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Apolipoprotein L1 Variants and Blood Pressure Traits in African Americans

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Abstract

BACKGROUND—African Americans (AA) are disproportionately affected by hypertension-related health disparities. Apolipoprotein L1 (*APOL1*) risk variants are associated with kidney disease in hypertensive AAs.

OBJECTIVES—This study assessed the *APOL1* risk alleles' association with blood pressure traits in AAs.

METHODS—The discovery cohort included 5,204 AA participants from Mount Sinai's Bio*Me* biobank. Replication cohorts included additional Bio*Me* (n = 1,623), Vanderbilt BioVU (n = 1,809), and Northwestern NUgene (n = 567) AA biobank participants. Single nucleotide polymorphisms determining *APOL1* G1 and G2 risk alleles were genotyped in Bio*Me* and imputed in BioVU/NUgene participants. *APOL1* risk alleles' association with blood pressure–related traits was tested in the discovery cohort, a meta-analysis of replication cohorts, and a combined meta-analysis under recessive and additive models after adjusting for age, sex, body mass index, and estimated glomerular filtration rate.

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APPENDIX For an expanded Methods section as well as a supplemental figure and tables, please see the online version of this article.

RESULTS—There were 14% to 16% of *APOL1* variant allele homozygotes (2 copies of G1/G2) across cohorts. *APOL1* risk alleles were associated under an additive model with systolic blood pressure (SBP) and age at diagnosis of hypertension, which was 2 to 5 years younger in the *APOL1* variant allele homozygotes (Cox proportional hazards analysis, p value for combined meta-analysis [p_{com}] = 1.9×10^{-5}). *APOL1* risk alleles were associated with overall SBP (p_{com} = 7.0×10^{-8}) and diastolic blood pressure ($p_{com} = 2.8 \times 10^{-4}$). After adjustment for all covariates, those in the 20- to 29-year age range showed an increase in SBP of 0.94 ± 0.44 mm Hg (p_{com} = 0.01) per risk variant copy. *APOL1*-associated estimated glomerular filtration rate decline was observed starting a decade later in life in the 30- to 39-year age range.

CONCLUSIONS—*APOL1* risk alleles are associated with higher SBP and earlier hypertension diagnoses in young AAs; this relationship appears to follow an additive model.

Keywords

allele; APOL1; estimated glomerular filtration rate; genetic association studies; kidney disease

Hypertension is a leading cause of morbidity and mortality worldwide. Data from the NHANES (National Health and Nutrition Examination Survey) for 2008 demonstrated a hypertension prevalence rate of 30% in the U.S. adult population (1). There are differences in prevalence between populations, with hypertension occurring earlier in life and more frequently in African Americans (AAs) (2). Additionally, compared with European Americans (EAs), AAs have a higher mortality from, and earlier onset of, complications of hypertension, in particular stroke, heart disease, and kidney disease (3). Average systolic blood pressure (SBP) and diastolic blood pressure (DBP) are 4 and 2 mm Hg higher, respectively, in AAs compared with EAs between 18 and 39 years of age (4). In addition to socioeconomic factors (5), heritability estimates indicate that genetic factors contribute to blood pressure (BP) traits in those of African or European ancestry (6,7). Numerous genetic loci for BP and hypertension have been identified, explaining approximately 2% of variation (8).

AAs are disproportionately affected by various kidney diseases (9). Genetic association studies demonstrated that 2 distinct alleles in the apolipoprotein L1 (*APOL1*) gene on chromosome 22 confer substantially increased risk for a number of kidney diseases in AAs, including focal segmental glomerulosclerosis, human immunodeficiency virus–associated nephropathy, and hypertension-attributable kidney disease (10–14). *APOL1* G1 (rs73885319/rs60910145; 2 missense variants in very high linkage disequilibrium) and G2 (rs71785313; 6 base pair deletion) risk alleles in the last exon of *APOL1* confer resistance to lethal *Trypanosoma brucei* infections in Sub-Saharan Africa, resulting in their selection and considerably higher frequency in individuals of African ancestry compared with other populations (15). This difference partly accounts for health disparities in kidney disease and end-stage renal disease in individuals of African ancestry (12,16,17). *APOL1* renal risk alleles were also associated with accelerated progression of chronic kidney disease (CKD) (18). The association between the *APOL1* risk alleles and kidney phenotypes is believed to follow a recessive model in which *APOL1* variant allele homozygotes (2 copies of G1/G2) are at increased risk. The underlying biological mechanisms, however, remain poorly understood (19).

Because of the increased prevalence and rate of progression of hypertensive kidney disease in individuals of African ancestry, we aimed to assess the association between *APOL1* risk variants and BP traits. For this purpose, we utilized genomic data linkable to electronic medical record (EMR) phenotypic data available in several biobanks that contribute to the Electronic Medical Records and Genomics (eMERGE) Network (20).

METHODS

This study was conducted as part of the eMERGE Network of the National Human Genome Research Institute (20). The study was designed by 2 authors (E.E.K., E.P.B), then was reviewed and approved for eMERGE II Network-wide participation by the eMERGE Steering Committee. The institutional review boards at all participating sites approved eMERGE II Network study protocols.

The Bio*Me* discovery cohort consisted of 5,204 self-reported AA participants who enrolled in the EMR-linked Bio*Me* Biobank at the Icahn School of Medicine at Mount Sinai on or before January 23, 2012. An additional 1,623 AA Bio*Me* participants who subsequently enrolled between January 24, 2012, and February 14, 2014, comprised the Bio*Me* replication cohort. External replication cohorts consisted of 1,809 AAs enrolled in the Vanderbilt University Medical Center BioVU Biobank (21), and 567 AAs enrolled in the Northwestern University NUgene Biobank.

GENOTYPING AND PHENOTYPING

Participants of the Bio*Me* discovery and replication cohorts were genotyped using a clinical genetic test to determine *APOL1* ancestral (G0), G1, and G2 allele status. All BioVU and NUgene samples were genotyped at their respective sites using a standard genotyping array with 1 million single nucleotide polymorphisms. Following standard genotype data quality control, variants on chromosome 22 were phased and imputed using the SHAPEIT and IMPUTE2 programs, respectively (22,23). The *APOL1* variant allele homozygotes were defined as carriers of 2 copies of rs73885319 (G1), 2 copies of rs71785313 (G2), or 1 copy of each. The *APOL1* variant allele heterozygotes were defined as carriers of 1 copy of these alleles, and *APOL1* ancestral allele homozygotes as carrying zero copies of these alleles. Under the additive model, the sum of the number of G1/G2 alleles was used, and under the recessive model, *APOL1* ancestral homozygotes and heterozygotes were joined in the same group.

