

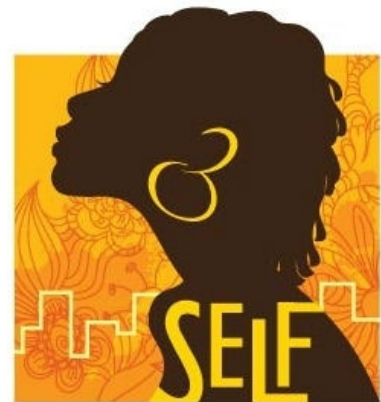


# Epidemiologic contribution to understanding environmental impact on women's health:

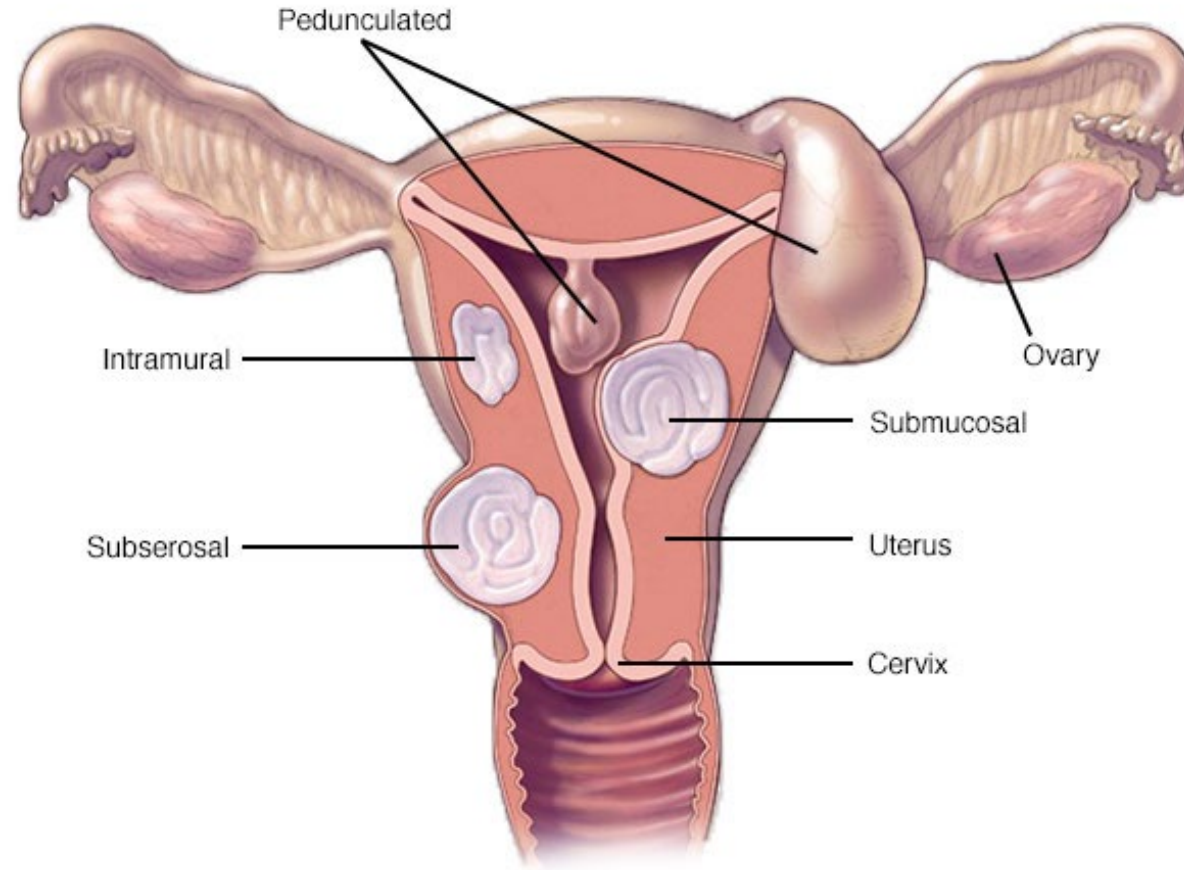
## Study of Environment, Lifestyle & Fibroids (SELF)

**Quaker Harmon, MD, PhD  
Staff Scientist (she, her)**

**National Institute of Environmental Health Sciences**



# Uterine leiomyoma, fibroids

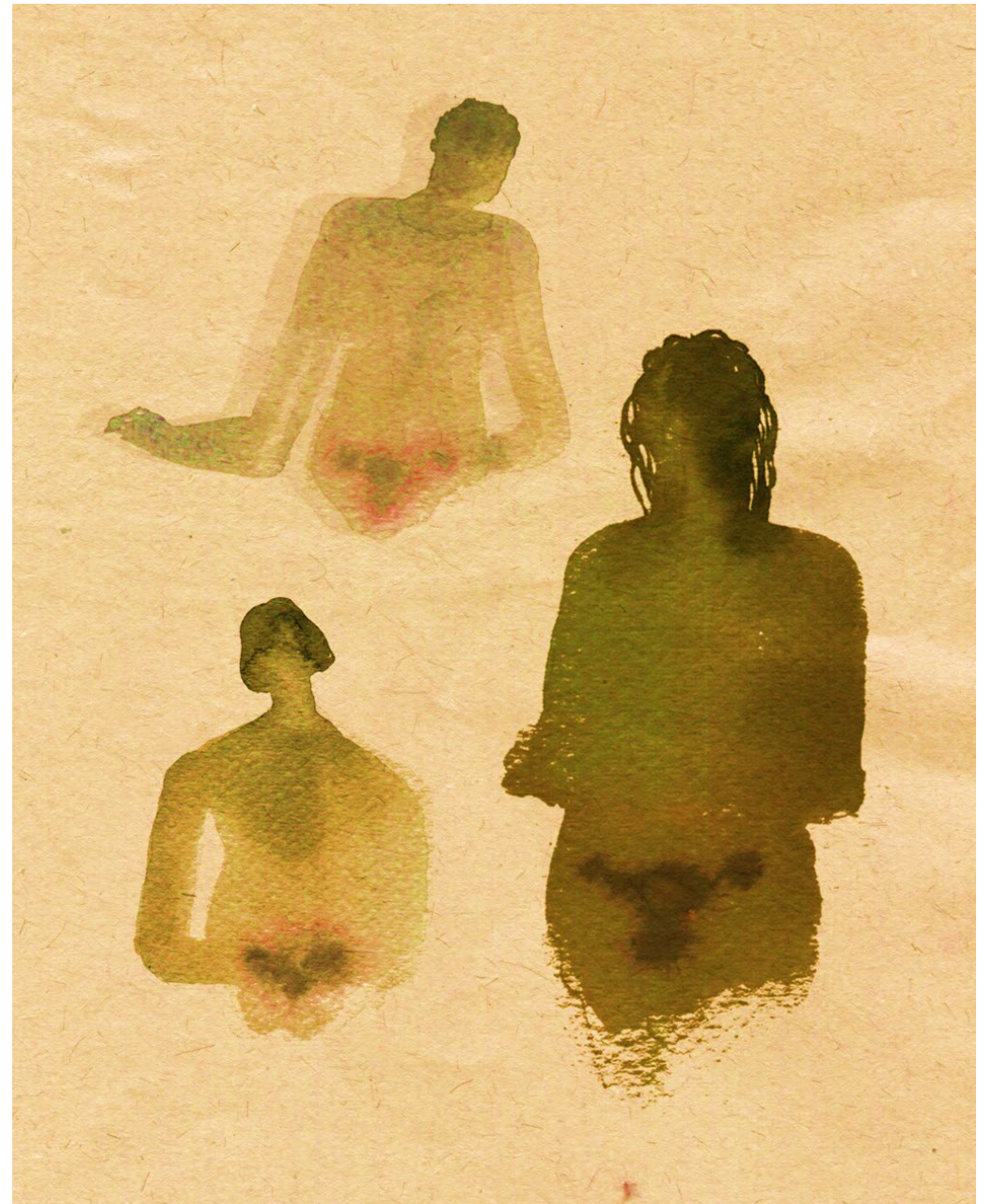


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- Non-cancerous smooth muscle tumors of the uterus

