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APOL1 renal risk variants are associated with obesity and body composition in African ancestry adults

An observational genotype–phenotype association study

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Abstract

While increased obesity prevalence among persons of African ancestry (AAs) compared to persons of European ancestry (EAs) is linked to social, environmental and behavioral factors, there are no gene variants that are common and significantly associated with obesity in AA populations. We sought to explore the association between ancestry specific renal risk variants in the apolipoprotein L1 (*APOL1*) gene with obesity related traits in AAs.

We conducted a genotype–phenotype association study from 3 electronic medical record linked cohorts (Bio*Me* Biobank, BioVU, nuGENE); randomized controlled trials (genetic testing to understand and address renal disease disparities) and prospective cohort study (Jackson Heart Study). We analyzed association of *APOL1* renal risk variants with cross-sectional measures of obesity (average body mass index (BMI), and proportion of overweight and obesity) and with measures of body composition (in Jackson Heart Study).

We had data on 11,930 self-reported AA adults. Across cohorts, mean age was from 42 to 49 years and percentage female from 58% to 75.3%. Individuals who have 2 *APOL1* risk alleles (14% of AAs) have 30% higher obesity odds compared to others (recessive model adjusted odds ratio 1.30; 95% confidence interval 1.16–1.41; $P = 2.75 \times 10^{-6}$). An additive model better fit the association, in which each allele (47% of AAs) increases obesity odds by 1.13-fold (adjusted odds ratio 1.13; 95% confidence interval 1.07–1.19; $P = 3.07 \times 10^{-6}$) and increases BMI by 0.36 kg/m^2 (~1 kg, for 1.7 m height; $P = 2 \times 10^{-4}$). *APOL1* alleles are not associated with refined body composition traits overall but are significantly associated with fat free mass index in women [0.30 kg/m^2 increment per allele; $P = .03$].

Thus, renal risk variants in the *APOL1* gene, found in nearly half of AAs, are associated with BMI and obesity in an additive manner. These variants could, either on their own or interacting with environmental factors, explain a proportion of ethnic disparities in obesity.

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Abbreviations: AA = African Americans, aOR = adjusted odds ratio, *APOL1* = apolipoprotein L1, BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, EA = European American, EHR = electronic health records, FFM = Fat free mass index, GUARDD = genetic testing to understand and address renal disease disparities, RCT = randomized controlled trial.

Keywords: apolipoprotein L1, disparities, obesity, outcomes

1. Introduction

In the US, beginning in the 1960's an upward trend in obesity occurred in adults of all major demographic groups.[1] The slope of these trends over the following 5 decades has been remarkably consistent across racial and gender groups, although blacks started at a higher baseline level and have continued to have a prevalence one third greater than among whites. Obesity and its adverse health consequences are now established as world-wide epidemics.[2–8] Obesity therefore represents a "common source" epidemic where exposure is widespread and the outcome is mediated by social, environmental, lifestyle and biological/genomic factors.[9–11] Twin and family studies estimate that 40% to 70% of obesity risk is heritable.[12] Large-scale genome-wide association studies have been performed in predominantly European American (EA) populations.[13–20] The majority of genetic variants associated with body mass index (BMI) and obesity in EA populations transfer to African Americans (AA) populations, however, some variants have been reported to be ancestry-specific, including African-derived variants,[21,22] emphasizing the importance of performing genomic studies in underrepresented ancestry groups. One rare genetic variant, rs80068415 in *SEMA4D* present in <1% of AAs and few, if any EAs, has been associated with increased obesity risk.[22] To date, no African-specific common variants have been significantly associated with increased BMI or obesity.

