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Association of *APOL1* With Heart Failure With Preserved Ejection Fraction in Postmenopausal African American Women

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IMPORTANCE *APOL1* genotypes are associated with kidney diseases in African American individuals and may influence cardiovascular disease and mortality risk, but findings have been inconsistent.

OBJECTIVE To discern whether high-risk *APOL1* genotypes are associated with cardiovascular disease and stroke in postmenopausal African American women, who are at high risk for these outcomes.

DESIGN, SETTING, AND PARTICIPANTS The Women's Health Initiative is a prospective cohort that enrolled 161 838 postmenopausal women into clinical trials and an observational study between 1993 and 1998. This study includes 11 137 African American women participants who had a clinical event from enrollment to June 2014. Data analyses were completed from January 2017 to August 2017.

EXPOSURES The variants of *APOL1* were genotyped or imputed from whole-exome sequencing.

MAIN OUTCOMES AND MEASURES Incident coronary heart disease, stroke and heart failure subtypes, and overall and cause-specific mortality were adjudicated from hospital records and death certificates. Estimated incidence rates were determined for each outcome and hazard ratios (HR) and 95% CIs for the associations of *APOL1* groups with outcomes.

RESULTS The mean (SD) age of participants was 61.7 (7.1) years. Carriers of high-risk *APOL1* variants (n = 1370; 12.3%) had higher prevalence of hypertension, use of cholesterol-lowering medications, and reduced estimated glomerular filtration rate (eGFR). After a mean (SD) of 11.0 (3.6) years, carriers of high-risk *APOL1* variants had a higher incidence rate of hospitalized heart failure with preserved ejection fraction (HFpEF) than low-risk carriers did but showed no differences for other outcomes. In adjusted models, there was a significant 58% increased hazard of hospitalized HFpEF (HR, 1.58 [95% CI, 1.03-2.41]) among carriers of high-risk *APOL1* variants compared with carriers of low-risk *APOL1* variants. The association with HFpEF was attenuated (HR = 1.50 [95% CI, 0.98-2.30]) and no longer significant when adjusting for baseline eGFR.

CONCLUSIONS AND RELEVANCE Status as a carrier of a high-risk *APOL1* genotype was associated with HFpEF hospitalization among postmenopausal women, which is partly accounted for by baseline kidney function. These findings do not support an association of high-risk *APOL1* genotypes with coronary heart disease, stroke, or mortality in postmenopausal African American women.

Supplemental content

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Cardiovascular disease is the leading cause of morbidity and mortality in African American women, who have higher rates of hypertension, coronary heart disease (CHD), stroke, and heart failure compared with women of other racial/ethnic backgrounds.[1] The incidence of myocardial infarction or fatal CHD for African American women is high and equivalent to that of white men.[1-3] Heart failure also becomes more common among African American women as they age.[4] The increased cardiovascular disease risk can be explained in part by socioeconomic factors and by a high burden of comorbidities in African American individuals, including hypertension, diabetes, obesity, and chronic kidney disease (CKD).[1,4] Genetic factors may also contribute to these racial/ethnic disparities.

Recent research suggested a role for African ancestry-specific alleles in the apolipoprotein L1 (*APOL1*) gene in cardiovascular disease and mortality in African American individuals.[5,6] Two high-risk *APOL1* genotypes (G1 and G2), combined, are present in approximately 13% in African American individuals and confer an estimated 20% lifetime risk of developing CKD.[7,8] These alleles are under positive selection in populations of African ancestry, as they confer resistance against a trypanosomal infection found in Africa.[9] The G1 allele comprises 2 highly correlated amino acid–changing variants, whereas G2 encodes a 6-base pair deletion that deletes 2 amino acids. The resulting protein, APOL1, is a minor apolipoprotein component of high-density lipoprotein cholesterol. It is expressed in vascular tissue[10,11] and may play role in atherosclerosis.[12]

Associations of *APOL1* alleles with cardiovascular disease and mortality were reported in African American participants of the Jackson Heart Study and among Medicare-eligible participants of the Cardiovascular Health Study but not in subsequent cross-sectional and longitudinal studies.[5,13-17] Differences in study design, outcome type, and the number of events in these studies may account for inconsistencies.