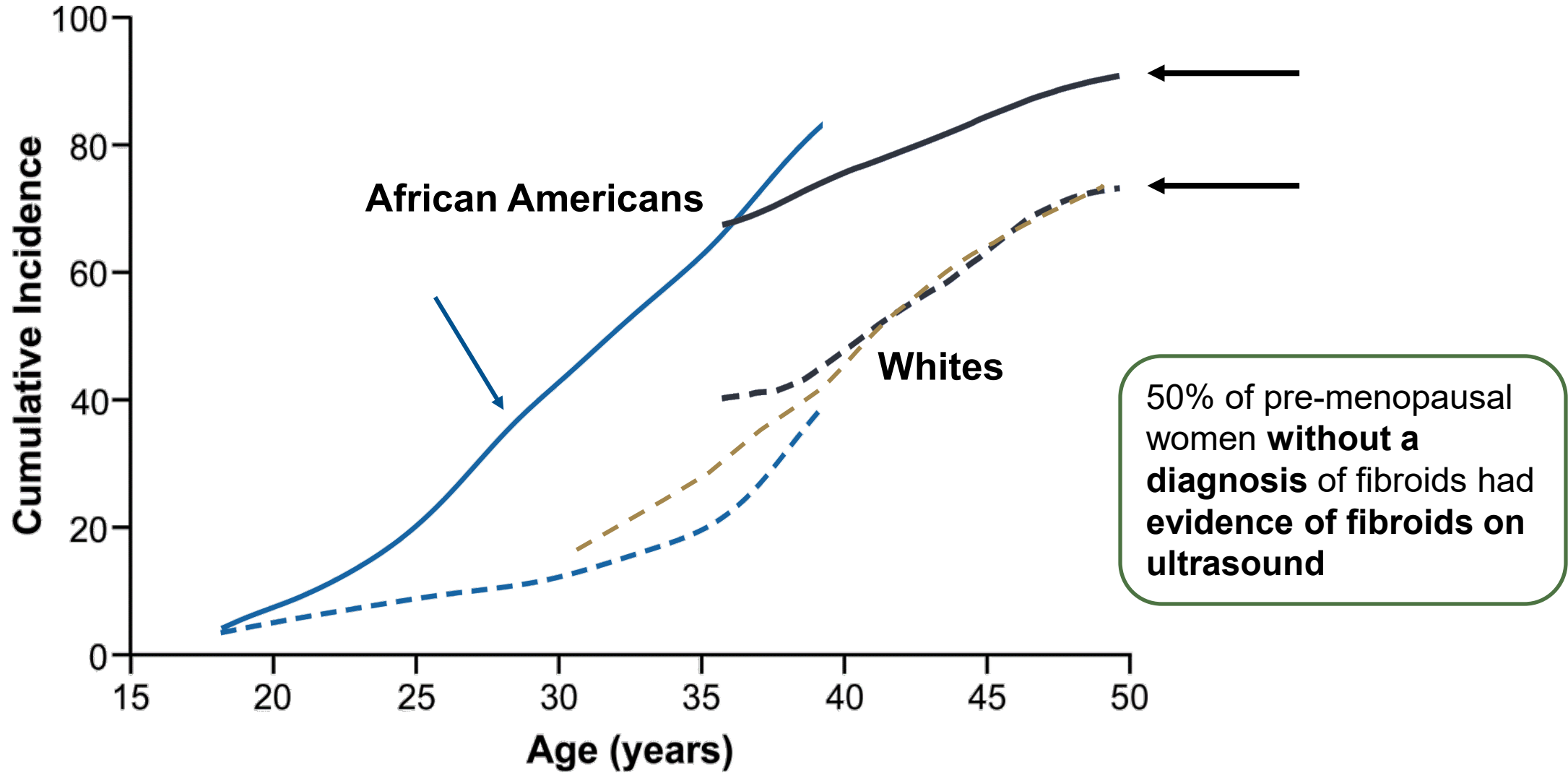
## Symptoms impact all aspects of life

- Symptoms
  - Heavy menstrual bleeding
  - Pain (during menstrual period, pelvic, back, during sex)
  - Abdominal bloating /pressure
  - Bladder and bowel symptoms
  - Fatigue
  - Difficulty getting pregnant or pregnancy complications
- Leading cause of hysterectomy



Chioma Ebinama New York Times April 15, 2020

# Common condition, earlier onset and higher prevalence for Black women



## **Few established risk factors, most non-modifiable**

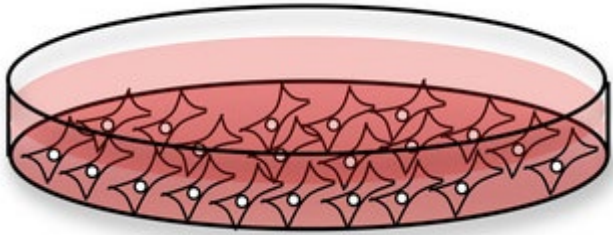
- Age
- Race/ethnicity
- Parity (protective)
- Earlier age at menarche

## **Modifiable risk factors – some supporting data but inconsistent**

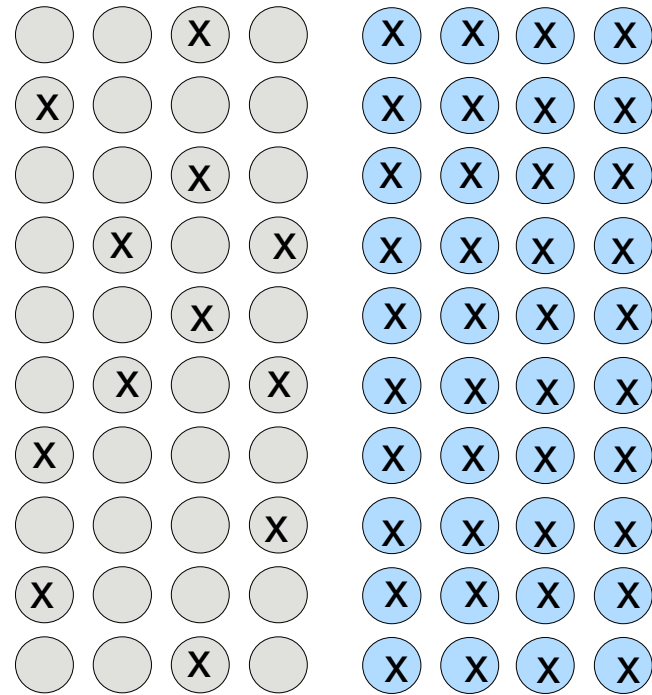
- Physical activity
- Dietary exposures
- Smoking
- Use of Depo-Provera<sup>®</sup> (protective, strong support)

