Diabetes, Kidney Disease, and Cardiovascular Outcomes in the Jackson Heart Study

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Abstract

Background and objectives Blacks have high rates of cardiovascular disease and mortality. Diabetes and CKD, risk factors for cardiovascular mortality in the general population, are common among blacks. We sought to assess their contribution to cardiovascular disease and mortality in blacks.

Design, setting, participants, & measurements This observational cohort study was of 3211 participants in the Jackson Heart Study (enrolled 2000–2004). Rates of incident stroke, incident coronary heart disease, and cardiovascular mortality were quantified in participants with diabetes, CKD (eGFR<60 ml/min per 1.73 m^2, urine albumin-to-creatinine ratio ≥30 mg/g, or both), or both through 2012, with a median follow-up of 6.99 years.

Results Four hundred fifty-six (14.2%) participants had only diabetes, 257 (8.0%) had only CKD, 201 (6.3%) had both, and 2297 (71.5%) had neither. Diabetes without CKD was associated with excess risks of incident stroke, incident coronary heart disease, and cardiovascular mortality after adjustment for demographic and clinical covariates, including prevalent cardiovascular disease (excess incidence rates, 2.6; 95% confidence interval, 0.5 to 4.7; 2.6; 95% confidence interval, 0.3 to 4.8; and 2.4; 95% confidence interval, 0.4 to 4.3 per 1000 person-years, respectively). CKD without diabetes was associated with comparable nonsignificant excess risks for incident stroke and coronary heart disease (2.5; 95% confidence interval, −0.1 to 5.2 and 2.4; 95% confidence interval, −0.8 to 5.5 per 1000 person-years, respectively) but a larger excess risk for cardiovascular mortality (7.3; 95% confidence interval, 3.0 to 11.5 per 1000 person-years). Diabetes and CKD together were associated with greater excess risks for incident stroke (13.8; 95% confidence interval, 5.3 to 22.3 per 1000 person-years), coronary heart disease (12.8; 95% confidence interval, 4.9 to 20.8 per 1000 person-years), and cardiovascular mortality (14.8; 95% confidence interval, 7.2 to 22.3 per 1000 person-years). The excess risks associated with the combination of diabetes and CKD were larger than those associated with established risk factors, including prevalent cardiovascular disease.

Conclusions The combination of diabetes and kidney disease is associated with substantial excess risks of cardiovascular events and mortality among blacks.

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Introduction

Blacks experience a higher rate of cardiovascular disease (CVD) than whites (1). Blacks residing in certain regions of the United States, such as Mississippi, have even higher rates of cardiovascular (CV) mortality than those residing elsewhere in the country (2–4). Diabetes and CKD are both significant risk factors for CVD and mortality. In fact, CVD is the predominant cause of mortality among people with diabetes and kidney disease (5,6). Previous studies, mostly in white or ethnically mixed populations, have shown that CKD is a powerful predictor of the excess mortality in diabetes (7–9). Using data from the National Health and Nutrition Examination Survey (NHANES III), we previously reported that, among people with diabetes, those with kidney disease have the highest cumulative incidence of 10-year mortality. Interestingly, absent kidney disease, mortality in people with diabetes was not drastically higher than that of a reference population without diabetes or kidney disease (9).

Blacks are 1.7 times more likely than whites to be diagnosed with diabetes (10), 2.5 times more likely to develop ESRD caused by diabetes (11), and 1.7 times more likely to die as a result of diabetes (12). In this study, we asked whether kidney disease is predictive of CV outcomes among blacks. To address this, we examined the association between diabetes, kidney disease, and excess risk for incident stroke and coronary heart disease (CHD) as well as CV mortality in the Jackson Heart Study (JHS) population.

Materials and Methods

Study Population

The JHS is a single–site, community–based, prospective cohort study of risk factors and course of CVD in noninstitutionalized adult blacks (13,14).

Between 2000 and 2004, the study enrolled 5301 blacks ages 21–94 years old residing in three counties within the Mississippi Metropolitan Area (Hinds, Madison, and Rankin). During this interval, the baseline data were collected using a self-administered questionnaire, an in-home interview, and a clinic visit. This study used data from 3211 JHS participants, excluding participants with missing data on baseline diabetes status (n=61), serum creatinine (n=34), serum cystatin C (n=81), and urine albumin and creatinine (n=1914). Follow-up clinical examinations were conducted in 4-year intervals, with examination 2 conducted between 2005 and 2008 and examination 3 conducted between 2009 and 2012. Median follow-up duration was 6.99 years. In addition, interim medical events and vital statistics were also collected using annual telephone interviews. The study was approved by the institutional review boards of Jackson State University, Tougaloo College, and the University of Mississippi Medical Center. All of the participants gave written informed consent. The use of deidentified data for this study was considered nonhuman subjects research by the Human Subjects Division of the University of Washington.

Diabetes Definition

Diabetes was defined as self-reported diabetes, hemoglobin A1c ≥6.5% (15), fasting glucose >126 mg/dl as per the 2010 American Diabetes Association guidelines (16), or use of glucose-lowering medications at baseline examination. Glycated hemoglobin A1c concentration was measured using an HPLC system (Tosoh Corporation, Tokyo, Japan) in blood samples collected after an overnight fast (17).

CKD Definition

CKD was defined as albuminuria, reduced eGFR, or both using data from the baseline visit. Albuminuria was defined as a urine albumin-to-creatinine ratio ≥30 mg/g. Reduced eGFR was defined as an eGFR≤60 ml/min per 1.73 m^2. More details on the definition of CKD and other covariates are in Supplemental Material.

Outcomes

The outcomes were incident CHD, incident stroke, and mortality from CV causes. These outcomes were captured during the annual telephone interviews with participants and their family members as well as the JHS examinations 2 and 3. During the interviews and examinations, trained staff identified interim medical events, including new health events, diagnostic tests, hospitalizations, new diagnoses, and death. These were subsequently confirmed by review of medical records, including discharge summaries, International Classification of Diseases, Ninth Revision codes, and procedure codes. Cohort deaths were additionally identified from the monthly printout of the Mississippi State Department of Health, systematic review of death certificates, hospital chart review, use of obituary notices, and linkage to the National Death Index. Final classification of all CV events required medical chart review and adjudication by trained physicians. Incident CHD was defined as myocardial infarction or need for coronary revascularization on the basis of data abstracted from medical records, which included presenting symptoms, relevant clinical data (cardiac biomarkers, electrocardiogram, *etc.*), and diagnostic and therapeutic procedures. A detailed description of other CV outcomes and statistical analysis is in Supplemental Material.

