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APOL1 Gene Kidney Risk Variants and Cardiovascular Disease: Getting to the Heart of the Matter

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Abstract

Apolipoprotein L1 gene (*APOL1*) renal-risk variants exhibit strong genetic association with a spectrum of non-diabetic kidney diseases in individuals with recent African ancestry. Relationships between *APOL1* kidney risk variants and cardiovascular disease (CVD) susceptibility and CVD-related death remain controversial. Some studies detected an increased risk for CVD, whereas others support protection from death and subclinical CVD and cerebrovascular disease. Because treatments for non-diabetic kidney disease may target this gene and its protein products, it remains critical to clarify the potential extra-renal effects of *APOL1* kidney risk variants. This review addresses the current literature on *APOL1* associations with CVD, cerebrovascular disease, and death. Potential causes of disparate results between studies are discussed.

Keywords

African Americans; apolipoprotein L1 (*APOL1)*; cardiovascular disease (CVD); kidney risk variants; genetic risk; atherosclerosis; nonmodifiable risk factor; racial disparities; chronic kidney disease (CKD); death; mortality; cerebrovascular disease; coronary artery calcification (CAC); review

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The apolipoprotein L1 gene (*APOL1*) association with a spectrum of non-diabetic kidney diseases is among the strongest genetic causes of complex disease.[1,2,3] Identification of *APOL1* has dramatically altered our understanding of susceptibility to glomerulosclerosis in populations with recent African ancestry.[4] In contrast, associations of *APOL1* kidney risk variants (KRVs) with cardiovascular disease (CVD) and death have been inconsistent; several studies suggest enhanced risk, while a growing body of evidence supports protection.[5,6,7,8] *APOL1* is expressed in the renal and systemic vasculature, [9,10] and its KRVs are associated with increased plasma small high-density lipoprotein (HDL)–

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cholesterol particle concentrations.[11] These findings support the potential for vascular involvement. Because therapies for *APOL1*-associated kidney disease will likely target the gene and its protein products, it is critical to fully understand extra-renal effects, including those involving blood vessels (Figure 1). It remains important to halt the development and progression of *APOL1*-associated chronic kidney disease (CKD) without increasing the potential risk of atherosclerotic complications.

Studies Finding an Association of *APOL1* and Increased Risk of CVD and Mortality

To assess effects of *APOL1* on CVD, Ito *et al.* examined two study cohorts containing African American participants.[12] First, they looked at 1,959 participants in the Jackson Heart Study (JHS), which followed a general African American population for five years. Of participants aged 35-84 years, 284, 892, and 783, respectively, had two, one, and zero *APOL1* KRVs. Baseline clinical CVD risk factors were similar between the three genotypic groups. The JHS participants with two *APOL1* KRVs had a significant increase in the composite outcome of myocardial infarction (MI), stroke, and therapeutic surgical or endovascular interventions, relative to those with zero KRVs (odds ratio [OR], 2.17; $p=9.4\times10^{-4}$). The increased risk for CVD remained significant in a Cox proportional hazard model that adjusted for age, sex, body mass index (BMI), diabetes, hypertension, smoking, lipids, and CKD (p=0.029). The expected *APOL1* associations with CKD, dialysis, and earlier age at onset of kidney disease were present in this population-based report.

In addition, an undisclosed number of JHS participants underwent computed tomography (CT) to measure coronary artery calcified atherosclerotic plaque (coronary artery calcification [CAC]). Surprisingly, despite its association with the composite of MI and stroke, those with two *APOL1* KRVs (versus zero KRVs) had *lower* CAC; however, CT imaging methods, CAC scores, and analysis results were not provided. Effects on CAC reportedly remained significant when participants with CKD were excluded. While lower CAC is protective from CVD events and mortality in all populations,[13,14] it has not been associated with an increased risk of CVD as in the JHS. Finally, analyses assessing JHS participants with one *APOL1* KRV in additive (zero versus one versus two KRVs) or recessive (zero/one versus two KRVs) models were not provided.

Ito *et al.* also evaluated 749 African American women aged 50-79 years from the Women's Health Initiative (WHI), a multi-center randomized control trial of postmenopausal hormone replacement therapy.[12] Women with advanced CKD were excluded. The WHI participants with two (n=103) and zero (n=302) *APOL1* KRVs were compared for rates of incident CVD and baseline estimated glomerular filtration rate (eGFR) after a mean follow-up of 2.5 years. Those with two *APOL1* KRVs had a significantly lower eGFR at baseline; they also had a higher risk of incident CVD (OR, 1.98) during follow-up.

