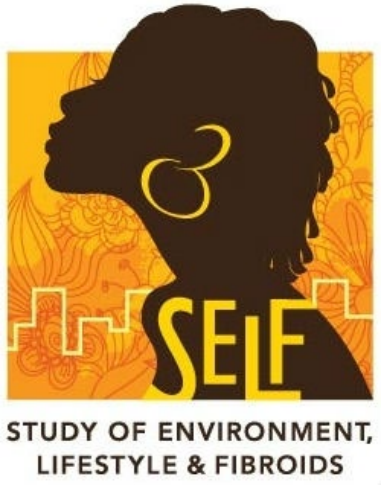
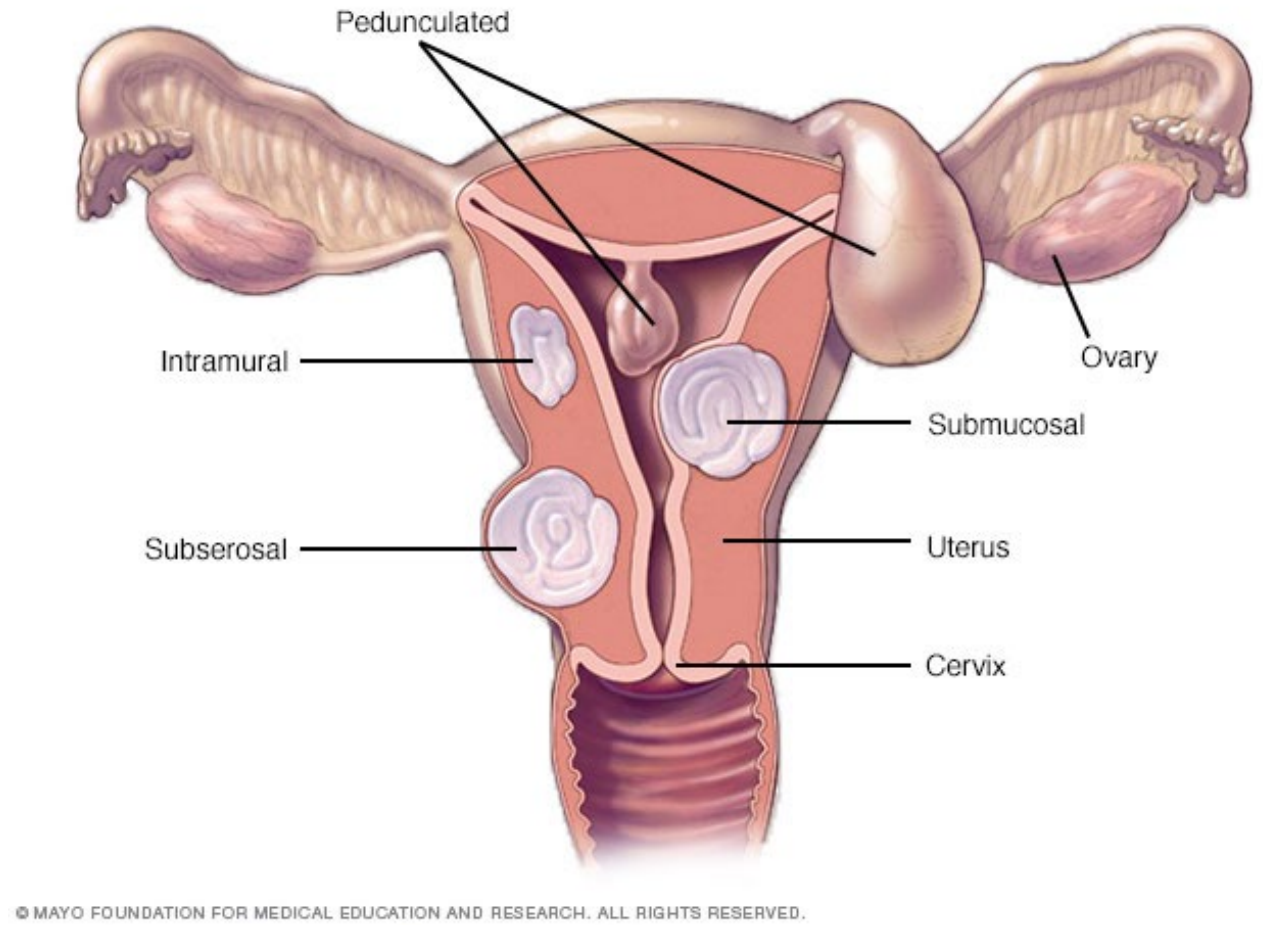
Epidemiologic contribution to understanding environmental impact on women's health:

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

Source: Mayo Foundation for Medical Education and Research http://www.mayoclinic.org/diseases-conditions/uterine-fibroids/home/ovc-20212509