# Common condition, high burden. Why don't we know more?

- Animal and human tissue studies
  - Eker rat model
  - Genetic mutations within fibroid tissue



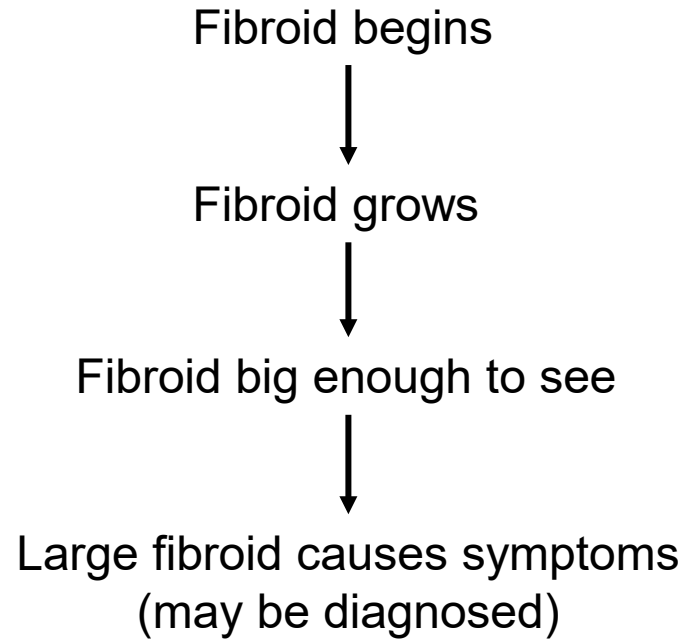
# Human studies



Non-Case  
or  
Controls

Cases

Misclassify non-cases



Too late!

Misclassification of exposure

## Existing human studies

- Do not learn about the early development of fibroids
- Miss exposures that occur before fibroids develop
- May be difficult to find associations that replicate
- **Until we know the natural history, it can be hard to identify important exposures**
- **We need good study designs to identify causes of fibroids**







NC Team,  
Social and Scientific Systems

Detroit Team  
Henry Ford Health



SELF

STUDY OF  
ENVIRONMENT,  
LIFESTYLE & FIBROIDS

- Black or African American women ages 23-35
- Detroit, MI area
- No clinical diagnosis of fibroids



## Visit 1

N=1693

2010–2012

*~18-20 mos.*

## Visit 2

88% response

2012–2015

*~18-20 mos.*

## Visit 3

86% response

2014–2016

*~18-20 mos.*

## Visit 4

91% response

2016–2018

**Every visit**  
 Ultrasound  
 Questionnaires  
 Clinical Measurements  
 Biospecimen



- Use ultrasound to detect new fibroids
- Measure fibroid growth
- Measure exposures before fibroids develop
- Many other important outcomes can be studied



- Natural history of a condition is fundamental → population burden, when and who to screen, know when to treat
- Finding exposures which slow the growth of small fibroids → reduce or delay symptoms and the need for invasive treatments
- Identifying exposures which increase the risk of new fibroids or increase the growth of small fibroids → opportunity to avoid or reduce exposure, prioritize screening

# Environmental exposures and natural history

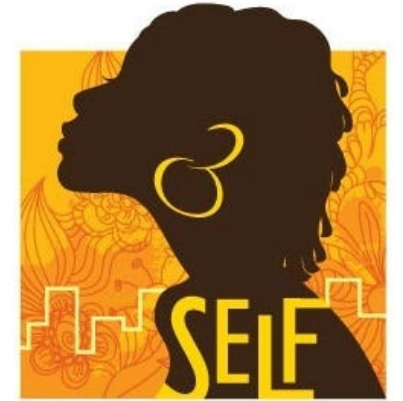
- Depo Provera



- Infant soy formula



- Natural history and impact of birth



STUDY OF ENVIRONMENT,  
LIFESTYLE & FIBROIDS

# Demographics at baseline among 1610 participants with at least one follow-up visit



Mean age 29 Y (SD 3.4)



