Original Contribution

Association of Age at Menarche With Increasing Number of Fibroids in a Cohort of Women Who Underwent Standardized Ultrasound Assessment


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Age at menarche has been associated with several reproductive conditions, and frequencies differ by race. Racial disparities also impact fibroid risk. We comprehensively examined the relationship between age at menarche, fibroid characteristics, and race. Women were enrolled in Right From the Start (2001–2010), a multistate study that systematically screened for fibroids during very early pregnancy. Endovaginal ultrasounds were conducted, and fibroid presence, number, type, volume, and diameter were recorded according to standardized definitions. Generalized estimating equations adjusted for correlations within study site were used to estimate associations between age at menarche and fibroid status and to test for interactions with race. Of 5,023 participants, 11% had a fibroid. Seven percent underwent menarche before 11 years of age and 11% at 15 years or later. We did not observe interactions between age at menarche and race. A 1-year increase in age at menarche was inversely associated with fibroids (adjusted risk ratio = 0.87, 95% confidence interval: 0.82, 0.91). Early age at menarche had a similar positive association in individual analyses with fibroid size, type, and location but was stronger for multiple fibroids (adjusted risk ratio = 0.75, 95% confidence interval: 0.68, 0.83). Our findings confirm other reports of an association between age at menarche and fibroid development (regardless of characteristics), demonstrate no effect modification by race, and suggest a stronger association for women with multiple fibroids, possibly reflecting a stronger association for early-onset disease.

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; RFTS, Right From the Start.

Early age at menarche has been associated with several health complications, including higher risk for obesity, cardiovascular disease, metabolic syndrome, type 2 diabetes, preeclampsia, and various forms of cancer (1–12). Early age at menarche is more common among black women relative to other racial groups (13). Prior studies have identified early age at menarche as a risk factor for the development of uterine leiomyomata, or fibroids (14–22).

Uterine fibroids are the most common female pelvic tumor. Incidence increases with age up to menopause, with cumulative incidence exceeding 70% (23, 24). An established risk factor for fibroids, in addition to age and early age at menarche, is black race (16, 23–26). Parity has been shown to be protective (27–29). Despite early age at menarche being an established risk factor, only one study of early age at menarche and fibroid risk has examined the relationship for separate fibroid types (focal submucosal fibroid, focal intramural/subserosal fibroid, and diffusely heterogeneous echopattern without focal fibroids) (14), and no study has comprehensively considered other fibroid characteristics (number and size). Furthermore, despite the association of both early age at menarche and uterine fibroids with black race, the relationship between race, age at menarche, and fibroid risk has not been examined in detail. The increased fibroid risk among black women might be the result of increased estrogen exposure that also increases the risk of earlier menarche, or it could be the result of interactions between genetic and environmental/lifestyle factors that lead to both earlier menarche and increased fibroid risk, such that the risk of fibroids associated with early menarche is stronger in blacks than in whites.
In the present study, we used data from the Right From the Start (RFTS) study (2001–2010), a nonclinical reproductive health cohort, to comprehensively examine the relationship between age at menarche and fibroids and fibroid characteristics, as well as to further assess the role of race in modifying the effect of age at menarche on fibroid risk. Although there have been some race-stratified analyses of age at menarche and fibroid risk, no study has directly tested whether there are racial differences in risk. RFTS is a unique study in which an endovaginal ultrasound is conducted as a part of participation in the study. At that examination, detailed data on fibroid characteristics are collected according to standardized definitions that require repeated measurements. Fibroid data collected include fibroid presence, number, type (submucous, subserous, or intramural), volume, and diameter.

