Building a search engine to find environmental exposures associated with disease and health

Epidemiological evidence from average and high-risk populations

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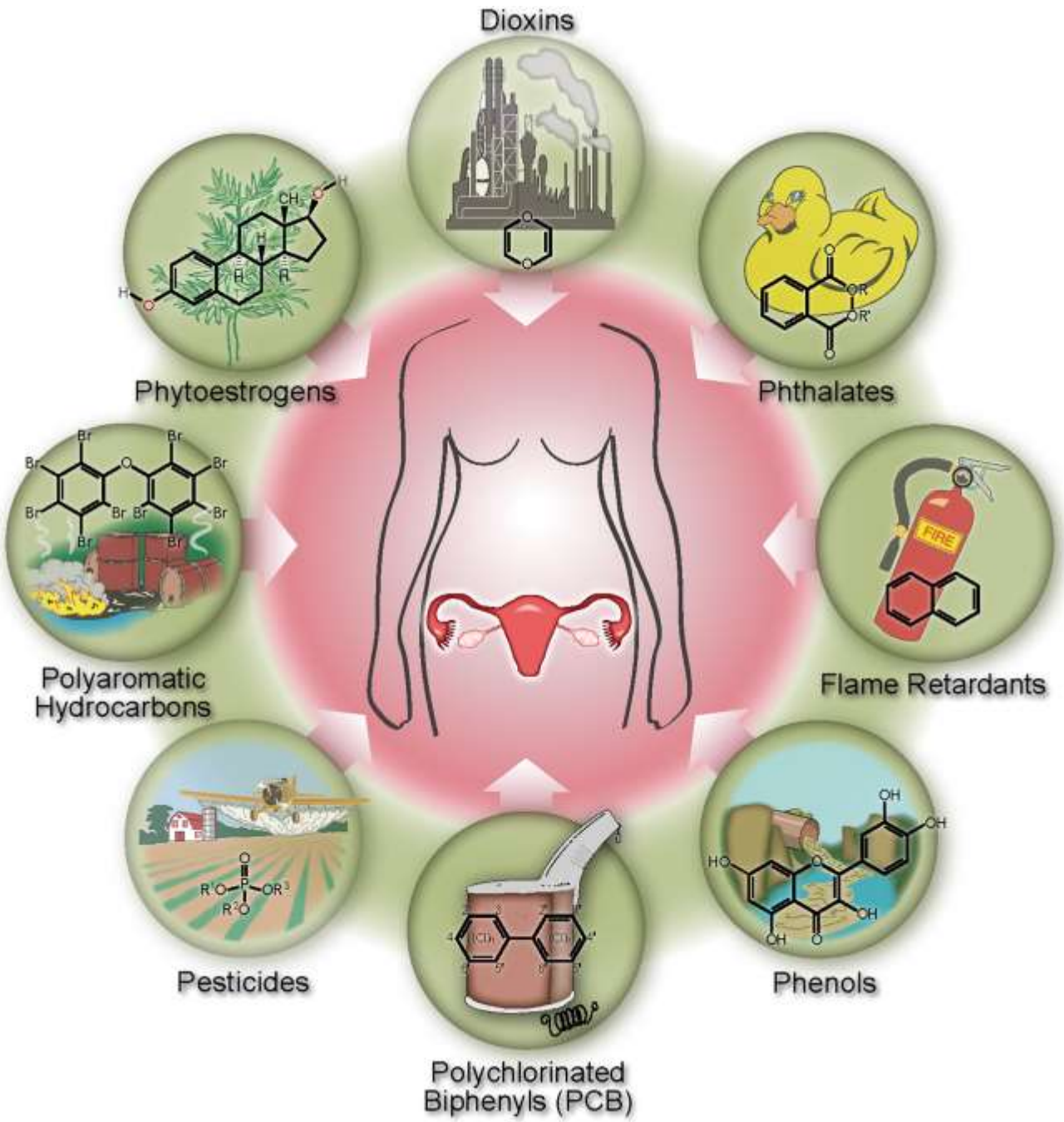
Overview

Goal = This work needs to be done!