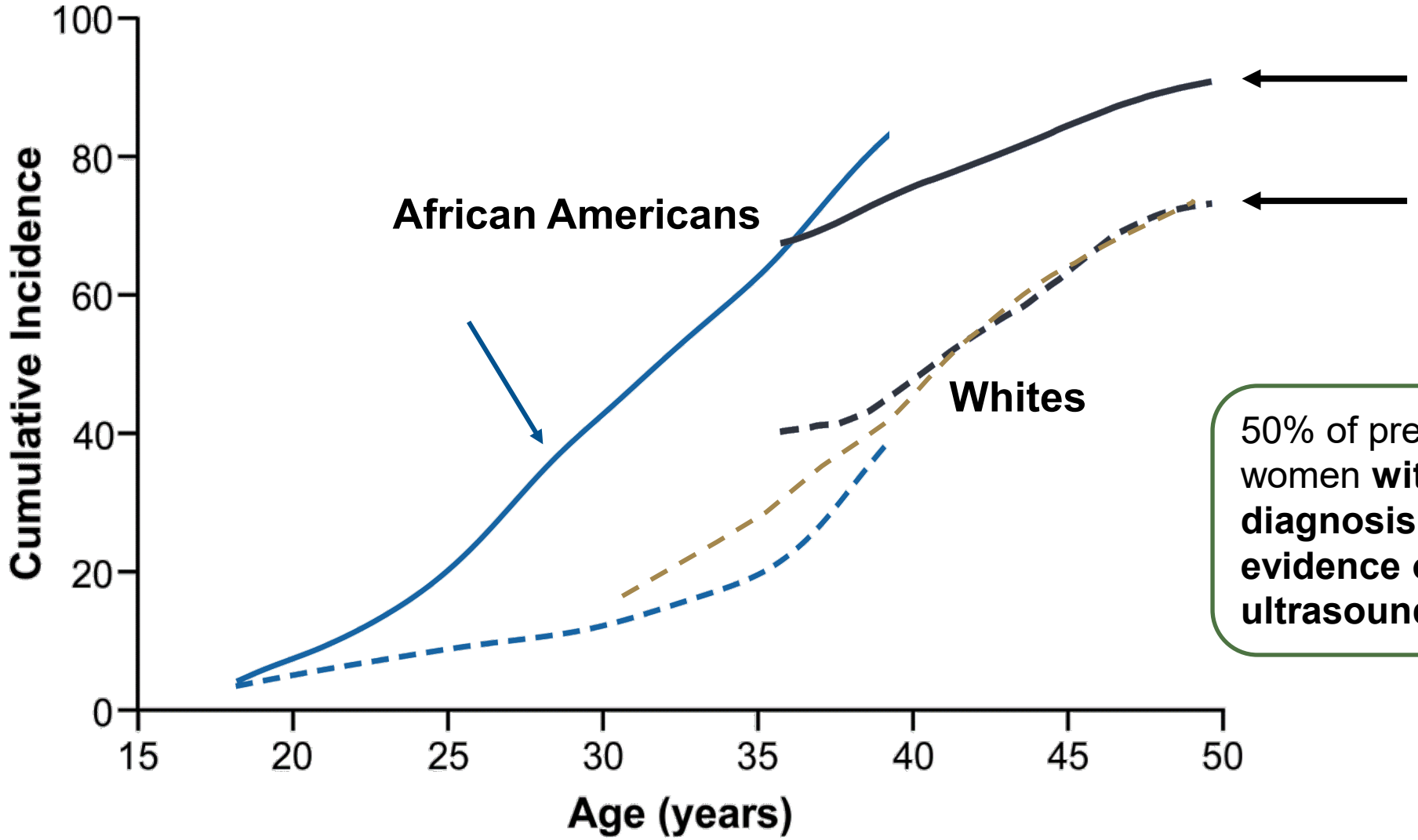
Symptoms impact all aspects of life

- 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



50% of pre-menopausal women **without a diagnosis** of fibroids had **evidence of fibroids on ultrasound**

Laughlin, Baird 2009; Eskenazi 2007; Baird, Dunson 2003

Few established risk factors, most non-modifiable

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

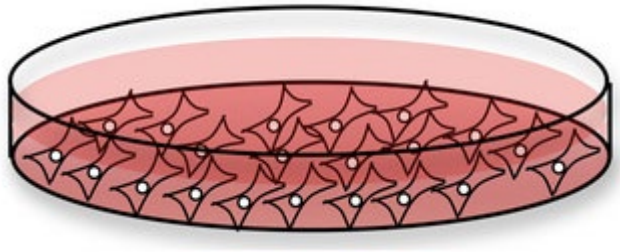
Modifiable risk factors – some supporting data but inconsistent

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

Wise, Laughlin-Tommaso, 2016

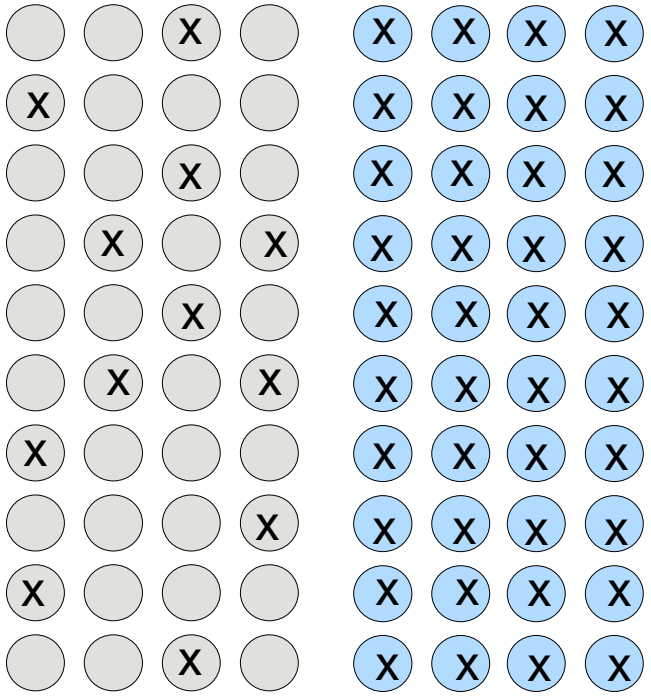
Common condition, high burden. Why don't we know more?

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



Newbold RR 1995, 2002; Flake GP 2003, 2018; Dixon D 2002, 2022, Mehine 2014

Human studies



Non-Case or Controls

Cases

Misclassify non-cases

Fibroid begins

↓

Fibroid grows

↓

Fibroid big enough to see

↓

Large fibroid causes symptoms (may be diagnosed)

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

SELF - Study Design

Visit 1	Visit 2	Visit 3	Visit 4
N=1693	88% response	86% response	91% response
2010–2012	2012–2015	2014–2016	2016–2018
	~18-20 mos.	*~18-20 mos.*	*~18-20 mos.*

Every visit

Ultrasound
Questionnaires
Clinical Measurements
Biospecimen

What can we do?

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

Why does it matter?

- 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

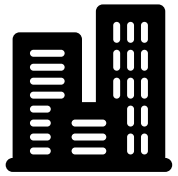
Demographics at baseline among 1610 participants with at least one follow-up visit

Mean age 29 Y (SD 3.4)