Apolipoprotein L1 (*APOL1*) risk variants are an example of an ancestry-specific genetic polymorphism associated with chronic disease burden. They confer resistance to lethal *Trypanosoma brucei* infections in sub-Saharan Africa, and thus are very common in AA individuals due to natural selection, but nearly nonexistent in other populations (14% in AA people with 2 risk variants, 47% in AAs with at least 1 variant and 0% to 0.01% in EAs).[23,24] Two distinct variants in the last exon of *APOL1* confer substantially increased risk and faster rates of progression of chronic kidney disease (CKD) in AAs, and explain a large proportion of the well-known AA–EA disparities in end stage renal disease. They have also been associated with other complex diseases, such as cardiovascular disease, earlier onset of hypertension and higher systolic blood pressure.[25,26] They confer resistance to lethal *T brucei* infections in sub-Saharan Africa, and thus are very common in AA individuals due to natural selection, but nearly nonexistent in other populations (14% in AA people with 2 risk variants, 47% in AAs with at least 1 variant and 0%–0.01% in EAs).[23,24]

A community–clinical–academic partnership[27] is conducting the Genetic Testing to Understand and Address Renal Disease Disparities (GUARDD) study, a randomized controlled trial (RCT) of the impact testing AA adults with hypertension for *APOL1* variants within the Implementing GeNomics In PracTicE Network. The GUARDD team decided to assess the association of *APOL1* renal risk variants with obesity among recruited patients, as both *APOL1* variants and obesity are prevalent in the study population.[28] After finding an initial association with obesity, we sought to determine the strength of this association in other AA populations in clinical trial and longitudinal study cohorts, in electronic health records (EHR)-linked biobanks, in rural and urban populations seen in both academic and community settings, and among persons residing in several US regions, as well as to study its association with body composition.

2. Methods

2.1. Study design and cohorts

We conducted a cross-sectional genetic association study among self-reported AA adults (>18 years). The discovery cohorts consisted of 1227 participants in GUARDD (N = 1277, age 18–70 years, with hypertension but without kidney disease) who receive care at one of 15 clinical sites throughout New York City,[28] and participants (N = 3835) who enrolled in the EHR-linked Bio*Me* Biobank at the Icahn School of Medicine at Mount Sinai before 2012. The internal replication cohort included an additional 1544 Bio*Me* participants who enrolled after 2012. External replication cohorts consisted of 1809 participants in the Vanderbilt University Medical Center BioVU Biobank, 567 participants in the Northwestern University NUgene Biobank,[29] and 3210 participants in the Jackson Heart Study.[30] No cohort, except for GUARDD (age < 75 years) and Jackson Heart Study (age < 84 years), had restrictions on comorbidities for inclusion, or upper age limits. We had institutional review board approval from all participating sites. Bio*Me*, Vanderbilt and BioVU are part of the eMERGE network and data is available in dbGAP under accession ID phs000888.v1.p1. Data for the GUARDD study will be available by request from the GUARDD DSMB. Data for JHS is available after completion of a manuscript submission proposal from JHS.

2.2. Genotyping

We genotyped Bio*Me* and GUARDD cohorts using a clinical genetic test to determine *APOL1* ancestral (G0), G1, and G2 variant status,[26,31] BioVU and NUgene cohorts using a standard genotyping array (with imputation of *APOL1* variant status), and the JHS cohort by exome sequencing.[32]

2.3. Outcomes and covariates

All sites obtained age and sex through questionnaires or EHR extractions, measured height and weight using standard procedures, calculated BMI (weight divided by height^2 [kg/m^2]) and removed BMI values within 9 months of a pregnancy. We calculated the estimated glomerular filtration rates from serum creatinine value using the CKD Epidemiology Collaboration study equation.[33] For the EHR cohorts we extracted time-stamped International Classification of Diseases-10-Clinical Modification codes for comorbidities, and laboratory values from EHR entries.

Although BMI is a generally good indicator of adiposity and disease risk, it does not distinguish between lean and fat body mass. The Jackson Heart Study had additional measures of adiposity and fat distribution and we thus performed association analyses with these more refined measures. These included body fat percentage, fat free mass (using bioelectrical impedance analysis and calculating relative lean mass with the fat free mass index – FFM/height^2), and body fat distribution (with measured waist and hip circumference, calculated waist-to-hip ratio, and visceral adipose tissue and subcutaneous adipose using computerized tomography).[34]

