Published in final edited form as:

Am J Kidney Dis. 2012 January ; 59(1): 41–49. doi:10.1053/j.ajkd.2011.08.015.

Association of Pulse Pressure, Arterial Elasticity, and Endothelial Function With Kidney Function Decline Among Adults With Estimated GFR > 60 mL/min/1.73 m²: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—The association of subclinical vascular disease and early declines in kidney function has not been well studied.

Study Design—Prospective cohort study

Setting & Participants—MESA participants with eGFR ≥60 mL/min/1.73m² with follow-up of 5 years

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Financial Disclosure: The authors declare that they have no other relevant financial interest.

Predictors—Pulse pressure (pulse pressure), small and large arterial elasticity (SAE, LAE), and flow mediated dilation.

Outcomes—kidney function decline

Measurements—SAE and LAE were measured by pulse contour analysis of the radial artery. Kidney function was measured by serum creatinine- and cystatin C-based eGFR.

Results—Among 4,853 adults, higher pulse pressure and lower SAE and LAE had independent and linear associations with faster rates of kidney function decline. Compared to persons with pulse pressure 40–50mmHg, eGFR_{SCysC} decline was 0.29 (p=0.006), 0.56 (p<0.001), and 0.91 (p<0.001) ml/min/1.73m²/year faster among persons with pulse pressure 50–60, 60–70, and >70mmHg, respectively. Compared to the highest quartile of SAE (most elastic), eGFR_{SCysC} decline was 0.26 (p=0.009), 0.35 (p=0.001), and 0.70 (p<0.001) ml/min/1.73m²/year faster for the second, third and fourth quartiles respectively. For LAE, compared to the highest quartile, eGFR_{SCysC} decline was 0.28 (p=0.004), 0.58 (p<0.001), and 0.83 (p<0.001) ml/min/1.73m²/year faster for each decreasing quartile of LAE. Findings were similar with creatinine-based eGFR. In contrast, among 2,997 adults with flow-mediated dilation and kidney function measures, flow-mediated dilation was not significantly associated with kidney function decline. For every 1-SD greater flow-mediated dilation, eGFR_{SCysC} and eGFR_{SCr} changed by 0.05 ml/min/1.73m²/year (p=0.3) and 0.06 ml/min/1.73m²/year (p=0.04), respectively.

Limitations—We had no direct measure of GFR, in common with nearly all large population based studies.

Conclusions—Higher pulse pressure and lower arterial elasticity, but not flow-mediated dilation, were linearly and independently associated with faster kidney function decline among persons with eGFR ≥60 ml/min/1.73m². Future studies investigate whether treatments to lower stiffness of large and small arteries may slow the rate of kidney function loss.

Keywords

kidney function; arterial elasticity; chronic kidney disease; atherosclerosis

Kidney disease is associated with vascular dysfunction at multiple anatomical and functional sites of the arterial system including increased large arterial stiffness(1–4), reduced large and small arterial elasticity(5) and endothelial dysfunction.(6) In turn, these measures of subclinical vascular dysfunction are independently associated with higher risk of mortality and cardiovascular events.(7–11) Subclinical vascular dysfunction may also contribute to the initiation and progression of kidney disease. Cross-sectional studies have associated higher stiffness with early stages of reduced kidney function.(1, 12) Increased arterial stiffness and markers of endothelial dysfunction have also been associated with faster progression in the setting of advanced CKD.(13–14) The role of subclinical vascular dysfunction as a determinant of early declines in kidney function among persons with eGFR >60 ml/min/1.73m² has not been well studied.(15) Moreover, no study has evaluated the association of subclinical vascular dysfunction with kidney function decline among persons with eGFR >60 ml/min/1.73m² using measures at multiple sites and that represent different functions of the arterial tree. Understanding the role of subclinical vascular dysfunction in the initiation of kidney disease is important given recent data from randomized trials suggesting that central blood pressure (a marker of stiffness) may be associated with progressive kidney function decline, independent of systolic or diastolic blood pressure levels.(16)

Therefore, we designed this study to understand the association between measures of subclinical vascular dysfunction with kidney function decline among persons with eGFR > 60 mL/min/1.73 m² at baseline. We specifically studied pulse pressure and vascular

measures that reflect different anatomical sites and represent different functions of the arterial tree: (1) arterial stiffness by pulse pressure, (2) small and large arterial elasticity by tonometry and (3) endothelial dysfunction by flow mediated dilation. We hypothesized that subclinical dysfunction at all sites of the arterial tree would be independently associated with kidney function decline.