Mukamal *et al.* examined 798 older African Americans in the Cardiovascular Health Study (CHS), a prospective cohort including 5,888 African American and European American participants aged 65 years or older from four US centers; greater than ten-year follow-up was available.[15] African American participants with two *APOL1* KRVs (n=91) had

significantly higher baseline albuminuria than the 707 participants with zero or one KRVs (p<0.001), without statistically significant differences in baseline eGFR or CVD. Changes in eGFR over time did not differ significantly between *APOL1* genotype groups; this may have been a result of the advanced age of this cohort. African Americans developing *APOL1*-related CKD typically do so at earlier ages; the CHS may contain a sample at lower risk of accelerated declines in eGFR, perhaps due to absence of requisite second hits necessary to initiate progressive kidney disease.[16] Compared to the group with zero or one *APOL1* KRV, the CHS group with two KRVs had significantly higher all-cause mortality (hazard ratio [HR], 1.3; p=0.05), non-cardiovascular mortality (HR, 1.4; p=0.05), and MI (HR, 1.8; p=0.02). In contrast, there were no statistically significant differences in cardiovascular mortality (HR, 1.3; p=0.31), stroke (HR, 1.2; p=0.80), or congestive heart failure (CHF; HR, 1.0; p=0.98). End points were generally similar between African Americans with less than two *APOL1* KRVs and European American CHS participants. Table 1 summarizes the major findings from the JHS, WHI, and CHS. None of these studies adjusted for the overall proportion of African ancestry in their cohorts.

Studies Not Finding an Association of *APOL1* and Increased Risk of CVD and Mortality

Prior to direct analysis of potential *APOL1* effects on CVD, the African American Study of Kidney Disease and Hypertension (AASK) detected a far higher frequency of kidney end points, relative to deaths, after ten-year follow-up of treated hypertension in non-diabetic African Americans with CKD attributed to high blood pressure.[17,18] The composite AASK primary end point included death, doubling of serum creatinine concentration, or initiation of dialysis. The AASK investigators reported higher frequencies of doubling of serum creatinine and dialysis, relative to death. Subsequently, *APOL1* KRVs were strongly associated with AASK kidney outcomes, rising serum creatinine concentrations, and albuminuria, whereas the blood pressure treatment arm (standard versus intensive control) and class of anti-hypertensive medications were not.[19,20] Kidney function declined relatively steadily among AASK participants with two *APOL1* KRVs—supporting the presence of an intrinsic kidney disease process, such as primary forms of glomerulosclerosis.[21] A recent AASK analysis failed to detect a significant effect of *APOL1* kidney risk variants on survival.[22] Results suggested that participants in the intensive blood pressure control arm with two *APOL1* kidney risk variants might have improved long-term survival; this effect was not seen in those in the less intensive blood pressure control arm.[22]

Results from four studies detecting protective or neutral effects of *APOL1* KRVs on CVD and mortality are summarized in Table 2. The African American–Diabetes Heart Study (AA-DHS) evaluated 717 participants: 91 with two, 350 with one, and 276 with zero *APOL1* KRVs.[23] The AA-DHS included only type 2 diabetes–affected individuals, and *APOL1* KRVs do not associate with classic diabetic kidney disease. Hence, unlike the JHS, WHI, and CHS, where *APOL1* KRVs were associated with kidney disease and/or albuminuria at baseline, confounding of *APOL1*-kidney disease risk on CVD and mortality outcomes were absent.[12,15] *APOL1* KRVs showed a significant negative association with CT-derived carotid artery calcified atherosclerotic plaque (p=0.02) and a trend toward negative association with

CAC (p=0.08) in dominant models adjusting for age, sex, overall African ancestry proportion, hemoglobin A1c, BMI, smoking, hypertension, renin-angiotensin system blockade, and statins. Mortality data in the AA-DHS came from the Social Security Death Index. The survival analysis demonstrated that participants with two *APOL1* KRVs lived significantly longer than those with one KRV, and those with one KRV lived longer than those with zero KRVs (additive genetic model; p=0.005).[23] Although AA-DHS and JHS both observed lower levels of calcified atherosclerotic plaque with increasing numbers of *APOL1* KRVs, results in AA-DHS demonstrated the expected protective effects of less subclinical CVD in the form of calcified plaque, whereas JHS saw paradoxical increases in risk for the composite CVD outcome.[12,23] The CVD events in the JHS were adjudicated and are therefore accurate. Similarly, the outcome of death in the AA-DHS was based on the Social Security Death Index and should be reliable.