MATERIALS AND METHODS

Study population and data collection protocol

RFTS is an ongoing community-based pregnancy cohort that began enrolling study participants in 2001. Over time, RFTS has been funded through 3 major phases with distinctive research questions (RFTS 1, 2, and 3) and has enrolled participants in Galveston, Texas; Memphis, Nashville, Knoxville, and Chattanooga, Tennessee; and the Research Triangle region (Raleigh, Durham, and Chapel Hill) in North Carolina. RFTS participants are 18 years of age or older, with a median age of 29 (interquartile range, 25–32) years and a maximum age of 45 years. As part of participation, study participants consented to their medical records being reviewed. Direct marketing and recruitment strategies have been described (30). The institutional review boards of Vanderbilt University, Nashville, Tennessee, and the University of North Carolina, Chapel Hill, North Carolina, approved this study.

At enrollment, a study transvaginal ultrasound was scheduled at a participating ultrasound site to assess embryonic development for the study pregnancy and to systematically assess embryonic ultrasound with self-reported fibroid status have been described previously (31, 32).

Participants completed an intake interview at enrollment and a computer-assisted telephone interview at the end of the first trimester. The first-trimester interview provided information on reproductive health history, including age at menarche. Information about candidate confounders was obtained from the intake interview and first-trimester interview.

Statistical methods

Descriptive statistics were expressed as frequencies and proportions for categorical variables. We used generalized estimating equations adjusted for candidate confounders to examine the relationship between age at menarche and risk for fibroids and fibroid characteristics. Study site was used as the correlated grouping variable. Analyses were conducted with an independence correlation matrix assuming a binomial distribution with a log function. Associations are presented as risk ratios with 95% confidence intervals. Fibroid outcomes examined included fibroid presence (any versus none), fibroid number (1, ≥2, and 0), fibroid type (any subserous, intramural, submucous, and none), fibroid total volume divided into quartiles (none, bottom quartile (0.003–0.91 cc), second quartile (0.92–4.71 cc), third quartile (4.72–20.7 cc), and top quartile (20.8–987.2 cc)), and fibroid maximum diameter divided into quartiles (none, bottom quartile (≤13.4 mm), second quartile (13.5–23.5 mm), third quartile (23.6–35.9 mm), and top quartile (36–132 mm)). Fibroid total volume was calculated from the total volume across all fibroids observed within a woman, whereas fibroid maximum diameter was based on the largest diameter observed across all fibroids within a woman. Fibroid characteristics were analyzed with no fibroids used as the control group and with separate analyses conducted for each subgroup of fibroid characteristic as a case group (e.g., for fibroid number, subjects with 1 fibroid and ≥2 fibroids were analyzed separately in case-control analyses, with no fibroids as controls). Analyses of fibroid presence outcome used age at menarche as a continuous variable as well as categorized (<10, 11, 12–13 (referent), 14, and ≥15 years), with the most common age at menarche (12–13 years) serving as the referent group. Analyses of fibroid characteristics were performed with only age at menarche as a continuous exposure. Interactions between age at menarche (continuous in years) and race (black, white (referent), Hispanic, other) were examined with likelihood ratio tests including and excluding the interaction terms from the statistical model. An α of 0.05 for the interaction term was considered evidence of effect modification by race.

Potential confounding factors consisted of known and strongly suspected influences on age at menarche or risk of fibroids, including participant age (in years), race (black, white (referent), Hispanic, other), educational level (high school or less, some college (referent), college or more), marital status (married or cohabiting (referent), other), household income (≤$40,000, $40,001–$80,000 (referent), ≥$80,001), parity (none (referent) versus ≥1), body mass index (weight in kilograms divided by the square of height in meters), and
smoking status (never, referent, current, former). Candidate confounders were analyzed for independent association with both age at menarche and fibroid status. Those that were independently associated with age at menarche and fibroid status and that resulted in a >5% relative change in age-at-menarche effect size estimates were retained in the model. Confounding was assessed through backward elimination. No variables remained as confounders by these criteria; however, to make our results comparable to prior studies, we included an adjustment for age for our models. Stata version 11 (StataCorp LP, College Station, Texas) was used for data analyses. We used a 2-sided 5% significance level for all statistical inferences.

