APOL1 Genotype and Race Differences in Incident Albuminuria and Renal Function Decline

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ABSTRACT

Variants in the *APOL1* gene are associated with kidney disease in blacks. We examined associations of *APOL1* with incident albuminuria and kidney function decline among 3030 young adults with preserved GFR in the Coronary Artery Risk Development in Young Adults (CARDIA) study. eGFR by cystatin C (eGFRcys) and albumin-to-creatinine ratio were measured at scheduled examinations. Participants were white (n=1700), high-risk black (two *APOL1* risk alleles, n=176), and low-risk black (zero/one risk allele, n=1154). Mean age was 35 years, mean eGFRcys was 107 ml/min per 1.73 m^2, and 13.2% of blacks had two *APOL1* alleles. The incidence rate per 1000 person-years (95% confidence interval) for albuminuria over 15 years was 15.6 (10.6–22.1) for high-risk blacks, 7.8 (6.4–9.4) for low-risk blacks, and 3.9 (3.1–4.8) for whites. Compared with whites, the odds ratio (95% confidence interval) for incident albuminuria was 5.71 (3.64–8.94) for high-risk blacks and 2.32 (1.73–3.13) for low-risk blacks. Adjustment for risk factors attenuated the difference between low-risk blacks and whites (odds ratio 1.21, 95% confidence interval 0.86–1.71). After adjustment, high-risk blacks had a 0.45% faster yearly eGFRcys decline over 9.3 years compared with whites. Low-risk blacks also had a faster yearly eGFRcys decline compared with whites, but this difference was attenuated after adjustment for risk factors and socioeconomic position. In conclusion, blacks with two *APOL1* risk alleles had the highest risk for albuminuria and eGFRcys decline in young adulthood, whereas disparities between low-risk blacks and whites were related to differences in traditional risk factors.

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Progression from CKD to ESRD affects black Americans disproportionately.[1,2] In addition, black persons in the United States experience faster rates of kidney function decline at early stages of disease, compared with white persons.[3–5] The reasons for these observations remain unclear. Two variants in the gene encoding apolipoprotein L1 (*APOL1*) (termed G1 and G2), which are common among individuals with African ancestry, but very rare in Caucasian persons, are linked to ESRD and CKD.[6–10] The presence of two of these *APOL1* variants was significantly associated with increased progression of CKD in studies that included black persons selected for established disease.[11] In one recent report, the association of *APOL1* with incident CKD in middle-aged black persons appeared to be weaker than that reported for advanced disease.[12] The association of *APOL*1 variants with the incidence of albuminuria and trajectories of kidney function decline among young black persons with preserved eGFR in a population-based cohort has not been examined.

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Furthermore, whether high-risk *APOL1* variants explain previously observed black versus white differences in the risk of albuminuria and early kidney function loss is not well understood. In one recent study among persons with established CKD, black participants without *APOL1* genetic variants remained at somewhat higher risk for disease progression, compared with white participants.[11] The degree to which differences in traditional risk factors and lifetime socioeconomic position (SEP) may also play a role in explaining race differences in albuminuria and early kidney function decline among black persons with and without the *APOL1* variants is not well established.

We have designed this study to evaluate the incidence of albuminuria and trajectories of kidney function decline among young black individuals with two *APOL1* risk alleles (high-risk black), black persons with zero or one *APOL1* variant (low-risk black) and white participants with preserved kidney function. We also sought to investigate the degree to which traditional kidney disease risk factors and markers of lifetime SEP may explain observed differences between the groups.

RESULTS

Cohort Characteristics

The sample size for these analyses was 3030, after we excluded 81 black persons without adequate genotyping results, 29 persons with eGFR by cystatin C (eGFRcys) <60 ml/min per 1.73 m^2 at baseline, and 37 persons with missing covariate data. Among these participants, mean age was 35 ± 4 years at baseline (Coronary Artery Risk Development in Young Adults (CARDIA) study year 10). A total of 176 (13.2%) black participants had two *APOL1* risk alleles (high-risk black). There were 424 black participants who had *APOL1* genotyping but lacked samples at follow-up years 15 and 20 who were not included in the trajectories ancillary study. Of these, 47 (11%) had two high-risk alleles.