2.4. Statistical analyses

Informed by the widely reported associations between *APOL1* risk variants and kidney disease evident only in a recessive model, we first tested a recessive model, comparing individuals with 2 high-risk G1/G2 variants (*APOL1* risk homozygotes) versus those carrying 1 (*APOL1* risk heterozygotes) or 0 high-risk variants (see Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A644 which shows differences in characteristics by risk allele). We tested association with BMI as a continuous outcome using linear regression, and with overweight and obesity as categorical outcomes using logistic regression (overweight, BMI $\geq$ 25 kg/m^2; obese, BMI $\geq$ 30 kg/m^2). We then further classified obesity as severe (BMI $>$ 35 kg/m^2) or extreme (BMI $>$ 40 kg/m^2). The control group was considered to be normal weight (18 kg/m^2 $\geq$ BMI $<$ 25 kg/m^2).

We adjusted all association analyses for age, sex, and percent African ancestry (assessed using ADMIXTURE with 2 founding populations [k = 2]) and fivefold cross-validations (available for all but the discovery cohort). We tested for interactions with age and sex by including their product term in the model. If interactions were significant, we repeated linear regression analyses in age/sex strata. After performing all analyses in each cohort, separately, we combined all cohorts using random effect meta-analysis.

Since more refined measures of adiposity were available in JHS, we tested association of *APOL1* risk variants with these traits using linear regression after adjusting for age and sex.

When studied phenotypes were correlated, we established a heuristic study-wide significance at $P \leq .01$ because we considered Bonferroni correction too punitive. We performed all analyses with R version 3.0.3, STATA 10.1 (College Station, TX) and SAS 9.4 (SAS Institute, Cary NC).

3. Results

3.1. Baseline characteristics of cohorts

We had data on 11,930 AA individuals across cohorts with mean age from 42 to 49 years and percentage female from 58% to 75.3%. All cohorts had well-preserved renal function at baseline with glomerular filtration rates from 78.4 to 85.8 mL/min (see Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A645 which illustrates the *APOL1* risk allele).

3.2. Association of APOL1 risk variants with body mass index, overweight and obesity status

Our meta-analysis showed that persons with 2 *APOL1* risk variants were 1.3 times more likely to be obese than others (recessive model adjusted odds ratio [aOR] 1.30; 95% confidence interval [CI] 1.16–1.41; $P = 2.75 \times 10^{-6}$). Assuming additive inheritance, we found that each risk variant increased the odds of obesity by 1.13-fold (aOR 1.13; 95% CI 1.07–1.19; $P = 3.07 \times 10^{-6}$) (Fig. 1), suggesting that the additive model better captured the association.

Severity of obesity did not strengthen the association; that is, association with severe obesity that is, BMI $>$ 35 kg/m^2 (aOR: 1.14/variant; 95% CI 1.07–1.22; $P < .01$) and extreme obesity that is, BMI $>$ 40 kg/m^2 (aOR 1.12/variant; 95% CI 1.03–1.22; $P < .01$) was similar to aOR for all obesity (BMI $\geq$ 30 kg/m^2), whereas the association with overweight was less pronounced (aOR 1.07/variant; 95% CI 1.00–1.15; $P = .03$) (Fig. 2).

Analysis of BMI revealed that homozygous carriers had a 0.58 kg/m^2 (equivalent to ~1.7 kg for a person 1.7 m tall) higher BMI than others ($P = 10^{-3}$). Assuming an additive mode, each risk variant increased BMI by 0.36 kg/m^2 (equivalent to ~1 kg, for person of 1.7 m tall; $P = 2 \times 10^{-4}$) (Fig. 3).

3.3. Associations with obesity traits stratified by sex

The association of *APOL1* risk variants with obesity risk was the same in women and men (women: aOR 1.13; men: aOR 1.15). However, the association with overweight (aOR 1.12) and with BMI (0.43 kg/m^2/variant) was only significant in women ($P_{\text{interaction}} < .05$) (Table 1).

3.4. Associations with refined body composition traits

APOL1 variants were not associated with any of the refined body composition traits under an additive model in men and women combined (Table 2). On stratification by sex, each copy of the *APOL1* variants was significantly associated with FFM in women (increment of 0.30 per *APOL1* risk variant; $P = 0.03$), but not in men (change of 0.22) ($P_{\text{interaction}} < .05$). There was no association of *APOL1* variants with any other body composition traits, either crude, or BMI adjusted, overall or when stratified by sex.

