Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Study populations

The Jackson Heart Study (JHS) is a community-based cohort study of African-Americans designed to evaluate risk factors for cardiovascular disease (CVD).[1,2] 5301 participants ages 21-94 years were recruited from the tri-county region (Hinds, Madison, and Rankin) of metropolitan Jackson, MS.[3] Participants were recruited during calendar years 2000-2004 and underwent a second in-person exam in 2005-2008 and a third exam in 2009-2013. For our study, participants were excluded if they were missing measures of serum creatinine (N=91) or cystatin C (N=81) at baseline, had prevalent CVD (N=1,072) or died prior to the second exam (N=236), which was when outcome ascertainment began for our analysis. Prevalent CVD was determined by self-report or occurrence of an adjudicated event prior to the second exam. We chose the second exam as our "baseline" for outcome ascertainment because this was the first point when all three study outcomes were adjudicated (HF was adjudicated after exam 2 while CHD and stroke adjudication started from exam 1). This left a final analytic sample of 3,821 participants.

The Cardiovascular Health Study (CHS) is a cohort study of older community-dwelling adults aged 65 or older.[4] Participants were recruited from HCFA Medicare eligibility lists at 4 locations: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. An initial 5201 participants were recruited between 1989 and 1990. An additional 687 African-American participants were added to the study in 1992–1993. For our study, we excluded participants who were missing measures of serum creatinine (N=80) or cystatin C (N=651) at baseline, or had prevalent CVD (based on self-report and review of prior

medical records for confirmation) (N=1260) leaving a final analytic sample of N=3,897 participants.

The Multi-Ethnic Study of Atherosclerosis (MESA) is a community-based cohort study of clinical and subclinical cardiovascular disease.[5] Between 2000 and 2002, MESA enrolled 6,814 adults 45-84 years of age from six field centers (New York and Bronx counties, New York; Baltimore City and County, Maryland; Forsyth County, North Carolina; Chicago, Illinois; St. Paul, Minnesota; and Los Angeles, California). Only individuals without known prevalent clinical cardiovascular disease, defined as myocardial infarction, angina, stroke, transient ischemic attack, heart failure, atrial fibrillation, use of nitroglycerin, prior angioplasty, coronary artery bypass grafting, valve replacement, pacemaker or defibrillator implantation, or any surgery on the heart or arteries, were eligible to participate. For our analysis, we excluded participants who were missing measures of serum creatinine (N=25) or cystatin C (N=40) at baseline or had no follow-up data available (N=5), leaving a final analytic sample of N=6,744 participants.

Chronic Kidney Disease

For all three cohorts, chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. Estimated glomerular filtration rate (eGFR) was calculated from serum concentrations of creatinine and cystatin C measured at baseline (from stored samples) using the 2012 CKD-EPI equation.[6]

In JHS, serum creatinine was measured using the Jaffe method and calibrated to measurements traceable to isotope dilution mass spec (IDMS).[7] In CHS, creatinine was measured using a colorimetric method (Ektachem700, Eastman Kodak, Rochester, NY) and also calibrated to Cleveland Clinic. In MESA, serum creatinine was measured by rate

reflectance spectrophotometry using thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics) and calibrated to the Cleveland Clinic. In the JHS and in MESA, serum cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Siemens AG, Munich). In CHS, serum cystatin C was measured using a BN II nephelometer (N Latex cystatin C, Dade Behring, Munich, Germany).[8]

Outcomes

The outcomes of our study were incident fatal and non-fatal heart failure (HF), fatal and non-fatal coronary heart disease (CHD) and fatal and non-fatal stroke. In all three cohorts, cardiovascular events and death were captured by study visits and/or telephone interviews with participants and their kin. During these regular contacts, interim health events, including diagnostic tests, new diagnoses, hospitalizations and death were ascertained. Information on events and deaths in each of the three cohorts triggered review of ICD 9 CM diagnosis codes, procedure codes, discharge summaries and medical records. Interviews with the next of kin and completed questionnaires by physicians and medical examiners or coroners were used to obtain information on deaths in CHS and MESA. In the JHS, information on deaths was limited to inpatient deaths. Medical chart review and adjudication by trained physicians was required for final, disease-specific event classification of all non-fatal cardiovascular events (HF, CHD and stroke). Deaths from HF, CHD and stroke were identified by review of obituaries, medical records (inpatient records for JHS), death certificates, National Death Index, the Centers for Medicare and Medicaid Services Healthcare-utilization database for hospitalizations (for CHS), and from household contacts (for CHS and MESA).[5,9-12]