Overall, as previously reported, black participants were more likely to have lower incomes and lower levels of education. At baseline, high-risk black individuals had the highest prevalence of albuminuria (14%), followed by low-risk black individuals (6%), compared with white participants (3%). The eGFRcys at baseline was slightly higher for black compared with white participants (Table 1). There were no significant differences between high-risk and low-risk black participants in income, education, access to care indicators, body mass index (BMI), smoking, diabetes or BP levels at baseline (all P values >0.1) (Table 1).

Incidence of Albuminuria by *APOL1* Risk Status and Race

For analyses of incident albuminuria, we additionally excluded 120 persons with an albumin-to-creatinine ratio (ACR) ≥30 mg/g at year 10, as well as an additional 18 with missing genotyping or follow-up albuminuria information, for a total sample size of 2893. Albuminuria was measured at years 10, 15, 20, and 25 in CARDIA. A total of 233 persons developed incident albuminuria over the 15-year follow-up period. Approximately 78% of incident albuminuria cases among black participants occurred in the *APOL1* low-risk group. The incidence rate in high-risk black individuals was 15.6 (95% confidence interval [95% CI], 10.6–22.2) per 1000 person years, compared with 7.8 (6.4–9.4) for low-risk black, and 3.9 (3.1–4.8) for white individuals. The cumulative prevalence of albuminuria by year 25 (including persons with albuminuria at year 10) was 30% for high-risk black, 15% for low-risk black, and 8% for white persons.

Compared with low-risk black participants, the age and sex adjusted odds ratio (OR) for incident albuminuria was 2.46 (1.59–3.81) for high-risk black persons. Differences were not attenuated by adjustment for clinical characteristics or SEP (Table 2). When we compared low-risk black persons with one risk allele to those with zero, there were no differences in incident albuminuria (OR, 1.24; 95% CI, 0.82–1.86, P=0.31).

In comparison with white persons, high-risk black persons had a 5.7-fold increased odds of incident albuminuria, and associations were robust after full adjustment. Low-risk black persons had over 2-fold increased odds of incident albuminuria, compared with white participants. Accounting for clinical characteristics attenuated the differences, and these became nonstatistically significant. Further addition of SEP variables attenuated the estimates further, but there were no statistically significant differences between the models (P=0.27) (Table 2). The population attributable fraction, *i.e.,* the increase in the incidence of albuminuria that can be explained by the *APOL1* high-risk genotype among black persons, was 10.8% in fully adjusted models.

We conducted two sensitivity analyses. First, we considered only persistent albuminuria, and findings were not materially different. For example, in adjusted models, OR (95% CI) were 3.44 (1.28–9.28) for high-risk and 1.60 (0.80–3.21) for low-risk black persons, compared with white individuals. Next, we evaluated the associations among persons with available data on participant wealth, and findings were not materially different. For example, in fully adjusted models, OR for incident albuminuria was 1.13 (95% CI, 0.79–1.61) for low-risk black compared with white persons.

eGFRcys Decline by Race and *APOL1* Risk Status

The mean follow-up time was 8.92 years for high-risk black, 9.15 for low-risk black, and 9.48 for white participants in this study. The mean (SD) eGFRcys decline for the CARDIA population was 0.86% (95% CI, 0.81–0.91) ml/min per 1.73 m^2 per year over the follow-up period. At 5 years of follow-up (CARDIA examination 15), the mean (SD) eGFRcys was 108 ± 19 ml/min per 1.73 m^2 among high-risk black persons, 110 ± 14 for low-risk black, and 107 ± 13 among white participants. At CARDIA examination 20, these were 101 ± 18, 103 ± 15, and 101 ± 14 ml/min per 1.73 m^2, respectively.