Statistical Methods

We categorized participants by presence or absence of diabetes and CKD and compared the distribution of demographics and covariates in these four mutually exclusive groups. Participants were considered at risk for each of the outcomes from their baseline visit until the first occurrence of the outcomes or censoring because of loss to follow-up, the end of available follow-up, or death from non-CV causes. Participants with a prior stroke were excluded from the analyses where the outcome was incident stroke. Participants with prior CHD were excluded from the analyses where the outcome was incident CHD. For the outcome of CV mortality, participants with prior stroke or CHD were included in the analyses. Incidence rates (per 1000 person-years with 95% confidence intervals [95% CIs]) for incident stroke, incident CHD, or CV mortality were calculated using Poisson regression in four groups: participants with no diabetes or CKD, participants with diabetes but no CKD, participants with CKD but no diabetes, and participants with both diabetes and CKD. Risk differences were estimated by comparing incidence rates in each group with those in the reference group (participants with no diabetes or CKD) from the Poisson regression. The 95% CIs for the risk differences were computed from a bootstrap analysis of 1000 samples. Cox proportional hazards regression was used to estimate the relative hazard of each outcome, adjusting for relevant covariates, in the same four groups. In each analysis, models were first adjusted for age, age^2, sex, and income (model 1). Given the large age range, adjustment for age was done using both simple and quadratic terms. Income was dichotomized by collapsing the four categories into two categories of low (combination of poor and lower middle) and high (combination of upper middle and affluent). Education was not included in the final model, because it did not remain significant in the presence of income. The final model was additionally adjusted for smoking status, hypertension, hyperlipidemia, and prevalent CVD (model 2).

To evaluate for additive interactions between diabetes and CKD (*i.e.*, to determine whether diabetes and CKD increased the risk difference of incidence rates of an event in an additive fashion), the risk difference for an event was calculated for each group (diabetes or CKD), and the effect modification between diabetes and CKD was evaluated by using the relative excess risk because of interaction (RERI) (18). The RERI is the difference of the observed effect of the joint exposure with the sum of the effects of each factor acting separately: $\mathrm{RERI} = \mathrm{RD}_{\mathrm{DM+CKD+}} - \mathrm{RD}_{\mathrm{DM+CKD-}} - \mathrm{RD}_{\mathrm{DM-CKD+}} + 1$, where DM is diabetes mellitus and $\mathrm{RD}_{\mathrm{DM+CKD+}}$ indicates risk difference of incidence rates for both diabetes and CKD. If diabetes is present but CKD is not, then the RD is $\mathrm{RD}_{\mathrm{DM+CKD-}}$; similarly, if diabetes is absent and CKD is present, the RD is $\mathrm{RD}_{\mathrm{DM-CKD+}}$. A value of zero implies exact additivity, a value greater than zero indicates a positive interaction between the two variables (or more

additivity), and a value less than zero implies less than additivity.

All analyses were conducted in STATA, version 13 (StataCorp., College Station, TX) and SPSS, version 22 (IBM SPSS, Chicago, IL), and P values <0.05 were considered statistically significant.

Results

Characteristics of Study Participants

Of the 5301 JHS participants, we excluded those with missing measures of diabetes (n=61), serum creatinine (n=34), cystatin (n=81), and urine albumin-to-creatinine ratio (n=1914), leaving 3211 who were included in this study (Supplemental Figure 1). The JHS participants excluded from this analysis (n=2090) were less affluent, were more likely to smoke, had lower mean GFR, and had higher percentages of albuminuria and prevalent CVD (Supplemental Table 1). Among the study population, 456 (14.2%) had only diabetes, 257 (8.0%) had only CKD, 201 (6.3%) had both, and 2297 (71.5%) had neither at study entry (Table 1). The majority of the participants with CKD had albuminuria (Supplemental Figure 2). Participants with diabetes and/or CKD were older and more obese. Presence of CKD and diabetes was associated with higher prevalence of hypertension and use of antihypertensive medications. Despite higher prevalence of antihypertensive use, the mean systolic BPs were higher in subgroups with CKD. More participants with diabetes were using hydroxymethyl glutaryl–CoA reductase inhibitors. However, total cholesterol as well as LDL cholesterol concentrations were comparable with or without CKD or diabetes. Participants with diabetes and/or CKD included more people with lower incomes. In addition, diabetes and CKD were more common in people with lower income: CKD was present in 16% of people in the combined poor and lower–middle categories versus 9% in the combined upper–middle and affluent categories. Diabetes was present in 25% of people in the combined poor and lower–middle categories versus 14% in the combined upper–middle and affluent categories.

CV Outcomes by Diabetes Status

The incidence rate of stroke was higher in JHS participants with diabetes than in those without diabetes: 6.5 (95% CI, 3.8 to 9.1) versus 1.3 (95% CI, 0.6 to 1.9) per 1000 person-years after adjustment for sociodemographic and clinical covariates (Table 2). Similarly, incident CHD and

Table 1. Baseline characteristics of the Jackson Heart Study participants by diabetes and CKD status

