Uterine Fibroids and the Risk of Cardiovascular Disease in the Coronary Artery Risk Development in Young Adult Women's Study

Shannon K. Laughlin-Tommaso, MD, MPH,^{1,2} Erika L. Fuchs, PhD, MPH,³ Melissa F. Wellons, MD,⁴
Cora E. Lewis, MD, MSPH, FACP, FAHA,⁵ Ronit Calderon-Margalit, MD, MPH,⁶
Elizabeth A. Stewart, MD,^{2,7} and Pamela J. Schreiner, PhD⁸

Abstract

Background: Uterine fibroids, the most common reproductive tract tumor in women, have been associated with hypertension and atherosclerotic cardiovascular disease (CVD). Prior studies of fibroids and CVD have examined the subset of women with symptomatic fibroids who undergo hysterectomy, itself a risk factor for CVD. We aimed to study the risk of subclinical CVD, as determined by coronary artery calcification (CAC), carotid intima media thickness (CIMT), and left ventricular (LV) mass, in women with ultrasound-diagnosed uterine fibroids.

Materials and Methods: Participants were 972 women from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a cohort recruited in 1985–1986. CARDIA screened black and white women aged 35–49 years by ultrasound for fibroids at 16 years of follow-up (2002–2004). Demographics and CVD risk factors were collected in 2000–2001 at 15 years of follow-up (baseline for this analysis). Women were tested at years 15, 20, and 25 for CAC, at year 20 for CIMT, and at year 25 for echocardiographic LV mass. Multivariable logistic regression was used to estimate the odds of CAC, CIMT, and LV mass.

Results: Fifty-two percent of women had fibroids (61.7% in black, 38.3% in white women). Most CVD risk factors were more common in women with fibroids. Adjusted odds of subclinical CVD, such as elevated CIMT and elevated LV mass, were not different for women with fibroids compared with those without (CIMT odds ratio [OR]=1.03; confidence interval [95% CI] 0.7–1.5 and LV mass OR=1.14; 95% CI 0.77–1.68), when adjusted for confounders.

Conclusions: Although women with fibroids had more CVD risk factors, presence of fibroids was not associated with subclinical CVD.

Keywords: cardiovascular disease, coronary artery calcification, carotid intima media thickness, fibroids, hysterectomy

Introduction

UTERINE FIBROIDS ARE the most common reproductive system tumor among women and the leading cause of hysterectomy in the United States. Fibroids have been asso-

ciated with hypertension and atherosclerosis, and some recommend using fibroids as a marker for future cardiovascular disease (CVD).^{1–4} However, the association between fibroids and CVD is unclear; whether the result could be due to confounding by other risk factors or by hysterectomy is unknown.⁵

¹Division of Gynecology, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota.

²Department of Surgery, Mayo Clinic, Rochester, Minnesota.

³Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, Texas.

⁴Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee.

⁵Division of Preventive Medicine, School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama.

⁶Hadassah-Hebrew University Braun School of Public Health, Jerusalem, Israel.

⁷Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota.

⁸Division of Epidemiology & Community Health, University of Minnesota, Minneapolis, Minnesota.

One hypothesis for the existence of an association is that fibroids and CVD share similar disordered wound-healing^{6,7} or plaque-formation^{1,8} pathways. These pathways could result in increased extracellular matrix formation in fibroids or plaque formation in arteries, leading to fibroids in the uterus and hypertrophy of the vascular walls or ventricles.^{1,8} A second hypothesis is based on the fairly strong association between hypertension and fibroids seen in many studies.^{2–4,9} Hypertension is multifactorial, but has been related to vascular wall thickness and stiffness, and leads to atherosclerosis.¹⁰ However, in most of these studies, hypertension was more strongly related to fibroid cases that led to hysterectomy rather than fibroid cases detected before needing surgical intervention.^{4,8,9}

We aimed to study the association between fibroids and CVD using markers of subclinical disease to further elucidate possible common pathways: (1) wall thickness and vascular stiffness using markers of carotid intima media thickness (CIMT) and left ventricular (LV) mass and (2) plaque formation using coronary artery calcification (CAC). In a sub-analysis, we excluded women who underwent hysterectomy to decrease confounding.

