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Associations between *APOL1* genetic variants and blood pressure in African American Mothers and Children from a U.S. Pregnancy Cohort: modification by air pollution exposures

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Institutional Review Board Approval

Written informed consent was obtained from all participants at enrollment. All CANDLE research activities were approved by the Institutional Review Board of the University of Tennessee Health Sciences Center, and this secondary analysis was approved by the University of Washington Human Subjects Division.

Disclosures

Dr. Csaba Kovesdy has served as consultant for Amgen, Astra Zeneca, Bayer, Cara Therapeutics, Reata, Sanofi Aventis, Takeda and Tricida. Dr. Adam Szpiro has served as consultant for the Health Effects Institute on the traffic-related air pollution panel. Their freedom to design, conduct, interpret and publish research is not compromised by these roles. The other authors declare they have no actual or potential competing financial interests.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The data from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) Study can be requested from the study website (https://candlestudy.uthsc.edu/research/guidelines-collaboration). The computing code in R can be obtained from the corresponding author via email request.

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Abstract

Introduction: Carriage of high-risk *APOL1* genetic variants is associated with increased risks for kidney diseases in people of African descent. Less is known about the variants' associations with blood pressure or potential moderators.

Methods: We investigated these associations in a pregnancy cohort of 556 women and 493 children identified as African American. Participants with two *APOL1* risk alleles were defined as having the high-risk genotype. Blood pressure in both populations was measured at the child's 4–6 years visit. We fit multivariate linear and Poisson regressions and further adjusted for population stratification to estimate the *APOL1*-blood pressure associations. We also examined the associations modified by air pollution exposures (particulate matter ≤2.5μm in aerodynamic

diameter [$PM_{2.5}$] and nitrogen dioxide) and explored other moderators such as health conditions and behaviors.

Results: Neither *APOL1* risk alleles nor risk genotypes had a main effect on blood pressure in mothers or children. However, each 2-μg/m^3 increase of four-year average $PM_{2.5}$ was associated with a 16.3 (95%CI: 5.7, 26.9) mmHg higher diastolic blood pressure in mothers with the *APOL1* high-risk genotype, while the estimated effect was much smaller in mothers with the low-risk genotype (i.e., 2.9 [95%CI: −3.1, 8.8] mmHg; $P_{interaction}$=0.01). Additionally, the associations of *APOL1* risk alleles and the high-risk genotype with high blood pressure (i.e., SBP and/or DBP≥90^{th} percentile) were stronger in girls vs. boys ($P_{interaction}$=0.02 and 0.005, respectively).

Conclusion: This study sheds light on the distribution of high blood pressure by *APOL1* genetic variants and informs regulatory policy to protect vulnerable population subgroups.

Keywords

APOL1 genetic variants; blood pressure; hypertension; air pollution exposures; child health; Gene–environment interaction

Introduction:

Adult hypertension is the most common chronic disease leading to office visits and the use of prescription drugs in the U.S (CDC, 2020; Whelton Paul K. et al., 2018) and is a major risk factor for adverse cardiovascular and renal outcomes (Flint et al., 2019; Tang et al., 2018). In children, elevated blood pressure may persist over time and progress to clinical hypertension in adulthood (Chen and Wang, 2008). Persistent racial disparities exist in many aspects of hypertension: compared to Whites, African Americans develop high blood pressure (HBP) earlier in life with a higher average blood pressure (Goulding et al., 2021; Wright et al., 2011). They are also disproportionally affected by complications attributed to hypertension, particularly chronic kidney disease (CKD) (Writing Group Members et al., 2016). Along with well-established risk factors for this health concern, including socioeconomic status and lifestyle factors, heritability estimates indicate that genetic polymorphisms also contribute to blood pressure traits in people of African descent.

Approximately half of African Americans carry at least one kidney disease-associated risk variant (G1 or G2 vs. G0) in the apolipoprotein L1 gene (*APOL1*) on chromosome 22, and 12-15% carry two risk variants (Friedman et al., 2011). *APOL1* G1 (rs73885319/rs60910145) and G2 (rs71785313) risk alleles, found only in people of African descent, confer resistance to some forms of African trypanosomiasis (Genovese et al., 2010a). Adult and pediatric data suggest individuals with two variant alleles are at higher risk for albuminuria and various forms of glomerular kidney disease (Kopp et al., 2011; Ekulu et al., 2019; Genovese et al., 2010b; Zahr et al., 2019; Ashley-Koch et al., 2011; Kopp, 2013). However, the role of *APOL1* risk variants in hypertension is unclear. To the best of our knowledge, only four studies, three in the U.S. and one in South Africa, have characterized this association in adults, with inconclusive results (Chen Teresa K. et al., 2020; Chen et al., 2017; Matsha et al., 2015; Nadkarni et al., 2017). The one pediatric study published to date reported a positive association between the *APOL1* high-risk genotype and

uncontrolled hypertension in American children with focal segmental glomerulosclerosis (FSGS) (Woroniecki et al., 2016). This relationship has not previously been examined in the general pediatric population.

Only some individuals with two *APOL1* risk variants develop hypertension and/or overt kidney disease, suggesting a possible role for gene-environment interactions (Langefeld et al., 2018). Mounting evidence from animal and human adult studies implicate air pollution in adverse cardiovascular and kidney outcomes (Brook et al., 2010; Wu et al., 2020). Particular attention has been directed toward ambient particulate matter ≤2.5μm in aerodynamic diameter ($PM_{2.5}$) and nitrogen dioxide (NO_2) (Giorgini et al., 2016; Li et al., 2020; Ni et al., 2021). To date, only one study in New York City has estimated the association between one-year average $PM_{2.5}$ and CKD by *APOL1* genotypes in older African Americans, and reported a significantly stronger association in the high-risk *APOL1* group (Paranjpe et al., 2020). However, there are no published data examining this *APOL1*-air pollution exposure interaction on blood pressure.

In the present study, we investigated associations between *APOL1* genetic variants and blood pressure in African American mothers and children, and we assessed modification of these associations by air pollution exposures, using data from a community-based pregnancy cohort in Southern U.S. Further, we explored potential modifications of the *APOL1*-blood pressure associations by history of hypertensive disorders in pregnancy, obesity, and smoking history in mothers, and the potential modifications by sex, preterm birth, prenatal smoking exposures, and obesity in children.

Methods:

Subjects

Study subjects were African American mothers and children from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study in Memphis, Tennessee. Participants were pregnant women with a singleton low risk pregnancy, aged 16-40, recruited at 16-27 weeks of gestation, residing in Shelby County, Tennessee. More details of the sampling, recruitment and data collection have been described elsewhere (Sontag-Padilla et al., 2015). Written informed consent was obtained from all participants at enrollment. All CANDLE research activities were approved by the Institutional Review Board of the University of Tennessee Health Sciences Center, and this secondary analysis was approved by the University of Washington Human Subjects Division.