Variables	All	No Diabetes		Diabetes	
		No CKD	CKD	No CKD	CKD
N, %	3211	2297 (71.5)	257 (8.0)	456 (14.2)	201 (6.3)
Age, yr	54 (13)	52 (13)	59 (14)	59 (11)	62 (11)
Men	1218 (38%)	912 (40%)	88 (34%)	137 (30%)	81 (40%)
Income					
Poor	354 (13%)	235 (12%)	31 (15%)	62 (17%)	26 (17%)
Lower middle	611 (23%)	402 (21%)	66 (31%)	92 (25%)	51 (33%)
Upper middle	828 (31%)	593 (31%)	63 (30%)	120 (32%)	52 (33%)
Affluent	882 (33%)	703 (36%)	52 (25%)	100 (27%)	27 (17%)
Smoking					
Never	2254 (71%)	1645 (72%)	170 (66%)	300 (66%)	139 (70%)
Former	555 (17%)	354 (16%)	50 (20%)	113 (25%)	38 (19%)
Current	375 (12%)	277 (12%)	36 (14%)	41 (9%)	21 (11%)
SBP, mmHg	126 (18)	124 (17)	136 (21)	127 (17)	138 (22)
DBP, mmHg	79 (10)	80 (10)	82 (13)	77 (11)	78 (11)
Use of antihypertensives	1578 (60%)	898 (50%)	164 (74%)	342 (79%)	174 (92%)
Hypertension	1940 (60%)	1180 (51%)	202 (79%)	371 (81%)	187 (93%)
Cholesterol, mg/dl	198 (39)	198 (39)	200 (42)	197 (38)	202 (44)
LDL, mg/dl	127 (36)	127 (36)	129 (37)	123 (33)	126 (41)
Use of HMG-CoA reductase inhibitors	377 (12%)	176 (8%)	24 (9%)	122 (27%)	55 (27%)
Hyperlipidemia	850 (27%)	537 (23%)	72 (28%)	166 (36%)	75 (37%)
Prevalent cardiovascular disease	317 (10%)	159 (7%)	46 (18%)	66 (15%)	46 (23%)
Creatinine, mg/dl	0.92 (0.32)	0.89 (0.18)	1.10 (0.71)	0.85 (0.19)	1.18 (0.61)
Cystatin C, mg/L	0.74 (0.25)	0.69 (0.12)	0.96 (0.58)	0.73 (0.15)	1.00 (0.46)
eGFR (CKD-EPI), ml/min per 1.73 m^2	104 (21)	108 (17)	88 (30)	103 (18)	82 (32)
ACR, mg/g	6 [4–13]	5 [4–8]	63 [35–169]	8 [5–12]	81 [41–359]
ACR≥30	399 (12%)	0 (0%)	220 (86%)	0 (0%)	179 (89%)

Data are presented as numbers (%), means (SDs), or medians [interquartile ranges]. Hypertension was defined as SBP≥140 mmHg, DBP≥90 mmHg, or use of antihypertensive medications. Hyperlipidemia was defined as LDL≥160 or use of HMG-CoA reductase inhibitors. eGFR was calculated using serum concentrations of creatinine and cystatin C measured at baseline using the 2012 CKD-EPI equation. To convert GFR in milliliters per minute to milliliters per second, multiply by 0.01667. To convert cholesterol in milligrams per deciliter to millimoles per liter, multiply by 0.0259. SBP, systolic BP; DBP, diastolic BP; HMG-CoA, hepatic hydroxymethyl glutaryl–CoA; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ACR, albumin-to-creatinine ratio.

CV mortality were more frequent in those with diabetes than in those without diabetes: 6.9 (95% CI, 4.1 to 9.6) versus 1.9 (95% CI, 1.1 to 2.7) and 6.0 (95% CI, 3.7 to 8.3) versus 1.3 (95% CI, 0.6 to 1.9) per 1000 person-years, respectively.

CV Outcomes by CKD and Diabetes Status

In the absence of diabetes and CKD, the unadjusted rate of incident stroke was 1.7/1000 person-years (95% CI, 1.1 to 2.4) (Table 3). In the presence of diabetes alone, CKD alone, or diabetes and CKD together, this rate was higher at 5.7 (95% CI, 2.1 to 9.8), 5.9 (95% CI, 2.1 to 9.8), and 17.0 (95% CI, 9.4 to 24.7) per 1000 person-years, respectively. Compared with the reference group without either diabetes or CKD, presence of diabetes only was associated with an excess risk for incident stroke of 2.6 (95% CI, 0.5 to 4.7) per 1000 person-years after adjustment for sociodemographic and clinical variables. CKD alone was associated with an excess risk of 2.5 (95% CI, −0.1 to 5.2) per 1000 person-years for stroke, which lost significance after adjustment for sociodemographic variables. The combination of diabetes and CKD was associated with an excess risk for incident stroke of 13.8 (95% CI, 5.3 to 22.3) per 1000 person-years in fully adjusted analyses.

Compared with the reference group, diabetes alone was associated with an excess risk for incident CHD of 2.6 (95% CI, 0.3 to 4.8) per 1000 person-years after full adjustment. The combination of diabetes and CKD was associated with an excess risk for incident CHD of 12.6 (95% CI, 4.9 to 20.8) per 1000 person-years after full adjustment. Presence of diabetes alone, CKD alone, or the combination of diabetes and CKD was associated with excess risks for CV mortality of 2.4% (95% CI, 0.4% to 4.3%), 7.3% (95% CI, 3.0% to 11.5%), and 14.8% (95% CI, 7.2% to 22.3%) per year after full adjustment. Modeling time to the first event using the Cox proportional hazard showed similar results: the combination of diabetes and CKD was associated with 3.3-fold (95% CI, 1.79 to 6.20) higher rates of incident CHD, 6.23-fold (95% CI, 3.22 to 12.09) higher rates of incident stroke, and 6.4-fold (95% CI, 3.53 to 11.78) higher rates of CV mortality (Table 4). There was a trend toward additive interaction between the risk differences associated with diabetes and CKD for incident stroke, incident CHD, and CV mortality. The RERIs and 95% CIs for incident stroke, incident CHD, and CV mortality were 0.87 (95% CI, 0.01 to 1.73), 0.78 (95% CI, −0.07 to 1.65), and 0.52 (95% CI, −0.27 to 1.30), respectively. However, only the interaction for incident stroke attained statistical significance (P value =0.004).

Table 2. Adjusted incidence rates of cardiovascular outcomes per 1000 person-years in people with and without diabetes in the Jackson Heart Study

Outcome	*N*	Events	Adjusted Incidence Rate (95% CI)
Incident stroke			
No diabetes	2473	35	1.3 (0.6 to 1.9)
Diabetes	615	36	6.5 (3.8 to 9.1)
Incident CHD			
No diabetes	2401	48	1.9 (1.1 to 2.7)
Diabetes	571	33	6.9 (4.1 to 9.6)
Cardiovascular mortality			
No diabetes	2554	52	1.3 (0.6 to 1.9)
Diabetes	657	46	6.0 (3.7 to 8.3)

Incidence rates were calculated using Poisson regression and adjusted for age, age^2, sex, income, hypertension, hyperlipidemia, current smoking, and prevalent cardiovascular disease. Participants with a prior stroke (or CHD) were excluded from the analyses where the outcome was incident stroke (or CHD). 95% CI, 95% confidence interval; CHD, coronary heart disease.