Materials and Methods

The Coronary Artery Risk Development in Young Adults (CARDIA) study provides a unique resource for studying uterine fibroids and CVD. In 1985–1986, CARDIA recruited 5,115 young adults of age 18–30 years balanced within each center (Birmingham, AL, Chicago, IL, Minneapolis, MN and Oakland, CA) on race, gender, age, and education.¹¹ Follow-up examinations were conducted 2, 5, 7, 10, 15, 20, and 25 years after baseline with response rates of 91%, 86%, 81%, 79%, 74%, 72%, and 72% of the surviving cohort, respectively. All hysterectomy and oophorectomy events were recorded. Study protocols were approved by the IRB committees of the participating institutions, and all participants provided written informed consents.

The CARDIA Women's study (CWS), an ancillary study to CARDIA, was designed to evaluate the role of polycystic ovarian syndrome in subclinical CVD. Women who were pregnant or who had both ovaries removed were excluded from the CWS. Ultrasound examinations were performed in 2002–2004, at approximately year 16 of the CARDIA study, to assess ovaries, but also measured any uterine fibroids detected; ~86% of eligible and invited women from CARDIA were examined in CWS ($n = 1,163$).

For this analysis, we considered the CARDIA year 15 follow-up examination, conducted in 2000–2001, as baseline. CAC was measured at this baseline examination (CARDIA year 15). Fibroids were measured at CARDIA year 16. Follow-up included data from CARDIA year 20 (CAC and CIMT measured) and CARDIA year 25 (CAC and LV mass measured). Sociodemographics, lifestyle data, and cardiovascular risk factor information were obtained from this examination using self- and interviewer-administrated questionnaires (Supplementary Table 1; Supplementary Data are available online at www.liebertpub.com/jwh). Dichotomous variables were created for race (black and white), ever use of birth control pills (yes/no), and menopausal status (yes/no). Smoking was categorized as never, prior, or current smoking. Height in centimeters and weight in kilograms were measured during clinical examination, and body mass index

(BMI) was calculated. Overweight was defined as $BMI \geq 25$ – 29.9 kg/m^2 and obesity as $BMI \geq 30 \text{ kg/m}^2$. Physical activity was estimated from an interviewer-administered questionnaire based on the amount of moderate and heavy physical activity performed during the past year. A score of 300 energy units is roughly equivalent to 150 minutes of moderate physical activity per week or five 30-minute sessions.¹²

In addition, hypertension was defined as $SBP \geq 140$, $DBP \geq 90$, or taking medications for hypertension. Diabetes is defined as fasting glucose >125 or on diabetes medication. Lipid profiles and C-reactive protein (CRP) from laboratory studies were reported. Hyperlipidemia was reported as a risk factor whether a participant was taking medication for hyperlipidemia or not.

A transvaginal pelvic ultrasound examination was performed using standard protocols for evaluation of the uterus and ovaries as previously described.¹³ American Registry of Diagnostic Medical Sonographers-certified sonographers performed the ultrasound examinations using a 5- to 7.5-MHz transvaginal probe. Fibroids were identified, counted, and the largest fibroid was measured in three perpendicular planes to allow for volumetric calculation. For this analysis, fibroid group status was assigned by the year 16 ultrasound and did not change even if fibroids were reported or pathologically diagnosed at a later time. In addition, reproductive health questionnaire data were collected at baseline and in the follow-up years 5 and 10 examinations and included information on menstrual patterns, hysterectomy or oophorectomy status, and menopause status. We used these data from baseline to determine reproductive health status. We excluded women who had a self-reported myocardial infarction or stroke before our baseline.

