Appendix 1. Additional Study Design Methods

Eligibility criteria[1]

The primary inclusion criteria were age at recruitment (23–34 years) and self-identified race/ethnicity (Black, African American, or part African American). Some participants were 35 by the time of enrollment. Women reporting a prior diagnosis of uterine leiomyomas were excluded. Women who reported that they were pregnant at the time of recruitment had their enrollment delayed until after the pregnancy in order to assure optimum ultrasound imaging. All inclusion and exclusion criteria are listed below:

Inclusion criteria

- Age 23-34 years at time of recruitment
- Self-identify as African American, Black, or partly African American
- Intact uterus (i.e., no previous hysterectomy)
- Residence in the United States
- Ability to attend clinic visits in Detroit, MI
- Stated commitment to remain in the study for 5 years
- Willing to provide contact information for tracing (contact information for three persons who could be asked about their whereabouts, or their social security number and contact information for 1 person who would know their whereabouts)

Exclusion criteria

- Any prior diagnosis of leiomyomas
- Any prior diagnosis of cancer that required radiation or chemotherapy
- Any prior diagnosis of lupus, Grave's disease, Sjogren's, scleroderma, or multiple sclerosis that required medication

Delayed entry

- Any woman who was pregnant at recruitment had enrollment delayed until 3 months after the pregnancy ended

Recruitment and enrollment procedures[1]

Recruitment was designed to saturate the Detroit, Michigan area with information about the study. For an early pilot phase, we began by sending letters describing the study to African-American women aged 23–34 years who had been seen in the past year at the Henry Ford Health System (HFHS), a large integrated health system in the Detroit area and a collaborating institution. We then expanded recruitment to the entire Detroit area with additional letters to older African-American women (35-65 years) seen at HFHS informing them of the study and asking them to tell eligible women about the study; a website (detroitself.org); fliers, brochures at health care clinics (all obstetrics and gynecology clinics were contacted and, if willing to participate, were sent brochures to display); local radio, television, newspaper, and magazine advertisements; and information booths at community events. The HFHS patient sample that was sent letters was selected with stratification by age to help maintain equal recruitment across the eligible age range.

Harmon QE, Patchel SA, Zhao S, Umback DM, Cooper TE, Baird DD. Depot medroxyprogesterone acetate use and the development and progression of uterine leiomyoma. Obstet Gynecol 2022;139.
The authors provided this information as a supplement to their article.

The enrollment process was designed to select for women motivated and able to continue in a long-term study. Women had to initiate the enrollment process (i.e., women who heard about the study and were interested in learning more about it phoned the study number). Enrollment required several steps: (1) a telephone eligibility screening; (2) completion of orientation—a detailed 30–60 minute description of the study procedures that could be done as a group activity at HFHS or individually by telephone; (3) completion of a self-administered ‘‘Pre-enrollment Questionnaire’’ that included questions about family history of leiomyomas, participant’s current health status, a checklist of medical conditions to identify prior health problems, and physical activity in the past 7 days; (4) provision of contact information for themselves and information to facilitate tracing if they could not be located; (5) signing the informed consent form; (6) scheduling and attending a clinic visit; and (7) completing three questionnaires either before or during the clinic visit (in rare instances after the visit). Required questionnaires included a computer-assisted telephone interview (CATI), a computer-assisted web interview (CAWI), and the Block 2005 Food Frequency Questionnaire (FFQ) that was adapted to a web format (www.nutritionquest.com). Enrollment was not complete until the clinic visit and the four questionnaires (CATI, CAWI, FFQ, and self-administered Pre-enrollment Questionnaire) were completed. Monetary compensation was provided.

During the enrollment period 3200 women were screened and 89% were found to be eligible for the study. Though nearly all those eligible agreed to participate, a substantial number did not attend an orientation or complete all enrollment activities. Final enrollment was 1693 (53% of those screened).

Study size[1]

The SELF cohort was powered based on 3 hypotheses unrelated to DMPA use. Initial power calculations indicated that given an exposure prevalence of 25% or 50%, SELF was powered to detect effect sizes of 1.4 or 1.3 (respectively) for 5 years cumulative incidence. These are comparable to effects of 0.7 or 0.8 if the exposure is inversely association with incidence. Given 25% exposed, the study was powered to find differences in growth of 25%.

