# Admixture mapping of uterine fibroid size and number in African American women

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**Objective:** To evaluate the relationship between genetic ancestry and uterine fibroid characteristics.
**Design:** Cross-sectional study.
**Setting:** Not applicable.
**Patient(s):** A total of 609 African American participants with image- or surgery-confirmed fibroids in a biorepository at Vanderbilt University electronic health record biorepository and the Coronary Artery Risk Development in Young Adults studies were included.
**Intervention(s):** None.
**Main Outcome Measure(s):** Outcome measures include fibroid number (single vs. multiple), volume of largest fibroid, and largest fibroid dimension of all fibroid measurements.
**Result(s):** Global ancestry meta-analyses revealed a significant inverse association between percentage of European ancestry and risk of multiple fibroids (odds ratio: 0.78; 95% confidence interval 0.66, 0.93; $P=6.05 \times 10^{-3}$). Local ancestry meta-analyses revealed five suggestive ($P<4.80 \times 10^{-3}$) admixture mapping peaks in 2q14.3-2q21.1, 3p14.2-3p14.1, 7q32.2-7q33, 10q21.1, 14q24.2-14q24.3, for number of fibroids and one suggestive admixture mapping peak ($P<1.97 \times 10^{-3}$) in 10q24.1-10q24.32 for volume of largest fibroid. Single variant association meta-analyses of the strongest associated region from admixture mapping of fibroid number (10q21.1) revealed a strong association at single nucleotide polymorphism variant rs12219990 (odds ratio: 0.41; 95% confidence interval 0.28, 0.60; $P=3.82 \times 10^{-6}$) that was significant after correction for multiple testing.
**Conclusion(s):** Increasing African ancestry is associated with multiple fibroids but not with fibroid size. Local ancestry analyses identified several novel genomic regions not previously associated with fibroid number and increasing volume. Future studies are needed to explore the genetic impact that ancestry plays into the development of fibroid characteristics. (Fertil Steril® 2017;108:1034–42. ©2017 by American Society for Reproductive Medicine.)
**Key Words:** Fibroids, leiomyomata, admixture mapping, local ancestry, global ancestry

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Uterine leiomyomata, or fibroids, are the most common female pelvic tumor (1) affecting most US women by menopause (2). Fibroids cost the United States 5.9–34.4 billion dollars annually for treatment, healthcare, and work loss costs (3). The incidence and progression of fibroids are highly heterogeneous, with some women developing a single small fibroid, whereas other women develop multiple and/or large fibroids. For example, African American (AA) women have a two- to threefold higher risk of fibroids when compared with European American (EA) women (4). The AA women also have more numerous and larger fibroids (2). In addition, AAs are two times

more likely than EAs to receive surgical treatments for fibroids such as hysterectomies (5).

Although the heritability of specific fibroid characteristics, such as fibroid size and number, is unknown, heritability estimates of fibroid risk from twin studies have ranged between 26% and 69% (6, 7). Additional support for genetic etiology for fibroids comes from racial differences in fibroid risk (2, 4, 8), as well as the racial differences in fibroid size and number between AA and EA women. A few studies have shown a direct relationship between increasing fibroid size and gene variants (9, 10). Edwards et al. (9) observed associations between increasing fibroid size in EAs with gene variants in trinucleotide repeat containing 6B (*TNRC6B*) and Bet1 golgi vesicular membrane trafficking protein like (*BET1L*) that were originally found in a genome-wide association study of fibroid risk (11). Aissani et al. (10) showed associations between fibroid risk and largest fibroid dimension when evaluating a set of candidate gene variants.

Admixture mapping is an analytic approach in genetics to evaluate the relationship between genetic ancestry and disease risk. Admixture mapping analyses are performed using admixed populations, such as AAs, where there are known prevalence differences in disease risk across racial groups. The AA women have on average approximately 80% African ancestry and 20% European ancestry (12). Admixture mapping has been successfully applied in studies examining multiple sclerosis (13), keloids (14), and prostate cancer (15) in AA populations. A few previous studies have performed admixture mapping analyses on fibroid risk using AA individuals (16, 17). In the first study by Wise et al. (16), the investigators performed an admixture mapping study using ultrasound- or image-confirmed 2,453 cases and 2,102 controls with no fibroid diagnosis from the prospective cohort, the Black Women's Health Study, with women throughout the United States. Using ANCESTRYMAP (18–20) and ADMIXMAP (21), they found that the mean percentage of African ancestry was significantly higher in fibroid cases when compared with controls but did not find a region in the genome that was significantly associated with fibroid risk (16). They did, however, find suggestive associations in chromosomal regions 2q33, 4p16, and 10q26 (16). In the second admixture mapping study on fibroid risk by Zhang et al. (17), the investigators performed a cross-sectional study using 393 ultrasound-confirmed cases and 132 ultrasound-confirmed controls from the National Institute of Environmental and Health Sciences-Uterine Fibroid Study. Using ADMIXMAP (21), they did not find a significant association between global ancestry and fibroid risk. Zhang et al. (17) did find a region within chromosome 1q42.2 with suggestive to significant associations where each African allele increased risk after stratifying by body mass index (BMI). In the most recent admixture mapping study by Giri et al. (22), the investigators performed a cross-sectional study using AA women from the biorepository at Vanderbilt University (BioVU) and the Coronary Artery Risk Development in Young Adults (CARDIA) cohorts. They found that BMI interacts with local European ancestry and fibroid risk in AA women in two genomic regions, 6p24 and 2q31-31 (22).

Fibroids are a heterogeneous disease. Each fibroid characteristic difference, such as single versus multiple fibroids or a small versus large fibroid, could be affected by a set of genetic loci. A study examining fibroid characteristics might have better power to detect genetic determinants of fibroid subphenotypes that might be more closely related to a potential targeted treatment than a genetic study on fibroid risk. To our knowledge, no study has performed an admixture mapping analysis on fibroid characteristics in AA individuals. The objective of this study is to examine the relationship between African ancestry and fibroid characteristics, namely size and number.

## MATERIALS AND METHODS

### Study Population

**Coronary Artery Risk Development in Young Adults.** The Coronary Artery Risk Development in Young Adults (CARDIA) study was initiated in 1985-1986 with the goal of measuring risk factors for coronary heart disease in a cohort of black and white Americans (23). The cohort consists of 5,115 AA and EA participants between the ages of 18 and 30 years who were selected based on approximately equal proportions of 18 to 24 and 25 to 30 year olds, sex, race (black and white), and education status with respect to high school graduation. Cohort recruitment took place at four locations in the United States: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California (23).

The CARDIA Women's Study is an ancillary study of CARDIA that conducted pelvic ultrasounds among women in the CARDIA cohort at 16 years after enrollment. The goal of the CARDIA Women's Study was to evaluate the association between risk factors of polycystic ovary syndrome (PCOS) and cardiovascular disease. Largest fibroid dimensions, fibroid number, and other relevant data to our project were collected and recorded by trained CARDIA Women's Study research staff (24). A transvaginal ultrasound was performed by sonographers who were certified by the American Registry of Diagnostic Medical Sonographers and who had performed at least 50 prior transvaginal ultrasound examinations. The sonographers used a 5- to 7.5-MHz transvaginal probe. The dimensions of the largest fibroid were measured and number of fibroids was noted (24).

Our analyses used lifestyle and sociodemographic information that was collected by self- and interviewer-administered questionnaires (24). Measurements for height and weight were collected using a standardized protocol described previously (25).

**The biorepository at Vanderbilt University.** The BioVU DNA Repository (2007–present) is a deidentified database of electronic health records that is linked to DNA. The BioVU consists of stored deidentified demographic and clinical information for each patient who visits the Vanderbilt University Medical Center (26). A detailed description of BioVU has been previously given (26, 27). The Office of Human Research Protections and the Institutional Review Boards deemed the BioVU DNA repository as non-human subjects research (27).

A validated phenotyping algorithm with a positive predictive value of 96% was used to identify fibroid cases (28). We included AA women who were at least 18 years old, who had at least one documented fibroid, and one pelvic imaging or surgery to treat fibroids, as indicated by the international classification of diseases, ninth revision, or current procedural terminology codes. Once fibroid cases were identified, we manually confirmed fibroid presence in patient electronic health records by verifying that fibroids were visualized in pelvic imaging or surgery. We then manually abstracted fibroid measurements for the largest fibroid, as well as total number of reported fibroids, indication for imaging, subsequent treatment for fibroids, mode for fibroid confirmation (ultrasound, computerized tomography [CT] scans, and magnetic resonance imaging [MRI] or from surgical reports comprising of hysterectomies and myomectomies), and pertinent demographic information. Our priority of recording patient information was from the first image report. If no image reports were available, we recorded patient information from surgical reports. If patient demographic information, such as BMI, was not listed in the image or surgical reports, we obtained the information from the nearest corresponding date.

Outcome measurements for analyses include largest dimension of all fibroid measurements, volume of largest fibroid, and number of fibroids (single vs. multiple). To obtain an accurate estimate on fibroid volume, we used the following equation to calculate the volume of an ellipsoid for both CARDIA and BioVU cohorts: (Length $\times$ Width $\times$ Height $\times$ 0.523). The product of the three dimensions was multiplied by 0.523 to estimate volume assuming an ellipsoid shape. The total volume measurement and largest dimension were $\log_{10}$ transformed to create a normally distributed outcome for regression analysis. Some individuals with volume measurements (BioVU - 33.6%) originally had only two measurements for their largest fibroid, but we imputed the third measurement by taking the average of the first two measurements.

