The NIEHS Uterine Fibroid Study
Epidemiologic Findings

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Disclaimer

Please note that many of the conclusions
in this presentation have been based
on unpublished data.

Please regard the information herein

as preliminary findings.

Epidemiologic Context

A decade ago: few epidemiologic studies, all surgery

    Parazzini: Italian case-control study of surgery cases vs. hospital controls

    Ross: British case-control study of surgery cases nested in Oxford Family Planning Cohort

    Romieu: U.S. case-control study of hysterectomy cases nested in Group Health sample

    Associations: menopause, smoking, parity; U.S. data on hysterectomy suggested African Americans at higher risk

New US cohorts: self-reported clinical fibroid diagnosis

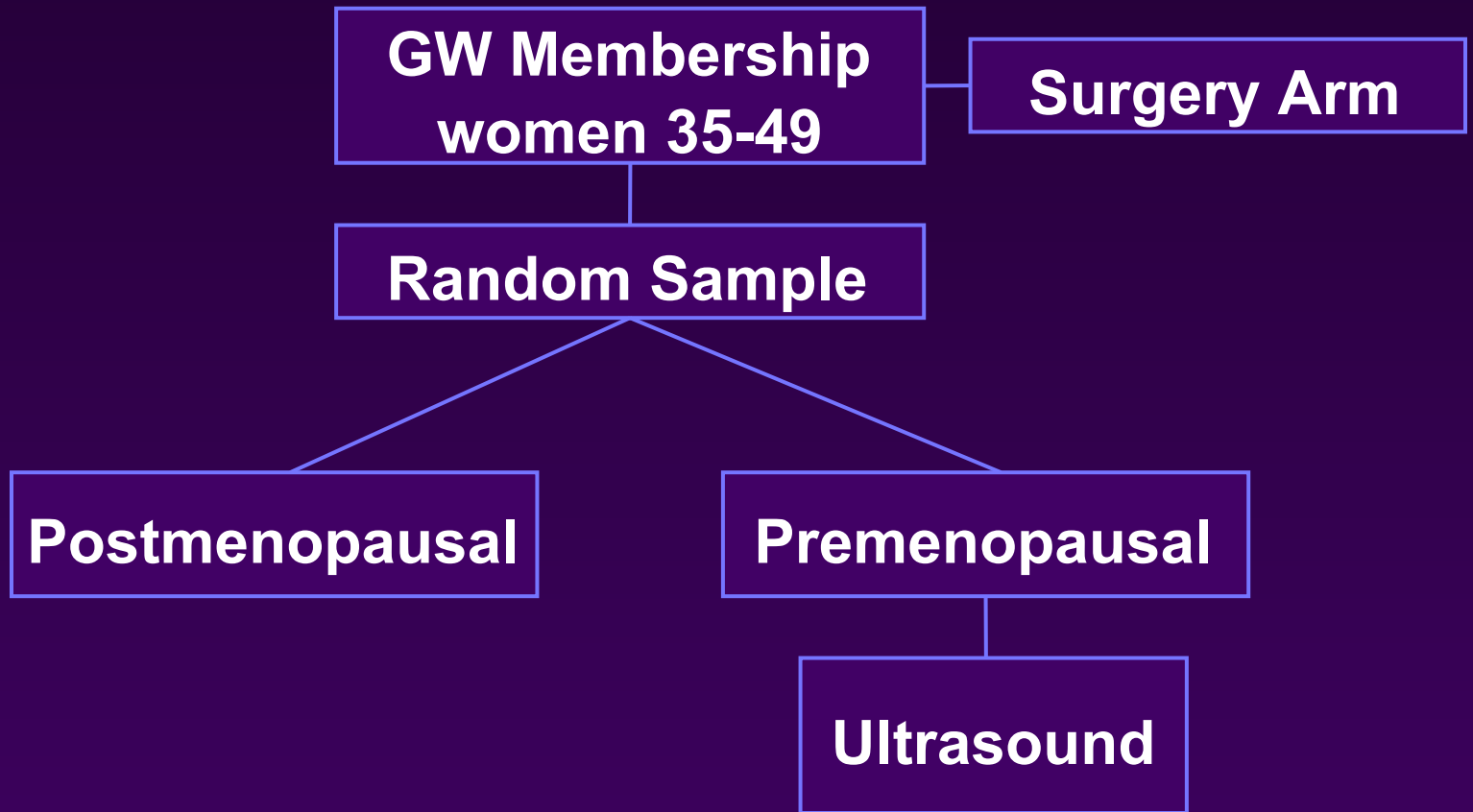   **Nurses Health**

    Black Women's Health

NIEHS Uterine Fibroid Study

Objectives

1. Estimate Fibroid Prevalence (ultrasound) Blacks vs Whites

2. Identify Risk Factors

3. Collect Tissue for Laboratory Study

Study Design

Data Collection Procedures

Telephone Invitation/Screener (1996-1999)

↓

Telephone Interview (~1 hr)
>   **self-administered Q**
>   **dietary Q**
>   **menstrual diary**
>   **early follicular phase urine**

↓

Clinic Visit
>   **blood draw**
>   **ultrasound**

↓

Followup Interviews (2001,2004)
>   **change in fibroid status**
>   **ultrasound and surgery records**
>   **symptoms**
>   **risk factor update**