Coronary artery calcification

CAC was measured at baseline, and at follow-up years 5 and 10 using computed tomography (CT) of the chest.¹⁴ Electron beam CT or multidetector CT scanners (GE Lightspeed or Siemens VZ/Siemens Biograph 16) were used to obtain consecutive 2.5–3 mm-thick transverse images from the root of the aorta to the apex of the heart in two sequential electrocardiogram-gated scanners.¹³ Data from both scans were transmitted electronically to the CARDIA CT Reading Center (Wake Forest University Health Sciences, Winston Salem, NC), where image analysts measured the calcified plaques in the left main, left anterior descending, circumflex, and right coronary arteries. The scores across all lesions within a given artery and across all arteries were summed for a total score. A calcium score in Agatston units was calculated for each calcified lesion. CT analysts were blinded to the participant's fibroid status. The outcome was a dichotomous variable wherein a positive score was any $CAC > 0$, as CAC is uncommon in young women and scores > 0 have been shown to predict CVD.¹⁵ We used prevalent CAC at each time point to align with intima media thickness (IMT) and LVM analyses, which were measured only once.

Intima media thickness

IMT was measured at the CARDIA year 20 (follow-up year 5).¹⁶ High-resolution B-mode ultrasound examinations of the common carotid artery, the carotid bifurcation, and the right and left internal carotid arteries were conducted by trained sonographers using the GE Logiq 700 device.¹³ Images were

read at a central reading center (Tufts Medical Center, Boston MA). Magnified gray-scale longitudinal images of the near and fall wall of each artery were obtained on both the right and left sides. The maximum IMT (in millimeters) at each segment was defined as the mean of the maximal IMT of the right and left side, near and far walls. CIMT was analyzed as a continuous measure; it was also examined as a dichotomous variable categorized at the 75th percentile of the overall IMT distribution.

Left ventricular mass

Doppler echocardiography and 2D-guided M-mode echocardiography were performed at 10 years of follow-up using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan). Examinations were performed in field centers by trained sonographers using standardized protocols.^{17,18} Measurements were performed in a central reading center (Johns Hopkins University, Baltimore MD) from the digitized images using a standard software off-line image analysis system (Digisonics, Inc., Houston, TX). LV mass was standardized to body surface area (BSA) and analyzed as a continuous measure of BSA-corrected LV mass.^{19,20} In addition, a dichotomous variable was created using a BSA-corrected LV mass >100 as abnormal.^{19,20}

Statistical analyses

All analyses were conducted using Stata SE Version 13.1.1. Differences in demographic and clinical characteristics by fibroid status were examined using chi-squared tests and *t*-tests for categorical and continuous variables, respectively. Unadjusted and adjusted logistic regression models estimated odds ratios for dichotomous outcomes (CAC), CIMT >75th percentile, and LV mass >100 for women with fibroids compared with those for women without fibroids. Unadjusted and adjusted linear regression models estimated β -coefficients for continuous outcomes (CIMT, LV mass) for women with fibroids compared with those for women without fibroids. Adjusted models were adjusted for race alone and fully adjusted models for race, BMI, age, smoking status, birth control use, hypertension (defined as systolic blood pressure ≥ 140 , diastolic blood pressure ≥ 90 , or using antihypertensive medications), menopause, education, income, study center, and physical activity obtained at the baseline examination. Statistical significance was assessed by two-sided $\alpha = 0.05$.

Because pelvic surgeries such as hysterectomy and oophorectomy can independently increase the risks of hypertension or CVD,^{5,21,22} we ran sensitivity models among women who did not report any pelvic surgery at the follow-up years 5 and 10 examinations. We tested for, but did not find, a significant interaction between BMI and race in the multivariable models. All results are presented with pooled analyses.

Results

Pelvic ultrasound scans were obtained from 972 women, and 52% had fibroids (61.7% in black women and 38.3% in white women, Table 1). At baseline CARDIA examination, mean age was ~40 years for both groups. Women without fibroids were more likely to be married or living with someone and more likely to have a higher income. Women with and without fibroids had similar gravidity and parity with nearly 50% of women having two or more children by