The hypothesis of these analyses was that there are different genetic risk factors for specific fibroid characteristics (e.g., you may have a different genetic risk factor for having a larger vs. multiple fibroids). Because there are known racial differences in fibroid number and size and as race is genetically determined, we evaluated the role of local genetic ancestry in risk for specific fibroid characteristics. These analyses are intended to better understand racial differences in fibroid phenotypic heterogeneity. Comparing subclasses of cases to controls would not necessarily tell us whether there are within case subphenotype (fibroid characteristics) differences, as evidence of an association from a case-control analysis may still be a result of fibroid risk and not risk specific to a fibroid subphenotype. Because of this, the individuals in this study are limited to fibroid cases only. The present study has been evaluated and approved by the Vanderbilt University Medical Center institutional review board.

## Genotyping

The CARDIA AA participants were genotyped as part of the Candidate Gene Association Resource study using the Affymetrix 6.0 array (Affymetrix). The BioVU AA participants were genotyped using the Affymetrix Axiom Biobank array (Affymetrix) and on the Axiom World Array 3 platform (Affymetrix). DNA was purified and quantitated by PicoGreen (Invitrogen).

## Genome-wide Association Study Quality Control

The same genome-wide association study quality control protocol was performed on both CARDIA and BioVU populations separately using PLINK1.7 software (29) and using the reference genome build GRCh37.p13 (Supplemental Figs. 1 and 2). The following steps were taken in our quality control analysis: [1] dropped subjects with inconsistent genetic versus reported sex, [2] dropped related subjects, meaning all individuals with $>0.95$ probability of identity by descent and only one individual from a pair with a probability of identity by descent between 0.2 and 0.95, [3] dropped single nucleotide polymorphism (SNP) without chromosomal locations, [4] dropped SNPs with a minor allele frequency of $\leq 1\%$, [5] dropped SNPs and subjects with low genotyping efficiency ($\leq 95\%$), and [6] dropped SNPs with a Hardy-Weinberg equilibrium $P \leq 1 \times 10^{-6}$. Alleles were aligned to the genomic + strand using the 1000 Genomes (build 37, 2013).

## Statistical Analyses

Demographic and covariate information were summarized using Stata/SE.

**Ancestry estimation.** Principal components of ancestry was estimated using EIGENSTRAT4.2 (Supplemental Figs. 3 and 4) (30). Assigning ancestry to SNPs using allele frequencies from the 1,000 Genomes Project as proxies to population allele frequencies (Phase 3 1,000 Genomes reference panels) (31) was accomplished using LAMP-ANC (Local Ancestry in adMixed Populations - ANCestral) (32–34). We used SNPs whose allele frequency difference between African ancestry and European ancestry was $\geq 20\%$ using PLINK1.7 software (29). Local ancestry was estimated using the following criteria as input: seven generations since admixture event, recombination rate at $1 \times 10^{-8}$, average ancestry composition per individual at 0.8 for African and 0.2 for European, respectively, proportion of overlap between windows of ancestry inference at 0.2, and r-squared threshold for LD-pruning at 0.1. Finally, local ancestry was coded as the number of European ancestry calls per each locus (0, 1, or 2). Global ancestry (percentage of European ancestry) was calculated for each individual by taking the number of European ancestry calls for all markers and dividing that number by the total number of ancestry calls.

**Global and local ancestry analyses.** Linear and logistic regression was performed for each outcome for BioVU and CARDIA, respectively, using PLINK 1.7 software (29). Outcomes included $\log_{10}$ transformed volume of largest fibroid, $\log_{10}$ transformed largest dimension of all fibroids, and number of fibroids (single vs. multiple). The exposure included global or local ancestry. Fixed effects inverse-variance weighted meta-analysis comparing global or local ancestry across CARDIA and BioVU AAs

**TABLE 1**

**Demographics of Coronary Artery Risk Development in Young Adults Study (CARDIA) and biorepository at Vanderbilt University (BioVU) African Americans.**

| Demographic characteristics | N | All (n = 609) | BioVU (n = 438) | CARDIA (n = 171) |
|---|---|---|---|---|
| Age (y; mean ± SD) | 609 | 41.4 ± 9.0 | 41.5 ± 11.0 | 41.3 ± 4.0 |
| BMI (kg/m$^2$) (mean ± SD) | 606 | 33.1 ± 8.0 | 32.9 ± 8.0 | 33.4 ± 8.0 |
| Underweight (<18.5 kg) (%) | 6 | 1 | 1 | 1 |
| Normal weight (18.5–24.9 kg) (%) | 87 | 14 | 16 | 11 |
| Overweight (25–29.9 kg) (%) | 142 | 23 | 23 | 24 |
| Obese (≥30 kg) (%) | 371 | 61 | 60 | 64 |
| Fibroid volume (cm$^3$) median (IQR) | 492 | 14.1 (3.6–47.2) | 19.6 (5.3–76.0) | 5.6 (2.1–19.3) |
| Largest fibroid dimension (cm) median (IQR) | 562 | 3.1 (2.0–5.0) | 3.5 (2.2–5.7) | 2.5 (1.8–3.7) |
| Fibroid number | 588 | | | |
| 1 (%) | 226 | 38 | 42 | 29 |
| >1 (%) | 362 | 62 | 58 | 71 |
| Percentage of European ancestry (mean ± SD) | 609 | 15.3 ± 10 | 15.5 ± 10 | 14.9 ± 10 |

*Note:* BMI = body mass index; IQR = interquartile range.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

was then performed for each outcome, respectively, using METAL software (35). Quantile-quantile (QQ) plots of local ancestry analyses were created for each outcome (Supplemental Figs. 5-13). A $P$ value of .05 or less denoted significance for all analyses involving global ancestry. The significance threshold for analyses of local ancestry was determined using 10,000 permutation tests for each outcome independently using PLINK1.7 software (29). The significance threshold for largest fibroid dimension, volume of largest fibroid, and fibroid number were determined to be $2.05 \times 10^{-5}$, $1.98 \times 10^{-5}$, and $4.80 \times 10^{-5}$, respectively. The suggestive threshold was found by taking two $\log_{10}$ down from the significance threshold. We adjusted for age and BMI for all analyses involving global genetic ancestry and adjusted for age, BMI, and five principal components for all analyses involving local genetic ancestry. We adjusted for BMI because BMI was found to be a confounder in a previous admixture mapping study on fibroid risk (17). We also performed admixture mapping analyses between local ancestry and fibroid number and volume for the reported admixture mapping peaks without adjustment for BMI and note that this did not significantly alter the association signals at these chromosomes (Supplemental Figs. 14–20). We also performed local ancestry analysis adjusting for the most significant single SNP association within the admixture mapping peak regions to identify any genetic/imputed SNPs that explain the ancestry peaks.

**Single SNP association analyses.** Nongenotyped SNPs in the suggestive mapping peak regions were imputed, and single SNP associations on BioVU and CARDIA were performed for each outcome, respectively. Suggestive mapping peak regions were defined as one $\log_{10}$ down from the most significant marker in a mapping peak above the suggestive threshold.

Suggestive peaks were further evaluated for single SNP associations in separate analyses by characteristics. A fixed effects inverse-variance weighted meta-analysis was performed comparing the single SNP association results across CARDIA and BioVU AAs using METAL software (35). The significance threshold for the single SNP association analyses was determined by calculating the effective number of independent SNPs among all genotyped SNPs within suggestive mapping peak regions of each outcome using simpleM software (36–38). The significance threshold for fibroid number and volume were determined to be $8.78 \times 10^{-6}$ and $5.42 \times 10^{-5}$, respectively. We adjusted for age, BMI, and five principal components for all analyses involving single locus test of association.

## RESULTS

### Demographic Data

There were 171 AAs in CARDIA and 438 in BioVU with information on fibroid characteristics (Table 1). The mean age and BMI were similar among AAs in CARDIA (age, 41.3 ± 4 years; BMI, 33.4 ± 8) and BioVU (age, 41.5 ± 11 years; BMI, 32.9 ± 8), and most subjects were obese (BioVU, 60%; CARDIA, 64%). The median volume of largest fibroid and largest fibroid dimension was smaller for CARDIA (volume, 5.6 cm$^3$; largest dimension, 2.5 cm) than for BioVU AAs (volume, 19.7 cm$^3$; largest dimension, 3.6 cm). In addition, CARDIA AAs were more likely to have multiple fibroids than BioVU AAs (71% vs. 58%). Finally, the mean percentage of European ancestry was less for CARDIA than for BioVU AAs (14.9% vs. 15.5%).

### Global Ancestry Analyses

We observed a significant association between percentage of European ancestry and number of fibroids. A 10% decrease in global European ancestry was significantly associated with multiple fibroids (odds ratio [OR]: 0.78; 95% confidence interval [CI] 0.66, 0.93; $P$=$6.05 \times 10^{-3}$) (Table 2). There were no significant associations in the meta-analyses between percentage of global European ancestry and volume of largest fibroid or largest dimension of all fibroids for BioVU and CARDIA AAs, although a 10% decrease in global European ancestry was near significantly associated with largest dimension (beta, -0.03; 95% CI -0.06, 0.00) (Table 2).