We defined the study population using self-reported race, as only a subset of participants had the entire set of genotype data available to determine ancestry. Starting with 999 mothers who self-identified as African American, we excluded those without DNA genotyping (N=83) or valid blood pressure measurements at the child 4-6 years visit (N=313), and further excluded those who were pregnant at blood pressure assessment (N=47). Among 786 parental-identified African American children, we excluded 141 without DNA genotyping and 152 without valid blood pressure measurement. The final analytic sample comprised 556 mothers and 493 children.

APOL1 genotype assessment

Maternal DNA was extracted from buffy coat specimens, separated from whole blood by centrifuging at 3000 rpm for 10 minutes and aliquoted to 500 μl in cryovials. Child DNA was isolated from either the buffy coat blood sample (N=289) or cells collected by buccal swabs (N=204). TaqMan assays (ThermoFisher Scientific, Waltham, MA) were used for DNA genotyping. The *APOL1* G1 allele is composed of two missense variants in very high linkage disequilibrium, rs73885319 (G1g) and rs60910145 (G1m), and we considered it sufficient to use only the G1g variant to define this risk allele (Kopp et al., 2011). The *APOL1* G2 allele consists of rs717185313, a 6 bp in-frame deletion. To examine whether allele dropout resulted in an excess of G2 homozygosity, we performed quality control measures of repeated PCR with and without a preamplification step, Sanger sequencing, and manual visualization of genotype clusters (Baak-Pablo et al., 2010). The results supported the robustness and reproducibility of our genotype assignments. We obtained the counts of *APOL1* risk alleles for each participant as follows: zero risk allele: G0/G0; one risk allele: G1/G0 or G2/G0; two risk alleles: G1/G1, G1/G2, or G2/G2. High-risk genotypes were further defined as those containing two high-risk alleles (G1/G1, G1/G2, or G2/G2), and low-risk genotypes were defined as those containing zero or one risk allele.

Blood pressure assessment

At the child age 4-6 years visit, maternal and child blood pressure measurements were obtained using a blood pressure monitor (model BPM-100 from BpTRU Medical Devices, Coquitlam, BC, Canada), according to a standardized protocol (NHANES 2015-2016 Procedure Manuals). Arm circumference was measured to select the correct cuff size. Following at least two minutes of rest in a quiet room, blood pressure was measured twice in the right arm at heart level. In mothers, measurements were repeated up to four times if there was a greater than 10 mmHg discrepancy in systolic blood pressure (SBP) and/or a greater than 6 mmHg discrepancy in diastolic blood pressure (DBP). Final blood pressure values were calculated by averaging the measurements within a 10-mmHg difference in SBP and a 6-mmHg difference in DBP among measurements. Maternal hypertension was defined as ≥130 mmHg SBP and/or ≥80 mmHg DBP (Whelton Paul K. et al., 2018). In children, up to four measurements were taken if there was a discrepancy >5 mmHg in either SBP or DBP. Final blood pressure values were calculated by averaging the measurements within a 5-mmHg difference among measurements. Following recommendations of the American Academy of Pediatrics 2017 Clinical Practice Guideline, we calculated sex-, age- and height specific blood pressure percentile based on the U.S. pediatric population with normal weight, and further characterized HBP as SBP and/or DBP at 90th percentile and above (Flynn et al., 2017).

Effect modifiers

Using participants' residential address history, point-based $PM_{2.5}$ and NO_2 exposures were estimated from a well-validated advanced spatiotemporal model (mean square error-based R^2: 0.80-0.93 for the $PM_{2.5}$ model and 0.74-0.89 for the NO_2 model) (Keller et al., 2015; Kirwa et al., 2021). The model was informed by monitoring data from regulatory networks and was further enhanced by air pollution measurements from intensive research

cohort-specific monitors. We used a geographic information system to identify covariates representing land-use characteristics that could reflect spatial variability in air pollution distribution, and the dimension-reduced regression covariates were obtained using partial least squares. The space-time features of pollution concentrations were decomposed into spatially varying long-term averages, spatially varying seasonal and long-term trends, and spatially correlated but temporally independent residuals. These components were fitted jointly in a likelihood-based spatiotemporal extension of universal kriging. Biweekly NO_2 and $PM_{2.5}$ predictions were estimated from region-specific models and were aggregated over the whole pregnancy and the postnatal windows from childbirth to four years old.

Other potential effect modifiers were also explored. History of hypertensive disorders in pregnancy was collected from both medical records and questionnaires. Mothers who reported smoking at enrollment or had urinary cotinine concentrations ≥200 ng/mL in the third trimester were classified as positive for pregnancy smoking (Benowitz et al., 2009). Maternal smoking history was determined using questionnaires that were administered from enrollment to the child age 4-6 years visit, combined with urinary cotinine aforementioned. Maternal and child body mass index (BMI) were derived from height and weight measured at the visit of outcome assessment. We characterized mothers as obese if they had a BMI ≥30 kg/m^2, and classified children as obese at or above the BMI 95^{th} percentile in the pediatric population of the same age and sex (Grummer-Strawn et al., 2010; Jensen et al., 2014). Child sex was obtained from birth records, and preterm birth was defined as birth before 37 completed weeks of gestation.

Covariates

Several maternal and child characteristics, mostly socioeconomic indicators, were considered precision variables in this study. Maternal characteristics included age at blood pressure assessment, income adjusted by household size (Burniaux et al., 1998), education, and insurance coverage. Child characteristics included age and height at outcome assessment, and current use of medication that may increase blood pressure, including albuterol, methylphenidate, and glucocorticoids. Other covariates included recruitment site and time splines of birthday date and visit date. Considering that African Americans manifest substantial population substructure, a well-established confounder in genetic association studies, we used standard protocols to apply principal component analysis (PCA) to a subset of study participants with complete genome-wide association study (GWAS) data to determine population stratification (Jolliffe, 2002). PCA was conducted using EIGENSOFT (Patterson et al., 2006; Price et al., 2006), and outliers were identified and removed before eigenvectors and eigenvalues were generated.

Statistical analysis

We summarized the maternal and child characteristics overall and by *APOL1* genetic variants and estimated the distributions of genetic polymorphisms and blood pressure measurements. Using the complete data, we performed linear regressions with robust standard error to estimate the associations of *APOL1* risk allele counts and *APOL1* risk genotypes with blood pressure in mothers and blood pressure percentiles in children. We performed Poisson regressions with robust standard error to quantify the relative risk (RR)

of hypertension in mothers and HBP in children. A hierarchical adjustment approach using two models for each population was implemented. In mothers, Model 1 (the minimally adjusted model) controlled for age and BMI at outcome assessment, overall smoking history, and recruitment site; Model 2 (the fully adjusted model) was additionally adjusted for education, income adjusted by household size, and insurance coverage. In children, Model 1 controlled for age, height, and BMI z-score at outcome assessment, sex, gestational age, medication use that may increase blood pressure, and recruitment site. Model 2 extended Model 1 and included maternal education levels, income adjusted by household size, and maternal insurance coverage.

