

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

Women's Risk of Endometriosis (WREN) Study

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Michigan State University

Advisory Committee on Research on Women's Health

October 18, 2022



Endometriosis

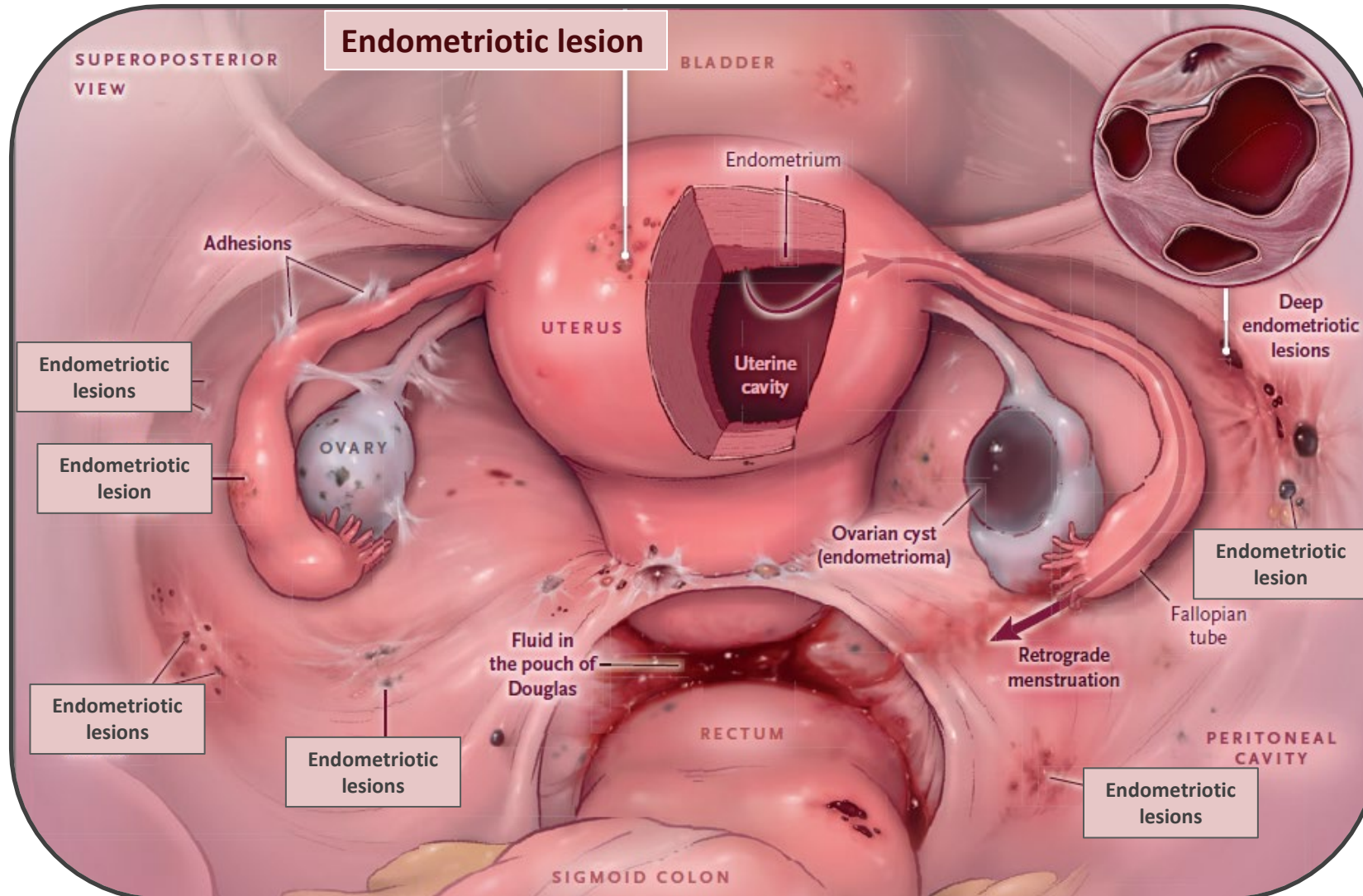


Image modified from: Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N England Journal of Medicine* 2020;382: 1244-1256.