Methods

Subjects

This study was conducted among participants from the Multi-Ethnic Study of Atherosclerosis (MESA), a large NHLBI sponsored study of adults without established cardiovascular disease designed to understand subclinical cardiovascular disease and its progression in a multi-ethnic cohort. Details on recruitment and design have been previously published.⁽¹⁷⁾ Briefly, MESA recruited 6,814 men and women between the ages of 45 and 84 who were free of cardiovascular disease and who self identified as White, Black, Hispanic or Chinese. Subjects were recruited from Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota between July 2000 and August 2002. Participants have returned for 3 visits, at years 2002–2004 (exam 2), years 2004–2005 (exam 3) and years 2005–2007 (exam 4). Repeat measures of kidney function were done at visits 3 and 4. The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

For these analyses, we excluded persons with no measure of albuminuria, serum creatinine, or serum cystatin C at baseline (n=94), persons who did not have any follow-up measures of creatinine or cystatin C (n=799), persons who had serum creatinine-based eGFR < 60 ml/min/1.73 m², and those who had missing data for subclinical measures; the total sample size comprised 4,853 persons. Only a subsample of MESA participants had available data on flow mediated dilation, thus the sample size for those analyses is 2,997.

Primary Outcome

Kidney function was measured by creatinine and cystatin C. All assays were performed in frozen serum specimens that were stored at –70°C. Serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., www.orthoclinical.com) at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, MN) and calibrated to Cleveland Clinic. Cystatin C was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Siemens AG) with a nephelometer (BNII, Siemens AG (formerly Dade Behring), www.siemens.com) and corrected for assay drift.

We estimated the GFR with the use of the CKD-EPI (CKD Epidemiology Collaboration) equations⁽¹⁸⁾: $eGFR_{SCr} = 141 \times \min(SCr/\kappa, 1)^a \times \max(SCr/\kappa, 1) - 1.209 \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black], where SCr is serum creatinine, and $eGFR_{SCysC} = 76.7 \times SCysC^{-1.19}$, where SCysC is serum cystatin C. This formula was developed from the pooling of several cohorts with GFR measured from iothalamate.⁽¹⁹⁾

Our outcome of interest was kidney function decline, assessed by both equations in separate models using repeated measures of eGFR.

Primary Predictors

Pulse Pressure—Pulse pressure (defined as resting seated systolic blood pressure – diastolic blood pressure) is thought to reflect arterial stiffness. Pulse pressure has also been shown to correlate with pulse wave velocity among hypertensive and non-hypertensive adults suggesting that it is a marker of a stiff aorta.(20–21) Pulse pressure is an independent predictor of cardiovascular events and death among persons with and without kidney disease.(22–23) In this study, resting brachial systolic and diastolic blood pressure measurements were obtained using the Dinamap® automated blood pressure device (Dinamap Monitor Pro 100®). Three sequential measures were obtained and the average of the second and third measurements was recorded.

