



ORIGINAL ARTICLE

Association between normal or mildly reduced kidney function, cardiovascular risk and biomarkers for atherosclerosis: results from the ENCORE trial

Crystal C. Tyson^{1,2}, Patrick J. Smith², Andrew Sherwood², Stephanie Mabe², Alan L. Hinderliter³ and James A. Blumenthal²

¹Department of Medicine, Duke University Medical Center, Durham, NC, USA, ²Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA and ³Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Correspondence and offprint requests to: Crystal C. Tyson; E-mail: cs206@dm.duke.edu

Abstract

Background: Moderate-to-severe kidney dysfunction is associated with atherosclerotic cardiovascular disease (ASCVD). Gradations of normal or mildly reduced kidney function may also associate with ASCVD risk.

Methods: We conducted a secondary analysis using baseline data from the Exercise and Nutritional Interventions for Cardiovascular Health (ENCORE) trial. Participants were sedentary, overweight and obese adults with unmedicated pre-hypertension or Stage I hypertension and an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m². The Pooled Cohorts Equations were used to estimate a 10-year risk for first ASCVD event. Carotid artery intima-media thickness (IMT) and brachial artery flow-mediated dilation (FMD) were measured to assess subclinical atherosclerosis and vascular endothelial function, respectively. Using linear regression, we examined the association between eGFR and ASCVD risk, IMT and FMD.

Results: Participants ($N = 139$) were predominantly women (65%), white (60%), with a mean age of 52.0 ± 9.6 years and mean eGFR of 89.1 ± 15.0 mL/min/1.73 m². Lower eGFR of 15 mL/min/1.73 m² was associated with higher ASCVD risk [$b = -2.7\%$ (95% confidence interval: $-3.7, -1.8\%$), $P < 0.001$], higher IMT [$b = 0.05$ mm (0.03, 0.08 mm), $P < 0.001$] and lower FMD [$b = -0.87\%$ ($-1.64, -0.11\%$), $P = 0.026$]. Compared with eGFR ≥ 90 mL/min/1.73 m², those with eGFR 60–89 mL/min/1.73 m² had higher mean ASCVD risk (7.6% versus 2.7%; $P < 0.001$), greater mean IMT (0.74 mm versus 0.66 mm; $P < 0.001$) and lower mean FMD (2.0% versus 3.7%; $P = 0.026$). After controlling for CVD risk factors, the association between eGFR and IMT remained significant ($P < 0.001$), and eGFR and FMD trended toward significance ($P = 0.08$).

Conclusions: Among overweight and obese adults with unmedicated high blood pressure and eGFR ≥ 60 mL/min/1.73 m², lower eGFR is associated with a greater 10-year risk for first ASCVD event, higher IMT and relatively impaired FMD.

Key words: cardiovascular risk, flow-mediated dilation, intima-media thickness, kidney function

Received: December 2, 2016. Editorial decision: March 3, 2017

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Introduction

Heart disease is the leading cause of death in adults with chronic kidney disease (CKD), largely caused by progressive coronary atherosclerosis [1]. For patients with CKD, the prevalence and severity of atherosclerotic cardiovascular disease (ASCVD) increases as kidney function declines, with the greatest risk for nonfatal and fatal ASCVD events occurring among those with end-stage kidney disease [2]. However, there is evidence that even minimally reduced kidney function may be associated with coronary atherosclerosis and cardiovascular events [3–5]. In a longitudinal, community-based cohort of 15 350 US adults 45–64 years old participating in the Atherosclerotic Risk in Communities (ARIC) study, the adjusted risk for CVD-related events was 16% higher for individuals with an estimated glomerular filtration rate (eGFR) between 60 and 89 mL/min/1.73 m² compared with those with an eGFR between 90 and 150 mL/min/1.73 m² [4]. Similarly, an analysis of 6354 participants of the Second National Health and Nutrition Examinations Survey Mortality Study demonstrated increasingly higher CVD mortality rates of 4.1, 8.6 and 20.5 deaths per 1000 person-years in adults with eGFR ≥90, 70–89 and <70 mL/min/1.73 m², respectively [5].