Study visits and retention

Follow-up visits were scheduled at approximately 20-month intervals and were delayed until at least 3 months post-partum if participants were pregnant. Participants who missed one or more visits were invited to attend later visits. Retention in the study was high; 91% attended the final study visit, 79% attended all 4 study visits and 95% attended at least 2 visits (Figure).

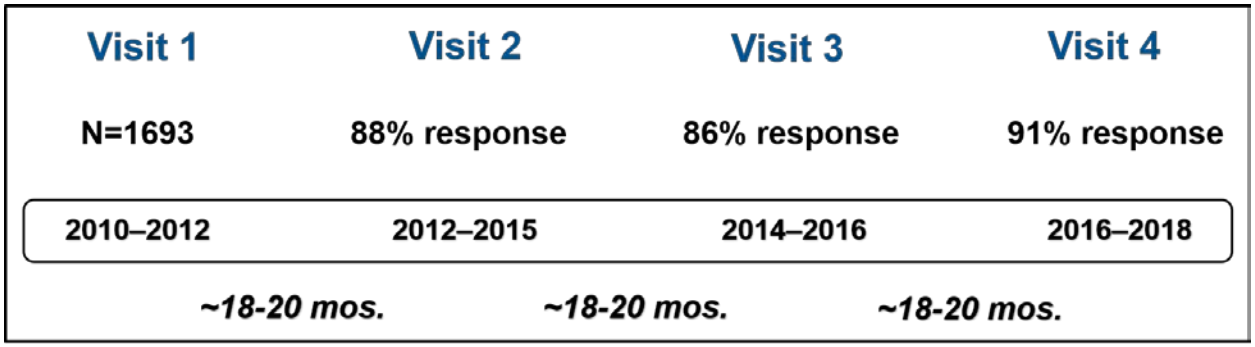

Figure. Study design and retention for the Study of Environment, Lifestyle & Leiomyomas. Detroit, Michigan 2010-2018

Ultrasound assessment of leioymomas[2]

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Ultrasound examinations were conducted throughout the study with Phillips IU-22s, with the exception of 1 GE Logic 9 machine with a consistent group of sonographers. The initial and refresher study trainings of sonographers included care in distinguishing leiomyomas from other pathologic changes in the uterus including adenomyosis and polyps, protocol for conducting the exam, and recording the data. If any leiomyomas with at least one diameter of 0.5 cm or greater were detected, the largest six were measured in three separate passes through the uterus. At each pass the 3 perpendicular diameters were measured and recorded for each leiomyoma, and caliper placement was from outer border to outer border. It was not logistically feasible to schedule study participants with the same sonographer at every visit. Ongoing quality control throughout the study by the lead sonographer included the review of archived video and still images for every sonographer each month.

Growth Analysis[2]

Leiomyoma growth was examined in leiomyomas identified as the same leiomyoma at consecutive visits. As in all prior studies of leiomyoma growth, lost leiomyomas could not be included. Identifying which of multiple leiomyomas were lost is not always possible, and just as importantly, their follow-up volume cannot be known. It could be anything as small as 0 cm^3 if the leiomyoma completely resolved or as large as just below our level of detection (~0.05 cm^3). Excluding lost leiomyomas will result in an over estimation of positive growth estimates and underestimation of shrinkage frequency. For each leiomyoma, we estimated an average change in the natural logarithm of volume (ln-volume) per day as the ratio of the change in ln-volume to the elapsed time in days between ultrasound examinations and re-expressed that as change in ln-volume per 18 months by multiplying by 540. The 18-month interval is close to our follow-up time for participants.

All our linear mixed models for leiomyoma growth used a growth rate estimated by the change in ln-volume per 18 months as the response variable. The random-effects portion of our mixed model included a variance component for woman (allowing correlations among leiomyomas from the same woman) and one for leiomyomas within woman (allowing correlations among the same leiomyoma at multiple intervals). Also, given the higher measurement variability among our triplicate measures of volume for small compared with large fibroids[3], we estimated the residual variance in growth rate separately for each level of a 4-level leiomyoma-size variable (<0.5 cm^3, 0.5-4.2 cm^3, 4.2-14.1 cm^3, ≥14.1 cm^3). The fixed-effects portion of our mixed model included a categorical variable for exposure to DMPA (*e.g.*, years since last use) with never-users as referent. We also included other covariates in the fixed-effects portion. These included, depending on the particular model: volume of leiomyoma, (<0.5 cm^3, 0.5-4.2 cm^3, 4.2-14.1 cm^3, ≥14.1 cm^3), number of leiomyomas (ordinal 1, 2, 3, 4+), age (continuous), years since last birth (within 5 years, 5+ years ago including no birth), income (<$20,000, $20-50,000, $50,000+), employment (employed yes/no), current use of oral contraception (yes, no), age at menarche (ordinal <11, 11, 12, 13, 13+).