Important questions remain about the broad influence of high-risk *APOL1* alleles on cardiovascular mortality and overall mortality for African American individuals who carry these *APOL1* variants, particularly postmenopausal women. Prior studies were underpowered to examine CHD and stroke (and its subtypes) as separate outcomes and have not examined the association of *APOL1* genotypes with heart failure subtypes or the association of these genotypes with outcomes in postmenopausal women. Chronic kidney disease is strongly associated with premature atherosclerosis, cardiovascular disease, and other health outcomes, including early mortality.[18-20] Therefore, *APOL1* associations with cardiovascular events could be associated with its role in promoting CKD. To examine these questions and address confounding, we used a large longitudinal sample of 11 137 African American participants in the Women's Health Initiative (WHI), composed of postmenopausal women, and we analyzed adjudicated outcomes including CHD, stroke, heart failure and its subtypes, and mortality. We also examined the associations of *APOL1* with end-stage renal disease (ESRD) in postmenopausal women and among those who had a hospitalization for heart failure.

Key Points

Question Are *APOL1* risk genotypes associated with cardiovascular disease and stroke in postmenopausal African American women?

Findings In this study of 11 137 participants in the Women's Health Initiative, high-risk *APOL1* genotypes were not associated with coronary heart disease, stroke, and all-cause and cardiovascular mortality. However, high-risk *APOL1* genotypes were associated with hospitalized heart failure with preserved ejection fraction, but associations were partly accounted for by baseline kidney function.

Meaning This study does not support a relationship among high-risk *APOL1* genotypes and cardiovascular disease in postmenopausal women, except for heart failure with preserved ejection fraction, mechanisms of which might include chronic kidney disease.

Methods

Study Population

The WHI is a prospective cohort study investigating postmenopausal women's health in the United States.[21] A total of 161 838 women aged 50 to 79 years old were recruited from 40 clinical centers between 1993 and 1998 to participate in an observational study and in 4 randomized clinical trials.[21-23] Recruitment was done through mass mailing to age-eligible women from lists obtained from voter registration, driver's license, and Health Care Financing Administration or other insurance lists, with emphasis on racial/ethnic minorities and older women.[21]

Study protocols and consent forms were approved by the institutional review boards at all participating institutions. Participants provided informed consent at the time of enrollment. This study adheres to the Declaration of Helsinki.

The WHI has collected comprehensive information on demographics, lifestyle and behaviors, medical history, medications, and cardiometabolic risk factors through clinical visits and questionnaire collections.[21] Anthropometrics and blood pressure were obtained through a physical examination. Serum creatinine was assayed using an enzymatic colorimetric method, traceable to an isotope dilution mass spectrometry reference method (coefficient of variation, 3.7%).[24] Glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology equation,[25] based on serum creatinine value, age, sex, and race/ethnicity.

Of a total of 14 618 African American women who were recruited into the WHI, we excluded women with missing data on genotypes and covariates at baseline or cardiovascular and kidney outcomes at follow-up. The final sample was 11 137 women (76.2%).

Exposure: *APOL1* Genotypes

The *APOL1* alleles G1 (rs73885319 and rs60910145) and G2 (rs71785313) were directly genotyped using the Taqman assay (Thermo Fisher Scientific) in 6293 individuals, of which 2491 overlapped with a genome-wide association study (GWAS) that includes 8515 African American individuals who were

genotyped using Affymetrix Genome-Wide Human SNP Array 6.0 (Thermo Fisher Scientific). The G1 variants were in high linkage disequilibrium (R^2 = 0.98), so only rs73885319 was used in analyses. Genotyping quality control included setting call rates to greater than 97% and Hardy-Weinberg equilibrium *P* to less than .05. The *APOL1* G1 variant was imputed in GWAS samples (n = 6024) using a reference panel from the Exome Sequencing Project (ESP), which also included the WHI samples with Exome Chip data.[26] For the G2 variant, a reference panel was built from 1530 African American individuals with overlapping sequencing from the ESP and GWAS data. The imputation quality for rs73885319 and rs71785313 (estimated R^2) were 0.76 and 0.78, respectively, which are considered moderate to high quality.[26] Correlation among genotyped and imputed *APOL1* data are shown in the eFigure in the Supplement; these demonstrate good quality of imputation for these variants using exome sequencing and exomechip data. Principal components of genetic variation were computed in the GWAS sample using standard methods and implemented in the EIGENSTRAT function of the EIGENSOFT package, version 6.1.4 (Price Lab, Harvard T. H. Chan School of Public Health).[27]