TABLE 1. BASELINE DEMOGRAPHICS OF WOMEN STRATIFIED BY FIBROID STATUS ON PELVIC ULTRASOUND: CARDIA STUDY, 2000–2001

	<i>Fibroids on US^a</i> N = 509 (52.37%)	<i>No fibroids on US^a</i> N = 463 (47.63%)
Age, mean (SD)	40.4 (3.6)	40.0 (3.7)
Race, <i>n</i> (%) ^b		
Black	309 (61.7)	151 (33.0)
White	192 (38.3)	307 (67.0)
Gravidity, <i>n</i> (%)		
0	76 (15.3)	81 (17.7)
1	80 (16.1)	66 (14.4)
2	98 (19.8)	99 (21.7)
3+	242 (48.8)	211 (46.2)
Parity, <i>n</i> (%)		
0	160 (31.9)	135 (29.5)
1	104 (20.8)	84 (18.3)
2+	237 (47.3)	239 (52.2)
Education ^b		
≤ 12 th grade	90 (18.0)	98 (21.4)
1–4 years college	329 (65.7)	258 (56.5)
Graduate school+	82 (16.4)	101 (22.1)
Marital status ^b		
Married/living with someone	272 (54.3)	280 (61.3)
Separated ^c	110 (22.0)	95 (20.8)
Never married	119 (23.8)	82 (17.9)
Income ^b		
<\$25,000	83 (16.7)	74 (16.3)
\$25,000 to <\$50,000	151 (30.4)	103 (22.7)
\$50,000+	262 (52.8)	276 (60.9)
Ever used birth control pills, <i>n</i> (%)	422 (84.2)	393 (85.8)
Smoking, <i>n</i> (%) ^b		
Never	311 (62.2)	257 (56.1)
Prior	84 (16.8)	110 (24.0)
Current	105 (21.0)	91 (19.9)
Center ^b		
Birmingham	106 (21.2)	106 (23.1)
Chicago	126 (25.2)	68 (14.9)
Minneapolis	88 (17.6)	131 (28.6)
Oakland	181 (36.1)	153 (33.4)
Physical activity, mean (SD)	279.43 (242.2)	308.5 (266.7)

^aUltrasound examination was performed in 2002–2004.

^b $p < 0.05$.

^cSeparated includes widowed, divorced, and other categories. CARDIA, Coronary Artery Risk Development in Young Adults.

baseline. Most women reported ever using birth control pills (>80%). Approximately 20% of women were current smokers, but women with fibroids were significantly less likely to report being prior smokers (16.8% compared with 24%) and more likely to report never smoking (62.2% vs. 56.1%).

For women with fibroids, number and size of fibroids are similar to other studies that used ultrasound screening.^{23–25} The average number of fibroids was 2.9 (SD 2.0). Nearly 80% were intramural with 5% submucosal, 12% subserosal, and 15% pedunculated. The mean largest diameter was 2.7 cm (SD 1.5) with mean largest volume of 16.1 cm³.