We estimated differences in eGFRcys decline between high and low-risk black persons, and each group to white persons,

Table 1. Characteristics of CARDIA participants by race and *APOL1* status at baseline

Characteristics	High-risk Black (*n*=176)	Low-risk Black (*n*=1154)	White (*n*=1700)	*P* Value Blacks Versus Whites	*P* Value High Versus Low-risk Blacks
Age	34±4	35±4	36±3	<0.001	0.01
Male	79 (45%)	503 (44%)	817 (48%)	0.06	0.75
Income				<0.001	0.41
<25k	52 (30%)	337 (29%)	177 (10%)		
25k–49k	74 (42%)	460 (40%)	543 (32%)		
50k-74k	37 (21%)	223 (19%)	444 (26%)		
≥75k	13 (7%)	134 (12%)	537 (32%)		
Education				<0.001	0.65
Less than HS	8 (5%)	73 (6%)	38 (2%)		
HS completed	47 (27%)	297 (26%)	225 (13%)		
College or more	121 (69%)	784 (68%)	1438 (85%)		
Wealth indicator[a]	64 (39%)	419 (39%)	905 (55%)	<0.001	0.88
Life hardship				<0.001	0.92
Very hard/hard	16 (9%)	110 (10%)	103 (6%)		
Somewhat hard	36 (20%)	246 (21%)	219 (13%)		
Not hard	124 (70%)	792 (67%)	1377 (81%)		
Caretaker education				<0.001	0.85
Less than HS	33 (19%)	221 (19%)	153 (9%)		
HS completed	72 (41%)	493 (43%)	621 (37%)		
College or more	71 (40%)	440 (38%)	927 (55%)		
Employment status				<0.001	0.04
Employed	139 (81%)	970 (90%)	1481 (88%)		
Unemployed	31 (18%)	132 (12%)	106 (6%)		
Homemaker	2 (1%)	27 (2%)	102 (6%)		
Hardship obtaining regular care				<0.001	0.53
Hard	25 (14%)	149 (13%)	132 (8%)		
Not hard	151 (86%)	992 (86%)	1560 (92%)		
Don't know	0 (0%)	7 (0.6%)	6 (0.3%)		
Hardship paying for care				<0.001	0.56
Hard	44 (25%)	311 (27%)	339 (20%)		
Not hard	132 (75%)	832 (72%)	1356 (80%)		
Don't know	0 (0%)	5 (0.4%)	3 (0.2%)		
Smoking	53 (30%)	341 (30%)	324 (19%)	<0.00	0.88
Diabetes	11 (6%)	91 (8%)	85 (5%)	0.01	0.44
Body mass index	28.82±7.21	29.11±6.93	25.98±5.30	0.00	0.60
Systolic BP	113.81±14.70	112.61±13.30	107.31±11.16	0.00	0.11
Diastolic BP	75.18±11.71	74.82±10.28	70.47±9.25	<0.001	0.17
eGFRcys ml/min per 1.73 m^2	111±15	113±12	109±12	<0.001	0.04
ACR ≥30 mg/g	22 (14%)	57 (6%)	41 (3%)	<0.001	<0.001
ACR mg/g[b]	4.52 (31.5–10.66)	3.95 (2.72–7.06)	3.98 (2.79–6.11)	<0.001	<0.001
Antihypertensive use	12 (7%)	55 (5%)	19 (1%)	<0.001	0.25

All values are mean±SD, except where otherwise noted. HS, high school.
[a]Wealth indicator was measured by whether a participant reported owning a house or not.
[b]Median (interquartile range).

separately. Among black participants, high-risk *APOL1* was associated with 0.38% ml/min per 1.73 m^2 per year (95% CI, 0.13–0.63) faster eGFRcys decline compared with low-risk black persons. These differences were not attenuated after adjustment (Table 3).

Compared with white persons, high-risk black persons had 0.64% ml/min per 1.73 m^2 per year (0.39–0.88) faster eGFRcys decline, and differences remained significant after adjustment. Low-risk black persons also had faster rates of eGFRcys decline compared with white persons, but adjustment for clinical risk factors attenuated the differences, and these became nonstatistically significant. The addition of SEP variables to the models including clinical risk factors further reduced differences between the groups ($P<0.001$ for added variables) (Table 3).