The Excess Risk of CV Outcomes Associated with CKD and Diabetes Compared with Other Clinical Risk Factors

To compare the excess risk of the CV outcomes associated with diabetes and CKD with that associated with other CV risk factors (particularly prevalent CVD), we examined the risk differences for each risk factor in the fully adjusted model (model 2 in Table 3). However, given our focus on incident outcomes, prevalent CVD is defined differently for each outcome. For incident stroke, prevalent CVD consisted of prevalent CHD, because the participants with prevalent stroke had to be excluded. Similarly, for the outcome of incident CHD, prevalent CVD consisted of prevalent stroke. Only for the outcome of CV mortality did prevalent CVD include both prevalent stroke and CHD. In the fully adjusted model, the combination of diabetes and CKD was associated with greater excess risks for incident stroke, incident CHD, and CV death than other CV risk factors, including prevalent CVD, hyperlipidemia, hypertension, and smoking. Diabetes and CKD individually were associated with comparable excess rates of incident stroke and CHD, excess risks that were of similar magnitude to those for hypertension and smoking but less than those of prevalent CVD. However, CKD alone was associated with much higher rates of CV mortality than diabetes alone, an excess risk that was comparable with that of prevalent CVD (Figure 1).

Discussion

In a black population with high incidence of CVD and mortality, diabetes alone was associated with excess risks of incident stroke, CHD, and CV mortality, whereas CKD alone was associated with excess risk for CV mortality. However, the combination of diabetes and kidney disease was associated with a greater excess risk for incident stroke, CHD, and CV mortality than established clinical risk factors, including a history of CVD.

Blacks, particularly in the southern low–income rural communities, have some of the highest rates of all-cause and CV mortality in the United States (2–4). Kidney disease and diabetes, both risk factors for CVD, are disproportionately more common in this population. CKD is associated with an excess risk of all-cause and CV mortality both in the general population (19–23) and among people with diabetes (5,6). In a nationally representative population, kidney disease captured a majority of the excess mortality risk associated with diabetes (9). Furthermore, absent kidney disease, diabetes was not associated

Table 3. Rates of incident stroke, coronary heart disease, and cardiovascular mortality (per 1000 person-years) by diabetes and CKD status in the Jackson Heart Study

Outcome	*N*	Events	Unadjusted Incidence Rate (95% Confidence Interval)	Risk Difference Per 1000 person-yr (95% Confidence Interval)	
				Model 1	Model 2
Incident stroke					
No diabetes or CKD	2235	26	1.7 (1.1 to 2.4)	Reference	Reference
Diabetes but no CKD	431	17	5.7 (2.1 to 9.8)	2.8 (0.5 to 5.1); *P*=0.02	2.6 (0.5 to 4.7); *P*=0.02
CKD but no diabetes	238	9	5.9 (2.1 to 9.8)	2.9 (−0.1 to 6.1); *P*=0.08	2.5 (−0.1 to 5.2); *P*=0.06
Diabetes and CKD	184	19	17.0 (9.4 to 24.7)	14.8 (6.0 to 23.7); *P*=0.001	13.8 (5.3 to 22.3); *P*=0.001
Incident coronary heart disease					
No diabetes or CKD	2186	39	2.7 (1.8 to 3.5)	Reference	Reference
Diabetes but no CKD	409	17	6.1 (3.2 to 9.0)	2.4 (−0.1 to 5.0); *P*=0.07	2.6 (0.3 to 4.8); *P*=0.03
CKD but no diabetes	215	9	6.4 (2.2 to 10.7)	2.4 (−1.2 to 5.9); *P*=0.20	2.4 (−0.8 to 5.5); *P*=0.15
Diabetes and CKD	162	16	15.7 (8.0 to 23.3)	12.4 (4.4 to 20.3); *P*=0.002	12.8 (4.9 to 20.8); *P*=0.002
Cardiovascular mortality					
No diabetes or CKD	2297	30	2.0 (1.3 to 2.7)	Reference	Reference
Diabetes but no CKD	456	16	5.1 (2.6 to 7.5)	2.4 (0.4 to 4.4); *P*=0.02	2.4 (0.4 to 4.3); *P*=0.02
CKD but no diabetes	257	22	13.6 (7.9 to 19.3)	7.7 (3.0 to 12.4); *P*=0.001	7.3 (3.0 to 11.5); *P*=0.001
Diabetes and CKD	201	30	23.5 (15.1 to 31.9)	14.8 (6.8 to 22.8); *P*<0.001	14.8 (7.2 to 22.3); *P*<0.001

Incidence rates were calculated using Poisson regression. Absolute risk differences were estimated by comparing the incidence rates in each group with those in the reference group (participants with no diabetes or CKD) using Poisson regression and adjusted for age, age^2, sex, and income (model 1) or additionally adjusted for hypertension, hyperlipidemia, current smoking, and prevalent cardiovascular disease (model 2). Participants with a prior stroke were excluded from the analyses where the outcome was incident stroke. Participants with prior coronary heart disease were excluded from the analyses where the outcome was incident coronary heart disease. However, participants with prior cardiovascular disease (stroke or coronary heart disease) were included in the analyses where the outcome was cardiovascular mortality.

with a large excess in mortality (9). Here, we extend that work by examining the association of diabetes and kidney disease with CV mortality as well as incident CV events in a high–risk black population. Risk differences were evaluated on an absolute scale to present the clinically relevant marginal risk associated with diabetes, kidney disease, or the combination over the baseline risk among the reference population without diabetes

Table 4. Relative hazards of incident stroke, coronary heart disease, and cardiovascular mortality by diabetes and CKD status in the Jackson Heart Study