In the secondary analyses of effect modifications, we included cross-product terms of each *APOL1* indicator (*APOL1* risk allele counts and *APOL1* risk genotypes) and the individual effect modifier in the fully adjusted models. To enable comparisons across studies, $PM_{2.5}$ and NO_2 were rescaled to two-unit increments of the predictions in each window, which were close to interquartile ranges (IQR) for exposures across different windows in Memphis, Tennessee. The other effect modifiers were treated as binary variables. In all the interaction models with air pollutions, time splines of visit date with 1 degree of freedom per year (df/year) were further adjusted to capture secular trends of blood pressure. In children, we extensively included time splines of conception date (4 df/year for prenatal $PM_{2.5}$; 1 df/year for NO_2 in each window and postnatal $PM_{2.5}$) to account for enrollment patterns.

In the first sensitivity analysis, we repeated the primary and secondary analyses with an additional adjustment of population stratification in Model 2 in 427 mothers and 290 children with available GWAS data. We were able to capture the majority of variation across the subpopulations by incorporating the first four principal components in the models of mothers, and the first three principal components in the models of children. Additionally, to verify that the observed associations were not biased by unmeasured CKD, we performed a deterministic sensitivity analysis to estimate an external CKD-adjusted RR of the *APOL1* high-risk genotype on maternal hypertension upon specification of three hypothetical values for the bias parameters, including the RR of CKD on hypertension, the prevalence of CKD in the *APOL1* high-risk and low-risk genotype groups (Greenland, 1996). Finally, we performed a post-hoc analysis to estimate linearity of the association between DBP and four-year average $PM_{2.5}$ by *APOL1* risk genotype in mothers using fully adjusted generalized additive models, and further truncated $PM_{2.5}$ at 9-11 $\mu g/m^3$. The analyses were conducted in R 3.6.1 (R Core Team) and Stata 15 (StataCorp).

Results

Characteristics of the study population

The retention of the CANDLE study from enrollment to the child 4-6 years visit as well as the sample sizes for primary and sensitivity analyses are illustrated in Figure 1. The analytic sample of 556 African American mothers was on average 30.5 (SD: 5.3) years old (Table 1). More than 70% had a high school education or less, and the median annual income adjusted for household size was $8,300. More than half were classified as obese, 22% had ever smoked, and 14% developed hypertensive disorders in previous pregnancies. The aggregated $PM_{2.5}$ and NO_2 from childbirth to age 4 were on average 10.0 (SD: 0.5) $\mu g/m^3$ and 9.7 (SD:

1.9) ppb, respectively. Most mothers had zero (43%) or one (46%) *APOL1* allele, and only 58 (10%) had the *APOL1* high-risk genotype with two risk alleles. Average SBP and DBP were 118.9 (SD: 14.8) and 77.5 (SD: 10.9) mmHg, respectively (Appendix Figure A.1). There were 231 (42%) mothers classified as hypertensive.

The 493 CANDLE children were on average 4.1 (SD: 0.5) years old, with an equal sex distribution (Table 2). Of these children, 12% had prenatal smoking exposures, 9% were born preterm, and 17% were classified as obese at the age 4-6 years visit. The average $PM_{2.5}$ in the overall pre- and postnatal period were 10.8 (SD: 0.9) and 10.0 (0.5) $\mu g/m^3$, respectively. Pre- and postnatal NO_2 had a corresponding average of 9.1 (SD: 2.5) and 9.7 (SD: 2.0) ppb. The proportions of children with zero, one, or two *APOL1* risk alleles were 43%, 42%, and 15%, respectively. SBP percentile was relatively normally distributed (Appendix Figure A.2), with an average of 49.8 (SD: 26.2), while DBP percentile was left skewed with a median of 83 (IQR: 29). There were 154 (31.2%) children with a SBP and/or DBP $\geq 90^{th}$ percentile classified as HBP.

Primary associations between *APOL1* and blood pressure

We did not find statistically significant evidence to support an overall association of *APOL1* risk allele counts or *APOL1* risk genotypes with blood pressure, as assessed by multivariate linear and Poisson regressions, in either mothers or children (Figure 2 and Appendix Table A.1). The associations with the greatest magnitude were found in the recessive models in children: the *APOL1* high-risk genotype was associated with a higher SBP percentile (β: 1.57, 95%CI: −5.41, 8.85), but a lower DBP percentile (β: −2.62, 95%CI: −8.27, 3.03), and these results had large statistical uncertainty as shown. The rest of the point estimates were very closer to null.

Effect Modification Analyses

There was a minor correlation between $PM_{2.5}$ and NO_2 (Spearman correlation: 0.28). We investigated whether these two air pollutants modified the associations between *APOL1* and blood pressure (Table 3). To enhance communication of findings, we present the results as the associations between air pollution exposures and blood pressure modified by *APOL1* risk variants. Significant interactions of $PM_{2.5}$ averaged from birth to four-year-old birthday with maternal *APOL1* risk genotypes were found for DBP: each 2-$\mu g/m^3$ higher $PM_{2.5}$ was associated with a 16.33 (95%CI: 5.73, 26.94) mmHg and a 2.85 (95%CI: −3.10, 8.79) mmHg higher DBP in mothers with the *APOL1* high-risk and low-risk genotypes, respectively ($P_{interaction}$: 0.01). We did not find similar interactive effects between *APOL1* risk alleles and $PM_{2.5}$ on the associations with either maternal SBP or DBP. Likewise, the *APOL1*-blood pressure associations were not modified by four-year average NO_2 in mothers. Similarly, the *APOL1*-air pollution exposure interactions did not affect the associations with blood pressure in children.

We further examined other potential effect modifiers, including history of hypertensive disorders in previous pregnancies, obesity and smoking history in mothers, and sex, obesity, preterm birth, and prenatal smoking exposure in children (Appendix Table A.2). The results suggested that there were sex-specific associations of HBP with *APOL1* risk alleles and risk

genotypes in children. The RR comparing those with one count increase of *APOL1* risk alleles to one count lower was 1.33 (95%CI: 0.95, 1.86) in girls and 0.82 (95%CI: 0.65, 1.04) in boys ($P_{interaction}$: 0.02). There was a 0.87 (RR: 1.87, 95%CI: 1.16, 3.03) higher risk of HBP in girls comparing those with the high-risk genotype to those with low-risk genotype, but a 0.34 (RR: 0.66, 95%CI: 0.38, 1.13) reduced risk in boys ($P_{interaction}$: 0.005). We did not find evidence to support a role for other modifiers.