45% household income <$20,000

78% have at least some college education

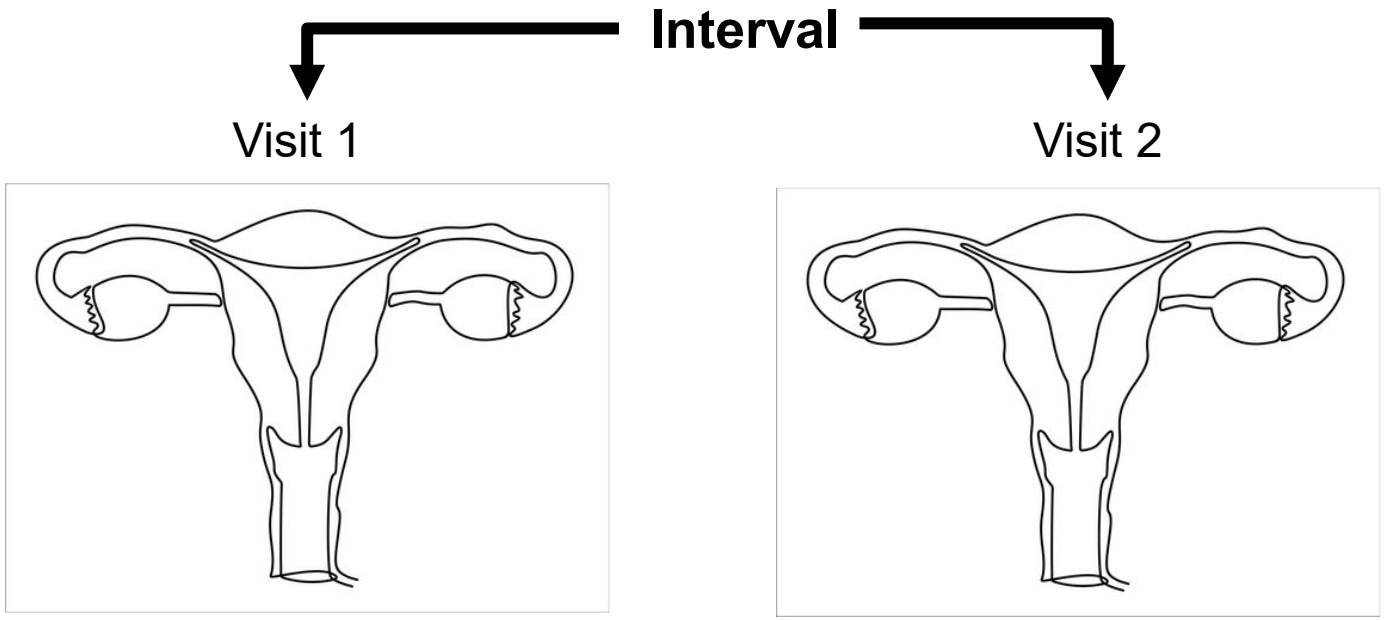
60% have had a birth



60% employed

Icons from the Noun project: SBTS, Imran Shaikh, Ralf Schmitzer, David Khai

Outcome overview



~18 mos.

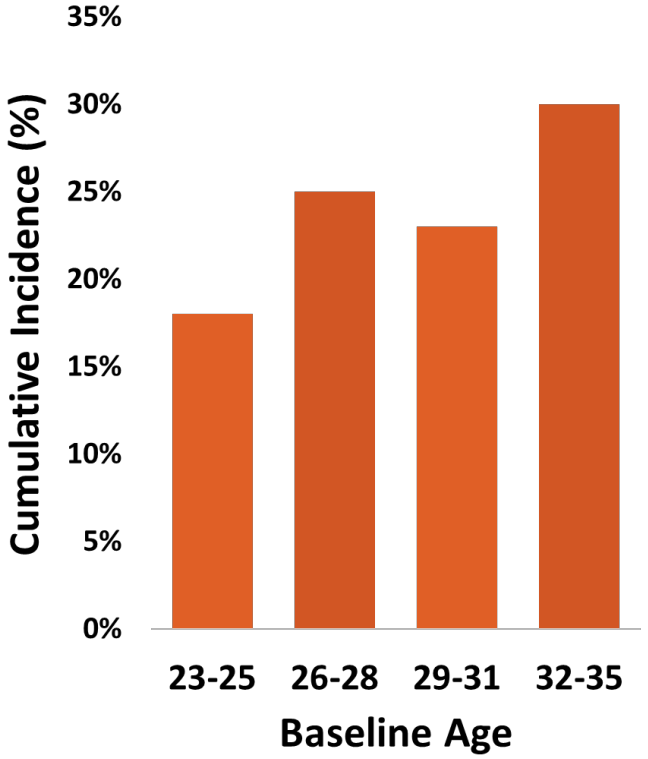
- Outcome based on comparison of consecutive ultrasounds

- Fibroid incidence (new fibroids)
- Fibroid growth

Fibroid incidence and growth by age

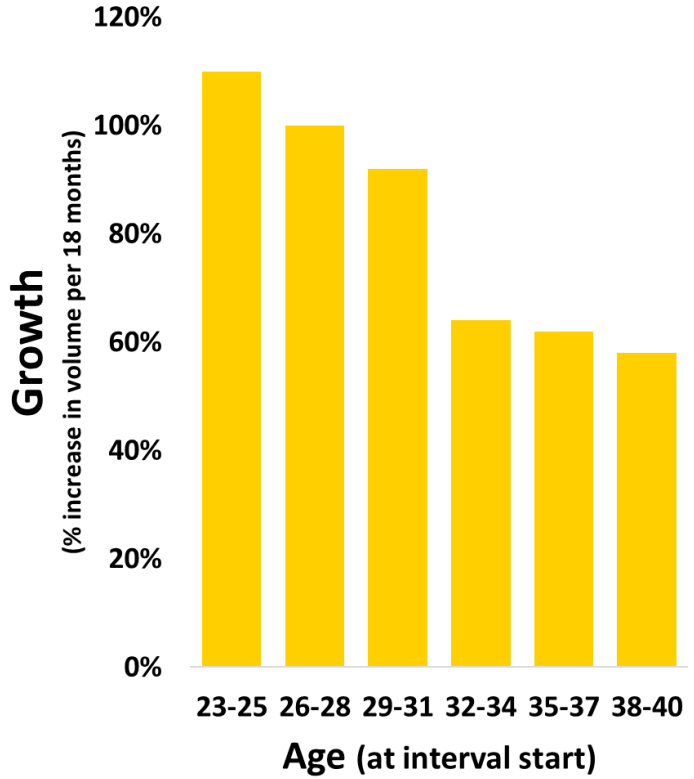
Dr. Donna Baird

Cumulative incidence by baseline age



↑ incidence with age

Growth rate by age



Growth rates ↓ with age

Baird 2020; Wegienka 2022

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)
Lumbiaganon (1985)	0.4 (0.3-0.5)
Wise (2004)	0.6 (0.4-0.9)
Harmon (2014)	0.7 (0.6, 0.9)

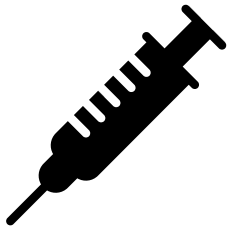
Cross-sectional OR clinical diagnosis

Lumbiganon P, 1996; Wise LA, 2004; Harmon QE, 2015.

