1.73 m\(^2\), and they were more likely to be older, have diabetes, and be on antihypertensive and lipid-lowering treatments. Among participants with cystatin C and arterial stiffness measure-
ments, 13.0% \((n = 283 \text{ of } 2177)\) had CKD by cystatin C–based eGFR (eGFRcys). The mean value of cystatin C for these 283 participants was 1.3 mg/L.

Among participants included for urinary albumin excretion–based cross-sectional analyses, 8.2% \((n = 479 \text{ of } 5818)\) had microalbuminuria. Individuals with microalbuminuria had a median urinary albumin-to-creatinine ratio (UACR) of 35 mg/g and a mean eGFRcrea of 89 ml/min/1.73 m².

### Arterial Measures and Kidney Function

In cross-sectional analyses, measures of central arterial stiffness, wave reflection, and mean arterial pressure did not differ by eGFRcrea-based CKD status (Table 2). This lack of association by eGFRcrea-based CKD status was observed in both age- and gender-adjusted and multivariable-adjusted models (Table 2). Higher CFPWV was associated with eGFRcys-based CKD status in age- and gender-adjusted models \((P = 0.003)\) but not in multivariable-adjusted models (Supplementary Table 1). Results were similar when CFPWV was related to eGFRcys as a continuous variable (Supplementary Table 1). Augmentation index was lower in individuals with CKD by eGFRcys in an unanticipated direction. However, this association was not observed when eGFRcys was modeled as a continuous trait (Supplementary Table 1).

In longitudinal analyses, higher arterial stiffness measures at baseline were not associated with incident CKD by eGFRcrea over a 7- to 10-yr follow-up (Table 3). This was observed in both age- and gender-adjusted and multivariable-adjusted models (Table 3).

### Arterial Measures and Urinary Albumin Excretion

In cross-sectional analyses, higher central arterial stiffness measures were associated with elevated urinary albumin excretion (Table 4). Higher CFPWV, forward pressure wave amplitude, and central pulse pressure were observed in individuals with microalbuminuria in both age- and gender-adjusted and multivariable-adjusted models (Table 4). Similar associations were observed when UACR was examined as a continuous variable (Table 4).

In longitudinal analyses, higher CFPWV at baseline was modestly associated with incident microalbuminuria over a 7- to 10-yr period in an age- and gender-adjusted model \((P = 0.04)\) but not in a multivariable-adjusted model (Table 5).

### Secondary Analyses

Exclusion of prevalent CVD or diabetes in cross-sectional analyses relating arterial stiffness to microalbuminuria did not produce significantly different results (data not shown). Similarly, addition of C-reactive protein level, a marker of inflammation, as a covariate in multivariable models in cross-sectional analyses relating arterial stiffness to urinary albumin excretion did not substantively alter the findings (Supplementary Table 2).

No interactions were observed for age and gender in

### Table 2. Age- and gender- and multivariable-adjusted least square means and SEMs of arterial stiffness measures by eGFRcrea-based CKD statusa

<table>
<thead>
<tr>
<th>Measures</th>
<th>No CKD (eGFRcrea ≥60 ml/min/1.73 m²) ((n = 2501))</th>
<th>CKD (eGFRcrea &lt;60 ml/min/1.73 m²) ((n = 181))</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid-femoral PWV (m/s)</td>
<td>Age and gender</td>
<td>9.9 ± 0.1</td>
<td>10.6 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>Multivariableb</td>
<td>9.9 ± 0.1</td>
<td>10.5 ± 0.2</td>
</tr>
<tr>
<td>Forward pressure wave amplitude (mmHg)</td>
<td>Age and gender</td>
<td>40.6 ± 0.2</td>
<td>41.3 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Multivariableb</td>
<td>41.0 ± 0.2</td>
<td>41.8 ± 0.8</td>
</tr>
<tr>
<td>Central pulse pressure (mmHg)</td>
<td>Age and gender</td>
<td>50.7 ± 0.3</td>
<td>52.1 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>Multivariableb</td>
<td>50.9 ± 0.3</td>
<td>52.0 ± 1.0</td>
</tr>
<tr>
<td>Augmentation pressure (mmHg)</td>
<td>Age and gender</td>
<td>8.7 ± 0.1</td>
<td>9.4 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>Multivariableb</td>
<td>8.6 ± 0.1</td>
<td>9.3 ± 0.5</td>
</tr>
<tr>
<td>Augmentation index (%)</td>
<td>Age and gender</td>
<td>15.4 ± 0.2</td>
<td>15.0 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Multivariableb</td>
<td>15.1 ± 0.2</td>
<td>14.8 ± 0.8</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>Age and gender</td>
<td>91.8 ± 0.2</td>
<td>91.4 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Multivariableb</td>
<td>91.6 ± 0.2</td>
<td>90.6 ± 0.9</td>
</tr>
</tbody>
</table>

