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Relationship between Hysterectomy and Admixture in African American Women

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Abstract

Objective—Most studies suggest that hysterectomies are more common in African Americans than in other ethnic groups. To assess this ethnic surgical disparity in a novel way, our main goal was to determine whether admixture (the proportion of sub-Saharan African or European origin in individuals) is associated with hysterectomy frequency in African American women in the Women's Health Initiative (WHI).

Study Design—In this retrospective study, we used ancestry informative single nucleotide polymorphisms (SNPs) to estimate admixture proportions in >10,000 African American women from the WHI. Logistic regression models were used to assess the association between admixture and self-reported history of hysterectomy with and without controlling for relevant covariates. Multinomial logistic regression models were used to assess the association between admixture and self-reported age of hysterectomy. We also considered other potential risk factors (adiposity, hypertension, and education) for hysterectomy accounting for admixture.

Results—African admixture was a strong risk factor after adjusting for multiple covariates (OR 1.85, $P<.0001$). The admixture risk for hysterectomy was highest for those performed in the 35–39 age range (OR 3.08, $P<.0001$) and least evident in oldest ages (45 or older). Our analyses also suggest that adiposity, hypertension and education were independently associated with hysterectomy in this population group.

Conclusion—These results suggest that higher African admixture is associated with higher frequencies of hysterectomy and that genetic studies specifically targeting African American

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women and diseases associated with hysterectomy may be especially useful in understanding the pathogenesis and underlying cause of this disparity in health outcome.

Keywords

ancestry; ancestry informative markers; fibroid tumors; Women's Health Initiative

Introduction

Hysterectomy is the most common gynecological surgery in the United States.[1] African American women have a higher risk of hysterectomy compared with other ethnic groups.[2,3] Explanations for this higher risk include less access to more conservative treatments due to lower socioeconomic status (SES), higher population density in the southern United States where hysterectomy is more common, and psychosocial factors that affect patient and/or physician preferences towards hysterectomy over other treatments.[3–6] However, the higher hysterectomy rates in African Americans may also reflect differences in the prevalence of diseases for which hysterectomy is performed. African Americans have a higher prevalence of uterine leiomyomas (fibroid tumors)[3] although the etiology is not well understood.

In African Americans, 60–70% of hysterectomies are performed for fibroids compared to 29–33% for non-Hispanic whites.[1,7,8] The odds of African Americans having fibroids as an indication for hysterectomy ranges from 2.7–9.4 compared to women without African ancestry.[3,9–11] African Americans develop fibroids at younger ages, and have more rapid fibroid growth and larger tumor volumes than women of European descent.[2] Although the effect of psychosocial or environmental factors should not be discounted, differences in fibroid behavior could also suggest an underlying biological etiology including genetic polymorphisms and/or expression.[12,13] Some estimates place genetics as a primary factor for fibroids, with heritability estimates ranging between 26% to 80% with most estimates above 50%,[14–16] and the diagnosis of fibroids is associated with several genetic loci in Japanese women.[17]

To explore the possible influence of genetics on the higher rate of hysterectomy in African Americans, we investigate whether the relative proportion of sub-Saharan African (referred to here as African) is associated with hysterectomy. We use a set of ancestry informative single nucleotide polymorphisms (SNPs)[18,19] to accurately estimate admixture in >10,000 self-identified African American participants of the Women's Health Initiative (WHI). In addition, we examine whether education, body mass index (BMI) and hypertension are associated with a history of hysterectomy (after adjusting for admixture) and whether these factors influence the admixture-associated risks for hysterectomy.

MATERIALS AND METHODS

This study is a cross-sectional analysis of self-identified African American participants in the WHI. WHI is the largest US health study of postmenopausal women aged 50–79 and includes over 160,000 women recruited between 1993 and 1998.[20,21] Our study included 10,439 African American women for whom both DNA samples were genotyped, and baseline hysterectomy information and other study covariates were available. The WHI provided access to clinical data and DNA samples under appropriate Human Institutional Review Board (IRB) approval and the study design was approved by the NHLBI as part of a BAA for the WHI. The study was otherwise exempt from IRB approval.