**TABLE 2**

**Associations between exposure of mean percentage of European ancestry and outcome.**

**Number of fibroids**[b]

| Cohort | Adjusted OR [95% CI][a] |
|---|---|
| BioVU | 0.77 [0.62, 0.94][e] |
| CARDIA | 0.83 [0.59, 1.16] |
| Meta-analysis | 0.78 [0.66, 0.93][f] |

**Volume of largest fibroid**[c]

| Cohort | Adjusted $\beta$ [95% CI][a] |
|---|---|
| BioVU | −0.04 [−0.14, 0.05] |
| CARDIA | 0.02 [−0.08, 0.13] |
| Meta-analysis | −0.01 [−0.08, 0.06] |

**Largest dimension of all fibroids**[d]

| Cohort | Adjusted $\beta$ [95% CI][a] |
|---|---|
| BioVU | −0.03 [−0.06, 0.00] |
| CARDIA | 0.01 [−0.02, 0.04] |
| Meta-analysis | −0.01 [−0.03, 0.01] |

*Note:* Exposure is in 10% increments of mean percentage of European ancestry. BioVU = biorepository at Vanderbilt University; BMI = body mass index; CI = confidence interval; CARDIA = Coronary Artery Risk Development in Young Adults Study; OR = odds ratio.
[a] Adjusted for age and BMI.
[b] Number is coded as single versus multiple fibroids.
[c] Volume is coded as $\log_{10}$ transformed largest fibroid volume in cubic centimeters.
[d] Largest dimension is coded as $\log_{10}$ transformed largest fibroid dimension of all fibroid measurements in centimeters.
[e] $P<.05$.
[f] $P<.007$.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

## Local Ancestry Analyses

We did not observe associations between local ancestry and number of fibroids, volume of largest fibroid, or largest dimension of all fibroids that were statistically significant after multiple comparisons. We did, however, observe five suggestive associations for number of fibroids ($P<4.80 \times 10^{-3}$) and one suggestive association for volume of largest fibroid ($P<1.97 \times 10^{-3}$) (Table 3). In addition, there were several statistically significant single SNP associations within the admixture mapping regions for number of fibroids and volume of largest fibroid.

The most significant admixture mapping signal was seen in number of fibroids within 10q21.1 near inositol polyphosphate multikinase (*IPMK*), where each European chromosome decreased the odds of multiple fibroids (OR: 0.51; 95% CI 0.36, 0.74; $P=3.23 \times 10^{-4}$) (Table 3 and Fig. 1). The most significant single SNP in this region was rs12219990, where each effect allele decreased the odds of multiple fibroids (OR: 0.41; 95% CI 0.28, 0.60; $P=3.82 \times 10^{-6}$) (Supplemental Table 1). After adjusting for the most significant SNP from the single SNP association analyses, rs12219990, the original admixture mapping signal was reduced (OR: 0.64; 95% CI 0.43, 0.94; $P=.0214$) (Table 3 and Fig. 1) suggesting the admixture mapping peak was due to this SNP. The effect allele for rs12219990 was more common among Europeans (35%) than among Africans (7%) (data not shown).

There was one suggestive admixture mapping peak in volume of largest fibroid in region 10q24.1-10q24.32 near leucine zipper tumor suppressor 2 (*LZTS2*), where each European allele decreased the probability of larger of fibroids (beta, −0.23; 95% CI −0.27, −0.09; $P=1.48 \times 10^{-3}$) (Table 3 and Supplemental Fig. 21). The most significant single SNP in this region was rs4919512, where each effect allele decreased the probability of larger fibroids (beta, −0.25; 95% CI −0.37, −0.13; $P=2.82 \times 10^{-5}$) (Supplemental Table 1). After adjusting for the most significant SNP from the single SNP association analyses, rs4919512, the original admixture mapping signal was slightly reduced (beta, −0.12; 95% CI −0.27, 0.08; $P=.145$) (Table 3 and Supplemental Fig. 21).

## DISCUSSION

This is the first admixture mapping study to examine the effects that African ancestry has on uterine fibroid characteristics. In this study we observed a strong inverse association between mean European ancestry and fibroid number, where increasing global African ancestry increases the odds of having multiple fibroids. Although there were no statistically significant local ancestry analyses of any fibroid characteristic, there were multiple suggestive regions of fibroid number (Fig. 1 and Supplemental Figs. 22-25) and volume (Supplemental Fig. 21). In addition, there were two statistically significant single SNP associations: one on 10q21.1 for fibroid number (rs12219990) and another on 10q24.31 for fibroid volume (rs4919512). Furthermore, the local ancestry analyses highlighted genes with potential biological significance in etiology of fibroid characteristics.

There were five genes (sin3A association protein 130 [*SAP130*], proteasome 26S subunit, non-ATPase 6 [*PSMD6*], plexin A4 [*PLXNA4*], *IPMK*, and SNW domain containing 1 [*SNW1*]) identified by local ancestry analyses of fibroid number and one gene (*LZTS2*) identified from our analyses of fibroid volume (Table 3). Four of the five genes identified in the fibroid number analyses (*SAP130*, *PLXNA4*, *IPMK*, and *SNW1*) have been previously associated with cancer susceptibility or tumor growth (39–42). The fifth gene (*PSMD6*) was previously associated with a delay in DNA repair when depleted (43). The only gene, *LZTS2*, that was identified by our analyses of fibroid volume has also been attributed in many cancers (44) where depletion of *LZTS2* increases probability of tumorigenesis (45). Further analyses evaluating the expression level of these genes in the Genotype-Tissue Expression (GTEx) project database, which aims to characterize the relationship between tissue-specific gene expression and genotype (46), demonstrated that *LZTS2*, *PSMD6*, *SAP130*, and *SNW1* were expressed (reads per kilobase of transcript per million mapped reads >5) in uterine tissue (GTEx Analysis Release V6p [dbGaP Accession phs000424.v6.p1]) (46). Of 53 tissues in total, *LZTS2* was expressed more in the uterus than in any other tissue. This supports our observed data that genetic variation around *LZTS2* may decrease gene expression, leading to a susceptibility of fibroid tumor growth. In addition, female-specific tissues including the endocervix, ectocervix, breast, ovary, fallopian tube, and vagina expressed *SNW1* to a higher degree than most non-female-specific tissue.

We also evaluated potential candidate regions that have been implicated in prior studies of fibroids and observed that the region 12q14.1-q14.3 contained a small admixture mapping peak associated with fibroid number

## TABLE 3

**Admixture mapping for number of fibroids and volume of largest fibroid in African American women.**

**Number**[c]

**10q21.1**

| Nearby gene | Cohort | OR [95% CI][a] | *P* value[a] | OR [95% CI][b] | *P* value[b] |
|---|---|---|---|---|---|
| *IPMK* | BioVU | 0.54 [0.62, 1.44] | $3.36 \times 10^{-3}$ | 0.68 [0.44, 1.04] | .076 |
| | CARDIA | 0.41 [0.18, 0.92] | .030 | 0.50 [0.21, 1.17] | .110 |
| | Meta-analysis | 0.51 [0.36, 0.74] | $3.23 \times 10^{-4}$ | 0.64 [0.43, 0.94] | .021 |

**14q24.2-14q24.3**

| Nearby gene | Cohort | OR [95% CI][a] | *P* value[a] | OR [95% CI][b] | *P* value[b] |
|---|---|---|---|---|---|
| *SNW1* | BioVU | 2.07 [1.34, 3.18] | $9.89 \times 10^{-4}$ | 1.81 [1.17, 2.82] | $8.12 \times 10^{-3}$ |
| | CARDIA | 1.62 [0.74, 3.55] | .226 | 1.54 [0.69, 3.44] | .289 |
| | Meta-analysis | 1.95 [1.34, 2.85] | $5.25 \times 10^{-4}$ | 1.75 [1.19, 2.57] | $4.66 \times 10^{-3}$ |

**2q14.3-2q21.1**

| Nearby gene | Cohort | OR [95% CI][a] | *P* value[a] | OR [95% CI][b] | *P* value[b] |
|---|---|---|---|---|---|
| *SAP130* | BioVU | 0.64 [0.43, 0.95] | .026 | 0.74 [0.48, 1.13] | .163 |
| | CARDIA | 0.47 [0.24, 0.93] | .024 | 0.85 [0.37, 1.96] | .701 |
| | Meta-analysis | 0.59 [0.42, 0.83] | $2.60 \times 10^{-3}$ | 0.76 [0.52, 1.11] | .157 |

**7q32.2-7q33**

| Nearby gene | Cohort | OR [95% CI][a] | *P* value[a] | OR [95% CI][b] | *P* value[b] |
|---|---|---|---|---|---|
| *PLXNA4* | BioVU | 2.02 [1.33, 3.08] | $1.05 \times 10^{-3}$ | 1.85 [1.20, 2.86] | $5.70 \times 10^{-3}$ |
| | CARDIA | 1.02 [0.46, 2.25] | .964 | 0.51 [0.20, 1.27] | .149 |
| | Meta-analysis | 1.74 [1.20, 2.52] | $3.54 \times 10^{-3}$ | 1.46 [0.98, 2.16] | .060 |

**3p14.2-3p14.1**

| Nearby gene | Cohort | OR [95% CI][a] | *P* value[a] | OR [95% CI][b] | *P* value[b] |
|---|---|---|---|---|---|
| *PSMD6* | BioVU | 1.56 [1.01, 2.40] | .045 | 1.45 [0.94, 2.25] | .095 |
| | CARDIA | 2.96 [1.25, 7.05] | .014 | 2.23 [0.92, 5.37] | .074 |
| | Meta-analysis | 1.77 [1.20, 2.60] | $3.86 \times 10^{-3}$ | 1.58 [1.07, 2.34] | .022 |

**Volume**[d]

**10q24.1-10q24.32**

| Nearby gene | Cohort | $\beta$ [95% CI][a] | *P* value[a] | $\beta$ [95% CI][b] | *P* value[b] |
|---|---|---|---|---|---|
| *LZTS2* | BioVU | −0.26 [−0.43, −0.08] | $4.62 \times 10^{-3}$ | −0.16 [−0.35, 0.04] | .116 |
| | CARDIA | −0.18 [−0.42, 0.06] | .138 | −0.04 [−0.30, 0.22] | .754 |
| | Meta-analysis | −0.23 [−0.27, −0.09] | $1.48 \times 10^{-3}$ | −0.12 [−0.27, 0.08] | .145 |

*Note:* BioVU = biorepository at Vanderbilt University; BMI = body mass index; CI = confidence interval; CARDIA = Coronary Artery Risk Development in Young Adults Study; OR = odds ratio; SNP = single nucleotide polymorphism.

