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# Association of intrauterine and early life factors with uterine leiomyomata in black women

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## Abstract

**Purpose—**Uterine leiomyomata (UL) are the primary indication for hysterectomy and are 2–3 times more common in black than white women. Previous studies indicate that early life may be a critical time window of susceptibility to UL. We assessed the association of UL with selected intrauterine and early life factors, expanding on previous research by using a prospective design and validated data on exposure and disease.

**Methods—**During 1997–2009, we followed 23,505 premenopausal women aged 23–50 for new diagnoses of UL in the Black Women's Health Study. We used Cox regression models to compute incidence rate ratios (IRR) and 95% confidence intervals, adjusting for potential confounders.

**Results—**During 12 years of follow-up, there were 7,268 incident UL cases diagnosed by ultrasound (N=5,727) or surgery (N=1,541). There was little evidence of an association between UL and birth weight, gestational age, or exposure to soy formula in infancy. Statistically significant associations were found for being first-born, foreign-born, or exposed to passive smoke in childhood, but the associations were weak, with IRRs ranging from 1.06 to 1.12.

**Conclusions—**These findings do not support the hypothesis that intrauterine and early life factors are strongly related to UL risk.

### MeSH keywords

leiomyoma; intrauterine; early life; African Americans; prospective studies; females; soy formula

## INTRODUCTION

Uterine leiomyomata (UL), benign tumors of the myometrium, are a major source of gynecologic morbidity in reproductive-aged women and the primary indication for hysterectomy in the United States (1). Both *in vitro* and *in vivo* studies suggest that UL are responsive to sex steroid hormones, including estradiol and progesterone (2, 3). UL incidence is 2–3 times higher in black women than white women, but reasons for the health disparity are unclear (4–6).

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In 2004, Baird postulated that *in utero* or early childhood exposures influence uterine development, thereby affecting steroid biosynthesis or uterine sensitivity to sex steroid hormones in later life (7). According to this theory, higher exposure to estrogens and progesterone in early life may increase vulnerability to uterine pathology in adult life. This hypothesis is supported by epidemiologic studies showing a greater incidence of UL among women with early menarche or prenatal exposure to diethylstilbestrol (DES), a synthetic estrogen. Although the evidence supporting a role for age at menarche in UL development is consistent across studies regardless of study design and method of disease ascertainment (8–12), the evidence supporting a role for prenatal exposure to DES is more mixed (13–17). DES was associated with an increased risk of ultrasound-detected UL in the cross-sectional NIEHS Uterine Fibroid Study (13), but not in two prospective cohort studies (14, 15), one of which used medical records to confirm exposure (15). In two recent cross-sectional analyses of white and black women that used self-reported baseline data from the NIEHS Sister Study, prenatal DES exposure (16, 17) was associated with early-onset UL (diagnosis by age 30 in blacks or age 35 in whites). Other early life factors that were associated with UL in both investigations from the Sister Study included younger maternal age (<20 vs. ≥40: RRs=1.19 to 1.43), being born ≥1 month preterm (RRs=1.43 to 1.64), and exposure to soy formula in infancy (RRs=1.25 to 1.26) (16, 17). Findings observed in one population but not the other were being a monozygotic twin (blacks: RR=1.94), maternal prepregnancy diabetes (whites: RR=2.05), maternal gestational diabetes (blacks: RR=2.09), and low childhood SES (whites: RR=1.28).

In an effort to replicate previous findings (16, 17), we evaluated the associations of selected intrauterine and early life factors with UL incidence among participants from the Black Women's Health Study (BWHS). Factors examined in both the Sister Study and BWHS include: maternal age, birth order, multiple gestation, birth weight, gestational age, feeding practices in infancy (breastfeeding, formula), passive smoke exposure (*in utero* and childhood), and childhood socioeconomic status. We expanded the range of factors investigated to include other factors related to prenatal or early life exposure to sex steroids (e.g., handedness) (18–23) as well as factors hypothesized to influence UL risk via other mechanisms such as the vitamin D pathway (e.g., latitude, season of birth) (16, 17, 24–26). The present study—the largest of any prior study on the topic—provides the first prospective data on early life factors in relation to UL, considers a wider range of ages at diagnosis, and validates UL and early life exposures.

## METHODS

### Study population

The Black Women's Health Study is an ongoing U.S. prospective cohort study of 59,000 African-American women aged 21–69 at entry (27). In 1995, *Essence* magazine subscribers (93.6%), black members of two professional societies (2.5%), and friends and relatives of early respondents (3.9%) responded to a mailed invitation to enroll in a long-term health study by completing a self-administered baseline questionnaire. Every two years, cohort members update their exposure and medical histories by questionnaire; follow-up of the baseline cohort has averaged over 80% across seven cycles of follow-up. Study participants reside in more than 17 states, with the majority residing in New York, California, Illinois, Michigan, Georgia, and New Jersey. The institutional review board of Boston University Medical Center approved the study protocol.

### Assessment of outcome

On the 1999 and 2001 follow-up questionnaires, women reported whether they had been diagnosed with "uterine fibroids" in the previous two-year interval, the calendar year in

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which they were first diagnosed, and whether their diagnosis was confirmed by "pelvic exam" and/or by "ultrasound/hysterectomy." On the 2003, 2005, 2007, and 2009 follow-up questionnaires, "hysterectomy" was replaced by "surgery (e.g., hysterectomy)" to capture women with other surgeries (e.g., myomectomy), and "ultrasound" and "surgery" were asked as two separate questions. Cases were classified as "surgically-confirmed" if they reported a diagnosis by "ultrasound/hysterectomy" (<2003) or "surgery" (≥2003 questionnaires) and also reported "hysterectomy" under a separate question on that respective questionnaire.

