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Apolipoprotein L1 & Chronic Kidney Disease Risk in Young Potential Living Kidney Donors

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STRUCTURED ABSTRACT

OBJECTIVE—To develop a novel chronic kidney disease (CKD) risk prediction tool for young potential living kidney donors.

SUMMARY BACKGROUND DATA—Living kidney donor selection practices have evolved from examining individual risk factors to a risk calculator incorporating multiple characteristics. Due to limited long-term data and lack of genetic information, current risk tools lack precision among young potential living kidney donors, particularly African Americans (AAs).

METHODS—We identified a cohort of young adults (18–30 years) with no absolute contraindication to kidney donation from the longitudinal cohort study CARDIA. Risk associations for CKD (eGFR <60 mL/min/1.73m²) were identified and assigned weighted points to calculate risk scores.

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Declaration of Interests

The authors have no conflicts of interest to disclose.

Disclaimers

The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the National Institutes of Health or the American Society of Transplantation.

Previous Presentation

This study was presented at the Living Donor Abdominal Organ Transplant Conference; September 9, 2016; Trieste, Italy, and at the American Society of Nephrology Kidney Week; November 17, 2016; Chicago, IL.

RESULTS—3,438 healthy adults were identified; mean age 24.8 years; 48.3% AA; median follow-up 24.9 years (IQR: 24.5–25.2). For 18-year-olds, 25-year projected CKD risk varied by ethnicity and gender even without baseline clinical and genetic abnormalities; risk was 0.30% for European American (EA) women, 0.52% for EA men, 0.52% for AA women, 0.90% for AA men. Among 18-year-old AAs with *apolipoprotein L1* gene (APOL1) renal-risk variants without baseline abnormalities, 25-year risk significantly increased: 1.46% for women and 2.53% for men; among those with two APOL1 renal-risk variants and baseline abnormalities, 25-year risk was higher: 2.53%–6.23% for women and 4.35%–10.58% for men.

CONCLUSIONS—Young AAs were at highest risk for CKD, and APOL1 renal-risk variants drove some of this risk. Understanding the genetic profile of young AA potential living kidney donors in the context of baseline health characteristics may help to inform candidate selection and counseling.

INTRODUCTION

Annually in the United States, over 6,000 healthy individuals undergo living donor nephrectomy for the purposes of kidney transplantation.^{1,2} Living kidney donors gain no medical benefit from donation, exposing themselves to health risks associated with major surgery and reduced renal mass, including chronic kidney disease (CKD), entirely for the benefit of another individual.^{3,4} Essential to this process is proper medical evaluation and informed consent to promote donor autonomy in medical decision-making, requirements that mandate accurate quantification and communication of donor candidate risk for CKD. This is particularly crucial for young potential living kidney donors, who have the lengthiest remaining risk exposure, and African Americans (AA), who are at enhanced risk of CKD.⁵

Recently, an online risk tool was developed using population-based data that quantified the combined effect of 10 health characteristics to estimate the risk of end-stage renal disease (ESRD) among living kidney donor candidates.⁶ While informative, this study of seven cohorts was limited by short follow-up (median 4 to 16 years), heterogeneity of cohort design (incorporating both longitudinal and cross-sectional cohorts), no data on family history, and older age of potential living kidney donors (40–63 years-old). These limitations compromise the accuracy of lifetime estimates for ESRD among young living kidney donors and do not address the risk of the more proximate endpoint of CKD.

Beyond the predictive value of baseline health characteristics is the rapidly evolving understanding of an individual's genetic-risk profile.^{7–9} Recently, *apolipoprotein L1* gene (*APOL1*) variants have been associated with nondiabetic CKD in AAs.^{10,11} About 40% of AAs have one of these renal-risk variants, with 13% of AAs demonstrating two.^{10,12,13} Previous work indicates that odds of CKD among individuals with one renal-risk variant were 1.3-fold higher and 7.3-fold higher among individuals with two variants compared to individuals without a variant allele.¹⁴ Independent of other risk factors, it is hypothesized that AA potential living kidney donors with *APOL1* variants may be at particularly high risk of CKD;¹⁵ however, incorporation of *APOL1* genotype into risk prediction models has not been done.

The goal of this study was to develop a novel CKD risk prediction tool for young potential living kidney donors by leveraging data from a longitudinal cohort of adults ages 18–30 with more than 25 years of follow-up and availability of *APOL1* genotyping.