Use of depo medroxyprogesterone acetate (DMPA)

Years since last use

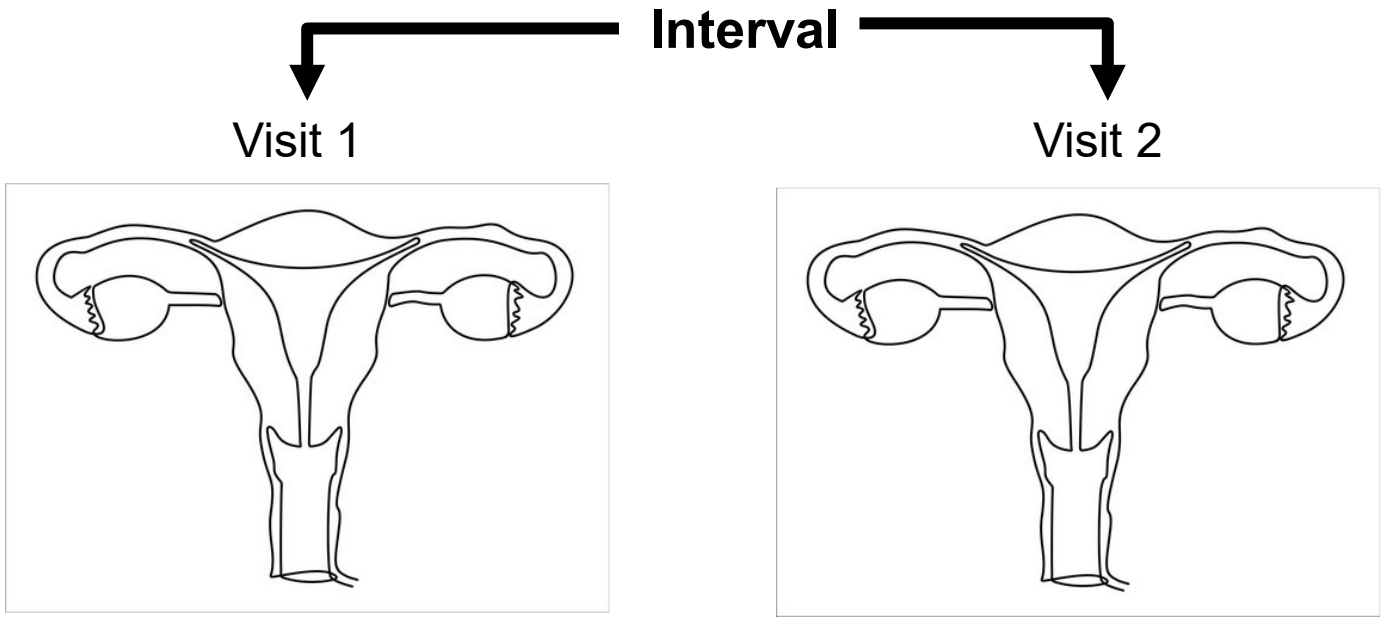
Use questionnaire data to calculate the number of years since last use of DMPA



40% ever used DMPA

Icon from the Noun Project David Khai

Statistical analysis, overview



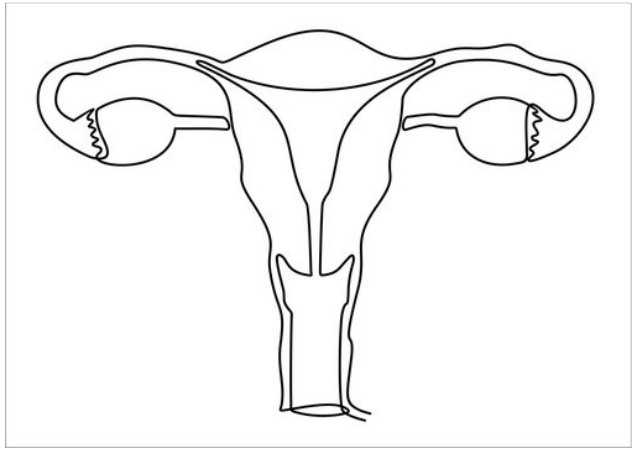
~18 mos.

- Up to 3 intervals for each participant

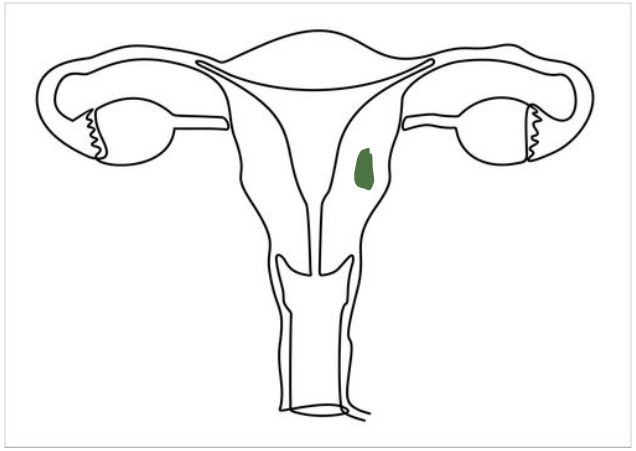
- Separate model for fibroid incidence and fibroid growth
- Account for repeated measures by participant and fibroid
- Censor following interventions to treat fibroids