45% household income <\$20,000



78% have at least some college education

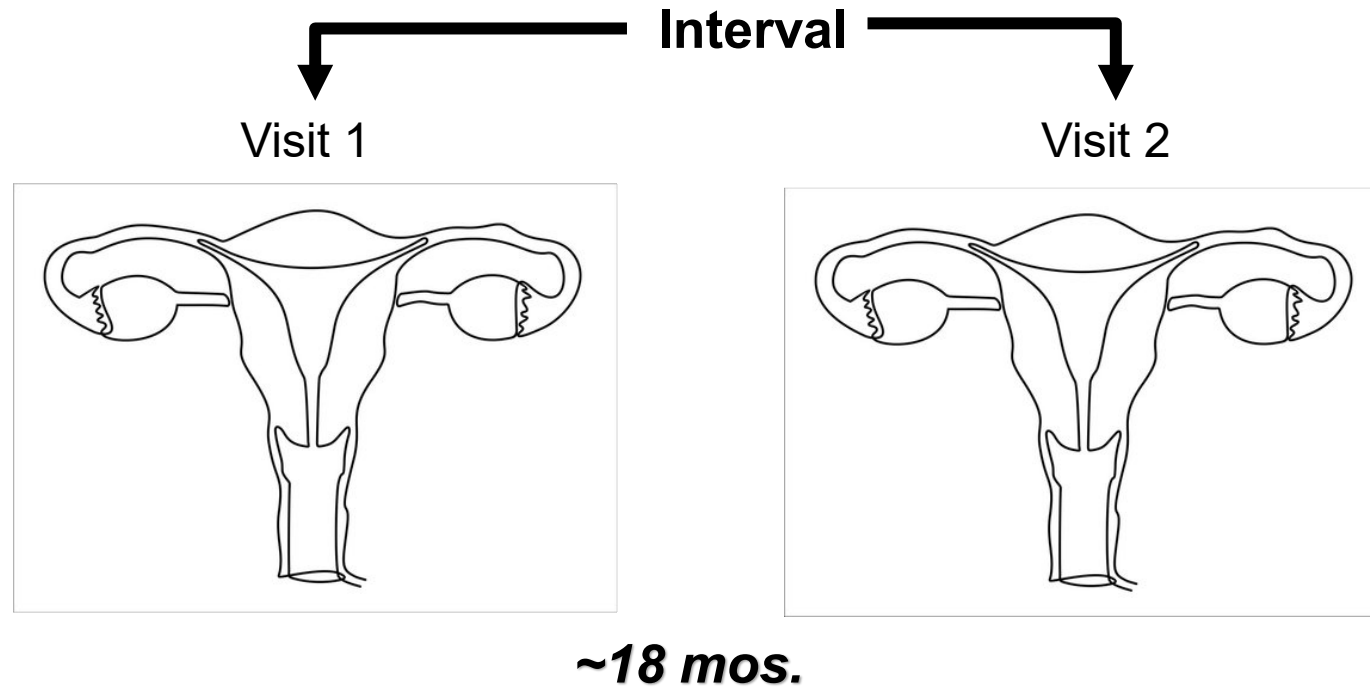


60% have had a birth



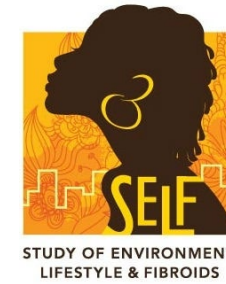
60% employed

## Outcome overview



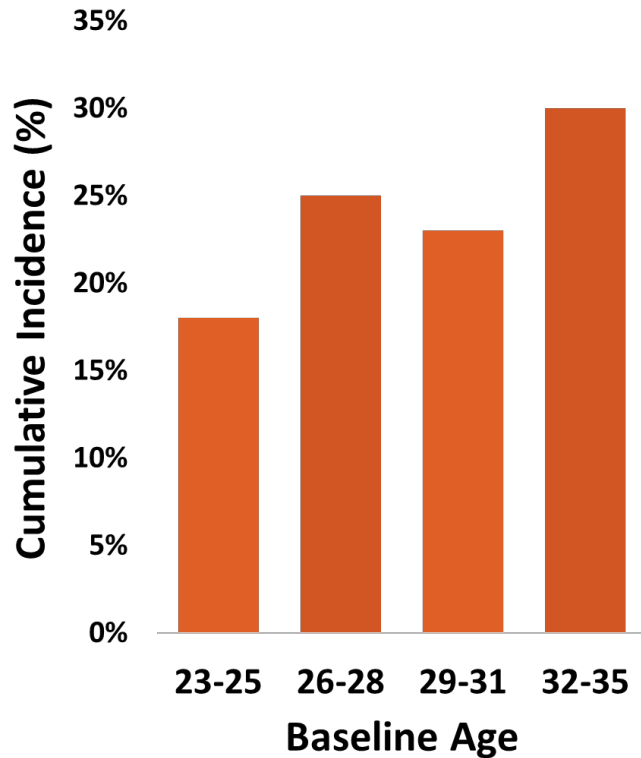
- Outcome based on comparison of consecutive ultrasounds
- Fibroid incidence (new fibroids)
- Fibroid growth

# Fibroid incidence and growth by age



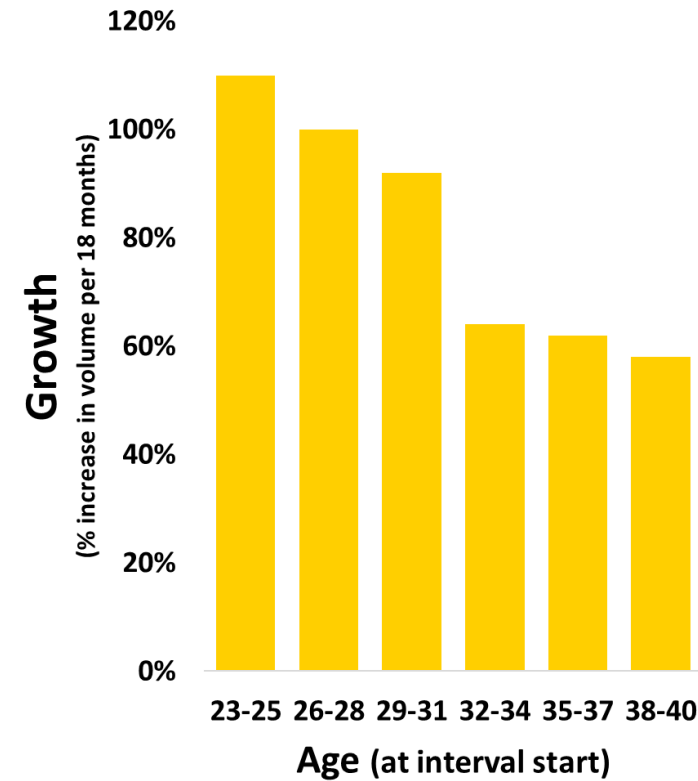
Dr. Donna Baird

## Cumulative incidence by baseline age



↑ incidence with age

## Growth rate by age



Growth rates ↓ with age



# Depo medroxyprogesterone acetate (DMPA) and fibroids

- An injectable progestin-only contraceptive

Depo-Provera®



## Studies of EVER vs. NEVER use of DMPA and fibroids

Study	Estimated RR (95% CI)
Lumbiganon (1985)	0.4 (0.3-0.5)
Wise (2004)	0.6 (0.4-0.9)
Harmon (2014)	0.7 (0.6, 0.9)

Cross-sectional OR clinical diagnosis

# Use of depo medroxyprogesterone acetate (DMPA)

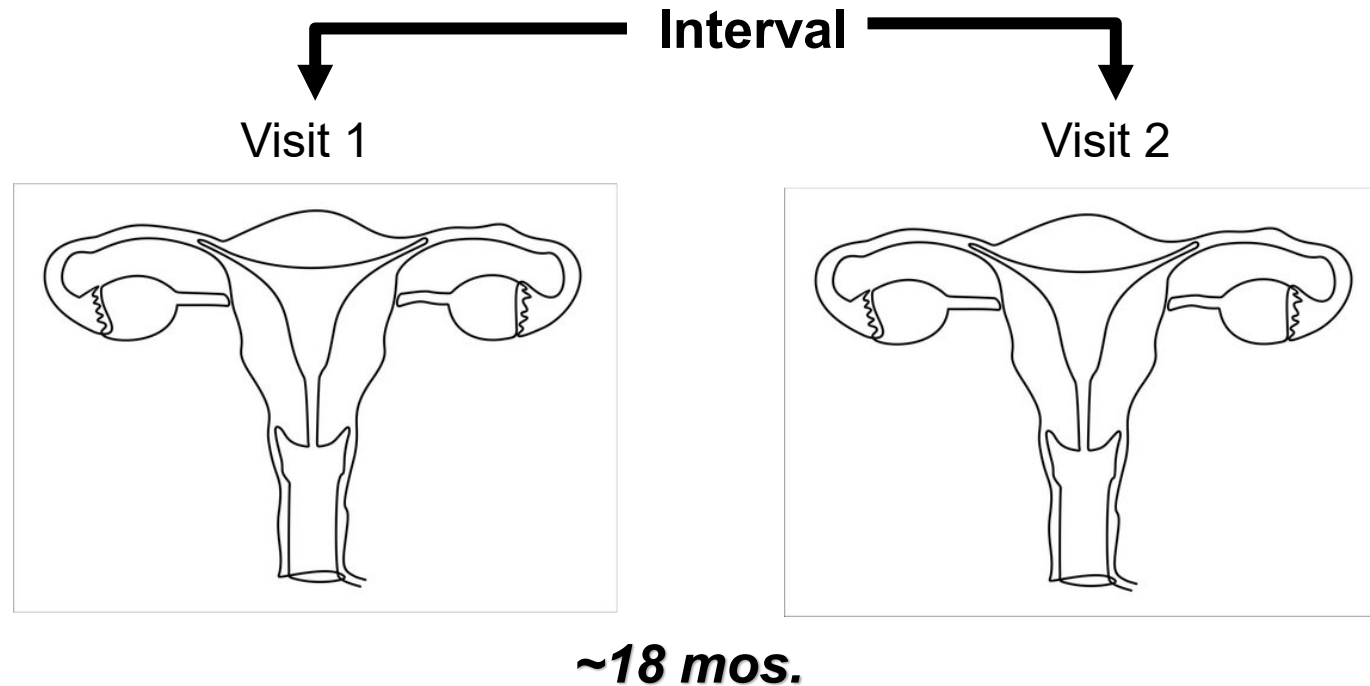
Years since last use

Use questionnaire data to  
calculate the number of years  
since last use of DMPA