RESULTS

We included a total of 5,023 women for whom we had both age at menarche and fibroid status from study ultrasound and who enrolled in the study between 2001 and 2010 (Table 1). The sample was multiethnic, with the majority white but a substantial number of black participants (19%). The majority of women were <30 years of age (55%). Age at menarche ranged between 8 and 19 years of age. Seven percent of women had age at menarche before 11 years, 13% at 11 years, 55% between 12 and 13 years, 14% at 14 years, and 11% at 15 years or older. In the RFTS cohort, earlier age at menarche was associated with younger participant age, being black or Hispanic, being overweight or obese, having <4 years of college, having an income ≤$40,000, not being married, and never having smoked.

The overall prevalence of fibroids in the cohort was 11% (n = 540). The majority of women with fibroids had a single fibroid (70%). The most common fibroid type was intramural (45%), followed by subserous (41%) and submucous (21%). Diameter of the largest fibroid varied between 4 and 132 mm, and volume varied between 0.003 and 987 cc.

Mean age at menarche was 12.71 (standard deviation, 1.48) years in whites and 12.32 (standard deviation, 11.83) years in blacks. Despite black race independently associating with age at menarche and fibroid risk, race did not interact with age at menarche to modify risk for fibroids (likelihood ratio test, P = 0.807). Race-stratified analyses of fibroid presence and age at menarche are provided in Table 2. Race-stratified analyses were consistent with the pooled race analyses. Older age at menarche (continuous) associated with a decreased risk of fibroids in analyses including all racial groups (for a 1-year increase in age at menarche, crude risk ratio = 0.90, 95% confidence interval (CI): 0.85, 0.95; adjusted risk ratio (aRR) = 0.87, 95% CI: 0.82, 0.91) (Table 2). Relative to age at menarche of 12–13 years, effect sizes were most protective among women with age at menarche ≥15 years (aRR = 0.63, 95% CI: 0.47, 0.86) and most elevated among women with age at menarche <11 years (aRR = 1.40, 95% CI: 1.07, 1.83), in analyses including all racial groups.

Further examination of fibroid characteristics in the pooled racial groups (Table 3) showed that age at menarche (analyzed as a continuous variable) associated similarly across most fibroid characteristics (type, total volume, and diameter). However, the association appeared stronger for women with multiple fibroids (aRR = 0.75) than for those with a single fibroid (aRR = 0.91).

DISCUSSION

We observed an association between early age at menarche and fibroid presence and number, and the association did not differ by race. To our knowledge, this is the first study to comprehensively examine the relationship between age at menarche and fibroid characteristics and the first to observe an inverse association between age at menarche and number of fibroids. Our results showed that age at menarche ≤11 years is associated with an increased risk of fibroids when compared with the mean age at menarche (12–13 years) and that age at menarche >13 years is associated with reduced risk. Furthermore, individuals with the earliest age at menarche (≤11 years) were most at risk of developing multiple fibroids compared with those with a mean age at menarche of 12–13 years (aRR = 2.31, 95% CI: 1.50, 3.59).

Our findings are consistent with prior studies that have shown that early age at menarche is associated with developing fibroids (14–18, 20–22, 33–35) (reviewed by Schwartz (21) and updated by Laughlin and colleagues (36)). An overview of these prior studies is provided in Web Table 1, available at http://aje.oxfordjournals.org/. Most studies did not evaluate age at menarche as a continuous age. Among studies that used 12 years as the referent age for age at menarche, the risk estimates ranged between 1.2 and 1.3 for the earliest age groups, with inconsistencies in estimates arising across studies as a result of which referent group was used (18, 34). Our risk estimate for the earliest age group, <11 years, was 1.40 and was higher than prior studies that also used 12 years as a referent age. This might reflect that we have a younger population of women, and therefore the early age at menarche could be associated with earlier onset or a more severe version of fibroids. Our race-stratified analyses were consistent with prior studies (15, 20), and we did not observe an interaction between race and age at menarche. Prior studies examined black, white, and multiethnic populations but did not investigate effect modification.