Fibroid Incidence, N=1232 participants

Visit 1



Visit 2

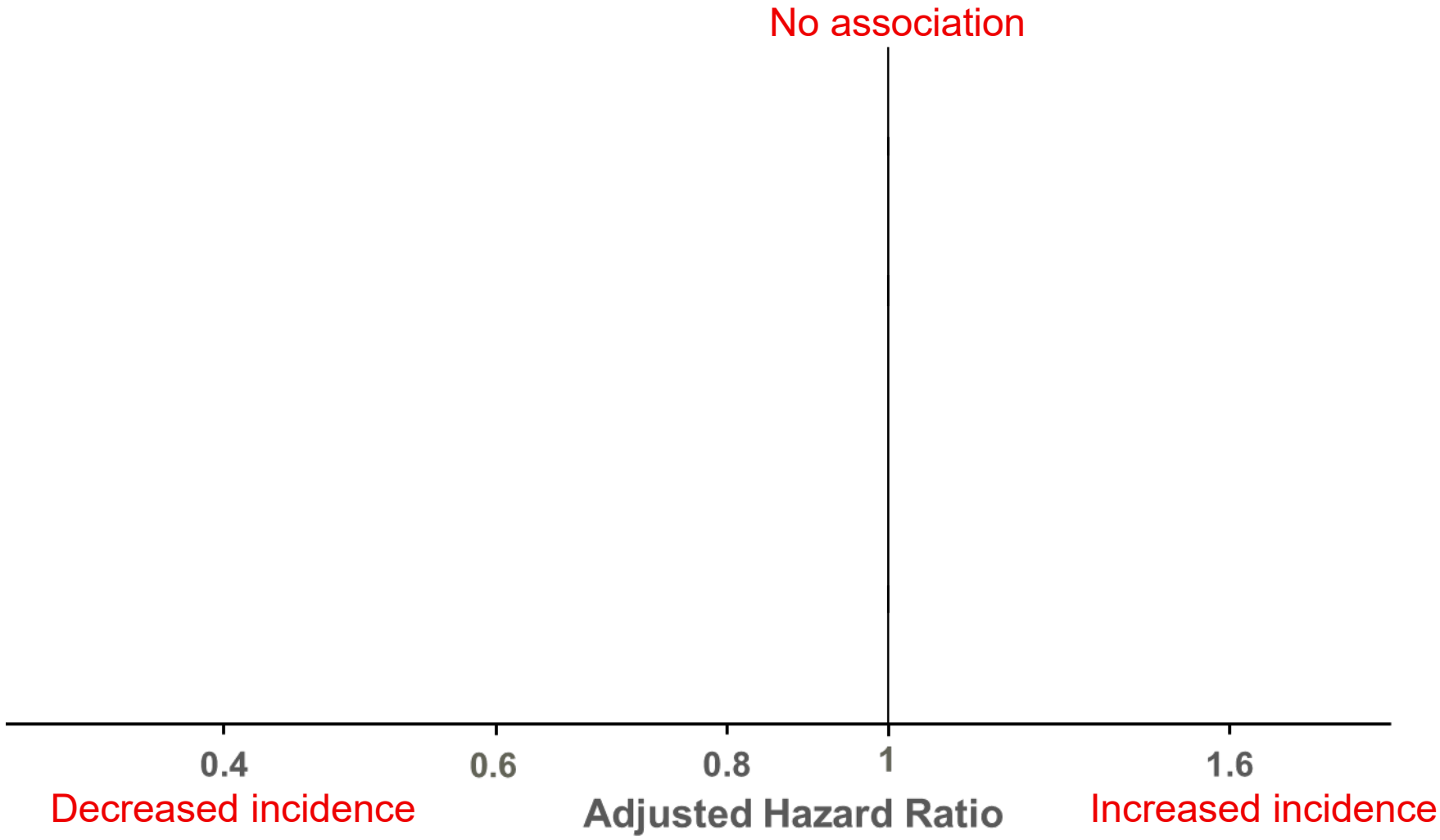


Eligible — No prior fibroid

Outcome — New fibroid case

Model — Cox Model with age as the time scale

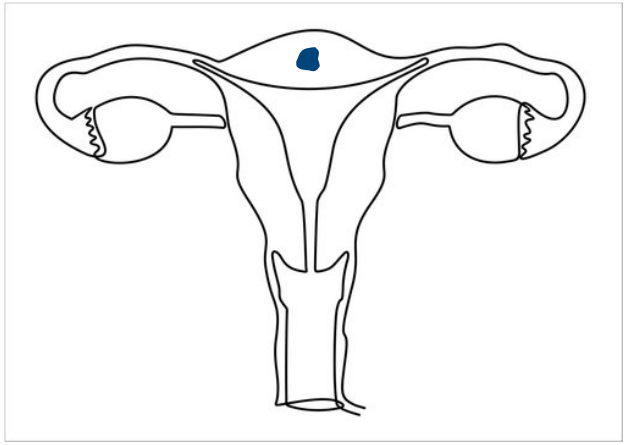
DMPA associated with reduced fibroid incidence



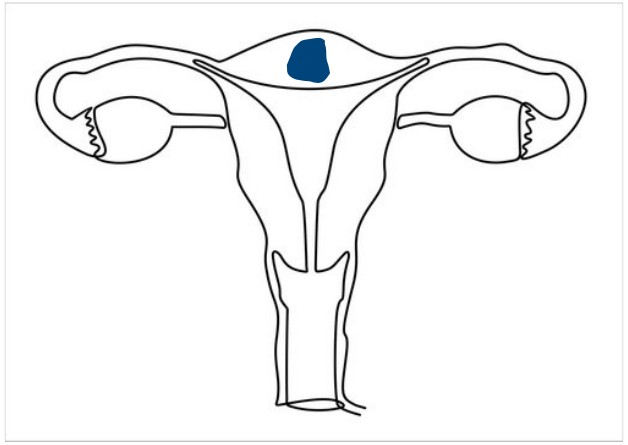
Adjusted for time since last birth, parity, BMI, smoking, income

