Metabolic Syndrome, Components, and Cardiovascular Disease Prevalence in Chronic Kidney Disease: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

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Key Words

Cardiovascular disease · Chronic kidney disease · Chronic Renal Insufficiency Cohort (CRIC) Study · Metabolic syndrome

Abstract

Background/Aims: Metabolic syndrome may increase the risk for incident cardiovascular disease (CVD) and all-cause mortality in the general population. It is unclear whether, and to what degree, metabolic syndrome is associated with CVD in chronic kidney disease (CKD). We determined metabolic syndrome prevalence among individuals with a broad spectrum of kidney dysfunction, examining the role of the individual elements of metabolic syndrome and their relationship to prevalent CVD. **Methods:** We evaluated four models to compare metabolic syndrome or its compo-

nents to predict prevalent CVD using prevalence ratios in the Chronic Renal Insufficiency Cohort (CRIC) Study. **Results:** Among 3,939 CKD participants, the prevalence of metabolic syndrome was 65% and there was a significant association with prevalent CVD. Metabolic syndrome was more common in diabetics (87.5%) compared with non-diabetics (44.3%). Hypertension was the most prevalent component, and increased triglycerides the least prevalent. Using the bayesian information criterion, we found that the factors defining metabolic syndrome, considered as a single interval-scaled variable, was the best of four models of metabolic syndrome, both for CKD participants overall and for diabetics and non-diabetics separately. **Conclusion:** The predictive value of this model for future CVD outcomes will subsequently be validated in longitudinal analyses.

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Introduction

Prospective cohort studies report a higher incidence of cardiovascular disease (CVD) or mortality among patients with chronic kidney disease (CKD) [1–3]. For example, Go et al. [1] reported a progressive increase in the hazard ratios for CVD events using the estimated glomerular filtration rate (eGFR) beginning with values of 45–59, and ending with values of <15 ml/min/1.73 m² in a large, community-based population. Similarly, in the Cardiovascular Health Study the presence of CKD doubled the CVD mortality risk in a cohort of 5,808 older subjects [2] and demonstrated that even early decrements in kidney function, where eGFR was >60 ml/min/1.73 m², assessed by cystatin C, were predictive of CVD [4]. Although it is not clear what contributes to such increased cardiovascular risk in patients with CKD, identifying the underlying risk factors associated with CVD among CKD patients could help to develop effective approaches for early screening and intervention in order to reduce the adverse CVD outcomes.

Metabolic syndrome, characterized by abdominal obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, elevated blood pressure (BP), and elevations in fasting glucose or diabetes, has been associated with an increased risk for the development of CVD as well as increased mortality from both CVD and all causes in the general population [5, 6]. Recent meta-analyses found that the metabolic syndrome increases the risk for incident CVD (relative risks (RRs) ranging from 1.53 to 2.18) and all-cause mortality (RR 1.27–1.60) in the general population [7–9]. Metabolic syndrome is common in patients with CKD and an important risk factor for development and progression of CKD [10, 11]. However, it is unclear whether metabolic syndrome predicts CVD in CKD. In this study, we examined the metabolic syndrome among individuals with a broad spectrum of kidney dysfunction, evaluating the syndrome itself compared with its individual elements and their relationship to prevalent CVD among participants of the Chronic Renal Insufficiency Cohort (CRIC) Study [12].

Methods

Study Population

The CRIC Study population includes a racially and ethnically diverse group of men and women aged 21–74 years with mild-to-moderate renal disease, 46% of whom have diabetes mellitus. CRIC participants were recruited between May 2003 and August

2008 from seven centers in the United States [12]. Patients were identified through laboratory database searches of recently measured serum creatinine values, referrals from physicians' offices, and self-referral. Patients with cirrhosis, HIV infection, polycystic kidney disease, renal cell carcinoma, a kidney transplant or on dialysis, or taking immunosuppressant drugs were excluded. Age-specific eGFR levels were used to define inclusion into the CRIC cohort: eGFR of 20–70 ml/min/1.73 m² for patients aged 21–44 years, 20–60 ml/min/1.73 m² for ages 45–64 years, and 20–50 ml/min/1.73 m² for ages 65–74 years. The current analysis is based on the experience of the 3,939 CRIC participants who completed the baseline study visit.