Age, sex, and AA/black race were extracted from participants' EMRs for BioVU participants and from enrollment questionnaires of Bio*Me* and NUgene participants. Concurrent Hispanic/Latino ethnicity was not considered. Time-stamped International Classification of Diseases-Ninth Revision-Clinical Modification (ICD-9-CM) codes, medication records, and laboratory values were extracted from longitudinal EMR entries. Body mass index (BMI) was calculated as the ratio between weight and the square of height in kg/m^2. The estimated glomerular filtration rates (eGFR) were calculated from serum creatinine value using the Chronic Kidney Disease Epidemiology Collaboration study equation (24). Office-based SBP and DBP represented the average (mean) of all recorded BP readings (referred to as "all") or average of BP readings prior to prescription of

antihypertensive medications (referred to as “untreated”). Medications were identified from electronic prescribing systems, structured problem list entries, and use of validated natural language processing tools (25). BMI and eGFR were averaged for overall and age range–specific values, where 2 or more determinations were available. For the age group–specific analyses, SBP, DBP, BMI, and eGFR values were stratified according to the age of participant at date of determination. Therefore, observations from an individual participant were represented only once in each group analysis, but individuals could have spanned age groups. The date of first recorded entry of hypertension-related ICD-9-CM codes (401.xx) was used to determine participant age at diagnosis of hypertension.

STATISTICAL ANALYSIS

All association tests were performed under both a recessive model and an additive model. For overall mean outpatient SBP and DBP, linear regressions were used with year of birth, sex, and mean BMI as covariates. We performed linear regressions for overall mean eGFR with year of birth, sex, and overall mean BMI as covariates. The association test for age at hypertension onset was performed by Cox proportional hazards analysis with covariates year of birth, sex, and overall mean BMI. For the SBP and DBP age group–specific analyses, linear regressions were performed under 2 models: 1) model 1 with covariates sex and mean BMI; and 2) model 2 with covariates sex, mean BMI, and mean eGFR. For the eGFR age group–specific analyses, linear regressions were performed under 3 models: 1) model 1 with sex and mean BMI as covariates; 2) model 2 with sex, mean BMI, and mean SBP as covariates; and 3) model 3 with sex, mean BMI, mean SBP, and mean DBP as covariates.

Because some of our studied phenotypes were correlated and we replicated our results independently, Bonferroni correction was considered to be too punitive and we established a heuristic study-wide significance at $p \leq 0.01$ and a test-wide significance at $p \leq 0.05$. All analyses were performed with R version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria). We used METAL software for meta-analyses of replication cohorts and combined association results (26).

RESULTS

All 9,203 participants with reported African ancestry meeting quality control criteria in the Bio*Me* discovery cohort and 3 replication cohorts (Bio*Me* replication, Vanderbilt BioVU, and Northwestern NUgene) were included. There were 14% to 16% of *APOL1* variant allele homozygotes and 40% to 47% of *APOL1* variant allele heterozygotes across cohorts. Mean follow-up, based on time between first and last BP measurements, ranged from 3.6 to 7.6 years, and mean number of BP measurements ranged from 19.9 to 37.9 depending on cohort and *APOL1* variant allele carrier status (Table 1). Robustness of the *APOL1* genotyping/imputation was validated by replication of prior associations between *APOL1* risk alleles and eGFR under a recessive model in each cohort, except in Northwestern NUgene ($p = 0.14$; consistent direction), which had the smallest sample size (Online Table 1).

In the discovery cohort, there was an association between *APOL1* risk alleles and overall SBP ($p = 3.3 \times 10^{-3}$) under a recessive model but no association with DBP (Online Table 1). The combined meta-analysis showed an association between *APOL1* risk alleles and overall

SBP (p value for the combined meta-analysis [p_{com}] = 1.6×10^{-7}) and DBP ($p_{com} = 4.5 \times 10^{-4}$) (Online Table 2) under a recessive model.

ASSOCIATIONS OF *APOL1* RISK ALLELES

APOL1 risk allele was associated with younger age at hypertension diagnosis in a Cox proportional hazards analysis (p value for the discovery cohort [p_{dis}] = 0.04; p value for the replication cohort [p_{rep}] = 3.2×10^{-4}; $p_{com} = 1.0 \times 10^{-4}$; with age, sex, and overall mean BMI as covariates) (Figure 1). The median age of hypertension diagnosis was 2 to 5 years earlier in the *APOL1* variant allele homozygotes, depending on the individual biobank cohort (Online Figure 1). *APOL1* variant allele homozygote separation of age at hypertension diagnosis manifested in the 20- to 39-year age range (Figure 1).

To test age-specific associations between *APOL1* risk alleles and BP, we conducted linear regression in 3 nonoverlapping 20-year age groups, including 20 to 39, 40 to 59, and 60 to 79 years, consistent with NHANES reports (4). Demographic and clinical characteristics are described for each of the 20-year age groups (Online Tables 3 to 5). Considering all BP measurements, irrespective of absence or presence of treatment in the 20- to 39-year group, *APOL1* variant allele homozygosity was associated with a study-wide significantly higher SBP after adjustment for sex and BMI (model 1: discovery cohort, 2.50 ± 0.93 mm Hg, $p_{dis} = 7.3 \times 10^{-3}$; replication cohort, 2.90 ± 0.83 mm Hg, $p_{rep} = 4.7 \times 10^{-4}$; and combined, 2.72 ± 0.62 mm Hg, $p_{com} = 1.1 \times 10^{-5}$) (Table 2), and remained associated after further adjustment for mean interval eGFR (model 2: replication cohort, 2.09 ± 0.86 mm Hg; p_{rep} = 0.01; and combined 1.91 ± 0.64 mm Hg; $p_{com} = 2.7 \times 10^{-3}$) (Table 2). We then excluded BP measurements obtained after participants were prescribed antihypertensive medications to eliminate potentially confounding effects of BP treatment and/or treatment response. *APOL1* variant allele homozygosity was associated with higher SBP obtained in the absence of treatment for the 20-to 39-year age range (model 1: discovery cohort, 1.98 ± 0.96 mm Hg; p_{dis} = 0.04; replication cohort, 2.61 ± 0.84 mm Hg, $p_{rep} = 1.9 \times 10^{-3}$; combined 2.34 ± 0.63 mm Hg; $p_{com} = 2.2 \times 10^{-4}$) and after further adjustment for interval eGFR (1.72 ± 0.63 mm Hg; $p_{com} = 6.6 \times 10^{-3}$) (Table 2). *APOL1* variant allele homozygosity was associated with higher DBP (discovery cohort, 1.71 ± 0.68 mm Hg; p_{dis} = 0.01; replication cohort, 1.33 ± 0.58 mm Hg; p_{rep} = 0.02; combined 1.49 ± 0.44 mm Hg; $p_{com} = 7.1 \times 10^{-4}$, respectively), but after additional adjustment for eGFR, this was attenuated to a nominal association achieved only in the combined analysis (model 2: 0.90 ± 0.45 mm Hg; p = 0.05) (Table 3). The *APOL1* risk alleles were not associated with BP in the 40- to 59-year age group (Online Table 6), and an association in the 60- to 79-year age range (2.07 ± 0.75 mm Hg; $p_{com} = 5.8 \times 10^{-3}$) was attenuated after adjusting for eGFR (model 2: 1.79 ± 0.74 mm Hg; p_{com} = 0.02) in this age group (Online Table 7).