- eGFRcrea, estimated GFR by creatinine-based Modification of Diet in Renal Disease study equation; PWV, pulse wave velocity.
- Multivariable models include: age, gender, Omni cohort status, body mass index, heart rate, mean arterial pressure (for models other than mean arterial pressure), diabetes, fasting blood glucose, total/high density lipoprotein cholesterol, lipid lowering medication use, triglycerides, hypertension treatment, hormone replacement therapy in women, current smoking status and prevalent cardiovascular disease.
analyses relating all six arterial stiffness measures to CKD by eGFRcrea or eGFRcys \( (P > 0.05) \). When interaction for gender was tested for microalbuminuria-based analysis, interactions were observed for forward pressure wave amplitude and central pulse pressure but not for other arterial measures (Supplementary Table 3). Similarly, when interaction for age was tested for microalbuminuria-based analysis, interaction was only observed for augmentation pressure (Supplementary Table 4).

**Power Calculations**

Our sample size in eGFRcrea-based cross-sectional analyses required a minimum difference in CFPWV of 0.8 m/s between participants with and without CKD by eGFRcrea to achieve
Carotid-femoral PWV (m/s) & Augmentation index (%) & Augmentation pressure (mmHg) & Forward pressure wave amplitude (mmHg) & Central pulse pressure (mmHg) & Measures & Odds ratio (95% CI) & P Value

| Age and gender | 1.19 (1.00, 1.40) | 0.04 |
| Multivariable | 1.14 (0.94, 1.42) | 0.17 |
| Age and gender | 1.15 (0.96, 1.37) | 0.14 |
| Multivariable | 1.24 (0.93, 1.66) | 0.15 |
| Age and gender | 1.19 (0.99, 1.43) | 0.06 |
| Multivariable | 1.33 (0.92, 1.93) | 0.13 |
| Age and gender | 1.12 (0.94, 1.34) | 0.22 |
| Multivariable | 1.0 (0.80, 1.27) | 0.96 |
| Age and gender | 1.04 (0.86, 1.26) | 0.70 |
| Multivariable | 0.92 (0.73, 1.16) | 0.46 |
| Age and gender | 1.02 (0.99, 1.03) | 0.06 |
| Multivariable | 1.02 (0.98, 1.06) | 0.37 |

**Table 5.** Logistic regression analysis testing association between per SD difference in baseline arterial stiffness measures and incident microalbuminuria in the Framingham Offspring Cohort (n = 1252)

aCI, confidence intervals; PWV, pulse wave velocity.
bMultivariable models include age, gender, baseline log urine albumin-to-creatinine ratio, body mass index, heart rate, mean arterial pressure (for models other than mean arterial pressure), diabetes, fasting blood glucose, total/HDL-cholesterol, lipid-lowering medication use, triglycerides, hypertension treatment, hormone replacement therapy in women, current smoking status, and prevalent cardiovascular disease.

80% statistical power and 5% α error. The observed difference in CFPWV between two groups was >0.8 m/s.

Our sample size in eGFRcrea-based longitudinal analyses only provided 30% statistical power to detect an 8% CKD incidence rate. Similarly, our sample size in albuminuria-based longitudinal analyses only provided 34% statistical power to detect a 10% microalbuminuria incidence rate.

**DISCUSSION**

Cross-sectional analyses in the Framingham Heart Study cohorts did not show a substantive difference in arterial stiffness between individuals with and without mild-to-moderate CKD by eGFRcrea. Higher CFPWV was associated with CKD by eGFRcys in a minimally adjusted model, but the association did not persist after multivariable adjustment. Augmentation index, contrary to our expectation, was lower in individuals with CKD by eGFRcys. The association between augmentation index and eGFRcys, however, was not observed when eGFRcys was examined as a continuous trait. Greater central arterial stiffness, on the other hand, was associated with urinary albumin excretion. Higher CFPWV, forward pressure wave amplitude, and central pulse pressure were associated with both microalbuminuria status and UACR as continuous traits. Conversely, augmentation pressure and augmentation index were not associated with urinary albumin excretion, and greater mean arterial pressure was only associated with urinary albumin excretion in an age- and gender-adjusted model.