Study Sample

Randomly Selected Participants
N = 1482
57% African American

Postmenopausal
N = 237 (16%)
Hysterectomy (11%)
Natural Menopause (5%)

Premenopausal
N = 1245 (84%)

Ultrasound data
N=1079
Study ultrasound (863)
Medical ultrasound (216)

Determination of Fibroid Status

findings at ultrasound   (73% of study)

> identified tumors > 0.5 cm
> premenopausal women

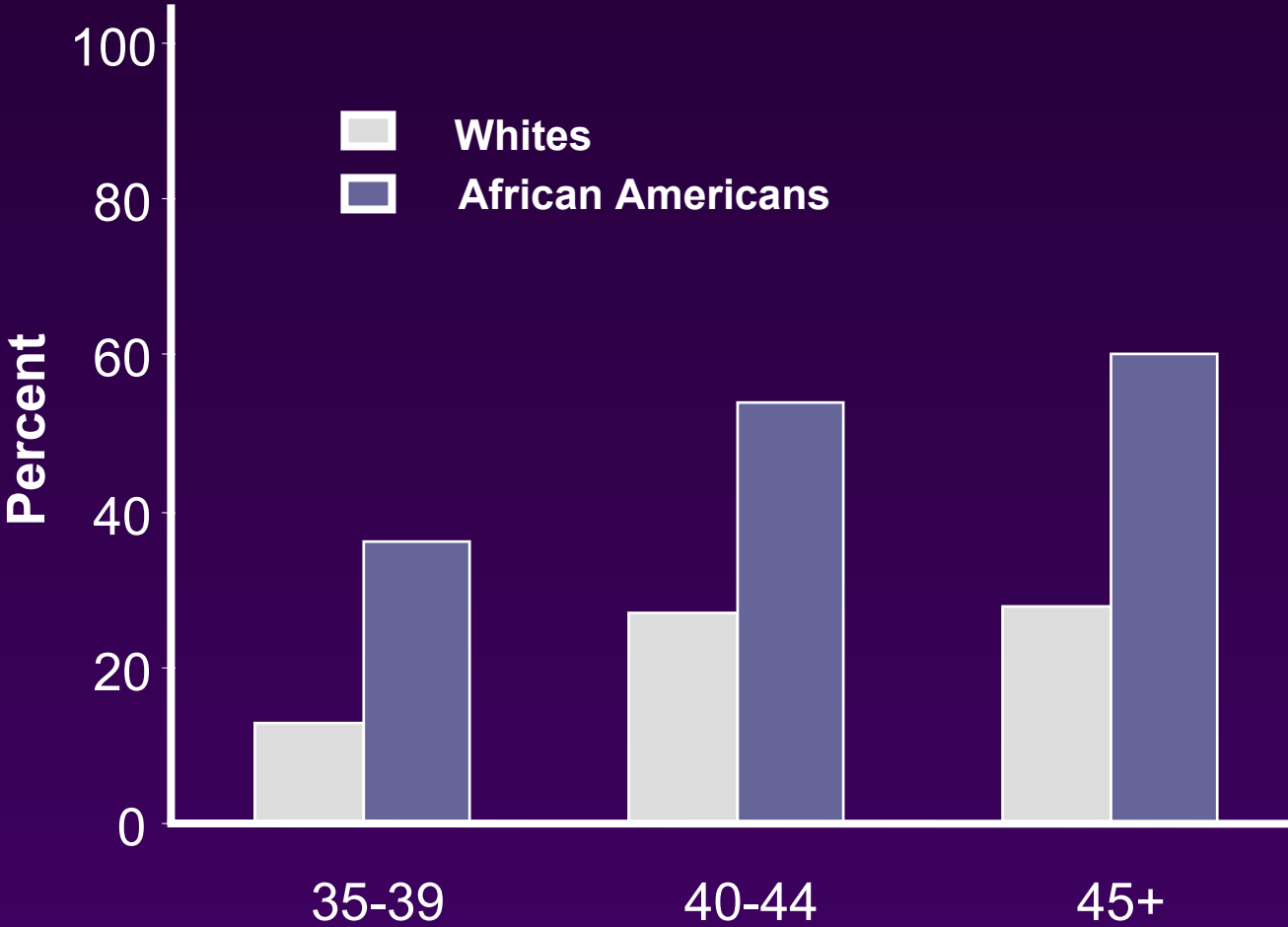**findings at surgery   (6% of study)**

> surgical pathology records
> women with prior hysterectomies
> data on 84/164

self report   (21% of study)