We next tested the association of eGFR with *APOL1* risk alleles in the 20- to 39-year age group, adding relevant covariates successively in 3 different models (Table 4). Compared with basic adjustment for sex and BMI (model 1: −4.83 ± 1.40 ml/min/1.73 m^2; $p = 5.7 \times 10^{-4}$), association of *APOL1* risk alleles with lower eGFR was attenuated largely by adjustment for SBP (model 2: −3.75 ± 1.39 ml/min/1.73 m^2; $p = 6.8 \times 10^{-3}$) and to a minor

degree by further adjustment for DBP (model 3: −3.67 ± 1.38 ml/min/1.73 m^2; p = 7.8 × 10^{-3}) (Table 4).

To refine further the temporal relationship between *APOL1* risk alleles and higher SBP or lower eGFR, we further divided the 20- to 39-year age group into 20- to 29-year and 30- to 39year age groups. The association between *APOL1* variant allele homozygosity and higher SBP was already observed in the 20- to 29-year age range replication meta-analysis and combined analysis (model 1: 3.80 ± 1.02 mm Hg replication; $p_{rep} = 1.8 \times 10^{-4}$; 3.24 ± 0.81 mm Hg combined; $p_{com} = 6.2 \times 10^{-5}$) (Table 2). Although attenuated, the association persisted after further adjustment for eGFR (model 2: 2.65 ± 1.08 mm Hg replication; p_{rep} = 0.01; 2.20 ± 0.87 mm Hg combined; p_{com} = 0.01). In contrast, we did not observe an association of lower eGFR with *APOL1* variant allele homozygosity in the 20- to 29-year age group (−0.59 ± 2.07 ml/min/1.73 m^2 combined; p_{com} = 0.77), but we did observe it in the 30- to 39-year age group (−5.37 ± 1.70 ml/min/1.73 m^2 combined; $p_{com} = 1.6 \times 10^{-3}$) (Table 4).

ASSOCIATION RESULTS UNDER RECESSIVE AND ADDITIVE MODELS

As expected, the overall eGFR association with *APOL1* risk alleles was stronger under a recessive model than under an additive model (recessive model: $p_{com} = 3.0 \times 10^{-16}$; additive model: $p_{com} = 4.2 \times 10^{-13}$) (Online Table 2). However, in the 20- to 39-year age range, the association with eGFR under an additive model was slightly stronger than the recessive model (recessive model: $p_{com} = 5.7 \times 10 = {}^{-4}$; additive model: $p_{com} = 1.6 \times 10^{-4}$) (Table 4).

The Cox proportional hazards analysis of age at hypertension diagnosis was also more significant under an additive model (recessive model: $p_{com} = 1.0 \times 10^{-4}$; additive model: $p_{com} = 1.9 \times 10^{-5}$), with *APOL1* variant allele heterozygotes in 3 of the 4 cohorts having a younger median age of hypertension diagnosis than *APOL1* ancestral allele homozygotes.

Both the overall associations with SBP (recessive model: $p_{com} = 1.6 \times 10^{-7}$; additive model: $p_{com} = 7.0 \times 10^{-8}$) and DBP (recessive model: $p_{com} = 4.5 \times 10^{-4}$; additive model: $p_{com} = 2.8 \times 10^{-4}$) with *APOL1* risk alleles were slightly stronger under an additive model (Online Table 2). In the 20- to 39-year age range, the association between the *APOL1* risk alleles with SBP was stronger under the additive model compared with the recessive model, except for untreated patients when eGFR was added to the model (Table 2). For DBP, the additive model was not more associated in any age range (Online Table 8). Testing for the additive model in the other age ranges did not uncover additional associations.

AGE-RELATED *APOL1* RISK STATUS

Next, we divided the 20- to 39-year age group in consecutive, nonoverlapping 4-year groups with average SBP, DBP, and eGFR measurements across all cohorts (Figure 2). SBP was significantly increased in *APOL1* variant allele homozygotes in 3 consecutive 4-year age groups between 20 and 31 years, respectively (Figure 2A). However, DBP was not significantly higher in *APOL1* variant allele homozygotes in any of the 4-year intervals, except for the 24- to 27-year interval (Figure 2B). In contrast, eGFR did not significantly decrease in *APOL1* variant allele homozygotes in 3 age groups between 20 and 31 years, but significantly decreased in 2 subsequent age groups between 32 and 39 years (Figure 2C).

Because urine albumin/protein laboratory data were largely missing in EMRs, we could only summarize the available results. In the 20- to 39-year age range, 23% of *APOL1* variant allele homozygotes and 19% of *APOL1* variant allele heterozygotes and *APOL1* ancestral allele homozygotes had a urine albumin/protein test recorded. Among those, 42% versus 55% manifested albuminuria or proteinuria at 29.9 ± 6.1 versus 30.8 ± 5.3 years in *APOL1* variant allele homozygotes versus combined *APOL1* variant allele heterozygotes and ancestral allele homozygotes, respectively (differences not significant). Thus, albuminuria/proteinuria was first documented nearly a decade after higher SBP and prior to significantly accelerated decline of eGFR in *APOL1* variant allele homozygotes.

DISCUSSION

Our findings demonstrated that *APOL1* risk alleles are associated with increased SBP and earlier onset of hypertension in young adults of African ancestry (Central Illustration). This association seems to be stronger under an additive model. After adjusting for major covariates such as BMI and eGFR, each copy of an *APOL1* risk allele accounted for 1.1-mm Hg higher SBP considering all BP measurements in the 20- to 39-year age group. When analysis was further limited to BP measured in the absence of antihypertensive medications, each copy of an *APOL1* risk allele accounted for a 0.8-mm Hg higher SBP, demonstrating that the association was independent of antihypertensive therapy.