Endometriosis



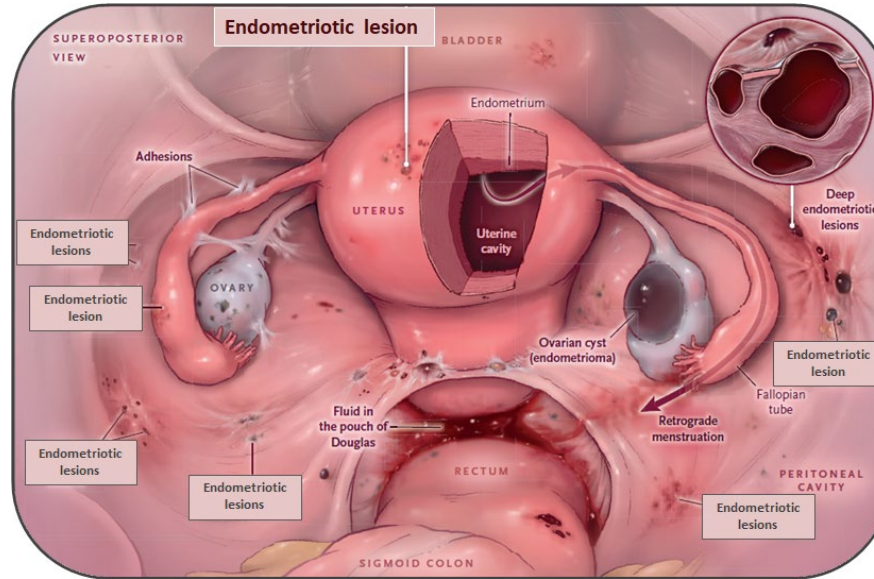
Chronic pelvic pain
Acyclic pelvic pain



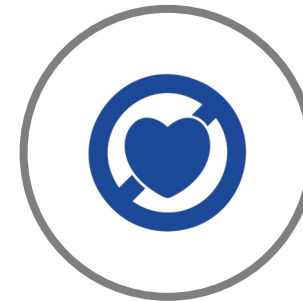
Painful menstrual periods



Painful bowel movements
Painful urination

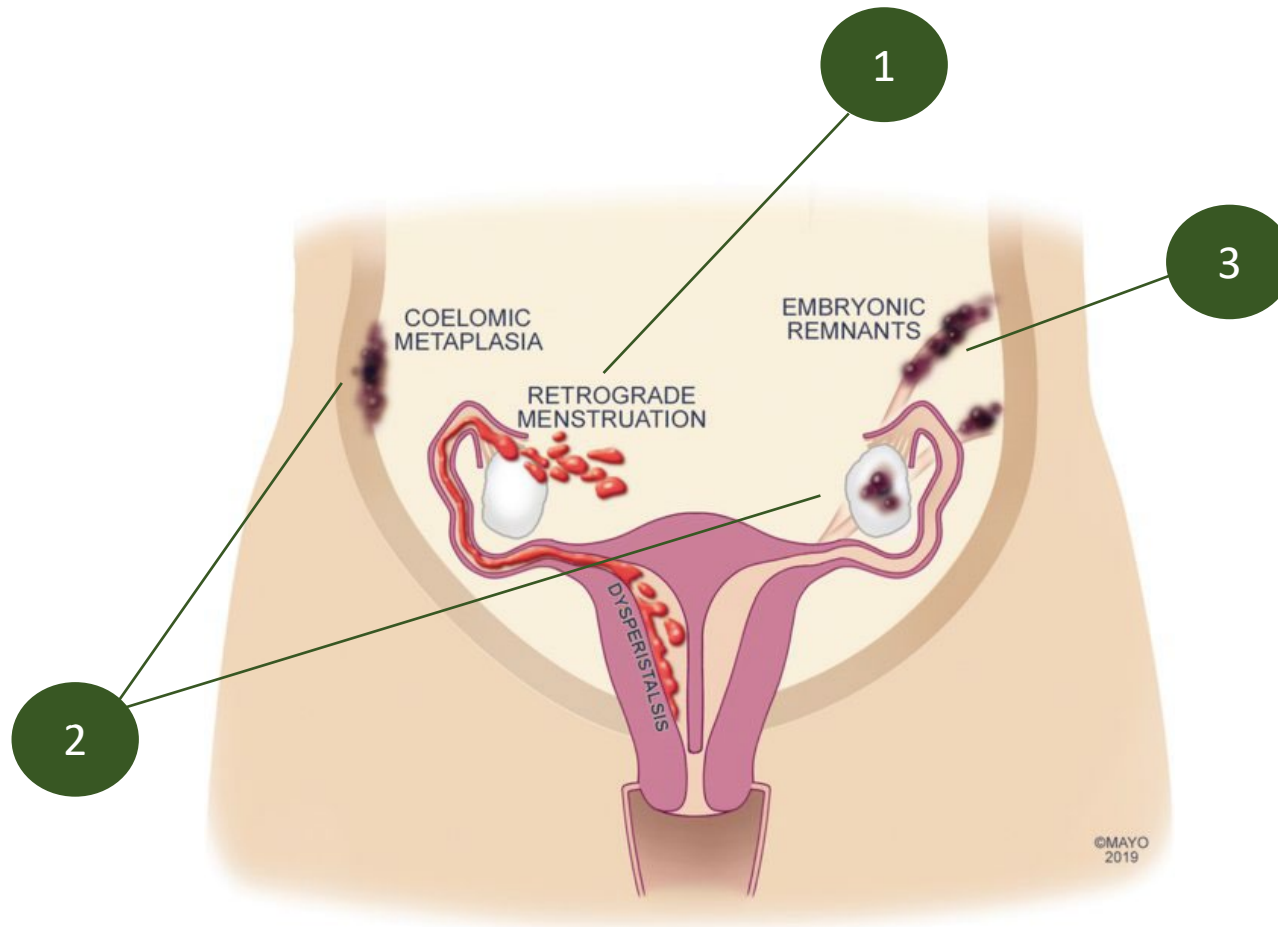


Fatigue



Pain during intercourse

Endometriosis: Pathogenesis



Separate etiologic pathways?

- Peritoneal endometriosis
- Ovarian endometriosis
- Deep infiltrating endometriosis

Multiple factors involved

- Anatomical
- Hormonal
- Immunological
- Genetic
- Environmental

Estrogen

- Regulates key pathological processes

Image from Pitot MA, et al. *Abdom Radiol (NY)* 2020;45: 1723-1740.

Lagana AS, et al. *International journal of molecular sciences* 2019;20.

Endometriosis: Environmental chemicals

POSITION STATEMENT

Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society

R. Thomas Zoeller, T. R. Brown, L. L. Doan, A. C. Gore, N. E. Skakkebaek, A. M. Soto, T. J. Woodruff, and F. S. Vom Saal

Endocrine disrupting chemical
“...is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.”