Sensitivity Analysis

After additionally adjusting for population stratification, the effect estimates for the *APOL1*-blood pressure associations were mostly augmented in children but were unchanged for mothers, although all the confidence intervals included null (Appendix Table A.3). In addition, significant interactive effects between $PM_{2.5}$ averaged from childbirth to four-year-old birthday and maternal *APOL1* risk genotypes on DBP remained (Appendix Table A.4). Sex-specific associations of child HBP with *APOL1* risk allele and risk genotypes were also identified (Appendix Table A.5). In the deterministic sensitivity analysis, we assumed that the prevalence of CKD was 6.7% and 1.7% in the *APOL1* high-risk and low-risk genotype group, respectively, based on the previous literature (Foster et al., 2013). When varying the RR of CKD on hypertension at 1.54 (Stage I CKD vs. non-CKD), 2.06 (Stage II CKD vs. non-CKD), 2.57 (Stage III CKD vs. non-CKD), and 3.61 (Stage IV CKD vs. non-CKD) (Tedla et al., 2011), the external CKD-adjusted RR of the *APOL1* high-risk genotype on maternal hypertension were 0.98, 0.96, 0.94, and 0.90, respectively, compared to the observed univariate RR of 1.01. In the post-hoc analysis with generalized additive model (Appendix Figure A.3), we observed an imprecise upward trend of SBP along with increasing $PM_{2.5}$ levels in mothers with the *APOL1* high-risk genotype (P: 0.08) but a flat inverted U-shape association in the low-risk genotype group (P: 0.83). After $PM_{2.5}$ being truncated at 9-11 $\mu g/m^3$, we still visualized an upward trend of $PM_{2.5}$-DBP associations in mothers with the *APOL1* high-risk genotype, with the possibility that the association was driven by the high $PM_{2.5}$ exposures.

Discussion

Using prospective data from the CANDLE cohort, we found no associations of *APOL1* risk alleles and *APOL1* risk genotypes with blood pressure in African American mothers or children. Analyses with and without population stratification adjustments both suggested two findings. First, four-year average $PM_{2.5}$ exposure was related to a greater increase in DBP in the mothers with the *APOL1* high-risk genotype, compared to their counterparts with the *APOL1* low-risk genotype. Second, girls with *APOL1* risk alleles or the high-risk genotype had a higher risk of HBP than boys with the same *APOL1* risk variants.

The null results for associations between *APOL1* risk variants and blood pressure in mothers are consistent with the two multi-site U.S. studies by Chen et al. (2017 and 2020), one from the Coronary Artery Risk Development in Young Adults cohort, and another from the Multi-Ethnic Study of Atherosclerosis study of an elderly population (Chen Teresa K. et al., 2020; Chen et al., 2017). However, another U.S. study using data from the Bio*Me* discovery cohort reported a positive association between *APOL1* risk alleles and SBP in the

20 to 39 year age group (Nadkarni et al., 2017). Similarly, a study of mixed-ancestry South Africans found relationships between the *APOL1* G2 risk allele and SBP, more pronounced in adults with diabetes (Matsha et al., 2015). The only analysis based on pediatric data, from the Chronic Kidney Disease in Children study, showed a higher prevalence of uncontrolled hypertension in the *APOL1* high-risk genotype group, but this study was limited to children with FSGS (Woroniecki et al., 2016).

Apart from the population heterogeneities across studies, two other factors may contribute to our null results. First, none of the known genetic variants associated with CKD, including *APOL1*, appear to fully explain the excess burden of hypertension in African Americans (Simino et al., 2012; Trudu et al., 2013; Tu and Pratt, 2013). Second, it remains obscure whether blood pressure is a mediator, a potentiator, or an aftereffect for the association between *APOL1* genetic variants and kidney diseases (Nadkarni and Coca, 2017). We conducted an external adjustment of CKD in the deterministic sensitivity analysis and found no change in our conclusions. Perhaps the *APOL1*-blood pressure association exists but cannot be detected in a young and low risk population, as exemplified by the CANDLE participants. It appears that subclinical *APOL1*-related nephropathy does not manifest itself as elevated blood pressure strongly early in life.

We found a stronger association between four-year average $PM_{2.5}$ and DBP in mothers with the *APOL1* high-risk genotype. To date, only one study in New York City has estimated similar interactive effects, and it reported a significantly greater risk of CKD with higher one-year average $PM_{2.5}$ exposures in the *APOL1* high-risk subgroup of adult African Americans (Paranjpe et al., 2020). Several other studies quantified the effects of gene-air pollution interactions on various cardiovascular outcomes, and mostly focused on individual polymorphisms in the angiotensin pathway or single candidate genes in the oxidative stress defense pathway (Mordukhovich et al., 2009; Wilker et al., 2010; Zanobetti et al., 2011). Akin to our study, a key feature of these studies is that the estimated effects of interaction terms were quite large, with the adverse response to air pollution essentially only found in subgroups with the unfavorable polymorphisms. As with other genetic variants being investigated, *APOL1* risk variants may share biomechanisms influencing $PM_{2.5}$-related cardiovascular outcomes, including inflammasome activation, endothelial dysfunction, and altered high-density lipoprotein profiles (Brook and Rajagopalan, 2012; Gaio et al., 2019; Lenters et al., 2010). This finding highlights the extra vulnerability to future vascular dysfunction and/or CKD in young women with the *APOL1* high-risk genotype when exposed to air pollution. Further investigations are required to explore the potential mechanism for this gene-environmental interaction.

We also detected sex-specific associations between *APOL1* risk variants and HBP in children from both additive and recessive genetic models, with more pronounced effects in girls. Nevertheless, the adult study based on the African American Study of Kidney Disease and Hypertension did not find a sex difference in the associations between *APOL1* risk alleles and CKD progression (Chen et al., 2015). Similarly, a South African study of mixed-ancestry adults also reported that sex did not modify the relationships of *APOL1* risk variants with blood pressure and kidney functions (Matsha et al., 2015). Adult studies indicated that CKD affects more women than men (Carrero et al., 2018). However, national

representative data showed a greater proportion of boys with elevated blood pressure than girls in the past decade (Al Kibria et al., 2019), but a comparable prevalence of hypertension between sex in African American adults (Fryar et al., 2017). Existing data have indicated that estrogens alone or combined with progestins may have beneficial cardiovascular effects in women (Vitale et al., 2009), although this potential protection can be inconsequential in early childhood. The variation in lifestyle factors between boys and girls may partially contribute to the sex-specific association found in this analysis. Previous studies also suggested that lipid-related genes may have sex-specific effects on metabolism of lipoproteins and atherogenesis in women, because the function of their encoded lectin-like oxidized low-density lipoprotein receptor relies on sex hormones and hormone receptors (Wang et al., 2011; Wittrup et al., 2000). At this time, pediatric data are insufficient to draw conclusions.