In contrast to longitudinal analyses in the JHS, WHI, CHS, and AA-DHS, cross-sectional associations between *APOL1* and CVD were assessed in 2,571 hypertensive African American Systolic Blood Pressure Intervention Trial (SPRINT) participants lacking diabetes.[24] A multicenter randomized trial, SPRINT was designed to determine optimal systolic blood pressure targets in high-risk hypertensive patients; the sample was enriched for hypertensive individuals with CKD, those with prior CVD (except stroke), and ethnic minorities.[25,26] The main SPRINT CVD outcome included MI, positive cardiac stress testing, coronary/carotid/peripheral vascular revascularization, ≥50% stenosis of a major artery, abdominal aortic aneurysm ≥5 cm, CAC score ≥400 Agatston units, ankle-brachial index ≤0.9, and left ventricular hypertrophy. In addition to this definition, a simpler CVD outcome limited to prior MI and coronary or carotid artery revascularization was employed. Analyses controlled for age, sex, BMI, number of blood pressure medicines, statins, smoking, overall African ancestry proportion, eGFR, and urine albumin-creatinine ratio (UACR). Among African American SPRINT participants, 14% had two *APOL1* KRVs (n=361) and 86% (n=2210) had less than two KRVs. Although presence of two *APOL1* KRVs was positively associated with greater UACR and reduced eGFR, it was not associated with prevalent CVD based on either the main trial definition or the simplified criteria.

Moreover, an analysis of *APOL1* kidney risk variant effects on Atherosclerosis Risk in Communities (ARIC) study outcomes showed significant relationships with the rate of decline in eGFR, development of ESKD, and diabetes mellitus (models adjusted for socioeconomic status and co-morbid conditions); however, relationships with CVD and survival were not observed in fully-adjusted models.[27]

Patient survival based on *APOL1* was also assessed in a cohort of 725 African Americans with end-stage kidney disease (ESKD) on hemodialysis (HD) from the Wake Forest and Emory University out-patient dialysis programs.[28] Many dialysis-related deaths are CVD-related; hence, mortality on dialysis was chosen to be a potential surrogate for CVD. Analyses adjusted for age at dialysis initiation, sex, number of comorbid conditions from the Centers for Medicare & Medicaid Services (CMS) Medical Evidence Report, and presence of an arteriovenous fistula or graft (versus a permanent catheter) at dialysis initiation, to represent access to pre-dialysis nephrology care. Among the 275 individuals with non-

diabetic ESKD, those with two *APOL1* KRVs (compared to those with fewer than two) had younger age at dialysis initiation, fewer comorbid conditions, and longer median survivals on dialysis. Results were consistent after full adjustment and when patients were stratified into groups with age <50 or ≥50 years at dialysis initiation to account for the earlier age at ESKD in those with *APOL1* high risk genotypes. In contrast, significant *APOL1* effects on survival were not observed in the 450 patients with diabetes-attributed ESKD.

Effects of *APOL1* KRVs on the brain and cognitive performance were assessed in 517 AA-DHS Memory in Diabetes (MIND) and 2,568 African American SPRINT Memory and Cognition in Decreased Hypertension (also MIND) participants; 483 of the AA-DHS MIND and 197 of the SPRINT MIND participants underwent cerebral magnetic resonance imaging (MRI).[29] In AA-DHS MIND, the presence of two *APOL1* KRVs was positively associated with cerebral gray matter volume, and negatively associated with white matter lesion volume (higher values for the latter reflect more severe cerebral small vessel disease) and cerebrospinal fluid volume (a measure of cerebral atrophy). *APOL1* was not significantly associated with white matter volume or performance on cognitive testing. The SPRINT sample was less well powered than AA-DHS MIND due to the smaller number with a cerebral MRI; however, directions of associations were consistent with those in AA-DHS MIND. A meta-analysis revealed that *APOL1* KRVs were positively associated with gray matter volume and negatively associated with white matter lesion volume. Although *APOL1* KRVs were associated with kidney disease and albuminuria in AA-DHS MIND and SPRINT participants, protective associations with cerebral volumes were detected. The reason that *APOL1* KRVs were associated with kidney disease in AA-DHS MIND, but not in the parent AA-DHS, likely reflects recruitment of an additional 220 MIND study participants for a cerebral MRI. The importance of these results is that cerebral white matter lesion volume reflects leukoaraiosis on MRI.[30] This volume increases as a result of cerebral hypoperfusion with subsequent ischemia related to white matter small vessel disease. Reductions in cerebral small vessel disease are protective to the brain; thus, they likely relate to the *APOL1* association with larger gray matter volume reflecting preservation of neuronal cell bodies and other brain cells.