Cardiovascular Disease Outcomes and Mortality

The WHI has standardized protocols for the ascertainment and classification of CHD, stroke and its subtypes, heart failure and its subtypes, and overall and cause-specific mortality. Annual follow-up visits (for the observational study) and semiannual visits (for randomized clinical trials) identifies self-reported events, including mortality. Clinical events were reviewed using hospital records, death certificates, and interviews of next of kin and classified by an expert panel of physicians.[28] Coronary heart disease was defined as a hospitalized acute myocardial infarction, definite silent myocardial infarction (defined on electrocardiogram), surgical or percutaneous procedures, or death associated with CHD. Acute myocardial infarction was based on cardiac pain, cardiac markers, and electrocardiogram readings. Stroke was defined as a rapid onset of a persistent neurological deficit attributed to a brain vascular event lasting more than 24 hours and without evidence for other causes, as obtained from hospitalization records; it did not included transient ischemic attacks. Strokes were classified into ischemic, hemorrhagic, or of indeterminate causative mechanisms. Given the small number of hemorrhagic strokes, we did not report this as a separate outcome. Heart failure (definitive or probable) was defined based on a first hospitalization for acute or chronic heart failure through medical history, medications, symptoms, signs, imaging, and biomarkers and other adjudication criteria previously published.[29,30] Events were classified into mutually exclusive categories: (1) preserved ejection fraction (HFpEF) (left ventricular ejection fraction [LVEF] ≥ 50%), (2) reduced ejection fraction (HFrEF) (LVEF < 50%), and (3) unknown ejection fraction heart failure (without documentation of LVEF) based on echocardiograms.[29] Unclassified heart failure (n = 95; 24.0% of 396 events [342 low-risk events and 54 high-risk events]) were only included in all-cause heart failure but not in analyses of heart failure subtypes. Participants with unclassified heart failure compared with patients with HFpEF or HFrEF were slightly older (unclassified heart failure: mean [SD] age, 65.8 [7.7] vs HFpEF: 64.9 [7.1] vs HFrEF: 63.8 [7.5] years, respectively), more likely to be obese (69 of 95 [72.6%] vs 108 of 154 [70.6%] and 70 of 144 [50.4%]), more likely to be hypertensive (78 of 95 [82.1%] vs 121 of 154 [78.6%] vs 113 of 144 [78.5%]), less likely to have diabetes (21 of 95 [22.1%] vs 49 of 154 [31.8%] and 41 of 144 [28.5%]), and less likely to have a high-risk *APOL1* genotype (10 of 95 [10.5%] vs 26 of 154 [16.8%] and 18 of 144 [12.5%]) (eTable 1 in the Supplement). The maximum serum creatinine levels during heart failure hospitalization were abstracted from medical records. End-stage renal disease events were drawn from the US Renal Data System for events occurring in or before 2014. Mortality was ascertained from death certificates and interviews of next of kin and adjudicated by expert physicians.[28]

Statistical Analyses

For descriptive analyses of baseline data, means, SDs, and frequencies were calculated as appropriate. The primary exposure was the presence of high-risk *APOL1* genotypes, using a recessive model (G1/G1, G2/G2, or compound heterozygotes G1/G2) compared with low-risk genotypes (G1/G0, G2/G0, or G0/G0). We estimated the incidence rate of each outcome for African American individuals carrying high-risk and low-risk *APOL1* genotypes using Poisson regression. Person-time at risk was defined as the time between baseline examination and the event or the last date of follow-up.

Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CIs for the associations of *APOL1* groups with outcomes. Model 1 was age adjusted. Model 2 was adjusted for age, education (high school or less vs some college or more), cigarette smoking (ever vs never), income (in US dollars), body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), systolic and diastolic blood pressures, use of lipid-lowering medications and antihypertensive drugs (including angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers), and history of diabetes mellitus. Model 3 further adjusted for baseline eGFR because early CKD is a determinant of ESRD and cardiovascular diseases.[31] Models 2 and 3 also included an indicator variable for participation in the observational study vs the clinical trials and another for geographic region.