4. Discussion

Our meta-analysis of 5 cohorts including 11,930 adults of African ancestry demonstrates that *APOL1* risk variants are strongly and robustly associated with BMI and obesity. This association best fit an additive model; that is, each additional risk variant increases BMI and risk of obesity, which is unlike their association with CKD progression for which a recessive model fits better,[35] although the association persists under a recessive model as well. We also found that the association with overweight status is only seen in women but not men, while the association with obesity does not show sexual dimorphism. Finally, we show that *APOL1* risk variants are associated with FFM in women, but not in men, while there is no association with any other adiposity traits.

The observed association between obesity and *APOL1* G1/G2 risk genotype is as large and prevalent as the association of obesity and *FTO* variation.[36] As we initially hypothesized, when examining the recessive model known to be associated with CKD progression, we discovered that presence of 2 high risk *APOL1* risk variants is strongly and robustly associated with BMI (adjusted increment of 0.69 kg/m^2) and obesity (adjusted OR of 1.32; $P = .02$). However, in contrast to CKD progression where

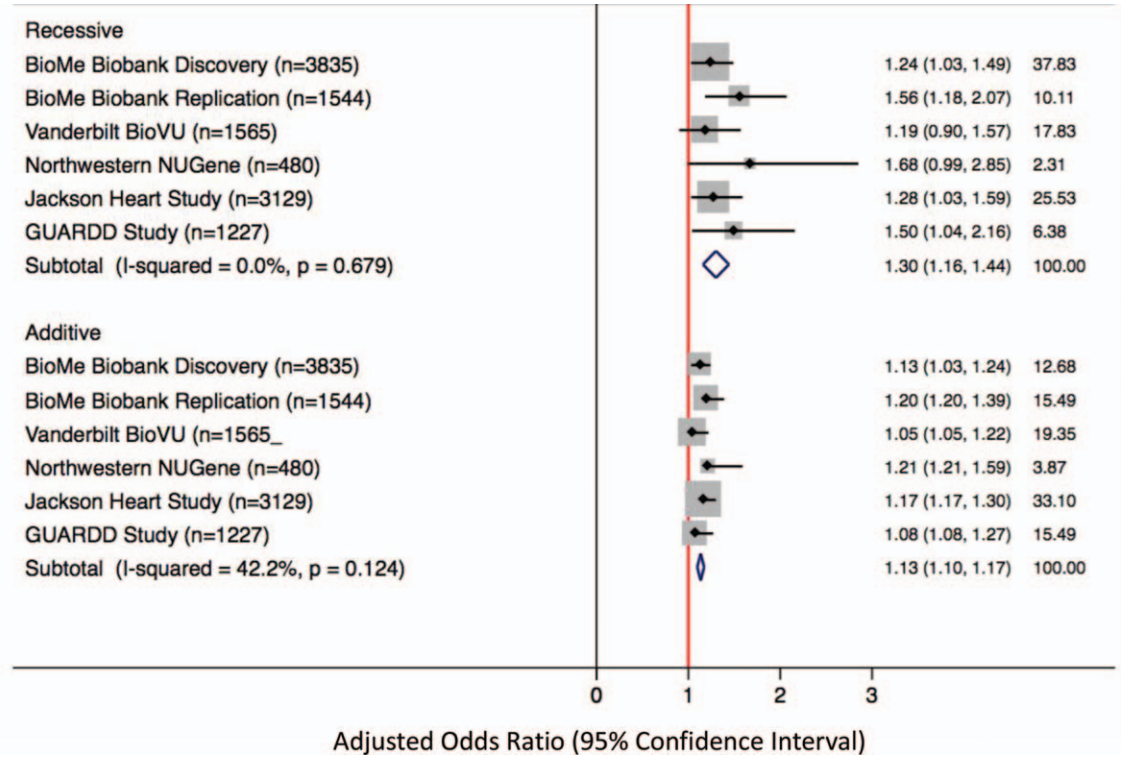

Figure 1. Association of *APOL1* risk variants with obesity status under a (A) recessive and (b) additive model. *APOL1* = apolipoprotein L1, GUARDD = genetic testing to understand and address renal disease disparities.