METHODS

Data Source

The Coronary Artery Risk Development in Young Adults (CARDIA) study is an ongoing, multicenter, longitudinal cohort whose study design has been previously described (Supplemental Digital Content 1- Supplemental Methods).^{16–21} At baseline examination (1985–1986), 5,114 adults, ages 18–30 years, were enrolled: Birmingham, AL; Minneapolis, MN; Chicago, IL; and Oakland, CA. All sites have Institutional Review Board approval, and all participants provided informed consent.

Study Population

There is significant transplant center variability in living kidney donor selection practices. The Joint Societies Work Group provides recommendations for evaluation of living kidney donors and recommends contraindications for donation, which we used to define a cohort eligible for living kidney donation: diabetes mellitus, hypertension (if AA or <55 years old), active malignancy, history of heart disease, evidence of a prior kidney problem, BMI > 40.0 kg/m², or pregnancy at the time of examination (Supplemental Digital Content 1- Supplemental Methods).²² Ethnicity was defined by self-report. Specifically, participants who identified as black or African American are heretofore referred to as African American (AA); participants who identified as white or Caucasian are heretofore referred to as European American (EA).

Outcome ascertainment

Uninephrectomy is associated with an immediate 50% reduction in renal clearance function, followed by an improvement related to renal hypertrophy to 60–70% of baseline; a living kidney donor with pre-donation eGFR 90 mL/min/1.73 m² should have long-term kidney function > 60 mL/min/1.73 m².^{23,24} Given these data, in our cohort of potential living kidney donors (*i.e.*, persons with two kidneys), the outcome of interest was development of at least Stage 3 CKD (eGFR < 60 mL/min/1.73 m²) or self-reported dialysis or kidney transplant. Time to CKD was from baseline examination to earliest examination with eGFR < 60 mL/min/1.73 m², initiation of dialysis, or kidney transplantation. Cases of CKD were confirmed by one of the following methods: a subsequent eGFR < 60 mL/min/1.73 m², microalbuminuria (two or more measurements of urine albumin/creatinine ratio ≥ 25 mg/g, adjusted for race and sex)²⁵, macroalbuminuria (one or more measurements of urine albumin/creatinine ratio ≥ 300 mg/g), eGFR < 60 mL/min/1.73 m² as calculated by the CKD-EPI equation using cystatin C (Supplemental Digital Content 1- Supplemental Methods), or a ≥ 25% decline in eGFR from baseline examination.^{19,25,26}

Statistical Analyses

Exploratory Data Analyses—Using data obtained at baseline examination, we described traditional risk factors for CKD, including demographics, social and family history, and

body composition, using measures of central tendency and spread for continuous factors and frequencies for categorical covariates. BMI was divided into the four World Health Organization categories and dichotomized at various cut points (overweight: 25.0 kg/m², obese: 30.0 kg/m², and morbidly obese: 35.0 kg/m²). Blood pressure was examined as a continuous measure, mean arterial pressure, and as a dichotomous variable for pre-hypertension (systolic blood pressure 120–139 mmHg or diastolic blood pressure 80–89 mmHg). eGFR was examined as a continuous measure and with a categorical cutpoint of 100 mL/min/1.73 m².

Risk prediction model development and discrimination—Univariate Cox proportional hazards regression was used, censoring for last recorded examination, by examining risk factors previously shown to be associated with development of CKD.^{5,27–34} Beginning with the standard baseline characteristics of age, race, and sex, additional risk factors were added with retention criterion $p < 0.10$ and the most parsimonious model chosen by minimizing Akaike's Information Criteria.

Factors identified in this model were assigned weighted points proportional to the β regression coefficient.³⁵ Given the size of the cohort and number of events, we derived the risk score using the entire cohort, a method shown to provide greater efficiency than split-sample validation.³⁶ Discrimination was assessed using an optimism-adjusted Harrell's concordance statistic, with bootstrap resampling of 500 replicates using the R package "RMS".³⁷ The risk score was then applied to the entire cohort to obtain estimates of 25-year risk of CKD for each possible value of the score. Martingale residuals were used to assess the adequacy of the risk score and the proportional hazards assumption.³⁸ Model calibration was assessed by comparing observed and expected rates of CKD using the Groennesby and Borgan score test.^{39,40}

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC), Stata 14.0 (StataCorp, College Station, TX), and R 3.2.5 (R Foundation, Vienna, Austria).