APOL1 risk alleles could account for a significant proportion of higher SBP in AAs compared with EAs between 18 and 39 years of age, although the entire difference in quantitative SBP cannot be explained by *APOL1* risk alleles. Significantly higher average SBP in *APOL1* variant allele homozygotes was already apparent in the 20- to 23-year age group, the youngest in our study. Future studies in adolescent and pediatric populations will be needed to identify an age range at which the effect of *APOL1* risk alleles on BP traits first manifests. Because an estimated 14% of AAs are *APOL1* variant allele homozygotes (27), and approximately 40% to 47% are *APOL1* variant allele heterozygotes, *APOL1* genetic testing in young AAs might define a new area to study health disparities associated with increased BP burden (28). The *APOL1* variant allele homozygotes subpopulation is also at increased risk for progressive renal (18) and possibly cardiovascular complications of hypertension (27).

Since the original report attributing substantial risk for focal segmental glomerulosclerosis and human immunodeficiency virus-associated nephropathy to the G1 and G2 *APOL1* risk alleles in a recessive model (12), the spectrum of *APOL1*-related nephropathies has expanded to a range of glomerular conditions (13,29–31), albuminuria and renal function decline (32), CKD and end-stage renal disease (33,34), and accelerated CKD progression (18). The intense search for how *APOL1* risk alleles contribute mechanistically to a range of distinct glomerulopathies has focused on their potential to exert direct toxicity and cell death in kidney cells. Indeed, findings of the trypanolytic activity of APOL1, forming pores in lysosomal membranes causing lysosomal permeabilization and cell death, have been observed following overexpression of *APOL1* ancestral (G0) and risk alleles (G1 and G2) in cultured human podocytes (35). However, *APOL1* is broadly expressed in human tissues,

raising the question of whether the *APOL1* risk allele toxicity is restricted to renal cells or whether other tissues manifest adverse phenotypes yet to be identified.

Our results raised the possibility that the effect of *APOL1* risk variants on hypertensive nephropathy could result, at least in part, from an increased BP burden demonstrated here, although subclinical nephropathy due to *APOL1* variant allele carrier status could also manifest itself as increased BP early in life (26). First, the SBP effect of *APOL1* risk alleles was already manifest in 20- to 29-year-old patients and persisted after adjustment for kidney function. In contrast, the *APOL1* association with reduced kidney function was not detectable in this age group but was evident in the 30- to 39-year-old group. Second, a kidney disease–independent, BP-dependent effect in *APOL1* variant allele homozygotes might underlie its previously reported association with cardiovascular disease burden (27), although this finding remains controversial (36). Third, APOL1 protein expression was observed in vascular media of preglomerular resistance vessels in diseased kidneys, but not in normal kidneys (37,38). It will be interesting to see whether vascular smooth muscle expression of *APOL1* is associated with BP levels.

The results suggesting an additive model for the genetic association between *APOL1* risk alleles and SBP, and possibly with eGFR, in 20- to 39-year-olds were surprising. Further studies, including participants of all ages, will be needed to clarify whether the underlying mechanism behind the association between *APOL1* and kidney phenotypes could follow an additive model where heterozygosity would not be sufficient to lead to kidney disease. Nonetheless, young *APOL1* variant allele heterozygotes showed elevated SBP, which increased the *APOL1*-related public health burden to the majority of young AAs.

STUDY LIMITATIONS

We were unable to adjust for albuminuria or proteinuria because of missing data in EMRs. Interestingly, in a community-based cohort of EA and AA young adults, albuminuria was first documented after age 30 years in *APOL1* variant allele homozygotes and combined *APOL1* variant heterozygotes and ancestral allele homozygotes, and excess incidence of albuminuria in AAs was largely explained by traditional risk factors including obesity, diabetes, and BP levels (32). However, in light of our results demonstrating an association between *APOL1* risk alleles and SBP, caution is warranted to apply adjustment for BP levels as independent covariate in association testing with *APOL1* risk alleles.

Although the effect size of an *APOL1* risk allele on SBP was larger than any previous common variant on BP, it is quantitatively low, was attenuated after exclusion of BP measurements obtained after participants were prescribed antihypertensive medications, and cannot explain the entire difference in BP between AAs and EAs ages 20 to 39 years. We did not find a significant independent association with DBP; the association of *APOL1* risk alleles and cardiovascular risk might not be mediated by BP alone. Due to the observational nature of the study, residual confounding cannot be excluded. Additionally, BP measurements were recorded during clinical care encounters, not as part of a research protocol; therefore, exact details of measurements methods were not available, and we could not use more robust measures such as 24-h ambulatory BP monitoring, because such monitoring is not routinely measured. However, there was no significant difference in

number of BP measurements and lengths of observation period between *APOL1* variant allele carrier status in individual bio-bank cohorts. Although administrative codes could have limitations, the hypertension ICD-9-CM codes have excellent sensitivity and specificity.

Ascertainment bias for some phenotypes, such as eGFR, for which patients with clinical signs/symptoms or family history of kidney disease would have been more likely to be tested more frequently and at a younger age, cannot be ruled out. We used self-reported AA race as inclusion criteria leading to a possibility of selection bias; however, because participants had predominantly African genetic ancestry, any bias was likely small and associations remained significant after correcting for principal components in cohorts for whom genome-wide genotyping data was available. Finally, because we only investigated the effect of *APOL1* risk alleles in AAs, it is unclear whether these findings are generalizable to Africans, Afro Caribbeans, and other populations of African descent.

CONCLUSIONS

In young AA adults, *APOL1* variant allele homozygotes manifested elevated SBP prior to eGFR decline and earlier hypertension diagnosis. Resolving whether *APOL1* initially affects vascular or renal cell biology requires further studies, including in adolescent and childhood populations. *APOL1* genetic testing can identify young individuals of African ancestry with increased BP burden and increased risk for hypertension-attributable cardiovascular and renal health disparities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

APOL1	apolipoprotein L1
BMI	body mass index
CKD	chronic kidney disease
DBP	diastolic blood pressure

eGFR	estimated glomerular filtration rate
EMR	electronic medical record
SBP	systolic blood pressure

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE

APOL1 alleles are strongly associated with elevated SBP and onset of hypertension in young AA adults before renal impairment develops.

TRANSLATIONAL OUTLOOK

Additional studies should examine whether the mechanisms underlying the association between *APOL1* and hypertensive kidney disease are additive and whether *APOL1* heterozygosity is associated with kidney disease.