Outlier analyses in our leiomyoma growth model revealed 14 leiomyomas with residuals for growth >3 SD from the mean; we present results after removing those outliers from the analysis as one of the sensitivity analyses in the Sensitivity Analysis section (Appendix 7) that follows.

To avoid possible confusion, we want to algebraically explain the interpretation of both the response variable in our mixed models and the model-based estimate that we use for the association of the response with a categorical DMPA exposure. First, consider the response variable itself. Though we measure the time interval between volume measurements in days and rescale volume change for each subject to an 18-month interval, we can conceptualize the variable without explicitly referencing that detail. Let V_F and V_I represent final and initial leiomyoma volumes measured 18 months apart. Our response variable, change in ln-volume over 18 months, can be represented as:

$Y = \ln(V_F) - \ln(V_I) = \ln\left({}^{V_F}/_{V_I}\right)$. In other words, a difference in ln-volume may be interpreted as the natural logarithm of a ratio expressing a fold-change in volume over 18 months. Y can be re-expressed as a change in volume relative to initial volume, *i.e.*, as a relative growth rate, through the following transformation:

$\exp(Y) - 1 = {V_{\mathrm{F}}}/{V_{\mathrm{I}}} - 1 = \frac{(V_{\mathrm{F}} - V_{\mathrm{I}})}{V_{\mathrm{I}}}$ (multiply by 100 to express as a percent). An analogous development applies to the mean of Y within any exposure category except that V_{F} and V_{I} then represent the geometric means of the corresponding volumes in that exposure category. We refer to such a transformed mean response as the "estimated change in leiomyoma volume over 18 months as a percentage of initial volume" or "estimated percent growth."

Next consider the model-based estimate of association with a binary exposure, that is, the difference in the mean value of Y between exposed (E) and referent (0) participants. Call this model-based estimate β.

$$\beta = \left[\ln\left(V_{\mathrm{E,F}}\right) - \ln\left(V_{\mathrm{E,I}}\right)\right] - \left[\ln\left(V_{0,\mathrm{F}}\right) - \ln\left(V_{0,\mathrm{I}}\right)\right] = \ln\left(\left.\frac{V_{\mathrm{E,F}}}{V_{\mathrm{E,I}}}\middle/\frac{V_{0,\mathrm{F}}}{V_{0,\mathrm{I}}}\right.\right),$$

where, for example, $V_{\mathrm{E,F}}$ represents the geometric mean of the final leiomyoma volume among the exposed group (with analogous meaning for the other subscripted volumes). Thus, β corresponds to a difference in differences on the logarithmic scale between volumes measured 18 months apart or, equivalently, to the logarithm of a ratio of fold changes, exposed over referent. We transform the model-based estimate as:

$$\exp(\beta) - 1 = \left(\left.\frac{V_{\mathrm{E,F}}}{V_{\mathrm{E,I}}}\middle/\frac{V_{0,\mathrm{F}}}{V_{0,\mathrm{I}}}\right.\right) - 1 = \frac{\left(\frac{V_{\mathrm{E,F}}}{V_{\mathrm{E,I}}}\right) - \left(\frac{V_{0,\mathrm{F}}}{V_{0,\mathrm{I}}}\right)}{\left(\frac{V_{0,\mathrm{F}}}{V_{0,\mathrm{I}}}\right)}.$$

Thus, the transformed version of β can be interpreted as a difference in fold change over 18 months between exposed and referent groups expressed as a proportion of the referent fold change. Multiplying this value by 100 expresses it as a percentage; we refer to this transformed association estimate as the "estimated percentage difference in growth over18 months" where 'growth' is assessed as fold change.