Small and Large Arterial Elasticity—To estimate the small (SAE) and large artery elasticity (LAE) indices, MESA used the HDI PulseWave CR-2000 Research CardioVascular Profiling Instrument (HDI, www.hdi-pulsewave.com) to acquire and analyze pulse waveforms from radial artery tonometry. The pulse contour analysis technique incorporates pressure fluctuations and provides a way to study changes in large and small arteries by measuring their response to distending pressures throughout the cardiac cycle. Briefly, the CR-2000 uses information about the waveforms to make inferences about the elastic properties of the arterial tree. This is done by analyzing the diastolic pulse contour, and calculating each parameter using a third order, four element Windkessel modified model. The LAE estimates have been shown to be comparable to corresponding findings using direct invasive methods, while the SAE measures are responsive to nitric oxide suppression.(24) LAE and SAE measures have been shown to have high reproducibility in repeated measures.(25–28) In MESA, two measures on the same day in a random sample of 131 participants showed that correlations were 0.74 for large arterial elasticity and 0.84 for small arterial elasticity measures.(28) Moreover, SAE has also been shown to be an independent predictor of cardiovascular events(11) and both SAE and LAE predicted incident hypertension.(29)

Endothelial Function by Flow-Mediated Dilation—Endothelial function was estimated using flow-mediated dilation (flow-mediated dilation). Detailed methods have been previously described.(7) Briefly, brachial flow-mediated dilation was measured by ultrasound (GE Logiq 700 Device) at the baseline MESA examination in a subset of participants. Participants were asked to rest for 15 minutes and fast for at least 6 hours. Blood pressure and pulse were monitored in the left arm every 5 minutes using an automated sphygmomanometer (Dinamap®). For flow-mediated dilation measurement, a standard blood pressure cuff was positioned around the right arm, 2 inches below the antecubital fossa, and the artery was imaged 5–9 cm above the antecubital fossa. Baseline images were obtained first. Then the cuff was inflated to 50 mmHg above the participant's systolic blood pressure for 5 minutes. Digitized images of the right brachial artery were captured continuously for 30 seconds before cuff inflation and for 2 minutes beginning immediately before cuff deflation to document dilation response. The ultrasound videotapes were read centrally at Wake Forest University Cardiology Image Processing Laboratory using previously validated methods. Baseline diameter, maximum diameter, and flow-mediated dilation were evaluated for intra-reader reproducibility, intra-subject variability and percent technical error and these have been previously reported.(7) Intra-class correlation coefficients for re-reads were 0.99, 0.99, and 0.93. Correlation coefficients for repeated measures in subjects two weeks apart were: 0.90, 0.90, and 0.54. Percent technical error was 1.39% for baseline diameter measurement, 1.47% for maximum diameter measurement, and 28.4% for flow-mediated dilation measurement.(7) We expressed flow-mediated dilation as a percentage, and calculated as [(maximum diameter during dilation phase– baseline

diameter)/baseline diameter]. flow-mediated dilation has been shown to be an independent predictor of cardiovascular events in MESA.(7)

Covariates of interest

Information on age, self-reported race/ethnicity, level of education, annual household income, and smoking history was obtained using standardized questionnaires. We categorized levels of education as less than high school, high school graduate, and college graduate or above. Income was categorized as annual household income <\$20,000, \$20,000 to \$39,999, \$40,000 to \$74,999 and $\geq$ \$75,000. Hypertension was defined as systolic pressure $\geq$ 140mmHg, diastolic pressure $\geq$ 90mmHg or current use of antihypertensive medication. Cigarette smoking was defined as current, former, or never. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Fasting blood was collected and stored at -70°F until needed for the appropriate assays. Diabetes was defined as either a fasting glucose $\geq$ 126mg/dl or use of oral hypoglycemic medication or insulin. High density lipoprotein (HDL) cholesterol was measured using the cholesterol oxidase cholesterol method (Roche Diagnostics, www.roche.com). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. Urine albumin and creatinine were measured in a single morning urine sample by nephelometry and the rate Jaffe reaction, respectively, and expressed as albumin-creatinine ratio (ACR) in mg/g.