[a] Model 1: adjusted for age, BMI, and five principal components.

[b] Model 2: adjusted for age, BMI, and five principal components + adjustment for most significant single SNP.

[c] Number is coded as single versus multiple fibroids.

[d] Volume is coded as $\log_{10}$ transformed largest fibroid volume in cubic centimeters.

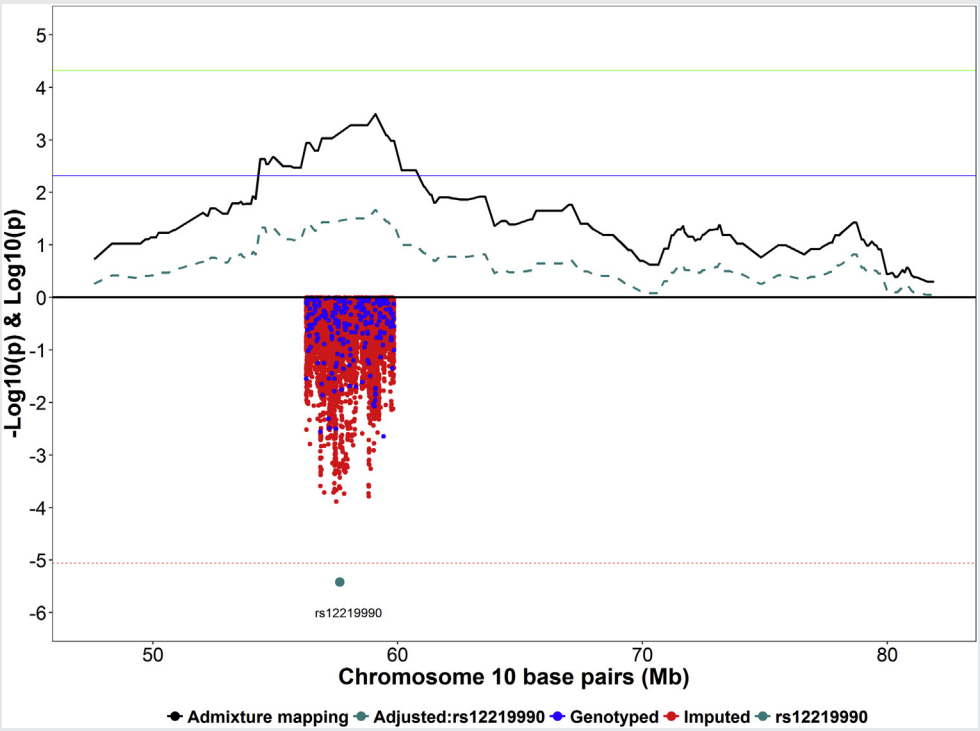
*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

($P$=7.21 × $10^{-3}$) and included high mobility group AT-hook 2 (*HMGA2*) (Supplemental Tables 2 and 3 and Supplemental Fig. 26), a gene previously implicated in fibroid risk in studies of the eker rat. The eker rat represents an animal model that spontaneously forms fibroid tumors similar to that of humans (47). Both the human *HMGA2* and the eker rat homologue are atypically expressed in fibroid tumors (47). The HMGA proteins are part of a family of transcription factors (47, 48). Progesterone and estrogen receptor (ER) activity has been shown to be regulated by the HGMA subfamily (47, 49–52).

The prior admixture mapping studies by Wise et al. (16), Zhang et al. (17), and Giri et al. (22) identified several suggestive associations; none overlapped with our study findings. However, the Wise et al. (16) global ancestry analyses showed a significant inverse association between global European ancestry and fibroid risk, consistent with our findings suggesting that African ancestry is not only associated with the development of a fibroid (or fibroid risk) but with the development of multiple fibroids. The second admixture study by Zhang et al. (17) used 393 AA cases, finding no association between global European ancestry and fibroid risk.

A difference between the two prior admixture mapping studies on uterine fibroids (16, 17) and ours included that our study used genome-wide association study data, allowing us to conduct single SNP association analyses within

## FIGURE 1




Admixture mapping analysis of chromosome 10 with overlapping single nucleotide polymorphism (SNP) association analysis results. The X-axis indicates the genomic position along chromosome 10 in Mb. The top of the Y-axis indicates -$\log_{10}$(*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs12219990; *dashed green line* = conditioned on rs12219990) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, body mass index (BMI), five principal components. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 56,258,202 to 59,854,651 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs12219990, was imputed (BioVU info score, 0.921; CARDIA info score, 0.922). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

identified regions. Wise et al. (16) and Zhang et al. (17) used panels of ancestry informative markers.

Previous estimations of ancestry place AA individuals having about 20% European ancestry and 80% African ancestry (12). The mean percentage of European ancestry for our study, however, was 15.5% for BioVU AAs and 14.9% for CARDIA AAs. The lower average percentage of European ancestry in our study could be an artifact of enriching for a trait (i.e., fibroids) that is more common in AAs (2).

There were limitations to our study. Our sample size was modest for each cohort (BioVU n = 438; CARDIA n = 171) matching the cohort size for admixture mapping study by Zhang et al. (17) (n = 525). We, however, performed meta-analyses between BioVU and CARDIA individuals, which served as a form of replication and validation for our findings. In addition, all fibroid characteristic information was assessed either by ultrasound or surgery, leading to a decrease in outcome misclassification. We also did not perform subanalyses, limiting to either image- or surgery-confirmed fibroid cases as all CARDIA individuals in this study had only ultrasounds to assess fibroid characteristics and as only some BioVU individuals had this information recorded during the abstraction process. It could be possible that BioVU individuals whose fibroids were discovered during surgery had a different tumor characteristic profile than women whose fibroids were confirmed by ultrasound, which could introduce bias in the analyses. Including women who had surgery could possibly inflate the effect sizes as these women may be more likely to have severe symptoms that may be due to larger size and/or number of fibroids. Finally, there is no overlap between the previous two admixture mapping studies on fibroid risk using AAs (16, 17) and our study. This could be because our study examined genetic risk factors with ancestry for differences in fibroid size and number and that these genetic factors by ancestry differ from the genetic factors for fibroid incidence.

Our study was the first admixture mapping study to access the association between ancestry and fibroid characteristics using AA populations. We found that global ancestry influences the number of fibroids and found many suggestive

mapping peaks influencing fibroid number and one mapping peak influencing fibroid volume. Further studies need to be performed to understand the biological mechanisms underlying the observed genetic associations.