Appendix 2. Baseline Characteristics (No. and %) of 1588 Participants by Analytic Group*: Study of Environment Lifestyle and Leiomyomas, Detroit, Michigan, 2010-2018

Characteristic†		Incident Analysis	Growth Analysis	Loss Analysis
	No. Participants	1232	434	539
Age (Years)	23-25	313 (25)	53 (12)	71 (13)
	26-28	320 (26)	102 (24)	134 (25)
	29-31	324 (26)	136 (31)	161 (30)
	32-35	275 (22)	143 (33)	173 (32)
Highest Education	High School/GED or Less	282 (23)	76 (18)	108 (20)
	Some College/Associates/Technical	635 (52)	206 (47)	252 (47)
	Bachelors/Masters/PhD	314 (25)	152 (35)	179 (33)
	Missing	1		0
Yearly Household Income	<20K	564 (46)	171 (39)	232 (43)
	20-50K	471 (38)	163 (38)	194 (36)
	50K+	186 (15)	98 (23)	110 (20)
	Missing	11	2	3
Employment Status	On leave	2 (0)	2 (0.5)	2 (0)
	Unemployed	487 (40)	138 (32)	186 (35)
	Employed	743 (60)	294 (68)	351 (65)
	Missing	1	0	0
Body Mass Index (kg/m^2)	<25	248 (20)	82 (19)	101 (19)
	25 to <30	260 (21)	88 (20)	97 (18)
	30 to <35	231 (19)	94 (22)	119 (22)
	35 to <40	205 (17)	75 (17)	97 (18)
	40 and above	288 (23)	95 (22)	125 (23)
Age at Menarche	Before Age 11	213 (17)	95 (22)	110 (20)
	Age 11	252 (20)	91 (21)	110 (20)
	Age 12	342 (28)	106 (24)	135 (25)
	Age 13	201 (16)	73 (17)	95 (18)
	After Age 13	224 (18)	69 (16)	89 (17)
Gravidity/ Parity	Never Pregnant	315 (26)	138 (32)	161 (30)
	0 Births	131 (11)	75 (17)	89 (17)
	1-2 Births	557 (45)	174 (40)	218 (40)
	3+ Births	229 (19)	47 (11)	71 (13)
Years since last birth	Within 3 years	312 (25)	64 (15)	78 (14)
	3-4.9 years	167 (14)	43 (10)	57 (11)
	5-9.9 years	223 (18)	63 (15)	95 (18)
	10+ years	84 (7)	51 (12)	59 (11)
	No birth	446 (36)	213 (49)	250 (46)
Using OCP at visit	Yes	138 (11)	57 (13)	59 (11)
Current Smoker	Yes	240 (19)	79 (18)	102 (19)

*For the analysis of leiomyoma growth and leiomyoma loss participants may not have been eligible in an interval starting at baseline. Baseline characteristics are shown for descriptive purposes only. In analyses, covariates were updated for every visit.

†Participants can be eligible for more than one analytic group. The No. Participants will not sum to 1588. Of the original 1610 participants with at least one follow-up ultrasound, N=22 were not included in any analysis. The reasons for exclusion are as follows: N=11 had a censoring surgery before their first follow-up, N=5 had poor ultrasound

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quality in every interval, N=5 had poor ultrasound quality coupled with a prevalent leiomyoma(s) that was subsequently lost, N=1 entered the study with too many leiomyomas to be eligible for the analysis of leiomyoma loss.

Abbreviations: DMPA Depo Medroxyprogesterone Acetate; K $1,000; GED General Education Diploma; OCP Oral Contraceptive Pill; PhD Doctoral Degree

Appendix 3. Estimated Growth* (95% Confidence Interval) Over 18 Months for Categories of Years Since Last Use of DMPA

Years since last use of DMPA	No. exposed leiomyomas	Leiomyoma volume change over 18 months as percentage of initial volume [% (95% CI)]
Never	964	72.8 (55.5 – 92.1)
Within 2 years	75	0.3 (-16.8 – 20.9)
2-4 years	28	52.0 (14.1 – 102.5)
4-8 years	63	84.6 (50.3 – 126.7)
8 or more years	229	73.8 (52.0 – 98.9)

*Based on a linear mixed model, estimates were calculated at the following specific covariate values: volume of leiomyoma at start of interval 0.5 cm^3-<4.2 cm^3, 32 years old, 2 leiomyomas, employed, income <$20,000, no birth within 5 years, age 12 at menarche, no use of oral contraception at visit.