We tested the a priori hypothesis of interactions with diabetes, hypertension, and CKD using models 2 and 3. We examined a composite outcome of CHD and ischemic stroke. In a secondary analysis restricted to the sample on whom GWAS had been performed, we used models 2 and 3 covariates and further adjusted for the first 3 principal components of ancestry. We also examined the additive genetic association of number of copies of *APOL1* genotypes with outcomes, stratified by high-risk and low-risk genotypes. Last, we estimated the proportion of women that developed ESRD after a heart failure hospitalization by *APOL1* risk status. For significant thresholds, we used an α of .05 in a 2-sided test. All analyses were performed using Stata version 11.0 (StataCorp) and SAS version 9.4 (SAS Institute). Data collection was completed from enrollment in 1993 to 1998 to June 2014. Data analyses were completed from January 2017 to August 2017.

Table 1. Baseline Characteristic of Participants Overall and by *APOL1* Genotypes: Women's Health Initiative (1993-1998)

Characteristic	Participants, No. (%)		
	Overall (n = 11 137)	Low-Risk *APOL1* Variant (n = 9767)	High-Risk *APOL1* Variant (n = 1370)
Age, mean (SD), y	61.7 (7.1)	61.7 (7.1)	61.5 (7.1)
Age range, y			
50-59	4556 (40.9)	571 (41.7)	3985 (40.8)
60-69	4807 (43.2)	604 (44.1)	4203 (43.0)
70 or more	1774 (15.9)	195 (14.2)	1579 (16.2)
Education			
<high school	1278 (11.5)	1096 (11.2)	182 (13.3)
≥High school	9859 (88.5)	1188 (86.7)	8671 (88.8)
Household Income, $			
<35 000	1937 (17.4)	1708 (17.5)	229 (16.7)
35 000-74 000	3616 (32.5)	3190 (32.7)	426 (31.1)
≥75 000	5584 (50.1)	4869 (49.9)	715 (52.2)
Have ever smoked	5719 (51.4)	5031 (51.5)	688 (50.2)
BMI, mean (SD)	31.1 (6.6)	31.1 (6.6)	31.3 (6.7)
Waist circumference, mean (SD), cm	91.8 (14.0)	91.7 (14.0)	92.2 (14.1)
Overweight/obese	3653 [33.1]/ 5597[50.7]	3198 [33.0]/ 4903 [50.6]	455 [33.6]/ 694 [51.3]
Diabetes	1472 (13.2)	1296 (13.3)	176 (12.9)
Hypertension	6207 (55.7)	5419 (55.5)	788 (57.5)
High cholesterol requiring medications	950 (8.5)	823 (8.4)	127 (9.3)
Systolic blood pressure, mean (SD), mm Hg	132.3 (17.9)	132.2 (17.8)	133.1 (18.4)
Diastolic blood pressure, mean (SD), mm Hg	78.3 (9.5)	78.2 (9.5)	78.6 (9.8)
History of cardiovascular disease[a]	2095 (19.1)	1825 (19.0)	270 (20.0)
eGFR,[b] mean (SD), mL/min/1.73 m^2	92.5 (19.0)	92.9 (18.8)	89.8 (20.1)
Chronic kidney disease[b]	607 (5.5)	506 (5.2)	101 (7.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate.

[a] Prevalent cardiovascular disease includes history of myocardial infarction, coronary heart disease procedures, or peripheral artery disease.

[b] Chronic kidney disease is defined by an eGFR less than 60 mL/min/1.73 m^2.

Results

Among 11 137 African American women, the mean (SD) age at recruitment was 61.7 (7.1) years, and the prevalence of high-risk *APOL1* genotypes was 12.3% (n = 1370). The baseline prevalence of risk factors was similar among individuals with high-risk and low-risk *APOL1* genotypes, except that high-risk *APOL1* variant carriers had a higher prevalence of hypertension (in low-risk variant carriers: 5419 [55.5%] vs high-risk variant carriers: 788 [57.5%]), higher use of cholesterol-lowering medications (low-risk variant carriers: 823 [8.4%] vs high-risk variant carriers: 127 [9.3%]), and lower mean eGFR (defined by a cutoff value of < 60 mL/min/1.73 m^2; low-risk variant carriers: mean [SD], 92.9 [18.8] mL/min/1.73 m^2 vs high-risk variant carriers: 89.8 [20.1] mL/min/1.73 m^2; **Table 1**).