RESULTS

Characteristics of Living Kidney Donor Candidates

3,438 participants met eligibility criteria to be a potential living kidney donor at the time of enrollment (Supplemental Digital Content 2- Flow chart of exclusions), with median follow-up of 24.9 years (IQR: 24.5–25.2). Mean age was 24.8 years, 54% were female, and 48.3% were AA (Table 1).

Mean BMI was 24.0 kg/m², 8.9% were obese, 3.7% had a high-risk waist-to-hip ratio, and 1.4% had impaired fasting plasma glucose level (FPG). The average systolic and diastolic blood pressures were 109 mmHg and 68 mmHg, respectively, and 19.9% were pre-hypertensive. Mean serum creatinine was 0.8 mg/dL, and mean eGFR was 124.6 mL/min/1.73 m². Forty-percent reported regular cigarette smoking, and 14.2% reported excessive alcohol use (Table 1).

Fourteen-percent had a first-degree relative with diabetes mellitus, and 49.6% reported a first-degree relative with hypertension. Among AA candidates, 41.5% had no *APOL1* renal-risk variant, 45.2% had one *APOL1* variant, and 13.3% had two *APOL1* variants (Table 1).

Fifty-five candidates developed CKD: 38 AA and 17 EA. Median time to CKD was 20.3 yrs (IQR: 15.0–24.8). Median time to CKD was 19.9 yrs (IQR: 14.9–24.8) among AA candidates and 24.4 yrs (IQR: 20.0–24.8) among EA candidates ($p=0.23$).

Associations of Health Characteristics and Family History with Development of CKD

Per one-year increase in age above 18 years there was an associated 1.09-fold increased risk of CKD (hazard ratio (HR): 1.09, 95%CI: 1.01–1.18). Compared to EA candidates, AA candidates had a 2.71-fold increased risk for CKD (HR: 2.71, 95%CI: 1.53–4.80). Risk of CKD was also significantly higher among potential candidates who were obese (HR: 3.37, 95%CI: 1.81–6.28), had impaired FPG (HR: 4.41, 95%CI: 1.38–14.12), or had a high-risk waist-to-hip ratio (HR: 2.81, 95%CI: 1.12–7.04) compared to non-obese candidates and candidates with normal FPG and low-risk waist-to-hip ratios, respectively. For each 1 mmHg increase in systolic blood pressure there was an associated 1.03-fold increased risk for CKD (HR: 1.03, 95%CI: 1.01–1.06). Potential candidates who smoked had a 1.94-fold higher risk of CKD compared to non-smokers (HR: 1.94, 95%CI: 1.14–3.31). Compared to potential candidates with no family history of diabetes mellitus or hypertension, candidates with a first-degree relative with diabetes had 3.43-fold higher risk of CKD (HR: 3.43, 95%CI: 1.97–5.99), and candidates with a first-degree relative with hypertension had 2.8-fold higher risk of CKD (HR: 2.80, 95%CI: 1.54–5.06), respectively (Table 2). On adjusted analyses, gender, family history (first-degree relative) of diabetes mellitus or hypertension, obesity, cigarette smoking, and low eGFR remained independently associated with increased risk for CKD (Table 3).

Associations of *APOL1* Genetic Risk Variants with Development of CKD

No *APOL1* renal-risk variants were present among EA candidates. There was a stepwise association between number of *APOL1* renal-risk variants and risk of CKD among AA candidates. Compared to potential EA candidates, potential AA candidates with no risk variant were not at statistically significantly higher risk for CKD (HR: 1.88, 95%CI: 0.88–4.01). Potential AA candidates with one risk variant were 2.55-fold more likely to develop CKD (HR: 2.55, 95%CI: 1.29–5.04) and those with two risk variants were 5.89-fold more likely to develop CKD (HR: 5.89, 95%CI: 2.76–12.58) than their EA counterparts (Table 2).

After controlling for multiple demographic and health characteristics, presence of *APOL1* renal-risk variants remained independently associated with an increased risk for CKD. Compared to EAs, AA potential candidates with one risk variant had 2.26-fold increased risk of CKD (adjusted HR (aHR): 2.26, 95%CI: 1.10–4.63) and those with two risk variants had a 4.94-fold increased risk of CKD (aHR: 4.94, 95%CI: 2.25–10.86) (Table 3).