We included cases diagnosed by ultrasound and surgery because surgical cases represent only a fraction of all cases and studies of surgical cases may spuriously identify risk factors associated with disease severity or treatment preference (28). Ultrasound has high sensitivity (99%) and specificity (91%) relative to histologic evidence (29, 30). To maximize specificity, pelvic exam cases (N=542) were treated as non-cases (31).

## Assessment of intrauterine and early life exposures and covariates

In 1997, women reported their country of birth and that of their parents, their birth weight (<4 lbs, 4lbs–5 lbs 8ozs, >5 lbs 8 ozs; or exact birth weight, if known), whether they were born preterm ("3 or more weeks early"), and whether they were a twin or triplet (identical vs. fraternal). Women also reported whether they were in the same room with a smoker for ≥ 1 hour/day for ≥1 years at home (age 0–10). In 2005, women reported the age at which their mothers gave birth to them and their state of residence at birth and age 15. In 2007, women reported how many brothers and sisters (half or full) they grew up with (sibship size) and how many were older than them. In 2009, women reported the highest level of education completed by their mother and father (<$12^{th}$ grade, high school degree or GED, some college or vocational school, college graduate or higher, don't know/not applicable), whether their home was rented or owned in childhood (age 0–11), whether they were breastfed as an infant (no, yes, don't know), duration of breastfeeding (months), and whether their mother smoked cigarettes while pregnant with them (no, yes, don't know).

The baseline (1995) and biennial follow-up questionnaires collected data on several known or suspected risk factors for UL, including reproductive and contraceptive history; weight and height; lifestyle factors (smoking, alcohol, physical activity); geographic region of residence; socioeconomic correlates (education, marital status, occupation, household income); medical history; and gynecologic surveillance (recency of pelvic exam, ultrasound). Reproductive factors, weight (to estimate body mass index (BMI), $kg/m^2$), smoking, marital status, physical activity, and region were updated on follow-up questionnaires and were analyzed as time-dependent covariates.

## Validation studies

**Uterine leiomyomata—**We assessed the accuracy of self-reported UL in a random sample of 248 cases diagnosed by ultrasound or surgery. Cases were mailed supplemental questionnaires regarding their initial date of diagnosis, method(s) of confirmation, symptoms, and treatment, and were asked for permission to review their medical records. We obtained medical records from 127 of the 128 women who gave us permission and corroborated the self-report in 122 (96%). Among the 188 (76%) providing supplemental survey data, 71% reported UL-related symptoms prior to diagnosis and 87% reported that their condition came to clinical attention because they sought treatment for symptoms or a tumor was palpable during a routine pelvic exam. There were no appreciable differences in UL risk factors by release of medical records (32).

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**Early life factors—**We validated self-reported data on infant birth weight, birth order, maternal age, and parental education against birth certificate data from the Massachusetts Department of Public Health among the 637 BWHS participants born in Massachusetts. Spearman correlation coefficients comparing self-reported vs. registry-supplied data were 0.99 for maternal age, 0.87 for birth weight, 0.78 for birth order, 0.66 for maternal education, and 0.68 for paternal education. Agreement for parental education may be greater than estimated because education could have increased since the participant's birth.

We also assessed the reliability of early life data among women who returned duplicate questionnaires in a given follow-up cycle. High agreement was found for being breastfed (kappa (k)=0.93), months of breastfeeding (Spearman correlation (r)=0.77), maternal age (r=0.96), sibship size (r=0.93), birth order (r=0.94), maternal smoking (k=0.89), passive smoking in childhood (k=0.73), maternal education (k=0.92), paternal education (k=0.93), preterm birth (k=0.86); and birth weight (categorical: k=0.86; exact: r=0.96). The time that elapsed between receipt of duplicate questionnaires ranged from 0 to 557 days (median=61 days), and there were no appreciable differences in correlations by time (data not shown).

## Restriction criteria

Of the 53,126 respondents to the 1997 questionnaire, we excluded women who were ≥50 years (N=11,475) or postmenopausal (N=6,580), women diagnosed with UL <1997 (N=9,846), those lost to follow-up >1997 (N=915), cases without a diagnosis year (N=139) or detection method (N=112), and women with missing covariate data (N=554), leaving 23,505 women for analysis. Those excluded had lower educational attainment than those included, but were similar with respect to parity, age at menarche, and other risk factors for UL.

## Data Analysis

Person-years were calculated from March 1997 until UL diagnosis, menopause, death, loss to follow-up, or the end of follow-up (March 2009), whichever came first. Age- and time period-stratified Cox regression models were used to estimate incidence rate ratios (IRR) and 95% confidence intervals (CI) for the associations of interest. Exposure variables were categorized in their original form or according to their frequency distribution in the analytic sample. We constructed two multivariable models: the first controlled for age (1-year intervals) and questionnaire cycle, while the second additionally controlled for potential early life confounders, including nativity (born outside the U.S., native born but ≥1 parent born outside U.S., native born with neither parent born outside of U.S.), birth weight (<2,000, 2,000–2,499, ≥2,500 grams), birth order (first-born, later-born), maternal age at participant's birth (<20, 20–24, 25–29, ≥30 years), and parental education (highest educational attainment by either parent: <12, 12, 13–15, ≥16 years). Secondary analysis involved additional control for adult risk factors that potentially mediate the associations, including age at menarche (years), parity (0, ≥1 births), age at first birth (years), years since last birth (<5, 5–9, 10–14, ≥15), age at first oral contraceptive use (years), history of oral contraceptive use (ever, never), BMI (<20, 20–24, 25–29, ≥30 kg/m$^2$), smoking (current, former, never), current alcohol intake (<1, 1–6, ≥7 drinks/week), participant's education (≤12, 13–15, 16, ≥17 years), marital status (married/living as married, divorced/separated/widowed, single), occupation (white collar, non-white collar, unemployed), annual household income (≤$25,000, $25,001–50,000, $50,001–100,000, >$100,000, missing), region of residence (South, Northeast, Midwest, West). Because results were largely consistent with the childhood-adjusted model, we did not present mediator-adjusted results.