The incidence rates of ESRD, CHD, stroke, heart failure, and mortality are shown in **Table 2**. After a mean (SD) follow-up of 11.0 (3.6) years, the most common outcomes were death of any cause, followed by fatal CHD, nonfatal CHD, ischemic stroke, hospitalization for heart failure, and hospitalization for ESRD. Carriers of high-risk *APOL1* variants vs low-risk variants had higher point estimates for incident rates of ESRD (low-risk variant carriers: incident rate [IR] per 1000 person-years: 1.85 [95% CI, 1.61-2.13] vs high-risk variant carriers: 2.68 [95% CI, 1.97-3.66]), CHD (low-risk variant carriers: IR per 1000 person-years, 6.02 [95% CI, 5.52-6.56] vs high-risk variant carriers: 6.50 [95% CI, 5.19-8.14]), all-cause heart failure (low-risk variant carriers: IR per 1000 person-years, 2.83 [95% CI, 2.54-3.15] vs high-risk variant carriers: 3.26 [95% CI, 2.50-4.26]), and hospitalization for heart failure with preserved ejection fraction (HFpEF) (low-risk variant carriers: IR per 1000 person-years, 1.05 [95% CI, 0.87-1.26] vs high-risk variant carriers: 1.57 [95% CI, 1.07-2.30]), but lower estimates for incidence rates of all-cause stroke (low-risk variant carriers: IR per 1000 person-years, 4.46 [95% CI, 4.10-4.87] vs high-risk variant carriers: 3.90 [95% CI, 3.02-5.05]) and ischemic stroke (low-risk variant carriers: IR per 1000 person-years, 3.14 [95% CI, 2.82-3.50] vs high-risk variant carriers: 2.56 [95% CI, 1.87-3.52]; Table 2).

Table 3 shows the hazard ratio for each health outcome comparing individuals carrying high-risk vs low-risk *APOL1* genotypes. In the age-adjusted models (model 1), high-risk *APOL1* status was significantly associated with ESRD (HR, 1.42 [95% CI, 1.01-1.99]), hospitalized HFpEF (HR, 1.54 [95% CI, 1.01-2.35]), and cardiovascular disease mortality (HR, 1.10 [95% CI, 1.09-1.12]). In the fully adjusted model (model 2), there was a 43% increased risk of ESRD (HR, 1.43 [95% CI, 1.01-2.02]) and a 58% increased risk of hospitalized HFpEF (HR, 1.58 [95% CI, 1.03-2.41]) among individuals with high-risk *APOL1* status com-

pared with those with low-risk *APOL1* status. However, the association of *APOL1* with cardiovascular mortality was attenuated and no longer significant in the fully adjusted models (HR, 1.05 [95% CI, 0.83-1.34]). After adjusting for baseline eGFR, the associations of *APOL1* genotypes with both ESRD and HFpEF were no longer significant, but estimates for association with HFpEF were only slightly reduced (model 2: HR, 1.58 [95% CI, 1.03-2.41]; model 3: 1.50 [95% CI, 0.98-2.30]). When excluding individuals with CKD at baseline, the HR for HFpEF was 1.42 (95% CI, 0.87-2.33). There were no significant interactions among *APOL1* genotypes and baseline diabetes, hypertension, or CKD (defined by an eGFR < 60 mL/min/1.73 m^2) for any of the outcomes ($P > .05$).

In the sensitivity analysis restricted to the GWAS sample (n = 7797), we assessed the association of *APOL1* with all outcomes, including HFpEF (events = 142) using model 2 covariates and further adjustments for principal components to account for population stratification. These analyses showed similar patterns of associations for high-risk *APOL1* genotypes with HFpEF (eTable 2 in the Supplement). Additional analyses using *APOL1* genotype copies (zero, 1 copy, or 2 copies, in an additive model) showed no significant association with cardiovascular outcomes (eTable 3 in the Supplement).

Women with a heart failure event had a higher prevalence of cardiovascular and kidney disease risk factors at baseline compared with the overall cohort (**Table 4**) and a higher prevalence of CKD (women with heart failure: n = 65 [16.4%] vs overall cohort: n = 607 [5.5%]). At baseline, high-risk *APOL1* carriers had lower mean eGFR and higher prevalence of CKD compared with low-risk *APOL1* carriers. Forty-four women with a heart failure event (11.1%) reached ESRD before or at the heart failure hospitalization, with similar frequency among carriers of high-risk *APOL1* variants (n = 6 of 54 [11.1%]) vs low-risk *APOL1* variants (n = 38 of 342 [11.1%]). Among 312 women without ESRD at the heart failure event, the maximum mean (SD) serum creatinine at hospitalization was 2.24 (1.89) mg/dL