Statistical Analyses

We first described baseline characteristics of the MESA participants in this study. To evaluate the association between each of the measures of vascular dysfunction and kidney function decline, we used linear mixed models with random intercepts and slopes to estimate and compare linear trends in mean eGFR. This approach takes into account the correlation of observations within subject. We truncated at eGFR >120 ml/min/1.73m². Each predictor was evaluated separately both as a continuous predictor per SD and categorized into quartiles (or per 10 mmHg increments for pulse pressure). The following cutpoints were used for pulse pressure categories based on prior literature of pulse pressure distributions among persons with and without kidney disease and association with outcomes (<40, 40–50, 50–60, 60–70, >70).(8, 10, 30–31)

We first evaluated the shape of the associations using restricted cubic splines. We examined the association of each predictor with kidney function decline after adjustment for CKD risk factors chosen *a priori* that might explain any observed differences by subclinical vascular dysfunction. We also adjusted for factors used in the calculation of the predictors. The following strategy was used: For the models with pulse pressure as the predictor, we adjusted for age and gender (Model 1). Model 2 adjusted for age, gender, race/ethnicity, education, household income, body mass index, diabetes, smoking, use of anti-hypertensive medications, LDL and HDL cholesterol, C-reactive protein, urine albumin to creatinine ratio, and systolic blood pressure. For the models of SAE, LAE and flow-mediated dilation as the predictors, Model 1 presents unadjusted associations. Model 2 is adjusted for age, gender, race/ethnicity, education, household income, height and weight, heart rate, diabetes, smoking, use of anti-hypertensive medications, LDL and HDL cholesterol, C-reactive protein, urine albumin-creatinine ratio and systolic and diastolic blood pressure. Because the estimates of LAE and SAE were calculated based upon measures including mean arterial blood pressure, heart rate, age, weight, and height, easily obtained physical measures that may be associated with kidney function, we performed a sensitivity analyses in an attempt to isolate the information given by the pulse waveform only. Because, where SVR is systemic vascular resistance, LAE*SVR and SAE*SVR are the quantities that arise directly from solution of the differential equations that are the source of the LAE and SAE estimates, we

multiplied LAE and SAE by SVR to isolate the information from the pulse waveform only and tested the association of LAE*SVR and SAE*SVR with kidney function decline. We also tested for interactions with race/ethnicity and gender in all models.

In a final step, we were interested in evaluating the independent association of large vs. small artery measures and kidney function decline. For this, we included SAE and pulse pressure in one model and tested the independent association of each predictor.

In a sensitivity analysis, we repeated the pulse pressure, SAE and LAE analyses in the subset of participants who had flow-mediated dilation measures to account for any potential differences due to the sample size or patient characteristics.

All analyses were performed using S-Plus (release 8.0, TIBCO, www.tibco.com) and SPSS statistical software (release 16.0.1, SPSS Inc., www.spss.com). Two-tailed p-values <0.05 were considered significant.

Results

Among 4,853 MESA participants in this study, mean age was 60 ± 10 (SD) years; 41% were hypertensive, and 11% diabetic (Table 1). Mean pulse pressure was 56 ± 16 mmHg. Mean SAE and LAE were 4.69 ± 2.88 ml/mmHg $\times$ 100 and 13.74 ± 5.52 ml/mmHg $\times$ 10, respectively. Less than 7% (n=328) of participants had ACR >30 mg/g. Mean kidney function decline was 1.07 ± 4.34 ml/min/1.73m² per year for eGFR_{SCysC} and 1.55 ± 2.83 ml/min/1.73m² per year for eGFR_{SCr} during a median follow up time of 4.76 years.

There was a linear association of higher pulse pressure, lower SAE, and lower LAE with faster kidney function decline (Figure 1). In contrast, there was no significant association between flow-mediated dilation and rate of kidney function decline (Figure 1). In models using linear predictors, each 1-SD (16 mmHg) increase in pulse pressure was associated with faster kidney function decline after full adjustment. Similarly, each standard deviation increment in SAE and LAE was associated with faster kidney function decline after full adjustment (Figure 2). In contrast, for every 1-SD increase in flow-mediated dilation, the rate of eGFR_{SCysC} decline changed by 0.05 (95% CI, -0.04 to 0.14) ml/min/1.73m² per year. Using creatinine to calculate eGFR, every 1-SD increase in flow-mediated dilation was associated with small effect on the rate of eGFR_{SCr} change, of 0.06 (95% CI, 0.002 to 0.130) ml/min/1.73m² per year.