Data Collection

During the baseline study visit, all CRIC study data were collected by trained study staff using procedures and equipment that were standardized across study sites. A baseline medical history questionnaire was administered in which participants were queried about prior history of CVD. Responses to these questions were used to identify prevalent CVD. Participants were asked: 'Have you ever been diagnosed with, or has a doctor or other health professional ever told you that, you have "coronary artery disease (heart attack, angina), prior revascularization of your heart blood vessels (e.g. balloon angioplasty, coronary stenting, coronary bypass surgery)"?' For these analyses, coronary artery disease was defined as an affirmative response to questions about either coronary artery disease or prior coronary revascularization. Separate questions queried about a history of heart failure, stroke or transient ischemic attack, or peripheral vascular disease (including claudication, amputation or angioplasty). Questionnaires also assessed demographic characteristics. Body weight and height were each measured twice and averaged for analysis. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the uppermost lateral border of the ilium with a Gulick II tape measure and repeated until two measures agreed within 1 cm. Three BP measurements were obtained in the sitting position after at least 5 min of quiet rest by trained and certified staff according to a standard protocol using an aneroid sphygmomanometer and averaged to calculate systolic BP (SBP) and diastolic BP (DBP). The BP criterion for metabolic syndrome was defined as either a SBP ≥ 130 mm Hg, DBP ≥ 85 mm Hg, or current anti-hypertensive medication use. Plasma glucose, HDL cholesterol and serum triglycerides were measured by standard laboratory methods. Diabetes mellitus was defined as a plasma glucose ≥ 126 mg/dl after fasting for a minimum of 8 h and/or self-reported current use of antidiabetes medication. Finally, serum creatinine was measured by the modified kinetic Jaffe reaction and re-calibrated in order to calculate eGFR using the Modification of Diet in Renal Disease study equation.

Metabolic syndrome was defined using recent ATP-III guidelines [13] as the presence of at least three of the following five criteria: (1) history of hypertension, SBP >130 mm Hg, or DBP >85 mm Hg, (2) history of diabetes mellitus or elevated plasma glucose (≥ 100 mg/dl), (3) waist circumference >102 cm for men and >88 cm for women, (4) triglycerides ≥ 150 mg/dl, and (5) HDL <40 mg/dl for men and <50 mg/dl for women. A metabolic syndrome score (Metscore) was computed by adding the number of metabolic syndrome components present.

Table 1. Demographics of those with and without metabolic syndrome (MS)

Characteristic	MS present	MS absent	Totals	p value
Number of participants	2,568 (65%)	1,371 (35%)	3,939	–
Age, years	58.9 ± 10.5	56.8 ± 11.8	58.2 ± 11.0	<0.0001
Male gender	1,391 (54.4%)	769 (55.7%)	2,160 (54.8%)	0.3752
Race				<0.0001
Non-Hispanic White	968 (37.8%)	670 (48.5%)	1,638 (41.6%)	
Non-Hispanic Black	1,115 (43.6%)	536 (38.8%)	1,651 (41.9%)	
Hispanic	381 (14.9%)	115 (8.3%)	496 (12.6%)	
Other	94 (3.7%)	60 (4.3%)	154 (3.9%)	
Diabetes (present)	1,666 (65.1%)	241 (17.5%)	1,907 (48.4%)	<0.0001
eGFR, ml/min/1.73 m ²	41.3 ± 13.0	45.6 ± 14.0	42.8 ± 13.5	<0.0001
Height, cm	168.7 ± 9.9	169.0 ± 9.4	168.8 ± 9.7	0.4715
Weight, kg	98.1 ± 22.9	79.3 ± 19.0	91.5 ± 23.4	<0.0001
BMI	34.4 ± 7.6	27.7 ± 6.2	32.1 ± 7.8	<0.0001
Waist circumference, cm	111.7 ± 16.3	94.8 ± 14.3	105.8 ± 17.6	<0.0001
Number with waist circumference qualifying for MS	2,140 (84.3%)	458 (34.1%)	2,598 (66.9%)	<0.0001
SBP, mm Hg	131.1 ± 22.1	123.6 ± 21.6	128.5 ± 22.2	<0.0001
DBP, mm Hg	71.4 ± 12.9	72.0 ± 12.7	71.6 ± 12.8	0.1110
Number with BP qualifying for MS	2,441 (95.1%)	1,011 (73.7%)	3,452 (87.6%)	<0.0001
Glucose, mg/dl	125.1 ± 54.6	97.2 ± 39.8	115.4 ± 51.7	<0.0001
Number with glucose qualifying for MS	2,039 (79.4%)	309 (22.5%)	2,438 (59.6%)	<0.0001
Serum creatinine, mg/dl	1.8 ± 0.6	1.7 ± 0.6	1.7 ± 0.6	<0.0001
Triglyceride, mg/dl	185.5 ± 131.2	104.2 ± 47.5	157.3 ± 116.3	<0.0001
Number with triglycerides qualifying for MS	1,376 (53%)	126 (9.2%)	1,502 (38.1%)	<0.0001
LDL, mg/dl	100.2 ± 36.2	106.9 ± 33.4	102.5 ± 35.4	<0.0001
HDL, mg/dl	42.8 ± 12.2	56.4 ± 17.0	47.5 ± 15.5	<0.0001
Number with HDL qualifying for MS	1,728 (67.3%)	231 (16.8%)	1,959 (49.7%)	<0.0001
Presence of any CVD	979 (38.1%)	337 (24.6%)	1,316 (33.4%)	<0.0001