Several other potential modifiers were examined in the current study, such as hypertensive disorder in mothers and preterm birth in children, and none were significant. To our knowledge, these modifiers have not been previously investigated for the *APOL1*-blood pressure association. However, these factors are well-established determinants of high blood pressure and were associated with *APOL1* risk variants in several other studies. Reidy and Hjorten et al. (2018) reported that fetal, not maternal, *APOL1* risk variants increased the risk of preeclampsia among young African American women (Reidy and Hjorten et al., 2018). Chen et al. (2015) concluded that obesity was associated with lower risk of *APOL1*-related CKD progression, but they found no difference in effect by smoking status (Chen et al., 2015). Additionally, the study by Ng et al. (2017) estimated an odds ratio of 4.6 for preterm birth comparing the *APOL1* high-risk genotype to low-risk genotype in African American children with glomerular disease (Ng et al., 2017). The current analysis is likely underpowered to reveal the modified associations by these factors, and future studies of larger cohorts of well-characterized populations are warranted to verify our hypotheses.

The present study has several strengths. First, it is one of the very few population studies to examine the associations between *APOL1* risk variant and blood pressure, particularly including general pediatric data. Second, to our knowledge, this is the first study to investigate several modifiable moderators for the *APOL1*-blood pressure associations, including spatiotemporally resolved $PM_{2.5}$ and NO_2 estimated from a well-validated advanced model. Third, we conducted PCA with a strict protocol to maximally remove linkage disequilibrium and capture population substructure.

There are also a few major limitations to be acknowledged. Firstly, we had a limited statistical power to detect effect modifiers, particularly in the analysis with population stratification adjustments, which caused a large uncertainty in our findings. Moreover, although the CANDLE study recruited women with a low-risk pregnancy, it is possible that some women developed chronic diseases such as hypertension and diabetes, and/or drug addiction during follow-up. Failure to account for these factors and their treatments/interventions due to data unavailability may distort the associations of interest. In addition, measurement of maternal and child blood pressure was performed at one time point (at child 4–6 years visit). As such, the ascertainment of hypertension and HBP do not meet the clinical definition, and potential misclassification may have occurred (Du et

al., 2019; Gillman and Cook, 1995; Pickering et al., 2005). Furthermore, we did not include longitudinal measurements of blood pressure and biomarkers of kidney function in this analysis, which could have provided additional insights to support the mechanistic hypotheses that *APOL1* risk variants contribute to CKD development with the involvement of increased blood pressure. Longitudinal blood pressure measurements may also reduce random error from outcome assessments on a single occasion. Lastly, our findings in the effect modifier analyses need to be interpreted with caution owing to the multiple comparisons.

Despite these limitations, our study concludes that *APOL1* risk variants are not associated with maternal or child blood pressure in a community-based cohort in the U.S. Importantly, there was suggestive evidence of gene-environmental interactions between *APOL1* risk variants and $PM_{2.5}$ in mothers and sex-specific associations in girls, and this finding warrants further exploration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

APOL1	the apolipoprotein L1 gene
BMI	body mass index
CANDLE	the Conditions Affecting Neurocognitive Development and Learning in Early Childhood
CKD	chronic kidney disease
DBP	diastolic blood pressure

df	degree of freedom
FSGS	focal segmental glomerulosclerosis
GWAS	genome-wide association study
HBP	high blood pressure
IQR	interquartile ranges
NO_2	nitrogen dioxide
PCA	principal component analysis
$PM_{2.5}$	particulate matter ≤2.5μm in aerodynamic diameter
RR	relative risk
SBP	systolic blood pressure

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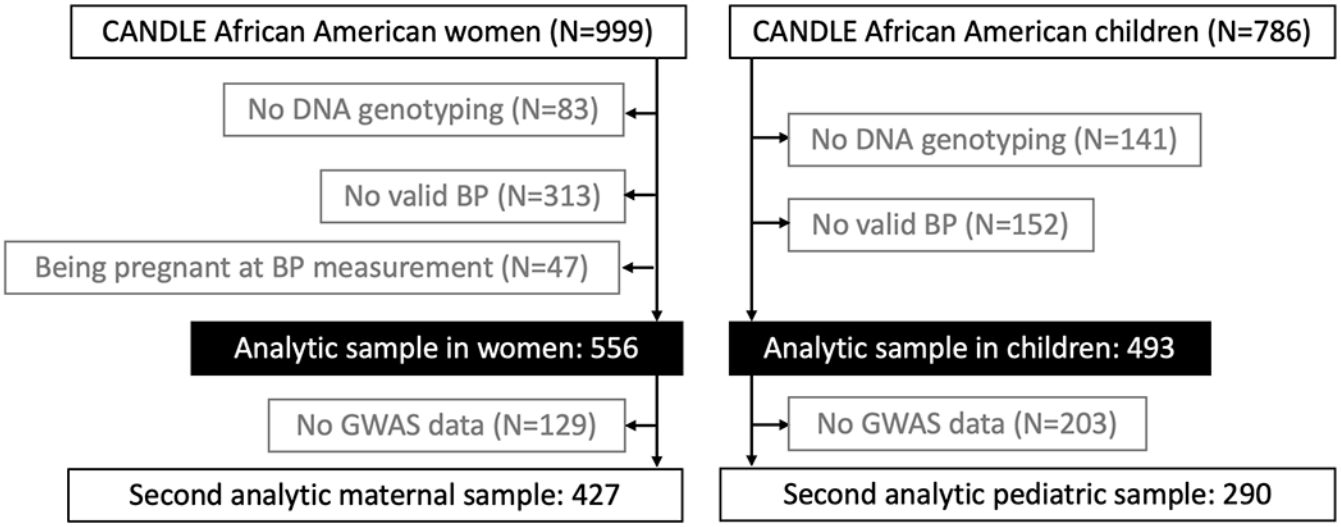

Figure 1. Inclusion Flowchart between enrollment and the child 4-6 years visit as well as sample sizes for the two analytic samples in CANDLE participants

Shown are the CANDLE cohort retention between enrollment and the child 4-6 years visit as well as sample sizes for the two analytic samples.