HF was defined as an inpatient or outpatient HF event/visit. (Fewer than 10% of captured HF events were outpatient events in CHS[11]). Central adjudicators assigned a diagnosis of HF by reviewing all pertinent data including history, physical examination, chest X-ray reports, and medication use. When available, ejection fraction was also considered during adjudication. An HF event was confirmed if, in addition to a physician diagnosis of HF, there was (1) documentation in the participants' medical records of a constellation of symptoms (such as shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea) and physical signs (such as edema, pulmonary rales, gallop rhythm, displaced left ventricular apical impulse); (2) supporting clinical findings such as evidence of pulmonary edema on chest X-ray; or (3) a record of medical therapy for CHF, including diuretics, digitalis, angiotensin-converting enzyme inhibitors, or beta-blockers. Based on these criteria, adjudicators assigned a diagnosis of no HF, probable HF or definite HF. For all three cohorts, reviewers classified HF as definite, probable, or absent. Definite or probable HF required heart failure symptoms, such as shortness of breath or edema. In addition to symptoms, probable HF required HF diagnosed by a physician and patient receiving medical treatment for HF. Definite HF required one or more other exam or imaging criteria listed above. Participants not meeting any criteria, including just a physician diagnosis of HF without any other evidence, were classified as having no HF. For this analysis, probable or definite HF was used as the HF outcome.

CHD was defined as myocardial infarction (MI) or coronary revascularization. Abstracted clinical information include presenting symptoms, presence and location of chest pain, history of MI, angina, other CVD, timing of onset of symptoms, use of medication, diagnostic procedures, and therapeutic procedures. The abstractors also

recorded cardiac biomarker levels during the hospitalization and used an algorithm to classify the cardiac enzymes. The cardiac biomarkers included troponin I, troponin T, creatine phosphokinase (CPK) and its isoenzyme CK-MB, serum lactate dehydrogenase (LDH) and its subfractions LDH1 and LDH2 along with their ratio of LDH1/LDH2. Copies of electrocardiograms (ECG) from the hospitalization were also obtained and reviewed for abnormalities on admission or evolution of abnormalities (e.g. Q-waves or ST-T abnormalities). Based on these data, adjudicators assigned a diagnosis of no MI, probable MI or definite MI. For this analysis, probable or definite MI was included as part of the CHD outcome.

Inpatient stroke was defined by adjudicators after review of medical records for stroke due to brain hemorrhage or infarction. Adjudicators reviewed the medical records, pertinent imaging/procedures and therapies to make a diagnosis of stroke. Stroke was defined as either definite or probable and for this analysis, and both of which were included in this analysis.

Covariates

Demographic characteristics (age, sex and race) were determined by self-report. Hypertension was defined by use of blood pressure medications or blood pressure >140/90 mmHg. Hyperlipidemia was defined as LDL cholesterol > 160 mg/dL or use of lipid lowering medications. Diabetes was defined as fasting glucose >126 mg/dl or use of oral hypoglycemic medications or insulin. Information on tobacco use was collected from self-report (never, former or current). Physical examination measures and laboratory values were obtained at the baseline study visit. Medication use was determined by medication inventory and was recorded by study personnel.

Statistical methods

We pooled participants from JHS, CHS and MESA for analysis on the individual participant level.

We calculated the unadjusted incidence rates (per 1000 person-years, with 95% confidence intervals) of each primary outcome (incident HF, CHD and stroke) by CKD status (eGFR <60 vs. ≥60 ml/min/1.73 m^2) using Poisson regression. Follow-up time was censored after the first occurrence of the event of interest, death not attributable to the event of interest, loss to follow-up, or the end of follow-up (maximum 6 years after baseline for JHS, truncated at 10 years after baseline for CHS and MESA). We then estimated risk differences, comparing participants with versus without CKD, from the Poisson regression and used a bootstrap analysis of 1000 samples to generate a 95% confidence interval for the risk differences.