We estimated the proportion of African and European admixture using a validated set of ancestry informative markers (AIMs)[18,19] that included 92 SNPs enabling accurate estimation of admixture proportions in African Americans.[18,19,22] Genotyping was

performed by our group as previously described[22] using the TaqMan® OpenArrays® system (https://products.appliedbiosystems.com/ab/en/US/adirect/ab?cmd=catNavigate2&catID=605783) (ABI, Foster City, CA, USA). The mean call rate was 97.1%. All AIM SNPs were in Hardy Weinberg equilibrium (P>.005) in parental populations, and the mean width of the 90% Bayesian confidence intervals (CIs) was 0.2 for admixture estimates in our studies of groups of African and Hispanic Americans.[18] While the mean width of CIs are larger for smaller AIM sets, the admixture proportions estimated in individuals assessed with these highly selected AIMs[18] are strongly correlated with larger AIMs sets. Correlations with larger sets of SNP AIMs (>500 SNPs) are >0.9 in testing with Mexican American and African American admixed populations (MFS, unpublished data). For the current study we did not include assessment of Amerindian admixture since the African American participants showed a very low frequency of Amerindian admixture(mean = 0.019).

The African and European admixture contribution (a proportion ranging from 0% to 100%) to each self-identified African American woman was assessed using STRUCTURE (v2.3.3)[23] analyses of genotyping results with AIMs as previously described.[24] The analyses were performed under the assumption of two populations (K = 2) with 100,000 replicates and 100,000 burn-in cycles and representatives of parental population groups as previously described.[24] The results were consistent with < 0.02 difference between each of three independent runs. We considered African admixture in data analyses because the results for European admixture mirror those for African admixture.

The primary outcome variable for all analyses was self-reported history of hysterectomy at baseline. We also investigated the association between African admixture and self-reported age at hysterectomy, comparing each age category with women who did not report hysterectomy. Age at hysterectomy was available in categories: “< 30”, “30–34”, “35–39”, “40–44”, “45–49”, “50–54”, “55–59”, and “60 or older”. We combined “50–54”, “55–59”, “60 or older” as “50 or older” to have a larger sample size for this category.

We considered the following baseline covariates: entry age, education, BMI, self-reported age at menarche, smoking history, alcohol intake, parity, and diastolic blood pressure. These covariates have been reported in previous studies as factors associated or potentially associated with the frequency of hysterectomy and/or fibroids.[3–6,11,25,26] BMI was computed as measured weight (kg) divided by the square of measured height (m^2). Parity included the following categories: never pregnant, no full-term pregnancy, 1 child, 2, 3, 4 children respectively and 5 or more children. We consider education with the following scale: high school or less, vocational, some college including associate degree and college degree (BA/BS and above). Alcohol intake had the following scale: non-drinker, past drinker, <1 drink/month, <1 drink/week, 1 to <7 drinks/week and 6, 7+ drinks/week. Smoking was categorized as: never smoker, < 5 years, 5–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, and 40–49 years. Diastolic hypertension status (hypertensive or normotensive) was determined based on the participants’ baseline diastolic blood pressure as previously defined.[27]

We conducted statistical analyses using SAS version 9.2 (SAS Institute, Cary, NC). All statistical tests were two sided and P<.05 was considered statistically significant. We used 10,439 participants for all analyses except when diastolic blood pressure was used as a covariate (N = 9,792) or for when we examined whether diastolic hypertension was associated with hysterectomy. This analysis included only individuals classified as hypertensive (blood pressure >90 mm Hg) or normotensive (blood pressure <80 mm Hg) (N = 7,593). Individuals with borderline blood pressures were not included in this analyses consistent with our previous study.[27] Baseline characteristics of the women with and

without hysterectomy were compared using chi-square tests for categorical variables and Student's *t* tests for continuous variables. To investigate the association between hysterectomy status and African admixture proportion, we obtained odds ratios (ORs) and 95% CIs using logistic regression models. The ORs described the effect of 100% African admixture compared to 0% African admixture, which corresponds to comparing one parental population to another parental population. We considered the following analysis models: 1) African admixture; 2) African admixture and education; 3) African admixture, education and BMI; 4) African admixture, education, BMI and parity; 5) African admixture, education, BMI, parity, age at menarche, smoking, and alcohol intake; 6) African admixture, education, BMI, parity, age at menarche, smoking, alcohol intake and diastolic blood pressure. All models included entry age and BMI was divided by its standard deviation consistent with our previous studies.[22,27–29]