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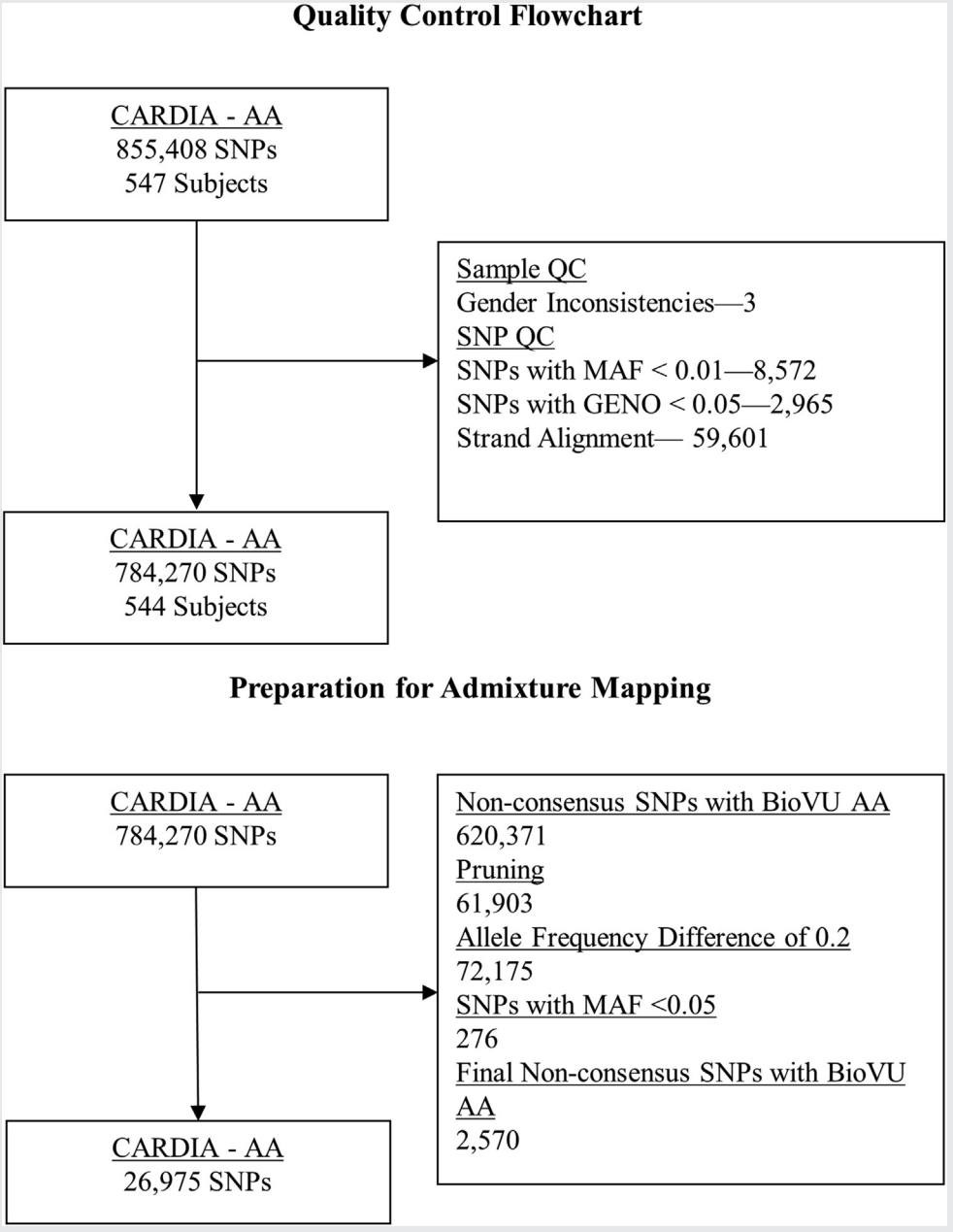
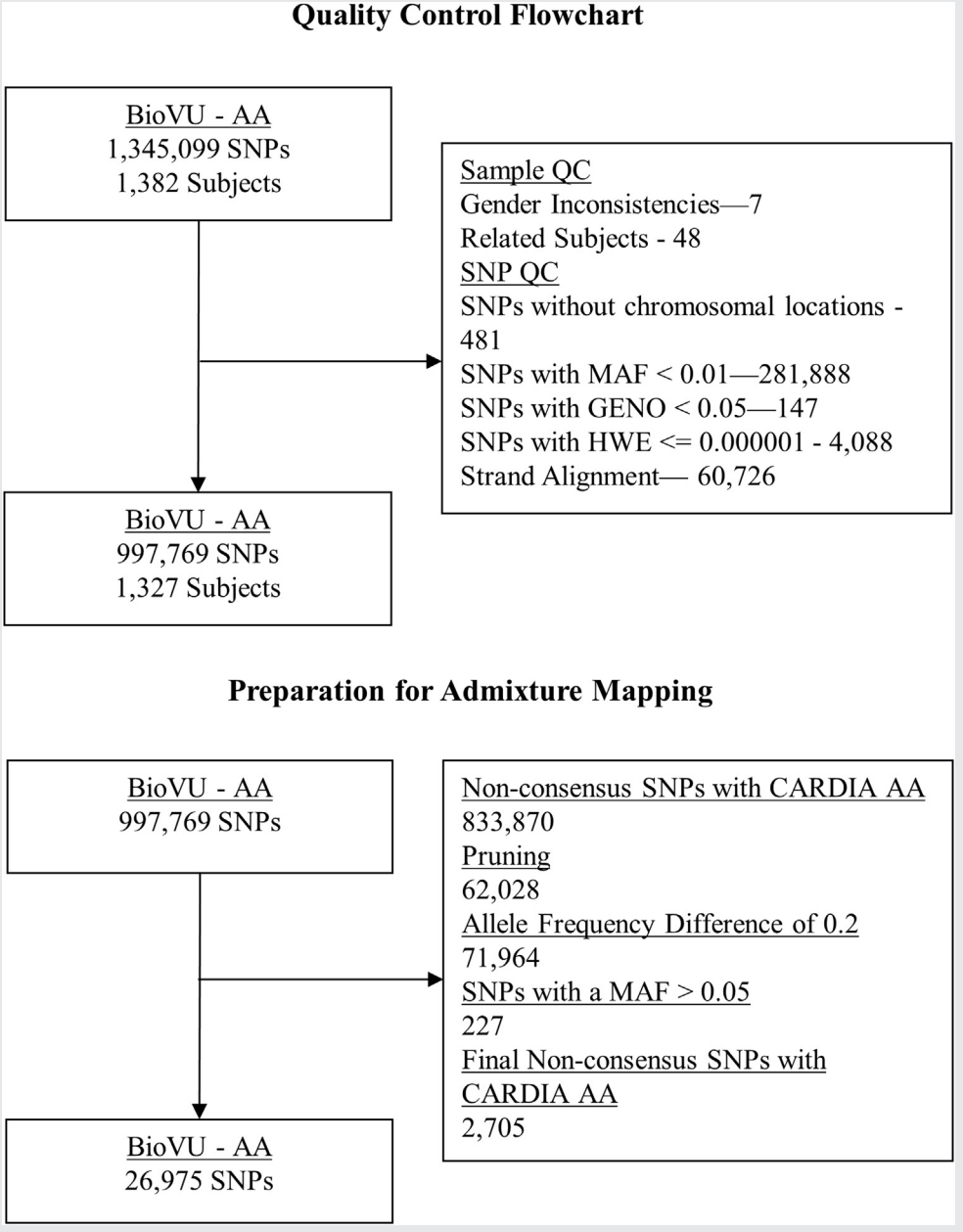
## SUPPLEMENTAL FIGURE 1




Quality control flow chart of Coronary Artery Risk Development in Young Adults Study (CARDIA) African American participants.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

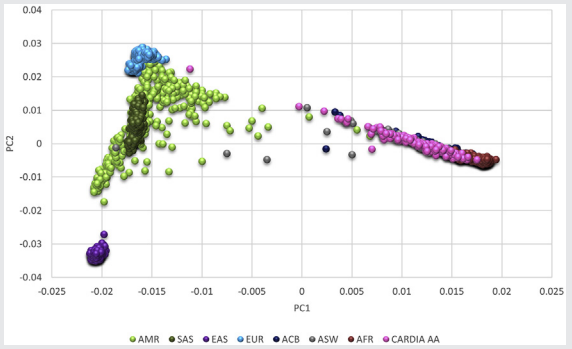
**SUPPLEMENTAL FIGURE 2**




Quality control flow chart of biorepository at Vanderbilt University (BioVU) African American participants.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

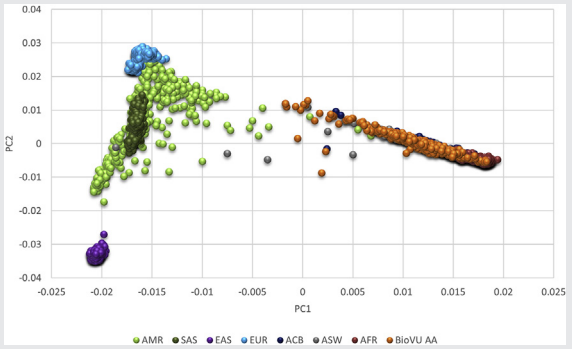
## SUPPLEMENTAL FIGURE 3




Graph of the principal component analysis of Coronary Artery Risk Development in Young Adults Study (CARDIA) African American participants plotted with individuals from the 1,000 Genomes Project. AMR =Ad Mixed American; EAS = East Asian; EUR = European; SAS = South Asian; ACB = African Caribbean in Barbados; ASW = Americans of African Ancestry in SW USA; AFR = African.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

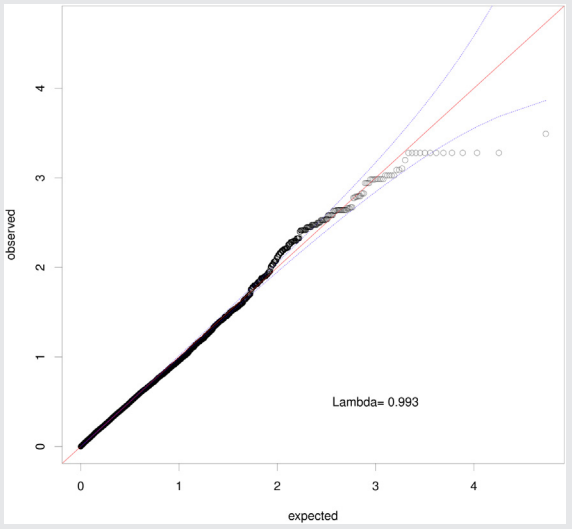
## SUPPLEMENTAL FIGURE 4




Graph of the principal component analysis of biorepository at Vanderbilt University (BioVU) African American participants plotted with individuals from the 1,000 Genomes Project. AMR =Ad Mixed American; EAS = East Asian; EUR = European; SAS = South Asian; ACB = African Caribbean in Barbados; ASW = Americans of African Ancestry in SW USA; AFR = African.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

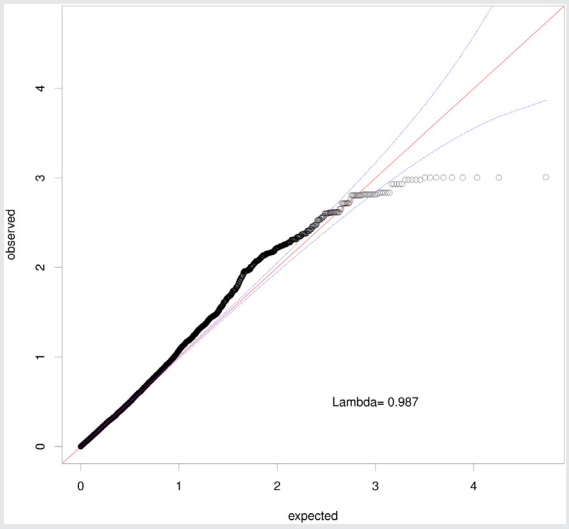
## SUPPLEMENTAL FIGURE 5




The QQ plot for the meta-analysis of the admixture mapping results for fibroid number (single vs. multiple) between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs). The regression analyses were adjusted for age, body mass index (BMI), five principal components. Markers with a minor allele frequency of at least 5% were used in the admixture mapping analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