Abbreviations: DMPA Depo Medroxyprogesterone Acetate; CI Confidence Interval; cm^3 cubic centimeters

Appendix 4. Absolute and Relative Risk of Leiomyoma Shrinkage for Leiomyomas Exposed to DMPA Within 2 Years of the Study Visit

Use of DMPA	No. shrinking*/ exposed leiomyomas	Percent of leiomyomas†,‡ that were shrinking (95% CI)	Relative risk† of shrinkage (95% CI)
Never use of DMPA	169/964	20.1 (16.5– 24.5)	Ref
Last use of DMPA within 2 years	34/75	40.4 (28.0– 58.4)	2.0 (1.4 – 2.9)
Last use of DMPA ≥ 2 years prior	59/320	20.9 (15.2–28.7)	1.0 (0.8 – 1.4)

* Leiomyoma shrinkage defined as % growth per 18-months <0%.
† Modelled using exposure categories: Last use of DMPA within 2 years, All other DMPA or Never (ref). Model covariates included: volume of leiomyoma (<0.5 cm^3, 0.5-4.2 cm^3, 4.2-14.1 cm^3, ≥14.1 cm^3), number of leiomyomas (ordinal 1, 2, 3, 4+), age (continuous), years since last birth (within 5 years, 5+ years ago including no birth), income (<$20,000, $20-50,000, $50,000+), employment (employed yes/no), current use of oral contraception (yes, no), age at menarche (ordinal <11, 11, 12, 13, 13+).
‡ Adjusted estimates from Poisson model using average values of covariates.

Abbreviations: CI confidence interval; cm^3 cubic centimeters; DMPA Depot Medroxyprogesterone Acetate

Appendix 5. Secondary Analysis Incorporating Cumulative Duration of Use

Exposure to DMPA and leiomyoma incidence, 1231 participants from SELF, Detroit, Michigan, 2010-2018. Years since last use of DMAP stratified by cumulative duration of use

	≤9 months of Cumulative Use		>9 months of Cumulative Use	
Time since last use of DMPA	**Incident/Exposed**	**aHR* (95% CI)**	**Incident/Exposed**	**aHR* (95% CI)**
Never	171/1597	REF	171/1597	REF
Within 2 years	4/56	1.0 (0.4 – 2.8)	16/325	0.6 (0.4 – 1.0)
2-4 years	5/48	1.0 (0.4 – 2.5)	11/127	1.0 (0.4 – 2.5)
4-8 years	7/101	0.9 (0.4 – 1.9)	20/243	0.9 (0.4 – 1.9)
8 or more years	21/180	1.1 (0.7 – 1.7)	40/384	1.1 (0.7 – 1.7)

*Hazard ratios and 95% confidence intervals from a single model with 8 categories of exposure and a single referent. Cox model adjusted for time varying parity (0, 1-2 births, 3+ births), time since last birth (within 4 years, 4+ years ago including no births), BMI kg/m^2 (<25, 25- <30, 30- <35, 35- <40, 40+), current smoking (yes, no) and household income (<$20,000, $20,000-$50,000, $50,000+). Referent is Never Use.

Abbreviations: DMPA Depot Medroxyprogesterone Acetate; SELF Study of Environment, Lifestyle and Leiomyomas; aHR adjusted hazard ratio; CI confidence interval; BMI body mass index

Exposure to DMPA and leiomyoma growth, 434 participants from SELF, Detroit, Michigan, 2010-2018. Years since last use of DMAP stratified by cumulative duration of use

	≤9 months of Cumulative Use		>9 months of Cumulative Use	
Time since last use of DMPA	**No. Growth Intervals**	**% Difference* (95% CI)**	**No. Growth Intervals**	**% Difference* (95% CI)**
Never	956	REF	956	REF
Within 2 years	12	-37.5 (-57.8 – -7.3)	63	-42.9 (-53.0 – -30.6)
2-4 years	7	-7.4 (-46.9 – 61.4)	21	-13.8 (-37.1 – 18.0)
4-8 years	26	-1.2 (-26.9 – 33.6)	37	12.2 (-12.1 – 43.3)
8 or more years	85	-2.7 (-18.5 – 16.0)	144	2.7 (-11.3 – 18.9)

*Estimated percent difference in growth. Estimates from a single model with 8 categories of exposure and a single referent. Fully adjusted linear mixed model with adjustment for volume of leiomyoma (<0.5 cm^3, 0.5-4.2 cm^3, 4.2-14.1 cm^3, ≥14.1 cm^3), number of leiomyomas (ordinal 1, 2, 3, 4+), age (continuous), years since last birth (within 5 years, 5+ years ago including no birth), income (<$20,000, $20-50,000, $50,000+), employment (employed yes/no), current use of oral contraception (yes, no), age at menarche (ordinal <11, 11, 12, 13, 13+). Referent is Never Use.