TABLE 2. CARDIOVASCULAR RISK FACTORS FOR WOMEN BY EXAMINATION YEAR AND PRESENCE OF FIBROIDS:
CARDIA STUDY

	<i>Fibroids on US</i>	<i>No fibroids on US</i>
	<i>Baseline</i>	
	<i>N = 501</i>	<i>N = 458</i>
Cardiovascular risk factors		
BMI, ^a kg/m ² , <i>n</i> (%)		
<25	147 (15.1)	198 (20.4)
≥25–29.9	148 (15.2)	106 (10.9)
≥30	214 (22.0)	159 (16.4)
SBP ^a (mmHg), mean (SD)	113.7 (15.4)	109.4 (15.0)
DBP ^a (mmHg), mean (SD)	74.4 (11.9)	71.4 (11.0)
Triglycerides (mg/dL), mean (SD)	87.1 (58.7)	87.7 (46.7)
Total cholesterol (mg/dL), mean (SD)	181.3 (32.7)	180.6 (29.7)
LDL-C (mg/dL), mean (SD)	109.3 (29.8)	107.2 (27.1)
HDL-C (mg/dL), mean (SD)	54.4 (14.3)	54.0 (13.6)
C-reactive protein (μg/mL), median (IQR)	1.8 (0.7–5.1)	1.5 (0.5–4.4)
Hypertension, ^{a,b} <i>n</i> (%)	96 (19.2)	52 (11.4)
Medications for hyperlipidemia, <i>n</i> (%)	2 (0.4)	2 (0.4)
Diabetes, ^c <i>n</i> (%)	14 (2.9)	9 (2.0)
Presence of CAC, <i>n</i> (%)	26 (5.3)	25 (5.6)
	<i>Follow-up year 5</i>	
	<i>N = 469</i>	<i>N = 429</i>
Cardiovascular risk factors		
BMI, ^a (kg/m ²), <i>n</i> (%)		
<25	120 (12.4%)	165 (17.0%)
≥25–29.9	127 (13.1%)	111 (11.4%)
≥30	262 (27.0%)	187 (19.2%)
SBP, ^a (mmHg), mean (SD)	115.8 (15.9)	112.0 (15.7)
DBP, ^a (mmHg), mean (SD)	74.0 (12.0)	70.8 (11.9)
Triglycerides (mg/dL), mean (SD)	95.5 (64.6)	93.3 (53.0)
Total cholesterol (mg/dL), mean (SD)	185.5 (34.3)	185.3 (31.1)
LDL (mg/dL), mean (SD)	107.9 (30.5)	107.3 (27.3)
HDL (mg/dL), mean (SD)	58.7 (16.5)	59.4 (15.3)
C-reactive protein (μg/mL), median (IQR)	1.6 (0.6–4.8)	1.2 (0.5–4.0)
Hypertension, ^{a,b} <i>n</i> (%)	138 (29.5)	73 (17.1)
Medications for hyperlipidemia, <i>n</i> (%)	34 (7.3)	24 (5.6)
Diabetes, ^c <i>n</i> (%)	41 (8.8)	25 (5.9)
Mean CIMT, ^a (mm), mean (SD)	0.7 (0.1)	0.7 (0.1)
Presence of CAC, <i>n</i> (%)	50 (11.6)	46 (11.7)
CIMT >75th percentile, <i>n</i> (%)	118 (27.1)	85 (21.6)
	<i>Follow-up year 10</i>	
	<i>N = 501</i>	<i>N = 458</i>
Cardiovascular risk factors		
BMI, ^a (kg/m ²), <i>n</i> (%)		
<25	102 (10.5%)	140 (14.4%)
≥25–29.9	121 (12.5%)	102 (10.5%)
≥30	286 (29.4%)	221 (22.7%)
SBP, ^a (mmHg), mean (SD)	119.9 (18.2)	114.6 (15.5)
DBP, ^a (mmHg), mean (SD)	75.4 (12.0)	72.2 (10.7)
Triglycerides (mg/dL), mean (SD)	100.6 (67.9)	99.0 (53.0)
Total cholesterol (mg/dL), mean (SD)	194.4 (35.9)	194.2 (34.5)
LDL (mg/dL), mean (SD)	111.2 (32.1)	111.1 (30.2)
HDL (mg/dL), mean (SD)	63.3 (18.3)	63.5 (17.1)
C-reactive protein (μg/mL), median (IQR)	1.7 (0.7–5.1)	1.6 (0.5–4.3)
Hypertension, ^{a,b} <i>n</i> (%)	188 (40.8)	119 (28.4)
Medications for hyperlipidemia, <i>n</i> (%)	59 (13.0)	49 (11.8)
Diabetes, ^c <i>n</i> (%)	56 (12.2)	37 (8.8)
Mean LV mass, ^{a,d} mean (SD)	155.3 (45.5)	147.0 (42.6)
Presence of CAC, <i>n</i> (%) ^a	88 (20.0)	55 (14.1)
LV mass >100 ^e , <i>n</i> (%)	153 (30.5)	122 (26.6)

^a*p* < 0.05.

^bHTN defined as SBP ≥140, DBP ≥90, or taking medications for hypertension.

^cDiabetes is defined as fasting glucose >125 mg/dL or on diabetes medication

^d*N*'s for LV mass at year 25 for women with fibroids=419 and women without fibroids=384.

^eAfter standardizing to body surface area.

BMI, body mass index; CAC, coronary artery calcification; CIMT, carotid intima media thickness; DBP, diastolic blood pressure; HTN, hypertension; LV, left ventricular; SBP, systolic blood pressure; SD, standard deviation; US, ultrasound.