Longitudinal analyses in the Framingham Offspring cohort did not show an association between baseline arterial measures and incident CKD over a 7- to 10-yr period. Higher CFPWV was modestly associated with incident microalbuminuria over a 7- to 10-yr period in the age- and gender-adjusted model but not in the multivariable-adjusted model. Low statistical power may have influenced our longitudinal results.

Various arterial stiffness measures are influenced by distinct but related hemodynamic variables. CFPWV depends on the wall thickness and elasticity of the central aorta and iliofemoral arteries and is regarded as the most important measure of central arterial stiffness.22–24 Forward pressure wave amplitude and central pulse pressure are specifically influenced by proximal aortic wall elasticity and diameter and cardiac function.24,25 Augmentation pressure, augmentation index, and mean arterial pressure are affected more by the peripheral arterial resistance and the impedance mismatch between the aorta and muscular arteries.24 Modest association observed between lower augmentation index and CKD by eGFRcys may potentially be a reflection of higher stiffness in central arteries relative to peripheral arteries in CKD. There is also a possibility that this was a false-positive finding because the association was statistically significant in only one of three analytic models testing augmentation index in relation to lower kidney function. Urinary albumin excretion, on the other hand, was found to be an important correlate of arterial stiffness measures that are dependent primarily on the properties of the aorta (CFPWV, forward pressure wave amplitude, and central pulse pressure) and not of measures that are influenced by peripheral arterial resistance and muscular arterial conduits (augmentation pressure, augmentation index, and mean arterial pressure).

Our results relating arterial stiffness to kidney function are in contrast to prior observations of higher arterial stiffness in individuals with advanced CKD.7–9 London et al.8 have reported elevated aortic pulse wave velocity in hemodialysis patients compared with controls. Subsequent studies have found similar findings in uremic predialysis patients8 and in patients with stages 4 and 5 CKD.7,9 The existing literature for mild to moderate kidney disease is variable. Our results are similar to findings in an elderly, primarily diabetic cohort examined in a recent Dutch report that did not show a significant difference in central arterial stiffness measures in individuals with eGFRcrea <56 ml/min/1.73 m² compared with individuals with higher eGFRcrea (n = 256 with eGFRcrea <56 ml/min/1.73 m²).15 CFPWV was not directly assessed in the Dutch
study. Nakagawa et al.,20 in contrast to our findings, reported that arterial stiffness correlated with decreased eGFrcrea and increased with increasing stages of CKD (n = 647, mean eGFrcrea 63.4 ± 14.5 ml/min/1.73 m², 37% with eGFrcrea <60 ml/min/1.73 m²). Lack of CFPWV, exclusion of important metabolic parameters from multivariable models, and the use of hospital-based samples may account for the contrasting results. Several other studies have reported an association between lower kidney function and arterial stiffness.16–19,21 These studies have been limited by small samples of patients with CKD,16–19,21 lack of CFPWV,18 or the use of eGFrcrea as a continuous exposure in samples without CKD.17,18,21 In longitudinal analyses, we found that baseline arterial stiffness measures were not associated with incident CKD over a 7- to 10-yr period. Our observations using widely accepted kidney function assessment tools and the standard array of tonometry measures suggest that central arterial stiffness is unlikely to be an important characteristic in community-dwelling individuals with primarily stage 3 CKD.

In contrast to measures of kidney function, we observed strong cross-sectional associations between central arterial stiffness and urinary albumin excretion. Our findings concur with the similar associations noted in prior reports involving individuals with diabetes,26,27 hypertension,28 and the general population.15,29 Our cross-sectional analysis, however, was unique for a large sample size, robust multivariable adjustment, and the use of gold standard tonometry measures for central arterial stiffness. However, in longitudinal analyses, we did not detect strong associations between baseline arterial measures and incident microalbuminuria over a 7- to 10-yr period. Our longitudinal analysis was limited by a low statistical power.