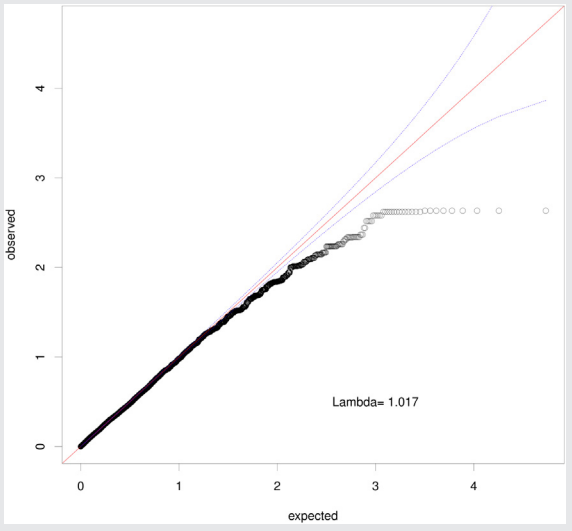
## SUPPLEMENTAL FIGURE 6




The QQ plot for the admixture mapping results for fibroid number (single vs. multiple) for biorepository at Vanderbilt University (BioVU) African Americans (AAs). The regression analyses were adjusted for age, body mass index (BMI), five principal components. Markers with a minor allele frequency of at least 5% were used in the admixture mapping analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

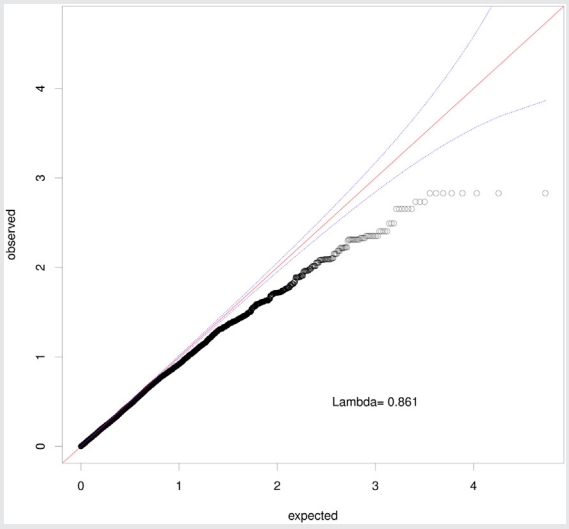
## SUPPLEMENTAL FIGURE 7




The QQ plot for the admixture mapping results for fibroid number (single vs. multiple) for Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs). The regression analyses were adjusted for age, body mass index (BMI), five principal components. Markers with a minor allele frequency of at least 5% were used in the admixture mapping analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

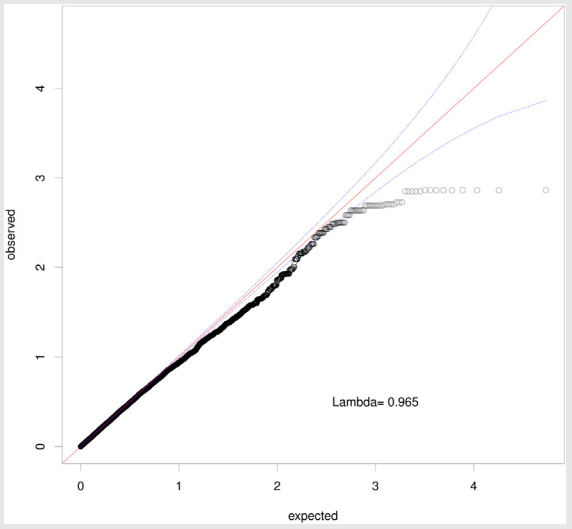
## SUPPLEMENTAL FIGURE 8




The QQ plot for the meta-analysis of the admixture mapping results for $\log_{10}$ transformed volume of largest fibroid between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs). The regression analyses were adjusted for age, body mass index (BMI), five principal components. Markers with a minor allele frequency of at least 5% were used in the admixture mapping analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

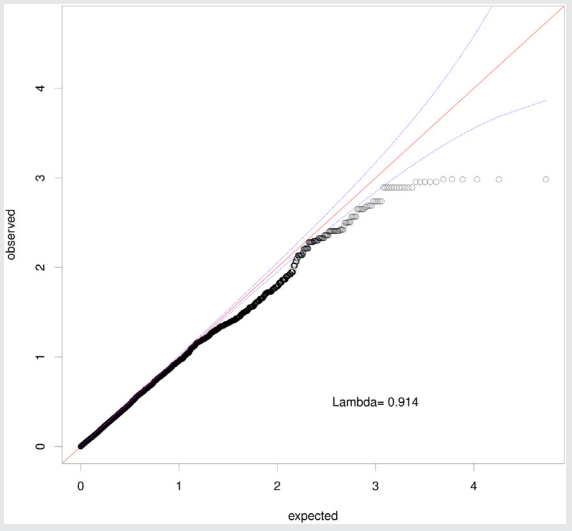
## SUPPLEMENTAL FIGURE 9




The QQ plot for the admixture mapping results for $\log_{10}$ transformed volume of largest fibroid for biorepository at Vanderbilt University (BioVU) African Americans (AAs). The regression analyses were adjusted for age, body mass index (BMI), five principal components. Markers with a minor allele frequency of at least 5% were used in the admixture mapping analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

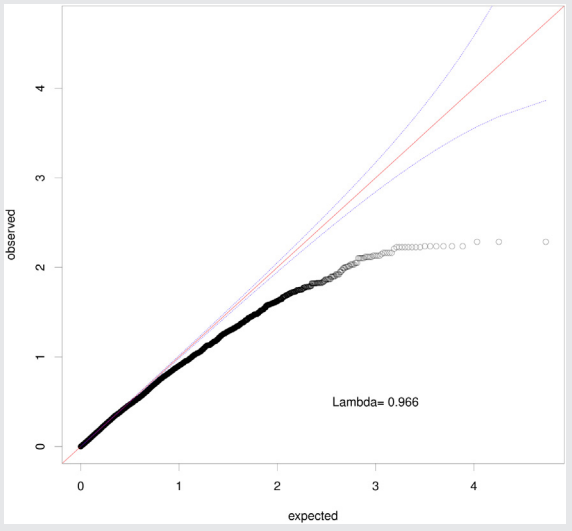
## SUPPLEMENTAL FIGURE 10




The QQ plot for the admixture mapping results for $\log_{10}$ transformed volume of largest fibroid for Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs). The regression analyses were adjusted for age, body mass index (BMI), five principal components. Markers with a minor allele frequency of at least 5% were used in the admixture mapping analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

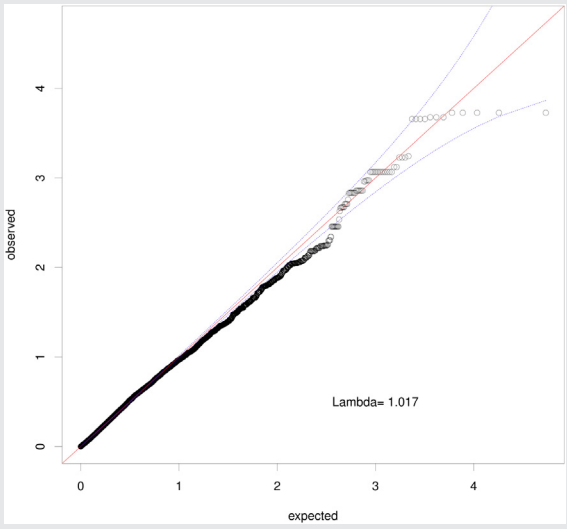
## SUPPLEMENTAL FIGURE 11




The QQ plot for the meta-analysis of the admixture mapping results for $\log_{10}$ transformed largest dimension of all fibroids between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs). The regression analyses were adjusted for age, body mass index (BMI), five principal components. Markers with a minor allele frequency of at least 5% were used in the admixture mapping analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

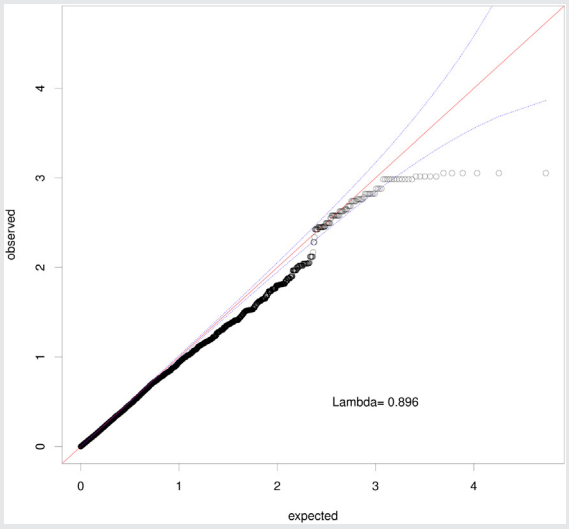
## SUPPLEMENTAL FIGURE 12




The QQ plot for the admixture mapping results for $\log_{10}$ transformed largest dimension of all fibroids for biorepository at Vanderbilt University (BioVU) African Americans (AAs). The regression analyses were adjusted for age, body mass index (BMI), five principal components. Markers with a minor allele frequency of at least 5% were used in the admixture mapping analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