**40% ever used DMPA**

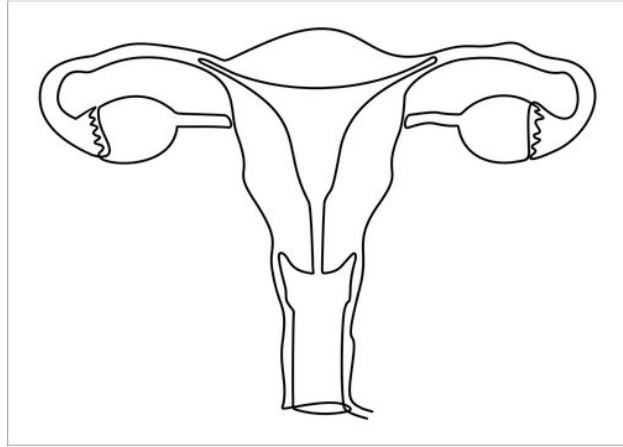
## Statistical analysis, overview



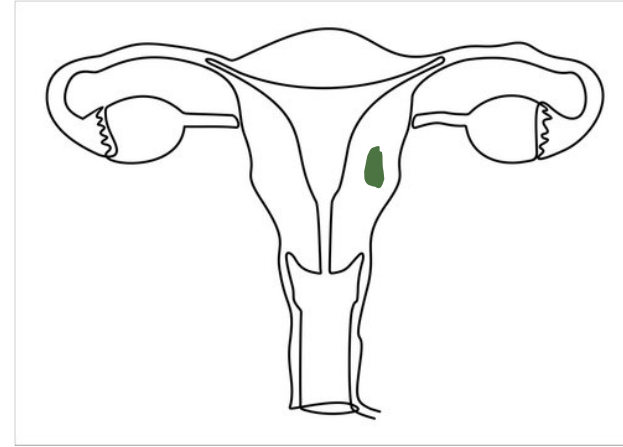
- Up to 3 intervals for each participant
- Separate model for fibroid incidence and fibroid growth
- Account for repeated measures by participant and fibroid
- Censor following interventions to treat fibroids