Individualized CKD Risk Projections

For an 18-year-old potential living kidney donor, the 25-year pre-donation projection of risk of CKD varied according to ethnicity and sex, even in the absence of baseline clinical and

genetic abnormalities; the risk was 0.30% for EA women, 0.52% for EA men, 0.52% for AA women, and 0.90% for AA men (Tables 4a–d; Figure 1). Corresponding estimates for a 30-year-old potential living kidney donor were 0.62%, 1.08%, 1.08%, and 1.86%, respectively (Supplemental Digital Content 3a–3d: Tables of estimated risk among 30-year-old potential living kidney donors). The projected risk of CKD was higher among potential candidates with additional risk factors, particularly in the context of impaired FPG, obesity, low eGFR, and family history of first-degree relative with diabetes mellitus or hypertension, than among those without additional risk factors (Tables 4a–d).

AA potential candidates with *APOL1* renal-risk variants were at highest risk of CKD. For an 18-year-old AA potential living kidney donor, the 25-year pre-donation projection of risk of CKD varied according to the presence of *APOL1* risk variants even in the absence of baseline clinical abnormalities; the risk was 1.46% for AA women with two risk variants and 2.53% for AA men with two risk variants. Among AAs with a baseline clinical abnormality or family history of a first-degree relative with diabetes mellitus and/or hypertension in addition to two *APOL1* risk variants, the 25-year pre-donation projection risk of CKD ranged from 2.53%–6.23% for 18-year-old women and 4.35%–10.58% for 18-year-old men (Tables 4c & 4d; Figure 1).

DISCUSSION

We estimated the 25-year risk for CKD among young potential living kidney donors, in whom a combination of individual demographic and health characteristics, family and social histories, and *APOL1* genotype were considered together. The 25-year projected pre-donation risk of CKD varied according to age, sex, and ethnicity, with the highest risk observed among AA men with a family history of a first-degree relative with diabetes mellitus and/or hypertension and two *APOL1* renal-risk variants (10.58%). Even in the absence of baseline clinical abnormalities and family history, the presence of two *APOL1* renal-risk variants in AA potential living kidney donors increased CKD risk five-fold compared to their EA counterparts (male: 2.53% vs. 0.52%; female: 1.46% vs. 0.30%, respectively). These findings suggest that knowledge of *APOL1* renal-risk variants significantly informs long-term risk prediction for CKD among young AA potential living kidney donors.

Recent studies of living kidney donor cohorts have reported increased risk for CKD among living kidney donors compared to healthy matched non-donors, but have failed to incorporate genetic variants in renal-risk genes such as *APOL1*.^{4,41} Our estimates leveraged data from a longitudinal cohort study of young participants (18–30 years-old) with median follow-up of 25-years that was enriched for AAs and contained genetic and health characteristics and family and social histories for participants, features not currently captured in living kidney donor study populations.^{4,42,43} Notably, our risk projections focused on development of CKD over a 25-year period in the absence of kidney donation and likely underestimate CKD risk in the setting of kidney donation; therefore, the magnitude of the added risk from kidney donation and the variation in this risk according to individual health characteristics and genetic variants remain uncertain. Nevertheless, a key component to an evidence-based framework for living donor selection involves assessment

of baseline, pre-donation CKD risk, and the value of utilizing healthy non-donor individuals to estimate this risk has been well established.⁶

Studies have documented that decline in kidney function and progression of CKD to ESRD are highly variable in the general population.^{44,45} eGFR trajectory has been shown to steadily decline in some individuals while others maintain stable eGFR with CKD for prolonged periods.⁴⁵ These patterns have important implications for clinical management, particularly for young living kidney donors, and the ability to identify young kidney donors *a priori* at greatest risk for a steady decline in eGFR and rapid progression to ESRD over time is of paramount importance. Recent data suggest that eGFR trajectory patterns differ by the number of *APOL1* renal-risk variants. In a longitudinal cohort study of 622 participants in the AA Study of Kidney Disease and Hypertension, participants with two *APOL1* renal-risk variants had 2.45-fold higher odds (95%CI: 1.62–3.69) of a steady decline in eGFR trajectory compared with participants with one or no *APOL1* renal-risk variant.⁴⁶ In addition, progression to ESRD has been shown to be more rapid in patients with two *APOL1* renal-risk variants,⁴⁷ and the attributable risk of having two *APOL1* renal-risk variants for the development of ESRD was 1.68 events per 1,000 person-years compared to a population-attributable risk of 0.21 events per 1,000 person-years with no *APOL1* renal-risk variant.¹¹