Fibroid Growth, N=1359 fibroid matches from 433 participants

Visit 1



Visit 2

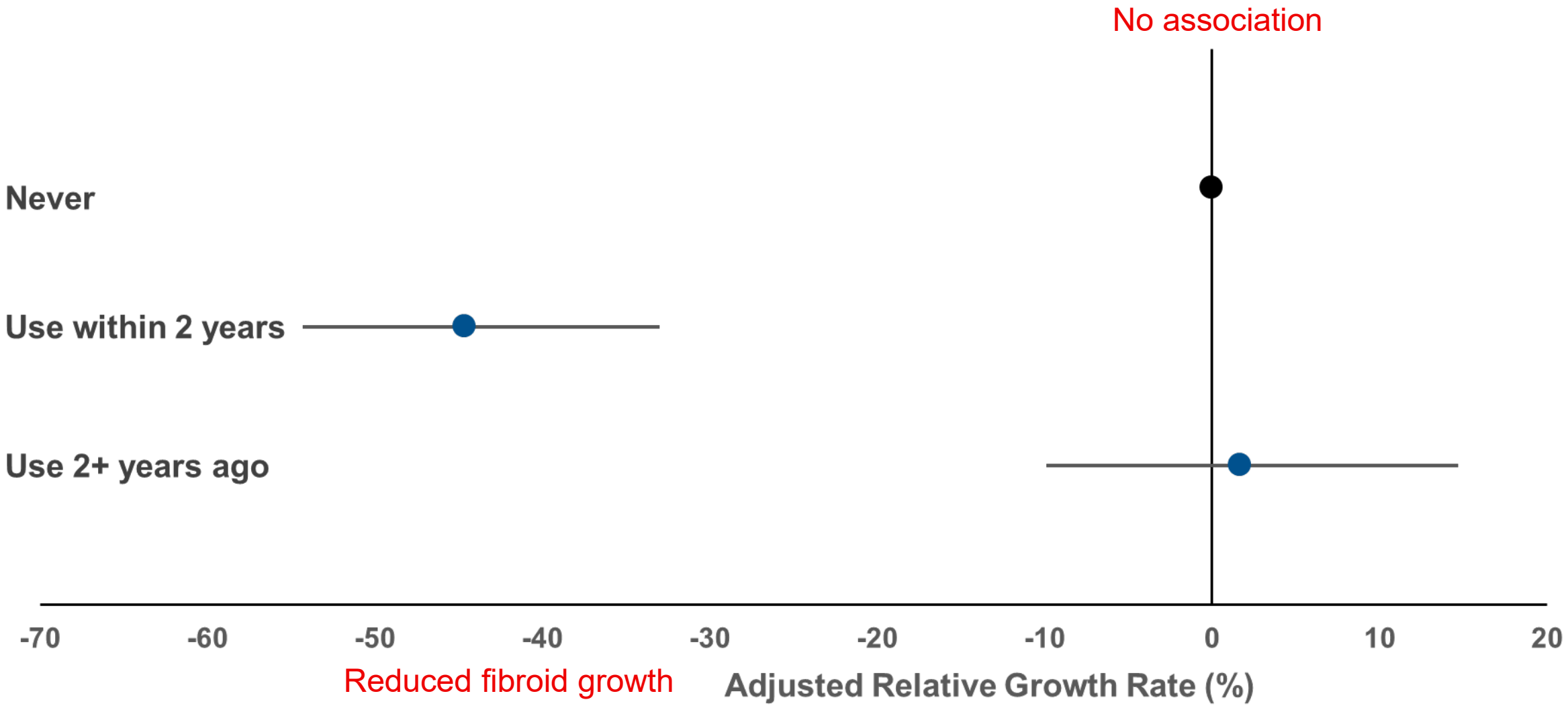


Eligible — Fibroids matched on position

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

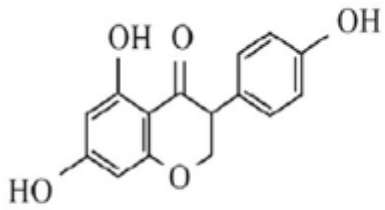
Exposure to DMPA within 2 years:

- ↓ **Incidence**: 40% reduction in fibroid incidence
- ↓ **Growth**: 45% lower growth
- ↑ **Loss**: 70% higher loss

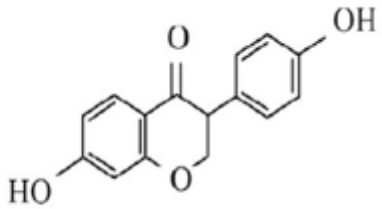
Important non-contraceptive benefit, needs to be studied in larger populations
Potential to delay symptoms in those with small fibroids

Harmon QE, OBGYN 2022

Soy has phytoestrogens



Genistein



Daidzein

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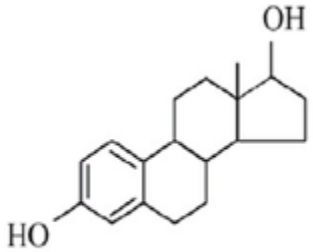


17-beta-estradiol

Dr. Christine Langton

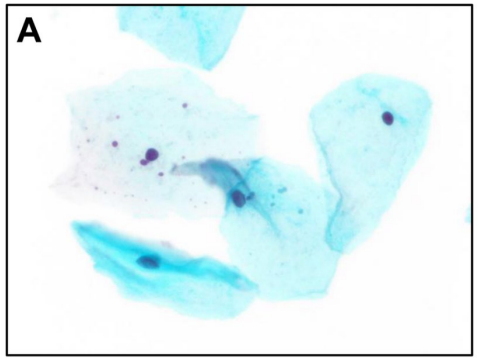
- Isoflavones act as endocrine disruptor
- Postnatal treatment to lab animals
  - alters rodent reproductive tract including uterus
  - increased fibroid development in Eker rats
- Exposure during sensitive developmental windows detrimental effects on reproductive systems

Image source adapted from: Pilšáková, L & Riecansky, Igor & Jagla, Fedor. (2010). Suen et al. 2021 Greathouse et al. 2012

Soy-based infant formula

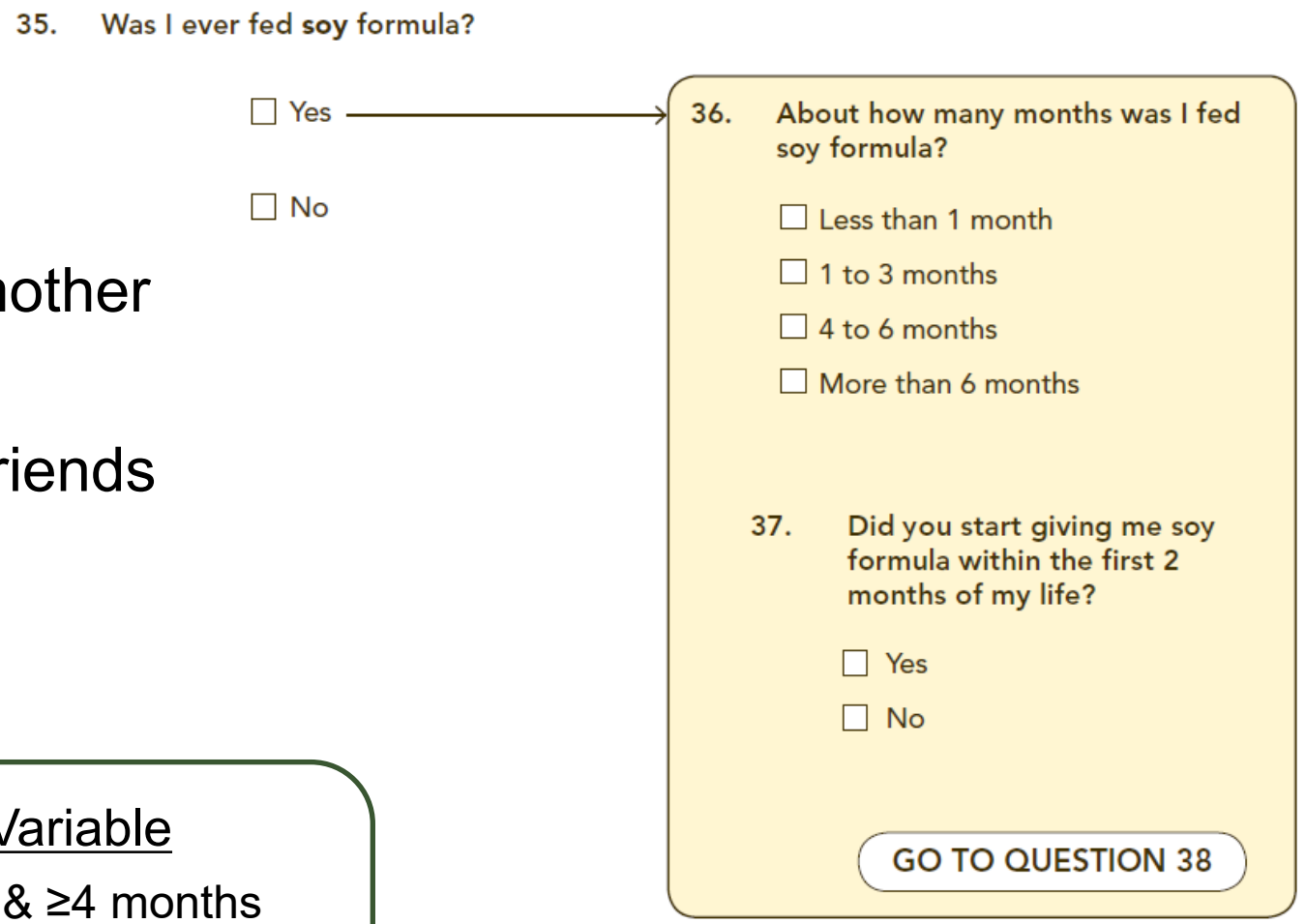
- Consumed by 12% of U.S. infants
- Contains high levels of phytoestrogens