# Fibroid Incidence, N=1232 participants

Visit 1



Visit 2



**Eligible**

No prior fibroid

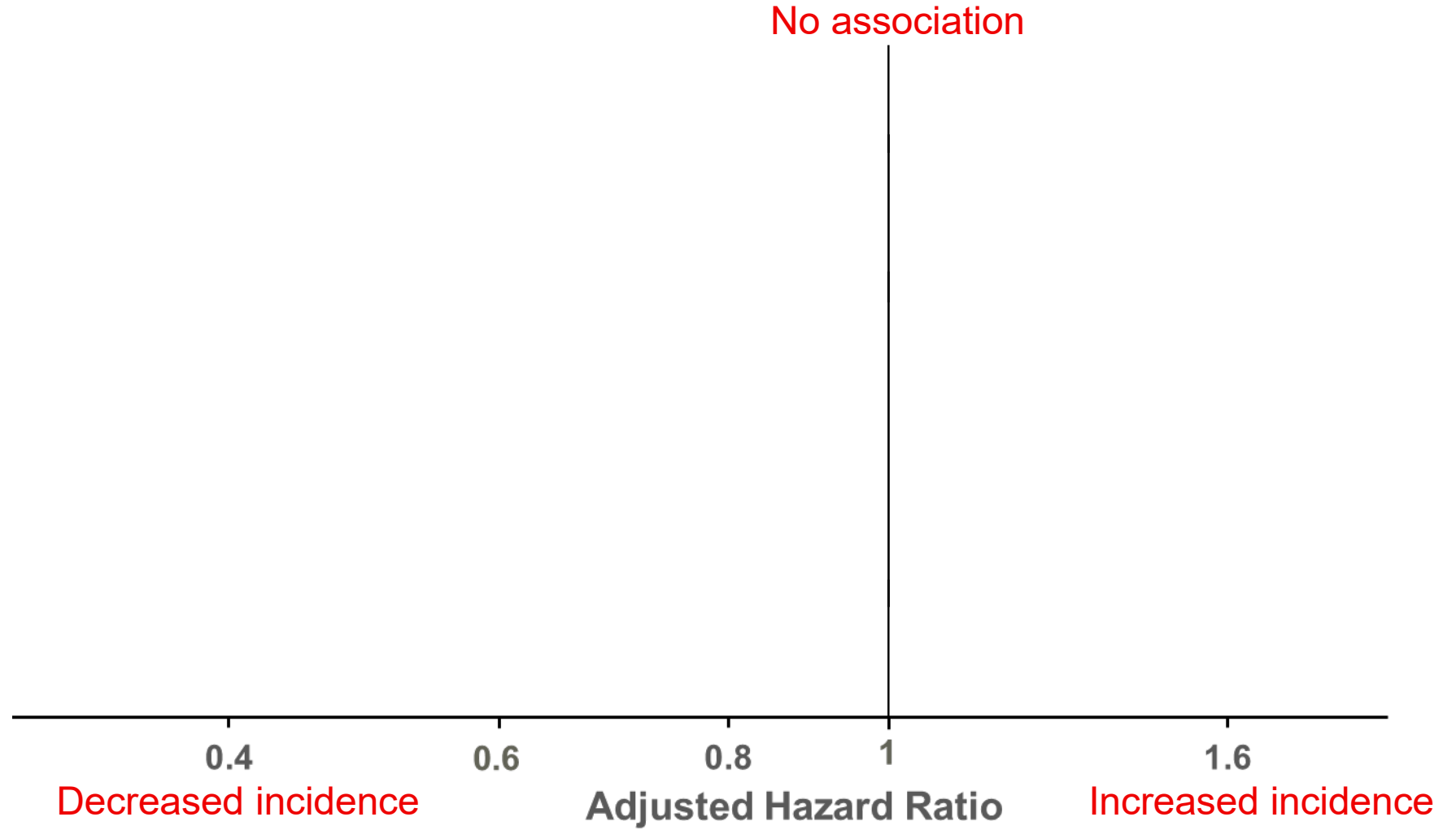
**Outcome**

New fibroid case

**Model**

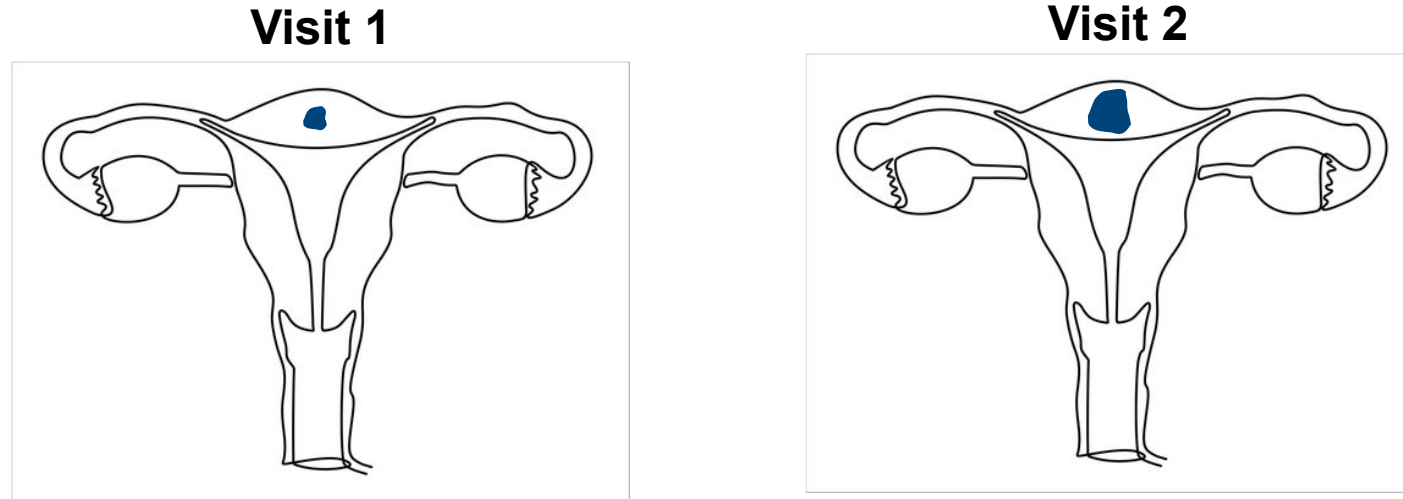
Cox Model with age as the time scale

# DMPA associated with reduced fibroid incidence



Adjusted for time since last birth, parity, BMI, smoking, income

# Fibroid Growth, N=1359 fibroid matches from 433 participants



**Eligible**

Fibroids matched on position

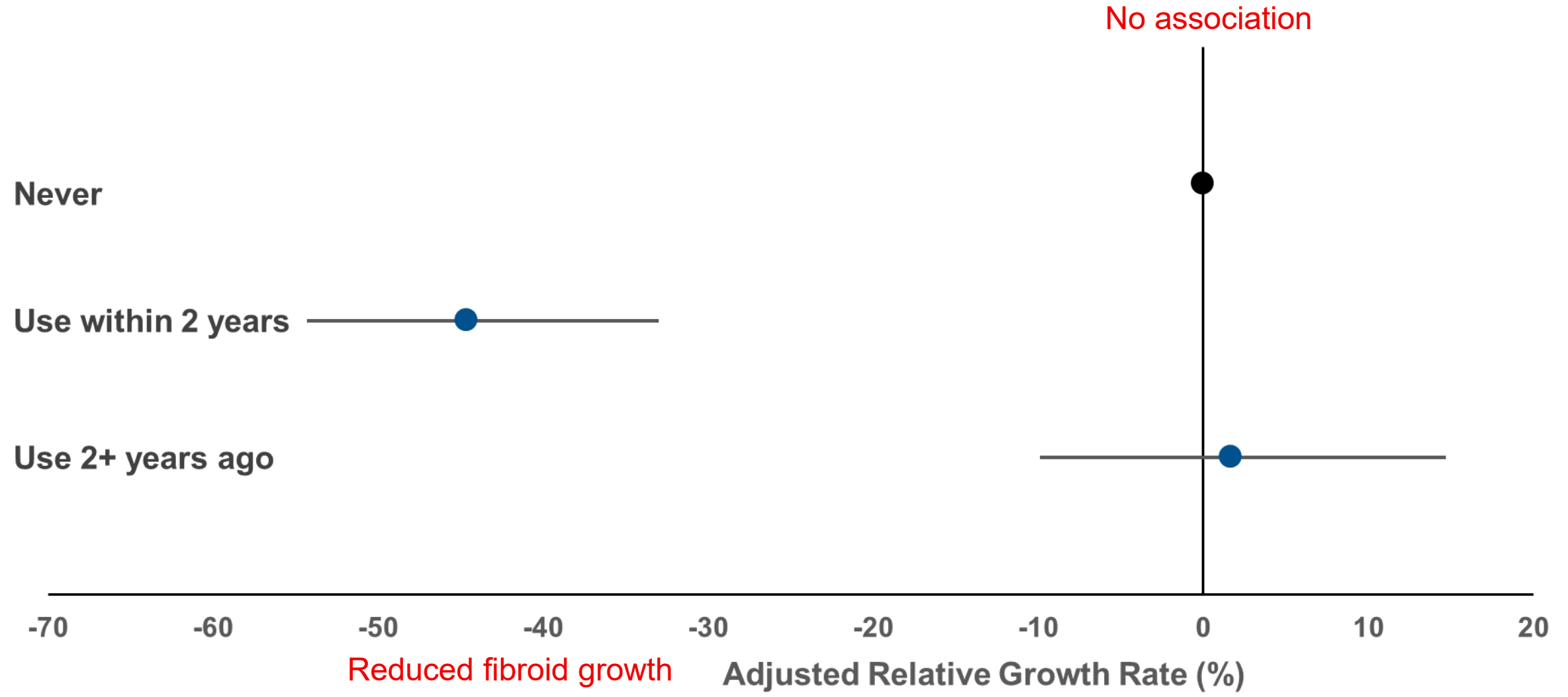
**Outcome**

Change in log volume scaled to 18 months

**Model**

Linear mixed model (fibroid level data)

# DMPA associated with reduction in fibroid growth over 18-months



Adjusted for age, time since last birth, number of fibroids, fibroid volume, employment, use of oral contraception, age at menarche

## Summary

Exposure to DMPA within 2 years:



**Incidence:** 40% reduction in fibroid incidence



**Growth:** 45% lower growth



**Loss:** 70% higher loss

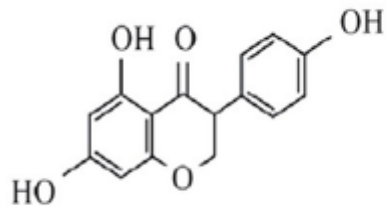
Important non-contraceptive benefit, needs to be studied in larger populations  
Potential to delay symptoms in those with small fibroids



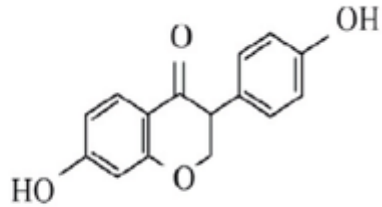
# Soy has phytoestrogens



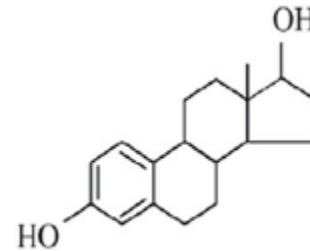
Dr. Christine Langton



Genistein



Daidzein



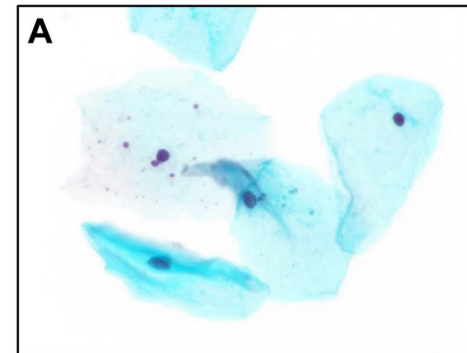
17-beta-estradiol

- Isoflavones act as endocrine disruptor
- Postnatal treatment to lab animals
  - alters rodent reproductive tract including uterus
  - increased fibroid development in Eker rats
- Exposure during sensitive developmental windows detrimental effects on reproductive systems