The purpose of the current study was to examine the relationship between kidney function, ASCVD risk and biomarkers for atherosclerosis among individuals with normal or mildly reduced kidney function. We used data from the Exercise and Nutritional Interventions for Cardiovascular Health (ENCORE) study, a randomized study that compared the effectiveness of the Dietary Approaches to Stop Hypertension (DASH) diet alone and the DASH diet combined with a behavioral weight loss program to lower blood pressure (BP) in sedentary, overweight or obese adults with unmedicated high BP and preserved kidney function [6]. In addition to completing baseline ASCVD risk assessments, structural and functional biomarkers for atherosclerosis were also assessed, including carotid artery intima-media thickness (IMT) and brachial artery flow-mediated dilation (FMD).

Materials and methods

Study design overview

Detailed descriptions of ENCORE trial methods and main results have been published previously [6]. Briefly, the ENCORE trial compared the effects of the DASH diet alone and the DASH diet combined with a behavioral weight loss program on BP, weight and CVD biomarkers compared with a usual diet control condition. The present study examined the relationship of eGFR with ASCVD risk and CVD biomarkers at baseline in a sample of 139 participants enrolled in the ENCORE trial. The study protocol was approved by Institutional Review Boards at Duke University and the University of North Carolina at Chapel Hill. All participants provided written informed consent.

Participants

ENCORE participants were sedentary adults aged 35 years or older, overweight or obese [body mass index (BMI) of 25.0–39.9 kg/m²], with no clinical history of coronary disease. All had a systolic blood pressure (SBP) 130–159 mmHg or diastolic blood pressure (DBP) 85–99 mmHg with no antihypertensive

medications. Participants with self-reported CKD were excluded. In the current study, we further excluded participants who met laboratory criteria for CKD based on eGFR <60 mL/min/1.73 m².

Assessments

Kidney function. A single measure of serum creatinine was performed at baseline prior to randomization. The CKD Epidemiology Collaboration (CKD-EPI) equation [7] was used to calculate eGFR. For purposes of the current study, ‘normal-high’ kidney function was defined as eGFR ≥90 mL/min/1.73 m² and ‘mildly decreased’ kidney function was defined as eGFR <90 mL/min/1.73 m² consistent with KDIGO 2012 Clinical Practice Guidelines [8].

Ten-year ASCVD risk. The Pooled Cohort Equations [9] were used to estimate participants’ 10-year risk for first occurrence of ASCVD event. An ASCVD event was defined as nonfatal myocardial infarction, nonfatal stroke and fatal cardiovascular disease event. Variables incorporated in this sex- and race-specific prediction model include age, systolic BP, total cholesterol, high-density lipoprotein cholesterol, current smoking and history of diabetes [9].

Because the ASCVD risk formula has only been validated among individuals aged 40–79 years, we eliminated individuals younger than 40 and older than 79 years from all ASCVD analyses.

Carotid artery IMT. IMT was measured using a high-resolution B-mode ultrasound vascular imaging system (Acuson Aspen, Mountain View, CA, USA) with a 10-MHz linear array transducer. Ultrasound examinations of the far wall of the left and right common carotid arteries (CCAs) were used to acquire longitudinal images spanning 2 cm proximal to the carotid bulb. IMT of the far wall of the left and right CCAs was measured over a 1-cm segment using edge detection software (Carotid Analyzer 5.0.5, Medical Imaging Applications LLC, Iowa City, IA, USA).

Brachial artery FMD. FMD was assessed using an Aspen Aspen ultrasound platform with a 11-MHz linear array transducer (Aspen). Participants relaxed in supine position for 10 min [10]. A forearm cuff was inflated to exceed SBP (~200 mmHg) for 5 min to induce reactive hyperemia. The distance between the proximal and distal arterial wall intima media interfaces were measured with PC-based software (Brachial Analyzer, version 4.0; Medical Imaging Applications LLC) to determine end-diastolic arterial diameters. FMD was defined as the maximum percentage change in arterial diameter relative to resting baseline from 10 to 120 s after deflation of the occlusion cuff.

Statistical analysis. All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and R 3.3.1 (<https://cran.r-project.org>). Standard descriptive statistics were performed to characterize the cohort. To determine the relationship between eGFR and CVD risk score, an unadjusted linear regression model was conducted. To determine the relationship between eGFR with IMT and FMD, both unadjusted and models adjusting for ASCVD risk factors, including clinic SBP, low-density lipoprotein/high-density lipoprotein