Abbreviations: DMPA Depot Medroxyprogesterone Acetate; SELF Study of Environment, Lifestyle and Leiomyomas; RR risk ratio; CI confidence interval; BMI, body mass index; cm^3 cubic centimeters.

Exposure to DMPA and leiomyoma loss, 539 participants from SELF, Detroit, Michigan, 2010-2018. Years since last use of DMAP stratified by cumulative duration of use

	≤9 months of Cumulative Use		>9 months of Cumulative Use	
Time since last use of DMPA	**Loss/Exposed**	**aRR* (95% CI)**	**Loss/Exposed**	**aRR* (95% CI)**
Never	143/663	REF	143/663	REF
Within 2 years	6/13	1.7 (1.0 – 2.8)	26/70	1.5 (1.1 – 2.2)
2-4 years	3/6	1.7 (0.7 – 4.1)	13/26	2.2 (1.4 – 3.4)
4-8 years	4/20	0.8 (0.3 – 2.1)	13/40	1.5 (0.9 – 2.4)
8 or more years	17/76	1.0 (0.6 – 1.6)	22/106	0.9 (0.6 – 1.3)

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*Risk ratios and 95% confidence intervals estimated from Poisson regression in a single model with 8 categories of exposure and a single referent. Fully adjusted model adjusted for number of leiomyomas (ordinal 1, 2, 3+), largest leiomyoma volume (<0.5 cm^3, 0.5-<4.2 cm^3, 4.2-33.5 cm^3, 33.5+ cm^3), age at visit (continuous), months between visits (continuous), years since last birth (within 4 years, 4+ years ago including no birth), BMI kg/m^2 (<25, 25 to <30, 30 to <35, 35 to <40, 40+) and education (≤High School, >High School). Referent is Never Use.

Abbreviations: DMPA Depot Medroxyprogesterone Acetate; SELF Study of Environment, Lifestyle and Leiomyomas; aRR adjusted risk ratio; CI confidence interval; BMI, body mass index; cm^3 cubic centimeters.

Appendix 6. Sensitivity Analysis

Six sets of sensitivity analyses were conducted to explore residual confounding, model assumptions, and the extent to which growth and loss results might be influenced by the inclusion in the model of leiomyoma number and size.

The sensitivity analyses were completed with the same adjusted models presented in Tables 2, 3 and 4 in the manuscript. Specifically, DMPA exposure was categorized as: never, last use within 2 years, last use 2- <4 years ago, last use 4- <8 years ago, last use 8+ years ago.

Rationale for each sensitivity analysis

1. In this population use of DMPA was more common among participants with births (Table 1). Given the strong association between recent birth and the outcomes of interest, we restricted to participants with no birth within 10 years.
2. We chose to model time since last birth and parity using the end of the interval as an anchor. This modelling choice allowed births between visits to be captured with the same detail as were other births. To test the influence of this modelling choice we re-ran models using time since last birth and parity anchored at the beginning of the interval.
3. When fitting Cox models, we assigned leiomyoma incidence as occurring at the end of the interval at the date of ultrasound. To test the robustness to alternate assumptions, we set the incidence of leiomyomas to the mid-point of the interval.
4. Models for leiomyoma loss and leiomyoma growth included leiomyoma volume and leiomyoma number, both of which influence the outcomes[2]. In as much as use of DMPA might cause smaller or less numerous leiomyomas, the growth and leiomyoma loss models were re-run without these variables to consider whether the leiomyoma factors might be influencing a DMPA association.
5. Consistent with prior work,[2,4] we examined the influence of outliers (positive or negative growth beyond 3SD) in the growth analysis.
6. The choice to use DMPA (and for how long) may be influenced by unmeasured behavioral, clinical, societal, or socio-economic factors. To rule out unmeasured confounding by the factors which would result in a participant or their clinician being more likely to use/prescribe DMAP, we explored the association with temporally remote use of DMPA (8+ years since last use). These remote users will share many characteristics with other users of DMPA, but they should not have sufficient recent exposure to DMPA to show associations with leiomyoma development. If, however, these unmeasured factors that result in women choosing to use DMPA or lead their providers to prescribe DMPA are driving the protective DMPA effect that we observed (introducing bias), the association for remote users will appear to be protective.

