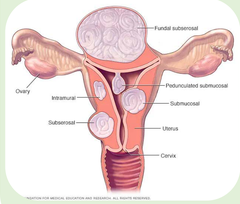
Blood lead concentrations and uterine fibroid incidence: A prospective study

Kristen Upson[1], Mandy S. Hall[1], Quaker E. Harmon[2], Robert O. Wright[3], Lauren A. Wise[4], Ganesa Wegienka[5], Ruth J. Geller[4], Amelia K. Wesselink[4], Birgit Claus Henn[6], Janet E. Hall[7], Erik J. Tokar[8], Donna D. Baird[2]

[1]Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, East Lansing, MI; [2]Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC; [3]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY; [4]Department of Epidemiology, Boston University School of Public Health, Boston, MA; [5]Department of Public Health Sciences, Henry Ford Health, Detroit, MI; [6]Department of Environmental Health, Boston University School of Public Health, Boston, MA; [7]Clinical Research Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC;[8]Mechanistic Toxicology Branch, Division of Translational Toxicology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC

Background

Uterine fibroids



- Smooth muscle non-cancerous uterine tumors
- Present in most women by age 50
- Substantial morbidity
  - Heavy menstrual bleeding
  - Pelvic pain
  - Leading indication for hysterectomy
- Disproportionately burdens U.S. Black women
  - 10-year earlier onset

Toxic metal lead

Sources

82 Pb Lead

- Leaded gasoline
- Lead paint
- Drinking water
- Foods
- Occupation: Manufacturing, construction, automotive, mining
- Cigarette smoke

- **Adversely affects all organ systems**
- **Affect all ages, including adults**
- **Displaces calcium** (cellular processes cofactor)
- **No safe blood Pb level**

82 Pb Lead

Fibroid pathogenesis — ***Biologic plausibility***

Two different biologic processes

1. Tumor initiation
   - Genetic mutations
   - Early event in fibroid development

   Probable human carcinogen
   (Genotoxic, mutagenic, epigenetic effects, oxidative stress and inflammation)
   ➢ Activate cell death pathways

2. Tumor growth
   - Estrogen, progesterone
   - Cellular proliferation of existing fibroids

   Promote tumor growth
   (Accumulation of mutations)

No direct investigation of lead on fibroid pathogenesis using in vitro or animal models

Objective

Blood lead (Pb) —?→ **↑Fibroid incidence**, **↑Fibroid growth**

Cohort characteristics (N=1,215)

- 29 (median) Age — ↑ Pb Lead
- 59% Higher BMI (≥30 kg/m²)
- 20% Current smokers — ↑ Pb Lead, ↓ fibroid
- 13% Depo-Provera (past 2 years) — ↑ Pb Lead, ↓ fibroid; Current Depo use
- 23% Lower education (≤ high school or GED) — ↑ Pb Lead
- 64% Given birth — ↓ fibroid
- 47% Lower income (annual household income <$20,000) — ↑ Pb Lead
- 25% Recent birth (past 3 years) — ↑ Pb Lead, ↓ fibroid; Birth past year

Methods

Cohort: Study of Environment, Lifestyle & Fibroids

- 1693 African-American women
- Ages 23-35 years at enrollment
- Residing in Detroit, MI area
- Community-recruited

STUDY OF ENVIRONMENT, LIFESTYLE & FIBROIDS

Data collection

Fibroids ≥0.5 cm in diameter

	Enrollment 2010-2012	Follow-up 1 2012-2015 (20 months)	Follow-up 2 2014-2016 (40 months)	Follow-up 3 2016-2018 (60 months)
Clinic visit	✓	✓	✓	✓
Ultrasound	✓	✓	✓	✓
Questionnaires	✓	✓	✓	✓
Biospecimens	✓	✓	✓	✓
	N=1693	88% response	86% response	91% response

Fibroid incidence analyses

Whole blood Pb

Icahn School of Medicine at Mount Sinai

5 years of follow-up

Enrollment — Follow-up 1 (20 months) — Follow-up 2 (40 months) — Follow-up 3 (60 months)

- Cox proportional hazards regression
- Age as the time scale
- Adjusted for time-varying covariates

Excluded those with fibroids on ultrasound at enrollment (20%)

Followed until:
- New fibroid detected
- Hysterectomy
- Loss to follow-up
- Final study visit

Fibroid growth analyses

Analyses among those with fibroids

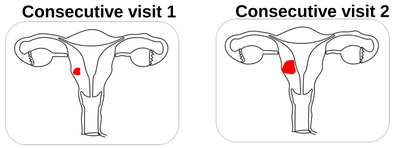
Same fibroid followed over 2 consecutive visits

Linear mixed effects model

Change in log volume per 18 months

Enrollment — Follow-up 1 (20 months) — Follow-up 2 (40 months) — Follow-up 3 (60 months)

Consecutive visit 1 **Consecutive visit 2**



Limitations & Strengths

Limitations

- Lead measured only at enrollment
- Residual confounding possible
- No evaluation of metal mixtures

Stay tuned!

Strengths

- Cohort of community-recruited participants
- Universal fibroid screening by ultrasound
- Time-varying covariates
- Detailed data on individual fibroids over time

Results

Lead and fibroid incidence, n=1,215

↓fibroid incidence

Follow-up over 5 years

	No. exposed	Incident cases	Person-years	HR (95% CI)[a]
Blood Pb (µg/dl) *(at enrollment)*				
Quartile 1 (≤0.36)	300	84	1258	Reference
Quartile 2 (>0.36 - ≤0.47)	308	72	1340	0.87 (0.63, 1.19)
Quartile 3 (>0.47 - ≤0.65)	304	60	1349	0.68 (0.48, 0.97)
Quartile 4 (>0.65)	303	78	1296	0.94 (0.65, 1.35)

[a]Age as the time scale. Adjusted for time-varying factors of parity, years since last birth, years since last DMPA use, BMI, smoking, education, and blood Cd concentrations.

Follow-up to 1st visit: **Similar associations**

Lead and fibroid growth, n=423

Follow-up over 5 years

	Growth intervals	% Difference (95% CI)[a]
Blood Pb (µg/dl) *(at enrollment)*		
Quartile 1 (≤0.36)	393	Reference
Quartile 2 (>0.36 - ≤0.47)	299	3.7% (-8.4%, 17.3%)
Quartile 3 (>0.47 - ≤0.65)	249	10.7% (-3.3%, 26.7%)
Quartile 4 (>0.65)	386	1.3% (-11.4%, 15.9%)

[a]Adjusted for fibroid volume, fibroid number, age, years since last birth, BMI, years since last DMPA use. smoking, education, and blood Cd concentrations.

Lead and fibroid growth, n=243

Follow-up to 1st visit (~20 months)

	Growth intervals	% Difference (95% CI)[a]
Blood Pb (µg/dl) *(at enrollment)*		
Quartile 1 (≤0.36)	103	Reference
Quartile 2 (>0.36 - ≤0.47)	79	14.6% (-9.0%, 44.2%)
Quartile 3 (>0.47 - ≤0.65)	57	45.1% (12.0%, 88.0%)
Quartile 4 (>0.65)	95	20.3% (-6.3%, 54.4%)

↑ fibroid growth

[a]Adjusted for fibroid volume, fibroid number, age, years since last birth, years since last DMPA use, BMI, smoking, education, and blood Cd concentrations.

Conclusions

- Blood lead associated with
  - ↓fibroid incidence
  - ↑fibroid growth
- Highlights
  - Importance of evaluating both fibroid incidence and growth
  - Supports need for *in vitro* and animal model investigation

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