- Linked to reproductive conditions
  - early/late menarche, menstrual irregularities, endometriosis
- Proliferative vaginal tissue in soy-fed infants



Adgent et al. *J Clin Endocrinol Metab*., Adgent et al. *PloS One 2013*

Soy formula assessment



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

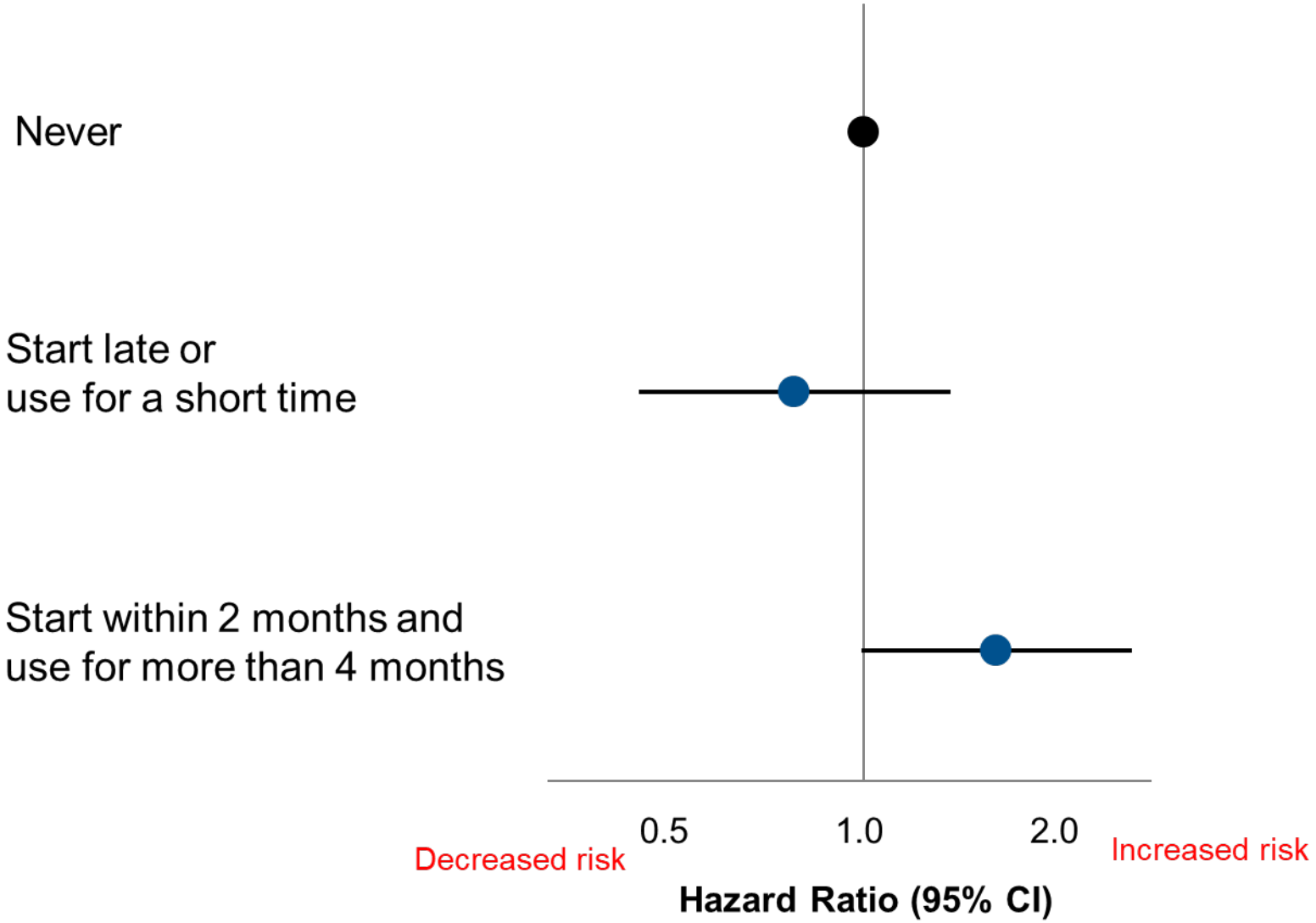
Composite Variable

Within 2 months & ≥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

Langton CR, under review EHP 2022

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

SELF
STUDY OF ENVIRONMENT, LIFESTYLE & FIBROIDS

Wise LA 2004, Marshall LM 1998, Baird DD 2003, Walker CL 2001, Laughlin SK 2010

Other exposures & outcomes