Data are expressed as mean ± SD for continuous variables and as percentages for categorical variables.

This study was approved by the Institutional Review Boards for each of the participating centers and the Scientific and Data Coordinating Center (University of Pennsylvania) and written informed consent was obtained from all participants. This study also conformed to the Health Insurance Portability and Accountability Act (HIPAA) guidelines.

Statistical Methods

Baseline characteristics and measures were summarized as means [standard deviation (SD)] for continuous variables and as percentages for categorical variables overall and by metabolic syndrome status. The prevalence of metabolic syndrome and metabolic syndrome score categories (0–5) were calculated overall and by age, gender, race/ethnicity, and eGFR category (<45, 45–59 and ≥60 ml/min/1.73 m²). The prevalence of CVD at baseline was summarized across metabolic syndrome status and scores with differences assessed using the χ^2 test. Next, prevalence ratios (PRs) adjusted for age, race/ethnicity, gender and eGFR were calculated using log binomial regression models. PRs are recommended, in lieu of odds ratios, for cross-sectional studies with common outcomes [14], and are calculated by determining the ratio of the {probability of disease present and exposure present} divided by the {probability of disease present when exposure is absent}. Anal-

ysis of Metscore as a class variable meant treating the number of components of metabolic syndrome being present (1–5, except that in the case of diabetes, 2–5, because everyone with diabetes has at least 1 component) and compared the PR for CVD at each level to the referent level of 0 components of metabolic syndrome (non-diabetics) and 1 component of metabolic syndrome (for the diabetics). The final multivariable-adjusted models were stratified by gender, race/ethnicity, eGFR and gender/race/ethnicity subgroups. We used the bayesian information criterion (BIC) to compare model fits. The BIC is calculated by regression software and equals the model deviance plus a penalty proportional to the number of parameters in the regression model and to the logarithm of the number of observations; model selection using BIC tends to produce parsimonious models. All analyses were conducted using SAS 9.2 (SAS Inc., Cary, N.C., USA).

Results

Characteristics of CRIC participants by metabolic syndrome status are provided in table 1. About two-thirds of the CRIC participants (65%) qualified for the

Table 2. Metabolic syndrome components frequency in CRIC – all participants, and by diabetic status

Metabolic syndrome score	All participants		Diabetes present (n = 1,907)		Diabetes absent (n = 2,032)	
	n	%	n	%	n	%
0	101	2.56			101	4.97
1	405	10.3	24	1.26	381	18.8
2	865	22.0	213	11.2	652	32.1
3	1,110	28.2	601	31.5	509	25.0
4	896	22.7	592	31.0	304	15.0
5	562	14.3	477	25.0	85	4.18