> missing ultrasound or medical records
> women with natural menopause
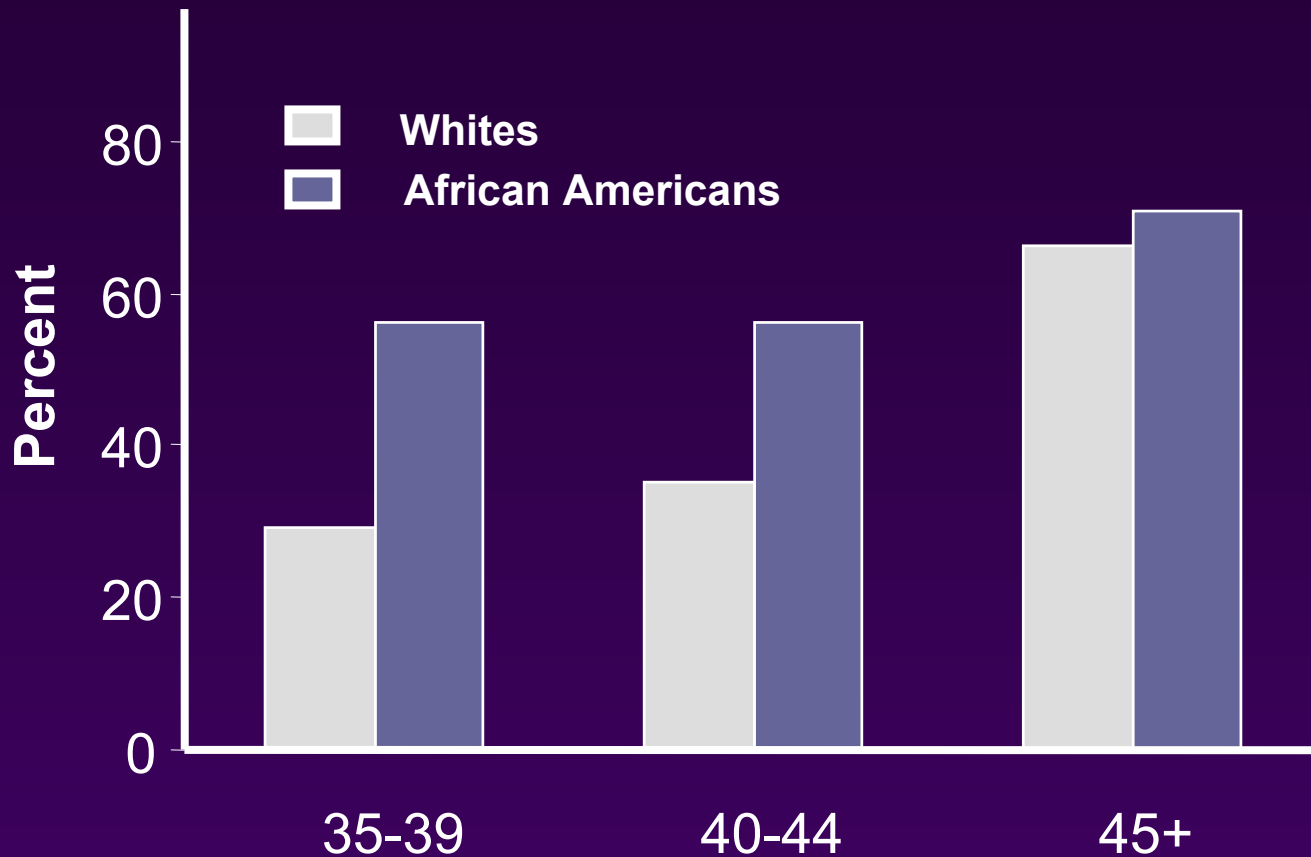> drop participants who self-reported "no fibroids" (10%)

Previously Diagnosed Fibroids
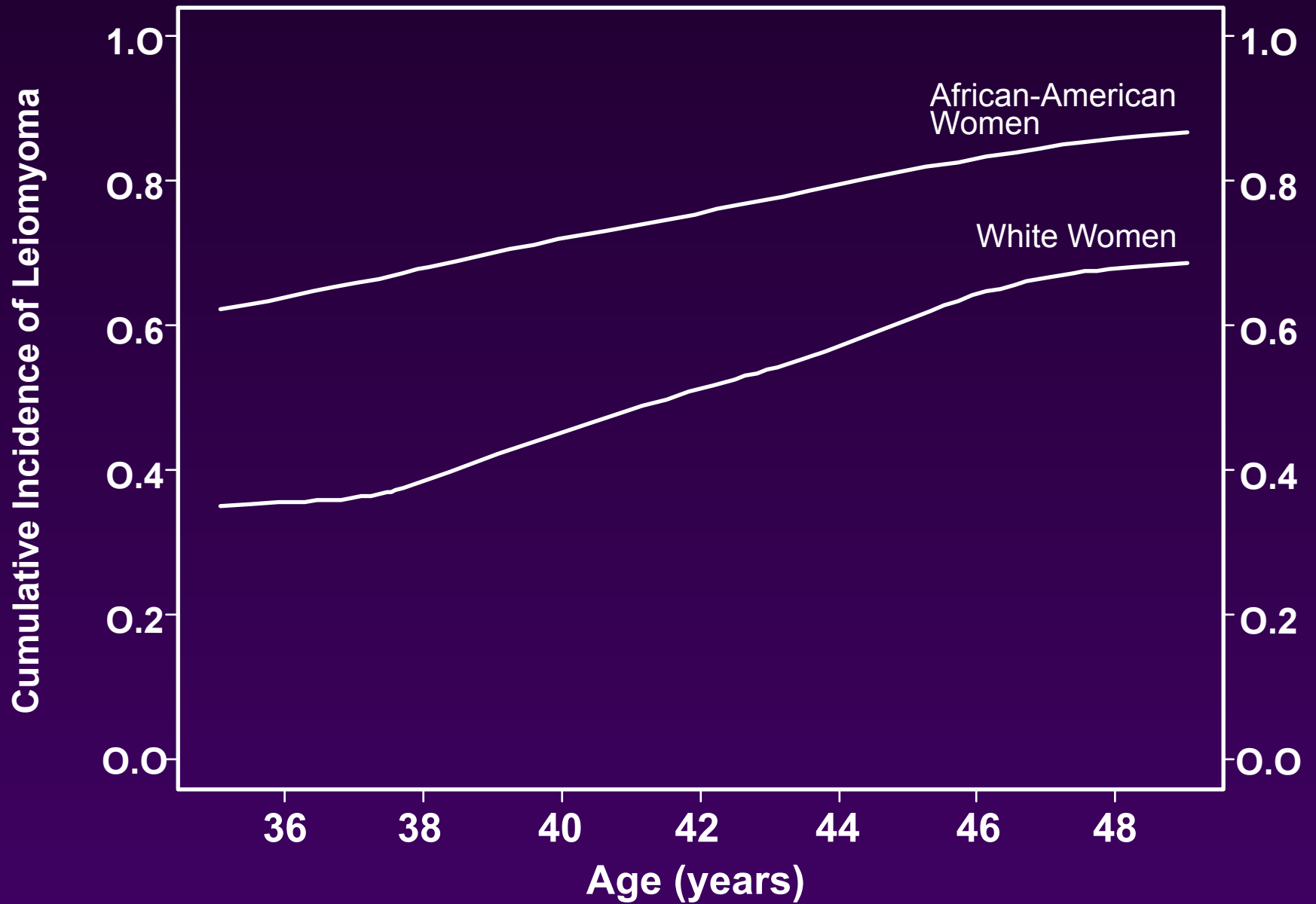**(self-report in entire sample)**