Finally, we were interested in comparing rates of eGFRcys decline accounting for the onset of albuminuria within each group (Figure 1). High-risk black persons had the earliest onset of albuminuria (mean age 34 years), compared with ages 37 for low-risk black and 39 for white individuals ($P<0.01$). Average eGFRcys decline among persons who had not yet developed albuminuria did not differ across groups. Specifically, in fully

Table 2. Incident albuminuria by race and *APOL1* risk genotype

Group	N	Incidence Rate per 1000 PY	Model 1	Model 2	Model 3
				Odds Ratio (95% CI)	
Comparison within blacks					
Low-risk black	1090	7.8	Ref	Ref	Ref
High-risk black	152	15.6	2.46[a] (1.59–3.81)	2.93[a] (1.86–4.62)	2.88[a] (1.81–4.59)
Comparison between whites and blacks					
White	1651	3.9	Ref	Ref	Ref
Low-risk black	1090	7.8	2.32[a] (1.73–3.13)	1.33 (0.96–1.84)	1.21 (0.86–1.71)
High-risk black	152	15.6	5.71[a] (3.64–8.94)	3.89[a] (2.43–6.22)	3.50[a] (2.14–5.71)

Multivariate analyses include young black and white adults with no albuminuria at baseline. Model 1 incorporated demographic variables (age, sex), global ancestry; model 2 incorporated demographic and pathophysiologic variables (smoking, BMI, systolic BP, use of antihypertensive medications and diabetes); and model 3 incorporated demographic, pathophysiologic and socioeconomic variables (participant income, participant education, caretaker education, employment status and access to care indicators). PY, person years.
[a]*P* values <0.05.

adjusted models, the average eGFRcys decline among high-risk black individuals was 0.68% (0.39–0.96) ml/min per 1.73 m^2, compared with 0.59 (0.40–0.77) for low-risk black and 0.58 (0.40–0.76) for white persons. However, there were statistically significant accelerations in the rate of eGFRcys decline after the development of albuminuria within each group (Figure 1). After the development of albuminuria, the fastest adjusted rate of decline was observed among high-risk black persons, 2.71 (2.07–3.34) ml/min per 1.73 m^2 per year, followed by low-risk black, 1.73 (1.32–2.14) and white persons, 1.11 (0.66–1.56).

DISCUSSION

In this large population-based cohort of young black and white adults with initially preserved kidney function, we found that 13.2% of black participants carried two *APOL1* gene variants. These individuals were significantly more likely to manifest early signs of kidney disease, albuminuria and accelerated eGFRcys decline, compared with white participants and black persons without the *APOL1* genotype. We also showed that black participants without the high-risk *APOL1* genotype remained at higher risk for albuminuria and eGFRcys decline compared with white persons, and these racial differences were attenuated after adjustment for traditional risk factors. Taken together, our data fit a model in which the onset and progression of *APOL1*-associated kidney disease is characterized by albuminuria and reduced eGFR, in a manner similar to the onset and progression of diabetic nephropathy. Our findings also highlight that black persons without this genetic variant remain at higher risk for albuminuria and kidney function loss compared with white persons, and that these disparities were largely related to differences in traditional risk factors.

Our findings are consistent with prior reports showing the strong association of G1 and G2 *APOL1* risk alleles with CKD, ESRD and progression of established disease in samples selected for kidney disease.[7–10] In a prior community-based sample of middle-aged black persons (mean age 53 years), the presence of two *APOL1* risk alleles was associated with prevalent albuminuria and incident CKD.[12] Our study expands current knowledge and extends findings to a young, unselected, community-based population with preserved eGFR. Our finding that the rate of kidney function loss significantly accelerated after albuminuria onset among high-risk black persons suggests that albuminuria may be an early marker of disease, and that it can distinguish those persons