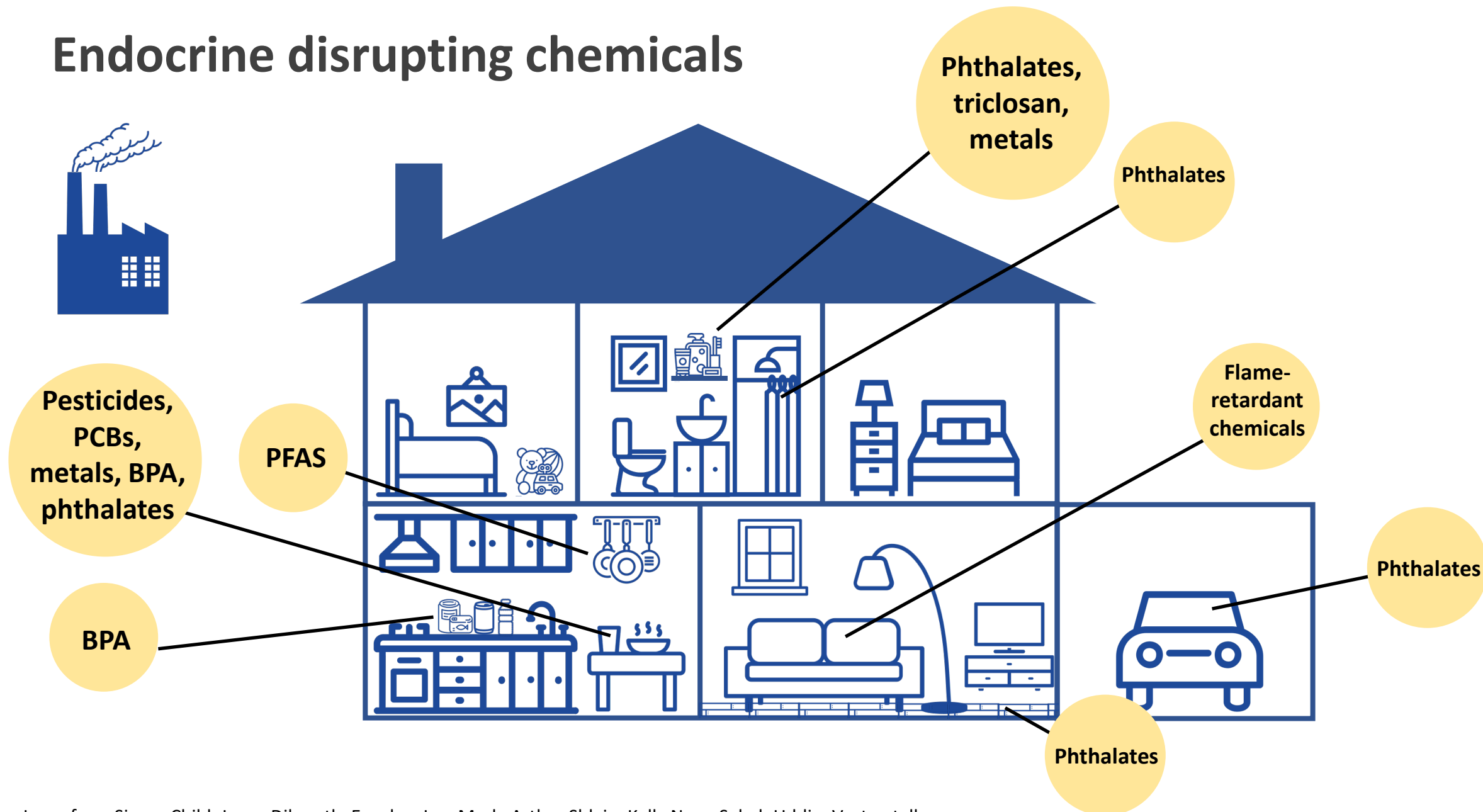
Endocrine disrupting chemicals



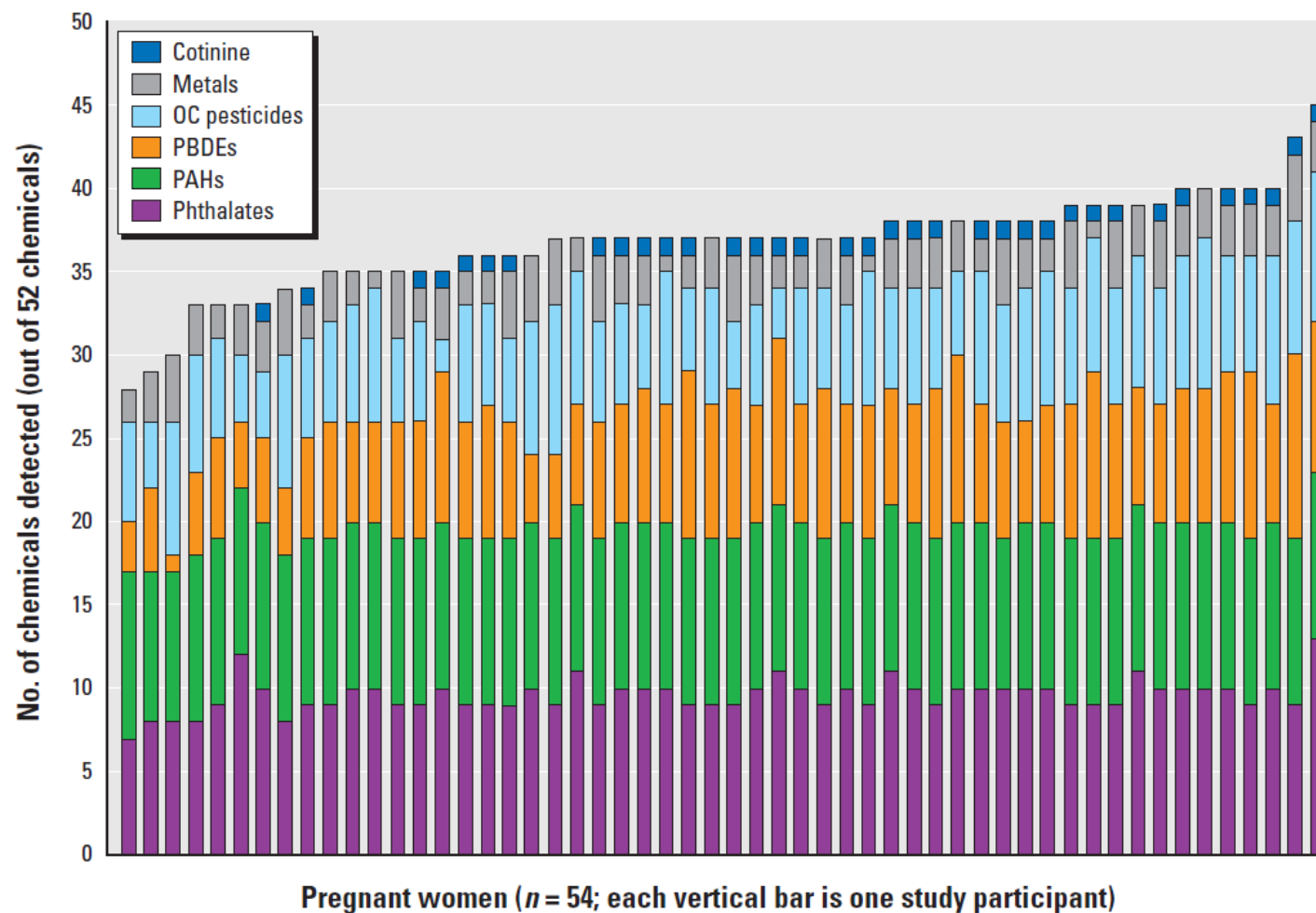
Endocrine disrupting chemicals



Endocrine disrupting chemicals

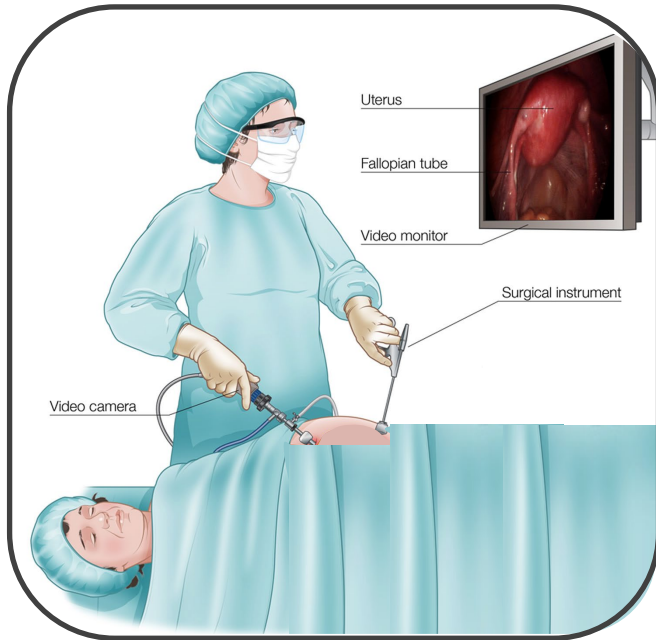


Endocrine disrupting chemicals

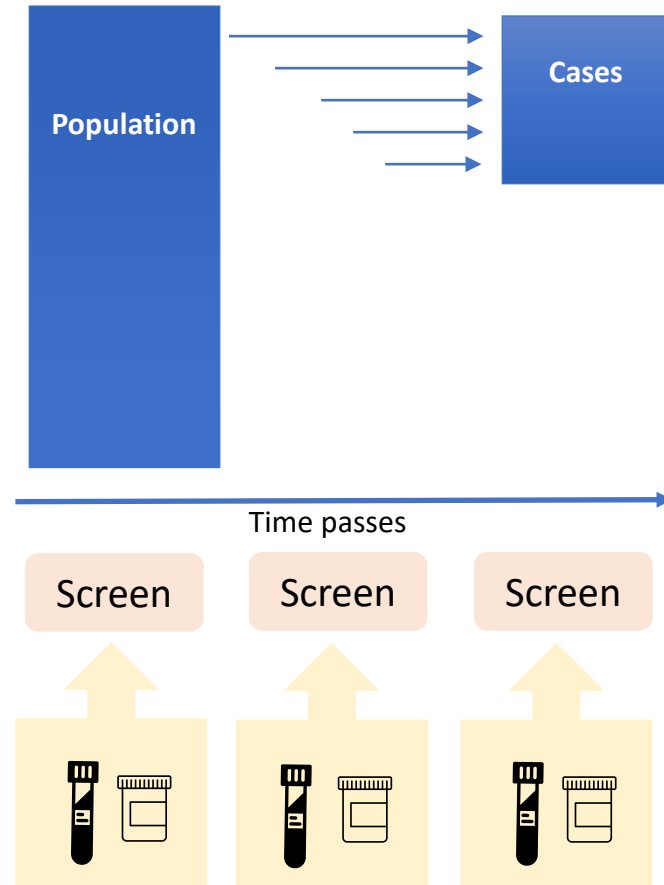


Endometriosis: Major challenge

Definitively diagnosed
by surgical visualization