Tests for trend were conducted by modeling the ordinal categorical version of the exposure and evaluating the associated Wald test statistic (33). P-values from interaction tests were

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obtained using the likelihood ratio test comparing models with and without cross-product terms between covariate and exposure variables. Departures from the proportional hazards assumption were tested by comparing models with and without cross-product terms between each exposure, age (<30, ≥30), and questionnaire cycle (1997–2003, 2003–2009). Analyses were performed using SAS statistical software version 9.2 (34).

Missing data ranged from 1% (country of birth for respondent and parents) to 36% (maternal age), with the latter variable's missingness attributable to its omission from the shortened 2005 questionnaire mailed to late-responders. Given the large proportion of women with missing data on at least one early life factor, secondary analyses were also conducted using multiple imputation (35). This involved using PROC MI in SAS to create five imputed datasets—including all known or suspected risk factors for UL in the imputation—and then combining results across imputed datasets using PROC MIANALYZE (34). Because both methods produced similar results (available upon request), we present the missing indicator method as our primary analysis.

To increase the sensitivity of disease classification, we repeated analyses after restricting non-cases to women with a recent ultrasound (<5 years ago). We also conducted secondary analyses that used the NIEHS Sister Study's UL case definition for black women (17): diagnosis before age 30, including prevalent and incident diagnoses regardless of detection method (N=6,642). Cases diagnosed ≥30 years were excluded from analysis. We used log-binomial regression to estimate prevalence ratios (PR) for the association between early life factors and UL.

## RESULTS

Baseline characteristics of BWHS participants at risk of UL are presented elsewhere (9). During 201,688 person-years of follow-up, there were 7,268 incident UL cases diagnosed by ultrasound (N=5,727) or surgery (N=1,541) (Table 1). Weak statistically significant associations were found between incident UL and foreign-born status (IRR=1.12, 95% CI, 1.02–1.24), passive smoke exposure in childhood (IRR=1.06; 95% CI, 1.01–1.11), and being a first-born child (IRR=1.06; 95% CI, 1.01–1.13). Although there was a small positive association among left-handed women with at least one left-handed parent (IRR=1.23, 95% CI, 1.07–1.42), the association was much weaker among left-handed women with no left-handed parents (IRR=1.06, 95% CI, 0.97–1.16). No appreciable differences in risk were found for participant's birth weight, gestational age, twinning, latitude of residence in early life, season of birth, parental education, home-ownership in childhood, and *in utero* smoke exposure. Likewise, there was little evidence of an association between UL and infant feeding practices, including being breastfed, duration of breastfeeding, and exposure to soy formula. When we used a reference group of women exclusively fed cow's milk formula, the association with soy formula was 1.00 (95% CI, 0.86–1.16).

Associations were not appreciably different across age strata (<30 vs. ≥30 years), with the exception of *in utero* smoke exposure, for which we observed a weak inverse association among women aged <30 (IRR=0.74; 95% CI, 0.53–1.04) but little association among those aged ≥30 (IRR=1.03; 95% CI, 0.95–1.11) (P-interaction=0.02) (Table 2). Likewise, results were similar when we restricted non-cases to those with a recent ultrasound (data not shown). Stratification by detection method (ultrasound vs. surgery) also revealed consistent results (data not shown).

Results based on the Sister Study case definition (Table 3) were largely similar to the original analyses (Table 1). Exceptions were that handedness and being born outside the US were no longer associated with risk, and maternal age and being breastfed for ≤3 months

were weakly associated with risk, albeit there was no consistent dose-response for either variable.

## DISCUSSION

In this large cohort study of black women, we found weak positive associations of UL with being foreign-born, first-born status, and exposure to passive smoking during childhood, and an inverse association with *in utero* exposure to cigarette smoke among women aged <30 years. None of the other early life factors examined, including those associated with UL in previous studies (young maternal age, preterm birth, soy formula) (16, 17), was related to risk. We did not have data on maternal prepregnancy diabetes, nor did we have any data on prenatal DES exposure (rare in black women). Our findings did not vary appreciably by age or case detection method, or among women who reported a recent ultrasound.

Our results for soy formula exposure and preterm birth disagree with those found in black and white women from the NIEHS Sister Study (16, 17). Our methods differ in that we examined incident cases of UL, we did not place any age restriction on our cases, and data on most early life factors (with the exception of infant feeding practices and *in utero* smoke exposure) were reported before the diagnosis of UL. We validated self-reported UL diagnoses in a random sample of women, demonstrating high accuracy of self-report (>96%). In addition, we validated many early life exposures using birth certificate data in a subset of women.

We chose early life factors based on their ability to influence UL risk via exposure to estrogens (e.g., dizygotic twin pregnancies) (36) or vitamin D (e.g., latitude, season of birth) (24–26). For example, twin pregnancies have higher levels of pregnancy-associated hormones than singleton pregnancies, and these levels may be higher in dizygotic than in monozygotic twin pregnancies (36). However, we found little evidence for an association between multiple gestation and UL, and no evidence that dizygotic pregnancies involving two placentas increased UL risk, although numbers of exposed cases were small. We also hypothesized that UL risk would be increased in first-born children of younger mothers, based on evidence that first pregnancies are associated with higher maternal endogenous estradiol levels than subsequent pregnancies (37, 38) and maternal levels of endogenous estrogens decrease with age (39). While we found evidence for a small positive association between first-born status and UL risk, there was only equivocal evidence for an association with maternal age. Finally, animal and human data suggest that left-handedness is influenced by higher prenatal exposure to estrogens or testosterone (18–23). To the extent that UL are influenced by intrauterine levels of sex steroid hormones, left-handedness could plausibly increase risk of adult-onset UL. However, we found only weak support for this hypothesis in incident analyses.