We studied the association between age at hysterectomy and admixture using multinomial logistic models where the response variable has seven categories: "women without a hysterectomy" which was used as the reference level, and "less than 30", "30–34", "35–39", "40–44", "45–49", and "50 or older" for women with hysterectomy. Multinomial logistic models generalize logistic regression by allowing response variables with more than two levels, and comparing different levels of the response variables to the reference level.

We also investigated the associations between hysterectomy status and education, BMI, diastolic hypertension, respectively, with and without controlling for admixture and other covariates using logistic regression models.

RESULTS

In our African American sample, there were significant differences in age at menarche, BMI, education and parity among the women who had hysterectomy compared with those who did not (Table 1). BMI was significantly higher among women with hysterectomy ($P<.0001$). Among women with hysterectomy a higher frequency of women reported high school or below education levels than among women who did not report hysterectomy. Women who were never pregnant had a markedly higher percentage of hysterectomy than those without hysterectomy. More women who reported hysterectomy had a higher frequency of hypertension as measured at study entry. Although the mean age at menarche for the study was significantly lower for those with hysterectomy this difference was small.

We examined the effect of admixture with and without adjusting for covariates (Table 2). African admixture was associated with hysterectomy when adjusting for entry age alone (OR 2.10, 95% CI 1.57–2.80). This association remained highly significant when controlling for education albeit with a slightly reduced OR (1.98, 95% CI 1.47–2.65). The ORs were similar when including BMI, parity, age at menarche, smoking and alcohol intake in the logistic regression model, but decreased to 1.85 when further adjusting for diastolic blood pressure. The admixture-hysterectomy association was highly significant in all models ($P<.0001$). In the full model, the association was also observed when adjusting for the recruitment region or when only women from southern recruitment centers were considered.

African admixture was significantly associated with age at hysterectomy with and without controlling for education, BMI, parity, age at menarche, smoking, alcohol intake and diastolic blood pressure ($P=.0002$ and $<.0001$, respectively). The ORs of African admixture for age at hysterectomy and the corresponding 95% CIs are presented in Figure 1. African admixture is significantly associated with hysterectomy at a younger age (< 45 years old). This association is especially strong for hysterectomies performed in 30–34 (adjusted OR 2.31, 95% CI 1.90–5.01) and 35–39 year-old women (adjusted OR 3.08, 95% CI 1.90–5.01).

We also investigated the association of education, BMI and hypertension with hysterectomy, respectively, with and without adjusting for admixture and other covariates (Table 3). For education, college degree was associated with decreased risk for hysterectomy when adjusting for entry age alone (OR 0.85, P=.001). The strength of the association was reduced after adjusting for African admixture (OR 0.87, P=.01), and when also including BMI in the model (OR 0.90, P=.04), but increased when adding parity and other covariates to the model (OR 0.81, P<.0001). BMI had a significant association with hysterectomy with or without adjusting for African admixture and other covariates (ORs ranged from 1.09 to 1.11, P<.0001) (Table 3). Diastolic hypertension was also positively related to hysterectomy with or without controlling for other covariates including African admixture (ORs ranged from 1.20 to 1.24, P<.0005) (Table 3).

COMMENT

The most important finding of the current study is that, amongst African American women, we found that a higher percentage of African admixture is associated with a higher frequency of hysterectomy. This association was significant with only a modest reduction in the odds ratio after controlling for socioeconomic and environmental covariates including education level, adiposity, and hypertension. Previous studies comparing rates of hysterectomy between African Americans and other race/ethnicities found higher rates of hysterectomy in African American women.[2,3] In a cross-sectional study of women aged 33–45, the adjusted frequency of hysterectomy in African Americans was estimated to be nearly four-fold higher frequency than in the non-Hispanic white population.[3] Our study, using a quantitative assessment of African admixture within an African American sample, suggests that hysterectomy is associated with African ancestry.