We adjusted for (1) demographic factors and cohort, and (2) demographic factors, cohort and CVD risk factors. The CVD risk factors we adjusted for included: age (continuous), sex, race/ethnicity, hypertension (dichotomous), diabetes (dichotomous), tobacco use (dichotomous), and dyslipidemia (dichotomous).

Prior to analyses, we decided to evaluate interactions of CKD with covariates for which we anticipated the absolute rate of CVD events may vary substantially: age (>= 65 or <65 years), gender, race/ethnicity, and study cohort. We adjusted for age as a linear term within each age stratum.

In a sensitivity analysis, we considered urine albumin to creatinine ratio (ACR) in the definition of CKD, consistent with international guidelines.[13] For this analysis, we included study participants in JHS and MESA who had measures of urine ACR available at baseline. Baseline measures of urine ACR were not available in CHS. In a second sensitivity analysis, we evaluated IR and risk differences across three categories of eGFR: >60, 45-59 and <45 ml/min/1.73 m^2.

All analyses were conducted in STATA version 13 (College Park, Tx, StataCorp LP) and SPSS version 22 (Armonk, NY: IBM Corp) and p-values < 0.05 were considered statistically significant.

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eTable 1. Baseline Characteristics of Study Participants From Each Cohort in the Pooled Analysis (N=14,462)

	Cardiovascular Health Study		Multi-ethnic Study of Atherosclerosis		Jackson Heart Study	
Characteristics	**eGFR≥60 ml/min/1.73 m^2**	**eGFR<60 ml/min/1.73 m^2**	**eGFR≥60 ml/min/1.73 m^2**	**eGFR<60 ml/min/1.73 m^2**	**eGFR≥60 ml/min/1.73 m^2**	**eGFR<60 ml/min/1.73 m^2**
N	3129	768	3141	603	3731	90
Age	71 (5)	75 (6)	61 (10)	72 (8)	54 (12)	67 (11)
Female	2062 (66%)	468 (61%)	3203 (52%)	358 (59%)	2348 (63%)	66 (73%)
Race						
White	2632 (84%)	649 (85%)	2313 (38%)	282 (47%)	--	--
Black	497 (16%)	119 (16%)	1714 (28%)	151 (25%)	3731 (100%)	90 (100%)
Hispanic	--	--	1377 (22%)	109 (18%)	--	--
Chinese	--	--	737 (12%)	61 (10%)	--	--
Hypertension	1661 (53%)	542 (71%)	2581 (42%)	450 (75%)	2013 (54%)	84 (93%)
Diabetes	402 (13%)	119 (16%)	727 (12%)	118 (20%)	625 (17%)	41 (46%)
Smoking						
Never	1493 (48%)	366 (48%)	3068 (50%)	319 (53%)	2625 (71%)	56 (62%)
Former	1236 (40%)	303 (40%)	2236 (37%)	223 (37%)	665 (18%)	25 (28%)
Current	395 (13%)	99 (13%)	819 (13%)	57 (10%)	432 (12%)	9 (10%)
Hyperlipidemia	620 (20%)	147 (19%)	1395 (23%)	182 (30%)	914 (25%)	25 (28%)
eGFR (ml/min/1.73 m^2)	80 (12)	49 (19)	87 (14)	50 (10)	107 (17)	46 (14)
Urine ACR*	--	--	5.2 [3.3, 10.2]	9.0 [4.3, 31.5]	5.5 [3.8, 10.2]	27.5 [6.4, 236.7]
>= 30 mg/g			485 (8%)	155 (26%)	218 (9%)	23 (47%)

*available only in 9160 participants from MESA and JHS

abbreviations: eGFR= estimated glomerular filtration rate

eTable 2. Adjusted Risk Differences* (per 1000 Person-years) for Adjudicated Incident Cardiovascular Events By Estimated Glomerular Filtration Rate (eGFR) and Urine Albumin-to-Creatinine Ratio (ACR) (N=9160)