Outcome	*N*	Events	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Incident stroke					
No diabetes or CKD	2235	26	1.00 (reference)	1.00 (reference)	1.00 (reference)
Diabetes but no CKD	431	17	3.23 (1.75 to 5.97)	1.94 (0.96 to 3.93)	1.83 (0.90 to 3.74)
CKD but no diabetes	238	9	3.65 (1.70 to 7.82)	2.43 (1.02 to 5.74)	1.91 (0.80 to 4.55)
Diabetes and CKD	184	19	10.33 (5.70 to 18.73)	7.41 (3.87 to 14.18)	6.23 (3.22 to 12.09)
Incident coronary heart disease					
No diabetes or CKD	2186	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
Diabetes but no CKD	409	17	2.23 (1.26 to 3.95)	1.59 (0.84 to 3.03)	1.36 (0.74 to 2.60)
CKD but no diabetes	215	9	2.44 (1.18 to 5.05)	1.65 (0.73 to 3.75)	1.32 (0.58 to 3.00)
Diabetes and CKD	162	16	5.90 (3.30 to 10.56)	4.32 (2.33 to 8.04)	3.33 (1.79 to 6.20)
Cardiovascular mortality					
No diabetes or CKD	2297	30	1.00 (reference)	1.00 (reference)	1.00 (reference)
Diabetes but no CKD	456	16	2.52 (1.37 to 4.62)	2.06 (1.03 to 4.20)	1.90 (0.94 to 3.84)
CKD but no diabetes	257	22	7.00 (4.04 to 12.13)	5.04 (2.70 to 9.40)	4.22 (2.24 to 7.97)
Diabetes and CKD	201	30	13.38 (7.45 to 20.56)	7.46 (4.15 to 13.43)	6.44 (3.53 to 11.78)

Relative hazard for each outcome was estimated using the Cox regression and adjusted for age, age^2, sex, and income (model 1) or further adjusted for hypertension, dyslipidemia, current smoking, and prevalent cardiovascular disease (model 2). Prevalent cardiovascular disease for each outcome was defined as in Table 3. HR, hazard ratio; 95% CI, 95% confidence interval.

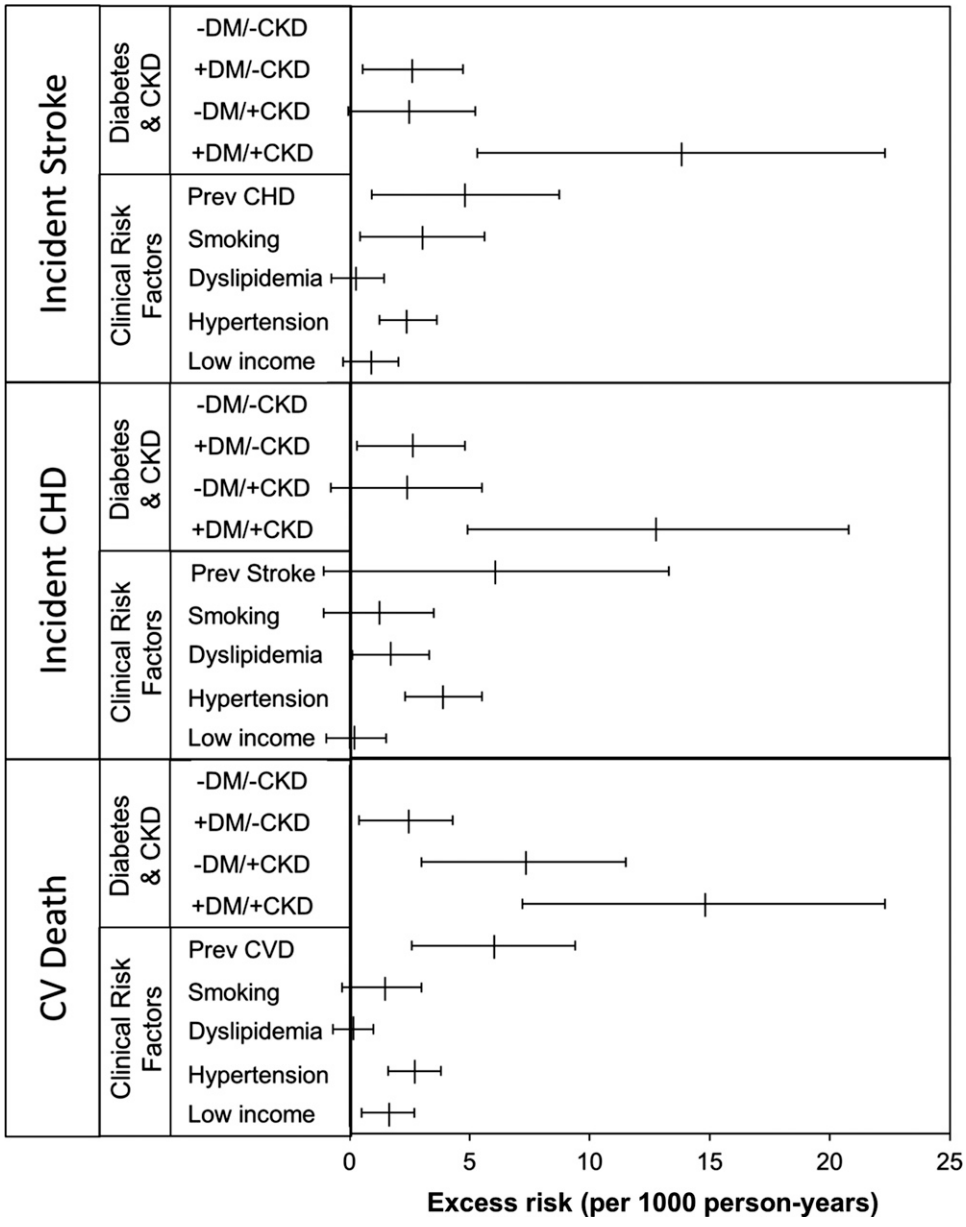

Figure 1. | Risk differences for incident stroke, coronary heart disease (CHD), and cardiovascular mortality (per 1000 person-years) by clinical risk factor in the Jackson Heart Study. Incidence rates were calculated using Poisson regression. Absolute risk differences were estimated by comparing the incidence rates in each group with those in the reference group (participants with no diabetes or CKD) using Poisson regression and adjusted for age, age^2, sex, hypertension, hyperlipidemia, smoking, and prevalent cardiovascular disease (CVD). Participants with a prior stroke were excluded from the analyses where the outcome was incident stroke; participants with prior CHD were excluded from the analyses where the outcome was incident CHD. CVD refers to a combination of stroke and CHD. CV death, cardiovascular death; DM, diabetes mellitus.

or CKD. Using this approach, we found a much larger excess risk for CV mortality in the presence of CKD than in the presence of diabetes, consistent with our findings in the NHANES III. Similarly, the combination of diabetes and CKD was associated with a much larger excess risk for CV mortality than either risk factor alone. Consistently, we found a trend toward an additive interaction between CKD and diabetes. However, except for incident stroke, this did not reach statistical significance.