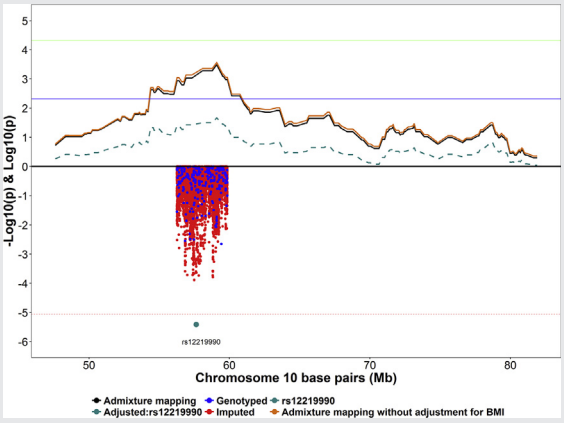
## SUPPLEMENTAL FIGURE 13




The QQ plot for the admixture mapping results for $\log_{10}$ transformed largest dimension of all fibroids for Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs). The regression analyses were adjusted for age, body mass index (BMI), five principal components. Markers with a minor allele frequency of at least 5% were used in the admixture mapping analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

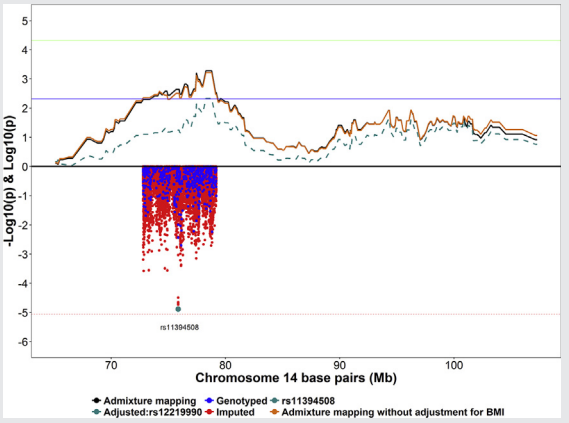
## SUPPLEMENTAL FIGURE 14




Admixture mapping analysis of chromosome 10 with overlapping single nucleotide polymorphism (SNP) association analysis results with and without adjustment for body mass index (BMI). The X-axis indicates the genomic position along chromosome 10 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs12219990; *dashed green line* = conditioned on rs12219990) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, BMI, five principal components. The *solid orange line* represents the admixture mapping analysis that was adjusted for age and five principal components only. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 56,258,202 to 59,854,651 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs12219990, was imputed (BioVU info score, 0.921; CARDIA info score, 0.922). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

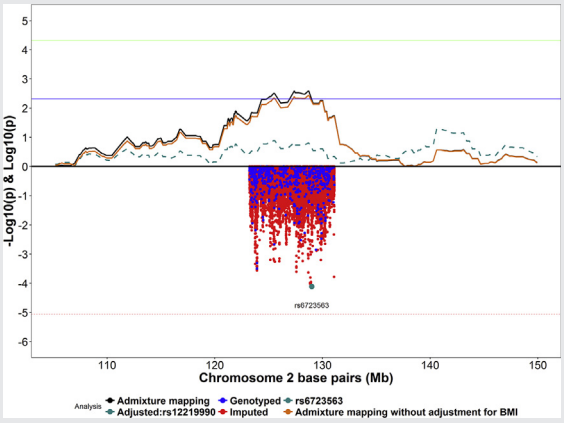
## SUPPLEMENTAL FIGURE 15




Admixture mapping analysis of chromosome 14 with overlapping single nucleotide polymorphism (SNP) association analysis results with and without adjustment for body mass index (BMI). The X-axis indicates the genomic position along chromosome 14 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs11394508; *dashed green line* = conditioned on rs11394508) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, BMI, five principal components. The *solid orange line* represents the admixture mapping analysis that was adjusted for age and five principal components only. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 72,802,666 to 79,205,619 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs11394508, was imputed (BioVU info score, 0.995; CARDIA info score, 0.956). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

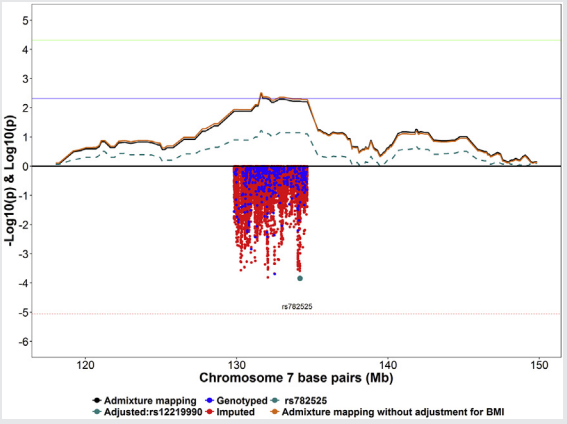
## SUPPLEMENTAL FIGURE 16




Admixture mapping analysis of chromosome 2 with overlapping single nucleotide polymorphism (SNP) association analysis results with and without adjustment for body mass index (BMI). The X-axis indicates the genomic position along chromosome 2 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs6723563; *dashed green line* = conditioned on rs6723563) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, BMI, five principal components. The *solid orange line* represents the admixture mapping analysis that was adjusted for age and five principal components only. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 123,221,985 to 131,110,097 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs6723563, was imputed (BioVU info score, 0.932; CARDIA info score, 0.885). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

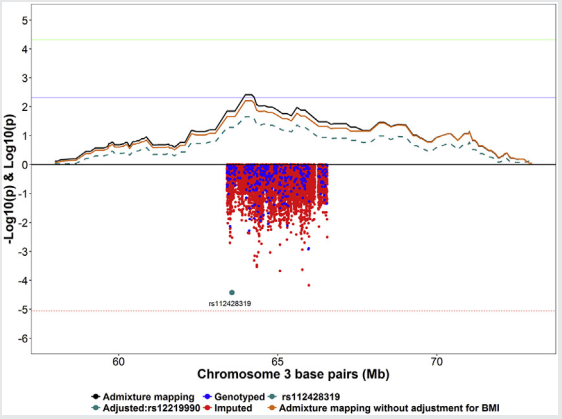
## SUPPLEMENTAL FIGURE 17




Admixture mapping analysis of chromosome 7 with overlapping single nucleotide polymorphism (SNP) association analysis results with and without adjustment for body mass index (BMI). The X-axis indicates the genomic position along chromosome 7 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs782525; *dashed green line* = conditioned on rs7872525) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, BMI, five principal components. The *solid orange line* represents the admixture mapping analysis that was adjusted for age and five principal components only. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 129,822,797 to 134,670,462 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs782525, was imputed (BioVU info score, 0.999; CARDIA info score, 0.985). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

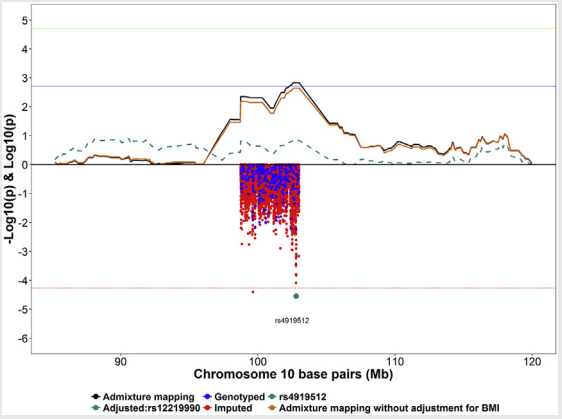
## SUPPLEMENTAL FIGURE 18




Admixture mapping analysis of chromosome 3 with overlapping single nucleotide polymorphism (SNP) association analysis results with and without adjustment for body mass index (BMI). The X-axis indicates the genomic position along chromosome 3 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs112428319; *dashed green line* = conditioned on rs112428319) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, BMI, five principal components. The *solid orange line* represents the admixture mapping analysis that was adjusted for age and five principal components only. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 63,405,151 to 66,558,036 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs112428319, was imputed (BioVU info score, 0.9998; CARDIA info score, 0.994). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

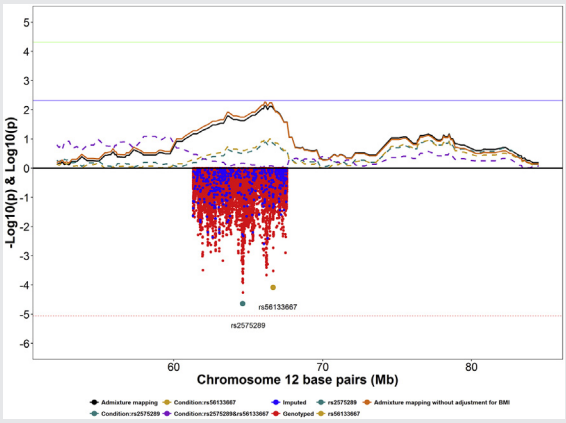
## SUPPLEMENTAL FIGURE 19




Admixture mapping analysis of chromosome 10 with overlapping single nucleotide polymorphism (SNP) association analysis results with and without adjustment for body mass index (BMI). The X-axis indicates the genomic position along chromosome 10 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs4919512; *dashed green line* = conditioned on rs4919512) with fibroid volume ($\log_{10}$ transformed) as the outcome. The admixture mapping analysis was adjusted for age, BMI, five principal components. The *solid orange line* represents the admixture mapping analysis that was adjusted for age and five principal components only. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid volume ($\log_{10}$ transformed) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 98,747,114 to 103,009,908 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs4919512, was genotyped for BioVU but imputed for CARDIA (BioVU info score, 1; CARDIA info score, 0.801). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