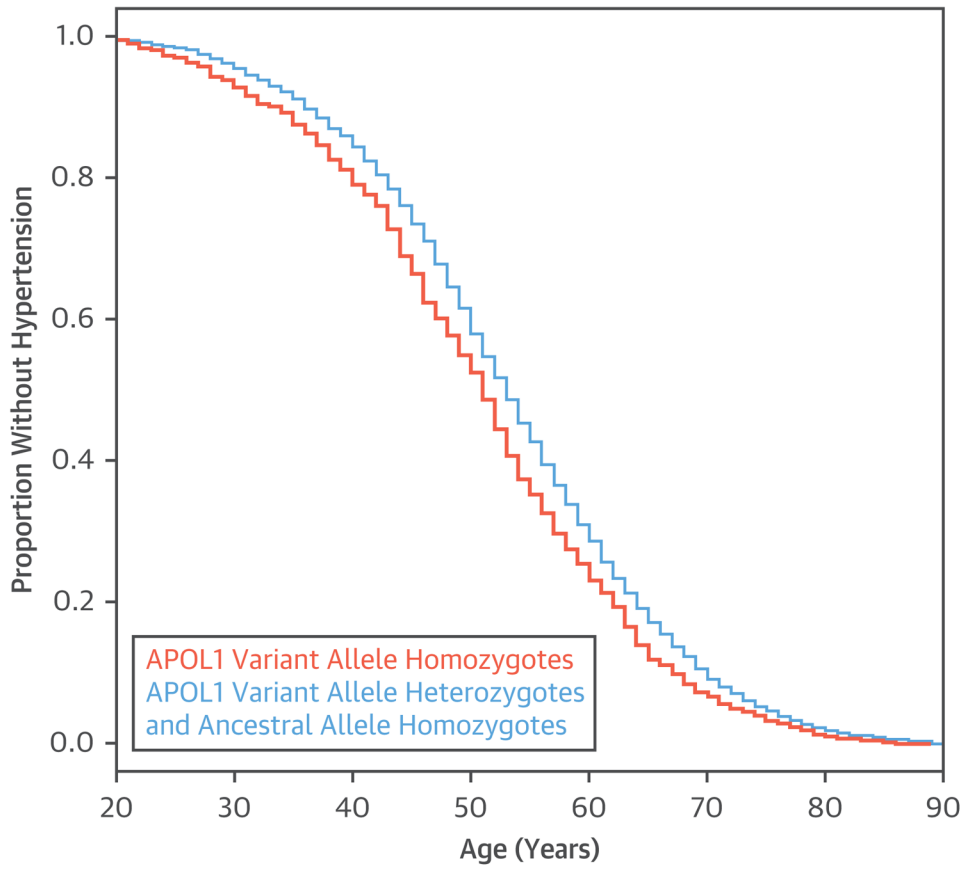


FIGURE 1. Age at First Diagnosis of Hypertension

Apolipoprotein L1 (*APOL1*) variant allele homozygotes (**orange**) were younger at diagnosis of hypertension than APOL1 ancestral allele homozygotes and variant allele heterozygotes (**blue**). A Cox proportional hazards analysis with age at hypertension diagnosis adjusted for year of birth, sex, and overall mean body mass index was significant in both the discovery cohort and replication meta-analysis.

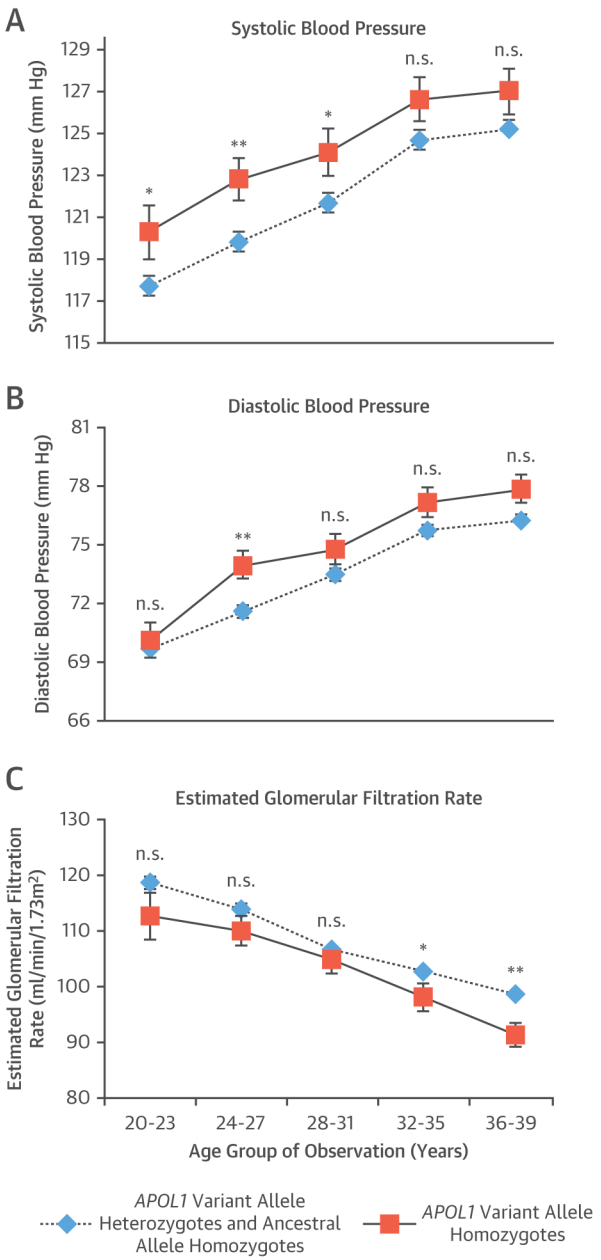
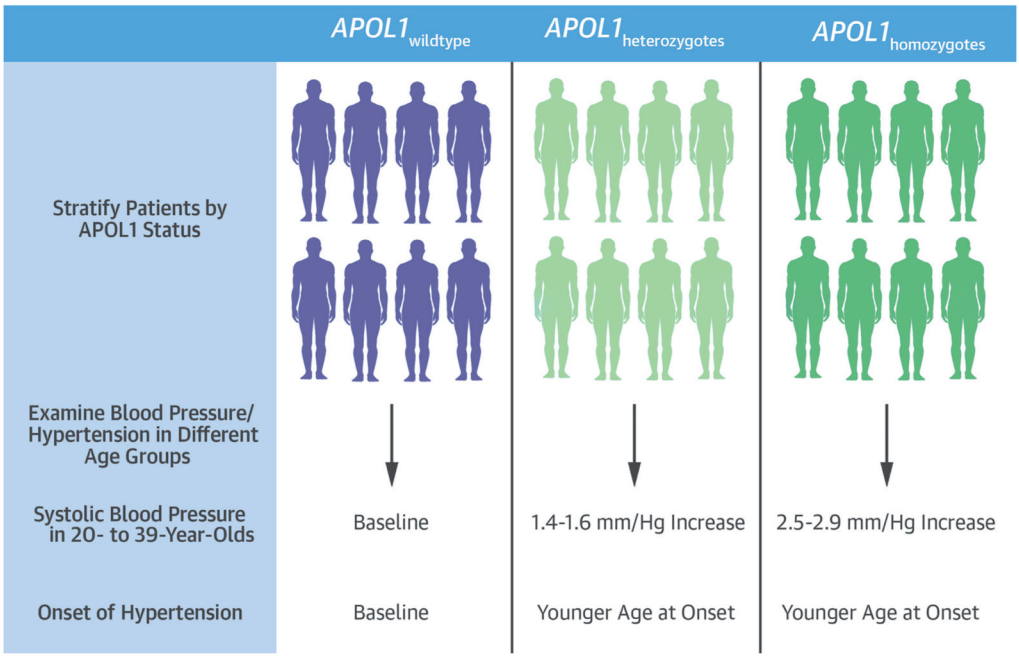