Systematic bias in the reporting of early life factors is unlikely in this analysis because information for most exposure variables was ascertained prior to UL diagnosis. However, some variables, particularly those assessed in later time periods (e.g., breastfeeding (2009), soy formula (2009), *in utero* smoke exposure (2009)), could have been influenced by disease status, resulting in differential misclassification of exposure. Random misclassification of early life factors is likely because women are being asked to recall events from early life that their mothers may not recall well. Such misclassification would have attenuated associations for the extreme categories of exposure. However, the high validity and reproducibility of our questionnaire data when compared with birth registry data suggest that the magnitude of reporting error is not large.



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Given that we did not screen all women with ultrasound to determine case status, disease misclassification was likely. Our validation study found high accuracy in UL reporting, indicating high specificity of disease classification. In prospective cohort studies, high specificity of disease classification ensures little bias in the IRR in the presence of non-differential disease misclassification (40). Findings were similar in subgroups for whom UL misclassification is lower (e.g., ultrasound-screened, younger women) (5). We also controlled for a wide range of potential confounders, which had little impact on the results. Cohort retention was high, thereby reducing potential for bias due to differential loss to follow-up. Finally, the large sample size and high incidence of UL in this population conferred excellent statistical power to detect small differences in risk.

In conclusion, our findings do not support the hypothesis that intrauterine and early life factors are materially associated with UL risk. We were unable to confirm selected findings from two previous cross-sectional studies on early life factors and UL from the NIEHS Sister Study (16, 17), with the exception of a weak association for first-born status. Further investigation in other prospective studies with validated data on early life factors is desirable.

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## Relevant Abbreviations

| | |
|---|---|
| **BWHS** | Black Women’s Health Study |
| **UL** | uterine leiomyomata |
| **IRR** | incidence rate ratio |
| **PR** | prevalence ratio |
| **CI** | confidence interval |
| **NIEHS** | National Institute of Environmental Health Sciences |

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**Table 1**

Early life factors and risk of uterine leiomyomata, Black Women's Health Study, 1997–2009.

| | | | Age-adjusted model[a] | | Multivariable model[b] | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Person-years** | **Cases** | **IRR** | **95% CI** | **IRR** | **95% CI** |
| Entire Sample | 201,688 | 7,268 | | | | |
| Born outside of the U.S. | | | | | | |
| No | 177,092 | 6,378 | 1.00 | Ref. | 1.00 | Ref. |
| No, but ≥1 parent born outside U.S. | 10,004 | 336 | 1.02 | 0.91, 1.14 | 1.02 | 0.91, 1.14 |
| Yes | 12,174 | 477 | 1.10 | 1.00, 1.21 | 1.12 | 1.02, 1.24 |
| Region of residence from birth to age 15 | | | | | | |
| Northern tier | 36,685 | 1,382 | 1.00 | 0.92, 1.07 | 1.00 | 0.92, 1.07 |
| Middle tier | 51,985 | 2,013 | 1.02 | 0.95, 1.08 | 1.01 | 0.94, 1.08 |
| Southern tier | 39,828 | 1,526 | 1.00 | Ref. | 1.00 | Ref. |
| Any combination of above | 19,730 | 742 | 0.98 | 0.90, 1.07 | 0.97 | 0.89, 1.06 |
| Season of birth | | | | | | |
| Spring | 44,988 | 1,602 | 0.99 | 0.93, 1.06 | 0.99 | 0.93, 1.06 |
| Summer | 52,869 | 1,893 | 1.00 | 0.94, 1.07 | 1.00 | 0.94, 1.07 |
| Fall | 53,975 | 1,982 | 1.02 | 0.96, 1.09 | 1.02 | 0.96, 1.09 |
| Winter | 49,856 | 1,791 | 1.00 | Ref. | 1.00 | Ref. |
| Highest education of either parent, y | | | | | | |
| <12 | 24,306 | 929 | 0.98 | 0.90, 1.06 | 1.01 | 0.93, 1.10 |
| 12 | 44,681 | 1,692 | 0.97 | 0.91, 1.04 | 0.98 | 0.92, 1.06 |
| 13–15 | 42,335 | 1,554 | 0.97 | 0.90, 1.04 | 0.97 | 0.91, 1.04 |
| ≥16 | 45,630 | 1,716 | 1.00 | Ref. | 1.00 | Ref. |
| *P*-trend[c] | | | $P=0.46$ | | $P=0.95$ | |
| Home ownership up to age 11 | | | | | | |
| Rented only | 68,128 | 2,600 | 1.03 | 0.98, 1.08 | 1.04 | 0.98, 1.09 |
| Rented and owned | 5,909 | 249 | 1.15 | 1.01, 1.31 | 1.13 | 0.99, 1.29 |
| Owned only | 83,070 | 3,078 | 1.00 | Ref. | 1.00 | Ref. |
| *In utero* exposure to cigarette smoke | | | | | | |
| No | 122,196 | 4,522 | 1.00 | Ref. | 1.00 | Ref. |