Cumulative Incidence

Risk Factors

Accepted
  age
  African American ethnicity
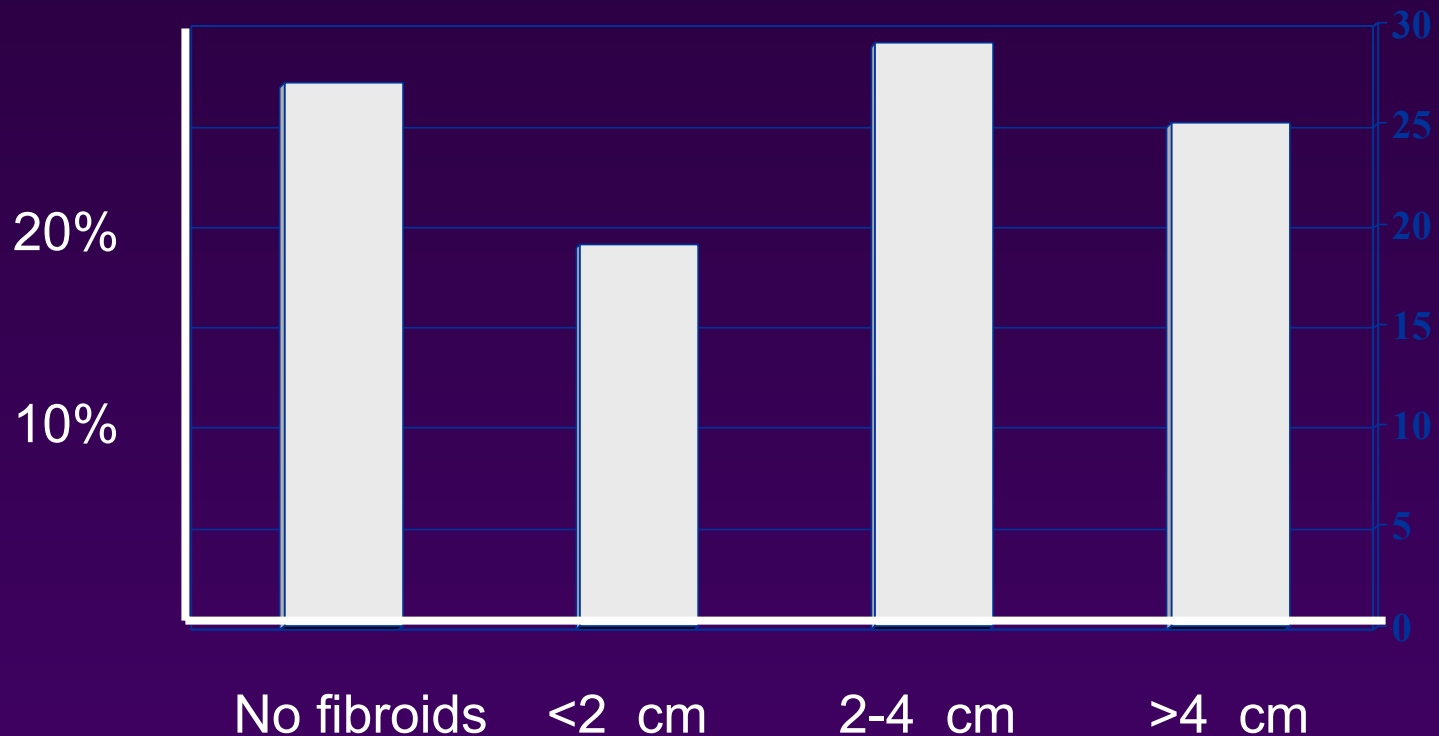
Others
  hormonal/reproductive
  infectious/inflammatory
  metabolism
  other

Analysis Method

Polytomous Logistic Regression: assesses relationship between variable of interest and several separate outcomes Small, medium, large fibroids are compared to no fibroids. Limit to "known" fibroid status (n=1189 blacks and whites)

Reproductive/Hormonal History Associated with Fibroids?