A critical consideration of the underlying explanation for these results is whether they have been influenced by societal factors including psychosocial and environmental factors. Education level although inversely associated with risk for hysterectomy (see below) does not account for the admixture association and is also a strong surrogate measure for socio-economic status. In addition, socio-economic status (measured by geocoding) showed almost identical results (data not shown), albeit this measured current rather than lifetime status. However, we cannot completely discount the possibility that unmeasured environmental factors and either patient or physician attitudes towards treatment options for underlying medical conditions could influence the current findings. However, it should be noted that in general there is some evidence for a physician bias against surgical intervention in ethnic minorities.[30] Moreover, other studies have found that adjusting for SES factors and many other variables such as knowledge of alternatives, physician practice preferences, and cultural factors, were not sufficient to eliminate the racial difference in hysterectomy rates.[3,10,31–33]

Our study had several important limitations including the lack of information on the underlying indication(s) for hysterectomy or whether oopherectomies were performed. There was also no information on whether other treatments including myomectomies or medical therapy were available. All information on hysterectomy including age at hysterectomy was self-reported. Given this restriction it is not possible to exclude recall bias that may have influenced results, however, the recall bias for a major surgical event as hysterectomy would be small. In the WHI dataset, another self-reported phenotype (diabetes) has been validated to be sufficiently accurate[34], which may also suggest low recall bias for the self-reported outcome. Another limitation is that the measurements of both hypertension and BMI were not contemporaneous with the time of hysterectomy but rather at WHI enrollment (at ages 55–75). Thus, we cannot distinguish whether these associations observed in our study are predisposing factors to, or a consequence of hysterectomy.

It is important to note that the highest proportion (40%) of the hysterectomies in our study participants occurred during the 1970's as a function of enrollment age and age at hysterectomy. Thus, our results predominantly reflect treatment decisions for this decade. In addition, ~50% of the participants in our study were enrolled from recruitment centers in southern U.S.A. Although our data showed a higher frequency of hysterectomy in the southern group (58.5%) compared to all other participants (52.8%) consistent with previous studies,[6] analyses adjusting for regional recruitment and those restricted to only southern participants showed a similar admixture association with hysterectomy (Table 2).

The current study also suggests association between hysterectomy and adiposity (BMI), education and hypertension. Although BMI measurements were obtained at WHI enrollment and not at the time of surgery, our results showed a significant association similar to findings from previous studies of hysterectomy rates where BMI at multiple time points before hysterectomy were examined.[25]

The lower rate of hysterectomy associated with higher education levels in our study are in accord with previous studies, suggesting that SES may play a role in the higher rate of hysterectomy among African Americans.[3–6,35] It has been hypothesized that women with lower SES might be more likely to delay care due to poorer knowledge about alternatives or less access to care. Such delay could result in a more serious condition at diagnosis precluding more conservative treatment. The decreased risk of hysterectomy associated with higher education levels was weakened when BMI was included in the analysis, consistent with our previous studies of adiposity in the WHI population group.[22]

For hypertension, our findings are consistent with others showing association of diastolic blood pressure and hysterectomy although more studies are needed.[26,36] The association between history of hysterectomy and hypertension was still observed in our study after inclusion of admixture as a covariate, which has not been considered in other studies. This is important since our previous investigation has shown an association of hypertension with African admixture.[27] We note that the analysis of systolic hypertension showed nearly identical results as diastolic hypertension (data not shown).

Although our study could not ascertain the indications for hysterectomy, our results suggest the possible association between African admixture and fibroids. In African Americans, fibroid tumors have been reported as the main indication for hysterectomy in 60–65% of cases compared to only 28–29% of cases in white women.[7] Studies have reported a higher prevalence of fibroid tumors in African Americans with younger age of onset, more rapid growth, a greater number of tumors, and larger tumor volume than in European Americans.[2,10, 11] The association we found between hysterectomy and African admixture may be a proxy for a genetic relationship between African admixture and fibroids.