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| Characteristic | Person-years | Cases | Age-adjusted model[a] IRR | Age-adjusted model[a] 95% CI | Multivariable model[b] IRR | Multivariable model[b] 95% CI |
|---|---|---|---|---|---|---|
| Yes | 21,338 | 816 | 1.01 | 0.94, 1.08 | 1.01 | 0.94, 1.09 |
| Passive smoke exposure up to age 10 | | | | | | |
| No | 84,980 | 2,953 | 1.00 | Ref. | 1.00 | Ref. |
| Yes | 102,118 | 3,815 | 1.06 | 1.01, 1.11 | 1.06 | 1.01, 1.11 |
| Mother's age at participant birth, y | | | | | | |
| <20 | 23,588 | 940 | 1.05 | 0.96, 1.14 | 1.02 | 0.93, 1.12 |
| 20–24 | 40,719 | 1,555 | 1.00 | 0.92, 1.07 | 0.98 | 0.91, 1.06 |
| 25–29 | 30,211 | 1,205 | 1.03 | 0.95, 1.12 | 1.02 | 0.95, 1.11 |
| ≥30 | 34,010 | 1,325 | 1.00 | Ref. | 1.00 | Ref. |
| First-born | | | | | | |
| No | 107,487 | 3,968 | 1.00 | Ref. | 1.00 | Ref. |
| Yes | 59,241 | 2,266 | 1.08 | 1.02, 1.14 | 1.06 | 1.01, 1.13 |
| Mother's age (y) and first-born status | | | | | | |
| <20 and first-born | 15,483 | 618 | 1.06 | 0.96, 1.16 | 1.06 | 0.96, 1.17 |
| <20 and later-born | 5,312 | 231 | 1.11 | 0.96, 1.28 | 1.11 | 0.96, 1.28 |
| 20–29 and first-born | 24,622 | 966 | 1.04 | 0.96, 1.14 | 1.04 | 0.95, 1.14 |
| 20–29 and later-born | 39,465 | 1,555 | 1.01 | 0.93, 1.09 | 1.01 | 0.93, 1.09 |
| ≥30 and first-born | 3,579 | 149 | 1.12 | 0.94, 1.33 | 1.12 | 0.94, 1.33 |
| ≥30 and later-born | 27,518 | 1,078 | 1.00 | Ref. | 1.00 | Ref. |
| Participant's birth weight, g | | | | | | |
| <2,000 | 5,012 | 165 | 0.92 | 0.78, 1.07 | 0.94 | 0.81, 1.10 |
| 2,000–2,499 | 20,984 | 786 | 1.03 | 0.96, 1.11 | 1.04 | 0.96, 1.12 |
| ≥2,500 | 134,397 | 4,878 | 1.00 | Ref. | 1.00 | Ref. |
| Participant preterm | | | | | | |
| No | 121,701 | 4,427 | 1.00 | Ref. | 1.00 | Ref. |
| Yes | 14,172 | 512 | 1.01 | 0.92, 1.11 | 1.05 | 0.94, 1.16 |
| Participant twin or triplet | | | | | | |
| No | 195,922 | 7,075 | 1.00 | Ref. | 1.00 | Ref. |
| Yes: | 3,796 | 120 | 0.88 | 0.73, 1.05 | 0.89 | 0.74, 1.07 |
| Identical | 841 | 24 | 0.79 | 0.53, 1.17 | 0.79 | 0.53, 1.18 |

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| Characteristic | Person-years | Cases | Age-adjusted model[a] IRR | Age-adjusted model[a] 95% CI | Multivariable model[b] IRR | Multivariable model[b] 95% CI |
|---|---|---|---|---|---|---|
| Fraternal | 2,693 | 86 | 0.89 | 0.72, 1.10 | 0.90 | 0.73, 1.12 |
| Left-handed | | | | | | |
| No | 139,297 | 5,169 | 1.00 | Ref. | 1.00 | Ref. |
| Yes: | 20,489 | 835 | 1.09 | 1.01, 1.17 | 1.09 | 1.02, 1.18 |
| Yes, as was ≥1 parent | 4,336 | 202 | 1.23 | 1.07, 1.42 | 1.23 | 1.07, 1.42 |
| Yes, but parents were not | 14,273 | 564 | 1.06 | 0.97, 1.15 | 1.06 | 0.97, 1.16 |
| Breastfed as infant | | | | | | |
| No | 94,961 | 3,438 | 1.00 | Ref. | 1.00 | Ref. |
| Yes | 45,017 | 1,751 | 1.07 | 1.01, 1.13 | 1.05 | 0.99, 1.12 |
| Duration of breastfeeding, mo. | | | | | | |
| ≤ 3 | 4,729 | 182 | 1.07 | 0.92, 1.25 | 1.05 | 0.90, 1.22 |
| 4–6 | 8,468 | 315 | 1.02 | 0.91, 1.15 | 1.00 | 0.89, 1.13 |
| 7–11 | 6,986 | 287 | 1.12 | 0.99, 1.26 | 1.10 | 0.97, 1.24 |
| ≥12 | 7,551 | 283 | 1.04 | 0.92, 1.17 | 1.01 | 0.89, 1.14 |
| *P*-trend[c] | | | $P = 0.16$ | | $P = 0.33$ | |
| Fed soy formula as infant | | | | | | |
| No | 126,118 | 4,666 | 1.00 | Ref. | 1.00 | Ref. |
| Yes | 7,284 | 265 | 1.01 | 0.89, 1.14 | 1.02 | 0.90, 1.16 |

IRR, incidence rate ratio; 95% CI, 95% confidence interval.

[a] Adjusted for age (1-year intervals) and questionnaire cycle (2-year intervals).

[b] Adjusted for age, questionnaire cycle, birth weight, birth order, maternal age at participant's birth, nativity, and parental education.

[c] *P*-value from Wald test of ordinal variable.