On the other hand, although CKD alone conferred a significant excess risk for CV mortality, it was not associated with significant excess risk for incident stroke or CHD. The combination of diabetes and kidney disease was associated with a significant excess risk for both incident stroke and CHD. However, each risk factor alone was associated with a small excess risk for these outcomes, which in the case of kidney disease, was not robust to adjustment, suggesting an additive interaction between diabetes and CKD. This observation raises the possibility

that, in absence of diabetes, CKD may contribute more to reduced survival after a CV event rather than a predisposition to it. In fact, presence and severity of kidney disease are associated with lower survival after CV events, including acute myocardial infarction, stroke, or congestive heart failure (24). In an interesting parallel, although blacks have comparable rates of CV events with whites (25,26), they experience higher CV mortality than whites (27–29). This suggests that the higher prevalence of kidney disease in blacks may contribute to the disparity in CV mortality in this population relative to whites.

The gap in socioeconomic status is believed to at least partly underlie the disparity in CV outcomes and mortality between blacks and whites (30–33). In the JHS, both diabetes and kidney disease were more prevalent in participants with lower socioeconomic status as assessed by income. Adjustment for age, sex, and socioeconomic status attenuated the excess risk for CV outcomes in the presence of the combination of diabetes and kidney disease. However, most of this attenuation was because of age (and not socioeconomic status). Furthermore, even after this adjustment, the excess risk for CV outcomes in the presence of concomitant diabetes and kidney disease remained sizable and significant. However, after adjustment for both diabetes and kidney disease, the excess risk associated with income was not significant for incident stroke and CHD but remained significant (although small) for CV mortality. These observations suggest that the previously observed associations between socioeconomic status and CVD outcomes may be mediated *via* higher rates of diabetes and CKD in people with lower socioeconomic status. They further suggest that socioeconomic status, similar to CKD, may have a greater influence on survival after a CV event than the predisposition to it.

Our findings are also relevant to the question of risk equivalence for the risk of CV outcomes associated with CKD compared with that from diabetes or prevalent CVD. Previous work in largely white populations has shown that CKD contributes significantly to CV risk stratification (34) and that the combination of diabetes and CKD is associated with comparable rates of incident myocardial infarction to preexisting CHD (35). Given our focus on incident outcomes (stroke and CHD), prevalent stroke (or CHD) could not be included in our assessment of risk factor for incident stroke (or CHD). As such, our findings address this question more fully for CV mortality, where prevalent CVD included prevalent stroke and CHD. Consistent with prior studies (34), we found that, in this black cohort, kidney disease, particularly in the presence of diabetes, was associated with a greater excess risk of CV outcomes and mortality than other clinically used CV risk factors, including preexisting CVD. This finding has direct clinical implications for CV risk stratification and intensive therapeutic targeting of the subpopulations at the highest risk for future CV events and mortality. For example, as pointed out in previous studies (34), full assessment of kidney function, including not only eGFR but also, urine albumin excretion, is likely to be beneficial for complete CV risk assessment.

Interestingly, the incidence of stroke was comparable with that of CHD in the JHS. This is counter to the general population, where incidence of CHD equals or exceeds that of all other CV events together (36,37). This may be related to the higher incidence of stroke noted in the southeastern United States compared with in the rest of the country (38,39). The higher rates of stroke observed in blacks versus whites may also contribute to this finding (40).

The observational nature of the study precludes differentiation of whether the combination of diabetes and kidney disease is causally related to CV outcomes, although this possibility is strongly supported by preexisting data (5,6,19–23). Additional limitations include assessment of kidney function and diabetes at one time point, the small number of events in some categories, and potential misclassification in determination of cause of mortality on the basis of International Classification of Diseases codes. The strengths of this study are use of a clinically relevant high–risk black population, use of physician–adjudicated CV outcomes, comparison with population internal references, uniform assessment of diabetes and kidney disease, and evaluation of associations on a clinically relevant additive scale.

In conclusion, this study highlights the significance of kidney disease as a risk factor for CVD and mortality in blacks, particularly in the presence of diabetes. Especially among blacks with diabetes, assessment of kidney function may be a helpful component of CV risk stratification for identification of a subpopulation for intensive risk modification.

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M.A. is the guarantor of this study and takes responsibility for the findings and interpretations presented in this manuscript.

Disclosures

None.

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Supplementary material for:

Title: Diabetes, kidney disease and cardiovascular outcomes in the Jackson Heart Study

Running title: diabetic kidney disease and cardiovascular disease

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Supplementary methods:

Definition of chronic kidney disease: Urine albumin and creatinine concentrations were measured in clean-catch random (N=2209) or 24-hour (N=1002) urine samples, collected at baseline visit after an overnight fast. There were 276 JHS participants with both 24-hour and spot urine ACR values with a correlation of 0.97. Urine albumin was measured using a human albumin kit (Dade Behring, Neward, Delaware) on a Dade Behring BN II nephelometer. Urine creatinine was measured at the University of Mississippi Medical Center Laboratory Reading Center using a multi-point enzymatic spectrophotometric assay (Vitros CREA dry reaction slides on a Vitros 950 Ortho-Clinical Diagnostics Analyzer, Raritan, New Jersey). Creatinine concentrations were calibrated to the Cleveland Clinic-equivalent Minnesota Beckman CX3 assay.(1) Serum creatinine was measured using the Jaffe method and calibrated to measurements traceable to isotope dilution mass spec (IDMS).(2) Serum cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Siemens AG, Munich). Estimated GFR was calculated from serum concentrations of creatinine and cystatin C measured at baseline using the 2012 CKD-EPI equation.(3)