The actual risk of CKD and ESRD among young AA living kidney donors with *APOL1* renal-risk variants is not known. Multiple studies have demonstrated that AA living kidney donors are at greater risk for kidney dysfunction following donation compared to their EA counterparts.^{4,43,48,49} Data from the United Network for Organ Sharing demonstrated that AAs represented 14.3% of all living kidney donors yet 44% of donors who developed ESRD.⁵⁰ More recently, data examining the risk of ESRD 15 years post-donation found the risk to be 74.7 per 10,000 AA donors compared with only 22.7 per 10,000 EA donors.⁴ While these data are important, understanding the increased risk for CKD and ESRD among otherwise healthy AA living kidney donors remains elusive. Interestingly, in one study a greater proportion of donors related to the recipient developed ESRD compared with unrelated donors.⁴¹ This finding suggests the potential for some underlying genetic susceptibility carried by family members, and supports the increased risk for CKD associated with strong family history and presence of *APOL1* renal-risk variants observed in our current study. These data, interpreted in the context of our findings, have key implications for *APOL1* genotype screening recommendations among potential AA living kidney donors, and may help inform candidate selection and counseling. It may be prudent to screen for *APOL1* renal-risk variants in any young AA living kidney donor candidate who presents with baseline clinical abnormalities or strong family history, and, if identified, counsel against living kidney donation.

The strengths of our study include the use of a single longitudinal cohort study with robust, granular health information, including *APOL1* genotype, enriched for AAs with more than 25 years of follow-up, allowing for more accurate prediction of the long-term risk for CKD among young potential living kidney donors. However, there are limitations specific to our study. ESRD was a relatively infrequent event, particularly among an incident cohort aged 18 to 30 years, and, as such, our main outcome was limited to development of CKD. We did

not model the incidence of risk factors for CKD such as diabetes mellitus and hypertension, and, therefore, an individual living donor candidate at greater risk for development of diabetes mellitus or hypertension than another candidate with identical health characteristics may be at higher risk for development of CKD than that predicted by our risk calculator. Furthermore, the risk calculator was developed in an incident cohort of young adults, and, as such, caution is warranted in utilizing this risk prediction tool for older potential living kidney donors.

This is the first study to examine the 25-year risk for development of CKD among a cohort of young potential living kidney donors that incorporates health characteristics, family and social history, and genetic variants. Young AA potential living kidney donors were at highest risk for development of CKD; variants in the *APOL1* gene drove a portion of this risk. Understanding the genetic profile of young AA potential living kidney donors in the context of other baseline health characteristics seems prudent. We believe our risk calculator can be used not only for donor screening and selection by the medical team, but, perhaps more importantly, in counseling patients about their individual risk for CKD and thereby improving informed consent and candidate autonomy in decision-making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Estimated 25-year risk for the development of chronic kidney disease among a cohort of 3,438 potential living kidney donor candidates from the CARDIA Study by baseline risk score.

Table 1

Baseline demographic and health characteristics, family and social histories, and genetic profiles among a cohort of potential living kidney donor candidates from the CARDIA Study (N=3,438).

Potential Living Kidney Donor Candidate Characteristics	N= 3,438
Demographics	
Age, yr, mean (SD)	24.8 (3.6)
Female sex, %	1,858 (54.0)
Ethnicity, %	
African American	1,661 (48.3)
European American	1,777 (51.7)
12 or more years of education, %	3,133 (91.1)
Marital status, %	
Married	749 (21.8)
Single, never married	2,418 (70.4)
Other/unknown (marriage-like relationship)	270 (7.9)
Health Characteristics	
BMI, kg/m ² , mean (SD)	24.0 (4.1)
Obese (BMI ≥ 30.0 kg/m ²), %	307 (8.9)
High-risk waist-to-hip ratio, %	128 (3.7)
Plasma glucose, mg/dL, mean (SD)	81.6 (10.4)
Impaired fasting glucose level, %	48 (1.4)
Systolic blood pressure, mmHg, mean (SD)	109.3 (9.9)
Diastolic blood pressure, mmHg, mean (SD)	67.7 (8.8)
Pre-hypertensive (SBP 120–139 or DBP 80–89 mmHg), %	685 (19.9)
HDL cholesterol, mg/dL, mean (SD)	53.3 (12.9)
Triglycerides, mg/dL, mean (SD)	70.3 (42.9)
eGFR (mL/min/1.73 m ²), mean (SD)	124.6 (14.8)
Low eGFR (90–99 mL/min/1.73 m ²), %	174 (5.1)
Serum creatinine, mg/dL, mean (SD)	0.80 (0.13)
Social History	
Regular cigarette smoking, %	1,435 (41.7)
Excessive alcohol use, %	488 (14.2)
Family History	
1 st degree relative with diabetes mellitus, %	491 (14.3)
1 st degree relative with hypertension, %	1,705 (49.6)
APOL1 renal-risk variants among African Americans, %	
0 risk variant	690 (41.5)
1 risk variant	750 (45.2)
2 risk variants	221 (13.3)