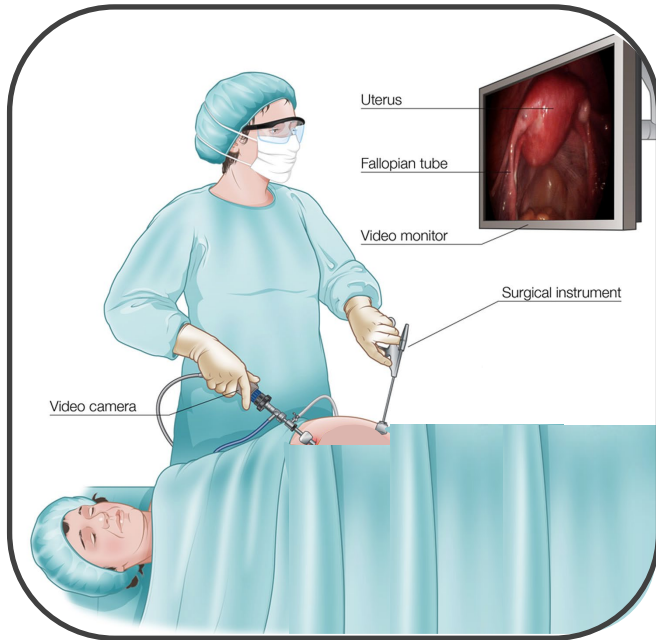


Prospective cohort study

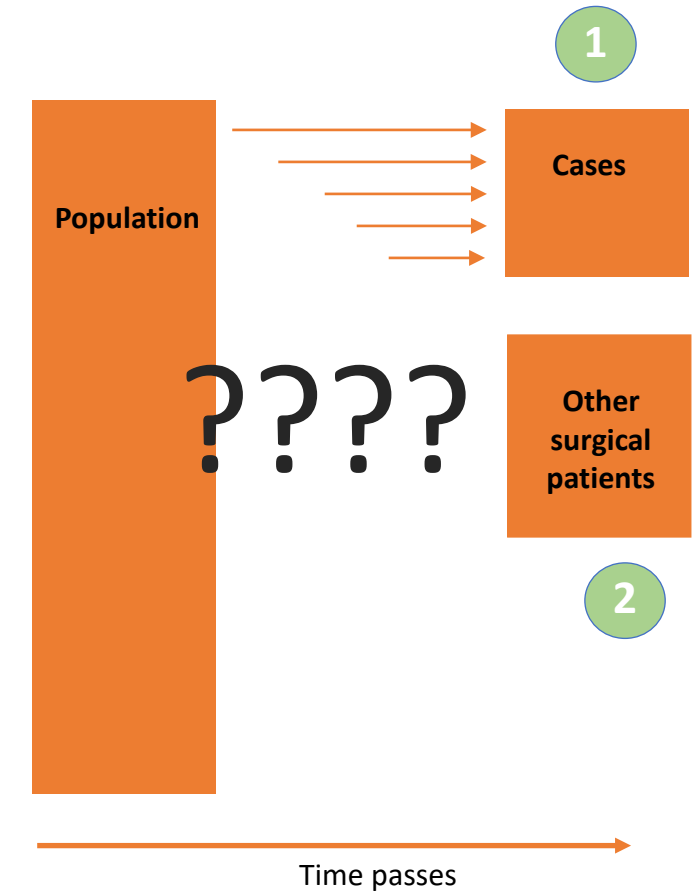


Endometriosis: Major challenge

Definitively diagnosed
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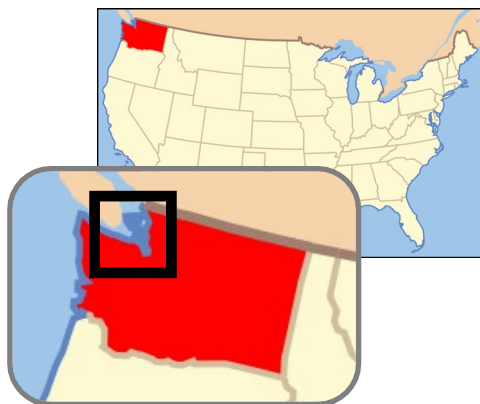
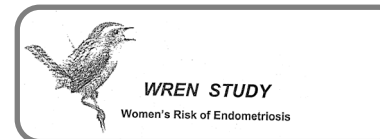
Case-control study



Upson K. *Curr Epidemiol Rep* 2020;7: 149-170.