Other characteristics: Demographic and socioeconomic variables (age, gender, income and education) as well as smoking history (never, former, current) were obtained during the baseline interview. Income was derived from family income and size, adjusted by the year of data collection to account for inflation and categorized in four groups (Table 1). Medications used in the two weeks preceding the interview were brought to the clinic and transcribed from bottles and coded by pharmacists using the Medispan dictionary. Blood pressure was measured by trained staff in seated participants after a 5-minute rest, using an appropriately sized cuff and a Hawksley random-zero sphygmomanometer (Hawksley and Sons, Ltd). Two blood pressure readings were taken one minute apart and the arithmetic average was recorded. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg and/or

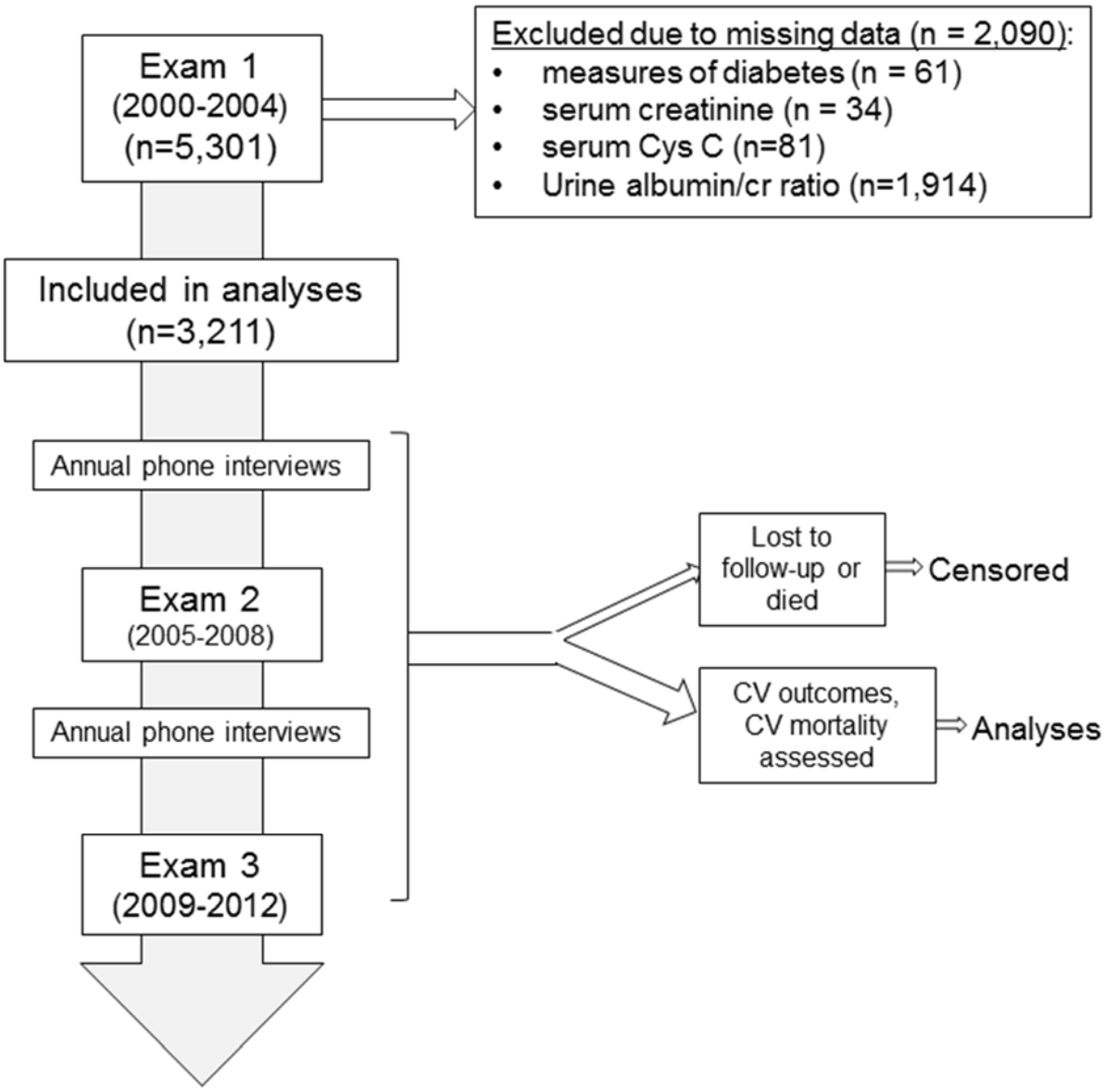
use of antihypertensive medications. Total cholesterol and triglyceride concentrations were measured in fasting blood samples using the Roche enzymatic methods using a Cobras centrifuge analyzer (Hoffman-La Roche).(4) Low-density lipoprotein (LDL) cholesterol concentrations were estimated using the Friedewald formula.(5) Hyperlipidemia was defined as a low-density lipoprotein cholesterol (LDL) $\geq$160 mg/dL and/or use of lipid-lowering medications

Definition of outcomes: Incident coronary heart disease was defined as myocardial infarction or need for coronary revascularization, based on data abstracted from medical records, which included presenting symptoms, relevant clinical data (cardiac biomarkers, electrocardiogram, etc) and diagnostic and therapeutic procedures. Adjudicating physicians assigned a diagnosis of no, probable, or definite myocardial infarction based on the abstracted data. For these analyses, probable or definite myocardial infarction was used as part of the coronary heart disease outcome. Incident stroke at outpatient or inpatient settings was defined as cerebrovascular accident due hemorrhagic or ischemic stroke based on review of medical records, including pertinent diagnostic and therapeutic procedures by qualified adjudicating physicians. An incident stroke defined as probable or definite based on this analysis was classified as an event for this outcome. Causes of death were identified by review of ICD-9 codes for the underlying and contributory causes of death, physician (and when indicated coroner or medical examiner) questionnaires, interviews with the next-of-kin and/or any non-family witnesses of death. Deaths from cardiovascular causes were ascertained by review of the causes of death by three physicians (all authors in this manuscript: M.A., N.B. and B.K.) and consisted of the following: acute coronary insufficiency, acute myocardial infarction, acute myocardial ischemia, advanced ischemic cardiomyopathy, (cardiac) arrhythmia, bradyarrhythmia, arteriosclerotic cardiovascular disease, asystole, intracerebral bleeding, cardiac standstill due to severe cardiopathy, cardiogenic failure, cardiomyopathy, cardiovascular events, cerebral hemorrhage, cerebral vascular accident/stroke, complication of cerebral vascular disease, complications of