# Soy-based infant formula

- Consumed by 12% of U.S. infants
- Contains high levels of phytoestrogens
- Linked to reproductive conditions
  - early/late menarche, menstrual irregularities, endometriosis
- Proliferative vaginal tissue in soy-fed infants



# Soy formula assessment

- Participants interviewed their mother when possible (89%)
- Answers from relatives/family friends present during infancy (11%)

35. Was I ever fed soy formula?

Yes

No

36. About how many months was I fed soy formula?

Less than 1 month

1 to 3 months

4 to 6 months

More than 6 months

37. Did you start giving me soy formula within the first 2 months of my life?

Yes

No

GO TO QUESTION 38

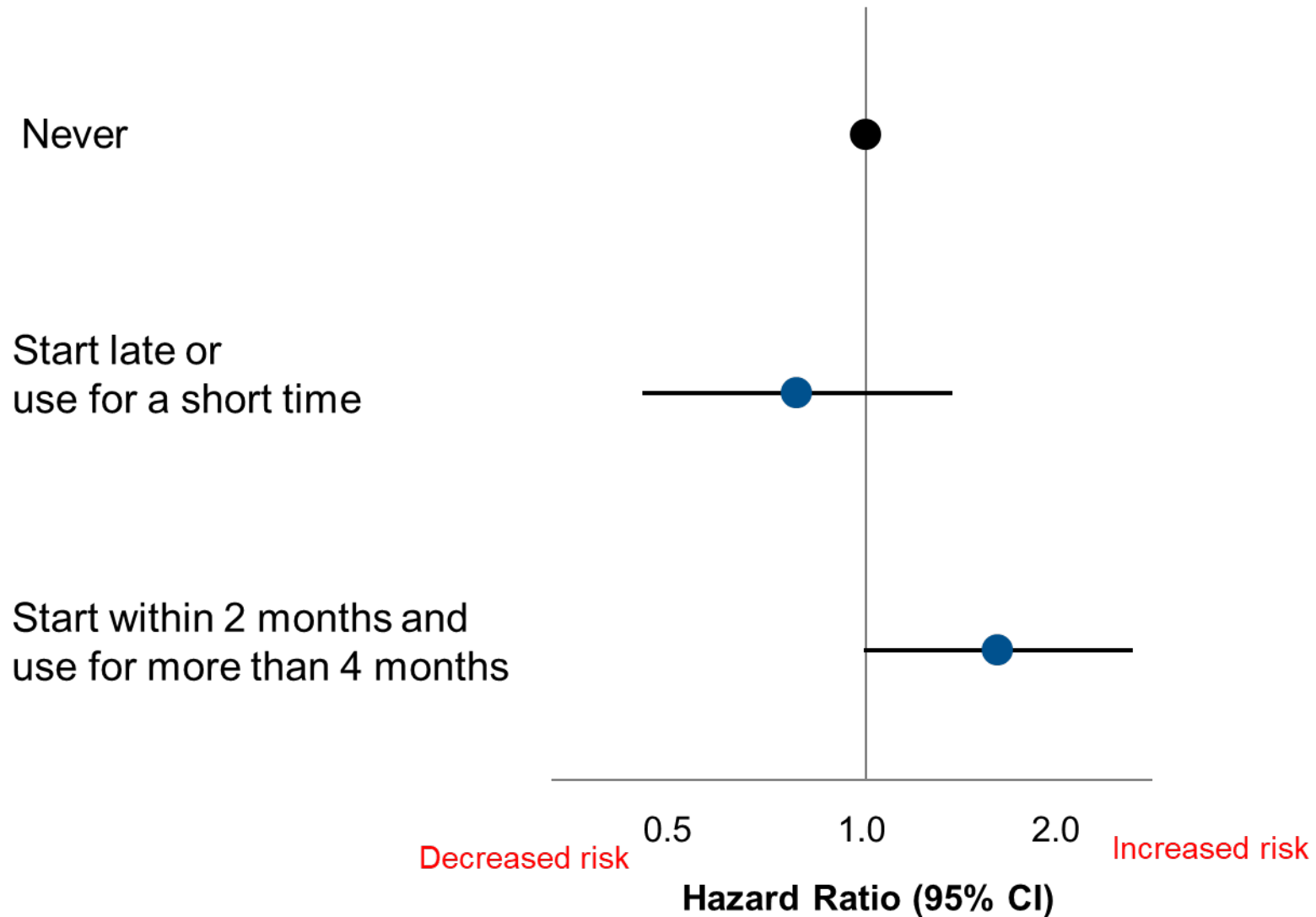
Composite Variable

Within 2 months &  $\geq 4$  months



More exposed

# Increased risk of incident fibroids with soy formula feeding



Adjusted for age (timescale), maternal pre-pregnancy diabetes/GDM, maternal HDP, mother's age at birth, mother's educational attainment, birth weight, time since last contraceptive injection, parity, time since last birth, smoking, BMI, and household income.

## Summary

- **Increased risk** of ultrasound-identified incident fibroids in adulthood for those fed soy formula **soon after birth and for a longer duration**
- Consistent with prior animal and human studies
- Examine fibroids and other outcomes in larger populations



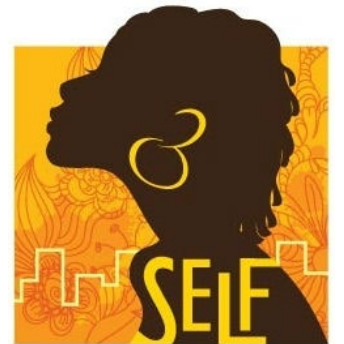
# Association between birth and fibroid growth

- Consistent observational data and animal studies showing that those with a birth are less likely to have fibroids



- Fibroid growth

- Birth within 5 years reduces fibroid growth by 30% [95% CI (-35%, -9%)]
- Stronger effects if also breastfeed for 6+ months



STUDY OF ENVIRONMENT,  
LIFESTYLE & FIBROIDS



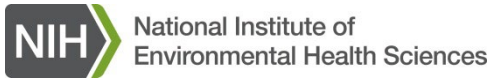
- Personal care products
- Sleep quality
- Early-life adversity
- Measured metals, endocrine disrupting compounds
- Inflammation
- Spatial and temporal exposures
- PCOS and hirsutism
- Body mass index
- Menstrual cycle characteristics
- Anti-Müllerian hormone
- Birth outcomes
- COVID experiences
- Infertility
- Vitamin D



## Summary & next steps

- SELF advances the science
- Highly engaged cohort and collaborative science a model for these types of studies
- Starting to use geocoding to capture neighborhood factors, toxic contamination sites, air quality
- Findings need to be replicated in other populations with high-quality study designs
- Life-course disease will require long-term investment