Accounting for Disparate Results Among Studies

It is widely accepted that albuminuria and reduced eGFR independently increase the risk of subclinical CVD and clinical CVD events.[31,32,33] Reciprocal relationships appear to exist, whereby CVD also associates with the development of CKD.[34] Therefore, studies in which *APOL1* KRVs are associated with the presence of CKD and/or albuminuria are at risk for confounding with CVD. In contrast, studies where *APOL1* KRVs are not associated (or weakly associated) with CKD have lesser likelihoods of confounding. Whether statistical adjustment is capable of fully accounting for the effects of CKD on the related CVD variable is unknown.

Three studies reported that increasing numbers of *APOL1* KRVs were associated with a higher risk for CVD events or death.[12,15] In contrast, three other studies reported reduced risk of death, subclinical CVD, and/or cerebrovascular disease in those with increasing numbers of *APOL1* KRVs.[23,28,29] Results in the AASK suggest the potential for minimal

effects of *APOL1* on CVD,[18] while cross-sectional results in SPRINT were neutral (*i.e.*, no significant relationships were seen).[24] Inaccuracy in estimating GFR in African Americans could result in misclassification of some participants with CKD as having normal kidney function, thereby affecting results.[35] Inclusion of prevalent patients with CKD or on dialysis, rather than incident patients, can lead to survival bias and might contribute to lower rates of subclinical CVD and cerebrovascular disease in African Americans.[36] Chen *et al.* and Kovesdy *et al.* reported higher mortality rates in African Americans with CKD, compared to European Americans.[37,38] However, lower mortality rates and reduced rates of coronary heart disease were reported in African Americans (versus European Americans) without CKD in the US Veterans Health Administration.[38] The "perfect" clinical study does not exist and every report has limitations. This includes all studies discussed in this review. However, a closer inspection of study populations, designs, and end points may provide clues to the different outcomes between these well-described cohorts.

The JHS, WHI, and CHS detected significant positive associations between *APOL1* KRVs and CVD events and/or death. The potential for confounding by *APOL1* association with CKD and/or albuminuria was present in all studies, and none adjusted for global African ancestry proportion. *APOL1* KRVs were significantly associated with baseline parameters of kidney disease in both JHS and WHI.[12] Of note, *APOL1* did not associate with the progression of CKD over time in JHS—potentially reducing confounding effects. The main JHS analysis focused on participants with the most extreme genotypes, comparing two versus zero *APOL1* KRVs; neither additive nor dominant models were presented for association with CVD or death. Those models might have provided interesting results, given subsequent reports.[23,28] Although the WHI attempted to recruit healthy post-menopausal women without CKD, significant *APOL1* associations with eGFR and hematocrit were evident, the latter potentially reflecting subclinical CKD.[12] In the CHS, *APOL1* KRVs were significantly associated with baseline albuminuria (but not eGFR).[15] Relatively few CVD events were observed during the thirteen-year CHS follow-up period: of 91 participants with high risk *APOL1* genotypes, there were 19 MIs, 12 strokes, and 23 CVD-related deaths. Relative to the other reports, the CHS evaluated an older study population. It is unclear what effects advanced age may have had on conclusions; *APOL1*-associated kidney disease typically develops in the fourth to fifth decades.[1] Finally, considering the clinical CVD associations with *APOL1* reported in JHS, the negative relationship between *APOL1* KRVs with CAC (subclinical atherosclerosis) appear paradoxical.[12] Lower degrees of subclinical CVD are widely accepted as protective from CVD.[13,14] Thus, the *APOL1* association with lower CAC despite greater numbers of CVD events in JHS participants with high-risk genotypes is difficult to reconcile. Details of the *APOL1* association analysis with CAC were not provided.