We expect hormonal factors to be related because fibroids are hormonally dependent tumors

1. arise after menarche; tend to shrink after menopause
2. HRT can increase development postmenopausally
3. GnRH agonist associated with shrinkage
4. anitprogestins associated with shrinkage

Estrogen and progesterone probably both important in fibroid development

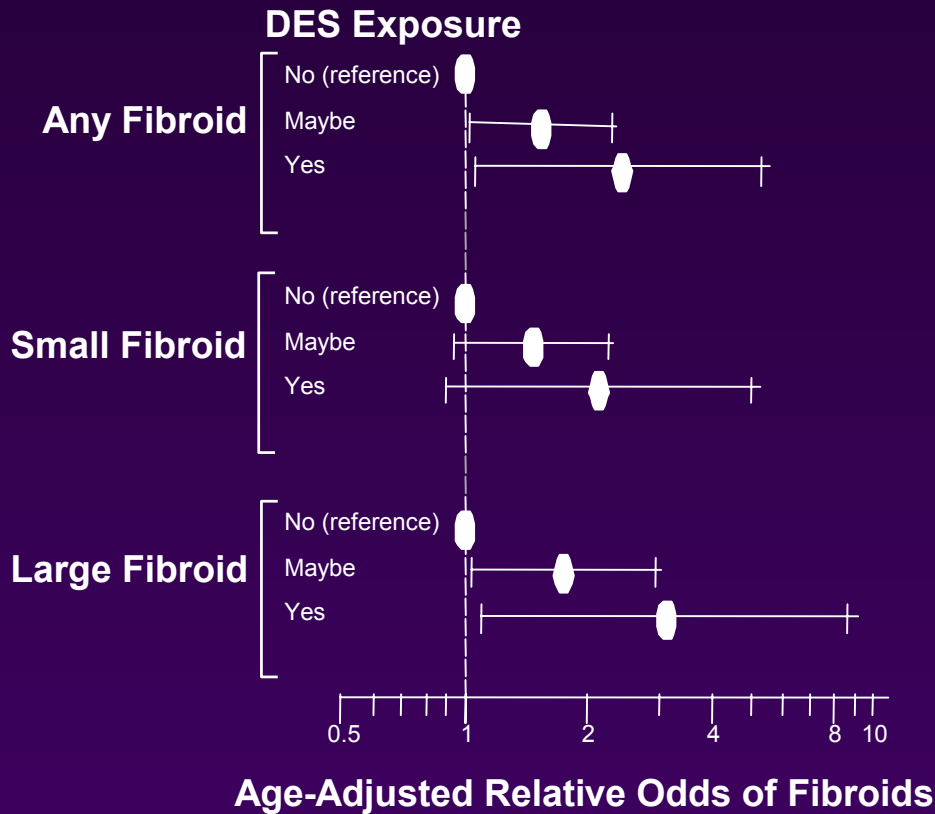# Prenatal DES Exposure
Prediction: exposure increases risk

African Americans – only 5 reported exposure, all with fibroids

Whites – 19 reported exposure

	No fibroids n (%)	Small fibroids (<4cm) n (%)	Large fibroids (≥4cm) n (%)
DES Exposure			
No	175 (48)	137 (38)	53 (15)
Maybe	27 (38)	30 (42)	14 (20)
Yes	5 (26)	9 (47)	5 (26)

Prenatal DES Exposure – Whites

DES Exposure

Any Fibroid
- No (reference)
- Maybe
- Yes

Small Fibroid
- No (reference)
- Maybe
- Yes

Large Fibroid
- No (reference)
- Maybe
- Yes

0.5 1 2 4 8 10

Age-Adjusted Relative Odds of Fibroids

Sensitivity Analyses
Adjust for:
- age menarche
- BMI
- exercise
- pregnancies
- mom's fibroids

Exclude:
- postmenopausal
- self-report fibroids
- women with old moms
- "maybe" exposure

Hormone/Reproduction-Related Factors

	African Americans aOR (95% CI)	Whites aOR (95% CI)
Prenatal DES	insufficient data	2.4 (1.1, 5.4)
Age of Menarche (yr)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)
Infertility	0.8 (0.5, 1.3)	1.4 (0.9, 2.1)
Age first birth		
<25	1.4 (0.9, 2.3)	1.4 (0.6, 3.2)
25+	0.9 (0.5, 1.6)	0.6 (0.3, 1.4)
Deliveries (# after 24)	0.8 (0.7, 1.0)	0.7 (0.6, 0.9)
Breastfeeding (6 mo diff)	0.9 (0.8, 1.0)	1.0 (0.9, 1.2)

Hormone/Reproduction-Related Factors (cont.)