- 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

National Institute of Environmental Health Sciences

National Institutes of Health
Office of Disease Prevention

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

NIEHS Collaborators


Dr. Anne Marie Jukic


Dr. Chandra Jackson

Extramural Collaborators





Dr. Erica Marsh


Dr. Lauren Wise


Dr. Ganesa Wegienka


Dr. Anissa Vines

NICHD Collaborators


Dr. Shyamal Peddada


Dr. Fasil Tekola Ayele

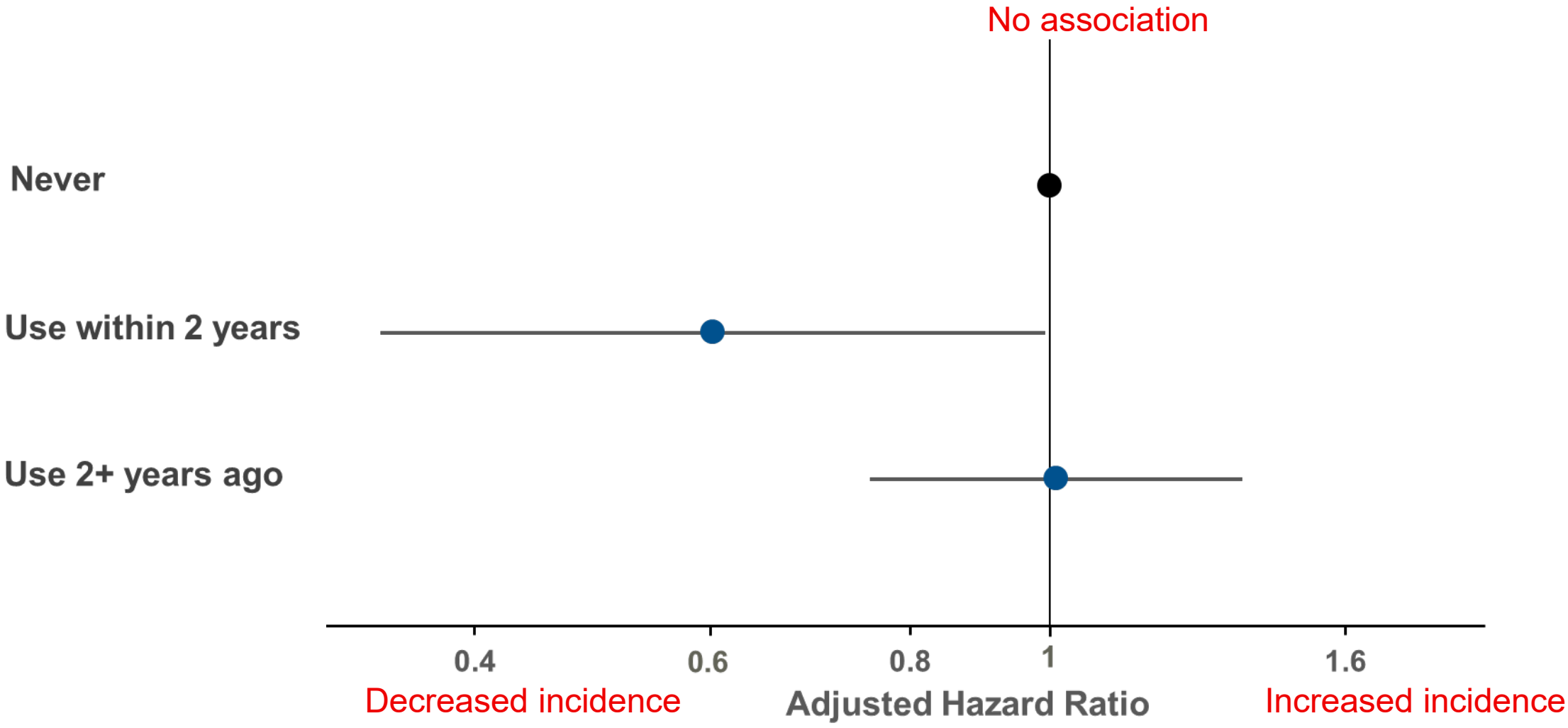

Dr. Symielle Gaston


Dr. Kyla Taylor


Questions

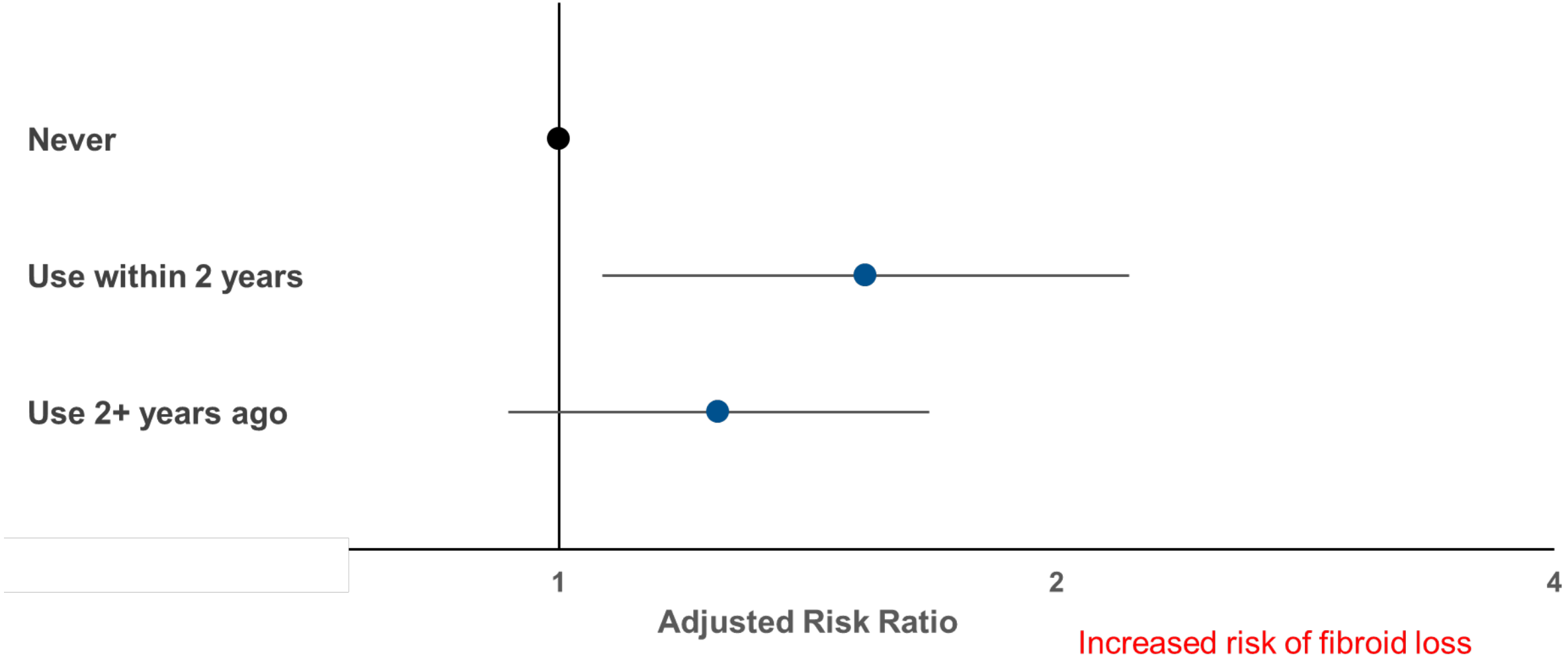
Additional slides

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