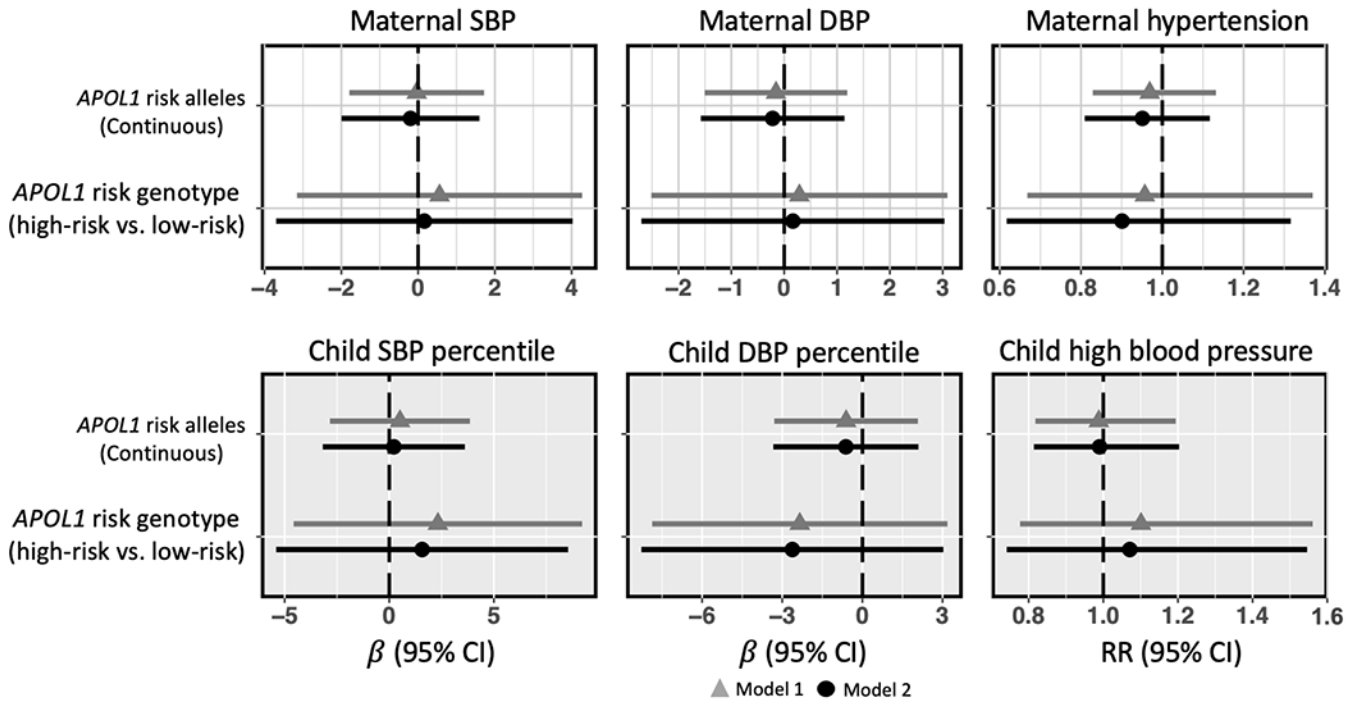

Figure 2. Estimated effects of APOL1 on blood pressure in the study population of the CANDLE cohort

Shown are the estimated effects of *APOL1* risk alleles and risk genotype on blood pressure in the CANDLE study population. The additive model was used for *APOL1* risk alleles, and the recessive model was used for *APOL1* risk genotype. In mothers, Model 1 was controlled for age and BMI at outcome assessment, overall smoking history and recruitment site; Model 2 was additionally adjusted for education levels, income adjusted by household size and insurance coverage. In children, Model 1 was controlled for age, height and BMI z score at outcome assessment, sex, gestational age, medication use that potentially increased blood pressure and recruitment site; Model 2 was extensively included maternal education levels, income adjusted by household size and maternal insurance coverage. Triangle/circle represent the effect estimates, error bars are 95% CIs, and dotted lines show null values. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HBP, high blood pressure; RR, relative risk

Table 1.

Characteristics of CANDLE African American mothers in the overall analytic sample and by *APOL1* risk allele counts and genotypes*

		***APOL1* risk allele count**			***APOL1* risk genotype**	
	Total (N=556)	**0 count (N=241)**	**1 count (N=257)**	**2 counts (N=58)**	**low risk (N=498)**	**high risk (N=58)**
Age (years)	30.5 (± 5.3)	30.3 (± 5.2)	30.6 (± 5.4)	30.8 (± 5.5)	30.5 (± 5.3)	30.8 (± 5.5)
Missing	11 (2.0%)	7 (3%)	3 (1%)	1 (2%)	10 (2%)	1 (2%)
BMI (kg/m^2)	32.5 (± 8.8)	32.4 (± 8.6)	33.0 (± 9.0)	31.0 (± 8.5)	32.7 (± 8.8)	31.0 (± 8.5)
Missing	10 (2%)	4 (2%)	3 (1%)	3 (5%)	7 (1%)	3 (5%)
Ever hypertensive disorder						
No	466 (84 %)	197 (82 %)	219 (85 %)	50 (86 %)	416 (84 %)	50 (86 %)
Yes	77 (14%)	35 (15 %)	34 (13 %)	8 (14 %)	69 (14 %)	8 (14 %)
Missing	13 (2%)	9 (4%)	4 (2%)	0 (0%)	13 (3%)	0 (0%)
Smoking						
No	431 (78 %)	185 (77 %)	205 (80 %)	41 (71 %)	390 (78 %)	41 (71 %)
Yes	124 (22 %)	55 (23 %)	52 (20 %)	17 (29 %)	107 (21 %)	17 (29 %)
Missing	1 (0.2%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)
Education level						
< High School	71 (13 %)	36 (15 %)	32 (12 %)	3 (5 %)	68 (14 %)	3 (5 %)
High School/GED	330 (59 %)	154 (64 %)	142 (55 %)	34 (59 %)	296 (59 %)	34 (59 %)
Technical School	66 (12 %)	22 (9 %)	31 (12 %)	13 (22 %)	53 (11 %)	13 (22 %)
College Degree	63 (11 %)	19 (8 %)	38 (15 %)	6 (10 %)	57 (11 %)	6 (10 %)
Grad/Professional Degree	25 (4 %)	10 (4 %)	13 (5 %)	2 (3 %)	23 (5 %)	2 (3 %)
Missing	1 (0.2%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.2%)	0 (0%)
BMI class						
Underweight	9 (2 %)	3 (1 %)	3 (1 %)	3 (5 %)	6 (1 %)	3 (5 %)
Normal weight	101 (18%)	48 (20 %)	40 (16 %)	13 (22 %)	88 (18 %)	13 (22 %)
Overweight	136 (24 %)	56 (23 %)	69 (27 %)	11 (19 %)	125 (25 %)	11 (19 %)
Obesity	300 (54 %)	130 (54 %)	142 (55 %)	28 (48 %)	272 (55 %)	28 (48 %)
Missing	10 (2%)	4 (2%)	3 (1%)	3 (5%)	7 (1%)	3 (5%)
Insurance coverage						
Medicaid or Medicare only	397 (71 %)	175 (73 %)	179 (70 %)	43 (74 %)	354 (71 %)	43 (74 %)