Central arterial stiffness, as measured by CFPWV, has been shown to be an independent risk factor for future cardiovascular events in individuals on dialysis.30,31 Chronic inflammation, increased oxidative stress, disorders of calcium-phosphate metabolism, activation of the renin-angiotensin system, and volume retention are some of the putative mechanisms for increased arterial stiffness in advanced kidney disease.30,31 Whether these mechanisms alter vascular hemodynamics and contribute to increased CVD risk in mild-to-moderate CKD remains unclear. Our group recently reported that endothelial dysfunction as measured by brachial reactivity measures does not correlate with mild-to-moderate CKD.32 Coronary artery calcification has also been recently shown to not correlate with eGFr in individuals with stages 3 to 5 CKD.33 The association observed in our study between CFPWV and CKD by eGFrcrea did not persist after multivariable adjustment, suggesting that shared risk factors likely influenced the findings. The non-GFR determinants of cystatin C, such as inflammation and adipose tissue mass, could have potentially affected our observations because arterial stiffness has modest relations to other markers of inflammation.34,35 Our results emphasize that arterial stiffness is not a crucial correlate of mild to moderate CKD in the community-based cohorts after adjustment for vascular risk factors known to affect both arterial measures and kidney function. The lack of relation does not rule out the possibility of higher arterial stiffness with lower kidney function in the presence of these various risk factors. It does, however, suggest that arterial stiffness likely does not play an important role in mild-to-moderate CKD above and beyond the traditional CVD risk factors.

Urinary albumin excretion has long been thought to reflect generalized vascular damage.36 Albuminuria has been associated with higher levels of circulating inflammatory markers.37 Albuminuria has also been linked with structural changes in capillary basement membrane38 and increased vessel wall intima-media thickness.39 The associations observed in our study between central arterial stiffness and albuminuria persisted in multivariable models that included traditional CVD risk factors and C-reactive protein. Our findings suggest that inflammation and traditional CVD risk factors alone cannot explain higher arterial stiffness observed in individuals with elevated urinary albumin excretion.

Our study has several strengths. We evaluated unselected samples from the long-term, community-based Framingham Heart Study cohorts. Kidney disease assessment was comprehensive with the use of cystatin C in addition to creatinine and UACR. CFPWV, a gold standard measure of central arterial stiffness, was available in most of our participants. Finally, our sample size in cross-sectional analyses gave us adequate power to detect modest associations.

This study also has some limitations. The longitudinal analyses were limited by low statistical power. We only had one time measurement of arterial stiffness and were not able to longitudinally assess the relationship between changes in arterial stiffness and kidney disease. Our samples were primarily white, which could limit the generalizability of our findings to other ethnic or racial groups. The use of eGFr equations that include age and gender may have resulted in potential confounding while testing for associations between arterial stiffness and CKD as age and gender are also strong determinants of arterial stiffness. We defined CKD based on an eGFr estimate derived from a single measure of serum creatinine or cystatin C. There may be miscategorization of individuals with eGFr close to 60 ml/min/1.73 m², because the Modification of Diet in Renal Disease (MDRD) study equation used in our study underestimates GFR in individuals without CKD.40 The impact of miscategorization when CKD is examined as a dichotomous trait is unclear. We also cannot rule out the possibility that lower muscle mass (the source of serum creatinine), particularly in older people where arterial stiffness is more prevalent, led to biased miscategorization and underestimation of the relation between arterial measures and CKD by eGFrcrea. However, eGFrcrea is less likely to have been affected by declining muscle mass. Our albuminuria measurements in the Offspring cohort were obtained an average of 2.9 yr before the tonometry measurements although this is unlikely to account for our positive finding.

Our study has important clinical and research implications.
We found that central arterial stiffness is an important correlate of elevated urinary albumin excretion but not of mild-to-moderate CKD in the Framingham Heart Study cohorts. Our findings suggest that the mechanisms for increased CVD in mild-to-moderate CKD may differ depending on the status of urinary albumin excretion. Future mechanistic research should focus on well-powered longitudinal studies to better understand the complex interplay between arterial function, vascular diseases, and kidney disease.

CONCISE METHODS

Study Sample
The samples for our community-based study were comprised of the Framingham Offspring (mean age, 61 yr), Omni (mean age, 56 yr) and Third Generation (mean age, 40 yr) cohort participants. The selection and design of these cohorts have been described elsewhere.41–43 The Offspring cohort was initiated in 1971 and includes the Framingham Original cohort’s adult children and their spouses. The Omni cohort was initiated in 1994 and includes adult residents of Framingham, MA, who describe themselves as members of a minority group. The Third Generation cohort was initiated in 2002 and includes adults with at least one parent in the Framingham Offspring cohort. All subjects provided written informed consent, and the Boston University Medical Center Institutional Review Board approved the study.