Table 2. Incidence Rates of End-stage Renal Disease and Cardiovascular Outcomes by *APOL1* Genotypes, Stratified by Risk Status

	Low-Risk *APOL1* Variant Carriers (n = 9767)		High-Risk *APOL1* Variant Carriers (n = 1370)	
Incident Outcome	Events, No.	Incidence Rate (95% CI) per 1000 Person-Years	Events, No.	Incidence Rate (95% CI) per 1000 Person-Years
End-stage renal disease	199	1.85 (1.61-2.13)	40	2.68 (1.97-3.66)
Coronary heart disease[a]	516	6.02 (5.52-6.56)	76	6.50 (5.19-8.14)
All-cause stroke	475	4.46 (4.10-4.87)	58	3.90 (3.02-5.05)
Ischemic stroke	334	3.14 (2.82-3.50)	38	2.56 (1.87-3.52)
All-cause heart failure	342	2.83 (2.54-3.15)	54	3.26 (2.50-4.26)
HFpEF[b]	128	1.05 (0.87-1.26)	26	1.57 (1.07-2.30)
HFrEF[c]	126	1.05 (0.88-1.25)	18	1.09 (0.68-1.72)
All-cause death	1526	14.1 (13.4-14.8)	211	14.1 (12.3-16.1)
Cardiovascular death	541	5.03 (4.63-5.47)	76	5.08 (4.06-6.36)
Composite coronary heart disease or ischemic stroke	710	8.39 (7.80-9.03)	97	8.39 (6.87-10.23)

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

[a] Among individuals without prevalent cardiovascular disease.

[b] n = 10 971.

[c] n = 10 961.

Table 3. Hazard Ratio of End-stage Renal Disease, Coronary Heart Disease, Stroke, and Mortality in African American Women With High-Risk *APOL1* Genotypes[a]

	Hazard Ratio (95% CI)		
Incident Outcome	Model 1	Model 2	Model 3
End-stage renal disease	1.42 (1.01-1.99)	1.43 (1.01-2.02)	1.02 (0.72-1.45)
Coronary heart disease[b]	1.13 (0.89-1.43)	1.15 (0.90-1.46)	1.13 (0.89-1.44)
All-cause stroke	0.92 (0.70-1.21)	0.88 (0.67-1.16)	0.84 (0.64-1.11)
Ischemic stroke	0.84 (0.60-1.18)	0.82 (0.58-1.14)	0.78 (0.56-1.10)
All-cause heart failure	1.19 (0.89-1.58)	1.18 (0.89-1.58)	1.13 (0.84-1.50)
HFpEF[c]	1.54 (1.01-2.35)	1.58 (1.03-2.41)	1.50 (0.98-2.30)
HFrEF[d]	1.07 (0.65-1.75)	1.05 (0.64-1.71)	1.00 (0.61-1.65)
All-cause death	1.06 (0.92-1.23)	1.06 (0.92-1.23)	1.02 (0.89-1.18)
Cardiovascular disease mortality	1.10 (1.09-1.12)	1.05 (0.83-1.34)	1.01 (0.79-1.29)
Composite coronary heart disease and ischemic stroke	1.02 (0.85-1.23)	1.01 (0.84-1.22)	1.00 (0.83-1.20)

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

[a] Model 1 was age adjusted. Model 2 was adjusted for age, waist, education, income, region, smoking, systolic blood pressure, diastolic blood pressure, hypertension treatment, diabetes, enrollment in observational study vs randomized clinical trial, and use of lipid medications. Model 3 was model 2, further adjusted for baseline glomerular filtration rate. All values are with reference to the low-risk *APOL1* variant carrier group.

[b] Among individuals without prevalent CVD.

[c] n = 10 971.

[d] n = 10 961.

Table 4. Clinical Characteristics and Kidney Outcomes of African American Participants in the Women's Health Initiative With Hospitalized Heart Failure, Stratified by Risk Status

