Deterioration in Renal Function Is Associated With Increased Arterial Stiffness

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BACKGROUND
Higher levels of baseline pulse wave velocity (PWV) have been associated with longitudinal decline in renal function in patients with kidney disease. We examined longitudinal decline in renal function in relation to levels of PWV. We hypothesized that longitudinal decline in renal function in a community-based, nonclinic sample would be associated with higher levels of PWV.

METHODS
We conducted a 4–5 year longitudinal study with 482 community-living individuals free from acute stroke, dementia, and end-stage renal disease (mean age = 60.9 years; 59% women; 93.2% white; 10% with diabetes mellitus; mean estimated glomerular filtration rate (eGFR) = 79.2 ml/min/1.73 m^2). Multiple linear regression analyses were used to examine the association between changes in renal function (eGFR and serum creatinine) from baseline to follow-up and PWV levels at follow-up, the outcome measure. Regression coefficients were adjusted for age, sex, education, race/ethnicity, weight, activity level, mean arterial pressure, treatment of hypertension, and cardiovascular risk factors.

RESULTS
With adjustment for covariables, decline in renal function was associated with higher levels of PWV over a mean follow-up of 4.68 years.

CONCLUSIONS
Decline in renal functioning from baseline levels measured 4–5 years before measurement of PWV is related to higher levels of PWV in a community sample.

Keywords: blood pressure; cardiovascular disease; chronic kidney disease; estimated glomerular filtration rate; hypertension; pulse wave velocity; renal disease.

doi:10.1093/ajh/hpt179

Pulse wave velocity (PWV) has become the gold standard indirect measure of arterial stiffness and has become a major measure of importance with regard to describing relations between arterial stiffness and chronic kidney disease (CKD).[1] Cross-sectional studies have shown associations between PWV and CKD,[2–8] but there have been relatively few, if any, longitudinal studies with community-based samples whose recruitment was not based upon a diagnosis of renal disease. Two studies, one with a community-based sample and one with a population-based sample, have been done. In the large community-based Framingham study, no association between multiple indices of arterial stiffness and incident CKD were found in multivariable analyses during a 10–17 year follow-up.[9] In the ABC study, baseline levels of PWV were related to decline in renal function over a median of 8.9 years, but this population-based sample was obtained from patient Medicare records.[10] Thus additional studies with community-based samples remain important.

There is an important difference between this study and the aforementioned studies. In each of these studies, PWV at baseline was the predictor and change in renal function was the outcome. In this study, we measured change in renal function from baseline to follow-up and assessed PWV levels at the follow-up occasion. Our study was stimulated by papers emphasizing the importance of studies in which decline in renal function over time (predictor) is related to arterial stiffness as an outcome.[11,12] These data are important given current efforts to relate risk factors for cardiovascular disease (CVD) to levels of PWV.[13–15] We hypothesized that decline in renal function from wave 6 to wave 7 of the study would be related to higher levels of PWV at wave 7, despite adjustment for demographic and cardiovascular risk factors related both to decline in renal function and PWV.

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Initially submitted June 4, 2013; date of first revision July 11, 2013; accepted for publication August 30, 2013; online publication September 30, 2013.

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METHODS

Sample

Data were obtained from the Maine Syracuse Longitudinal Study (MSLS).[16,17] MSLS participants were recruited for studies of blood pressure (BP) and cognitive performance with no recruitment exclusions other than institutionalization, diagnosed psychiatric disorder, and alcoholism. Data necessary to estimate change in renal function were obtained at the 6th and 7th waves; PWV was obtained at the 7th wave. The mean between waves was 4.68 years (SD = 0.61). Eight hundred eight participants with data on renal function and with residences in New York State at wave 6 were invited back to the laboratory for repeated renal studies and PWV data collection at wave 7; 536 returned for wave 7. Of these, participants were excluded in the following order: (i) missing data (n = 29); (ii) history of acute stroke at baseline (n = 5); (iii) on dialysis at baseline (n = 0); (iv) probable dementia at baseline (n = 0); and (v) suboptimal quality of data on arterial stiffness as defined by SphygmoCor as a PWV error of estimate >20% (n = 20). Acute stroke was defined as a focal neurological deficit persisting for >24 hours, and probable dementia was defined by multidisciplinary review, hospital records, and cognitive measures. The final longitudinal sample consisted of 482 participants.