Heart Failure			
eGFR < 60 ml/min/1.73 m^2	**ACR ≥ 30 mg/g**	**Events/N at risk**	**Risk Difference** (95% CI**
No	No	178/7811	0 (ref)
No	Yes	50/703	1.9 (0.5, 3.2); p=0.006
Yes	No	33/468	1.2 (-0.2, 2.5); p=0.084
Yes	Yes	30/178	5.2 (2.2, 8.3); p=0.001
CHD			
eGFR < 60 ml/min/1.73 m^2	**ACR ≥ 30 mg/g**	**Events/N**	**Risk Difference ** (95% C**
No	No	197/7811	0 (ref)
No	Yes	38/703	1.3 (-0.02, 2.7); p=0.053
Yes	No	40/468	2.0 (0.5, 3.5); p=0.011
Yes	Yes	24/178	4.7 (1.3, 8.1); p=0.007
Stroke			
eGFR < 60 ml/min/1.73 m^2	**ACR ≥ 30 mg/g**	**Events/N**	**Risk Difference ** (95% C**
No	No	136/7811	0 (ref)
No	Yes	33/703	1.3 (0.2, 2.5); p=0.023
Yes	No	25/468	0.7 (-0.4, 1.8); p=0.222
Yes	Yes	13/178	1.8 (-0.3, 3.9); p=0.086

*Adjusted IR = incidence rate per 1000 person yrs adjusted for age, sex, race, cohort, hypertension, diabetes, tobacco use, dyslipidemia, prevalent CHD, prevalent HF and prevalent stroke.
** RD= risk difference of the adjusted IRs, compared with eGFR<60 ml/min/1.73 m^2 and ACR<30 mg/g.

eTable 3. Incidence Rates (IR) and Risk Differences (per 1000 person-years) of Adjudicated Incident Cardiovascular Events in Participants by eGFR Category

	Events/N at ri	Unadjusted Incidence Rate (95% CI)	Unadjusted risk difference (95% CI)	Adjusted risk difference (95% CI) (comparison group: >60 ml/min/173 m2) Model 1	Adjusted risk difference (95% CI) (comparison group: >60 ml/min/173 m2) Model 2
Incident Heart Failure					
eGFR≥60	666/13001	6.2 (5.8, 6.7)	11.2 (8.2, 14.0); p<0.001	2.1 (1.0, 3.2); p<0.001	1.4 (0.5, 2.4); p=0.004
eGFR 45 - 5	150/1087	17.4 (14.6, 20.1			
eGFR < 45	95/374	38.3 (30.6, 46.1	32.1 (24.7, 39.6); p<0.001	7.0 (4.1, 9.9); p<0.001	4.6 (2.4, 6.7); p<0.001
Incident Coronary Heart Disease					
eGFR≥60	826/13001	8.4 (7.9, 9.0)	13.1 (9.8, 16.3); p<0.001	2.6 (1.2, 3.9); p<0.001	1.9 (0.8, 3.0); p=0.001
eGFR 45 - 5	181/1087	21.5 (18.4, 24.7			
eGFR < 45	86/374	34.6 (27.3, 42.0	26.2 (18.9, 33.5); p<0.001	5.4 (2.9, 7.9); p<0.001	3.6 (1.6, 5.5); p<0.001
Incident Stroke					
eGFR≥60	479/13001	4.8 (4.4, 5.3)	6.8 (4.5, 9.0); p<0.001	1.0 (0.1, 2.0); p=0.03	0.6 (-0.2, 1.4); p=0.134
eGFR 45 - 5	100/1087	11.6 (9.3, 13.8)			
eGFR < 45	50/374	19.7 (14.2, 25.1	14.9 (9.3, 20.4); p<0.001	1.6 (0.7, 4.5); p=0.007	1.4 (-0.04, 2.8); p=0.057

Model 1: adjusted for age, sex, race and cohort
Model 2: adjusted for age, sex, race, cohort, hypertension, diabetes, tobacco use, and dyslipidemia