Table 3. Breakdown of metabolic syndrome component frequency

Metabolic syndrome score	Metabolic syndrome component, %				
	elevated glucose	increased waist circumference	low HDL BP	increased BP	increased triglycerides
<i>All participants</i>					
0	0.0	0.0	0.0	0.0	0.0
1	6.9	14.9	10.6	64.0	4.0
2	32.5	47.1	21.7	86.9	12.7
3	66.4	73.0	41.5	92.5	28.0
4	82.6	88.2	78.7	95.1	56.1
5	100	100	100	100	100
<i>Diabetics</i>					
0	–	–	–	–	–
1	100	0.0	0.0	0.0	0.0
2	100	9.3	2.8	86.9	1.4
3	100	72.3	22.3	93.0	14.3
4	100	86.0	75.0	94.3	45.6
5	100	100	100	100	100
<i>Non-diabetics</i>					
0	0.0	0.0	0.0	0.0	0.0
1	1.0	15.8	11.3	68.0	4.2
2	10.4	59.2	27.9	87.0	16.4
3	26.7	73.8	64.2	91.9	44.2
4	48.7	92.4	85.9	96.7	76.6
5	100	100	100	100	100

diagnosis of metabolic syndrome. The race/ethnicity distribution of participants differed across those with and without metabolic syndrome, with fewer non-Hispanic Whites as well as more non-Hispanic Blacks and Hispanics meeting the criteria for the syndrome. Most characteristics itemized in table 1 were significantly different in

Fig. 1. Pie charts showing prevalence of metabolic syndrome in CKD in participants without (upper row) or with (lower row) diabetes. Each row is divided into three eGFR ranges, as labeled. Those with <3 metabolic syndrome components are the white slices beginning at the 12 o'clock position going counterclockwise. The next slices, continuing counterclockwise, represent 3, 4 or all 5 metabolic syndrome components.

those with compared with those without metabolic syndrome, except for DBP and height.

Table 2 shows the distribution of metabolic syndrome components among CRIC participants. Fewer than 3% of the CRIC participants had no metabolic syndrome component and nearly 15% of the CRIC participants had all 5 components. When broken down by diabetes status, 87.5% of our participants with diabetes and 44.3% of our non-diabetic participants had metabolic syndrome. Figure 1 presents the prevalence of metabolic syndrome by diabetes and kidney function status, showing the substantial prevalence of 3 or more components in participants with diabetes and CKD.

Table 3 shows, by the total number of metabolic syndrome components present, the distribution of the metabolic syndrome components. The most common component was the presence of a BP >130/85 mm Hg or use of antihypertensive medications. The least common component was a serum triglyceride concentration >150 mg/dl.

Table 4 compares the PR of any CVD for a diagnosis of metabolic syndrome and for each of the individual com-

Table 4. Adjusted¹ models of PRs of metabolic syndrome and presence of any CVD

Model No.	Model characteristic	All participants	p value	Diabetics (only)	p value	Non-diabetics (only)	p value
1	Metabolic syndrome	1.16 (1.04–1.30)	0.0087	1.08 (0.91–1.28)	0.3544	1.22 (1.06–1.42)	0.0063
2	Metscore 1 (class)	1.45 (0.76–2.77)	<0.0001	referent		1.24 (0.65–2.38)	0.0007
	Metscore 2	1.93 (1.03–3.59)	–	0.82 (0.47–1.42)	0.0138	1.69 (0.90–3.16)	–
	Metscore 3	1.91 (1.03–3.56)	–	0.80 (0.47–1.35)	–	1.77 (0.94–3.32)	–
	Metscore 4	2.25 (1.21–4.19)	–	0.98 (0.58–1.66)	–	1.83 (0.97–3.46)	–
	Metscore 5	2.26 (1.21–4.22)	–	0.94 (0.55–1.59)	–	2.52 (1.30–4.88)	–
3	Metscore (continuous)	1.09 (1.05–1.14)	<0.0001	1.07 (1.01–1.12)	0.0152	1.14 (1.07–1.21)	<0.001
4	Glucose	1.18 (1.01–1.39)	<0.0471	–	–	1.10 (0.94–1.29)	0.2606
	HDL cholesterol	1.20 (1.10–1.31)	<0.0001	1.25 (1.12–1.40)	<0.0001	1.12 (0.96–1.30)	0.1487
	Hypertension	1.10 (0.91–1.32)	0.3059	0.80 (0.67–0.95)	0.0238	1.69 (1.22–2.34)	0.0005
	Triglycerides	0.98 (0.90–1.07)	0.7238	0.96 (0.86–1.07)	0.4601	1.04 (0.88–1.22)	0.6474
	Waist circumference	1.08 (0.97–1.19)	0.1559	1.04 (0.91–1.18)	0.5677	1.19 (1.01–1.39)	0.0338

¹ Models adjusted for age, gender, ethnicity, eGFR and clinical site; data are 'mean (95% confidence intervals)'.