Procedures

The University of Maine human subjects Institutional Review Board approved this study. Except for assessment of PWV at wave 7, procedures were identical at waves 6 and 7. A blood sample, multiple brachial artery BP measurements, and PWV were obtained before breakfast in the morning after an overnight fast. After a light breakfast, including decaffeinated tea or coffee, participants' medical and drug histories were updated.[18] After each wave of the study, participants were advised to meet with their physicians for treatment as usual for any risk or disease factor discovered during that wave or any previous wave of the study.

Assay methods for covariable data have been defined previously.[18,19] Serum creatinine (sCR) was determined using a 2-point rate test type on a Johnson and Johnson Vitros Instrument (Ortho Clinical Diagnostics, Rochester, NY, USA). Coefficients of variation for these procedures were <5.0%. We estimated eGFR using the Modification of Diet in Renal Disease (MDRD)[20] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas.[21] A reciprocal transformation of sCR (1/sCR) was also employed.[18,19]

Brachial BP and pulse wave velocity

Brachial artery pressure was assessed at waves 6 and 7 using the traditional pressure-cuff method with a Critikon Dinamap Pro Care 100 (oscillometeric method; GE Health Care, Chalfont St. Giles, UK). After 10 minutes of supine rest, 5 measurements were taken in the supine, sitting, and standing positions and then averaged. After BP measurement, PWV was assessed noninvasively in a supine position, using the SphygmoCor system and procedure (AtCor Medical, Itasca, Illinois, USA) with applanation tonometry. Carotid–femoral path length was measured as the difference between the surface distances joining (i) the suprasternal notch, the umbilicus, and the femoral pulse and (ii) the suprasternal notch and the carotid pulse. Carotid–femoral transit time was estimated in 8–10 sequential electrocardiogram-gated femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. The foot of the pulse wave was identified using the intersecting tangent method. PWV was calculated as the carotid–femoral path length divided by the carotid–femoral transit time.[22,23] This is a noninvasive and reproducible method to determine arterial stiffness.[24,25] The coefficient of variation in our laboratory is 1.79%.

Covariables and descriptive data

The data collected for covariance analyses and statistical adjustment are summarized as sample-descriptive data in the "Results" section with units of measurement. Standard assays and diagnostic criteria were used and were fully described in a previous study.[16–18] Self-report variables were as follows: alcohol consumption (ounces per week including 0), cigarette smoking (number per week including 0), and depressed mood (defined as a score of ≥16 on the Center for Epidemiologic Studies Depression Scale).[26] Physical activity was indexed using the Nurses' Health Study leisure time physical activity questionnaire and converted to metabolic equivalent of task (MET) units.[27] Prevalent CVD was defined by the self-reported presence of coronary artery disease, myocardial infarction, congestive heart failure, transient ischemic attack, or angina pectoris and was confirmed by medical records. Obesity was defined as a body mass index ≥30 kg/m^2. Waist circumference was measured using a nonextendable tape at the level of the iliac crest. Diabetes mellitus was defined as treatment with insulin, oral antihypoglycemic diabetic agents, or by fasting glucose level of ≥126 mg/dl (7 mmol/L). Hypertension was defined as treatment for hypertension or a BP of ≥140/90 mm Hg. Albuminuria, hemoglobin levels, and complete blood count data were not collected at wave 6 or 7 because renal function was not a focus of the study at the time of data collection.

Statistical analyses

Natural log and reciprocal transformations of eGFR and creatinine, respectively, were done to meet assumptions of linear regression analyses. Log PWV was expressed as a continuously distributed outcome variable and regressed onto measures of change in eGFR and 1/sCR. Change in renal functioning was defined as renal functioning at follow-up adjusted for baseline renal functioning. This well-recognized longitudinal method[28] allowed us to determine whether greater deterioration in renal functioning between wave 6 and 7 was related to higher PWV values at wave 7. Analyses were conducted using Stata 12 (StataCorp, College Station, TX). The selection of covariables for regression models was based on their significant associations with PWV and change

in renal function. For the primary analyses, covariables were based on wave 6 data, except for heart rate, which was taken from wave 7 at the time of PWV assessment. Weight at wave 6 and intraindividual change in weight scores (wave 6–7) were used as covariables given the importance of change in weight with respect to PWV.[29] Each model builds on the other in a hierarchical manner, and the full model includes all the covariables:

1. Basic (demographic) covariate set: age + sex + education + ethnicity.
2. Intermediate covariable set: demographic set + mean arterial pressure (MAP).
3. Full model: demographic + MAP + height + weight + weight change (wave 6 to wave 7) + activity level in total MET units + heart rate + treatment for hypertension + diabetes mellitus + high-density lipoprotein (HDL) cholesterol + homocysteine.

