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Original Investigation

Kidney Function and Cardiovascular Events in Postmenopausal Women: The Impact of Race and Ethnicity in the Women's Health Initiative

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Background: Kidney disease disproportionately affects minority populations, including African Americans and Hispanics; therefore, understanding the relationship of kidney function to cardiovascular (CV) outcomes within different racial/ethnic groups is of considerable interest. We investigated the relationship between kidney function and CV events and assessed effect modification by race/ethnicity in the Women's Health Initiative.

Study Design: Prospective cohort study.

Setting & Participants: Baseline serum creatinine concentrations (assay traceable to isotope-dilution mass spectrometry standard) of 19,411 postmenopausal women aged 50 to 79 years who self-identified as either non-Hispanic white (n = 8,921), African American (n = 7,436), or Hispanic (n = 3,054) were used to calculate estimated glomerular filtration rates (eGFRs).

Predictors: Categories of eGFR (exposure); race/ethnicity (effect modifier).

Outcomes: The primary outcome was the composite of 3 physician-adjudicated CV events: myocardial infarction, stroke, or CV-related death.

Measurements: We evaluated the multivariable-adjusted associations between categories of eGFR and CV events using proportional hazards regression and formally tested for effect modification by race/ethnicity.

Results: During a mean follow-up of 7.6 years, 1,424 CV events (653 myocardial infarctions, 627 strokes, and 297 CV-related deaths) were observed. The association between eGFR and CV events was curvilinear; however, the association of eGFR with CV outcomes differed by race ($P = 0.006$). In stratified analyses, we observed that the U-shaped association was present in non-Hispanic whites, whereas African American participants had a rather curvilinear relationship, with lower eGFR being associated with higher CV risk, and higher eGFR, with reduced CV risk. Analyses among Hispanic women were inconclusive owing to few Hispanic women having very low or high eGFRs and very few events occurring in these categories.

Limitations: Lack of urinary albumin measurements; residual confounding by unmeasured or imprecisely measured characteristics.

Conclusions: In postmenopausal women, the patterns of association between eGFR and CV risk differed between non-Hispanic whites and African American women.

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INDEX WORDS: Cardiovascular disease (CVD); CV risk; CV events; myocardial infarction (MI); stroke; CV death; renal function; estimated glomerular filtration rate (eGFR); serum creatinine; race/ethnicity; Hispanic; African American; kidney disease; Women's Health Initiative (WHI).

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Editorial, p. 169

Chronic kidney disease (CKD), defined as glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 or albumin-creatinine ratio (ACR) ≥ 30 mg/g, affects more than 25 million Americans, and its prevalence is increasing.[1,2] Both markers of kidney function are directly and independently associated with all-cause and cardiovascular (CV) mortality.[3,4] Furthermore, evidence is accumulating that minority populations are disproportionately affected by kidney disease, with African Americans having a higher risk of CKD that is more likely to progress to end-stage renal disease compared with whites.[5] Faster kidney function decline and increased risk of end-stage renal disease also exist in Hispanics compared with non-Hispanics.[6,7]

Recent evidence suggests that the association between CKD and CV outcomes may differ by race.[4,8] Although previous studies have reported sex differences in the associations of estimated GFR (eGFR) and albuminuria with CV and all-cause mortality, relatively little is known about the association between decreased kidney function and CV risk and its potential modification by race or ethnicity among postmenopausal women in the United States.[9-13] Because most existing studies have predominantly examined white women, more information is needed on women of other racial/ethnic groups.

The multiethnic Women's Health Initiative (WHI) prospective cohort study of postmenopausal women, for whom creatinine concentrations were measured in a large subset at baseline, provides an opportunity to assess the associations of GFR with myocardial infarction (MI), stroke, and CV death. We hypothesized that these associations would differ among racial and ethnic groups.