ratio, insulin sensitivity index, BMI and current smoking status (yes or no), were conducted. For separate linear regression models, ASCVD risk score and each biomarker served as the criterion variable with eGFR as the predictor of interest. None of the models was adjusted for demographic factors (i.e. age, sex and race), because these factors were incorporated in the calculation of eGFR. Because several variables (e.g. age, sex, SBP, total cholesterol, high-density lipoprotein, current smoking and history of diabetes) were used to calculate the ASCVD risk score, the model using ASCVD risk score as a criterion variable was not adjusted for ASCVD risk factors. In order to provide a more clinically meaningful interpretation of any observed associations, eGFR was scaled in 15 mL/min/1.73 m² increments. Results are reported as means and 95% confidence intervals (CIs) unless otherwise stated. For descriptive purposes, we also compared individuals with 'normal-high' kidney function to those with 'mildly decreased' kidney function in a set of secondary, explanatory analyses. Between-group differences were compared using t-test for continuous variables and chi-square test for categorical variables.

We evaluated the extent to which any of the observed associations were nonlinear using Harrell's restricted cubic spline function within R. We evaluated the extent to which models met assumptions, including additivity, linearity and distribution of residuals, and found no evidence of significant violations of these assumptions.

Results

Participant characteristics

Although ENCORE participants (N = 144) self-reported having normal kidney function, five were excluded from our analyses with an eGFR <60 mL/min/1.73 m² (i.e. range 53–59 mL/min/1.73 m²). Demographic and baseline characteristics of the remaining 139 participants included in our analyses are shown in Table 1. The sample was predominantly women (65%), white race (60%) and average age was 52.0 ± 9.6 years. Median eGFR was 89.1 mL/min/1.73 m².

Ten-year ASCVD risk and biomarkers for atherosclerosis

ASCVD risk score was determined only for participants whose age was in the validated range (N = 134). There was a strong positive correlation between ASCVD risk and IMT ($r = 0.40$, $P < 0.001$) and a moderate negative correlation between ASCVD risk and FMD ($r = -0.25$, $P = 0.008$). IMT and FMD were negatively correlated (N = 139; $r = -0.34$, $P < 0.001$).

Kidney function and 10-year ASCVD risk

The overall mean [± standard deviation (SD)] ASCVD risk was 5.4 ± 5.5%. There was a strong, inverse association between eGFR and ASCVD risk [$b = -2.7$ (-3.7, -1.8), $P < 0.001$], with a lower eGFR of 15 mL/min/1.73 m² corresponding to an approximate increase in ASCVD risk of 2.7% (Table 2). Participants with mildly decreased kidney function had higher mean ASCVD risk

Table 1. Demographic and clinical characteristics of included ENCORE trial participants by eGFR

	All (n=139)	Normal-high kidney function eGFR ≥90 (n=74)	Mildly decreased kidney function eGFR 60–89 (n=65)	P-value
Age, years	52.0 (9.6)	47.9 (7.0)	56.3 (10.2)	<0.001
Female gender, n (%)	94 (65)	56 (79)	32 (46)	0.001
Race, n (%)				
White	86 (60)	40 (54)	46 (66)	
Black	56 (39)	32 (43)	24 (34)	
Asian	2 (1)	2 (3)	0 (0)	0.21
Years of education	15.2 (2.6)	15.3 (2.5)	15.0 (2.7)	0.42
Annual household income, n (%)				
<\$25 000	21 (17)	13 (21)	8 (13)	
\$25 000–50 000	31 (25)	17 (27)	14 (23)	
\$50 000–100 000	44 (36)	21 (33)	23 (38)	
≥\$100 000	27 (22)	12 (19)	15 (25)	0.28
Weight, kg	94.0 (14.1)	94.2 (14.7)	93.9 (13.6)	0.84
BMI, kg/m ²	33.2 (3.9)	33.9 (4.1)	32.3 (3.5)	0.01
BP, mmHg				
Clinic SBP	137.7 (8.8)	136.5 (8.1)	139.0 (9.3)	0.08
Clinic DBP	85.5 (6.4)	87.0 (5.9)	84.0 (6.5)	<0.01
Serum creatinine, mg/dL	0.94 (0.17)	0.85 (0.12)	1.04 (0.16)	<0.01
eGFR, mL/min/m ²	89.1 (15.0)	99.9 (9.5)	77.3 (9.6)	<0.001
Fasting cholesterol, mg/dL	205 (40)	206 (41)	204 (38)	0.80
LDL cholesterol	126 (36)	125 (36)	127 (35)	0.83
HDL cholesterol	54 (14)	55 (15)	53 (14)	0.32
LDL/HDL ratio	2.45 (0.93)	2.37 (0.87)	2.54 (1.0)	0.27
Stumvoll ISI, μmol/kg/min/pM	0.089 (0.017)	0.086 (0.017)	0.092 (0.016)	0.05
Current smoker, %	12 (9)	7 (9)	5 (8)	0.71
ASCVD risk, %	5.0 (5.4) ^a	2.7 (2.7)	7.6 (6.5) ^a	<0.001 ^a
IMT mm	0.70 (0.15)	0.66 (0.11)	0.74 (0.17)	<0.01
FMD % dilated	2.9 (4.0)	3.7 (4.5)	2.0 (3.2)	0.03