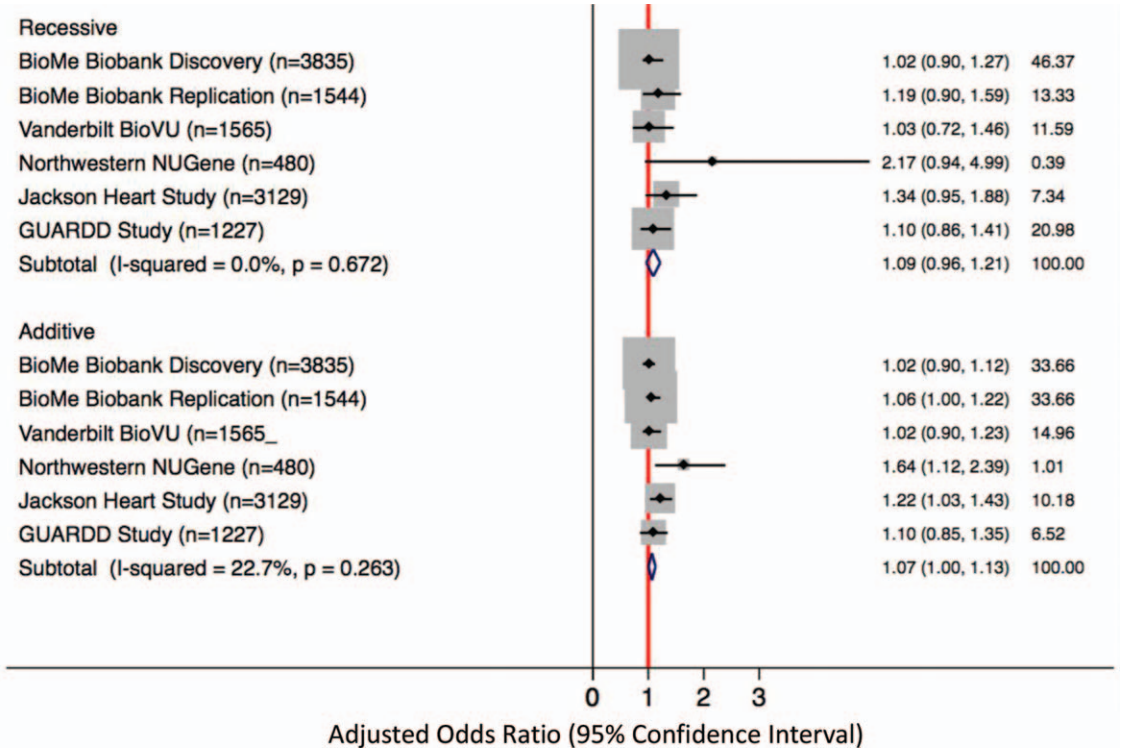

Figure 2. Association of *APOL1* risk variants with overweight status under a (A) recessive and (b) additive model. *APOL1* = apolipoprotein L1, GUARDD = genetic testing to understand and address renal disease disparities.