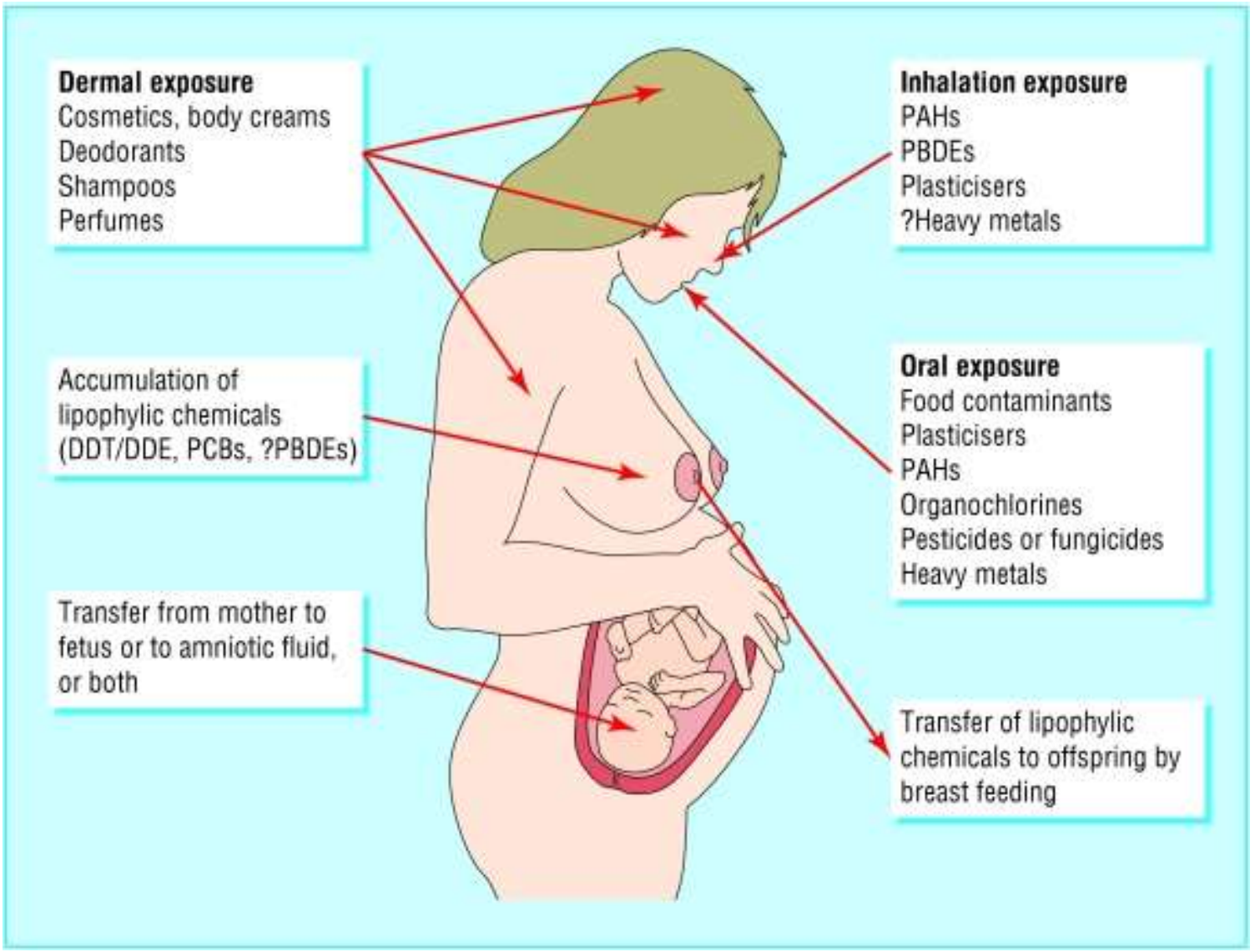
- Overview of endocrine disrupting chemicals (EDCs)
- Background on associations between EDCs and pregnancy health
- Example of specific EDC and pregnancy complication
  - Average risk
  - Higher risk (women seeking care at a fertility center)
- Next steps toward improving research and informing clinical care in environmental and pregnancy health

What is an environmental endocrine disruptor?