Table 3. Differences in eGFRcys decline by race and *APOL1* genotype

Group	N	eGFRcys decline ml/min per 1.73 m^2 (% per year)	β coefficient (95%CI) eGFRcys (% ml/min per 1.73m^2 per year)		
			Model 1	Model 2	Model 3
Comparison within blacks					
Low-risk black	1154	0.82	Ref	Ref	Ref
High-risk black	176	1.19	0.38[a] (0.13–0.63)	0.38[a] (0.14–0.62)	0.40[a] (0.17–0.64)
Comparison between whites and blacks					
White	1700	0.56	Ref	Ref	Ref
Low-risk black	1154	0.82	0.26[a] (0.14–0.38)	0.10 (–0.01–0.22)	0.04 (–0.08–0.16)
High-risk black	176	1.19	0.64[a] (0.39–0.88)	0.48[a] (0.24–0.72)	0.45[a] (0.21–0.68)

Model 1 incorporated demographic variables (age, sex, visit, global ancestry); model 2 incorporated demographic and pathophysiologic variables (smoking, BMI, systolic BP, use of antihypertensive medications, and diabetes); model 3 incorporated demographic, pathophysiologic and socioeconomic variables (participant income, participant education, caretaker education, employment status, access to care indicators).
The beta coefficients indicate the direction and magnitude of GFR decline: positive β coefficients can be interpreted as % ml/min per 1.73 m^2 faster decline. For example, compared with low-risk black persons, high-risk black persons declined by 0.40% ml/min per 1.73 m^2 per year faster. eGFRcys, estimated GFR by cystatin C.
[a]*P* values <0.05.

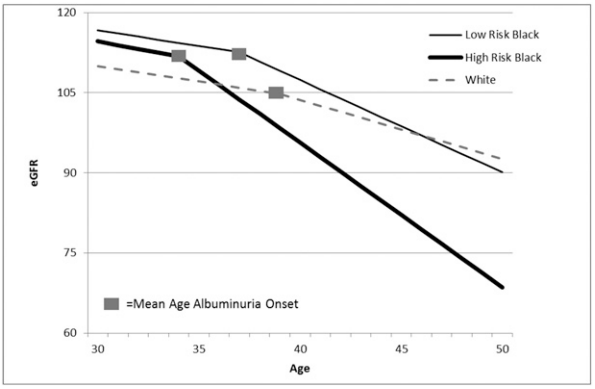

Figure 1. eGFRcys decline before and after onset of albuminuria by race and *APOL1* status.

with two *APOL1* gene variants who are at the highest risk for kidney function loss. It is noteworthy that a recent report showed that, among persons with and without proteinuria, *APOL1* high-risk variants still conferred an increased risk for CKD progression in persons with established disease.[11] In contrast to these studies, our population is limited to young persons with preserved eGFR. Moreover, as ACR was not measured in the prior studies, whether some participants in those studies without elevated protein to creatinine ratios had low levels of albuminuria is not known. Our data also support the current models of HIV-associated nephropathy and FSGS, which suggest that the pathogenic role of *APOL1* may involve disruption of podocyte[7] and vascular architecture.[13] Our findings that the eGFRcys slope did not significantly differ by *APOL1* status prior to the onset of albuminuria among black persons suggest that the benefits of screening for *APOL1* among young black adults with preserved eGFR should consider determination of albuminuria first to identify the persons at highest risk for kidney function loss, as screening for microalbuminuria may be cost effective in black populations.[14] As the momentum for genetically informed medicine grows, further studies are required to determine the benefits of *APOL1* determination coupled with periodic albuminuria screening among black persons.

Our observations that black persons without the *APOL1* risk alleles remain at higher risk for albuminuria and kidney function loss compared with white individuals is also important, and consistent with a prior report.[6] While high-risk *APOL1* may explain about 10% of the excess incidence of albuminuria among black participants, incident albuminuria among low-risk black persons accounted for the highest proportion of albuminuria cases among black persons. We showed that race differences between low-risk black and white participants were mostly explained by adjustment for traditional risk factors such as obesity, smoking, diabetes and BP levels. Among these black persons without two *APOL1* variants, research is necessary in order to determine whether kidney disease risk may be modifiable with current therapies.