Results and Interpretation of Each Sensitivity Analysis

Results of sensitivity analyses for the comparison of DMPA use within 2 years to never use are presented below in the table below. The sensitivity analyses did not appreciably alter the interpretation of results. Results and interpretation for each sensitivity analysis are listed below.

1. Estimates were slightly stronger when the population was restricted to those with no birth in the last 10 years. We conclude that, although there may be some residual confounding by time since last birth in the original model, this bias is not generating the observed association.
2. Estimates were unchanged when parity and time since last birth were anchored at the beginning of the interval, indicating that our choice to anchor these events at the end of the interval is not introducing bias.
3. In the incidence model, assigning leiomyoma onset to the mid-point of the interval did not alter the estimate. We conclude that our choice to assign incidence at the time of ultrasound is not introducing bias.
4. Removing leiomyoma volume and leiomyoma number from the loss and growth models did not change the estimates, suggesting that these variables are not influencing the observed association.
5. Removal of outliers from the growth model showed a small attenuation of the original estimate, but a strong negative growth estimate persisted. The attenuation is likely due to the removal of 3 rapidly shrinking leiomyomas from the group of women who had used DMPA within 2 years.

Finally, with regard to unmeasured confounding due to factors associated with choice/prescription of DMPA:

6. We observed null estimates for remote (8+ years since last use) users of DMPA. The lack of an association suggests that unmeasured factors associated with DMPA use are unlikely to be affecting our findings.

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Sensitivity Analyses* for Leiomyoma Incidence, Leiomyoma Growth, and Leiomyoma Loss Analyses

Sensitivity Analysis	Leiomyoma Incidence		Leiomyoma Growth		Leiomyoma Loss	
	No. incident/ No. exposed	aHR (95% CI)	No. leiomyomas in model	% difference (95% CI)	No. loss/ No. exposed	aRR (95% CI)
Original Estimate: DMPA use within 2 years v Never	20/381	**0.6 (0.4 – 1.0)**	**1351**	**-42.0 (-51.4 – -30.7)**	32/83	**1.6 (1.1 – 2.2)**
In the absence of bias these estimates should be similar to the original estimate						
1. Restrict to those with no birth/ last birth 10+ years ago	7/112	0.5 (0.2 – 1.0)	871	-50.3 (-60.9 – -36.9)	9/31	1.8 (1.0 – 3.2)
2. Use birth/parity at beginning of interval	20/381	0.6 (0.4 – 1.0)	1351	-42.8 (-52.3 – -31.4)	32/83	1.7 (1.2 – 2.3)
3. Assign incident leiomyoma to midpoint of interval	20/381	0.6 (0.4 – 1.0)	--	N/A	--	N/A
4. Remove leiomyoma characteristics from models	--	N/A	1351	-40.1 (-50.5 – -27.6)	32/83	1.6 (1.2 – 2.2)
5. Remove outliers† from growth models	--	N/A	1326	-35.1 (-45.0 – -23.3)	--	N/A
In absence of unmeasured differences between users and non-users of DMPA that could bias the results, the estimate should be null (aHR and aRR=1, % difference= 0)						
6. Last use of DMPA 8+ years ago	61/564	1.1 (0.8 – 1.5)	1351	0.6 (-10.7 – 13.3)	39/182	0.9 (0.7 – 1.3)

* All analyses were conducted with the same model specification and adjustment covariates as in the main analyses.

† N=14 leiomyomas with residuals whose absolute value exceeds 3SD were removed from the model of leiomyoma growth.

Abbreviations: DMPA Depot Medroxyprogesterone Acetate; aRR Adjusted Risk Ratio; aHR adjusted Hazard Ratio; CI Confidence Interval; N/A not estimated for this outcome

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