RESULTS

Descriptive statistics at baseline (wave 6) and follow-up (wave 7) are shown in Table 1. Supplementary Table 1 displays the proportion of persons on various classes of hypertensive medications. Both the MDRD and CKD-EPI GFR estimates decreased by 15% from wave 6 to wave 7, and sCR levels increased. Pulse pressure decreased from wave 6 to wave 7, as only diastolic, not systolic, BP increased from wave 6 to 7.

Total cholesterol, triglycerides, low-density lipoprotein (LDL), and HDL declined, with modest decline for HDL. Smoking rates declined, and homocysteine increased. Percentage of hypertensive and diabetic individuals increased, but so did treatment for these risk factors. There was no significant change in mean weight from wave 6 to wave 7 nor was there a change in waist circumference. Prevalent CVD increased from 11% to 14%, but this change was unrelated to PWV. The percentage of the sample being treated for anemia was 0.62% at wave 6, with no change at wave 7; a history of anemia was unrelated to PWV.

There were no significant ($\alpha = 0.05$) interactions of risk factor covariables with changes in renal function (eGFR and 1/sCR). Thus variables from wave 6 were employed as covariables for the primary analyses, with the exception of heart rate.

After log transformation of eGFR and calculating the inverse of sCR (1/sCR), all variables met assumptions underlying linear regression analyses, and results were replicated using bootstrapped standard errors with 1,000 replicate samples.

Table 2 summarizes raw regression coefficients expressing associations between changes in renal function in log units (wave 6 to wave 7) to PWV (wave 7) for the 3 regression models. The sign for 1/sCR is reversed so that for all renal measures positive regression coefficients indicate that greater decreases in renal function are associated with higher levels of PWV. It may be seen that associations between measures of change in renal function and levels of PWV were statistically significant for each of the renal measures. The magnitude of the relations was reduced when the full covariable set (model) was employed.

While raw score coefficients (b) are important in terms of comparison among studies, they are difficult to interpret given the need for normalization procedures (log and reciprocal transformations); thus Table 3 provides standardized regression coefficients (β) (i.e., each unit increase in 1 SD for the predictor (renal decline over time) related to a 1 SD difference in PWV levels at wave 7). These coefficients may be interpreted as follows using the CKD-EPI formula as an example. An individual with a 1 SD decrease in eGFR for the CKD-EPI formula would experience a 0.18–0.20 SD increment in PWV for the basic and intermediate covariable sets and a 0.11 SD increment with adjustment for the full covariable set. Renal change (wave 6 and wave 7) was associated with higher values of PWV at wave 7, and the magnitude of this association was attenuated, but remained significant, with adjustment for the full model covariable set. The relative importance of this change expressed in SD units is indicated by the observation that each SD increment in MAP was associated with a 0.15 SD increase in PWV, whereas each SD decrease in renal function was associated with a 0.11 increase in PWV at wave 7.

Figure 1, based on the full covariable model and the CKD-EPI formula, expresses results in terms of less than average change (M − 1 SD), average change (M), and greater than average change (M + 1 SD) in renal function and also for change scores at the 25th (lower) percentile, median, and the 75th (higher) percentile of the distribution of change scores. These cut points are arbitrary but are often used to illustrate magnitude of relations, as is the purpose here.

Individuals who experienced less than average decrease (lesser decrease) went from approximately 78 to 84 ml/min/1.73 m^2 for M − 1SD and from 79 to 77 ml/min/1.73 m^2 for the 25th percentile. Individuals who experienced typical levels of change in renal functioning between wave 6 and wave 7 (average decrease) went from approximately 79 to 68 ml/min/1.73 m^2 for mean and 78 to 76 ml/min/1.73 m^2 for median. Individuals who experienced greater than average decrease (greater decrease) went from approximately 79 to 55 ml/min/1.73 m^2 for M + 1 SD and from 78 to 58 ml/min/1.73 m^2 for the 75th percentile. The highest levels of PWV are shown (Figure 1) for those who showed the greater decline in eGFR from wave 6 to wave 7, and the lowest levels are shown for those who showed the lesser change.