Our examination of the associations between early age at menarche and different types and sizes of fibroids is also novel. To our knowledge, only the Uterine Fibroid Study examined fibroid types with regard to early age at menarche (14). Our results, showing associations with early age at menarche across all 3 fibroid types examined, are consistent with the Uterine Fibroid Study findings, in which similar associations were seen across fibroid types (14).

In prior studies examining the relationship between early age at menarche and fibroids, researchers have speculated on the potential biological relationship, focusing primarily on the role of hormones in fibroid risk. A common explanation for the observed associations between these 2 factors is that each additional year of hormonal cycles confers additional risk for developing a fibroid (reviewed by Schwartz (21)). Another mechanism could be that women with early age at menarche might have a hormonal milieu different from that of women with later age at menarche. Early age at menarche has been associated with increased levels of estradiol and estrone, as well as with lower levels of sex hormone–binding globulin (9, 37–40). Both of these hypotheses seem plausible because higher progesterone and estrogen exposures are thought to increase a woman’s risk for fibroid development.
### Table 1. Study Participant Characteristics by Race in the Right From the Start Study, 2001–2010

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
<th>Age at Menarche, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;11 (n = 360)</td>
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<tr>
<td>Age, years</td>
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<td>No.</td>
</tr>
<tr>
<td>&lt;25</td>
<td>1,735</td>
<td>35</td>
<td>119</td>
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<tr>
<td>25–29</td>
<td>1,003</td>
<td>20</td>
<td>128</td>
</tr>
<tr>
<td>30–34</td>
<td>1,596</td>
<td>32</td>
<td>74</td>
</tr>
<tr>
<td>≥35</td>
<td>688</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>3,515</td>
<td>70</td>
<td>177</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>940</td>
<td>19</td>
<td>134</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>344</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>Other</td>
<td>217</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Educational level</td>
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<tr>
<td>High school or less</td>
<td>889</td>
<td>18</td>
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<tr>
<td>Some college</td>
<td>920</td>
<td>64</td>
<td>98</td>
</tr>
<tr>
<td>College or more</td>
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<td>18</td>
<td>163</td>
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<tr>
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<td>306</td>
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<tr>
<td>Other</td>
<td>543</td>
<td>11</td>
<td>54</td>
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<td>Household income</td>
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<tr>
<td>≤$40,000</td>
<td>1,513</td>
<td>31</td>
<td>142</td>
</tr>
<tr>
<td>$40,001–$80,000</td>
<td>1,804</td>
<td>38</td>
<td>120</td>
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<tr>
<td>≥$80,001</td>
<td>1,488</td>
<td>31</td>
<td>77</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>2,343</td>
<td>48</td>
<td>164</td>
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<tr>
<td>≥1</td>
<td>2,563</td>
<td>52</td>
<td>188</td>
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<tr>
<td>Body mass indexa</td>
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<tr>
<td>Underweight (&lt;20)</td>
<td>488</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Normal weight (20–24.9)</td>
<td>2,294</td>
<td>46</td>
<td>101</td>
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<tr>
<td>Overweight (25–29.9)</td>
<td>1,194</td>
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<tr>
<td>Obese (≥30)</td>
<td>1,010</td>
<td>20</td>
<td>135</td>
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<tr>
<td>Smoking status</td>
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<tr>
<td>Never</td>
<td>3,635</td>
<td>73</td>
<td>255</td>
</tr>
<tr>
<td>Current</td>
<td>188</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td>Former</td>
<td>1,144</td>
<td>23</td>
<td>69</td>
</tr>
<tr>
<td>Prior self-reported fibroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>141</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>No</td>
<td>2,767</td>
<td>95</td>
<td>165</td>
</tr>
<tr>
<td>Study site</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>North Carolina</td>
<td>2,893</td>
<td>58</td>
<td>177</td>
</tr>
<tr>
<td>Tennessee</td>
<td>1,756</td>
<td>35</td>
<td>144</td>
</tr>
<tr>
<td>Texas</td>
<td>374</td>
<td>7</td>
<td>39</td>
</tr>
</tbody>
</table>