In contrast, the AA-DHS was not confounded by *APOL1* associations with kidney disease or albuminuria.[23] Not only were reduced levels of subclinical CVD seen based on CT vascular imaging in those with higher numbers of *APOL1* KRVs (paralleling JHS results), this finding translated to the expected improved survival in those with lower levels of subclinical CVD. Potential limitations of the AA-DHS are that results may not be generalizable to populations lacking diabetes, and adjudicated CVD events were not captured. In this regard, SPRINT may be informative. The SPRINT study excluded individuals with diabetes and

prior strokes.[24] However, just as in the JHS, WHI, and CHS, *APOL1* KRVs were associated with baseline kidney disease in SPRINT. This association was weak and likely related to SPRINT inclusion criteria that permitted recruitment of patients with low level proteinuria (<1 g/d) and reduced eGFR. Compared with the 13% of African Americans in the general population who possess two *APOL1* KRVs (*i.e.*, have high risk for CKD genotypes), a similar percentage of African American SPRINT participants had two KRVs (14%). Thus, the relatively weak *APOL1*-association with kidney disease in SPRINT participants, whose KRV frequencies mirrored the general African American population, could reduce the confounding between CKD and CVD. Despite recruitment of participants enriched for prior CVD or at high risk for future CVD in SPRINT, *APOL1* was not significantly associated with prevalent CVD. SPRINT limitations include the lack of longitudinal follow-up; however, those analyses are underway given early cessation of SPRINT due to significant reductions in CVD with more intensive lowering of systolic blood pressure.[26]

Potential support for vascular protection related to *APOL1* KRVs was seen with improved survival of African Americans with non-diabetic etiologies of ESKD.[28] The effects of *APOL1* KRVs on the brain also appeared to parallel those in the systemic vasculature. Similar to the lower levels of calcified atherosclerotic plaque in African Americans with increasing numbers of *APOL1* KRVs, lesser degrees of cerebral white matter small vessel disease (and larger volumes of gray matter) were present in African Americans with greater numbers of *APOL1* KRVs.[29] This observation was robust to adjustment for *APOL1* KRV association with CKD, which is important because these protective relationships were observed despite association between *APOL1* with non-diabetic ESKD[28] and with parameters of kidney disease in AA-DHS MIND.[29]

We note that many of the studies in Table 2 (relative to those in Table 1) included participants with type 2 diabetes. Several cellular pathways appear to differ between those with diabetic and non-diabetic forms of kidney disease, including autophagy. The APOL1 protein contains a single BH3 domain; members of the so-called BH3-only family are involved in the autophagy pathway,[39] which is down-regulated in diabetic kidney disease. Consistent with this, several modifiers of kidney disease progression in AASK had effects in obese individuals with *APOL1* kidney risk alleles.[40]

Study End Points

These studies employed potentially related, but markedly different, end points. As such, end point selection may have contributed to the differing conclusions. The JHS evaluated the composite end point of MI, stroke, or therapeutic surgical or endovascular procedure, whereas the WHI evaluated all major adverse cardiovascular events.[12] The CHS studied MI, stoke, CHF, total mortality, CVD mortality, and non-CVD mortality.[15] The possible *APOL1* KRV effect of increasing risk for MI in these three studies would be expected to yield higher rates of CVD mortality. However, CHS saw significantly higher all-cause mortality and non-CVD mortality, whereas effects on CVD mortality were non-significant.[15] In contrast, the AA-DHS and a study of hemodialysis patients with non-diabetic ESKD assessed overall participant survival (all cause-mortality); independent CVD events were not measured.[23,28] These two studies detected lower rates of death with increasing numbers of *APOL1* KRVs. It

was presumed that the majority of deaths in African Americans with type 2 diabetes and with ESKD would be CVD-related, but this was not formally tested. Subclinical CVD differs from adjudicated CVD events.