	African Americans	Whites
	aOR (95% CI)	aOR (95% CI)
OC Use (5 yr diff < age 30)	1.1 (0.9, 1.3)	0.9 (0.7, 1.2)
OC Use <age 18	1.2 (0.8, 1.9)	1.0 (0.5, 2.0)
Short cycles (<27 days)	0.9 (0.6, 1.4)	1.3 (0.7, 2.8)

<u>Luteinizing Hormone</u> (high tertile vs low) <u>1.8 (1.0, 3.0)</u>

Infectious/Inflammatory Factors

Hypothesis: similarity to atheroma
(vascular smooth muscle)

Infectious Stimulus (CMV, Chlamydia)
↓ apoptosis
↑ mitosis

Infectious/Inflammatory Factors

	African Americans aOR (95% CI)	Whites aOR (95% CI)
Prior STD diagnosis	1.4 (0.9, 2.0)	1.2 (0.8, 1.8)
Sexual partners (>5 vs 1)	0.7 (0.5, 1.1)	0.9 (0.6, 1.4)
Age first sex (<16 vs 21+)	1.2 (0.7, 2.0)	0.9 (0.4, 2.0)
IUD (ever use)	1.5 (1.0, 2.3)	1.4 (0.9, 2.3)
Talc exposure	0.8 (0.5, 1.4)	0.9 (0.5, 1.5)

Infectious/Inflammatory Factors

Test for Organisms in Tumor Tissue (selected for exposure)
    Viral DNA
        herpes symplex I, II
        human herpes virus 6, 7, 8
        cytomegalovirus
        Epstein-Barr virus
   Histopathology
        Chlamydia trachomatis (intracellular bacteria)

Result: no evidence of organisms in tumor tissue

Metabolism-Related Factors

Hypothesis: insulin exposure → fibroid growth

      insulin receptors in fibroid tissue
      insulin is mitogenic in cultured smooth muscle

Test: analysis of data from questionnaire
      clinic measurements
      markers in serum or plasma

Metabolism-Related Factors

	African Americans	Whites
	aOR (95% CI)	aOR (95% CI)
Exercise	0.6 (0.4, 1.1)	0.5 (0.3, 1.0)
BMI (25+)	1.5 (1.0, 2.2)	1.0 (0.6, 1.5)
Insulin (high vs low tertile)	0.8 (0.4, 1.4)	0.8 (0.6, 1.7)
IGF-I (high vs low tertile	1.1 (0.7, 1.9)	0.7 (0.4, 1.2)
IGF BP-3 (high vs low tertile)	1.1 (0.6, 1.8)	1.0 (0.5, 1.7)
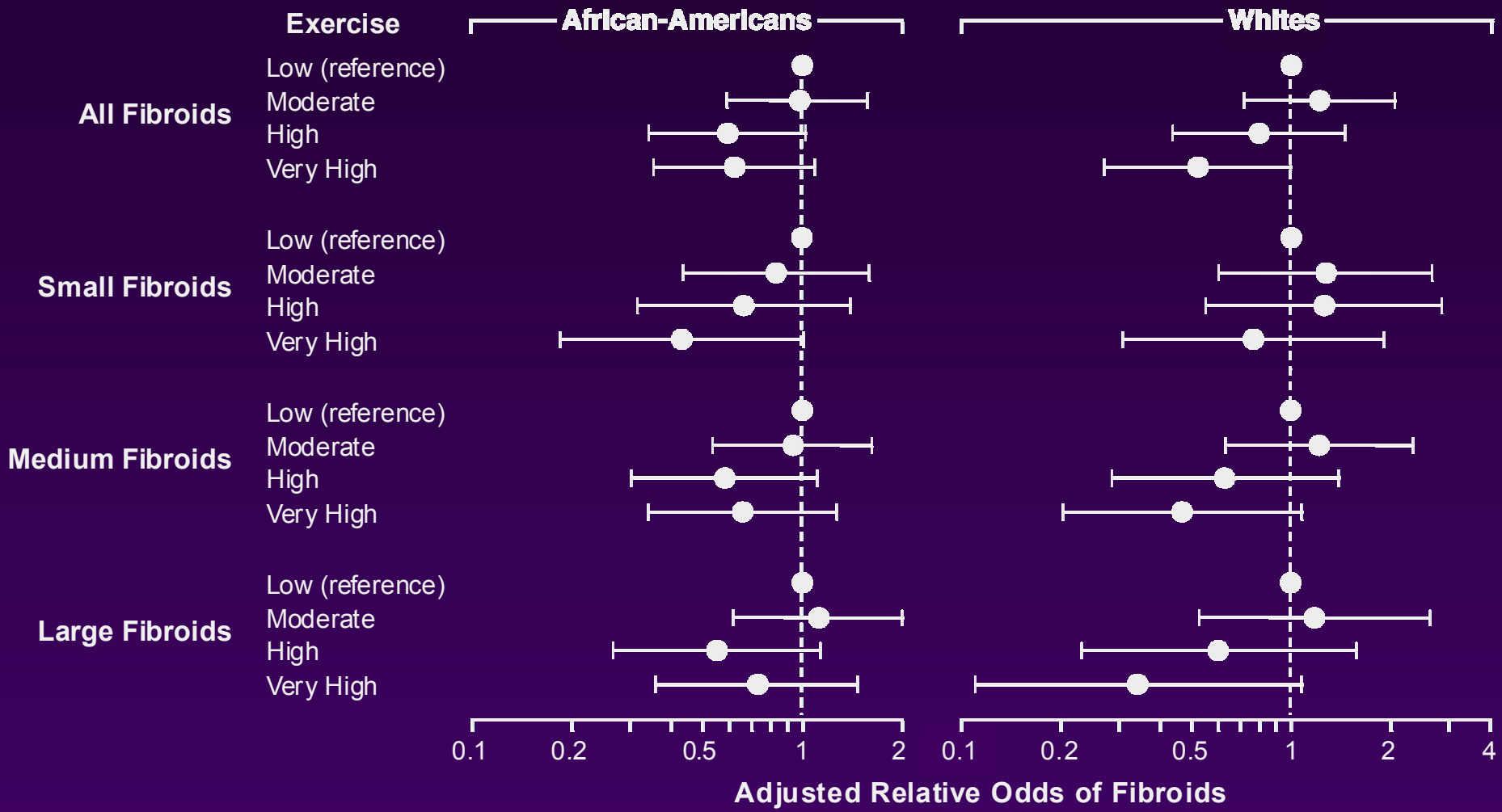
Exercise Findings Confirmed by Bayesian Analysis