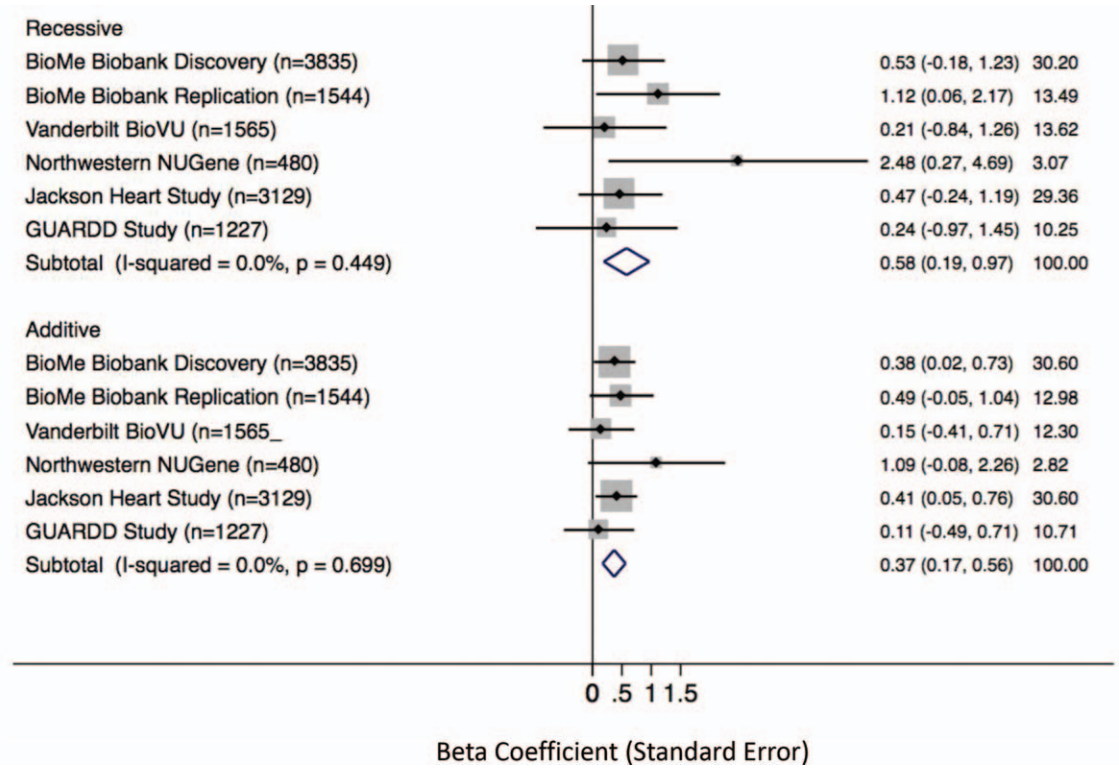

Figure 3. Association of *APOL1* risk variants with body mass index under a (A) recessive and (b) additive model. *APOL1* = apolipoprotein L1, GUARDD = genetic testing to understand and address renal disease disparities.

the *APOL1* risk is recessive, we also found that the association with obesity seems to follow an additive mode l – having only 1 high risk *APOL1* variant, which is the case for about half of AAs, is associated with a higher odds of obesity (adjusted OR of 1.13). Although other obesity-associated African-derived variants have been discovered, including *SEMA4D*, the minor variant frequencies have been extremely low, from 0.0058 to 0.0086 and these variants thus are unlikely to account for a large proportion of ethnic differences in obesity.[22]

The ancestry specific *APOL1* variants analyzed here have significant BMI effect size and high prevalence in AAs. Until now, the principal associations of *APOL1* risk variants had been with kidney disease, where homozygosity is associated with CKD progression and end stage renal disease.[35] Although BMI-related traits and kidney disease are correlated,[37] the association of heterozygous *APOL1* variants with obesity-related traits may represent true pleiotropy of *APOL1* risk variants and indicate that their impact on ancestry-related disparities may extend beyond renal phenotypes.

As stated, *APOL1*'s association with BMI and obesity is one of the strongest genetic associations discovered for these traits.[36,21,22] With a significant minority of AAs (14%) having 2 *APOL1* risk variants and nearly half (40%–47%) having at least 1 risk variant, these variants could explain some of the differences in BMI traits between AAs and EAs. It is important to note that this association neither contradicts nor minimizes the known social determinants of racial disparities in obesity, including access to healthy food, economic disparities, poverty and stress.[9–11] Additional research is needed to explore the interactions of *APOL1* risk variants with clinical, behavioral and environmental factors that also contribute to obesity in AAs, as race is a social construct, but ancestry has biological underpinnings.