To our knowledge, this is the first report evaluating the importance of genetic risk, traditional risk factors and SEP in explaining black-white differences in the development of albuminuria and eGFR loss in young adults with preserved kidney function. We were able to examine trajectories because we used cystatin C measured at the same laboratory, at the same time, from frozen samples. We were able to account for markers of SEP and BP levels throughout young adulthood. We must note several important limitations. We did not have direct measures of GFR. However, this is impractical in large epidemiologic studies. We could not investigate each individual's eGFRcys trajectory. Rather, our analyses using repeated measures over time (up to three per individual) allow the trajectories to be interpretable as typical patterns for CARDIA participants. The eGFR and albuminuria data are available for just two follow-up visits 5 years apart, and the eGFR decline slopes are composites based on these values. We cannot specifically account for the exact temporal association of the development of albuminuria and the start of eGFR loss within each individual, as the data are insufficiently granular. We are unable to make inferences related to the importance of *APOL1* in middle age or more advanced kidney disease. Future studies with larger sample sizes and availability of kidney biopsy tissue are required to elucidate pathologic mechanisms of *APOL1*-associated disease.

Black individuals with two *APOL1* risk alleles had the highest risk for albuminuria and eGFRcys decline in young adulthood, compared with low-risk black and white persons. Disparities between low-risk black and with white persons were related to differences in traditional risk factors.

CONCISE METHODS

Study Participants

We used data from 3030 participants in the kidney function trajectories ancillary study within the CARDIA study. We have previously described the development of this cohort, which was designed to examine factors associated with early kidney function loss among young black and white adults.[5] Briefly, the parent CARDIA study was designed to study early determinants of cardiovascular disease. CARDIA recruited 5115 black and white persons age 18–30 years between 1985 and 1986 from four sites in the United States (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA).[15] Serum cystatin C and urinary albumin and creatinine were measured at years 10, 15 and 20 visits (corresponding to calendar years 1995–1996, 2000–2001 and 2005–2006), and an additional albuminuria measure is also available at CARDIA year 25. Persons who had a visit at year 10 or later (15 or 20) and with at least two consecutive cystatin C measures are included in the kidney function trajectories study.[5] All participants gave informed consent, and the appropriate institutional review boards approved this study.

Measurement of Urinary Albumin and Kidney Function

Urinary albumin and creatinine were measured at years 10, 15, 20, and 25 and the urine ACR was expressed in mg/g. Kidney function was assessed by serum cystatin C. Cystatin C was measured at visits 10, 15 and 20 from frozen samples by nephelometer using the N Latex cystatin C kit (Dade Behring, now Siemens, Munich, Germany). All cystatin C

measurements were performed simultaneously at the University of Minnesota and were calibrated for drift as previously described.[5] We estimated the eGFR using the most recent CKD Epi cystatin C (eGFR-cys) equation: eGFRcys=133*(min(cysC/0.8, 1)**(–0.499))*(max (cysC/0.8, 1)**(–1.328))*(0.996**age)*(0.932**if female).[16] As previously described,[5] we specifically chose to use cystatin C to estimate GFR trajectories in this population because it is less biased by race and because measures performed at the same time, in the same laboratory, from frozen samples, are better suited for estimation of trajectories.

Our main outcomes of interest were incident albuminuria and annualized changes in eGFRcys (in percentages). We defined incident albuminuria as having an ACR ≥30 mg/g at years 15, 20, or 25 among persons with ACR <30 mg/g at year 10. In a sensitivity analysis, we considered only persons with persistent albuminuria, in which persons who had one ACR ≥30 and a subsequent ACR <30 mg/g were coded as noncases.