Values indicate mean (SD) unless otherwise indicated.

LDL, low-density lipoprotein; HDL, high-density lipoprotein; ISI, insulin sensitivity index.

^aFor ASCVD risk analysis, total group N = 134 and mildly decreased kidney function group N = 65 after excluding five participants with age <40 or >79 years.

Table 2. Associations between eGFR scaled in 15 mL/min/1.73m² increments with 10-year ASCVD risk and biomarkers of atherosclerosis

	Unadjusted			Adjusted ^a		
	b	95% CI	P-value	b	95% CI	P-value
ASCVD risk score, % ^b	-2.7	-3.7, -1.8	<0.001			
IMT, mm ^c	-0.05	-0.03, -0.08	<0.001	-0.05	-0.02, -0.07	<0.001
FMD, % ^c	0.9	0.1, 1.6	0.026	0.69	-0.1, 1.5	0.081

^aModel adjusted for clinic SBP, low-density lipoprotein/high-density lipoprotein ratio, insulin sensitivity index, BMI and current smoking status.

^bN = 134.

^cN = 139.

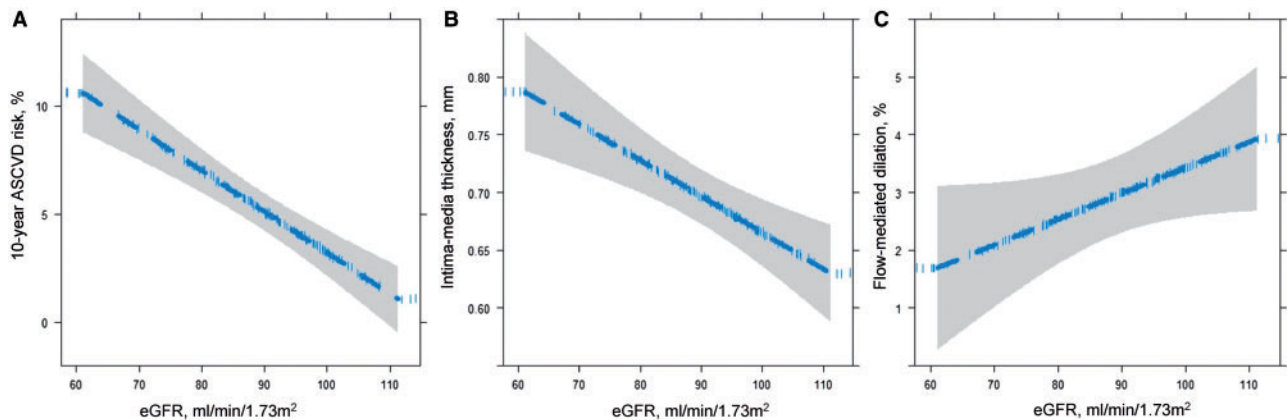


Fig. 1. Unadjusted correlates of eGFR with 10-year ASCVD risk (A), intima-media thickness (B) and flow-mediated dilation (C).

compared with participants with normal-high kidney function [8.0% (95% CI: 6.3, 9.6%) versus 3.0% (2.3, 3.7%); $P < 0.001$].

Kidney function and biomarkers for atherosclerosis

Carotid artery IMT. The mean (\pm SD) IMT for the total sample was 0.70 ± 0.15 mm. There was a significant inverse association between eGFR and IMT in both the unadjusted [$b = -0.05$ mm ($-0.08, -0.03$ mm), $P < 0.001$; Figure 1B] and adjusted models [$b = -0.05$ mm ($-0.02, -0.07$ mm), $P < 0.001$], with a lower eGFR of 15 mL/min/1.73 m² corresponding to 0.05 mm greater IMT (Table 2). Participants with mildly decreased kidney function had greater mean IMT compared with participants with normal-high kidney function [0.74 mm (0.70, 0.77 mm) versus 0.66 mm (0.63, 0.70 mm); $P < 0.001$].