Genetic Risk for Atherosclerosis in African Americans

In contrast to CKD, recent African ancestry is protective from the development of calcified atherosclerotic plaque (subclinical atherosclerosis, including CAC) in admixed populations with and without diabetes.[41,42] European ancestry increases the risk for CAC. Therefore, we typically adjust for global African ancestry proportion in genetic studies evaluating subclinical CVD in African Americans. Despite more severe conventional CVD risk factors (*e.g.*, hypertension, albuminuria, higher low-density lipoprotein cholesterol, and poorer glycemic control among patients with diabetes), African Americans have substantially lower levels of CAC and calcified atherosclerotic plaque in the aorta and carotid arteries relative to European Americans.[43,44,45] This radiologic observation has great clinical relevance. It translates to an approximate 50% reduction in MIs among African Americans with equal access to healthcare as European Americans in the Kaiser Permanente Health Maintenance Organization and Veterans Health Administration.[46,47] African Americans with ESKD are also known to live significantly longer on CMS-supported renal replacement therapy and have fewer MIs relative to European Americans with ESKD.[48]

The majority of reports from our group observed *APOL1*-associated protection from the development of subclinical CVD or cerebrovascular disease. It is possible that part of the increased risk of CVD and MI reported by JHS, WHI, and CHS was affected by the *APOL1* association with baseline CKD or albuminuria.[12,15] Potentially protective effects of *APOL1* KRVs on death, CVD, and subclinical cerebrovascular disease are supported by AA-DHS, AA-DHS MIND, and studies in prevalent patients receiving hemodialysis.[18,23,28,29] Therefore, we feel that there is a need for additional studies to elucidate relationships between *APOL1* KRVs and CVD. Ideally, studies will incorporate designs that are only minimally confounded by the *APOL1* association with progressive kidney disease, perhaps large population-based samples without over-representation of patients with advanced CKD (controlling for participant age and relevant CVD risk factors) and studies in cohorts with type 2 diabetes where *APOL1* is not associated with kidney disease (additionally controlling for diabetes duration and glycemic control). These studies will need to be well-powered with sufficient follow-up time to detect extra-renal effects of *APOL1*, which are likely weaker than those for kidney disease. Future studies should also consider overall African ancestry proportion, since it strongly and reproducibly associates with the risk of subclinical CVD. It should be kept in mind that even if studies support that *APOL1* kidney risk variants confer some protection from CVD, the effect will have to be weighed against the powerful CVD risk that is conferred by CKD itself. If APOL1 inhibitors are identified, their clinical role needs to balance mitigation of CKD progression (with its attendant risk for CVD and mortality outcomes) versus potential direct adverse CVD effects of such inhibition. Nephrologists are respected for treating many of our patient's medical problems, not simply kidney disease. In a similar fashion, while we focus on eradicating *APOL1*-associated kidney disease, we must remain vigilant for the vascular effects of *APOL1*.

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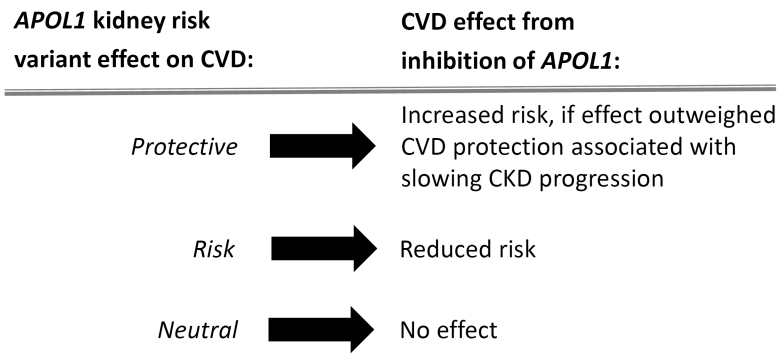

Figure 1.
Postulated effects of *APOL1* inhibition on CVD.

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Table 1

Studies finding an association of *APOL1* risk for CVD and mortality

Study: Population	Comparisons	End Point - Outcome	Comments
JHS[^](12): 1959 African Americans from general population	African Americans: *APOL1* 2 KRVs (n=284) vs *APOL1* 0 KRVs (n=783)	CV: CVD [*] - significant positive association	Significant association after CKD adjustment; Dominant and recessive models not reported
		CV: CAC score - Significant negative association	Significant association in participants lacking CKD; Dominant and recessive models not reported
		Renal: CKD [†] - Significant positive association	Earlier age at CKD onset
WHI[^](12): 749 postmenopausal African American women	African Americans: *APOL1* 2 KRVs (n=103) vs *APOL1* <2 KRVs (n=646)	CV: Major adverse CV event - Significant positive association	None
		Renal: eGFR - Significant negative association	Significant negative association with hematocrit
CHS[^](15): 798 older African Americans; 4964 older European Americans	African Americans: *APOL1* 2 KRVs (n=91) vs *APOL1* <2 KRVs (n=707)	Mortality: All-cause - Significant positive association	None
		Mortality: CVD - Non-significant	Low event numbers
		Mortality: Non-CVD - Significant positive association	Low event numbers
		CV: MI - Significant positive association	Low event numbers
		CV: Stroke - Non-significant	Low event numbers
		CV: CHF - Non-significant	Low event numbers
		Renal: eGFR - Non-significant	None
		Renal: Albuminuria - Significant positive association	None
	African Americans with <2 *APOL1* KRVs (n=707) vs European Americans (n=4964)	No significant differences in mortality, CVD, or renal end points	None

