

## RESEARCH LETTER

**APOL1 Risk Alleles, Cardiac Markers, and Risk of ESKD in African Americans: The Atherosclerosis Risk in Communities Study**

To the Editor:

African Americans face a higher risk for chronic kidney disease and kidney failure compared with people of European ancestry. Part of this risk has been attributed to genetic factors. The presence of 2 risk alleles in the *APOL1* gene, a genotype present in 13% of African Americans, is associated with 2-fold increased risk for end-stage kidney disease (ESKD).<sup>1</sup> However, not everyone with the high-risk genotype progresses to ESKD. It has been suggested that a “second hit,” an exposure that increases the risk of the *APOL1* high-risk genotype, is required for kidney function decline.<sup>2</sup>

Cardiovascular damage could play a role in precipitating kidney function decline. Cardiac troponin T, troponin I, and N-terminal pro-brain natriuretic peptide (NT-proBNP) are markers of cardiac damage that are used in diagnosing myocardial infarction and heart failure and are increasingly recognized as prognostic markers, even at subclinical levels.<sup>3-5</sup> High-sensitivity cardiac troponin T (hs-cTnT) and NT-proBNP have been associated with ESKD.<sup>6</sup> The *APOL1* gene is widely expressed, including in the vasculature. A recent study<sup>7</sup> suggested minimal association between *APOL1* genotype and clinical cardiovascular disease; however, this has not been tested using the more

sensitive markers of subclinical disease, such as hs-cTnT, high-sensitivity troponin I (hs-TnI), and NT-proBNP. Using data from African American participants in the Atherosclerosis Risk in Communities (ARIC) Study,<sup>8</sup> we examined the associations of *APOL1* genotypes with these cardiac markers and tested whether higher levels increased the risk of *APOL1* associated with ESKD.

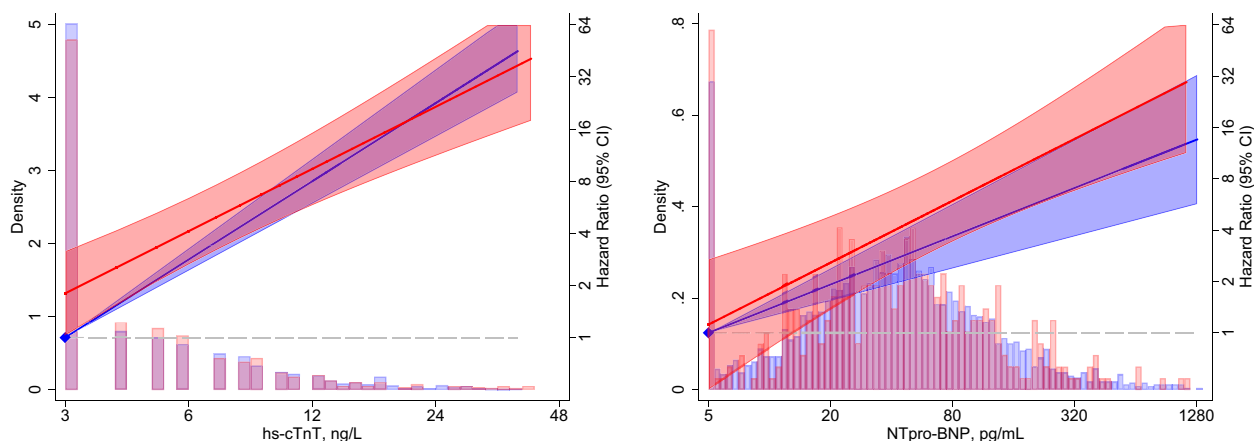
The ARIC Study is a prospective community-based cohort of adults aged 45 to 64 years that began in 1987. For this study, only African American participants without prevalent ESKD consenting to genotyping were included (N = 2,992). Hs-cTnT and NT-proBNP were assayed at study visit 2 (1990-1992), which was considered the baseline for our study, and visits 4 (1996-1998), 5 (2011-2013), and 6 (2016-2017; *Item S1*). We tested cross-sectional differences in cardiac markers by *APOL1* genotype using Wilcoxon rank sum tests. For longitudinal change in cardiac marker levels, we used mixed models with random intercepts and slopes. For risk for ESKD, defined as entry into the US Renal Data System registry, we used Cox regression to estimate the risk associated with *APOL1* by tertiles of hs-cTnT and NT-proBNP and as continuous log-transformed variables. Models were adjusted for age, sex, study center, and percentage of African ancestry. Analyses were repeated using ARIC Study visit 4 as baseline to evaluate hs-TnI, which was available only at visits 4 and 5. The ARIC Study has been approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (IRB number: H.34.99.07.02.A1), and all participants provided informed consent.