Several sensitivity analyses were done. All significant associations remained when all covariables were taken from wave 6 and change in weight was deleted from the analysis (e.g., full model: b = 2.71, 2.19, and 2.16, for 1/SCR, MDRD, and CKD-EPI, respectively; all Ps < 0.002).

To determine the effect of excluding variables that did not relate to PWV from the extended primary model, we added these previously excluded variables (CVD, depressed mood, ounces of alcohol per week including 0, cigarettes per week including 0) to the full model in sensitivity analyses. We also conducted a series of sensitivity analyses in which total cholesterol, LDL, and triglycerides replaced HDL in separate analyses and a series in which the variables height and weight were replaced with body mass index and waist circumference and hypertension was replaced with treatment for hypertension. None of these analyses significantly improved the regression model, and all previously reported relations between renal decline and PWV remained statistically significant.

Table 1. Demographic and medical history variables obtained at one or both waves

	Wave 6		Wave 7		
Variable	**M or %**	**SD**	**M or %**	**SD**	***P* value**
Age, y	60.9	11.5	65.6	11.5	<0.001
Education, y	14.8	2.7	14.8	2.8	0.23
PWV, m/s			10.5	2.9	
Pulse pressure, mm Hg	59.2	16.0	52.8	16.0	<0.001
SBP, mm Hg	128.7	21.1	129.5	20.3	0.34
DBP, mm Hg	69.5	9.7	76.6	9.8	<0.001
MAP, mm Hg	89.3	12.4	94.3	12.0	<0.001
Heart rate, bpm	66.4	10.1	63.9	9.2	<0.001
MDRD eGFR, ml/min/1.73 m^2	79.2	16.5	67.3	13.9	<0.001
CKD-EPI eGFR, ml/min/1.73 m^2	78.9	16.1	66.3	14.7	<0.001
Creatinine, mg/dl	0.9	0.3	1.1	0.3	<0.001
Height, cm	167.7	9.8	167.4	10.0	0.07
Weight, kg	82.5	18.8	82.6	18.7	0.83
Waist Circumference, cm	94.1	14.5	94.2	15.4	0.83
BMI, kg/m^2	29.3	5.8	29.5	6.3	0.19
Physical Activity, MET h/wk	21.1	26.1	21.3	27.5	0.79
Glucose, mg/dl	97.4	25.9	97.7	20.9	0.78
HDL, mg/dl	54.7	15.8	53.2	15.3	<0.001
LDL, mg/dl	121.2	34.1	112.7	32.9	<0.001
Triglycerides, mg/dl	137.4	114.0	115.6	80.6	<0.001
Total cholesterol, mg/dl	202.4	40.4	188.5	39.3	<0.001
Smoking, cigarettes/wk	8.6	34.0	5.6	26.1	0.002
Alcohol consumption, oz/wk	1.5	2.5	1.4	2.4	0.71
Plasma homocysteine, μmol/L	9.4	2.8	10.4	3.6	<0.001
% in stages based on eGFR					<0.001
1: >89	25.1		5.6		
2: 50–89	62.0		61.0		
3: 30–49	12.7		32.6		
4: 15–29	0.2		0.6		
5: <15			0.2		
% *APOE*-ε4	30				
% Female	59				
% Black	6				
% Obese, BMI ≥ 30	39		38		0.52
% Diabetes	10		15		<0.001
% Diabetics treated	86		89		<0.001
% Hypertension	57		63		<0.001
% Hypertensives treated	83		95		<0.001

Continued

Table 1. Continued

Variable	Wave 6 M or %	Wave 6 SD	Wave 7 M or %	Wave 7 SD	*P* value
% CVD[a]	11		14		<0.001
% Depressed mood	8		10		0.22
% Anemic	0.6		0.6		

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; PWV, pulse wave velocity; SBP, systolic blood pressure.

[a]Includes myocardial infarction, coronary artery disease, heart failure, angina pectoris, and transient ischemic attack.

Table 2. Raw regression coefficients (*b*) relating decline in renal function to pulse wave velocity levels[a]

Measure of change in eGFR	Basic covariables[b] PWV/ unit decrease	95% CI	*P* value	Intermediate covariable set[c] PWV/ unit decrease	95% CI	*P* value	Full covariable set[d] PWV/ unit decrease	95% CI	*P* value
1/sCR	3.09	1.57–4.61	<0.001	2.71	1.14–4.28	<0.001	1.72	0.29–3.15	0.02
MDRD	2.50	1.21–3.80	<0.001	2.19	0.82–3.55	0.002	1.35	0.10–2.60	0.04
CKD-EPI	2.44	1.19–3.69	<0.001	2.16	0.83–3.48	0.002	1.33	0.12–2.55	0.03

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PWV, pulse wave velocity; sCR, serum creatinine.