		APOL1 risk allele count			*APOL1* risk genotype	
	Total (N=556)	**0 count (N=241)**	**1 count (N=257)**	**2 counts (N=58)**	**low risk (N=498)**	**high risk (N=58)**
Medicaid/Medicare and private insurance	27 (5 %)	11 (5 %)	13 (5 %)	3 (5 %)	24 (5 %)	3 (5 %)
Private insurance only	132 (24 %)	55 (23 %)	65 (25 %)	12 (21 %)	120 (24 %)	12 (21 %)
Income adjusted by household size (thousand dollar)	8.3 [3.1, 16.7]	7.8 [3.1, 14.3]	9.4 [3.0, 17.5]	9.8 [3.6, 19.0]	8.3 [3.1, 15.8]	9.8 [3.6, 19.0]
Missing	4 (1%)	1 (0.4%)	2 (0.8%)	1 (2%)	3 (1%)	1 (2%)
Recruitment site						
General recruitment	405 (73 %)	179 (74 %)	183 (71 %)	43 (74 %)	362 (73 %)	43 (74 %)
Safety net hospitals	151 (27 %)	62 (26 %)	74 (29 %)	15 (26 %)	136 (27 %)	15 (26 %)
4-year average $PM_{2.5}$ ($\mu g/m^3$)	9.99 (± 0.53)	9.96 (± 0.49)	10.03 (± 0.56)	9.97 (± 0.55)	10.00 (± 0.53)	9.97 (± 0.55)
Missing	10 (2%)	6 (3%)	3 (1%)	1 (2%)	9 (2%)	1 (2%)
4-year average NO_2 (ppb)	9.66 (± 1.94)	9.75 (± 1.97)	9.64 (± 1.98)	9.32 (± 1.58)	9.69 (± 1.97)	9.32 (± 1.58)
Missing	31 (6%)	15 (6%)	12 (5%)	4 (7%)	27 (5%)	4 (7%)

*Shown are mean (± SD), counts (%), and median [25th percentile, 75th percentile].

Abbreviations: BMI, body mass index; GED, graduate equivalency degree

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Table 2.

Characteristics of CANDLE African American children in the overall analytic sample and by *APOL1* risk allele counts and genotypes *

		***APOL1* risk allele count**			***APOL1* risk genotype**	
	Total (N=493)	**0 count (N=212)**	**1 count (N=208)**	**2 counts (N=73)**	**low risk (N=420)**	**high risk (N=73)**
Age (years)	4.1 (± 0.5)	4.1 (± 0.5)	4.1 (± 0.6)	4.1 (± 0.4)	4.1 (± 0.5)	4.1 (± 0.4)
Height (cm)	106.0 (± 5.8)	106.0 (± 5.9)	107.0 (± 6.0)	106.0 (± 5.0)	106.0 (± 6.0)	106.0 (± 5.0)
Gestational week	38.9 (± 1.9)	38.8 (± 2.0)	38.8 (± 1.9)	39.2 (± 1.3)	38.8 (± 2.0)	39.2 (± 1.3)
Missing	12 (2%)	7 (3%)	4 (2%)	1 (1%)	11 (3%)	1 (1%)
Child sex						
Female	252 (51 %)	100 (47 %)	114 (55 %)	38 (52 %)	214 (51 %)	38 (52 %)
Male	241 (49 %)	112 (53 %)	94 (45 %)	35 (48 %)	206 (49 %)	35 (48 %)
Preterm birth						
No	439 (89 %)	188 (89 %)	182 (88 %)	69 (95 %)	370 (88 %)	69 (95 %)
Yes	42 (9 %)	17 (8 %)	22 (11 %)	3 (4 %)	39 (9 %)	3 (4 %)
Missing	12 (2%)	7 (3%)	4 (2%)	1 (1%)	11 (3%)	1 (1%)
Maternal pregnancy smoking						
No	428 (87 %)	190 (90 %)	178 (86 %)	60 (82 %)	368 (88 %)	60 (82 %)
Yes	65 (13 %)	22 (10 %)	30 (14 %)	13 (18 %)	52 (12 %)	13 (18 %)
Maternal education						
< High School	70 (14 %)	33 (16 %)	29 (14 %)	8 (11 %)	62 (15 %)	8 (11 %)
High School/GED	282 (57 %)	122 (58 %)	116 (56 %)	44 (60 %)	238 (57 %)	44 (60 %)
Technical School	56 (11 %)	22 (10 %)	25 (12 %)	9 (12 %)	47 (11 %)	9 (12 %)
College Degree	61 (12 %)	22 (10 %)	29 (14 %)	10 (14 %)	51 (12 %)	10 (14 %)
Grad/Professional Degree	23 (5 %)	12 (6 %)	9 (4 %)	2 (3 %)	21 (5 %)	2 (3 %)
Missing	1 (0.2%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)
Medical use that potentially increases blood pressure						
No	434 (88 %)	184 (87 %)	183 (88 %)	67 (92 %)	367 (87 %)	67 (92 %)
Yes	59 (12 %)	28 (13 %)	25 (12 %)	6 (8 %)	53 (13 %)	6 (8 %)
BMI class						
Underweight	12 (2 %)	5 (2 %)	5 (2 %)	2 (3 %)	10 (2 %)	2 (3 %)
Normal weight	324 (66 %)	142 (67 %)	133 (64 %)	49 (67 %)	275 (65 %)	49 (67 %)

		APOL1 risk allele count			*APOL1* risk genotype	
	Total (N=493)	**0 count (N=212)**	**1 count (N=208)**	**2 counts (N=73)**	**low risk (N=420)**	**high risk (N=73)**
Overweight	71 (14 %)	25 (12 %)	36 (17 %)	10 (14 %)	61 (15 %)	10 (14 %)
Obesity	85 (17 %)	39 (18 %)	34 (16 %)	12 (16 %)	73 (17 %)	12 (16 %)
Missing	1 (0.2%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)
Maternal insurance coverage						
Medicaid or Medicare only	357 (72 %)	155 (73 %)	142 (68 %)	60 (82 %)	297 (71 %)	60 (82 %)
Medicaid/Medicare and private insurance	19 (4 %)	9 (4 %)	9 (4 %)	1 (1 %)	18 (4 %)	1 (1 %)
Private insurance only	117 (24 %)	48 (23 %)	57 (27 %)	12 (16 %)	105 (25 %)	12 (16 %)
Income adjusted by household size (thousand dollar)	8.3 [2.9, 17.0]	8.3 [3.2, 16.7]	9.2 [2.9, 18.1]	6.3 [1.4, 15.7]	8.6 [3.1, 17.3]	6.3 [1.4, 15.7]
Missing	2 (0.4%)	1 (0.5%)	0 (0%)	1 (1%)	1 (0.2%)	1 (1%)
Recruitment site						
General recruitment	372 (75 %)	167 (79 %)	154 (74 %)	51 (70 %)	321 (76 %)	51 (70 %)
Safety net hospitals	121 (25 %)	45 (21 %)	54 (26 %)	22 (30 %)	99 (24 %)	22 (30 %)
Prenatal $PM_{2.5}$ ($\mu g/m^3$)	10.80 (± 0.88)	10.80 (± 0.90)	10.81 (± 0.85)	10.76 (± 0.91)	10.81 (± 0.87)	10.76 (± 0.91)
Missing	12 (2%)	7 (3%)	4 (2%)	1 (1%)	11 (3%)	1 (1%)
Postnatal $PM_{2.5}$ ($\mu g/m^3$)	9.95 (± 0.50)	9.92 (± 0.46)	9.96 (± 0.52)	9.99 (± 0.54)	9.94 (± 0.49)	9.99 (± 0.54)
Missing	9 (2%)	7 (3%)	2 (1%)	0 (0%)	9 (2%)	0 (0%)
Prenatal NO_2 (ppb)	9.05 (± 2.54)	8.89 (± 2.49)	9.18 (± 2.52)	9.12 (± 2.76)	9.03 (± 2.51)	9.12 (± 2.76)
Missing	12 (2%)	7 (3%)	4 (2%)	1 (1%)	11 (3%)	1 (1%)
Postnatal NO_2 (ppb)	9.67 (± 2.02)	9.71 (± 2.07)	9.66 (± 1.98)	9.55 (± 2.03)	9.69 (± 2.02)	9.55 (± 2.03)
Missing	26 (5%)	13 (6%)	8 (4%)	5 (7%)	21 (5%)	5 (7%)

*Shown are mean (± SD), counts (%), and median [25th percentile, 75th percentile].