Age at hysterectomy and indication for surgery vary by ethnicity.[2,3] In the early reproductive years, hysterectomies are most commonly performed for symptomatic endometriosis and menstrual disorders, with little difference in ethnic distribution. In the mid and late reproductive years, symptomatic fibroid tumors predominate as the major indication for hysterectomy, with higher rates in African Americans than in non-Hispanic white population groups. After menopause, fibroid tumors generally decrease in size and become asymptomatic. Rates of hysterectomy also drop with prolapse and cancer becoming the predominant indications for hysterectomy, and rates are higher in white women than in African Americans.[8] In our study, African admixture has the strongest association for hysterectomies in 35–39 year-olds (adjusted OR 3.08) where fibroids are more likely to be the primary indication for hysterectomies. The association between African admixture and

hysterectomy is lower in the 45–49 (adjusted OR 1.14) and 50 or above groups (adjusted OR 1.35) (Figure 1) as other indications for hysterectomy begin to increase.

The admixture association with hysterectomy in the adjusted model is not significant when hysterectomies are performed at less than 30 years of age and shows a more moderate effect for hysterectomies performed before 35 years of age. This suggests that environmental or psychosocial factors may be more important for these younger women where indications for hysterectomy are predominantly endometriosis and women are potentially less informed about their health care choices.

The association between hysterectomy and African admixture amongst African American women reported here has an important implication. Our findings suggest that there is genetic variation within ethnic categories that should be more fully explored. Admixture mapping[37] and genetic association studies focusing on African Americans may identify specific genetic variations that more fully identify women at risk for hysterectomy, thus stimulating investigations to better define disease pathways that may be important in the etiology for ethnic disparities in hysterectomy rates.

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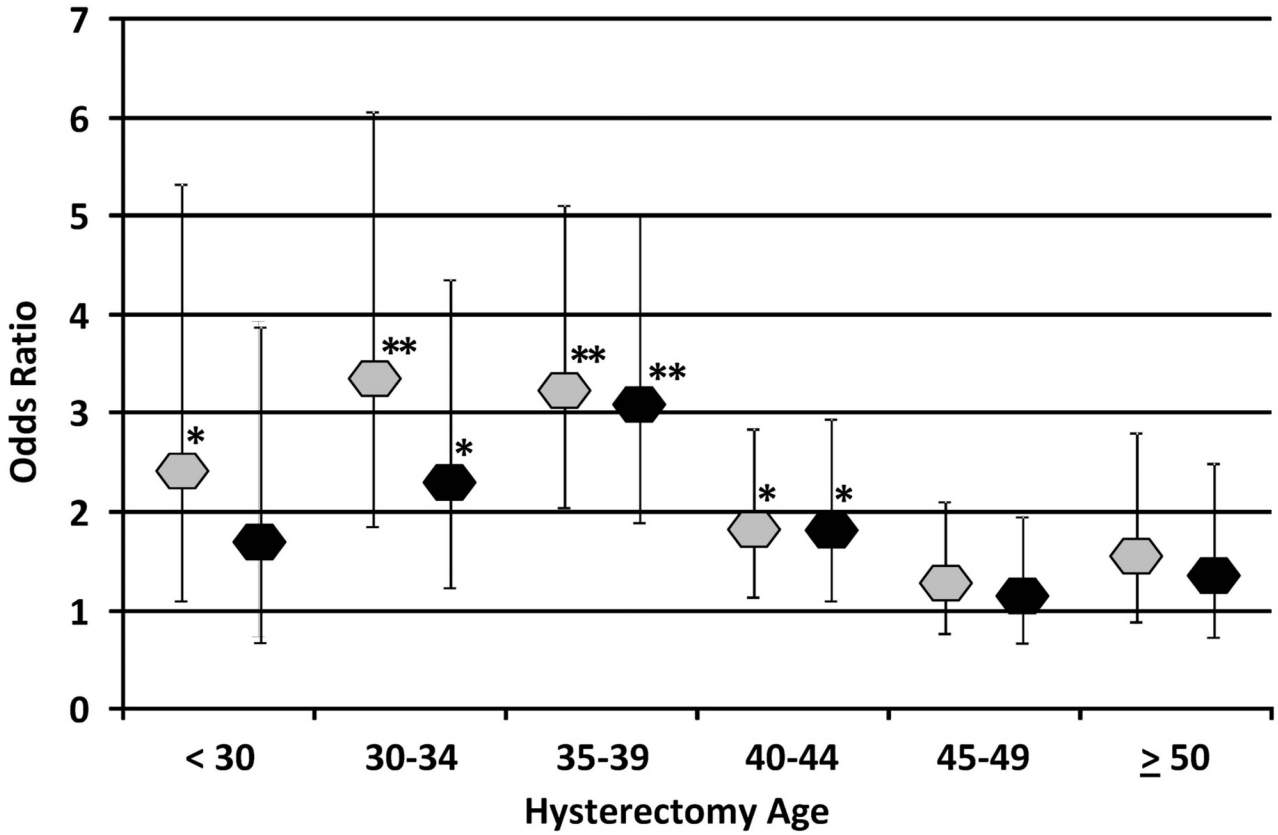