Image (modified) from: <https://healthjade.com/laparoscopy/>

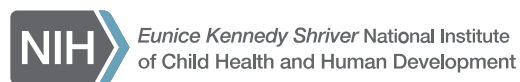
Women's Risk of Endometriosis (WREN) Study



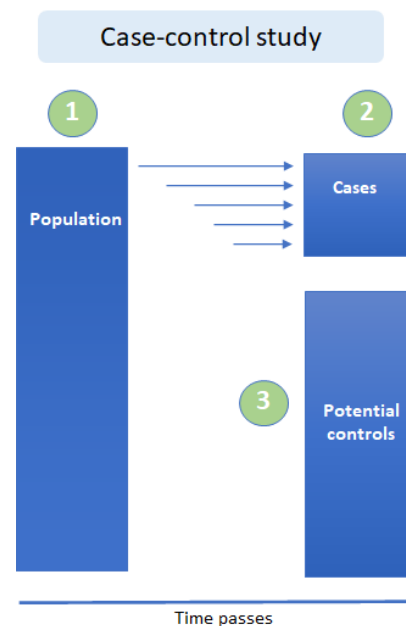
Victoria Holt, PhD



Delia Scholes, PhD



R01 HD033792



Endometriosis cases

- Ages 18-49
- Diagnosed years 1996-2001
- Surgically-confirmed

Population controls

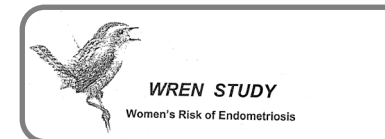
- Ages 18-49
- Randomly selected enrollees
- Age-matched to cases

Eligibility criteria:

- Pre-menopausal
- Ages 18-49
- Intact uterus
- At least one ovary
- No prior endometriosis diagnosis
- Enrolled >6 months before reference date

Date of first visit for symptoms leading to endometriosis diagnosis

Women's Risk of Endometriosis (WREN) Study



Endometriotic disease case definition

Focus on endometriosis with

- Tissue invasiveness
- Interference with physiologic processes

Benefits

- ↑ likelihood of observing true etiologic associations
- ↓ frequency of undiagnosed disease in study population

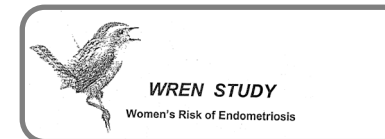
Data on:

- Ovarian endometriosis
- Non-ovarian pelvic endometriosis

Table 1. Proposed Standard Definition of Endometriotic Disease for Epidemiologic Studies of Endometriosis

Status	Signs and Symptoms
Definite disease	Ovarian endometriomas of any size Pelvic endometriotic implants of any size >5 mm deep Pelvic endometriotic implants of any size with adhesions not attributable to another cause
Possible disease	Pelvic endometriotic implants not meeting above criteria, plus one or more of the following symptoms: <ul style="list-style-type: none">• Infertility• Moderate to severe dysmenorrhea (painful menstrual periods)• Moderate to severe dyspareunia (pain during intercourse)• Moderate to severe pelvic pain

Women's Risk of Endometriosis (WREN) Study



WREN participants:

310 Endometriosis cases

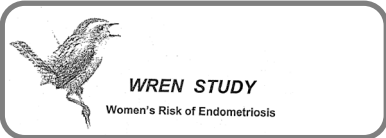
727 Population controls

In-person structured interview

- Conducted by trained female interviewers
- At participant home or Fred Hutch
- Questions covered range of health histories
 - e.g., menstruation, reproductive, pregnancy, contraception
- Methods employed to aid recall



Women's Risk of Endometriosis (WREN) Study



Matrix



Laboratory



Analytes



Funding



11 Organochlorine pesticides (OCPs)
34 Polychlorinated biphenyl
congeners (PCBs)
(non-dioxin-like)



Science to Achieve Results
(STAR) grant R829438



Institut für Prävention und Arbeitsmedizin
der Deutschen Gesetzlichen Unfallversicherung
Institut der Ruhr-Universität Bochum

Bisphenol A (BPA)



National Institute of
Environmental Health Sciences

R03ES019976

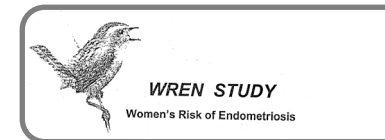



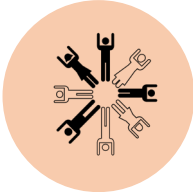


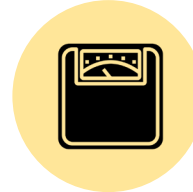


8 Phthalate metabolites



University of Washington
Doctoral Dissertation Small
Grants Program

Women's Risk of Endometriosis (WREN) Study

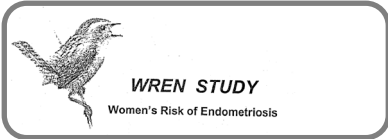


							
	Median age (IQR)	White race	College graduate	Income (≥\$70,000)	BMI (≥30)	Current smoker	Nulli- parous
Cases (n=310)	39 years (IQR: 33-44)	85%	46%	23%	21%	20%	48%
Controls (n=727)	39 years (IQR: 33-44)	83%	41%	28%	20%	17%	30%