Table 5. BIC statistic for the four models of the relationship of metabolic syndrome and its components to prevalent CVD

Model No.	BIC statistic		
	all participants	diabetics (only)	non-diabetics (only)
Covariates ¹ only	4,576.4	2,534.1	2,133.9
1 Metabolic syndrome (binary)	4,577.8	2,540.8	2,134.1
2 Metabolic syndrome (class)	4,589.0	2,551.7	2,150.7
3 Metabolic syndrome as a score (continuous)	4,564.2	2,535.7	2,124.9
4 Metabolic syndrome components (binary subcomponents of metabolic syndrome definition)	4,588.9	2,540.0	2,146.8

¹ Age, race, sex, eGFR, and clinical site.

ponents of metabolic syndrome separately. In addition, these relationships were stratified by the presence or absence of diabetes. Four models of metabolic syndrome are presented. In model 1, metabolic syndrome is treated as a dichotomous variable (yes or no). Interestingly, the PR for CVD of non-diabetics with metabolic syndrome was actually higher than that of diabetics with metabolic syndrome. In model 2, metabolic syndrome is treated as a class variable. The statistical comparisons are the individual Metscore values to a value of 0. The indicated p values are for the overall model, showing some predictive potential overall, but little or no significant prediction in the

diabetic or non-diabetic subgroups. In model 3, metabolic syndrome score was treated as a single interval-scaled variable. This model showed the best prediction (table 5). In model 3, we observed that each increment in the number of metabolic syndrome factors present increased the PR for CVD by 9%. In model 4, we examined metabolic syndrome by the individual components of the definition of metabolic syndrome in a binary fashion. This model performed well in the non-diabetics but not as well in the diabetics. Of note, in the diabetics, the hypertension criterion (BP >130/85 mm Hg or on antihypertensive medications) had a PR that appeared protective against CVD.

In table 5, we present the results of four models of metabolic syndrome testing the model fit characteristics using the BIC, where smaller values indicate a better fit. BIC substantially penalizes more complex models, as is appropriate in coming up with simple models for clinical use. Thus, some variables with statistically significant associations with outcome were not included. The best fit appeared to be model 3 which treated metabolic syndrome as a single interval-scaled variable taking on values of 1 through 5.

Discussion

Our data present four important findings derived from a large diverse population of participants with CKD. The first finding is the high prevalence of metabolic syndrome in CKD. Nearly 2 out of 3 participants (65%) in the CRIC Study satisfy the ATP-III diagnostic criteria for metabolic syndrome, with a noteworthy proportion (44.3%) of participants without diabetes fulfilling metabolic syndrome criteria. Such a high proportion of metabolic syndrome in diabetics (87% in the current study) was also noted by Alexander et al. [15] in the NHANES-III population. Reported prevalence of metabolic syndrome in the USA has been increasing, in step with the growing problem of obesity. In recent studies, the metabolic syndrome prevalence in adults in the USA increases with age and ranges from 22 to 35% [10, 16, 17]. Even in the absence of diabetes, the prevalence of metabolic syndrome in our CKD population is nearly twice as high as in other recently reported cohorts. The recently reported association between metabolic syndrome and decline in kidney function with more components of the syndrome showing a greater decline underscores the clinical importance of this finding. In the Atherosclerosis Risk in Communities (ARIC) Study, those with all 5 metabolic syndrome components had a nearly 2.5-fold higher odds of developing CKD compared with no components during a 9-year follow-up [18]. The mechanism by which metabolic syndrome participates in accelerating the loss of kidney function may be through hyperfiltration, supported by studies such as that of Chagnac et al. [19], which demonstrated a greater degree of hyperfiltration in subjects with severe obesity compared with similar aged controls. In addition, elevated insulin concentrations, a consequence of the insulin resistance thought to underlie the metabolic syndrome, is another potential mediator by increased renal blood flow through its vasodilatory effects on the kidney circulation [20].

Secondly, there is substantial variability in the prevalence of the individual components of the metabolic syndrome with elevated BP present more than twice as often as elevated triglyceride levels. Non-CKD populations like NHANES [15] show a higher prevalence of elevated triglyceride concentration, but similar prevalence in waist circumference, HDL and BP criterion.