APOL1, *apolipoprotein L1* gene; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SD, standard deviation

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Table 2

Associations of baseline demographic and health characteristics, family and social histories, and *APOL1* genetic risk variants with risk for development of chronic kidney disease among a cohort of potential living kidney-donor candidates in the CARDIA Study (N=3,438).

	Unadjusted		
	HR	95% CI	p-value
Demographic Factors			
Age (per 1-year increase above age 18 yr)	1.09	1.01–1.18	0.03
Female sex	0.73	0.43–1.24	0.24
African American ethnicity	2.71	1.53–4.80	< 0.001
12 or more years of education	0.54	0.24–1.19	0.12
Baseline Health Risk Factors			
BMI (kg/m ²) (per 1-unit increase)	1.08	1.03–1.14	0.005
BMI- WHO categories (reference=BMI <25.0 kg/m ²)			
Overweight (25.0–29.9 kg/m ²)	0.53	0.22–1.25	0.15
Obese (30.0–34.9 kg/m ²)	3.50	1.82–6.72	< 0.001
Morbidly obese (≥ 35.0 kg/m ²)	1.08	0.15–7.91	0.94
Overweight (BMI ≥ 25.0 kg/m ²)	1.21	0.69–2.10	0.51
Obesity (BMI ≥ 30.0 kg/m ²)	3.37	1.81–6.28	< 0.001
Morbidly obese (BMI ≥ 35.0 kg/m ²)	1.02	0.14–7.37	0.98
Impaired fasting glucose (100–125 mg/dL)	4.41	1.38–14.12	0.01
High-risk waist-to-hip ratio	2.81	1.12–7.04	0.03
Systolic BP (mmHg)	1.03	1.01–1.06	0.03
Diastolic BP (mmHg)	1.00	0.97–1.03	0.89
Systolic categories (reference= <120 mmHg)			
120–129 mmHg	1.26	0.61–2.57	0.54
130–139 mmHg	2.64	0.82–8.52	0.10
Pre-hypertension (SBP 120–139 or DBP 80–89 mmHg)	1.52	0.84–2.76	0.16
Hypercholesterolemia	0.94	0.23–3.85	0.93
eGFR at baseline (mL/min/1.73 m ²) (per 1-unit increase above 90 mL/min/1.73 m ²)	1.00	0.98–1.02	0.81
eGFR 90–99 mL/min/1.73 m ² at baseline	2.27	0.97–5.29	0.06
Social History Risk Factors			
Regular cigarette smoking	1.94	1.14–3.31	0.01
Family History Risk Factors			
1 st degree relative with diabetes mellitus	3.43	1.97–5.99	< 0.001
1 st degree relative with hypertension	2.80	1.54–5.06	< 0.001
Genetic Risk Variants			
<i>APOL1</i> risk group (reference=European Americans)			
African Americans with 0 risk variant	1.88	0.88–4.01	0.10

	Unadjusted		
	HR	95% CI	p-value
African Americans with 1 risk variant	2.55	1.29–5.04	0.007
African Americans with 2 risk variants	5.89	2.76–12.58	< 0.001
<i>APOLI</i> risk group among African Americans (reference=0)			
1 risk variant	1.35	0.63–2.91	0.44
2 risk variants	3.14	1.36–7.24	0.007

APOLI, apolipoprotein L1 gene; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; WHO, World Health Organization

Table 3

Adjusted hazard ratios, beta coefficients, and risk score points of risk factors for the development of chronic kidney disease among a cohort of potential living kidney donor candidates from the CARDIA Study (N=3,438).