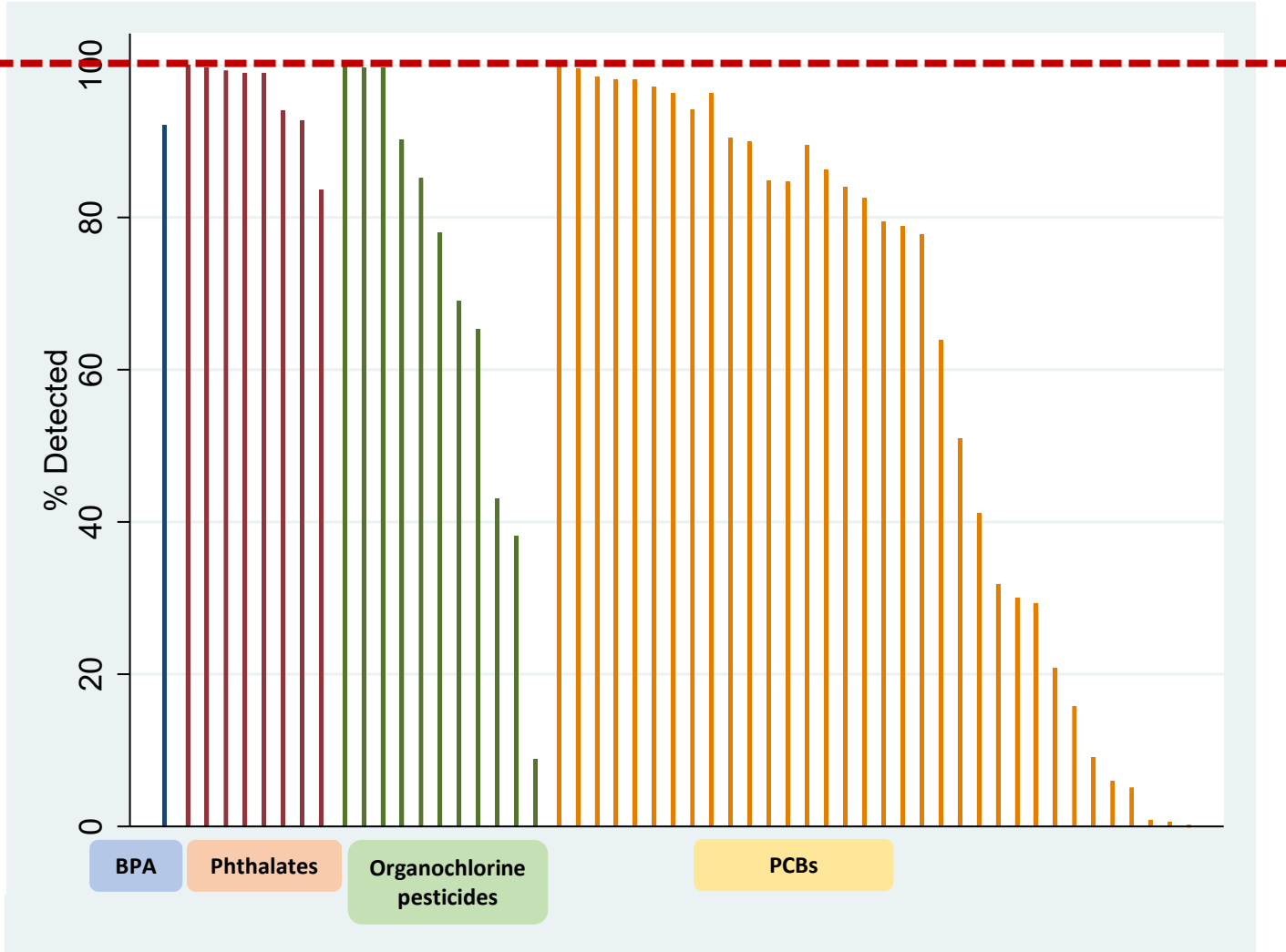
Upson K, et al. *Fertil Steril* 2015;104: 964-971 e965.

Icons from Alexa, Deemak Daksina, Adrien Coquet, Nikita Kozin, dDara, and Yeong Rong Kim at the Noun Project

Women's Risk of Endometriosis (WREN) Study

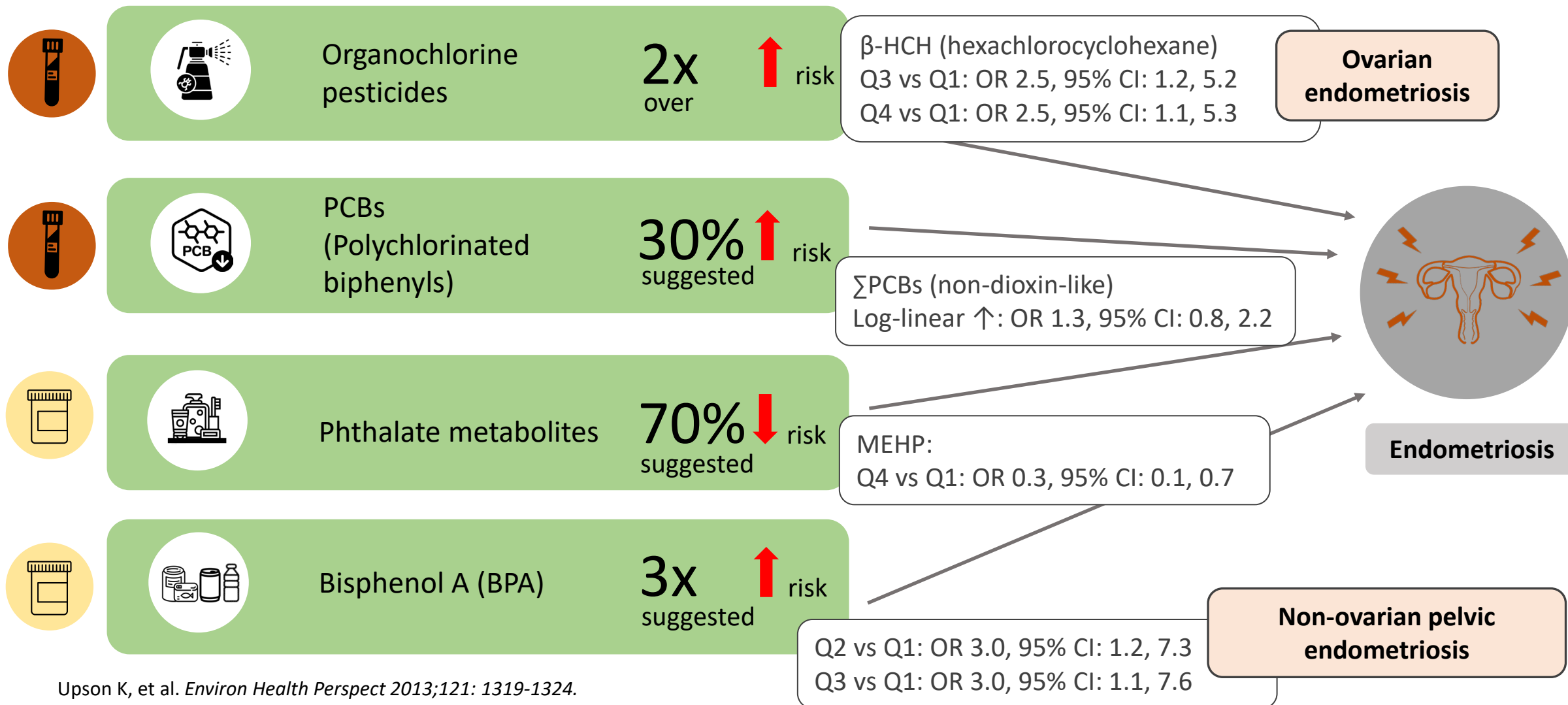
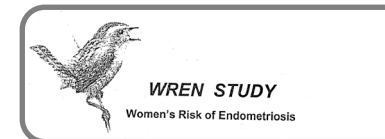