Cardiovascular risk factors

Cardiovascular risk factors were slightly more common for women with fibroids than for women without fibroids (Table 2) at baseline and follow-up years 5 and 10. BMI was significantly higher among women with fibroids (30.1, SD 7.8) than for women without fibroids (28.5, SD 8.0, p -value of the difference=0.002) at baseline and a statistically significant difference was maintained through 10 year follow-up. Hypertension was significantly higher in women with fibroids, a difference that increased at each follow-up. At baseline, women with fibroids had an 8% higher prevalence of hypertension that increased to a 12% difference by 10 years follow-up. Hypercholesterolemia, diabetes, lipid profiles, and CRP were similar between groups. We tested for the multiplicative interaction between fibroid status and race, which was not statistically significant. Therefore, all models are presented with race groups pooled.

Subclinical disease

The presence of CAC was similar between women with and without fibroids at baseline and at 5 years follow-up (Table 2). At 10 years, the difference in presence of CAC was significantly higher in women with fibroids (20.0% vs. 14.1%, $p=0.03$). There was no correlation between volume of the largest fibroid and CAC at baseline (data not shown).

At 5 years, mean CIMT was higher among women with fibroids (mean 0.69, SD 0.12 vs. 0.67, SD 0.13, $p=0.01$). The proportion of women with CIMT above the 75th percentile was higher in women with fibroids, but not statistically significant (27.1% vs. 21.6%, $p=0.06$, Table 2). At 10 years, LV mass was significantly higher among women with fibroids

(155.3 g, SD 45.5 g) than women without fibroids (147.0 g, SD 42.6 g, $p=0.008$), but no difference in stratified analyses (Table 2). After standardizing for BSA, 30.5% ($n=153$) of women with fibroids and 26.6% ($n=122$) of women without fibroids had an LV mass >100 ($p=0.2$). There was no association between fibroid volume and either CIMT or LV mass.

In univariate analyses (Table 3), fibroids were associated with presence of CAC at 10 years (odds ratio 1.52, 95% confidence interval 1.05–2.20). Once adjusted for all confounders, fibroids were not associated with presence of CAC at any time point. CIMT and LV mass values also did not differ between groups.

Women without hysterectomy or oophorectomy

At 5 years, 4.0% ($n=36$) of women reported hysterectomy of which 78.1% ($n=25$) had fibroids as the indication. Of the 36 women who reported hysterectomy, less than half of the women had oophorectomy ($n=17$). At 10 years follow-up, 90 (9.7%) women reported hysterectomy of which 56 (62.2%) had hysterectomy for fibroids. Of women undergoing hysterectomy at 10 years follow-up, more than half had ovarian surgery ($n=49$); most ($n=33$, 70.2%) had both ovaries removed, 13 ($n=27.7$ %) had one or part of one removed, and one was unknown. After exclusion of the women who had undergone pelvic surgery, odds ratios remained similar and there was no significant association between fibroids and subclinical disease in univariate and multivariate analyses (Table 3).

Discussion

We found that cardiovascular risk factors were higher in women with fibroids than in women without fibroids,

TABLE 3. ASSOCIATION OF SUBCLINICAL CARDIOVASCULAR DISEASE WITH PRESENCE OF FIBROIDS BY YEAR OF EXAMINATION: CARDIA STUDY

	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)	Adjusted OR ^b (95% CI)
Presence of CAC			
Baseline	0.95 (0.54, 1.67)	1.13 (0.63, 2.04)	1.12 (0.60, 2.11)
Year 5	0.99 (0.65, 1.52)	1.02 (0.62, 1.59)	0.89 (0.54, 1.46)
Year 10	1.52 (1.05, 2.20)	1.51 (1.03, 2.22)	1.50 (0.95, 2.37)
>75 th percentile CIMT			
Year 5	1.35 (0.98, 1.86)	1.19 (0.85, 1.66)	1.03 (0.70, 1.50)
Corrected LV Mass > 100			
Year 10 ^c	1.21 (0.91, 1.60)	1.08 (0.80, 1.45)	1.14 (0.77, 1.68)
<i>Women with prior surgery</i>			
Presence of CAC			
Year 5	0.91 (0.57, 1.43)	0.91 (0.56, 1.47)	0.77 (0.45, 1.32)
Year 10	1.34 (0.90, 1.99)	1.34 (0.87, 2.02)	1.40 (0.86, 2.28)
>75 th percentile CIMT			
Year 5	1.38 (0.98, 1.93)	1.18 (0.83, 1.68)	1.04 (0.70, 1.55)
Corrected LV Mass > 100			
Year 10 ^c	1.36 (1.00, 1.87)	1.19 (0.86, 1.66)	1.22 (0.80, 1.85)

^aAdjusted for race.