FIGURE 2. Change of Blood Pressure and eGFR

Variations in **(A)** systolic blood pressure, **(B)** diastolic blood pressure, and **(C)** estimated glomerular filtration rate (eGFR) were seen in apolipoprotein L1 (*APOL1*) ancestral allele homozygotes and *APOL1* variant allele heterozygotes versus *APOL1* variant allele homozygotes for all cohorts combined between the ages of 20 and 39 years. Line graphs show mean values with 95% confidence intervals. *p < 0.05; **p < 0.01. n.s. = not significant.



CENTRAL ILLUSTRATION. *APOL1* Genotypes and Phenotypic Data From EMRs

Hypertension-related health problems affect African Americans (AAs) to a greater degree than other groups, and apolipoprotein L1 (*APOL1*) risk variants are associated with kidney disease in hypertensive AAs. Analyzing data from electronic medical records (EMRs) from 3 major health systems in discovery and replication cohorts using recessive and additive models demonstrated that *APOL1* risk alleles were associated with higher systolic blood pressure in AAs of 20 to 39 years of age and younger at diagnosis of hypertension.

TABLE 1

Demographic and Clinical Characteristics

	BioMe Discovery			BioMe Replication			Vanderbilt BioVU			Northwestern NUgene		
	APOL1 Variant Allele Copies			*APOL1* Variant Allele Copies			*APOL1* Variant Allele Copies			*APOL1* Variant Allele Copies		
	0 or 1 (n = 4,496)	2 (n = 708)	p Value	0 or 1 (n = 1,356)	2 (n = 267)	p Value	0 or 1 (n = 1,524)	2 (n = 285)	p Value	0 or 1 (n = 482)	2 (n = 85)	p Value
Age at first blood pressure measurement, yrs	49.4 ± 14.9	48.9 ± 14.6	0.34	42.5 ± 16.5	42.0 ± 15.7	0.68	48.3 ± 16.0	46.0 ± 15.1	0.03	46.8 ± 13.0	43.3 ± 12.6	0.03
Female	63.4	65.8	0.22	61.8	58.4	0.30	66.0	68.8	0.38	70.1	75.3	0.37
Genetic African ancestry, %	80.9 ± 16.0	86.8 ± 8.3	2.2×10^{-16}	NA	NA	NA	79.5 ± 11.3	82.8 ± 8.8	8.5×10^{-8}	78.3 ± 12.6	81.9 ± 9.2	2.3×10^{-3}
Time between first and last blood pressure measurements, yrs	4.8 ± 2.7	4.7 ± 2.6	0.34	3.5 ± 2.7	3.7 ± 2.8	0.22	6.0 ± 3.8	6.3 ± 3.8	0.25	7.5 ± 4.7	7.7 ± 4.9	0.72
Discrete outpatient encounters with blood pressure recordings, n	32.1 ± 31.6	30.1 ± 27.9	0.09	21.5 ± 23.2	19.9 ± 17.4	0.19	30.9 ± 33.5	33.8 ± 33.0	0.18	35.6 ± 35.8	37.9 ± 35.0	0.60
Hypertension diagnosis *	61.1	64.5	0.08	36.7	43.8	0.03	65.3	70.9	0.08	57.9	58.8	0.91
Antihypertensive medications †	66.5	67.7	0.58	45.6	51.3	0.09	73.5	78.6	0.08	62.2	58.8	0.55
SBP, mm Hg	130.8 ± 13.9	132.2 ± 13.9	0.02	128.0 ± 14.5	131.8 ± 14.8	1.7×10^{-4}	131.4 ± 14.5	132.3 ± 13.7	0.32	126.8 ± 12.5	127.6 ± 13.4	0.61
DBP, mm Hg	75.8 ± 8.0	76.5 ± 8.5	0.07	74.6 ± 8.5	75.7 ± 8.4	0.05	77.5 ± 8.0	79.1 ± 7.7	3.5×10^{-3}	77.4 ± 7.4	78.3 ± 7.5	0.34
eGFR, ml/min/1.73 m^2 ‡	83.9 ± 26.9	78.4 ± 30.9	1.6×10^{-5}	90.1 ± 27.4	82.8 ± 38.8	6.0×10^{-3}	82.1 ± 28.3	80.2 ± 31.4	0.35	85.8 ± 24.9	85.8 ± 25.5	0.99
BMI, kg/m^2 §	30.6 ± 7.9	31.4 ± 8.0	0.01	29.2 ± 8.0	30.0 ± 8.0	0.13	31.9 ± 7.9	32.3 ± 7.6	0.52	32.9 ± 9.5	35.7 ± 10.1	0.02

Values are mean ± SD or %.

* Hypertension diagnosis status was assessed with presence of hypertension International Classification of Diseases-Ninth Revision-Clinical Modification diagnostic code.

† Percentage of participants prescribed any antihypertensive medications.

‡ Estimated glomerular filtration rate (eGFR) was calculated from measured serum creatinine values by the Chronic Kidney Disease Epidemiology estimating equation.

§Body mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

APOL1 = apolipoprotein L1; DBP = diastolic blood pressure; SBP = systolic blood pressure.