Quasi-longitudinal Bayesian analysis estimates tumor onset and tumor growth (using data on age at any prior clinical diagnosis of fibroids, age of participant at time of study, and size of tumor at age of ultrasound; censoring at menopause)

Bayesian Results	African Americans	Whites
exercise variable	includes chores	excludes chores
tumor onset (protective)	BF=217	BF=1000
ex. category of most impact	mod-high	mod-high
tumor progression	BF=3	BF=8

Other Factors

	African Americans	Whites
Smoking	no	no
Alcohol*	risk	risk
Caffeine	no	no
Shift work	no	no
Solvent exposure	no	no
Radiation/chemo (wk)	protective	protective
Pesticides	no	no
Insect repellent (child)	risk	risk

*see Aimee D'Aloisio poster

Adjusting for Risk Factors Doesn't Explain Higher Risk for African Americans

Prevalence Odds Ratio (95% CI)
(African-Americans Relative to Whites)
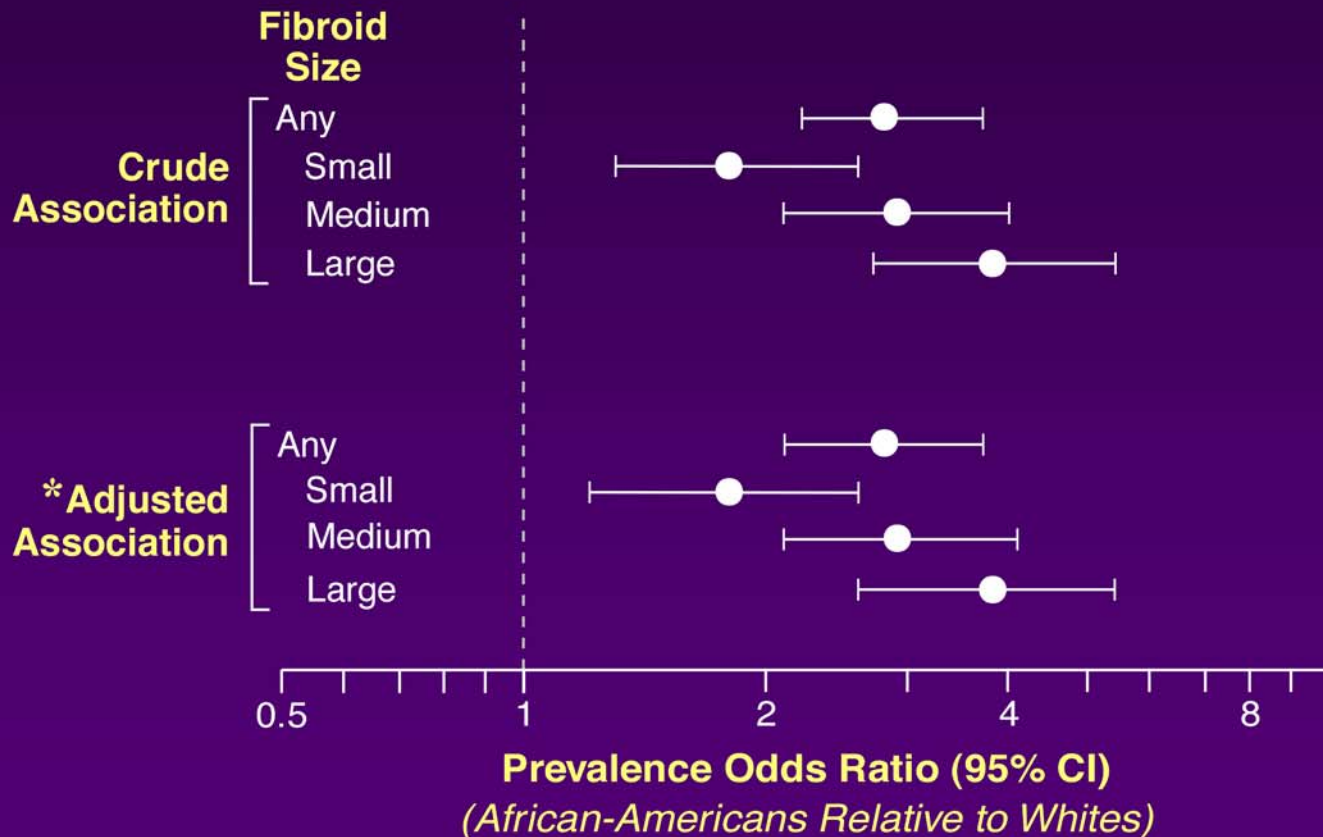
*Adjusted for age, BMI, age of menarche, fullterm prenancies after age 24, exercise