Detected in 100%
of participants



Trabert B, et al. *Environ Health Perspect* 2010;118: 1280-1285.
Upson K, et al. *Environ Health Perspect* 2013;121: 1319-1324.
Upson K, et al. *Environ Res* 2013;126: 91-97.
Upson K, et al.. *Hum Reprod* 2014;29: 2457-2464.

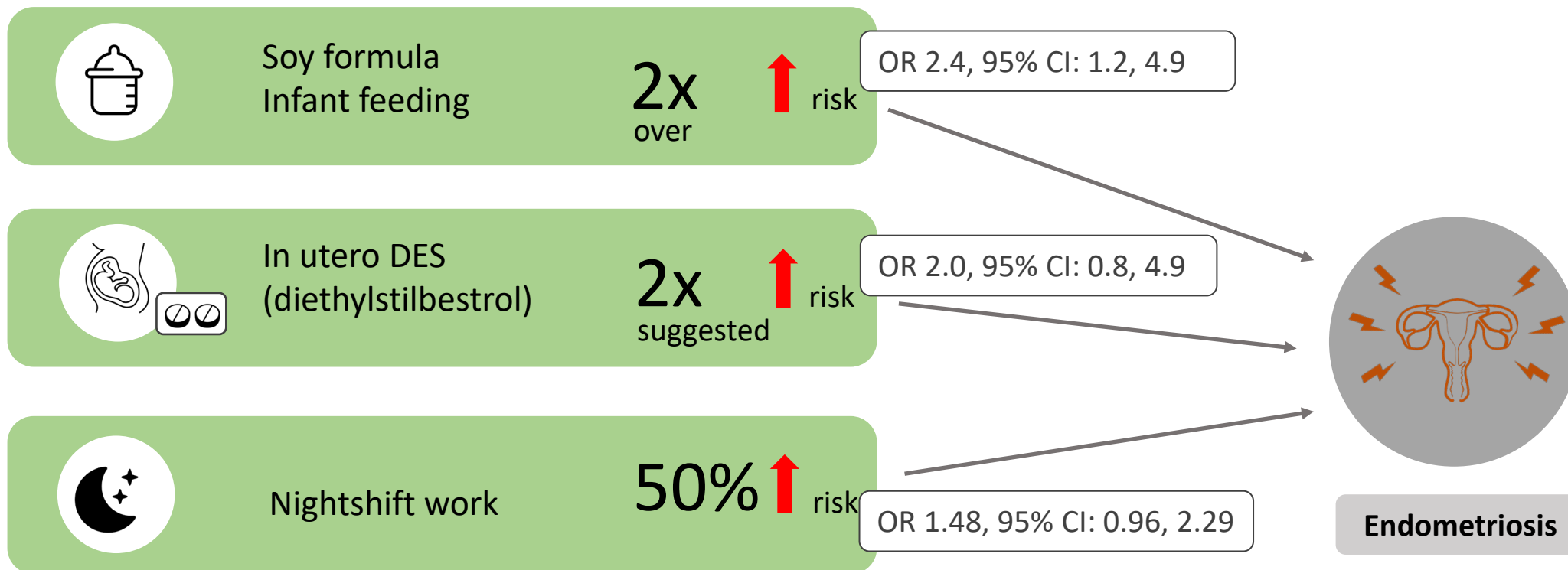
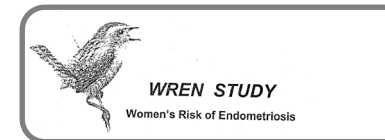
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Icons from Lia Rahdiah, Foodicons, Collection, Eucalyp, IconMark, Arthur Shlain, Kelly Ness, Sahab Uddin, Vectorstall, Hermine Blanquart, Visualeat, Justin Blake, and Jonathan Li at the Noun Project

Women's Risk of Endometriosis (WREN) Study

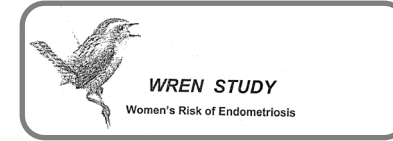


Upson K, et al. *Fertil Steril* 2015.

Marino JL, et al. *Epidemiology* 2008;19: 477-484.

Icons from Flatart, arif fajar yulianto, fibo junior, Hermine Blanquart, and Justin Blake at the Noun Project