TABLE 2

Association of *APOL1* Risk Alleles With SBP

	BioMe Discovery							Replication Meta-Analysis		Combined Analysis	
	N	0 or 1 Copy	0 Copies	1 Copy	2 Copies	β ± SE	p Value	β ± SE	p Value	β ± SE	p Value
Model 1: Adjusted for Sex and BMI*											
All patients											
20–39 yrs											
Recessive	1,132	122.4 ± 12.0			125.9 ± 14.4	2.50 ± 0.93	7.3×10^{-3}	2.90 ± 0.83	4.7×10^{-4}	2.72 ± 0.62	1.1×10^{-5}
Additive	1,132		121.8 ± 11.5	123.1 ± 12.6	125.9 ± 14.4	1.40 ± 0.45	2.1×10^{-3}	1.68 ± 0.43	9.6×10^{-5}	1.55 ± 0.31	7.4×10^{-7}
20–29 yrs											
Recessive	472	119.7 ± 11.1			122.3 ± 11.4	2.27 ± 1.34	0.09	3.80 ± 1.02	1.8×10^{-4}	3.24 ± 0.81	6.2×10^{-5}
Additive	472		119.7 ± 10.6	119.8 ± 11.8	122.3 ± 11.4	1.01 ± 0.64	0.11	1.84 ± 0.53	4.5×10^{-4}	1.51 ± 0.41	2.0×10^{-4}
30–39 yrs											
Recessive	814	124.0 ± 12.8			127.6 ± 15.2	2.59 ± 1.18	0.03	2.28 ± 1.11	0.04	2.42 ± 0.81	2.8×10^{-3}
Additive	814		123.1 ± 12.3	125.1 ± 13.2	127.6 ± 15.2	1.64 ± 0.58	5×10^{-3}	1.22 ± 0.58	0.04	1.43 ± 0.41	5.3×10^{-4}
Untreated patients											
20–39 yrs											
Recessive	946	120.5 ± 10.8			123.1 ± 12.6	1.98 ± 0.96	0.04	2.61 ± 0.84	1.9×10^{-3}	2.34 ± 0.63	2.2×10^{-4}
Additive	946		120.2 ± 10.3	120.8 ± 11.3	123.1 ± 12.6	1.07 ± 0.46	0.02	1.54 ± 0.43	3.1×10^{-4}	1.32 ± 0.31	2.3×10^{-5}
20–29 yrs											
Recessive	424	118.6 ± 10.0			121.8 ± 10.9	2.97 ± 1.30	0.02	2.69 ± 1.00	7.2×10^{-3}	2.79 ± 0.79	4.2×10^{-4}
Additive	424		118.5 ± 10.1	118.7 ± 10.2	121.8 ± 10.9	1.29 ± 0.63	0.04	1.38 ± 0.50	6.1×10^{-3}	1.34 ± 0.39	6.0×10^{-4}
30–39 yrs											
Recessive	626	121.5 ± 11.1			123.8 ± 13.5	1.30 ± 1.24	0.30	2.78 ± 1.19	0.02	2.07 ± 0.86	0.02
Additive	626		121.0 ± 10.6	122.0 ± 11.6	123.8 ± 13.5	1.00 ± 0.59	0.09	1.54 ± 0.61	0.01	1.26 ± 0.42	3.0×10^{-3}
Model 2: Adjusted for Sex, BMI, and eGFR†											
All patients											
20–39 yrs											

	BioMe Discovery						Replication Meta-Analysis		Combined Analysis	
	N	0 or 1 Copy	0 Copies	1 Copy	2 Copies	β ± SE	p Value	β ± SE	p Value	β ± SE	p Value
Model 1: Adjusted for Sex and BMI*											
Recessive	1,022	122.7 ± 12.2			126.4 ± 14.5	1.69 ± 0.95	0.08	2.09 ± 0.86	0.01	1.91 ± 0.64	2.7×10^{-3}
Additive	1,022		122.2 ± 11.6	123.3 ± 12.7	126.4 ± 14.5	0.91 ± 0.47	0.05	1.22 ± 0.45	6.5×10^{-3}	1.07 ± 0.32	9.2×10^{-4}
20–29 yrs											
Recessive	390	120.2 ± 11.4			122.1 ± 11.0	1.37 ± 1.45	0.35	2.65 ± 1.08	0.01	2.20 ± 0.87	0.01
Additive	390		120.4 ± 10.8	120.0 ± 12.1	122.1 ± 11.0	0.35 ± 0.70	0.61	1.32 ± 0.56	0.02	0.94 ± 0.44	0.03
30–39 yrs											
Recessive	736	124.1 ± 12.9			128.3 ± 15.1	1.51 ± 1.21	0.21	1.93 ± 1.13	0.09	1.74 ± 0.83	0.04
Additive	736		123.0 ± 12.3	125.5 ± 13.4	128.3 ± 15.1	1.36 ± 0.59	0.02	0.91 ± 0.60	0.13	1.14 ± 0.42	6.9×10^{-3}
Untreated patients											
20–39 yrs											
Recessive	822	120.2 ± 10.0			123.0 ± 12.3	1.70 ± 0.93	0.07	1.73 ± 0.86	0.04	1.72 ± 0.63	6.6×10^{-3}
Additive	822		120.1 ± 9.8	120.4 ± 10.3	123.0 ± 12.3	0.74 ± 0.45	0.10	0.94 ± 0.44	0.03	0.84 ± 0.31	7.0×10^{-3}
20–29 yrs											
Recessive	341	118.8 ± 9.9			121.0 ± 8.9	1.82 ± 1.35	0.18	1.80 ± 1.13	0.11	1.81 ± 0.87	0.04
Additive	341		118.9 ± 9.7	118.7 ± 10.2	121.0 ± 8.9	0.68 ± 0.66	0.30	1.05 ± 0.56	0.06	0.89 ± 0.43	0.04
30–39 yrs											
Recessive	536	120.8 ± 9.9			124.5 ± 13.6	1.83 ± 1.21	0.13	2.38 ± 1.17	0.04	2.12 ± 0.84	0.01
Additive	536		120.4 ± 9.8	121.3 ± 10.0	124.5 ± 13.6	1.06 ± 0.57	0.06	0.88 ± 0.60	0.15	0.97 ± 0.41	0.02

Values are mean ± SD.

*All mean values listed are for individuals with nonmissing BMI values.

†All mean values listed are for individuals with nonmissing BMI and eGFR values.

β = effect size in mm Hg for *APOL1* variant allele homozygotes versus *APOL1* variant allele heterozygotes and ancestral allele homozygotes under the recessive model and for 1 copy of *APOL1* risk allele under the additive model; SE = standard error; other abbreviations as in Table 1.