Pulse pressure values of 50–60, 60–70 and >70 mmHg were independently and incrementally associated with faster kidney function decline compared with pulse pressure levels between 40–50 mmHg. A pulse pressure <40 mmHg was not significantly associated with changes in rate of eGFR decline compared with the referent. Adjustment for demographics, comorbidities and systolic blood pressure did not attenuate this association (Table 2).

Compared with individuals in the highest quartiles of SAE and LAE (most elastic), persons in the lowest quartile had their serum cystatin C-based eGFR decrease faster, with the rate of decline greater by 0.70 ml/min/1.73m² (for SAE) and 0.83 ml/min/1.73m² (for LAE) per year. Similar patterns were observed when using eGFR_{SCr}. In contrast, among 2,997 adults in MESA, no significant association was seen between decreasing quartiles of flow-mediated dilation and rate of kidney function decline (Table 3).

Associations of SAE*SVR and LAE*SVR were significant after full adjustment (p<0.001 for all). There were no significant interactions by race/ethnicity or gender in any of the models (p-values >0.05 for all).

In a model including both pulse pressure and SAE, each of these predictors was independently associated with kidney function decline. After full adjustment, each 1-SD increase in pulse pressure was associated with faster decrease of $eGFR_{SCysC}$, with the rate of decline greater by 0.35 (95% CI, -0.43 to -0.28) ml/min/1.73m² per year. After adjustment for SAE, this was only mildly attenuated to 0.32 (95% CI, -0.42 to -0.23) ml/min/1.73m² greater decline per year. Similarly, every 1-SD decrease in SAE was associated with a 0.23 (95% CI, -0.16 to -0.30) ml/min/1.73m² greater $eGFR_{SCysC}$ decline per year. Adjustment for pulse pressure moderately attenuated this association to 0.12 (-0.04 to -0.19) ml/min/1.73m² greater decline per year.

Sensitivity analyses including only 2,997 persons who had flow-mediated dilation measurement resulted in similar results. Higher pulse pressure was associated with faster decrease of kidney function, with a 0.32-ml/min/1.73m² greater decline per year for each 1-SD increment in pulse pressure. Compared with those in the highest quartiles of SAE and LAE (most elastic), persons in the lowest quartiles had their serum cystatin C-based GFR estimates decline faster, by an additional 0.65 ml/min/1.73m² (for SAE) and 0.75 ml/min/1.73m² (for LAE) per year.

Discussion

In this large multi-ethnic cohort, we found that higher large arterial stiffness measured by pulse pressure and decreased small (SAE) and large arterial elasticity (LAE) were significantly and linearly associated with faster decline in kidney function among persons with $eGFR > 60$ ml/min/1.73m². Moreover, the associations between pulse pressure and SAE were independent of each other. In contrast, endothelial dysfunction, measured by flow mediated dilation, was not associated with differences in rates of kidney function decline. Our findings were consistent whether kidney function was assessed by cystatin C- or creatinine-based $eGFR$.

Our finding that pulse pressure is associated with kidney function decline is in accordance with prior literature showing that wider pulse pressure is associated with progression from stages 4 and 5 CKD to ESRD,(32) and with kidney function decline in a sample of Japanese factory workers with preserved $eGFR$.(15) Our study expands these findings to show that increased pulse pressure is independently associated with kidney function decline across a large, diverse cohort of persons with initial $eGFR > 60$ ml/min/1.73m² and no cardiovascular disease. Increased pulse pressure is thought to reflect arterial stiffness, likely a process mediated by atherosclerosis. The combination of higher SBP and lower DBP (wider pulse pressure) may result in increased work load to the myocardium and lower perfusion pressures to the kidney during diastole.(33) How these mechanisms may explain the association of higher pulse pressure and kidney function decline remains unknown. It is particularly interesting that pulse pressure predicted kidney function decline independently of SBP among adults without established CKD or CVD. Recently, long term follow up studies of large cohorts have shown that lower blood pressure goals did not universally succeed in attenuating the slope of GFR decline.(34) Future studies should evaluate whether agents that reduce SBP without widening pulse pressure (that is, reduce SBP more than they reduce DBP) may be uniquely beneficial for slowing GFR decline and preventing cardiovascular adverse events, even among persons with only mildly reduced $eGFR$.