Brachial artery FMD. The overall mean (\pm SD) FMD was $2.9 \pm 4.0\%$. There was a significant association between eGFR and FMD in the unadjusted model [$b = 0.87\%$ (0.11, 1.64%), $P = 0.026$; Figure 1C] and a trend toward significance in the model adjusted for ASCVD risk factors [$b = 0.69\%$ ($-0.09, 1.47\%$), $P = 0.08$], with a lower eGFR of 15 mL/min/1.73 m² corresponding to lower FMD of 0.9% and 0.7%, respectively (Table 2). Participants with mildly decreased eGFR had a lower mean FMD compared with participants with normal-high eGFR [2.0% (1.0, 3.0%) versus 3.7% (2.8, 4.7%); $P = 0.026$].

Post hoc analyses by age. Because age is an important determinant of both atherosclerosis and eGFR, we performed a post hoc analyses in which we considered eGFR and atherosclerotic biomarkers by age tertiles (35–45, 46–55, ≥ 56 years). Among middle-aged and older adults, we observed comparable associations

between eGFR with IMT (age 35–45: $b = -0.01$, age 46–55: $b = -0.07$, age ≥ 56 : $b = -0.08$), as well as between eGFR and FMD (age 35–45: $b = 0.38$, age 46–55: $b = 0.66$, age ≥ 56 : $b = 0.71$), suggesting that the observed associations between eGFR and atherosclerotic activity were not driven solely by increasing age.

Discussion

The relationship between kidney function and ASCVD risk is well established among individuals with CKD, with lower kidney function associating with more severe atherosclerosis and higher nonfatal and fatal ASCVD events [1, 2, 11]. The current study extends these findings by suggesting a similar relationship for individuals with mildly reduced or normal kidney function. In our sample of overweight and obese adults with high BP and eGFR ≥ 60 mL/min/1.73 m², we observed an inverse relationship between eGFR and estimated 10-year risk for first ASCVD event, suggesting that even mildly reduced eGFR is associated with higher CVD risk. This observation is further supported by our findings that lower eGFR was also associated with increased atherosclerosis as evidenced by greater IMT, and impaired endothelial function manifested by a lower FMD. Findings of the present study suggest that eGFR as a measure of kidney function may correlate with early atherosclerotic changes, and perhaps serve as a surrogate biomarker for subclinical atherosclerosis in individuals with normal or mildly reduced kidney function.

Our current findings are consistent with results from prior epidemiologic studies of adults with normal kidney function that observed eGFR values of ≥ 60 mL/min/1.73 m² to be associated with nonfatal and fatal ASCVD event rates [4, 5]. Despite mounting evidence supporting the prognostic value of eGFR to

predict CVD outcomes, markers of kidney function and/or the presence of CKD are not routinely included in ASCVD event prediction models. For example, during the development of the Pooled Cohorts Equations, which we used to estimate ASCVD risk in our sample, moderate or severe CKD (defined as $eGFR < 60 \text{ mL/min/1.73 m}^2$ based on the CKD-EPI equation [12]) was tested as a predictor in the final, base model. However, CKD was ultimately rejected because it did not significantly improve the model's discrimination for ASCVD events. Whether $eGFR$ as a continuous variable improved the accuracy of the ASCVD prediction model was not reported. Nonetheless, the common practice of excluding kidney function markers from ASCVD prediction models should not negate the important impact that kidney function has on the incidence of nonfatal ASCVD events and mortality.

IMT and FMD are structural and functional biomarkers of atherosclerosis that predict CVD events independent of traditional risk factors [13, 14]. A meta-analysis of eight population-based studies involving 37 000 subjects estimated that higher IMT of 0.1 mm was associated with higher age- and sex-adjusted relative risk for myocardial infarction and stroke of 15% and 26%, respectively [15]. With regards to FMD, a meta-analysis of 14 studies involving 5500 subjects observed that per 1% decrement in FMD, the pooled relative risk for cardiovascular events increased by 8% [14]. We observed a clinically relevant difference in both IMT and FMD between individuals with normal-high kidney function compared with mildly decreased kidney function.