Characteristic	No. (%)		
	Overall	Low-Risk *APOL1* Variant Carriers	High-Risk *APOL1* Variant Carriers
Baseline, No.	396	342	54
Age, mean (SD), y	64.7 (7.4)	64.8 (7.4)	64.2 (7.6)
Have ever smoked	219 (55.3)	190 (55.6)	29 (53.7)
Obese[a]	249 (63.9)	211 (62.4)	38 (73.1)
Diabetes	112 (28.3)	97 (28.4)	15 (27.8)
Hypertension	315 (79.6)	275 (80.4)	40 (74.1)
History of cardiovascular disease	157 (40.1)	136 (40.1)	21 (39.6)
eGFR, mean (SD), mL/min/1.73 m^2	84.1 (23.2)	84.9 (22.4)	78.7 (27.2)
Chronic kidney disease[b]	65 (16.4)	52 (15.2)	13 (24.1)
Heart failure hospitalization, No.	396	342	54
End-stage renal disease before or at hospitalization	44 (11.1)	38 (11.1)	6 (11.1)
HFpEF	154 (38.9)	128 (37.4)	26 (48.2)
HFrEF	144 (36.4)	126 (36.8)	18 (33.3)
Kidney outcomes after heart failure event,[c] No.	312	271	41
Maximum inpatient serum creatinine, mean (SD), mg/dL	1.72 (1.34)	1.64 (1.21)	2.24 (1.89)
End-stage renal disease events at follow-up	37 (11.9)	29 (10.7)	8 (19.5)
Time from heart failure to incident end-stage renal disease, y	3.4 (3.5)	3.3 (3.4)	3.9 (3.9)

Abbreviations: eGFR, estimate glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

[a] Obesity is defined by a body mass index (calculated as weight in kilograms divided by height in meters squared) equal to or greater than 30.

[b] Chronic kidney disease is defined by an eGFR less than 60 mL/min/1.73 m^2.

[c] Among women without end-stage renal disease at hospitalization.

for carriers of high-risk *APOL1* variants compared with 1.64 (1.21) mg/dL for carriers of the low-risk *APOL1* variants. In addition, 8 of 41 of carriers of high-risk *APOL1* variants (19.5%) and 29 of 271 carriers of low-risk *APOL1* variants (10.7%) newly developed ESRD after hospitalization for heart failure after a mean (SD) follow-up time of 3.9 (3.9) and 3.3 (3.4) years, respectively. Overall, among women with a hospitalization for heart failure, 11 of 54 high-risk (20.4%) and 38 of 342 (11.1%) low-risk genotype carriers developed ESRD at a mean (SD) follow-up time of 11.0 (4.0) and 10.5 (4.1) years. In comparison, among women without a hospitalization for heart failure, 29 of 1311 high-risk *APOL1* carriers (2.2%) and 160 of 9408 (1.7%) low-risk *APOL1* carriers developed ESRD at a mean (SD) follow-up time of 11.0 (3.6) and 10.8 (3.6) years, respectively.

Discussion

In this large longitudinal study of postmenopausal African American women at risk for cardiovascular events, we confirmed the association of high-risk *APOL1* status with incident ESRD and identified an association of high-risk *APOL1* variant carriers with hospitalization for heart failure with preserved LVEF (HFpEF). The main findings are also notable for the lack of association of high-risk *APOL1* variant carrier status with CHD, stroke (all-cause and subtypes), mortality (all-cause and cardiovascular-associated) and a composite outcome (fatal and nonfatal CHD and ischemic stroke) when accounting for known risk factors. High-risk *APOL1* genotypes were associated with a 58% increase risk in hospitalized HFpEF but not overall heart failure or heart failure because of reduced LVEF (HFrEF). Post hoc power analyses showed that this study has excellent power to detect a hazard difference of 1.2 to 1.4 among high-risk and low-risk *APOL1* variant carrier groups for all cardiovascular outcomes (eTable 4 in the Supplement). Supporting our findings, a recent publication from the Multiethnic Study of Atherosclerosis showed an 82% increased hazard of overall heart failure for carriers of high-risk *APOL1* variants (95% CI, 1.01-3.28), although the study did not report associations with heart failure subtypes.[16]

The diagnosis of HFpEF is based on typical symptoms and signs of heart failure in a patient with normal LVEF as detected by echocardiography.[32] The condition is present in 30% to 50% of all patients with heart failure, and the prevalence is 2-fold higher in older women than older men.[33] Current evidence suggests distinct pathophysiological mechanisms and different responses to therapy in HFpEF compared with HFrEF,[32] although hospitalization and mortality rates are similar.[34] Several risk factors have been identified for HFpEF including CKD, obesity, and inflammation,[35-37] which is also shown in a prior study of heart failure in the WHI, although eGFR was not examined as a risk factor.[30] The APOL1 protein is involved in innate immunity,[12] and *APOL1*-associated CKD occurs in inflammatory states, such as HIV infection and lupus.[7,38] Further research is needed to understand the relationship of *APOL1*, inflammation, and HFpEF after the findings of this study are replicated.