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a Total numbers for variables might not sum to 5,023 because of missing data.
b Weight (kg)/height (m)^2.
Fibroids have been found to have increased numbers of estrogen receptors, reduced capacity for metabolizing estradiol to the less active estrone, and enhanced transcriptional response to estrogen exposure compared with myometrium (41–44). Thus, fibroids promote an estrogen-enriched environment and might respond more vigorously than normal myometrium to estrogens. Animal models further support the role of hormonal regulation in fibroid growth. The Eker rat spontaneously develops fibroids, with a prevalence of 65% by age 16 months among rats that have never been bred. In vivo and in vitro studies in Eker rats have confirmed that the tumors have enhanced proliferation in response to hormonal stimuli and decreased apoptosis. Research in Eker rats further supports an interpretation of fibroid tissue as “hypersensitive to steroid hormone stimulation perhaps by reacquiring the responsive phenotype of . . . pregnant animals” (43, p. 830).

In addition to the direct role on hormonal factors that early age at menarche plays, an association between early age at menarche and fibroids could arise from causal networks that emerge from prenatal and early life exposures. In 2 cross-sectional analyses from the National Institute of Environmental Health Sciences (NIEHS) Sister Study, researchers identified prenatal and early life factors that might influence fibroid development (20, 45), and these factors could also influence early age at menarche. Maternal obesity might also be such a candidate early life exposure. It can impact fetal metabolic programming through epigenetic mechanisms that could either directly or indirectly impact childhood obesity.
is possible that women with
ally, the majority of our participants were in their twenties. It
veloped
able to determine the age at which a study participant devel-
(32). However, even with ultrasound screening we were not
should be very low, as has been shown from our prior studies
of developing a
opathy case at ultrasound was approximately 6.7 weeks. At this early ges-
tional age, there should be minimal distortion of the uterus to
impact identification of a fibroid. Finally, although fibroid types
were defined on the basis of mutually exclusive categories, women with multiple fibroids might have been included in
analyses of multiple fibroids types. However, we do not believe
this significantly modified our findings because the majority
of participants in our cohort had a single fibroid (70%). An
additional analysis limited to only those women with a single
fibroid resulted in comparable findings (data not shown).

In summary, we observed an association between early age at
menarche and fibroid presence that was apparent across dif-
f erent tumor types and sizes, and we saw no evidence of effect
modification by race. The stronger association for multiple
fibroids could re
ect earlier onset or more severe disease for
women with early menarche, but further research is required to
understand the signi-
ficance of these
findings and the poten-
tially different influences on the formation as opposed to the
growth of fibroids.

ACKNOWLEDGMENTS

Author affiliations: Vanderbilt Epidemiology Center, Institute
of Medicine and Public Health, Department of Obstetrics