Figure 1. Association of African Admixture with Hysterectomy Age

African admixture odds ratios and 95% confidence intervals for hysterectomy are shown for different age at hysterectomy groups based on the multinormial logistic regression model adjusting for entry age (grey diamonds) and for the fully adjusted model (black diamonds). Significant P values as indicated at P<.05 (*) and at P<.0001 (**). The fully adjusted model included the following covariates: entry age, education, parity, body mass index, age at menarche, smoking, alcohol intake, and diastolic blood pressure (see Methods for details). The frequency of the reference group and each hysterectomy defined age group is as below for the two models respectively: women without a hysterectomy: 4637, 4363; < 30: 414, 394; 30–34: 808, 748; 35–39: 1459, 1383; 40–44: 1352, 1255; 45–49: 1020, 943; ≥ 50: 719, 680.

Table 1

Descriptive Statistics of Variables by Hysterectomy Status

Variable	No Hysterectomy (N = 4637, 44.4%)	Hysterectomy (N = 5802, 55.6%)	p*
Entry age (y)	61.7±7.0	61.5±7.2	0.09
Age at menarche (y)	12.7±1.6	12.6±1.6	<.0001
BMI (kg/m^2)	30.8±6.5	31.4±6.5	<.0001
DBP (mm Hg)+	79.3±9.9	80.0±10.0	0.0009
Education			<.0001
high school or below	1154 (24.9)	1500 (25.9)	
Vocational	562 (12.1)	749 (12.9)	
some college	1161 (25.0)	1601 (27.6)	
college degree	1760 (38.0)	1952 (33.6)	
Parity			<.0001
Never Pregnant	269 (5.8)	506 (8.7)	
No term pregnancy	254 (5.5)	366 (6.3)	
1 Child	682 (14.7)	887 (15.3)	
2 Children	1087 (23.4)	1315 (22.7)	
3 Children	827 (17.8)	1048 (18.1)	
4 Children	624 (13.5)	687 (11.8)	
5 Children or more	894 (19.3)	993 (17.1)	
Smoke			0.51
Never smoker	2373 (51.2)	2949 (50.8)	
Less than 5 years	273 (5.9)	343 (5.9)	
5–9 years	182 (3.9)	258 (4.5)	
10–19 years	493 (10.6)	612 (10.6)	
20–29 years	533 (11.5)	710 (12.2)	
30–39 years	483 (10.4)	560 (9.7)	
40–49 years	222 (4.8)	290 (5.0)	
50 or more years	78 (1.7)	80 (1.4)	
Alcohol intake			0.27
Non drinker	809 (17.5)	995 (17.2)	
Past drinker	1530 (33.0)	1981 (34.1)	
<1 drink per month	612 (13.2)	750 (12.9)	
<1 drink per week	840 (18.1)	1044 (18.0)	
1 to <7 drinks per week	663 (14.3)	764 (13.2)	
7+ drinks per week	183 (4.0)	268 (4.6)	
HTN			<.0001
No	2120 (62.9)	2445 (57.9)	
Yes	1248 (37.1)	1780 (42.1)	

BMI, body mass index; DBP: diastolic blood pressure; smoke: years of a regular smoker; HTN: hypertension status based on baseline diastolic blood pressure.