"An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations" WHO, 2013

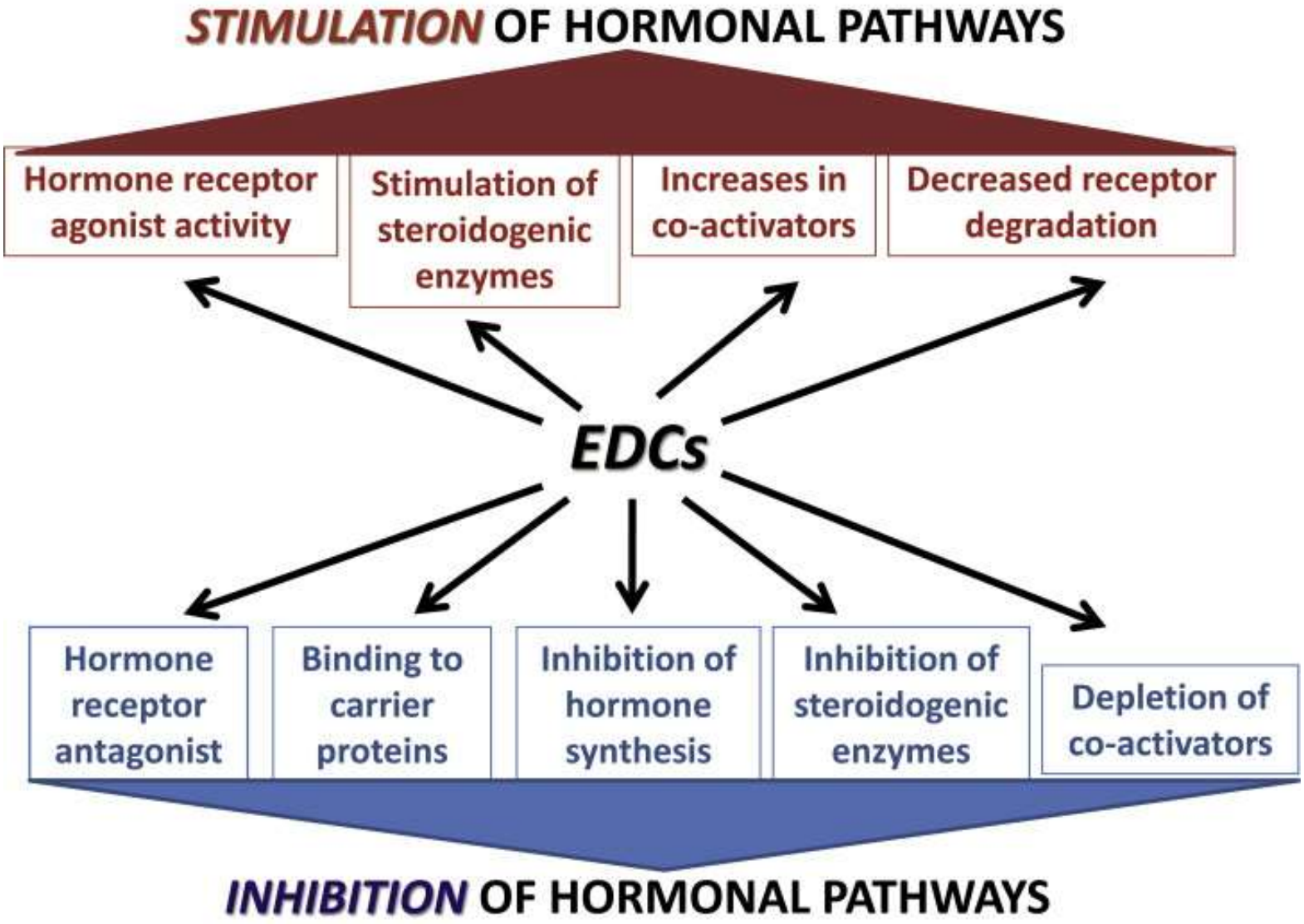


Routes of exposure



Sharpe et al, BMJ 2004

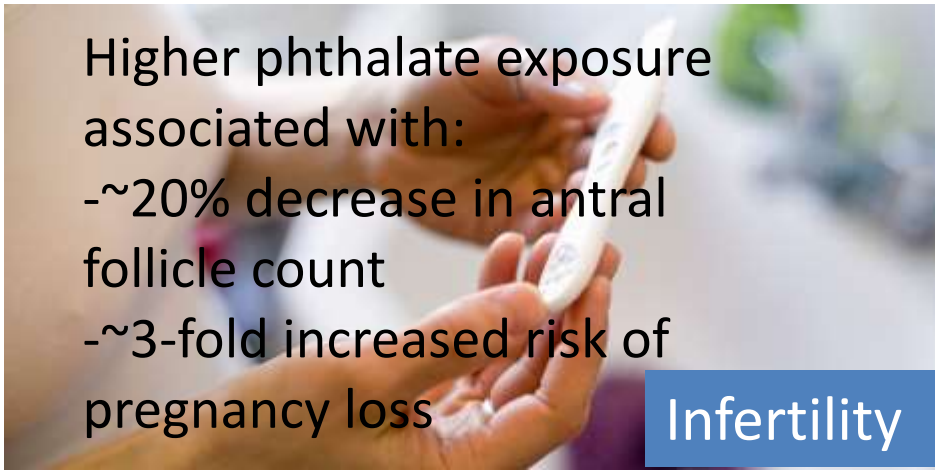
Mechanisms of Endocrine Disruption

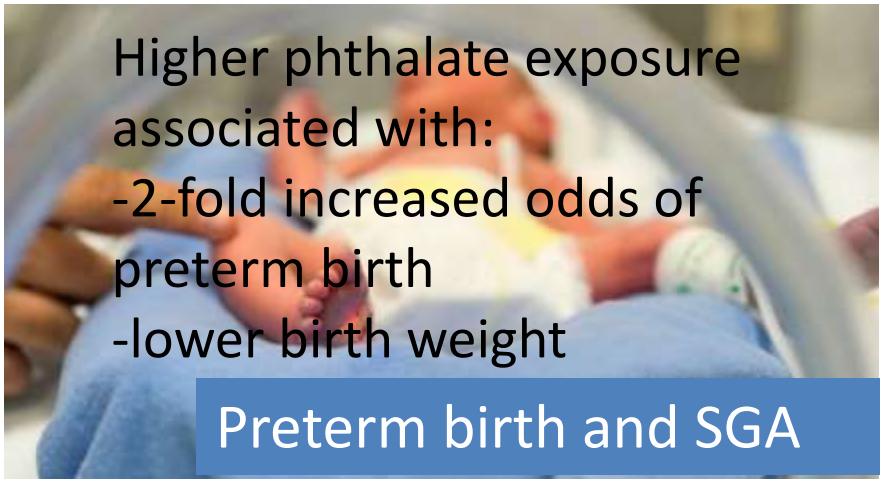