CHS, Cardiovascular Health Study; JHS, Jackson Health Study; KRV = kidney risk variant, CVD = cardiovascular disease, CKD = chronic kidney disease, CAC = coronary artery calcification, eGFR= estimated glomerular filtration; WHI, Women's Health Initiative; CHF, congestive heart failure; MI, myocardial infarction; CV, cardiovascular

[*] myocardial infarction, stroke or therapeutic surgical or endovascular procedure;

[†] eGFR <60 ml/min/1.73m^2 or urine albumin-creatinine ratio >30 mg/g'

[^] CHS eGFR used cystatin C-based eGFR; eGFR methodology in JHS and WHI was not specified.

Table 2

Studies not finding an association of *APOL1* risk and CVD and mortality

Study: Population	Comparisons	End Point - Outcome	Comments
AA-DHS[^] (23): 717 African Americans with T2DM	African Americans with *APOL1* 2 KRVs (n=91) vs *APOL1* 1 KRVs (n=350) vs *APOL1* 0 KRVs (n=276)	Mortality: All-cause - Significant negative association	p=0.005 (fully-adjusted additive model)
		CV: CAC score - Non-significant trend toward negative association	p=0.08 (fully-adjusted dominant model)
		CV: Carotid artery calcium - significant negative association	p=0.02 (fully-adjusted dominant genetic model)
		Renal: eGFR - Non-significant	None
		Renal: Albuminuria - Non-significant	None
Wake Forest - Emory Dialysis Cohort (28): 725 prevalent African American HD patients	African Americans with non-DM ESKD *APOL1* 2 KRVs (n=129) vs *APOL1* <2 KRVs (n=146)	HD survival: Non-DM ESKD - Significant positive association	p=0.0235 (fully-adjusted additive model); p=0.0385 (fully-adjusted recessive model)
	African Americans with DM-attributed ESKD *APOL1* 2 KRVs (n=82) vs *APOL1* <2 KRVs (n=368)	HD survival: DM ESKD - Non-significant	None
SPRINT [*^] (24): 2460 African Americans with HTN	African Americans with *APOL1* 2 KRVs (n=361) vs *APOL1* <2 KRVs (n=2210)	CV: CVD[*] - Non-significant	Prevalent CVD (incident data unavailable)
		Renal: eGFR - Significant negative association	Prevalent data
		Renal: Albuminuria - Significant positive association	Prevalent data
AA-DHS MIND and SPRINT MIND meta-analysis [*^] (29): 680 African Americans with cerebral MRI	African Americans with *APOL1* 2 KRVs (n=87) vs *APOL1* <2 KRVs (n=593)	MRI: GMV - Significant positive association	All intracranial measurements associations were also significant in AA-DHS alone but none were in SPRINT before meta-analysis
		MRI: WMLV - Significant negative association	
		Renal: eGFR - Significant negative association	None
		Renal: Albuminuria - Significant positive association	None

African American-Diabetes Heart Study (AA-DHS); AA-DHS MIND, AA-DHS Memory in Diabetes; KRV = kidney risk variant, CVD = cardiovascular disease, CAC = coronary artery calcification, eGFR = estimated glomerular filtration rate, ESKD = end-stage kidney disease, MRI = magnetic resonance imaging, GMV = gray matter volume, WMLV = white matter lesion volume, SPRINT = Systolic Blood Pressure Intervention Trial; SPRINT MIND, SPRINT Memory and Cognition in Decreased Hypertension; T2DM, type 2 diabetes mellitus; HD, hemodialysis; HTN, hypertension; DM, diabetes mellitus

[*] CVD defined as myocardial infarction, positive cardiac stress test, coronary/carotid/peripheral artery revascularization, ≥50% stenosis of major artery, abdominal aortic aneurysm ≥5cm, CAC score ≥400 Agatston units;

[^] AA-DHS and SPRINT used creatinine-based eGFR