* Two-sample t-tests were used for continuous variables; Chi-squared tests were used for BMI.

[+] N = 4363, 44.6% for no hysterectomy, N = 5429, 55.4% for hysterectomy.

Data are mean ± standard deviation, or n (%). For education, some college included associate degrees and college degree includes BA/BS and above.

The hysterectomies were primarily performed during three decades: 21.9% in the 1960's; 40.2% in the 1970's; and 26.3% in the 1980's.

Table 2

Association of African Admixture With Hysterectomy Status

Model*	Odds Ratio	95% CI		P
		Lower	Upper	
AFR	2.10	1.57	2.80	<.0001
AFR, EDU	1.98	1.47	2.65	<.0001
AFR, EDU, BMI	1.90	1.42	2.55	<.0001
AFR, EDU, BMI, parity	1.92	1.43	2.58	<.0001
AFR, EDU, BMI, parity, menarche, smoke, alcohol	1.94	1.44	2.62	<.0001
AFR, EDU, BMI, parity, menarche, smoke, alcohol, DBP	1.85	1.36	2.52	<.0001
Full Model, Region^	1.86	1.36	2.54	<.0001
Full Model (Southern)&	2.02	1.26	3.25	0.004

CI: confidence interval; AFR: African admixture; EDU: education; BMI: body mass index; menarche: age at menarche; smoke: years of a regular smoker; alcohol: alcohol intake; DBP: diastolic blood pressure.

* Logistic regression models were used to study the association between African admixture and hysterectomy status. All models included entry age. The odds ratios attributed to the difference in 0% and 100% African admixture.

^ Full model (AFR; EDU, BMI, age at menarche, smoke, alcohol and DBP) was also adjusted for region of recruitment (South, East, Midwest, and Northwest).

& Analyses restricted to only South recruitment region (no hysterectomy, 1870 women; hysterectomy, 2642 women).

Table 3

Association of Education, BMI and Hypertension With Hysterectomy Status

Model*	Odds Ratio	95% CI		P
		Lower	Upper	
EDU+	0.85	0.76	0.93	0.001
EDU, AFR	0.87	0.79	0.97	0.01
EDU, AFR, BMI	0.90	0.81	1.00	0.04
EDU, AFR, BMI, parity	0.82	0.74	0.91	0.0003
EDU, AFR, BMI, parity, menarche, smoke, alcohol	0.81	0.72	0.90	<.0001
BMI#	1.11	1.06	1.15	<.0001
BMI, AFR	1.10	1.05	1.14	<.0001
BMI, AFR, EDU	1.09	1.05	1.13	<.0001
BMI, AFR, EDU, parity	1.10	1.05	1.14	<.0001
BMI, AFR, EDU, parity, menarche, smoke, alcohol	1.09	1.04	1.13	<.0001
HTN	1.24	1.13	1.36	<.0001
HTN, AFR	1.23	1.12	1.35	<.0001
HTN, AFR, BMI	1.22	1.11	1.34	<.0001
HTN, AFR, EDU, BMI, parity	1.20	1.09	1.32	0.0002
HTN, AFR, EDU, BMI, parity, menarche, smoke, alcohol	1.20	1.09	1.32	0.0002

CI: confidence interval; EDU: education; AFR: African admixture; BMI: body mass index; menarche: age at menarche; smoke: years of a regular smoker; alcohol: alcohol intake; HTN: hypertension status based on baseline diastolic blood pressure.

* All models included entry age. BMI was divided by its standard deviation.

+ Logistic regression models were used to study the association between education, BMI and hypertension and hysterectomy status. The odds ratio and *P* value are presented for the education category “college degree BA/BS and above” versus “high school and below”. Results for “vocational school” and “some college including associate degree” versus “high school and below” are not significant.

BMI was divided by its standard deviation.