[a]Unit of decrease for independent variable (eGFR) is change in logged eGFR (ln(ml/min/1.73 m^2)) and units of 1/sCR. All regression coefficients have been scaled to represent the association between greater renal impairment and increments in PWV, and all models adjust follow-up renal function for baseline renal function. Covariables were taken from wave 6 unless otherwise specified below.

[b]Basic set: age + sex + education + race/ethnic group.

[c]Intermediate set: basic set + mean arterial pressure.

[d]Full set: basic set+ mean arterial pressure + height + weight + weight change (wave 6 to wave 7) + activity metabolic equivalent of task total + heart rate (wave 7) + treatment for hypertension + diabetes + high-density lipoprotein cholesterol + homocysteine.

Table 3. Standardized regression coefficients (β) relating decline in renal function to pulse wave velocity levels[a]

Measure of change in eGFR	Basic covariables[b] PWV/ SD decrease	95% CI	*P* value	Intermediate set 1[c] PWV/ SD decrease	95% CI	*P* value	Full set 3[d] PWV/ SD decrease	95% CI	*P* value
1/sCR	0.21	0.11–0.31	<0.001	0.18	0.08–0.29	<0.001	0.12	0.02–0.13	0.02
MDRD	0.19	0.09–0.29	<0.001	0.17	0.06–0.27	0.002	0.10	0.008–0.20	0.04
CKD-EPI	0.20	0.10–0.31	<0.001	0.18	0.07–0.29	0.002	0.11	0.01–0.21	0.03

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PWV, pulse wave velocity; sCR, serum creatinine.

[a]Unit of decrease is SD for independent variables (eGFR and 1/sCR). All regression coefficients have been scaled to represent the association between greater renal impairment and increments in PWV, and all models adjust follow-up renal function for baseline renal function. Covariables were taken from wave 6 unless otherwise specified.

[b]Basic set: age + sex + education + race/ethnic group.

[c]Intermediate set: basic set + mean arterial pressure.

[d]Full set: Basic set + mean arterial pressure + *height + weight + weight change (wave 6 to wave 7) + activity metabolic equivalent of task total + heart rate (wave 7) + treatment for hypertension + diabetes + high-density lipoprotein cholesterol + homocysteine.*

Attrition

Heckman's selection-bias procedure was used[30] to determine the effects of attrition from baseline to follow-up. Results were identical to ordinary least squares (OLS) regression models. Persons with higher systolic BP at baseline were 1% less likely per 1 mm Hg to return for the wave 7 assessment of PWV.

DISCUSSION

Greater longitudinal decline in renal function (wave 6 to wave 7) in a community-based sample was associated with higher levels of PWV, with adjustment for age, sex, education, ethnicity, weight, physical activity, MAP, and CVD risk factors. We also adjust for baseline renal function and

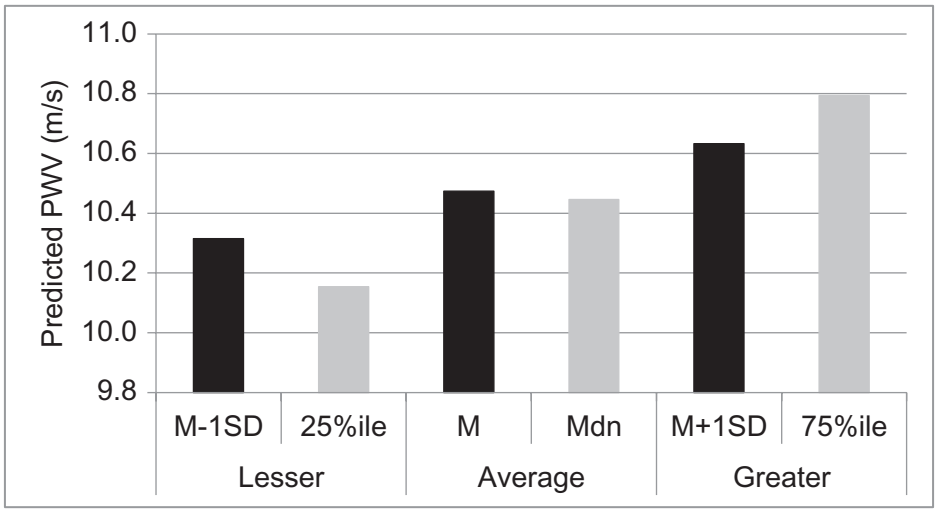

Figure 1. Predicted values of pulse wave velocity (PWV) as a function of the extent of change in renal functioning estimated using the Chronic Kidney Disease Epidemiology Collaboration formula.

changes in renal function. Thus the regression coefficients reported reflect associations between change in renal function and level of PWV net normative physiological change.