Results of the present study overlap with a previous study that examined how serum cystatin C, which is an endogenous filtration marker for $eGFR$, related to estimated CVD risk (using the Framingham score), IMT and FMD in a cross-sectional study of 103 adults with hypertension and a mean measured creatinine clearance of $94.8 \pm 43.3 \text{ mL/min/1.73 m}^2$ [16]. Similar to our study, the investigators found that higher CVD risk was associated with poorer kidney function, and also found a strong, inverse association between IMT and FMD. In contrast to the present findings, however, they did not observe kidney function to be associated with IMT or FMD. There are important differences in the demographic and clinical characteristics of the respective samples. Compared with our sample of US adults, participants in the study conducted by Monteiro Junior et al. were Brazilian, older in age (57 versus 52 years), predominantly non-white (64% versus 40%), treated with anti-hypertensive medications and had higher clinic SBPs (145 versus 137 mmHg). The cohort also included patients with diabetes (16% versus 0%) and creatinine clearance $< 60 \text{ mL/min/1.73 m}^2$ (18% versus 0%), and had a higher mean IMT (1.09 mm versus 0.70 mm) [16]. Results from other studies examining how serum cystatin C relates to IMT and/or FMD have been inconsistent [17–19].

The larger sample size in ENCORE and our use of $eGFR$ as a marker of kidney function instead of cystatin C alone may have contributed to our positive study findings. Using $eGFR$ as a measure of kidney function allowed us to first account for demographic factors that influence the development and progression of atherosclerosis (i.e. age, sex and race) in the context of kidney function prior to examining the relationship between kidney function and subclinical atherosclerosis. Our findings that the relationship between $eGFR$ and biomarkers for atherosclerosis tended to remain significant after adjusting for traditional CVD risk factors, and was comparable in magnitude for the middle and older aged tertiles, suggest that $eGFR$ may be

independently associated with subclinical atherosclerosis for individuals with mildly reduced or normal kidney function.

There is good reason to believe that $eGFR$ is a biomarker for subclinical atherosclerosis in individuals without CKD. Glomerulosclerosis, which is chronic scarring of glomerular capillaries, has been likened to atherosclerosis [20]. Pathologic changes that ultimately cause IMT, intraluminal narrowing and diffuse stiffening of large- and medium-size arteries (i.e. atherosclerosis) throughout the vascular system not only affect the renal arteries but have also been reported to induce lipoprotein-mediated inflammation and injury in glomerular capillaries [21]. Injured glomerular cells share similar features with cells of atherosclerotic vessels [21]. The measurement of $eGFR$, in part, reflects the integrity of glomerular capillaries and subtle changes in $eGFR$ may suggest early atherosclerotic activity. Additional studies are needed to establish the relationship between kidney function, subclinical atherosclerosis and risk for ASCVD events among individuals without CKD.

A strength of the current study is the concurrent measurement of IMT and FMD in a single cohort, which provided objective evidence that atherosclerotic markers were more pronounced at lower ranges of $eGFR$ in individuals with preserved kidney function. Our study has several limitations. A single measurement of serum creatinine and use of creatinine-based $eGFR$, rather than cystatin C-based $eGFR$, is a less than optimal measure of kidney function for individuals without known kidney disease. However, our findings are consistent with other studies that have demonstrated a relationship between creatinine-based $eGFR$ and cardiovascular outcomes [4, 5]. Another limitation is our inability to determine the CKD status of our participants, which requires quantification of urine protein. Urine albumin excretion rates were not measured, which prevented detection of mild CKD and the ability to examine how albuminuria relates to biomarkers of atherosclerosis. Because albuminuria is an independent risk factor for CVD and mortality [22–24], it will be important for future studies to examine the relationship between urine albumin excretion rates and biomarkers for atherosclerosis. Nontraditional cardiovascular risk factors that are of particular relevance in CKD, such as serum albumin, phosphorus, parathyroid hormone and vitamin D, were not measured in ENCORE participants. Although we suspect that our participants, who had preserved $eGFR$ s ($\geq 60 \text{ mL/min/1.73 m}^2$), had normal or mildly abnormal values for these nontraditional risk factors, our inability to determine their impact on results is a limitation. A further limitation is that as an index of atherosclerosis, our measurement of carotid IMT is less robust than carotid intima-media area, which also incorporates carotid lumen diameter and provides a more complete index of atherosclerotic disease activity that is more resistant to potential effects of changes in arterial pressure [25, 26]. Because age affects both kidney function and atherosclerosis, another potential limitation was our inability to eliminate the contribution of age to the relationship between $eGFR$ and atherosclerotic biomarkers. However, our *post hoc* analyses by age tertiles demonstrated a comparable relationship between kidney function and atherosclerotic biomarkers for the middle and older age groups with $eGFR$ associating with increased atherosclerotic activity, suggesting that the observed associations were not simply a result of older age.