Abbreviations: BMI, body mass index; GED, graduate equivalency degree

Table 3.

Modified associations between *APOL1* variants and blood pressure by $PM_{2.5}$ and NO_2 from the fully adjusted interaction models

	Maternal *APOL1* risk allele*				Maternal risk genotype*		
	0 count	1 count	2 counts	P†	Low risk	High risk	P†
4-year average $PM_{2.5}$ ‡							
SBP, β (95% CI)	−1.6 (−11.58, 8.38)	2.05 (−6.48, 10.58)	5.7 (−7.47, 18.87)	0.37	−0.11 (−8.18, 7.95)	14.11 (−3.07, 31.29)	0.09
DBP, β (95% CI)	2.27 (−5.49, 10.04)	4.72 (−1.34, 10.77)	7.16 (−2.04, 16.36)	0.42	2.85 (−3.1, 8.79)	16.33 (5.73, 26.94)	0.01
Hypertension, RR (95% CI)	1.01 (0.42, 2.42)	1.22 (0.62, 2.39)	1.47 (0.54, 3.95)	0.57	1.03 (0.52, 2.05)	2.94 (0.9, 9.56)	0.09
4-year average NO_2 ‡							
SBP, β (95% CI)	−0.52 (−1.75, 0.72)	0.2 (−1.24, 1.65)	0.92 (−1.95, 3.8)	0.40	−0.2 (−1.3, 0.91)	1.81 (−2.64, 6.26)	0.38
DBP, β (95% CI)	0.28 (−1.17, 1.74)	0.26 (−0.8, 1.31)	0.23 (−1.91, 2.37)	0.97	0.18 (−0.84, 1.2)	1.83 (−1.11, 4.78)	0.29
Hypertension, RR (95% CI)	0.96 (0.82, 1.12)	0.96 (0.83, 1.1)	0.96 (0.72, 1.27)	0.99	0.94 (0.84, 1.06)	1.24 (0.78, 1.98)	0.25
	Child *APOL1* risk allele*				Child risk genotype*		
	0 count	1 count	2 counts	P†	Low risk	High risk	P†
Prenatal $PM_{2.5}$ ‡							
SBP, β (95% CI)	9.41 (−7.32, 26.14)	5.74 (−9.1, 20.58)	2.08 (−15.26, 19.42)	0.39	5.52 (−9.82, 20.86)	6.62 (−12.76, 26.01)	0.89
DBP, β (95% CI)	9.32 (−2.16, 20.8)	11.16 (1, 21.33)	13.01 (0.35, 25.67)	0.58	8.91 (−1.47, 19.28)	17.27 (2.41, 32.14)	0.23
HBP, RR (95% CI)	1.55 (0.6, 4.01)	1.44 (0.61, 3.44)	1.35 (0.5, 3.62)	0.12	1.4 (0.57, 3.46)	1.53 (0.56, 4.16)	0.83
Postnatal $PM_{2.5}$ ‡							
SBP, β (95% CI)	10.98 (−12.86, 34.81)	9.72 (−10.84, 30.27)	8.46 (−17.37, 34.28)	0.86	10.28 (−10.56, 31.11)	8.75 (−21.16, 38.66)	0.91
DBP, β (95% CI)	0.1 (−16.37, 16.57)	7.03 (−7.72, 21.78)	13.96 (−5.39, 33.32)	0.19	4.71 (−9.63, 19.05)	10.64 (−12.79, 34.07)	0.56
HBP, RR (95% CI)	1.58 (0.42, 5.95)	1.79 (0.52, 6.17)	2.01 (0.4, 10.1)	0.77	1.81 (0.53, 6.17)	1.33 (0.24, 7.35)	0.66
Prenatal NO_2‡							
SBP, β (95% CI)	3.62 (0.65, 6.6)	1.69 (−0.8, 4.19)	−0.24 (−4.52, 4.04)	0.16	2.8 (0.32, 5.29)	−0.78 (−5.76, 4.19)	0.18
DBP, β (95% CI)	0.96 (−1.37, 3.3)	2.19 (0.36, 4.02)	3.42 (0.14, 6.69)	0.27	1.7 (−0.16, 3.56)	2.64 (−1.47, 6.75)	0.68
HBP, RR (95% CI)	1.08 (0.91, 1.28)	1.06 (0.91, 1.23)	1.04 (0.81, 1.32)	0.79	1.09 (0.94, 1.25)	0.96 (0.74, 1.25)	0.36
Postnatal NO_2 ‡							

	Maternal *APOL1* risk allele*				Maternal risk genotype*		
	0 count	1 count	2 counts	P†	Low risk	High risk	P†
SBP, β (95% CI)	0.74 (−2.81, 4.29)	1.33 (−1.56, 4.22)	1.92 (−3.37, 7.21)	0.74	1.13 (−1.73, 4)	1.58 (−4.95, 8.12)	0.90
DBP, β (95% CI)	0.72 (−1.79, 3.23)	1.64 (−0.39, 3.66)	2.55 (−1.42, 6.53)	0.49	1.42 (−0.57, 3.41)	0.9 (−4.46, 6.25)	0.86
HBP, RR (95% CI)	1.06 (0.87, 1.28)	1.11 (0.93, 1.33)	1.18 (0.85, 1.63)	0.60	1.09 (0.92, 1.28)	1.13 (0.77, 1.67)	0.85

*The additive model was used for *APOL1* alleles, and the recessive model was used for *APOL1* risk genotype. In mothers, the models were adjusted for age and BMI at outcome assessment, overall smoking history, recruitment site, education levels, income adjusted by household size, insurance coverage, and an interaction term between *APOL1* variants and individual modifiers. Time splines of visit date with 1 df/year were further included in the models. In children, the models controlled for age, height and BMI z score at outcome assessment, sex, gestational age, medication use that potentially increased blood pressure, recruitment site, maternal education levels, income adjusted by household size, maternal insurance coverage, and an interaction term between *APOL1* variants and individual modifiers. Time splines of visit date with 1 df/year and date of conception with varied df/year were further included in the models.

†P value was for the interaction term.

‡$PM_{2.5}$ and NO_2 in each window were rescaled to two-unit increment.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HBP, high blood pressure; RR, relative risk