^bAdjusted for race, BMI category, age, smoking status, hypertension, ever use of birth control, menopause status, income, education, physical activity, and study center.

^cCorrected for standardized body surface area.

CI, confidence interval; OR, odds ratio.

particularly BMI and hypertension. Crude measures of subclinical disease, including presence of CAC, mean CIMT, and mean LV mass, were all higher in women with fibroids. However, in multivariable analyses, there was no association between fibroids and subclinical CVD.

The results of our study suggest that fibroids alone may not increase the risk of CVD, but that there could be shared risk factors. Similar to other studies, we found an association between fibroids and hypertension, as well as fibroids and BMI.^{2,4,9,26,27} We did not find an association between fibroids and lipid profiles, but other studies have.^{3,28} Thus, fibroids may serve a marker of a group of women at higher risk of CVD due to underlying risk factors.⁴ Screening and preventive efforts have reduced the occurrence of CVD events for women at high risk^{29,30}; it would be interesting to determine whether fibroids could be similarly prevented. Boynton-Jarrett et al. found that fibroid incidence was higher in women with higher diastolic blood pressure; whether controlling blood pressure would decrease fibroid risk or not has not been shown.⁴ Statin use has been associated with a lower risk of fibroids and fibroid symptoms in one study, but further research on preventative medications is needed.³¹

An issue with observational data is that some fibroids can be severe enough to lead to hysterectomy with or without oophorectomy, which may increase the risk of CVD independent of fibroid status.^{21,22,32} One strength of this study was including women who were ultrasound screened for fibroids but did not proceed to hysterectomy ($n=882$) to reduce potential bias from the effects of surgery on ovarian function.^{21,22} We did not find any association between fibroids and CVD among women without pelvic surgery.

Additional strengths of this study are that women originally recruited from four communities were evaluated by ultrasound for polycystic ovaries with both clinical and subclinical fibroids noted, reducing initial misclassification of controls and detection bias.³³ By the time fibroids are clinically significant enough to lead to hysterectomy, it is difficult to determine whether the fibroids or CVD had earlier onset; thus, the screening ultrasound aided in confirming fibroid diagnosis. However, clinically significant fibroids may be stronger predictors of future CVD than ultrasound-screened cases. Because ultrasound examination was performed only once, the future progression or regression of fibroids is unknown. Misclassification of cases into controls would decrease the magnitude of the associations. A final strength includes the direct measurement of subclinical CVD.

Lastly, few studies have been able to show a link between clinically diagnosed CVD, rather than subclinical markers, and fibroids due to the same limitations we have in CARDIA. Fibroids are a disease of the reproductive years, whereas CVD increases with age after menopause. The best study design is one that screens women in their reproductive years for fibroids and has long-term follow-up to allow for the natural occurrence of CVD. In another 10 years, when these women are 55–70 years old, CARDIA will be ideal for re-evaluating this association. Our current end points are still few in number due to young age, so our power is limited to detect small associations. Also, the subclinical CVD we studied may differ in pathophysiology so that relationships between fibroids and CVD may depend on CVD subtype.

Conclusions

Fibroids and CVD share risk factors. We did not find a direct association with subclinical CVD once analyses were adjusted for CVD risk factors. Longer follow-up for clinical CVD is needed.

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Address correspondence to:

Shannon K. Laughlin-Tommaso, MD, MPH
 Division of Gynecology
 Department of Obstetrics and Gynecology
 Mayo Clinic
 200 1st Street SW
 Rochester, MN 55905

E-mail: laughlintommaso.shannon@mayo.edu