Samples for Cross-Sectional Analyses
For eGFR-based analyses, 3539 participants from the Offspring cohort who attended the seventh (1998 to 2001) examination cycle and 405 participants from the Omni cohort who attended the second (1999 to 2001) examination cycle were eligible. We excluded participants with missing vascular tonometry measures (n = 905), as well as those with missing creatinine (n = 277), missing covariates (n = 61), eGFRcys <15 ml/min/1.73 m² (n = 2), and UACR >300 mg/g (n = 17), resulting in a final sample size of 2682 individuals. Of these, cystatin C measurements were available for 2177 Offspring participants, and CFPWV was available for 2332 participants.

For urinary albumin excretion–based analyses, 6858 participants from the Offspring cohort who attended the seventh examination cycle and the Third Generation cohort who attended the first (2002–2005) examination cycle were eligible. We excluded participants with missing vascular tonometry measures (n = 738), missing UACR or UACR >300 mg/g (n = 37), and missing covariates (n = 265), resulting in a final sample size of 5818 individuals. CFPWV was available for 5531 participants.

Samples for Longitudinal Analyses
Longitudinal data on kidney function and urinary albumin excretion were only available in the Framingham Offspring cohort.

For eGFR-based analyses, 1995 Offspring participants who attended the seventh examination cycle were eligible after excluding participants who did not attend the eighth (2005 to 2008) examination cycle (n = 404) and those with missing creatinine (n = 302) and missing vascular tonometry measures (n = 838). We further excluded individuals with baseline CKD (n = 128) and those with missing CFPWV (n = 187) and missing covariates (n = 5), resulting in a final sample size of 1675 participants.

For urinary albumin excretion–based analyses, 1660 Offspring participants who attended the seventh examination cycle were eligible after excluding participants who did not attend the eighth examination cycle (n = 364) and those with missing UACR (n = 539) and missing vascular tonometry measures (n = 969). We further excluded individuals with baseline microalbuminuria (n = 355) and those with missing CFPWV (n = 49) and missing covariates (n = 4), resulting in a final sample size of 1252 participants.

Kidney Function Assessment
Serum creatinine (mg/dl) was measured using the modified Jaffe method (interassay coefficient of variation [CV] = 2.8%, intra-assay CV = 4.0%) and calibrated for the MDRD Study equation using a previously described two-step process to minimize any potential interlaboratory variability.44 The four-variable MDRD Study equation was used to calculate eGFRcys.45,46 CKD was defined as eGFRcys of <60 ml/min/1.73 m².47

Cystatin C concentrations (mg/L) were measured by nephelometry (Dade Behring Diagnostic, Marburg, Germany) on previously frozen serum samples stored at −80°C (interassay CV = 3.3%, intra-assay CV = 2.4%). The following age- and gender-adjusted equation was used to calculate eGFRcys: eGFRcys = 127.7 × CysC⁻¹.17 × age⁻⁰.⁰³ × (0.91 if female).48 CKD by eGFRcys was defined as an eGFRcys of <60 ml/min/1.73 m².

Urinary albumin concentration was measured on stored spot urine samples using a Tia-quant immunoturbimetric assay (intra-assay CV = 2.1% for the Third Generation cohort and 7.2% for the Offspring cohort; Roche Diagnostics, Indianapolis, IN). Offspring measurements were performed at the sixth examination cycle (1995 to 1998). Urinary creatinine concentration was measured using a modified Jaffe method (intra-assay CV = 1.0% for the Third Generation cohort and 2.3% for the Offspring cohort). Microalbuminuria was defined as UACR of >17 mg/g for men and >25 mg/g for women.49 The UACR is a validated and reliable measure of urinary albumin excretion.50

Arterial Stiffness Assessment
Arterial stiffness was assessed using a commercially available tonometer (SPT-301; Millar Instruments, Houston, TX) for the Offspring and Omni cohorts and a custom tonometer (Cardiovascular Engineering, Inc., Norwood, MA) for the Third Generation cohort. Arterial tonometry data with simultaneous electrocardiographic recordings were obtained with participants in supine position from radial, brachial, carotid, and femoral arteries. The distance between pulse acquisition site for each artery and the suprasternal notch was obtained with body surface measurements. CFPWV was calculated using body surface measurements and tonometry data and denotes the speed of propagation of aortic pressure waveforms from the proximal aorta to the femoral artery. CFPWV is affected by thickness and stiffness of the entire central arterial tree including aorta, iliac arteries, and femoral arteries.51 Forward pressure wave amplitude was defined as the difference between pressures at the foot and the first systolic peak or inflec-
tion point of the carotid pressure waveform. Forward pressure wave amplitude indicates the amplitude of aortic pressure wave created by ventricular ejection and depends on the elasticity of the proximal aortic wall, cardiac function, and aortic diameter.25 Central pulse pressure was obtained from tonometry waveforms and depends on the aortic compliance and stroke volume.25 Augmented pressure was defined as the difference between the central systolic pressure and the forward wave peak pressure. Augmentation pressure describes the amplitude of the summated reflected wave that returns to the central aorta as a result of forward pressure wave encountering reflections at the arterial tree branch points.24 Augmentation index was defined as the percentage of central pulse pressure attributable to the augmented pressure. Both augmentation pressure and augmentation index are affected by heart rate, cardiac function, peripheral arterial resistance, and impedance mismatch between aorta and muscular arteries.24 Mean arterial pressure (MAP) was obtained from brachial pressure waveforms calibrated to the brachial blood pressure. Higher values of CFPWV, forward pressure wave amplitude, and central pulse pressure are generally indicative of increased central arterial stiffness, and each of these measures is influenced by related but distinct hemodynamic variables.