It is well established that kidney function is associated with ASCVD risk and atherosclerosis among individuals with CKD. We showed that normal or mildly reduced $eGFR$ is associated with ASCVD risk and biomarkers for atherosclerosis even among

individuals with preserved kidney function. This suggests that subtle impairments in kidney function, measured by eGFR, may be indicative of increased atherosclerotic activity among overweight and obese adults with high BP.

Funding

This work was supported, in part, by grants HL074103 and HL122836 from the National Heart, Lung, and Blood Institute, and grant M01-RR-30 from the General Clinical Research Center, National Institutes of Health. C.C.T. was also supported by grant HL122836-01A1S1 from the National Heart, Lung, and Blood.

Conflict of interest statement

None declared.

References

- Thompson S, James M, Wiebe N et al. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol* 2015; 10: 2504–2511
- Chonchol M, Whittle J, Desbien A et al. Chronic kidney disease is associated with angiographic coronary artery disease. *Am J Nephrol* 2008; 28: 354–360
- Reis SE, Olson MB, Fried L et al. Mild renal insufficiency is associated with angiographic coronary artery disease in women. *Circulation* 2002; 105: 2826–2829
- Manjunath G, Tighiouart H, Ibrahim H et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003; 41: 47–55
- Muntner P, He J, Hamm L et al. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 2002; 13: 745–753
- Blumenthal JA, Babyak MA, Hinderliter A et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Arch Intern Med* 2010; 170: 126–135
- Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Inter* 2013; 3 (Suppl 3): 1–150
- Goff DC, Lloyd-Jones DM, Bennett G et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2935–2959
- Celermajer DS, Sorensen KE, Gooch VM et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992; 340: 1111–1115
- United States Renal Data System. 2015 USRDS annual data report: Epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2015
- Levey AS, Bosch JP, Lewis JB et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470
- Simon A, Gariepy J, Chironi G et al. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. *J Hypertens* 2002; 20: 159–169
- Yeboah J, Folsom AR, Burke GL et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation* 2009; 120: 502–509
- Lorenz MW, Markus HS, Bots ML et al. Prediction of clinical cardiovascular events with carotid intima-media thickness - a systematic review and meta-analysis. *Circulation* 2007; 115: 459–467
- Monteiro Junior F, Ferreira PA, Nunes JA et al. Correlation between serum cystatin C and markers of subclinical atherosclerosis in hypertensive patients. *Arq Bras Cardiol* 2012; 99: 899–906
- Potter K, Hankey GJ, Green DJ et al. Homocysteine or renal impairment: which is the real cardiovascular risk factor? *Arterioscler Thromb Vasc Biol* 2008; 28: 1158–1164
- Watanabe S, Okura T, Liu J et al. Serum cystatin c level is a marker of end-organ damage in patients with essential hypertension. *Hypertens Res* 2003; 26: 895–899
- Rodondi N, Yerly P, Gabriel A et al. Microalbuminuria, but not cystatin C, is associated with carotid atherosclerosis in middle-aged adults. *Nephrol Dial Transplant* 2007; 22: 1107–1114
- Chade AR, Lerman A, Lerman LO. Kidney in early atherosclerosis. *Hypertension* 2005; 45: 1042–1049
- Wheeler DC, Chana RS. Interactions between lipoproteins, glomerular cells and matrix. *Miner Electrolyte Metab* 1993; 19: 149–164
- Gerstein HC, Mann JF, Yi Q et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286: 421–426
- Ljungman S, Wikstrand J, Hartford M et al. Urinary albumin excretion—a predictor of risk of cardiovascular disease. A prospective 10-year follow-up of middle-aged nondiabetic normal and hypertensive men. *Am J Hypertens* 1996; 9: 770–778
- Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. *Arch Intern Med* 1997; 157: 1413–1418
- Guerin AP, Marchais SJ, Metivier F et al. Arterial structural and functional alterations in uraemia. *Eur J Clin Invest* 2005; 35 (Suppl 3): 85–88
- Henareh L, Jogestrand T, Agewall S. Microalbuminuria in patients with previous myocardial infarction. *Kidney Int* 2006; 69: 178–183