Women's Risk of Endometriosis (WREN) Study



Limitations

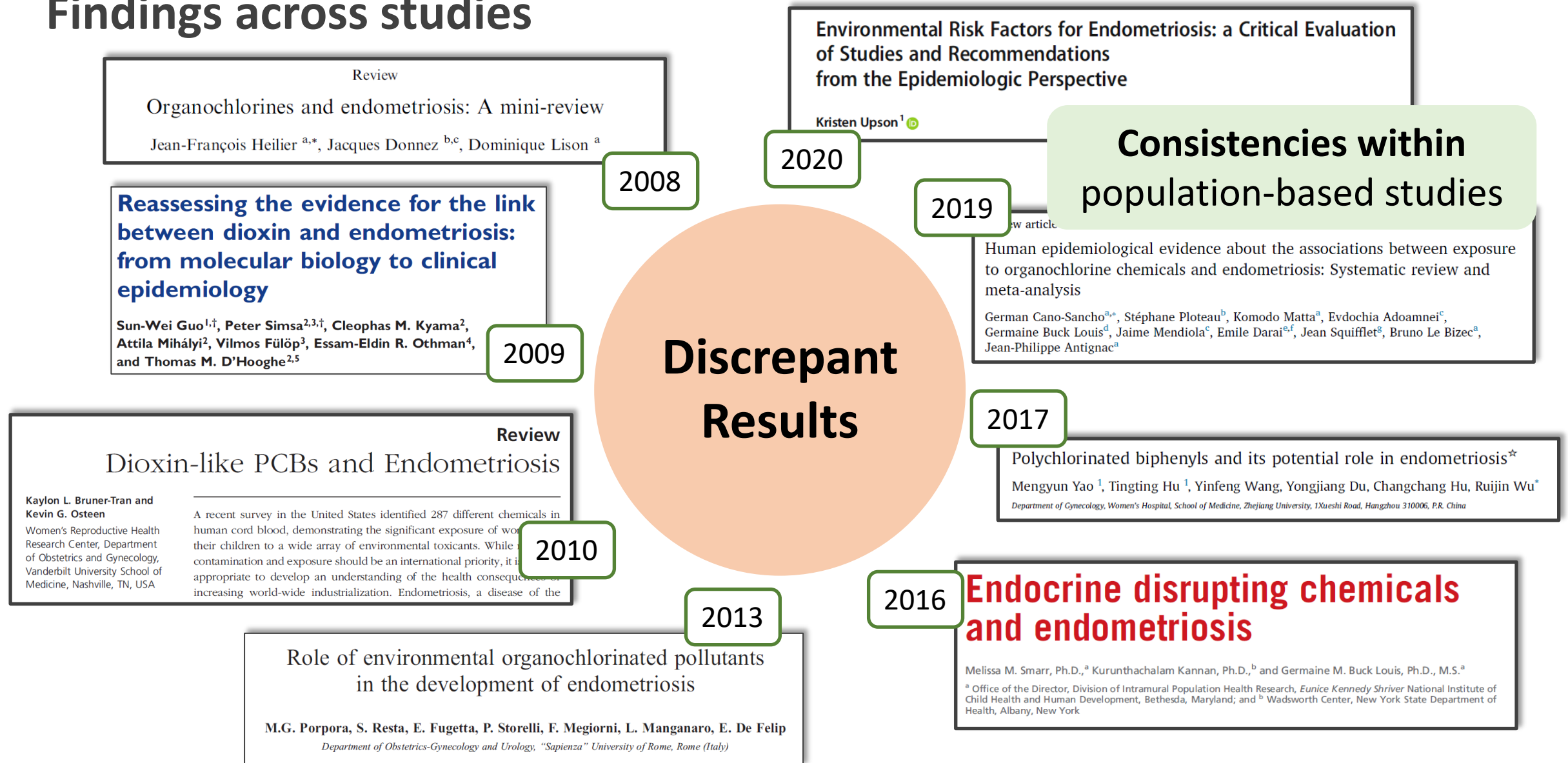
- Biologic sample collection after case diagnosis
- Single sample for non-persistent chemicals (BPA, phthalates)
- Research conducted before recent developments in mixtures analyses
- Undiagnosed disease among controls



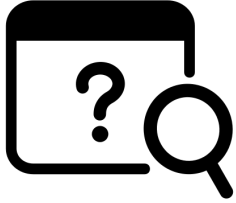
Strengths

- Population-based sampling
- Collection of biologic samples
- Years of biologic sample collection (before EDCs widely known)
- Data on ovarian and non-ovarian pelvic endometriotic lesion location

Findings across studies



Heilier JF, et al. *Chemosphere* 2008;71: 203-210; Guo SW et al. *Mol Hum Reprod* 2009;15: 609-624; Bruner-Tran et al. *Systems biology in reproductive medicine* 2010;56: 132-146; Porpora MG, et al. *Clin Exp Obstet Gynecol* 2013;40: 565-567; Smarr MM, et al. *Fertil Steril* 2016;106: 959-966; Yao M, et al. *Environmental pollution* 2017;229: 837-845; Cano-Sancho G et al. *Environment international* 2019;123: 209-223; Upson K. et al. *Curr Epidemiol Rep* 2020;7: 149-170.



Reasons for disparate results

Study population differences

Exposure measurement

Confounder adjustment

Undiagnosed disease in
controls

Environmental Risk Factors for Endometriosis: a Critical Evaluation of Studies and Recommendations from the Epidemiologic Perspective

Kristen Upson¹ 

Reasons for disparate results

Study population sampling

Sample collection at
diagnosis

Statistical analysis issues

Single disease entity

Heilier JF, et al. *Chemosphere* 2008;71: 203-210; Guo SW et al. *Mol Hum Reprod* 2009;15: 609-624; Bruner-Tran et al. *Systems biology in reproductive medicine* 2010;56: 132-146; Porpora MG, et al. *Clin Exp Obstet Gynecol* 2013;40: 565-567; Smarr MM, et al. *Fertil Steril* 2016;106: 959-966; Yao M, et al. *Environmental pollution* 2017;229: 837-845; Cano-Sancho G et al. *Environment international* 2019;123: 209-223; Upson K. et al. *Curr Epidemiol Rep* 2020;7: 149-170.

Recommendations

1

Population-based sampling

Novel avenues:

- Build capacity to collect endometriosis data in large, epidemiologic cohort studies

2

Exposure during etiologically-relevant window

Novel avenues:

- Archived newborn dried blood spots
- Baby teeth
- Link with existing data (e.g., air pollution)

3

Disaggregating endometriosis

Novel avenues:

- Collect operative and pathology reports

4

Environmental exposures unique to menstruators

Novel avenues:

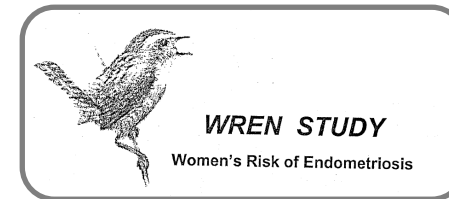
- Menstrual product use
- Menstrual blood loss
- Hormonal contraceptive use

5

Team science

- Epidemiology
- Biostatistics
- Toxicology
- Exposure science
- Gynecology

Women's Risk of Endometriosis (WREN) Study



WREN Researchers

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Delia Scholes, PhD

Jennifer Marino, PhD, MPH

Britton Trabert, PhD, MS

Kristen Upson, PhD, MPH

WREN Collaborators

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Dana Barr, PhD

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Science to Achieve Results (STAR)
grant R8294538 (Holt)

National Institute of Environmental
Health Sciences
R03ES019976 (Holt)

Eunice Kennedy Shriver National
Institute of Child Health and Human
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Research F31NR013092
(Upson)

National Institute of Nursing
Research F31NR009164
(Marino)

University of Washington
Department of Epidemiology
Doctoral Dissertation Small
Grants Program (Upson)

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