Cumulative Incidence
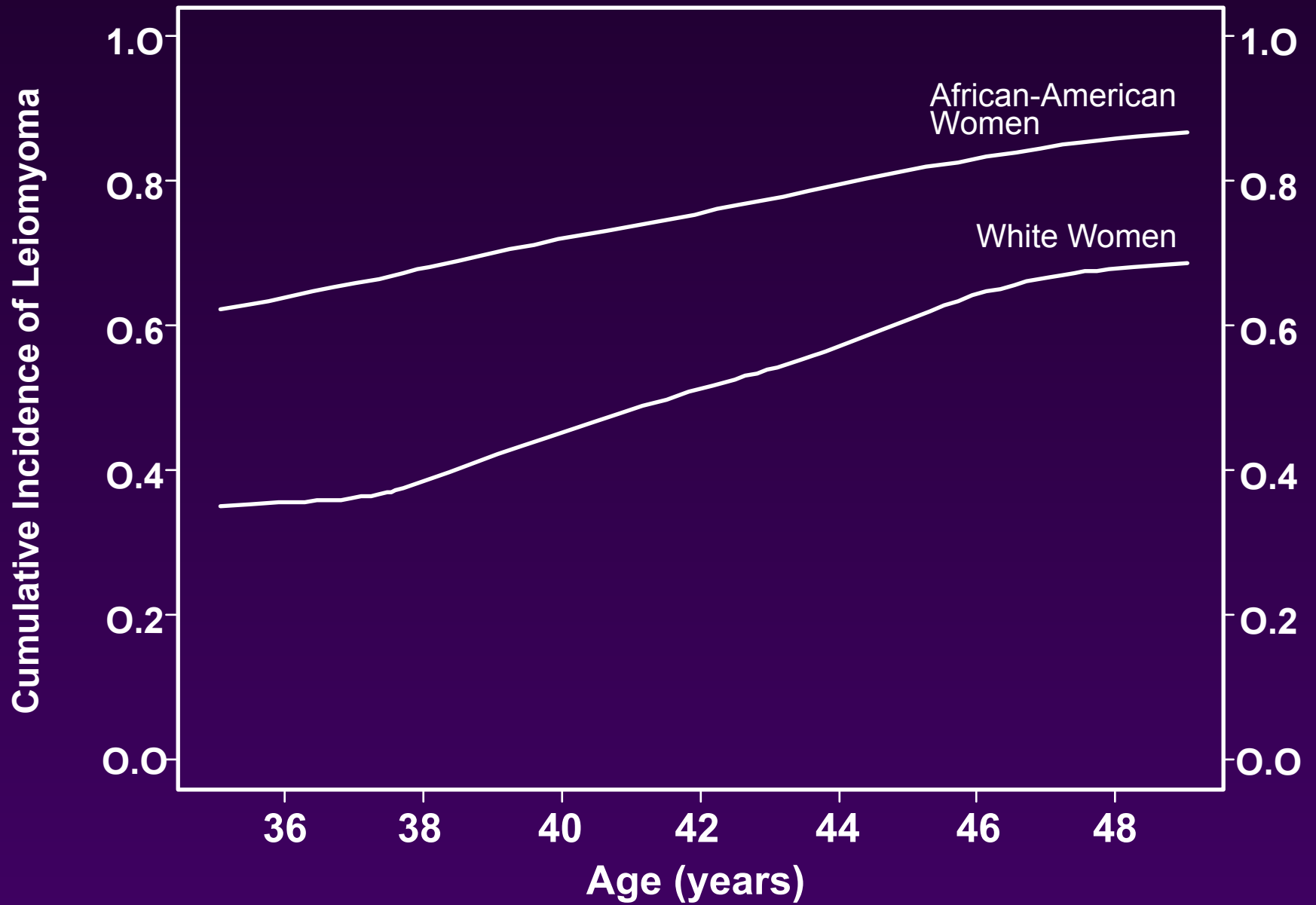
Where Do We Go From Here?

Cohort Study: Incidence, Fibroid Growth

Enroll women before they develop fibroids

Monitor annually with ultrasound

Recruit from women at high risk

mom or sister had surgery for fibroids

Contributors

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+ +

Other

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NIEHS Uterine Fibroid Study Continuing Epidemiologic Work

1. Complete risk factor analysis
2. Follow-up of premenopausal participants
    2000-2001, 2004-2005

    Analyze symptom development & treatments

    Can we predict who will have symptoms

    and require major treatment based on initial fibroid characteristics and participant characteristics?