APOL1 has not been associated previously with obesity or related traits, perhaps because *APOL1* risk variants are not represented on standard genotyping arrays; the initial associations with kidney disease were in fact a result of admixture mapping in a small sample, showing a peak of African ancestry

Table 1

Associations of APOL1 risk variants with body mass index, overweight and obesity stratified by sex under an additive model.

	Beta/aOR (SE/95% CI)		
	All	**Female**	**Male**
Body mass index	0.58 (0.41)	0.43 (0.27)	0.22 (0.27)
Overweight	1.12 (1.00–1.27)	1.12 (1.02–1.22)	1.01 (0.91–1.12)
Obese	1.13 (1.07–1.19)	1.13 (1.05–1.20)	1.15 (1.05–1.26)

Adjusted for age and percentage of African ancestry.
APOL1 = apolipoprotein L1, aOR = adjusted odds ratio, CI = confidence interval.

Table 2

Association of *APOL1* risk variants with adiposity measures under an additive model stratified by sex.

	All* Mean (SE)	Female† Mean (SE)	Male† Mean (SE)
Waist/hip ratio	0.001 (0.004)	0 (0.005)	0.003 (0.005)
Waist/hip ratio (BMI adjusted)	0 (0.004)	−0.000005 (0.005)	0.002 (0.005)
Visceral adipose tissue	19.3 (24.5)	10.7 (15.1)	33.7 (43.8)
Visceral adipose tissue (BMI adjusted)	8.5 (22.2)	−0.64 (25.8)	23.8 (40)
Subcutaneous adipose tissue	54.7 (59.6)	41.7 (79.6)	77.3 (86.6)
Subcutaneous adipose tissue (BMI adjusted)	0.36 (38.7)	−16.7 (52)	29.4 (55.3)
Percentage of body fat	0.27 (0.40)	0.14 (0.48)	0.48 (0.72)
Fat free mass index	0.27 (0.15)	0.30 (0.19)	0.22 (0.24)

APOL1 = apolipoprotein L1, BMI = body mass index.
* Adjusted for age, sex.
† Adjusted for age.

spanning the *APOL1* locus in association with nondiabetic end stage renal disease.[23,38] Following this initial report some studies have considered only a recessive model, and have adjusted for BMI/obesity when assessing association between *APOL1* risk variants and kidney disease. In light of our results, caution is warranted when adjusting for BMI/obesity as a confounder in association testing with *APOL1* risk. This also points towards the importance of including more diverse populations in genomic research; ethnic minorities have been traditionally underrepresented in genome wide association studies.[39]

We also show an interaction with sex in the association of *APOL1* risk variants with BMI. Such an interaction has previously been observed at multiple GWAS loci for BMI and adiposity traits.[40] While association between the risk variants and BMI was limited to women, the association with obesity extended to both sexes, perhaps reflecting a threshold effect. We did not find an association between any regional adiposity trait and *APOL1* risk variants. Association of these variants with fat free mass in women could in fact reflect a contribution to BMI through increased nonadipose tissue, including muscle mass, suggesting the need for mechanistic studies. Our limited sample size (JHS only) with extensive body composition measures argues, in addition, for an expansion of deep body composition phenotyping in human cohorts.

Strengths of our study include this being largest cohort of AAs with and without *APOL1* risk variants analyzed, data from a variety of sources including EHR based cohorts, RCTs and observational cohort studies, and analysis of refined measures of body composition in 1 observational cohort study. However, the results should be interpreted in the light of some limitations. We used self-reported AA race leading to a possibility of selection bias, however associations remained significant even after correcting for principal components which was available for over 70% of our pooled cohort. There might be limited generalizability due to the EHR based nature of some cohorts; however, the associations remained robust in both RCT and traditional observational cohort studies. And, since we only had refined measures of adiposity in one of the cohorts; a larger sample may uncover other associations.

In conclusion, we demonstrate a statistically strong and quantitatively substantial association of BMI and obesity with *APOL1* risk variants, which are present in nearly half of persons with African ancestry. These risk variants account for a nontrivial contribution to disparities in obesity between AA and EA. It will be important to assess the impact of sharing this information with patients and clinicians, and to study the role of *APOL1* gene–environment interactions in obesity.

Author contributions

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