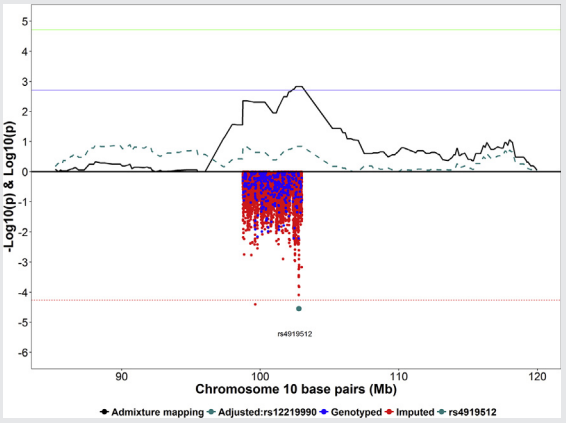
## SUPPLEMENTAL FIGURE 20




Admixture mapping analysis of chromosome 12 with overlapping single nucleotide polymorphism (SNP) association analysis results with and without adjustment for body mass index (BMI). The X-axis indicates the genomic position along chromosome 10 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs2575289 or rs56133667; *dashed teal line* = conditioned on rs2575289; *dashed yellow line* = conditioned on rs56133667; *dashed purple line* = conditioned on rs2575289 and rs56133667) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, BMI, five principal components. The *solid orange line* represents the admixture mapping analysis that was adjusted for age and five principal components only. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 61,300,873 to 67,610,913 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs2575289, was imputed (BioVU info score, 0.976; CARDIA info score, 0.991). The SNP, rs56133667, was imputed (BioVU info score, >0.999; CARDIA info score, >0.999). The *dotted red line* represents the significance threshold of the single SNP association analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

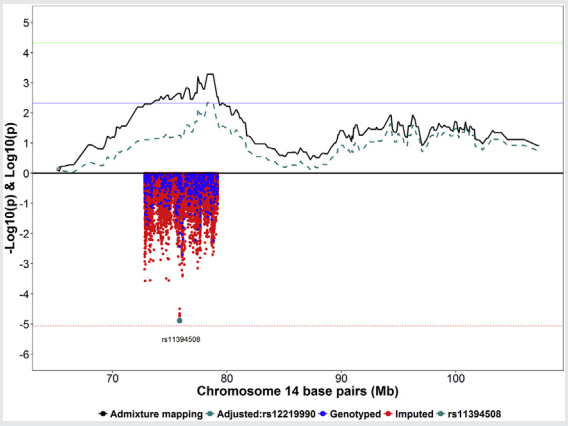
## SUPPLEMENTAL FIGURE 21




Admixture mapping analysis of chromosome 10 with overlapping single nucleotide polymorphism (SNP) association analysis results. The X-axis indicates the genomic position along chromosome 10 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs4919512; *dashed green line* = conditioned on rs4919512) with fibroid volume ($\log_{10}$ transformed) as the outcome. The admixture mapping analysis was adjusted for age, body mass index (BMI), five principal components. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid volume ($\log_{10}$ transformed) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 98,747,114 to 103,009,908 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs4919512, was genotyped for BioVU but imputed for CARDIA (BioVU info score, 1; CARDIA info score, 0.801). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

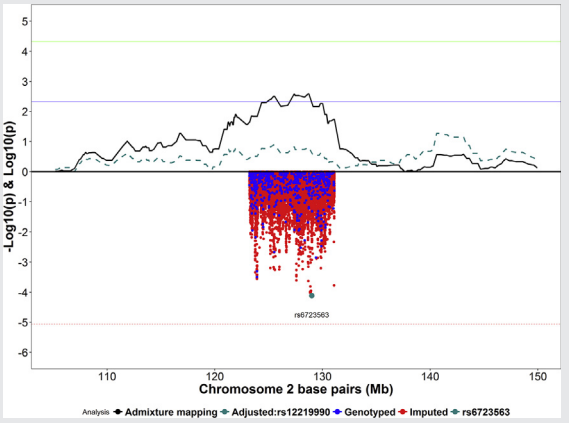
## SUPPLEMENTAL FIGURE 22




Admixture mapping analysis of chromosome 14 with overlapping single nucleotide polymorphism (SNP) association analysis results. The X-axis indicates the genomic position along chromosome 14 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) AAs from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs11394508; *dashed green line* = conditioned on rs11394508) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, body mass index (BMI), five principal components. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 72,802,666 to 79,205,619 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs11394508, was imputed (BioVU info score, 0.995; CARDIA info score, 0.956). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

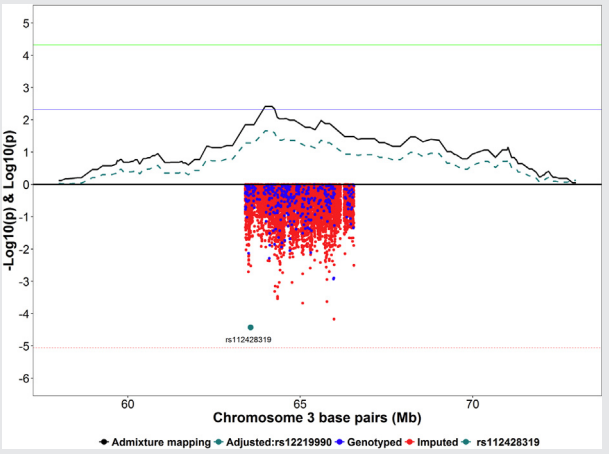
## SUPPLEMENTAL FIGURE 23




Admixture mapping analysis of chromosome 2 with overlapping single nucleotide polymorphism (SNP) association analysis results. The X-axis indicates the genomic position along chromosome 2 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs6723563; *dashed green line* = conditioned on rs6723563) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, body mass index (BMI), five principal components. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 123,221,985 to 131,110,097 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs6723563, was imputed (BioVU info score, 0.932; CARDIA info score, 0.885). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

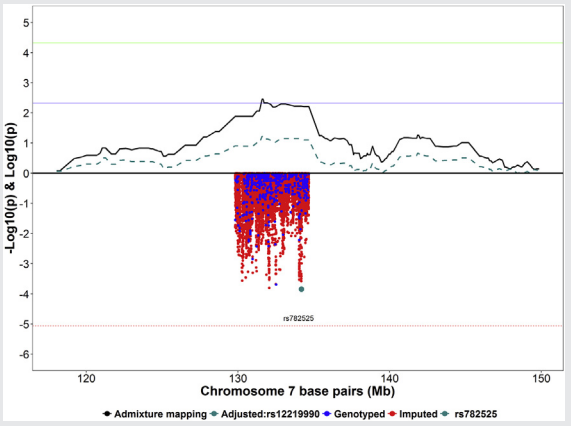
## SUPPLEMENTAL FIGURE 24




Admixture mapping analysis of chromosome 3 with overlapping single nucleotide polymorphism (SNP) association analysis results. The X-axis indicates the genomic position along chromosome 3 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs112428319; *dashed green line* = conditioned on rs112428319) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, body mass index (BMI), five principal components. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 63,405,151 to 66,558,036 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs112428319, was imputed (BioVU info score, 0.9998; CARDIA info score, 0.994). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

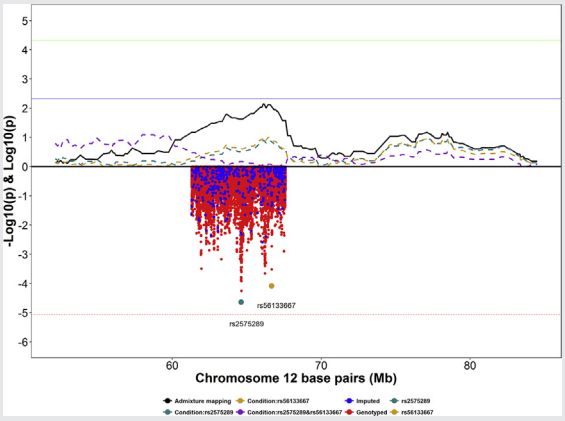
## SUPPLEMENTAL FIGURE 25




Admixture mapping analysis of chromosome 7 with overlapping single nucleotide polymorphism (SNP) association analysis results. The X-axis indicates the genomic position along chromosome 7 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs782525; *dashed green line* = conditioned on rs7872525) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, body mass index (BMI), five principal components. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 129,822,797 to 134,670,462 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs782525, was imputed (BioVU info score, 0.999; CARDIA info score, 0.985). The *dotted red line* represents the significance threshold.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*

## SUPPLEMENTAL FIGURE 26




Admixture mapping analysis of chromosome 12 with overlapping single nucleotide polymorphism (SNP) association analysis results. The X-axis indicates the genomic position along chromosome 10 in Mb. The top of the Y-axis indicates -$\log_{10}$ (*P* value) from the meta-analysis between biorepository at Vanderbilt University (BioVU) and Coronary Artery Risk Development in Young Adults Study (CARDIA) African Americans (AAs) from logistic regression of admixture mapping values that were generated from LAMP-ANC (*solid black line* = not conditioned for rs2575289 or rs56133667; *dashed teal line* = conditioned on rs2575289; *dashed yellow line* = conditioned on rs56133667; *dashed purple line* = conditioned on rs2575289 and rs56133667) with fibroid number (single vs. multiple) as the outcome. The admixture mapping analysis was adjusted for age, body mass index (BMI), five principal components. The *solid green line* represents the significance threshold. The *solid blue line* represents the suggestive threshold. The bottom portion of the Y-axis indicates the $\log_{10}$ (*P* value) for the single SNP association analyses (*blue circles* = genotyped SNPs; *red circles* = imputed SNPs) with fibroid number (single vs. multiple) as the outcome. The imputed region was found by taking 1 –log down from the most significant mapping peak above the suggest threshold. The imputed region encompassed 61,300,873 to 67,610,913 bp. The single SNP association analysis was adjusted for age, BMI, and five principal components. The SNP, rs2575289, was imputed (BioVU info score, 0.976; CARDIA info score, 0.991). The SNP, rs56133667, was imputed (BioVU info score, >0.999; CARDIA info score, >0.999). The *dotted red line* represents the significance threshold of the single SNP association analysis.

*Bray. Admixture mapping of fibroid characteristics. Fertil Steril 2017.*