	aHR	95% CI	p-value	β	Risk points
Age (per 1-year increase above age 18 yr)	1.06	0.98–1.15	0.13	0.06139	1 per year > 18
Male sex	1.73	1.00–2.97	0.05	0.54562	9
Impaired fasting glucose (100–125 mg/dL)	3.00	0.91–9.90	0.07	1.09980	18
First degree relative with diabetes mellitus	2.25	1.25–4.05	0.007	0.81051	13
First degree relative with hypertension	1.92	1.04–3.54	0.04	0.65110	11
Obese (BMI 30.0 kg/m ²)	2.05	1.05–3.99	0.04	0.71698	12
History of regular cigarette smoking	1.79	1.04–3.06	0.03	0.58050	9
eGFR 90–99 mL/min/1.73 m ² at baseline	3.11	1.29–7.48	0.01	1.13339	18
APOL1 risk group (ref= European Americans)					
AA with 0 risk variant	1.75	0.80–3.82	0.16	0.55750	9
AA with 1 risk variant	2.26	1.10–4.63	0.03	0.81497	13
AA with 2 risk variants	4.94	2.25–10.86	< 0.001	1.59725	26

* Bootstrapped c-index of the risk score= 0.7639

AA, African American; *APOL1*, apolipoprotein L1 gene; BMI, body mass index; eGFR, estimated glomerular filtration rate

Estimated 25-year risk of chronic kidney disease among 18-year-old *European American female* potential living kidney donor candidates from the CARDIA Study (N=3,438).

Table 4a

Score	Baseline fasting glucose	Family history of DM	Family history of HTN	Obese at baseline (BMI ≥ 30)	Baseline eGFR 90–99	APOL1 risk variants	Regular smoking	25-year risk (95% CI)
0	Normal	None	None	No	No	0	No	0.30% (0.08–0.52)
9	Normal	None	None	No	No	0	Yes	0.52% (0.20–0.84)
11	Normal	None	Yes	No	No	0	No	0.58% (0.23–0.93)
12	Normal	None	None	Yes	No	0	No	0.62% (0.26–0.98)
18	Impaired	None	None	No	No	0	No	0.90% (0.43–1.36)
18	Normal	None	None	No	Yes	0	No	0.90% (0.43–1.36)
24	Normal	Yes	Yes	No	No	0	No	1.29% (0.70–1.88)

APOL1, apolipoprotein L1 gene; BMI, body mass index as kg/m²; CI, confidence interval; DM, diabetes mellitus; Family history, first-degree relative; HTN, hypertension; eGFR, estimated glomerular filtration rate as mL/min/1.73 m²

Estimated 25-year risk of chronic kidney disease among 18-year-old *European American male* potential living kidney donor candidates from the CARDIA Study (N=3,438).

Table 4b

Score	Baseline fasting glucose	Family history of DM	Family history of HTN	Obese at baseline (BMI ≥ 30)	Baseline eGFR 90–99	<i>APOL1</i> risk variants	Regular smoking	25-year risk (95% CI)
9	Normal	None	None	No	No	0	No	0.52% (0.20–0.84)
18	Normal	None	None	No	No	0	Yes	0.90% (0.43–1.36)
20	Normal	None	Yes	No	No	0	No	1.01% (0.51–1.52)
21	Normal	None	None	Yes	No	0	No	1.08% (0.55–1.60)
27	Impaired	None	None	No	No	0	No	1.55% (0.89–2.22)
27	Normal	None	None	No	Yes	0	No	1.55% (0.89–2.22)
33	Normal	Yes	Yes	No	No	0	No	2.24% (1.38–3.09)

APOL1, apolipoprotein L1 gene; BMI, body mass index as kg/m²; CI, confidence interval; DM, diabetes mellitus; Family history, first-degree relative; HTN, hypertension; eGFR, estimated glomerular filtration rate as mL/min/1.73 m²

Estimated 25-year risk of chronic kidney disease among 18-year-old *African American female* potential living kidney donor candidates from the CARDIA Study (N=3,438).