Covariate Assessment
Body mass index was defined as weight in kilograms divided by height in meters squared. Brachial blood pressure and heart rate were measured by an oscillometric device (Dinamap; Critikon Inc, Tampa, FL) for the Offspring and Omni cohorts and a semiautomated auscultatory device (Cardiovascular Engineering, Inc.) for the Third Generation cohort. Fasting plasma glucose, total cholesterol, HDL-cholesterol, triglyceride, and C-reactive protein levels were obtained from fasting blood samples. Diabetes was defined as having a fasting blood glucose of $\geq 126\text{mg/dL (}\geq 7 \text{mmol/L})$ or as being treated with insulin and/or oral hypoglycemic medications. Current smoking status was defined as smoking at least one cigarette a day for the past 1 yr. Prevalent CVD was defined as the presence of any of the following: history of myocardial infarction, angina pectoris, coronary insufficiency, transient ischemic attack, ischemic or hemorrhagic cerebrovascular accident, intermittent claudication, and congestive heart failure. These CVD categorizations were based on medical records and assessed by blinded adjudication panels consisting of at least two physicians. The detailed criterion used for CVD events are described elsewhere.25

Statistical Analysis
Cross-Sectional Analyses
Descriptive statistics were used to tabulate demographic, clinical, and tonometry variables by eGFR and microalbuminuria status. CKD by eGFRcra and eGFRcys status, microalbuminuria status, eGFRcys as a continuous trait, and UACR as a continuous trait were defined as exposure variables. Arterial stiffness measures (CFPWV, forward pressure wave amplitude, central pulse pressure, augmentation pressure, and mean arterial pressure) were defined as dependent variables. In primary analyses, linear regression models were implemented to examine the arterial stiffness measures in relation to CKD, microalbuminuria, eGFRcys, and UACR. The models were first adjusted for age and gender and then multivariable adjusted for the following covariates: age, gender, Omni cohort status (for analyses using Omni data), body mass index, heart rate, mean arterial pressure (for models other than mean arterial pressure), diabetes status, fasting blood glucose level, total to HDL-cholesterol ratio, triglyceride level, use of medications (for hypertension, lipid lowering, and hormone replacement in women), current smoking status, and prevalent CVD. As a secondary analysis, log C-reactive protein level was added as a covariate in multivariable models in analyses relating arterial stiffness measures to urinary albumin excretion.

Longitudinal Analyses
Arterial stiffness measures in the Offspring seventh examination cycle were defined as the exposure variables. Incident CKD and incident microalbuminuria at the Offspring eighth examination cycle were defined as outcome variables. Logistic regression models were implemented to test the association between baseline arterial stiffness measures and incident CKD and incident microalbuminuria. The models were first age and gender and then multivariable adjusted for the same set of covariates as in cross-sectional analyses in addition to baseline eGFR (for CKD analyses) and baseline log UACR (for microalbuminuria analysis). All covariates were assessed during the Offspring seventh examination cycle.

In both cross-sectional and longitudinal analyses, generalized estimating equations were used to account for familial correlation when testing for urinary albumin excretion. CFPWV was inverse transformed to normalize variance, and regression coefficients of least square means and SEMs were inversed to present data in native units.

SAS version 9.1 (SAS Institute, Cary, NC) was used to perform all analyses. Two-sided $P \leq 0.05$ was considered statistically significant.

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DISCLOSURES
G.F.M. is the President of Cardiovascular Engineering, Inc., a company that designs and manufactures devices that measure vascular stiffness.
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