<table>
<thead>
<tr>
<th>Fibroid Outcomes</th>
<th>No. of Cases</th>
<th>Crude Risk Ratio</th>
<th>95% CI</th>
<th>Adjusted Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroid number</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vs. 0</td>
<td>380</td>
<td>0.94</td>
<td>0.88, 1.00</td>
<td>0.91</td>
<td>0.85, 0.96</td>
</tr>
<tr>
<td>≥2 vs. 0</td>
<td>160</td>
<td>0.80</td>
<td>0.72, 0.88</td>
<td>0.75</td>
<td>0.68, 0.83</td>
</tr>
<tr>
<td>Fibroid type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any subserous vs. no fibroid</td>
<td>224</td>
<td>0.92</td>
<td>0.85, 1.00</td>
<td>0.88</td>
<td>0.81, 0.96</td>
</tr>
<tr>
<td>Any intramural vs. no fibroid</td>
<td>243</td>
<td>0.83</td>
<td>0.77, 0.90</td>
<td>0.79</td>
<td>0.73, 0.86</td>
</tr>
<tr>
<td>Any submucous vs. no fibroid</td>
<td>112</td>
<td>0.92</td>
<td>0.82, 1.03</td>
<td>0.88</td>
<td>0.78, 0.99</td>
</tr>
<tr>
<td>Total fibroid volume, cc a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom quartile vs. no fibroid</td>
<td>134</td>
<td>0.94</td>
<td>0.85, 1.05</td>
<td>0.90</td>
<td>0.81, 1.00</td>
</tr>
<tr>
<td>Second quartile vs. no fibroid</td>
<td>134</td>
<td>0.89</td>
<td>0.80, 0.99</td>
<td>0.85</td>
<td>0.76, 0.95</td>
</tr>
<tr>
<td>Third quartile vs. no fibroid</td>
<td>136</td>
<td>0.83</td>
<td>0.75, 0.92</td>
<td>0.79</td>
<td>0.71, 0.89</td>
</tr>
<tr>
<td>Top quartile vs. no fibroid</td>
<td>133</td>
<td>0.90</td>
<td>0.81, 1.00</td>
<td>0.86</td>
<td>0.77, 0.96</td>
</tr>
<tr>
<td>Largest fibroid diameter, mm b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom quartile vs. no fibroid</td>
<td>134</td>
<td>0.95</td>
<td>0.85, 1.05</td>
<td>0.90</td>
<td>0.81, 1.00</td>
</tr>
<tr>
<td>Second quartile vs. no fibroid</td>
<td>134</td>
<td>0.88</td>
<td>0.79, 0.98</td>
<td>0.85</td>
<td>0.76, 0.95</td>
</tr>
<tr>
<td>Third quartile vs. no fibroid</td>
<td>130</td>
<td>0.82</td>
<td>0.74, 0.92</td>
<td>0.79</td>
<td>0.70, 0.88</td>
</tr>
<tr>
<td>Top quartile vs. no fibroid</td>
<td>139</td>
<td>0.90</td>
<td>0.81, 1.00</td>
<td>0.87</td>
<td>0.78, 0.97</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

a Women with no fibroids (n = 4,483) served as the control group.

b Multivariate regression with generalized estimating equations adjusted for participant’s age.

c Bottom quartile, 0.003–0.91 cc; second quartile, 0.92–4.71 cc; third quartile, 4.72–20.7 cc; and top quartile, 20.8–987.2 cc.

d Bottom quartile, 4–13.4 mm; second quartile, 13.5–23.5 mm; third quartile, 23.6–35.9 mm; and top quartile, 36–132 mm.

and contribute to future outcomes like age at menarche and
fibroids (46, 47). Further research is needed to understand
the biological basis for the relationship between age at men-
arche and fibroids.

A significant strength of the present study is that all women
were systematically screened for fibroids with a standard pro-
tocol that included an endovaginal ultrasound. The majority
of other uterine fibroid studies did not have imaging data
available but instead relied on clinical diagnosis of fibroids.
As a result, misclassification of fibroids within our cohort
should be very low, as has been shown from our prior studies
(32). However, even with ultrasound screening we were not
able to determine the age at which a study participant devel-
oped fibroids. This limits our ability to assess the time at risk
of developing a fibroid since the start of menarche. Addition-
ally, the majority of our participants were in their twenties. It
is possible that women with fibroids in the cohort represented
a group with early onset of the condition, given that estimates
of age-specific cumulative incidence suggest that many women
develop fibroids later in their premenopausal years (36). Fur-
thermore, although women were recruited during early preg-
nancy, the distortion of the pregnant uterus could affect the
ability to detect a fibroid. However, the median gestational age
at ultrasound was approximately 6.7 weeks. At this early ges-

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