Third, metabolic syndrome was associated with prevalent CVD at enrollment into CRIC overall, but it improves model fit as measured by BIC only among those without diabetes when stratified for this. This latter point is particularly noteworthy and suggests that perhaps the designation of metabolic syndrome is less important than understanding the individual risk factors present among CKD patients with diabetes.

Lastly our data show that simply counting up the number of metabolic syndrome components (i.e. 1–5 components being present in any individual) showed the best model characteristics as evaluated using the BIC compared with the presence of metabolic syndrome or the individual components of it. This suggests that dichotomization into a binary diagnosis of metabolic syndrome unnecessarily reduces information for predicting CVD. While the use of the score or its individual components may somewhat improve prediction, this comes at a price of increased model complexity and difficulty of interpretation and use which may not be warranted in many clinical settings.

The metabolic syndrome was described to characterize cardiovascular risk capitalizing on the well-known finding that CV risk factors tend to ‘cluster’ in individuals with upper body obesity [21]. In recent years, the association of metabolic syndrome with CVD has been called into question by arguments that cast doubt on its value in CVD risk recognition since the components alone appear to be equally predictive [22]. As depicted in table 4, the only individual component with a stronger association with prevalent CVD among participants without diabetes as assessed by the adjusted PR was hypertension, which was present in 87.6% of our participants. The presence of hypertension doubles the likelihood of having metabolic syndrome when compared to the general non-hypertensive population and metabolic syndrome in hypertensives generally heightens the risk of CVD [23]. Our data showed that hypertension appeared to be ‘protective’ from CVD in the diabetics with metabolic syndrome. Although this at first seems counterintuitive, it may be that those with diabetes and increased BP were treated earlier and more aggressively compared to those diabetics without a diagnosis of hypertension with drugs blocking the

renin-angiotensin system. Sixty-seven percent of the diabetics without metabolic syndrome reported taking an ACE inhibitor or an angiotensin receptor blocker, while 80% of the diabetics with metabolic syndrome were treated with these drugs in CRIC. Each of these drug classes has an agent with an indication for high cardiovascular risk ('Expanded indication for Telmisartan FDA' <http://www.theheart.org/article/1014115.do> and 'Ramipril FDA approval for high CV risk' <http://www.pslgroup.com/dg/1e36a6.htm> both accessed January 11, 2011). In addition, the dialysis experience also somewhat paradoxically suggests that lower BPs are associated with a greater risk of cardiovascular death [24].

Our findings regarding metabolic syndrome in CKD add to the literature, given the large size of our CKD population, about half of whom were diabetic and about half of whom were African-American. We acknowledge several limitations including the cross-sectional nature of the analyses and the self-report of prevalent CVD.

In summary, we observed a high prevalence of metabolic syndrome in a population of subjects all of whom

have CKD compared to that reported in the general population without diabetes. Hypertension was the component most often present in our CKD population fulfilling the criteria for metabolic syndrome. The presence of metabolic syndrome was associated with a significant PR for CVD at enrollment into the CRIC study, but only among those without diabetes. The longitudinal nature of the CRIC study provides an ideal setting to determine prospectively the predictive value of metabolic syndrome, compared to individual components, both on kidney function decline and on worsening of existing CVD and incident cardiovascular outcomes in an already high-risk population, those with established CKD.

Acknowledgments

This work was supported by NIH grants U01-DK-060984 and UL1-RR-024134. R.R.T. was funded by a grant from NIH/NIDDK.

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Erratum

In reference to the manuscript entitled 'Metabolic Syndrome, Components, and Cardiovascular Disease Prevalence in Chronic Kidney Disease: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study' by Townsend et al. [Am J Nephrol 2011;33:477–484], the following grant acknowledgments were inadvertently omitted by the authors: (a) University of Pennsylvania Scientific & Data Coordinating Center U01DK060990; (b) The Johns Hopkins University UL1 RR-025005; (c) University of Maryland GCRC M01 RR-16500; (d) Case Western Reserve University Clinical and Translational Science Collaborative (University Hospitals of Cleveland, Cleveland Clinic Foundation, and Metro-Health) UL1 RR-024989; (e) University of Michigan M01 RR-000042 and UL1 RR-024986; (f) University of Illinois at Chicago CTSA UL1RR029879; (g) Tulane/LSU/Charity Hospital General Clinical Research Center RR-05096, and (h) Kaiser NIH/NCRR UCSF-CTSI UL1 RR-024131.