TABLE 3

Association of *APOL1* Risk Alleles With DBP

	Bio*Me* Discovery					Replication Meta-Analysis		Combined Analysis	
	N	0 or 1 Copy	2 Copies	β ± SE	p Value	β ± SE	p Value	β ± SE	p Value
Model 1: Adjusted for Sex and BMI*									
All patients									
20–39 yrs	1,132	73.4 ± 8.2	75.7 ± 10.0	1.71 ± 0.68	0.01	1.33 ± 0.58	0.02	1.49 ± 0.44	7.1×10^{-4}
20–29 yrs	472	70.9 ± 7.9	73.6 ± 8.7	2.59 ± 1.03	0.01	1.31 ± 0.76	0.08	1.76 ± 0.61	3.9×10^{-3}
30–39 yrs	814	74.9 ± 8.4	76.8 ± 10.4	1.34 ± 0.84	0.11	1.48 ± 0.76	0.05	1.42 ± 0.56	0.01
Untreated patients									
20–39 yrs	946	72.2 ± 7.6	73.5 ± 7.9	0.93 ± 0.71	0.19	1.13 ± 0.63	0.07	1.04 ± 0.47	0.03
20–29 yrs	424	70.2 ± 7.2	72.6 ± 6.6	2.29 ± 0.97	0.02	0.51 ± 0.78	0.52	1.21 ± 0.61	0.05
30–39 yrs	625	73.3 ± 7.8	74.1 ± 8.8	0.23 ± 0.92	0.81	2.06 ± 0.88	0.02	1.19 ± 0.63	0.06
Model 2: Adjusted for Sex, BMI, and eGFR†									
All patients									
20–39 yrs	1,022	73.9 ± 8.1	75.9 ± 10.2	0.82 ± 0.68	0.23	0.96 ± 0.60	0.11	0.90 ± 0.45	0.05
20–29 yrs	392	71.5 ± 8.0	73.5 ± 8.7	1.60 ± 1.08	0.14	0.93 ± 0.82	0.25	1.18 ± 0.65	0.07
30–39 yrs	736	75.2 ± 8.5	77.2 ± 10.4	0.62 ± 0.86	0.47	1.22 ± 0.77	0.11	0.95 ± 0.57	0.10
Untreated patients									
20–39 yrs	822	72.4 ± 7.1	73.2 ± 7.8	0.21 ± 0.70	0.77	1.09 ± 0.67	0.10	0.67 ± 0.49	0.17
20–29 yrs	343	70.7 ± 7.0	72.1 ± 5.7	1.11 ± 1.02	0.28	0.54 ± 0.91	0.56	0.79 ± 0.68	0.24
30–39 yrs	535	73.1 ± 7.2	74.2 ± 8.6	0.13 ± 0.92	0.88	1.96 ± 0.92	0.03	1.05 ± 0.65	0.11

Values are mean ± SD.

*All mean values listed are for individuals with nonmissing BMI.

†All mean values listed are for individuals with nonmissing BMI and eGFR. Abbreviations as in Tables 1 and 2.

TABLE 4

Association of *APOL1* Risk Alleles with eGFR*

	BioMe Discovery							Replication Meta-Analysis		Combined	
	N	0 or 1 Copy	0 Copies	1 Copy	2 Copies	β ± SE	p Value	β ± SE	p Value	β ± SE	p Value
20–39 years of age											
Model 1 recessive	1,047	105.0 ± 22.8			97.2 ± 31.2	−7.13 ± 2.10	7.0×10^{-4}	−2.97 ± 1.89	0.12	−4.83 ± 1.40	5.7×10^{-4}
Model 1 additive	1,047		106.0 ± 22.9	103.8 ± 22.6	97.2 ± 31.2	−3.56 ± 1.03	5.6×10^{-4}	−1.88 ± 0.99	0.06	−2.69 ± 0.71	1.6×10^{-4}
Model 2 recessive	1,022	105.1 ± 22.8			97.4 ± 30.6	−5.84 ± 2.07	4.9×10^{-3}	−2.05 ± 1.87	0.27	−3.75 ± 1.39	6.8×10^{-3}
Model 2 additive	1,022		106.1 ± 23.0	103.9 ± 22.5	97.4 ± 30.6	−2.88 ± 1.02	4.7×10^{-3}	−1.21 ± 0.97	0.21	−2.01 ± 0.70	4.2×10^{-3}
Model 3 recessive	1,017	105.1 ± 22.8			97.4 ± 30.6	−5.76 ± 2.05	5.2×10^{-3}	−1.95 ± 1.86	0.29	−3.67 ± 1.38	7.8×10^{-3}
Model 3 additive	1,017		106.1 ± 23.1	103.9 ± 22.5	97.4 ± 30.6	−3.04 ± 1.01	2.7×10^{-3}	−1.22 ± 0.97	0.21	−2.10 ± 0.70	2.8×10^{-3}
20–29 years of age											
Model 1 recessive	403	111.8 ± 22.9			111.1 ± 20.3	−0.18 ± 3.27	0.96	−0.87 ± 2.67	0.75	−0.59 ± 2.07	0.77
Model 1 additive	403		113.0 ± 22.8	110.4 ± 23.0	111.1 ± 20.3	−1.22 ± 1.57	0.44	−1.48 ± 1.40	0.29	−1.36 ± 1.04	0.19
Model 2 recessive	390	112.0 ± 22.6			110.0 ± 19.9	−0.98 ± 3.24	0.76	0.27 ± 2.66	0.92	−0.24 ± 2.06	0.91
Model 2 additive	390		113.3 ± 21.8	110.3 ± 23.4	110.0 ± 19.9	−1.77 ± 1.55	0.25	−0.82 ± 1.39	0.55	−1.25 ± 1.03	0.23
Model 3 recessive	390	112.0 ± 22.6			110.0 ± 19.9	−0.23 ± 3.18	0.94	0.14 ± 2.71	0.96	−0.02 ± 2.06	0.99
Model 3 additive	390		113.3 ± 21.8	110.3 ± 23.4	110.0 ± 19.9	−1.83 ± 1.52	0.23	−0.89 ± 1.40	0.52	−1.32 ± 1.03	0.20
30–39 years of age											
Model 1 recessive	762	101.1 ± 22.8			91.0 ± 32.6	−9.46 ± 2.49	1.6×10^{-4}	−1.80 ± 2.33	0.44	−5.37 ± 1.70	1.6×10^{-3}
Model 1 additive	762		101.4 ± 22.6	100.6 ± 23.0	91.0 ± 32.6	−3.78 ± 1.23	2.3×10^{-3}	−1.03 ± 1.23	0.40	−2.40 ± 0.87	5.9×10^{-3}
Model 2 recessive	736	101.1 ± 22.8			90.7 ± 32.0	−8.28 ± 2.46	8.0×10^{-4}	−1.18 ± 2.31	0.61	−4.51 ± 1.68	7.4×10^{-3}
Model 2 additive	736		101.4 ± 22.8	100.7 ± 22.9	90.7 ± 32.0	−2.83 ± 1.22	0.02	−0.47 ± 1.22	0.70	−1.65 ± 0.86	0.06
Model 3 recessive	731	101.1 ± 22.9			90.7 ± 32.0	−8.32 ± 2.46	7.7×10^{-4}	−1.04 ± 2.31	0.65	−4.45 ± 1.69	8.3×10^{-3}
Model 3 additive	731		101.4 ± 22.8	100.8 ± 22.9	90.7 ± 32.0	−2.86 ± 1.23	0.02	−0.41 ± 1.22	0.73	−1.63 ± 0.86	0.06

Values are mean ± SD.

*Models were adjusted as follows: model 1, adjusted for sex and BMI; model 2, model 1 + additional adjustment for SBP; and model 3, model 2 + additional adjustment for DBP. Abbreviations as in Tables 1 and 2.