The findings that reduced SAE and LAE are associated with faster kidney function decline are also noteworthy. Reduced SAE and LAE are thought to represent an impaired ability of the microvasculature to withstand distending pressures during the diastolic portion of the cardiac cycle (capacitive and oscillatory). Our findings build upon prior literature suggesting that glomerular capillaries are very sensitive to small changes in upstream pressures.(33)

Mechanisms for these associations remain unexplained but may include increased inflammatory response, oxidative stress or dysregulation of vascular matrix architecture and remodeling.(35) Future studies should be aimed at understanding whether agents that increase elasticity such as statins(36–37) may be beneficial to reduce kidney function loss.

In contrast to pulse pressure and elasticity measures, flow-mediated dilation was not associated with kidney function decline. Some cross-sectional studies have shown an association with flow-mediated dilation and CKD,(6) while other large population based studies have not.(38) Markers of endothelial dysfunction have been shown to predict reduced kidney function, and to predict death among persons with CKD.(6, 39) One possible explanation for our findings is that only some, but not all, of the mechanisms that regulate endothelial function are altered in the setting of kidney disease. For example, animal studies have shown that subtotal nephrectomy results in preserved endothelial function that is mediated by nitric oxide, despite abnormalities in sympathetic activity and increased vascular stiffness.(40) Recent evidence in humans suggests that abnormalities in acetylcholine-stimulated forearm blood flow, but not nitric oxide (NO) mediated flow, are associated with CKD progression.(41) In addition, flow-mediated dilation may not be able to accurately capture the association between endothelial dysfunction and kidney function decline due to measurement errors in the technique. Whether alterations of non-NO mediated endothelial function pathways are associated with early kidney function decline remains unclear.

To our knowledge, this study is the first to show that measures of subclinical vascular disease at multiple sites of the arterial tree and that reflect different functions of the arterial system are independent predictors of kidney function decline among persons with eGFR >60 ml/min/1.73m². Our study has the advantage of being a well-characterized multi-ethnic cohort with repeated measures of eGFR using two filtration markers (creatinine and cystatin C). However, we are limited by having no direct measure of GFR, in common with nearly all large population-based studies. Moreover, we used pulse pressure as a marker of stiffness rather than pulse wave velocity. However, pulse pressure has been shown to be strongly correlated with pulse wave velocity. In addition, our sample size for flow mediated dilation analyses was smaller, thus reducing power to detect small effect sizes; these measures are not normalized to flow, thus limiting physiological interpretations. However, our results were robust when limiting to the subsample with flow-mediated dilation measures. The association between vascular dysfunction and kidney function decline may also be bi-directional and/or parallel processes. We are unable to test for bi-directionality in the present study. In summary, we found that increased pulse pressure and reduced small and large arterial elasticity are independently associated with kidney function decline among persons with eGFR >60ml/min/1.73m². Given recent literature on promising agents that may attenuate stiffness, elasticity and endothelial dysfunction,(13, 33, 42–44) future studies should investigate whether these agents may have a role in primary prevention of CKD among high risk groups.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at www.mesa-nhlbi.org.

Support: This research was supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by the NIDDK (grant 1K23DK082793-01, Dr Peralta). These funding sources had no involvement in the design or execution of this study.