In the current study, the association among high-risk *APOL1* genotypes and ESRD was reduced from 1.43 to 1.02 when adjusting for baseline eGFR, which was consistent with baseline kidney function as a risk factor for progression to ESRD. However, the association of *APOL1* with HFpEF was partially attenuated (HR, 1.58 to 1.50) when adjusting for baseline eGFR and slightly reduced to 1.42 when excluding

participants with CKD. In the Multiethnic Study of Atherosclerosis, the association with overall heart failure was unchanged when adjusting for baseline eGFR or urine albumin excretion.[16] These findings suggest that additional factors account for the *APOL1*-HFpEF associations. Variants of *APOL1* may modulate furosemide-induced diuresis in heart failure.[39] A meta-analysis of 3 randomized trials of intravenous furosemide conducted in patients with decompensated heart failure identified associations of *APOL1* variants (including G1) with fluid loss. (The G2 variant was not examined.) Because worsening kidney function and heart failure are interassociated, longitudinal assessments of kidney function will be needed to clarify their complex causal relationships, specifically in association with *APOL1* risk.

An important finding of this study is the lack of association of *APOL1* with several cardiovascular outcomes. Two prior studies showed significant association of *APOL1* genotypes with cardiovascular disease.[5,6] These studies had a small number of cardiovascular events and/or used composite cardiovascular outcomes. Ito et al[5] reported a 2-fold increased risk in the Jackson Heart Study for a composite outcome of myocardial infarction, stroke or transient ischemic attacks, and surgical or percutaneous intervention among 1959 African-American men and women carrying high-risk vs low-risk *APOL1* genotypes, although carriers of high-risk *APOL1* variants had lower coronary artery calcification scores. Replication was performed in 749 women in the WHI cohort, who were selected for extreme values of low-density lipoprotein cholesterol and blood pressure or early myocardial infarction and stroke for exome sequencing, and sampling selection could explain some of the results.[40] In contrast, our samples included most of the recruited African American women in the WHI study, and it reflects more closely the general population. The Cardiovascular Health Study reported 80% and 30% increased hazard of myocardial infarction and total mortality, respectively, among 798 Medicare-eligible participants carrying high-risk compared to low-risk *APOL1* genotypes.[6] There were no significant associations of *APOL1* with heart failure and stroke, although the number of events were small (n = 12 and 23, respectively). Genotypes of *APOL1* have not been associated with imaging differences in cardiac hypertrophy, left ventricular geometry, subclinical atherosclerosis, or longitudinal increases in blood pressure.[5,41,42]

This study provides new information on incidence rates of ESRD for high-risk *APOL1* variants in postmenopausal women, which were lower than described in population studies[43] that combined men and women (2.6 and 3.4 per 1000 person-years, respectively). The women in the WHI cohorts who had high-risk *APOL1* genotypes had higher prevalence of CKD at baseline, higher serum creatinine on heart failure hospitalization, and more commonly developed ESRD at follow-up. However, the overall and cardiovascular-associated mortality were similar among carriers of high-risk or low-risk *APOL1* variants. Our prior research has shown that early mortality is not a competing risk for ESRD in women in the WHI cohort.[44]

Limitations

This study is limited to women, which prevented assessment of sex differences in *APOL1* risk in association with outcomes. We could not assess the associations of *APOL1* with subclinical atherosclerosis or albuminuria, which are not available in the WHI data. The main hypotheses were tested without correction for multiple testing, given that this is a hypothesis-driven study. The associations of *APOL1* with HFpEF should be confirmed in additional studies that focus on heart morphology and function.

Conclusions

To our knowledge, this is the largest study of the association of *APOL1* alleles with cardiovascular disease and CKD in postmenopausal African American women, and it includes a long follow-up time and adjudicated and validated clinical events. We examined the most clinically relevant outcomes, including CHD, ischemic stroke, heart failure and its subtypes, and mortality, and provided evidence for the association of *APOL1* with HFpEF. While the function of *APOL1* remains to be elucidated, these findings identify potential genetic susceptibility to detrimental consequences of kidney disease and HFpEF that disproportionately affect African American women, as well as important information on the lack of association of *APOL1* variants with CHD, stroke, and mortality in postmenopausal African American women.[15,45]

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