METHODS

Study Design and Population

The WHI is a large prospective multicenter cohort study that focuses on strategies for preventing heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women aged 50 to 79 years recruited from September 1993 through December 1998. Participants were postmenopausal if they had had some combination of the following: hysterectomy, double oophorectomy, conclusion of menstrual bleeding, vasomotor symptoms, or prescribed hormone therapy. The WHI Study consists of an observational study cohort and 3 clinical trial components (a hormone therapy component, a dietary modification component, and a calcium/vitamin D component). Details of eligibility criteria, data collection, and ascertainment of health outcomes have been reported previously (see Item S1, available as online supplementary material, for WHI clinical trial and observational study design).[14,15]

Our analysis was restricted to a subset of WHI participants who participated in the WHI Core Biomarker Studies, including 8,505 African American and 3,503 Hispanic participants who constituted the WHI Single Nucleotide Polymorphism (SNP) Health Association Resource (SHARe) cohort and 10,300 participants of European ancestry who had participated in the WHI Memory Study,[16] an ancillary study of the WHI hormone trials, or whose samples were analyzed in another WHI ancillary study, the Genomic and Randomized Trials Network (GARNET) Study (Fig 1).[17] African American and Hispanic participants in the SHARe cohort were drawn from the observational study and the clinical trial components. Participants of European ancestry were drawn from the hormone therapy components. Participants in these trials provided baseline data on various CV disease biomarkers, including creatinine, cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, insulin, glucose, and C-reactive protein. After excluding participants whose serum creatinine measurements were not available (n = 197) and/or those with missing data on covariates of interest (n = 2,700), the final cohort included 19,411 participants. There were no clear patterns of missingness in our covariates and none of the variables we excluded had missing rates > 5%.

Primary Exposure of Interest

The exposure of interest was eGFR at baseline. Stored frozen serum specimens were sent to the University of Minnesota−Fairview laboratory for measurement of baseline creatinine concentrations and other CV risk markers (discussed next). Serum creatinine was measured by the Roche enzymatic method on a Roche Modular P Chemistry Analyzer (Roche Diagnostic Corp) and calibrated against

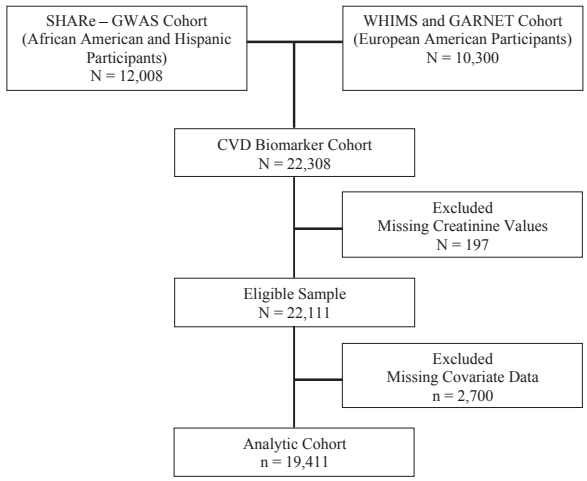

Figure 1. Flow diagram of Women's Health Initiative (WHI) cardiovascular disease (CVD) biomarker study cohort. Our analysis was restricted to a subset of WHI participants who participated in the WHI Core Biomarker Studies, including 8,505 African American and 3,503 Hispanic participants who constituted the WHI Single Nucleotide Polymorphism (SNP) Health Association Resource (SHARe) cohort and 10,300 participants of European ancestry who had participated in the WHI Memory Study (WHIMS) or whose samples were analyzed in another WHI ancillary study, the Genomic and Randomized Trials Network (GARNET) Study.[17] African American and Hispanic participants in the SHARe cohort were drawn from the observational study and the clinical trial components. Participants of European ancestry were drawn from the hormone therapy components. Participants in these trials provided baseline data on various CVD biomarkers, including creatinine. After excluding participants whose serum creatinine measurements were not available (n = 197) and/or those with missing data for covariates of interest (n = 2,700), the final cohort included 19,411 participants. Abbreviation: GWAS, genome-wide association study.