Table 4c

Score	Baseline fasting glucose	Family history of DM	Family history of HTN	Obese at baseline (BMI ≥30)	Baseline eGFR 90–99	APOL1 risk variants	Regular smoking	25-year risk (95% CI)
9	Normal	None	None	No	No	0	No	0.52% (0.20–0.84)
13	Normal	None	None	No	No	1	No	0.66% (0.28–1.04)
26	Normal	None	None	No	No	2	No	1.46% (0.82–2.10)
18	Normal	None	None	No	No	0	Yes	0.90% (0.43–1.36)
22	Normal	None	None	No	No	1	Yes	1.14% (0.60–1.69)
35	Normal	None	None	No	No	2	Yes	2.53% (1.59–3.45)
20	Normal	None	Yes	No	No	0	No	1.01% (0.51–1.52)
24	Normal	None	Yes	No	No	1	No	1.29% (0.70–1.88)
37	Normal	None	Yes	No	No	2	No	2.85% (1.83–3.86)
21	Normal	None	None	Yes	No	0	No	1.08% (0.55–1.60)
25	Normal	None	None	Yes	No	1	No	1.37% (0.76–1.99)
38	Normal	None	None	Yes	No	2	No	3.03% (1.96–4.09)
27	Impaired	None	None	No	No	0	No	1.55% (0.89–2.22)
31	Impaired	None	None	No	No	1	No	1.98% (1.20–2.76)
44	Impaired	None	None	No	No	2	No	4.35% (2.89–5.79)
27	Normal	None	None	No	Yes	0	No	1.55% (0.89–2.22)
31	Normal	None	None	No	Yes	1	No	1.98% (1.20–2.76)
44	Normal	None	None	No	Yes	2	No	4.35% (2.89–5.79)
33	Normal	Yes	Yes	No	No	0	No	2.24% (1.38–3.09)
37	Normal	Yes	Yes	No	No	1	No	2.85% (1.83–3.86)
50	Normal	Yes	Yes	No	No	2	No	6.23% (4.13–8.28)

APOL1, apolipoprotein L1 gene; BMI, body mass index as kg/m²; CI, confidence interval; DM, diabetes mellitus; Family history, first-degree relative; HTN, hypertension; eGFR, estimated glomerular filtration rate as mL/min/1.73 m²

Estimated 25-year risk of chronic kidney disease among 18-year-old *African American male* potential living kidney donor candidates from the CARDIA Study (N=3,438).

Table 4d

Score	Baseline fasting glucose	Family history of DM	Family history of HTN	Obese at baseline (BMI ≥ 30)	Baseline eGFR 90–99	APOL1 risk variants	Regular smoking	25-year risk (95% CI)
18	Normal	None	None	No	No	0	No	0.90% (0.43–1.36)
22	Normal	None	None	No	No	1	No	1.14% (0.60–1.69)
35	Normal	None	None	No	No	2	No	2.53% (1.59–3.45)
27	Normal	None	None	No	No	0	Yes	1.55% (0.89–2.22)
31	Normal	None	None	No	No	1	Yes	1.98% (1.20–2.76)
44	Normal	None	None	No	No	2	Yes	4.35% (2.89–5.79)
29	Normal	None	Yes	No	No	0	No	1.75% (1.03–2.47)
33	Normal	None	Yes	No	No	1	No	2.24% (1.38–3.09)
46	Normal	None	Yes	No	No	2	No	4.90% (3.27–6.51)
30	Normal	None	None	Yes	No	0	No	1.86% (1.11–2.61)
34	Normal	None	None	Yes	No	1	No	2.38% (1.48–3.26)
47	Normal	None	None	Yes	No	2	No	5.21% (3.47–6.91)
36	Impaired	None	None	No	No	0	No	2.68% (1.71–3.65)
40	Impaired	None	None	No	No	1	No	3.42% (2.24–4.58)
53	Impaired	None	None	No	No	2	No	7.44% (4.87–9.94)
36	Normal	None	None	No	Yes	0	No	2.68% (1.71–3.65)
40	Normal	None	None	No	Yes	1	No	3.42% (2.24–4.58)
53	Normal	None	None	No	Yes	2	No	7.44% (4.87–9.94)
42	Normal	Yes	Yes	No	No	0	No	3.86% (2.55–5.15)
46	Normal	Yes	Yes	No	No	1	No	4.90% (3.27–6.51)
59	Normal	Yes	Yes	No	No	2	No	10.58% (6.62–14.36)

APOL1, apolipoprotein L1 gene; BMI, body mass index as kg/m²; CI, confidence interval; DM, diabetes mellitus; Family history, first-degree relative; HTN, hypertension; eGFR, estimated glomerular filtration rate as mL/min/1.73 m²