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Figure 1. Splines of the Association of pulse pressure, SAE, LAE and FMD (flow-mediated dilation) with Kidney Function Decline in MESA (Multi-Ethnic Study of Atherosclerosis)

Figure 2. The Association of SAE and LAE (per 1-SD decrease) and pulse pressure (per 1-SD increase) with Kidney Function Decline among 4,853 Adults without CKD in MESA*

*Models adjusted for age, gender, race, education, household income, body mass index, diabetes, smoking, anti-hypertensive medications, low density lipoproteins, high density lipoproteins, C-reactive protein, urine albumin-creatinine ratio, and systolic blood pressure. Point estimates are as follows for eGFR_{cys} (serum cystatin C-based estimated glomerular filtration rate): SAE: -0.23; LAE: -0.29; pulse pressure: -0.35; FMD: 0.05. Point estimates for eGFR_{cr} (serum creatinine-based estimated glomerular filtration rate) are: SAE: -0.16; LAE: -0.15; pulse pressure: -0.26; FMD: 0.06.

Table 1Characteristics of MESA Participants with eGFR > 60 mL/min/1.73 m² at baseline*

Characteristic	Value
Age (years)	60 ± 10
Male	2352 (49)
Race/Ethnicity	
White	1851 (38)
Chinese	592 (12)
Black	1296 (27)
Hispanic	1114 (23)
Education	
<High School	806 (17)
Completed High School, No College	2243 (46)
Completed College or More	1797 (37)
Income	
<\$20,000	1008 (21)
\$20,000–\$39,999	1234 (25)
\$40,000–\$74,999	1315 (27)
≥\$75,000	1139 (24)
Diabetes	555 (11)
Hypertension	1966 (41)
Smoking status	
Never	2455 (51)
Former	1758 (36)
Current	633 (13)
Systolic blood pressure (mmHg)	125 ± 20
Diastolic blood pressure (mmHg)	72 ± 10
Use of Hypertension Medications	4603 (33)
LDL Cholesterol (mg/dL)	117 ± 31
HDL Cholesterol (mg/dL)	51 ± 15
Triglycerides (mg/dL)	111 (77; 161)
Use of Lipid-Lowering Medications	710 (15)
Body Mass Index (kg/m ²)	28 ± 6
Height (cm)	167 ± 10
Weight (lbs)	174 ± 38
Heart rate (beats/min)	63 ± 9
Glucose (mg/dL)	96 ± 29
Insulin (μU/mL)	5.3 (3.5; 8.4)
C-Reactive Protein	1.80 (0.79; 1.12)
Interleukin-6	1.14 (0.73; 1.79)
eGFR _{MDRD} (mL/min/1.73m ²)	83 ± 14
eGFR _{SCr} (mL/min/1.73m ²)	82 ± 13

Characteristic	Value
eGFR _{SCysC} (ml/min/1.73m ²)	95 ± 17
UACR (mg/g)	5.0 (3.2; 9.7)

Note: N = 4,853. Categorical variables given as number (percent); continuous variables as mean +/- SD or median (25th; 75th percentile).

* *Abbreviations:* eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Low-density lipoprotein (LDL), High-density lipoprotein (HDL, Estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) Study equation (eGFR_{MDRD}), Estimated glomerular filtration rate using the serum creatinine-based CKD-EPI equation (eGFR_{SCr}), Estimated glomerular filtration rate using a serum cystatin C-based equation (eGFR_{SCysC}), Urinary albumin-creatinine ratio (UACR); MESA, Multi-Ethnic Study of Atherosclerosis. Conversion factors for units: serum creatinine in mg/dL to μ mol/L, $\times 88.4$; glucose in mg/dL to mmol/L, $\times 0.05551$; HDL-C and LDL-C in mg/dL to mmol/L, $\times 0.02586$; Insulin in μ U/mL to pmol/L, $\times 6.00$; Triglycerides in mg/dL to mmol/L, $\times 0.01129$; eGFR in mL/min/1.73 m² to mL/s/1.73 m², $\times 0.01667$.