# Collaborators and Funding

American Recovery and Reinvestment Act

## Current and Recent Trainees



Dr. Christine Langton



Dr. Kristen Moore



Dr. Kristen Upson  
Michigan State



Dr. Ky'Era Actkins



Sherice Simpson



Dr. Helen Chin  
George Mason



Dr. Anne Marie Jukic



Dr. Chandra Jackson



Dr. Symielle Gaston



Dr. Kyla Taylor

## Extramural Collaborators



Dr. Erica Marsh



Dr. Lauren Wise



Dr. Ganesa Wegienka



Dr. Anissa Vines

## NICHD Collaborators



Dr. Shyamal Peddada

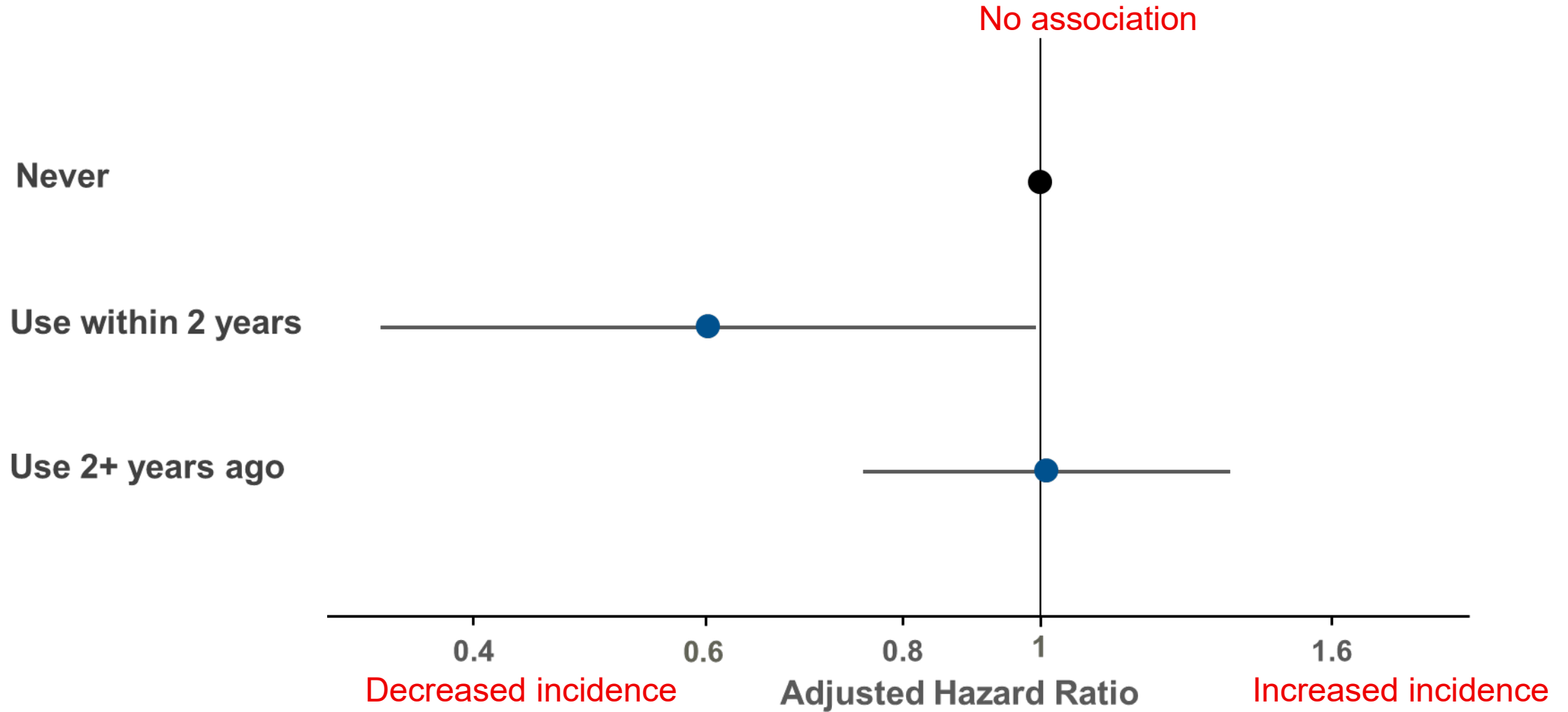


Dr. Fasil Tekola Ayele



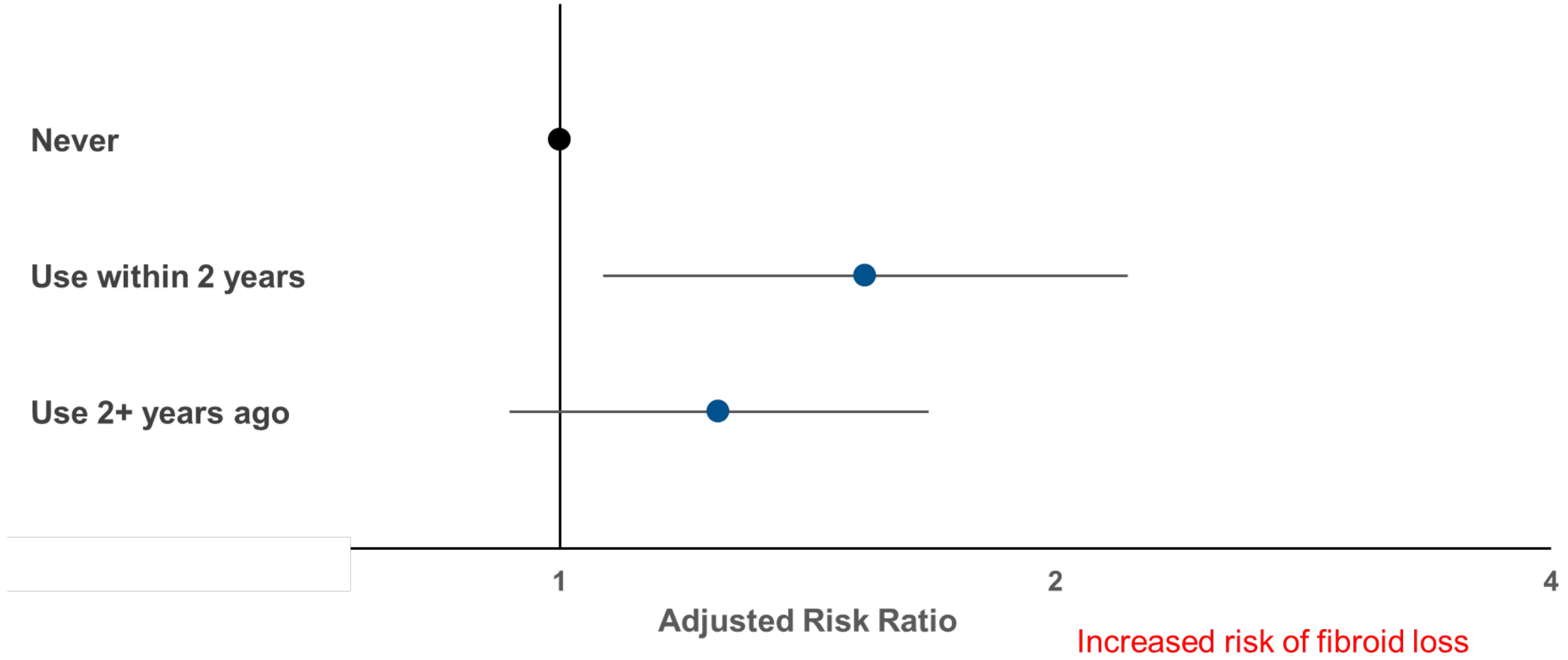
# Additional slides

# DMPA associated with reduced fibroid incidence



Adjusted for time since last birth, parity, BMI, smoking, income

# DMPA associated with increased fibroid loss



Adjusted for age, time since last birth, months between visits, number of fibroids, fibroid volume, BMI, education