Genotyping

In CARDIA, the *APOL1* G1 and G2 variant alleles were genotyped in black participants using samples collected at year 0 by TaqMan assays (ABI, Foster City, CA). The G1 haplotype is defined by rs73885319, which is in near-absolute linkage disequilbrium (d'=1) with the second G1 allele rs60910145, and the G2 is a six base pair deletion (rs71785313). Based on the previously described recessive model for *APOL1* and kidney disease, high-risk *APOL1* genotype status was based on the carriage of two risk variants, which includes homozygosity at G1 or G2 or compound heterozygosity (G1/G2).[7,11,12] Persons of European ancestry are known to have extremely low frequencies of these variants.[17,18] Global ancestry was estimated using the software Eigenstrat.[19]

Covariates

Age, sex and race were ascertained by self-report using standardized questionnaires. At each visit, BP measurements were taken by trained staff using sphygmomanometry, and use of antihypertensive medication was recorded. Blood was collected at each study visit and stored at –70°C until measurements were performed. Diabetes was defined as fasting blood glucose ≥126 mg/dL or use of insulin and/or oral hypoglycemic agents.

Lifetime SEP was evaluated by using several metrics previously shown to be associated with poor health in CARDIA.[20] As a marker for childhood SEP, we used the highest level of parental education. As markers of adult SEP, we used participant income, employment status (working, unemployed, housemaker) and highest level of education by self-report up to year 10. Participants also reported whether they had a usual place for medical care, and the level of hardship in obtaining or paying for medical care (access to care). In sensitivity analyses, we also considered participant wealth, defined as whether the participant owned their home. Level of life hardship was obtained by self-report at CARDIA year 5. Wealth and lifetime hardship are included as sensitivity analyses due to missing observations or reported at earlier visits from baseline for this study.

Statistical Analyses

We first compared characteristics of high-risk black, low-risk black and white participants at baseline (CARDIA year 10). We then estimated the incidence of albuminuria over the 15-year follow-up period within each group. We evaluated differences between high-risk and low-risk black persons, and each group to white persons, using generalized estimating equation pooled logistic models. In order to investigate the importance of traditional risk factors and SEP in explaining observed differences, we built sequential models. Model 1 adjusted for age, sex, global ancestry and study visit. Model 2 added smoking, BMI, and systolic BP and the use of antihypertensive medication as time-updated covariates, and diabetes. Model 3 added caretaker education, participant income and education, employment status and access to care (regular place for medical care and hardship paying for medical care). We evaluated differences between each subsequent model using the Wald test. We estimated the population attributable fraction for high-risk *APOL1* on the incidence of albuminuria among black participants, using imputation-based causal inference methods.[21] The population attributable fraction can be interpreted as the increase in the incidence of albuminuria that can be explained by the *APOL1* high-risk genotype among black persons.

Next, we compared kidney function trajectories over 10 years among high-risk black, low-risk black and white persons. We have previously reported on methods for eGFRcys trajectory evaluation in CARDIA.[5] For these analyses, we used log-transformed eGFRcys to reduce the influence of large changes at the high eGFR range observed in this population, and to reduce skewness.[22,23] To estimate and compare overall annualized percentage changes in kidney function among the groups, we used linear mixed models with random intercepts and slopes to account for within-subject correlation of repeated measures. We present annualized percentage changes in eGFRcys, obtained by nonlinear back transformation of the regression coefficients. Models were adjusted sequentially as above.

Finally, we were interested in comparing kidney function trajectories before and after the onset of albuminuria among black persons with and without the *APOL1* renal risk variants and whites, separately. Consistent with the reported peak onset age for *APOL1*-associated focal segmental sclerosis[9] and with hypothesized mechanisms,[7,13] we tested whether there was a significant acceleration in eGFRcys decline after the onset of albuminuria in each group. As above, we tested for differences in eGFRcys decline between groups, among persons who had not/had already developed albuminuria. For these analyses, albuminuria was considered as a time-dependent covariate, with time of onset imputed 2.5 years prior to the CARDIA visit at which albuminuria was first noted (midpoint of the interval since the previous visit). We used linear splines to model annualized percentage changes in eGFRcys, allowing for changes in slope at the imputed time of onset of albuminuria. All models were adjusted as above. Analyses were performed using Stata (StataCorp, College Station, TX), and P values <0.05 were considered statistically significant.

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DISCLOSURES

None.

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