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**Table 2**

Association of early life factors and risk of uterine leiomyomata, by age, Black Women's Health Study, 1997–2009.

| Characteristic | *AGE <30* | | | | *AGE ≥30* | | | | P-value, test for age interaction[†] |
|---|---|---|---|---|---|---|---|---|---|
| | Person-years | Cases | Multivariable model[a] IRR | 95%CI | Person-years | Cases | Multivariable model[a] IRR | (95%CI) | |
| Born outside of the U.S. | | | | | | | | | |
| No | 21,484 | 496 | 1.00 | Ref. | 155,608 | 5,882 | 1.00 | Ref. | 0.56 |
| No, but ≥1 parent born outside U.S. | 2,563 | 61 | 1.10 | 0.84, 1.44 | 7,441 | 275 | 1.01 | 0.89, 1.14 | |
| Yes | 1,830 | 51 | 1.26 | 0.94, 1.69 | 10,344 | 426 | 1.11 | 1.01, 1.22 | |
| Region of residence from birth to age 15 | | | | | | | | | |
| Northern tier | 5,127 | 136 | 0.95 | 0.74, 1.21 | 31,558 | 1,246 | 1.00 | 0.92, 1.08 | 0.09 |
| Middle tier | 6,430 | 138 | 0.76 | 0.60, 0.97 | 45,556 | 1,875 | 1.03 | 0.96, 1.11 | |
| Southern tier | 4,452 | 126 | 1.00 | Ref. | 35,376 | 1,400 | 1.00 | Ref. | |
| Any combination of above | 2,223 | 55 | 0.86 | 0.62, 1.18 | 17,507 | 687 | 0.98 | 0.89, 1.07 | |
| Season of birth | | | | | | | | | |
| Spring | 6,173 | 128 | 0.96 | 0.75, 1.22 | 38,815 | 1,474 | 1.00 | 0.93, 1.07 | 0.19 |
| Summer | 6,933 | 178 | 1.20 | 0.96, 1.50 | 45,936 | 1,715 | 0.98 | 0.92, 1.05 | |
| Fall | 6,958 | 171 | 1.12 | 0.89, 1.40 | 47,018 | 1,811 | 1.01 | 0.94, 1.08 | |
| Winter | 6,190 | 136 | 1.00 | Ref. | 43,666 | 1,655 | 1.00 | Ref. | |
| Highest education of either parent, y | | | | | | | | | |
| <12 | 1,475 | 49 | 1.30 | 0.94, 1.80 | 22,831 | 880 | 1.00 | 0.91, 1.08 | |
| 12 | 4,383 | 105 | 0.93 | 0.73, 1.18 | 40,298 | 1,587 | 0.99 | 0.92, 1.06 | |
| 13–15 | 6,133 | 143 | 0.93 | 0.74, 1.15 | 36,203 | 1,411 | 0.98 | 0.91, 1.05 | 0.30 [P-interaction = 0.06 if one IX term for education <12 yrs with age] |
| ≥16 | 7,537 | 191 | 1.00 | Ref. | 38,093 | 1,525 | 1.00 | Ref. | |
| *P*-trend[c] | | | | *P* = 0.58 | | | | *P* = 0.81 | |
| Home ownership up to age 11 | | | | | | | | | |
| Rented only | 7,998 | 203 | 1.01 | 0.83, 1.22 | 60,130 | 2,397 | 1.04 | 0.98, 1.10 | 0.84 |
| Rented and owned | 955 | 27 | 1.11 | 0.75, 1.66 | 4,955 | 222 | 1.13 | 0.98, 1.29 | |
| Owned only | 10,449 | 258 | 1.00 | Ref. | 72,621 | 2,820 | 1.00 | Ref. | |
| *In utero* exposure to cigarette smoke | | | | | | | | | |
| No | 16,219 | 396 | 1.00 | Ref. | 105,976 | 4,126 | 1.00 | Ref. | 0.02 |