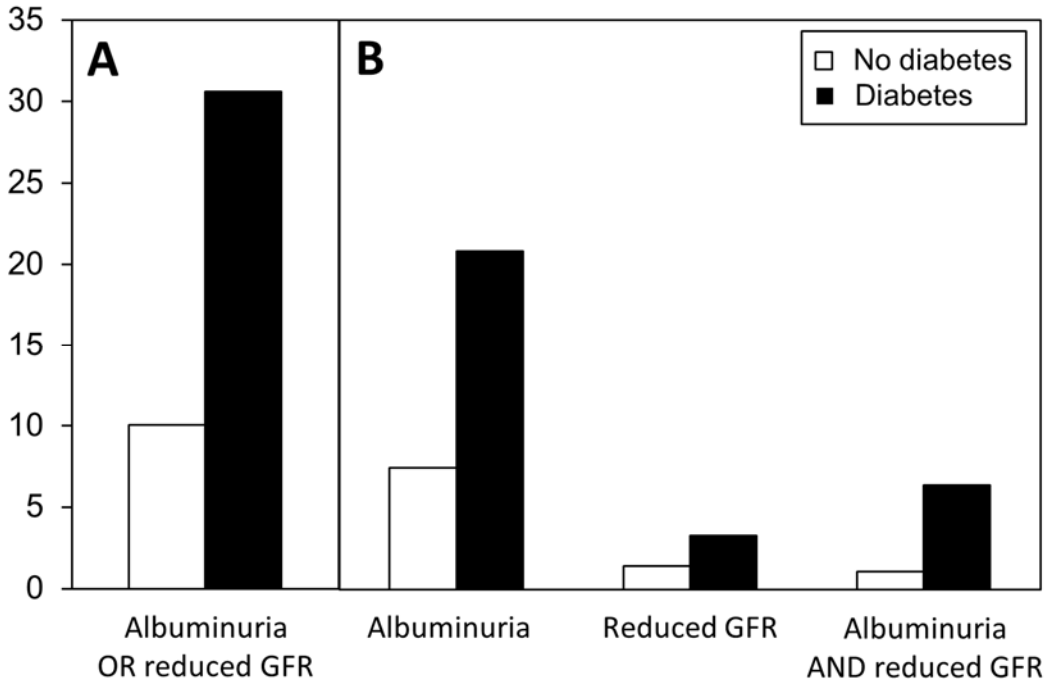
(hypertensive) heart disease, (end-stage) congestive heart failure, consistent with atherosclerotic coronary vascular disease, dissecting abdominal aneurysm, end-stage cardiomyopathy, end-stage heart disease, end-stage stroke, hemorrhagic shock due to abdominal aneurysm, hemorrhagic stroke, history of CVD with chronic decompensation, hypertensive cardiovascular disease, hypertensive heart disease, intracerebral hemorrhage, ischemic cardiomyopathy, ischemic stroke, multiple embolic strokes, myocardial infarction, no cerebral blood flow, possible (or probable) acute myocardial infarction (or insufficiency), probable cardiovascular accident, probable stroke, pulmonary edema and acute left heart failure, severe atherosclerosis with focal occlusive thrombo-embolus, sudden cardiac arrest, ventricular fibrillation, cardiopulmonary arrest, (acute) cardiac arrest.

SUPPLEMENTARY DATA

Supplementary Figure 1. Consort diagram demonstrating the flow of participants whose data was used in these analyses.



Supplementary Figure 2. Prevalence (A) and manifestations (B) of kidney disease in people with and without diabetes in the Jackson Heart Study. Closed (■) and open(□) bars indicate people with and without diabetes, respectively.



Supplementary Table. Baseline characteristics of Jackson Heart Study participants: whole cohort vs. excluded.

	Current study	Excluded	Whole Cohort
Variables			
N (%)	3211	2090	5301
Age	54 (13)	57 (13)	55 (13)
Male	1218 (38%)	716 (34%)	1934 (37%)
Income			
Poor	354 (13%)	347 (19%)	701 (16%)
Lower-middle	611 (23%)	486 (27%)	1097 (25%)
Upper-middle	828 (31%)	497 (28%)	1325 (30%)
Affluent	882 (33%)	476 (26%)	1358 (30%)
Smoking			
Never	2254 (71%)	1320 (64%)	3574 (68%)
Former	555 (17%)	431 (21%)	986 (19%)
Current	375 (12%)	318 (15%)	693 (13%)
SBP (mmHg)	126 (18)	128 (19)	127 (18)
DBP (mmHg)	79 (10)	78 (11)	79 (11)
Use of anti-hypertensives	1578 (60%)	1077 (60%)	2655 (62%)
Hypertension	1940 (60%)	1312 (63%)	3252 (61%)
Cholesterol (mg/dL)	198 (39)	201 (41)	199 (40)
LDL (mg/dL)	127 (36)	127 (37)	127 (36)
Use of HMG-CoA reductase inhibitors	377 (12%)	225 (11%)	602 (11%)
Hyperlipidemia	850 (27%)	535 (26%)	1385 (26%)
Prevalent cardiovascular disease	317 (10%)	255 (12%)	572 (11%)
Creatinine (mg/dL)	0.92 (0.32)	0.99 (0.78)	0.95 (0.54)
Cystatin C (mg/L)	0.74 (0.25)	0.80 (0.54)	0.76 (0.39)
eGFR (CKD-EPI)	104 (21)	99 (23)	102 (22)
ACR (mg/g)*	6 [4, 13]	8 [5, 14]	6 [4, 13]
ACR $\geq$ 30	399 (12%)	14/79 (18%)	413 (16%)

Data are presented either as numbers (percent), means (SD) or median [interquartile range]. Hypertension and hyperlipidemia were defined as in Table 1. Estimted GFR (eGFR) was calculated as described in Table 1. To convert GFR in ml/min to ml/s, multiply by 0.01667. To convert cholesterol in mg/dl to mmol/L, multiply by 0.0259. SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein cholesterol; HbA1c: hemoglobin A1c; ACR: Albumin to creatinine ratio.

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