**Table 1.** Characteristics of Study Participants

Variable	Overall	0 or 1 <i>APOL1</i> Allele	2 <i>APOL1</i> Alleles	P
N	2,992	2,593	399	
hs-cTnT, ng/L	5.0 (1.9)	4.9 (1.9)	5.1 (2.0)	
hs-cTnT, ng/L	4.0 [3.0-7.0]	4.0 [3.0-7.0]	4.0 [3.0-7.0]	0.42
NT-proBNP, pg/mL	41.2 (3.3)	41.1 (3.3)	41.3 (3.4)	
NT-proBNP, pg/mL	40.5 [19.7-82.1]	40.5 [19.7-81.7]	39.9 [19.2-85.4]	0.89
Age, y	56.1 (5.8)	56.2 (5.8)	55.6 (5.6)	0.05
Female sex	1,907 (63.7%)	1,648 (63.6%)	259 (64.9%)	0.60
Percentage African ancestry	82.5 (10.0)	82.0 (10.3)	85.3 (7.8)	<0.001
Current smoker	763 (25.6%)	644 (25.0%)	119 (30.0%)	
Former smoker	866 (29.1%)	756 (29.3%)	110 (27.7%)	
Never smoker	1,348 (45.3%)	1,180 (45.7%)	168 (42.3%)	0.10
BMI, kg/m <sup>2</sup>	30.0 (6.3)	30.0 (6.2)	30.3 (6.4)	0.36
Systolic blood pressure, mm Hg	126.5 (20.5)	126.5 (20.4)	126.7 (21.3)	0.88
Cardiovascular disease	354 (12.1%)	292 (11.5%)	62 (16.0%)	0.01
Hypertension	1,631 (54.9%)	1,393 (54.1%)	238 (59.9%)	0.03
Diabetes	739 (24.9%)	638 (24.8%)	101 (25.4%)	0.78
eGFR, mL/min/1.73 m <sup>2</sup>	104.1 (19.7)	104.2 (19.5)	103.6 (21.0)	0.60
Incident ESKD events	165 (5.5%)	133 (5.1%)	32 (8.0%)	0.02
Time to ESKD, y	23.9 [15.2-26.1]	24.0 [15.0-26.1]	23.5 [16.3-26.1]	0.58

Note: Values are shown as number (percentage) for female sex, smoking, hypertension, cardiovascular disease, and diabetes; geometric mean (geometric SD) and median [interquartile range] for hs-cTnT and NT-proBNP and mean (SD) for the rest. Geometric mean and SD are calculated on a multiplicative scale and better represent the central value and spread in highly skewed data. eGFR is from the Chronic Kidney Disease Epidemiology Collaboration equation. Cardiovascular disease is defined as history of stroke, coronary artery disease, or heart failure.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; ESKD, end-stage kidney disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation.



**Figure 1.** Hazard ratios (95% confidence intervals [CIs]) for end-stage kidney disease by *APOL1* status and high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) measures at baseline. Hazards are adjusted for age, sex, Atherosclerosis Risk in Communities Study center, and percentage of African ancestry. Values less than the minimum level of detection were imputed with the minimum. Hazards are relative to the minimum level of detection: 3 ng/L for hs-cTnT and 5 pg/ml for NT-proBNP. *APOL1* low risk is in blue and high risk is in red.

Mean age of the study population was 56 years, and mean estimated glomerular filtration rate was 104 mL/min/1.73 m<sup>2</sup>. There were no baseline differences in hs-cTnT or NT-proBNP levels by *APOL1* risk status, but slightly higher cardiovascular disease and hypertension among the 399 (13%) participants with the *APOL1* high-risk genotype (Table 1). There were no differences in change in hs-cTnT (7.7% vs 7.5% increase per year; *P* for interaction = 0.43) or change in NT-proBNP levels (7.9% vs 8.8% increase per year; *P* for interaction = 0.14) by *APOL1* genotype. After visit 2, there were 165 ESKD events over a median follow-up of 24 years. hs-cTnT and NT-proBNP levels were both significant risk factors for ESKD. Risks for ESKD associated with the *APOL1* high-risk genotype were not different across tertiles of hs-cTnT or NT-proBNP (interaction *P* > 0.05 for all comparisons; Table S2). Results were similar when cardiac markers were modeled continuously (interaction *P* > 0.05 for both; Fig 1).

When visit 4 was used as a baseline, results were consistent. hs-TnI at visit 4 and subsequent change in hs-TnI levels did not differ by *APOL1* genotype. After visit 4, there were 86 ESKD events occurring over a median follow-up of 19 years (Table S1). Risk for ESKD increased with higher hs-TnI levels, but the risk associated with *APOL1* did not vary significantly by hs-TnI level (Table S2; Fig S1). Results were similar after accounting for the competing risk for death using the model of Fine and Gray (Table S3).

In a large well-characterized cohort of African Americans with preserved kidney function and long follow-up, we found no significant cross-sectional or longitudinal associations between *APOL1* genotype and hs-cTnT, NT-proBNP, or hs-TnI levels. Consistent with previous studies,<sup>6</sup> we found that cardiac marker levels were strongly associated with the development of ESKD. However, there

were no significant differences in risk for ESKD associated with the *APOL1* high-risk genotype at different levels of these markers. The relatively small number of events in our study may have limited our power. There were no visit 2 echocardiogram data to evaluate cardiorenal physiology. Our results suggest that *APOL1* high-risk genotype is not a risk factor for subclinical cardiovascular disease and the second hit for *APOL1*-associated ESKD may not manifest through cardiac damage.

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## SUPPLEMENTARY MATERIAL

### Supplementary File (PDF)

**Figure S1:** Hazard ratios (95% CI) for ESKD by *APOL1* status and hs-cTnT, NT-proBNP, and hs-TnI measures at baseline visit 4

**Item S1:** Genotyping and assay methods for cardiac markers.

**Table S1:** Characteristics of Study Participants at Visit 4 (1996-1998)

**Table S2:** Hazard Ratios of *APOL1* High Risk by Tertile of hs-cTnT, NT-proBNP, and hs-TnI at Visits 2 and 4

**Table S3:** Subhazard Ratios of *APOL1* High Risk by Tertile of hs-cTnT, NT-proBNP, and hs-TnI at Visits 2 and 4 Accounting for the Competing Risk of Death

## ARTICLE INFORMATION

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