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| Characteristic | *AGE <30* | | | | *AGE ≥30* | | | | P-value, test for age interaction[†] |
|---|---|---|---|---|---|---|---|---|---|
| | Person-years | Cases | Multivariable model[a] IRR | 95%CI | Person-years | Cases | Multivariable model[a] IRR | (95%CI) | |
| Yes | 2,055 | 37 | 0.74 | 0.53, 1.04 | 19,284 | 779 | 1.03 | 0.95, 1.11 | |
| Passive smoke exposure up to age 10 | | | | | | | | | |
| No | 12,434 | 279 | 1.00 | Ref. | 72,546 | 2,674 | 1.00 | Ref. | 0.62 |
| Yes | 12,343 | 304 | 1.10 | 0.94, 1.30 | 89,775 | 3,511 | 1.06 | 1.00, 1.11 | |
| Mother's age at participant birth, y | | | | | | | | | |
| <20 | 3,276 | 94 | 1.08 | 0.79, 1.47 | 20,313 | 846 | 1.01 | 0.92, 1.11 | 0.67 |
| 20–24 | 5,316 | 142 | 1.01 | 0.77, 1.33 | 35,403 | 1,413 | 0.97 | 0.90, 1.05 | |
| 25–29 | 3,866 | 97 | 0.96 | 0.72, 1.28 | 26,345 | 1,108 | 1.03 | 0.95, 1.12 | |
| ≥30 | 3,749 | 96 | 1.00 | Ref. | 30,261 | 1,229 | 1.00 | Ref. | |
| First-born | | | | | | | | | |
| No | 11,611 | 267 | 1.00 | Ref. | 95,876 | 3,701 | 1.00 | Ref. | 0.83 |
| Yes | 8,893 | 230 | 1.12 | 0.92, 1.36 | 50,348 | 2,036 | 1.06 | 1.00, 1.13 | |
| Mother's age (y) and first-born status | | | | | | | | | |
| <20 and first-born | 2,275 | 65 | 1.16 | 0.84, 1.62 | 13,208 | 553 | 1.05 | 0.95, 1.17 | 0.98 |
| <20 and later-born | 551 | 17 | 1.18 | 0.70, 2.00 | 4,761 | 214 | 1.11 | 0.95, 1.28 | |
| 20–29 and first-born | 3,804 | 102 | 1.06 | 0.78, 1,43 | 20,818 | 864 | 1.04 | 0.94, 1.14 | |
| 20–29 and later-born | 4,345 | 113 | 1.03 | 0.77, 1.37 | 35,120 | 1,442 | 1.01 | 0.93, 1.09 | |
| ≥30 and first-born | 424 | 11 | 1.07 | 0.57, 2.02 | 3,155 | 138 | 1.12 | 0.94, 1.34 | |
| ≥30 and later-born | 3,001 | 77 | 1.00 | Ref. | 24,517 | 1,001 | 1.00 | Ref. | |
| Participant's birth weight, g | | | | | | | | | |
| <2,000 | 810 | 17 | 0.93 | 0.57, 1.52 | 4,202 | 148 | 0.94 | 0.80, 1.11 | 0.59 |
| 2,000–2,499 | 2,651 | 57 | 0.90 | 0.68, 1.19 | 18,334 | 729 | 1.05 | 0.97, 1.13 | |
| ≥2,500 | 18,219 | 434 | 1.00 | Ref. | 116,178 | 4,444 | 1.00 | Ref. | |
| Participant preterm | | | | | | | | | |
| No | 16,314 | 406 | 1.00 | Ref. | 105,387 | 4,021 | 1.00 | Ref. | 0.18 |
| Yes | 2,383 | 47 | 0.80 | 0.56, 1.16 | 11,789 | 465 | 1.08 | 0.96, 1.20 | |
| Participant twin or triplet | | | | | | | | | |
| No | 25,516 | 603 | 1.00 | Ref. | 170,405 | 6,472 | 1.00 | Ref. | 0.30 for all twins; 0.19 for sub-categories |
| Yes: | 496 | 7 | 0.64 | 0.30, 1.36 | 3,300 | 113 | 0.91 | 0.75, 1.10 | |

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| Characteristic | AGE <30 | | | | AGE ≥30 | | | | P-value, test for age interaction[†] |
|---|---|---|---|---|---|---|---|---|---|
| | Person-years | Cases | Multivariable model[a] IRR | 95%CI | Person-years | Cases | Multivariable model[a] IRR | (95%CI) | |
| Identical | 124 | 3 | 0.99 | 0.32, 3.11 | 717 | 21 | 0.76 | 0.50, 1.18 | |
| Fraternal | 355 | 3 | 0.40 | 0.13, 1.24 | 2,338 | 83 | 0.95 | 0.76, 1.18 | |
| Left-handed | | | | | | | | | |
| No | 17,227 | 421 | 1.00 | Ref. | 122,069 | 4,748 | 1.00 | Ref. | |
| Yes: | 2,408 | 71 | 1.21 | 0.94, 1.55 | 18,082 | 764 | 1.08 | 1.00, 1.17 | 0.41 for all left-handers, 0.86 with parental handedness |
| Yes, as was ≥1 parent | 556 | 18 | 1.32 | 0.82, 2.12 | 3,781 | 184 | 1.22 | 1.06, 1.42 | |
| Yes, but parents were not | 1,682 | 47 | 1.14 | 0.84, 1.54 | 12,591 | 517 | 1.05 | 0.96, 1.16 | |
| Breastfed as infant | | | | | | | | | |
| No | 12,886 | 304 | 1.00 | Ref. | 82,074 | 3,134 | 1.00 | Ref. | 0.17 |
| Yes | 4,994 | 139 | 1.18 | 0.95, 1.45 | 40,023 | 1,612 | 1.04 | 0.98, 1.11 | |
| Duration of breastfeeding, mo. | | | | | | | | | |
| ≤ 3 | 664 | 17 | 1.09 | 0.66, 1.78 | 4,065 | 165 | 1.05 | 0.90, 1.23 | 0.38 |
| 4–6 | 1,075 | 31 | 1.21 | 0.83, 1.77 | 7,393 | 284 | 0.99 | 0.87, 1.12 | |
| 7–11 | 731 | 26 | 1.50 | 1.00, 2.25 | 6,255 | 261 | 1.07 | 0.94, 1.21 | |
| ≥12 | 998 | 20 | 0.86 | 0.54, 1.36 | 6,553 | 263 | 1.03 | 0.90, 1.17 | |
| *P*-trend[c] | | | | *P* = 0.55 | | | | *P* = 0.39 | |
| Fed soy formula as infant | | | | | | | | | |
| No | 14,874 | 357 | 1.00 | Ref. | 111,245 | 4,309 | 1.00 | Ref. | 0.19 |
| Yes | 1,254 | 38 | 1.28 | 0.91, 1.79 | 6,030 | 227 | 0.99 | 0.87, 1.13 | |

IRR, incidence rate ratio; 95% CI, 95% confidence interval.

[a] Adjusted for age, questionnaire cycle, birth weight, birth order, maternal age at participant's birth, nativity, and parental education.

[b] Test for interaction using cross-product terms for each level of exposure variable and binary age (<30 vs. ≥30); degrees of freedom equal to the number of levels of exposure.

[c] *P*-v alue from Wald test of ordinal variable.