Table 2

Association of Pulse Pressure and Kidney Function Decline

	Pulse Pressure (mmHg)				
	<40 (n=1,095)	40-50 (n=1,338)	50-60 (n=1,014)	60-70 (n=690)	>70 (n=716)
eGFR _{SCysC}					
Model 1 *	0.08 (0.5)	Reference	-0.29 (0.004)	-0.58 (<0.001)	-0.90 (<0.001)
Model 2 **	0.07 (0.5)	Reference	-0.29 (0.006)	-0.56 (<0.001)	-0.91 (<0.001)
eGFR _{Scr}					
Model 1 *	0.13 (0.06)	Reference	-0.12 (0.1)	-0.37 (<0.001)	-0.63 (<0.001)
Model 2 **	0.13 (0.06)	Reference	-0.13 (0.08)	-0.33 (<0.001)	-0.62 (<0.001)

Note: Values shown are β (p-value) among MESA Participants with eGFR > 60 mL/min/1.73 m² at baseline. Estimated glomerular filtration rate using the serum creatinine-based CKD-EPI equation (eGFR_{SCysC}). Estimated glomerular filtration rate using a serum cystatin C-based equation (eGFR_{SCysC}). MESA, Multi-Ethnic Study of Atherosclerosis; eGFR, estimated glomerular filtration rate.

* Model 1: age and gender adjusted

** Model 2: adjusted for age, gender, race/ethnicity, education, household income, body mass index, diabetes, smoking, use of anti-hypertensive medications, LDL and HDL cholesterol, C-reactive protein, urine albumin-creatinine ratio, and systolic blood pressure

Table 3

Decline in eGFR over five years by quartile of SAE, LAE and Flow-mediated dilation

	Q3 [†]	Q2 [‡]	Q1 [‡]
eGFR _{SCysC}			
SAE			
Model 1 *	−0.27 (0.006)	−0.34 (0.001)	−0.72 (<0.001)
Model 2 **	−0.26 (0.008)	−0.35 (0.001)	−0.70 (<0.001)
LAE			
Model 1 *	−0.29 (0.003)	−0.56 (<0.001)	−0.81 (<0.001)
Model 2 **	−0.28 (0.004)	−0.58 (<0.001)	−0.83 (<0.001)
Flow-mediated dilation			
Model 1 *	0.26 (0.03)	−0.03 (0.8)	−0.18 (0.2)
Model 2 **	0.25 (0.04)	−0.03 (0.8)	−0.13 (0.3)
eGFR _{SCr}			
SAE			
Model 1 *	−0.19 (0.005)	−0.29 (<0.001)	−0.47 (<0.001)
Model 2 **	−0.17 (0.01)	−0.29 (<0.001)	−0.45 (<0.001)
LAE			
Model 1 *	−0.18 (0.009)	−0.33	−0.50 (<0.001)
Model 2 **	−0.18 (0.008)	−0.33 (<0.001)	−0.50 (<0.001)
Flow-mediated dilation			
Model 1 *	0.13 (0.1)	−0.08 (0.4)	−0.17 (0.05)
Model 2 **	0.12 (0.2)	−0.10 (0.3)	−0.16 (0.06)

Note: Values shown are β (p-value). Q4 is the reference group for each. Population is MESA participants with eGFR > 60 ml/min/1.73 m² at baseline.

Abbreviations: Estimated glomerular filtration rate using the serum creatinine-based CKD-EPI equation (eGFR_{SCr}), Estimated glomerular filtration rate using a serum cystatin C-based equation (eGFR_{SCysC}), MESA, Multi-Ethnic Study of Atherosclerosis; eGFR, estimated glomerular filtration rate; Q, quartile.

* Model 1: age and gender adjusted

** Model 2: adjusted for age, gender, race, education, household income, height & weight, heart rate, diabetes, smoking, systolic blood pressure, diastolic blood pressure, anti-hypertension medications, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, C-reactive protein, and urinary albumin-creatinine ratio

[†] Quartiles SAE (mm/mmHg×100): Q4, >5.79; Q3, 3.71–5.79; Q2, 2.40–3.70; Q1, <2.40

[‡] Quartiles LAE (mm/mmHg×100): Q4, >16.20; Q3, 12.53–16.20; Q2, 9.47–12.52; Q1, <9.47.

[‡] Quartiles for flow-mediated dilation: Q4, >6.0; Q3, 4.0–6.0; Q2, 2.3–3.9; Q1, ≤2.3.