In the Framingham community-based study, PWV values measured once at baseline and with a 7–10-year follow-up were unrelated to incident renal disease in a multivariable model.[9] However, in a recent population-based ABC study of elderly individuals drawn from Medicare beneficiary records, higher levels of baseline PWV were related to more rapid decline in renal function over a median of 8.9 years in covariable-adjusted models.[10] The ABC investigators argue for the importance of adjustment for BP. In this study, we adjusted for MAP and hypertension.

The ABC study provides indirect support for our findings, but, as was true of the Framingham study, the investigators examined baseline levels of PWV in relation to change in renal function. In contrast, we prospectively measured renal change over time and related it to PWV, but we do not argue that relations between renal decline and PWV are unidirectional (renal decline → higher PWV). The design of our study does not permit this conclusion, and it is inconsistent with the literature previously reviewed. Our goal was to describe the relationship between change in renal function and levels of PWV.

There is a need for large, community-based samples in which longitudinal data for both renal decline and PWV are measured concurrently or using a prospective design. Briet *et al.*[31] employed this design but with a sample of patients. Carotid artery, but not aortic stiffness, increased with decline in renal function over 3.5 years. The study involved 180 patients with mild to moderate CKD, but 91% of the study participants had hypertension and 68% had dislipidemia. Briet *et al.* discussed the possibility that change in pulse wave velocity may not have been observed because remodelling of the arteries had taken place.

In terms of mechanisms, it has been hypothesized that decline in renal functioning is associated with atherosclerosis due to endothelial dysfunction and to arteriosclerosis related to thickening of the media, calcification, and fibrosis. It has also been hypothesized that oxidative stress, inflammation, uremic toxins, and dyslipidemia play a role in endothelial dysfunction and vascular calcification, vascular smooth muscle hypertrophy, and collagen deposition and that cross-linking influences medial thickening, calcification, and fibrosis.[32,33]

Persons lost to the study from attrition were generally in poorer health, and those who remained were treated after baseline. Consequently, we may have underestimated the magnitude of relations between change in decline in renal function and arterial stiffness that would occur in an absence of attrition. However, Heckman selection models used to evaluate sample bias corroborated all observed associations found with our multivariable models.

There were no data on albuminuria because at the time the data were collected kidney disease was not a focus of the MSLS study. As discussed previously, there are no longitudinal data on PWV; we cannot assert that changes in PWV are associated with changes in renal function or that this relationship is unidirectional.

The strength of our study is that we related decline in renal functioning over 4–5 years to PWV for persons in a community-based sample, for whom a majority of hypertensive individuals were treated as usual with antihypertensive medications and investigators were blind to kidney disease status at both waves of data collection.

In a community-based sample, including individuals with early-stage kidney disease, decline in renal function was associated with higher PWV values and, by inference, higher levels of arterial stiffness. These results were seen with adjustment for baseline renal function, age, sex, education, and cardiovascular risk factors associated with renal function and PWV. We found modest associations between decline in renal function and PWV levels, but even modest associations constitute unacceptable risks at a population level. We hypothesize that effective management of the multiple CVD risk factors associated with renal disease and PWV could possibly be an avenue for successful early intervention in these processes.[34–38] Clinical trials are necessary to test this hypothesis.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

ACKNOWLEDGMENTS

This work was supported by grants R01HL067358, and R01HL081290 from the National Heart, Lung and Blood Institute, National Institutes of Health and by research grant R01AG03055 from the National Institute on Aging, National Institutes of Health to the University of Maine. A. Davey's contribution was supported by PENR-2008–05011, PENR-2010–04643, R21CA158877, R01HD069769, R01CA158361, and R01AG13180. We thank Amanda Goodell and Rachael Torres, University of Maine, for reading and commenting on earlier versions of this manuscript.

DISCLOSURE

The authors declared no conflict of interest.

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