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## Table 3

Early life factors in relation to lifetime prevalence of UL at age 30 years, Black Women's Health Study, 1997–2009.

| Characteristic | Persons | Cases | Age-adjusted model[a] | |
|---|---|---|---|---|
| | | | PR | 95% CI |
| Entire Sample | 56,933 | 6,642 | | |
| Born outside of the U.S. | | | | |
| No | 46,057 | 5,479 | 1.00 | Ref. |
| No, but ≥1 parent born outside U.S. | 1,962 | 229 | 0.97 | 0.85, 1.09 |
| Yes | 2,695 | 339 | 1.04 | 0.94, 1.15 |
| Region of residence from birth to age 15 | | | | |
| Northern tier | 8,296 | 990 | 1.00 | 0.92, 1.08 |
| Middle tier | 12,884 | 1,560 | 1.02 | 0.95, 1.09 |
| Southern tier | 11,358 | 1,341 | 1.00 | Ref. |
| Any combination of above | 5,407 | 634 | 0.99 | 0.91, 1.09 |
| Season of birth | | | | |
| Spring | 12,912 | 1,535 | 1.01 | 0.92, 1.08 |
| Summer | 14,931 | 1,731 | 0.99 | 0.93, 1.05 |
| Fall | 14,804 | 1,701 | 0.98 | 0.92, 1.04 |
| Winter | 14,286 | 1,675 | 1.00 | Ref. |
| Highest education of either parent, y | | | | |
| <12 | 9,172 | 1,091 | 1.00 | 0.92, 1.08 |
| 12 | 10,746 | 1,300 | 1.00 | 0.92, 1.08 |
| 13–15 | 9,031 | 1,155 | 1.05 | 0.97, 1.14 |
| ≥16 | 8,311 | 1,019 | 1.00 | Ref. |
| *P*-trend[b] | | | $P = 0.61$ | |
| Home ownership up to age 11 | | | | |
| Rented only | 17,749 | 2,186 | 1.03 | 0.97, 1.08 |
| Rented and owned | 1,154 | 158 | 1.12 | 0.97, 1.30 |
| Owned only | 18,762 | 2,266 | 1.00 | 1.00 |
| *In utero* exposure to cigarette smoke | | | | |
| No | 29,229 | 3,520 | 1.00 | Ref. |
| Yes | 4,991 | 632 | 1.05 | 0.97, 1.13 |
| Passive smoke exposure up to age 10 | | | | |
| No | 20,032 | 2,333 | 1.00 | Ref. |
| Yes | 25,304 | 3,168 | 1.08 | 1.02, 1.13 |
| Mother's age at participant birth, y | | | | |
| <20 | 6,248 | 787 | 1.11 | 1.02, 1.22 |
| 20–24 | 9,974 | 1,255 | 1.11 | 1.02, 1.20 |
| 25–29 | 7,004 | 889 | 1.11 | 1.02, 1.22 |
| ≥30 | 7,970 | 906 | 1.00 | Ref. |
| First-born | | | | |

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| Characteristic | Persons | Cases | Age-adjusted model[a] | |
|---|---|---|---|---|
| | | | PR | 95% CI |
| No | 26,133 | 3,100 | 1.00 | Ref. |
| Yes | 14,449 | 1,822 | 1.06 | 1.01, 1.12 |
| Mother's age (y) and first-born status | | | | |
| <20 and first-born | 3,955 | 508 | 1.11 | 1.00, 1.23 |
| <20 and later-born | 1,383 | 175 | 1.09 | 0.94, 1.28 |
| 20–29 and first-born | 5,650 | 714 | 1.09 | 0.99, 1.20 |
| 20–29 and later-born | 9,421 | 1,202 | 1.10 | 1.01, 1.20 |
| ≥30 and first-born | 869 | 97 | 0.96 | 0.79, 1.18 |
| ≥30 and later-born | 6,259 | 726 | 1.00 | Ref. |
| Participant's birth weight, g | | | | |
| <2,000 | 1,217 | 143 | 0.98 | 0.84, 1.14 |
| 2,000–2,499 | 5,220 | 647 | 1.04 | 0.96, 1.12 |
| ≥2,500 | 31,158 | 3,741 | 1.00 | Ref. |
| Participant preterm | | | | |
| No | 29,088 | 3,442 | 1.00 | Ref. |
| Yes | 2,929 | 377 | 1.08 | 0.98, 1.19 |
| Participant twin or triplet | | | | |
| No | 49,646 | 5,913 | 1.00 | Ref. |
| Yes: | 931 | 110 | 0.99 | 0.83, 1.18 |
| Identical | 218 | 27 | 1.04 | 0.73, 1.48 |
| Fraternal | 625 | 71 | 0.95 | 0.76, 1.18 |
| Left-handed | | | | |
| No | 33,606 | 4,083 | 1.00 | Ref. |
| Yes: | 4,867 | 618 | 1.04 | 0.97, 1.13 |
| Yes, as was ≥1 parent | 1,013 | 122 | 0.99 | 0.83, 1.17 |
| Yes, but parents were not | 3,391 | 436 | 1.06 | 0.96, 1.16 |
| Breastfed as infant | | | | |
| No | 19,204 | 2,286 | 1.00 | Ref. |
| Yes | 13,507 | 1,693 | 1.08 | 1.01, 1.14 |
| Duration of breastfeeding, mo. | | | | |
| ≤ 3 | 988 | 150 | 1.28 | 1.10, 1.49 |
| 4–6 | 1,939 | 244 | 1.07 | 0.94, 1.20 |
| 7–11 | 2,014 | 258 | 1.10 | 0.97, 1.24 |
| ≥12 | 2,216 | 302 | 1.16 | 1.04, 1.30 |
| *P*-trend[b] | | | $P = 0.65$ | |
| Fed soy formula as infant | | | | |
| No | 31,211 | 3,834 | 1.00 | Ref. |
| Yes | 1,330 | 183 | 1.10 | 0.96, 1.26 |

PR=prevalence ratio. Excludes cases that were diagnosed after age 30 years.

[a]Adjusted for age (1-year intervals).

[b] *P*-value from Wald test of ordinal variable.

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