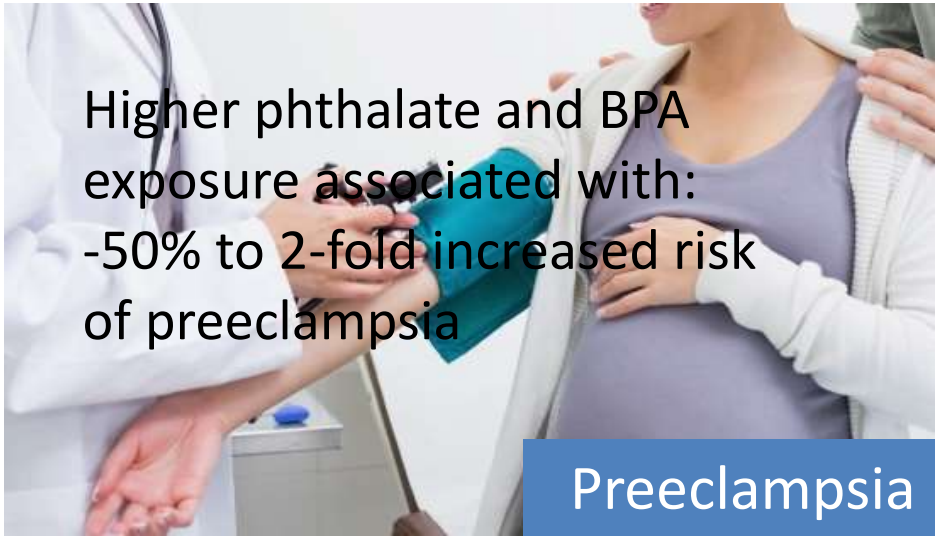
Cooke, et al., Haschek and Rousseaux's Handbook on Toxicologic Pathology, 2013

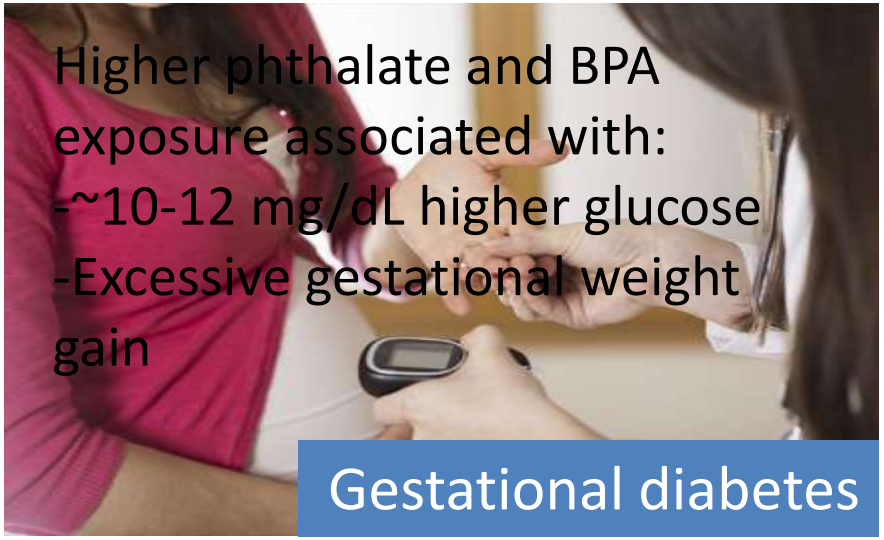
EDCs and pregnancy health

Once pregnant, ~25% of pregnancies in the United States have one of these 4 complications





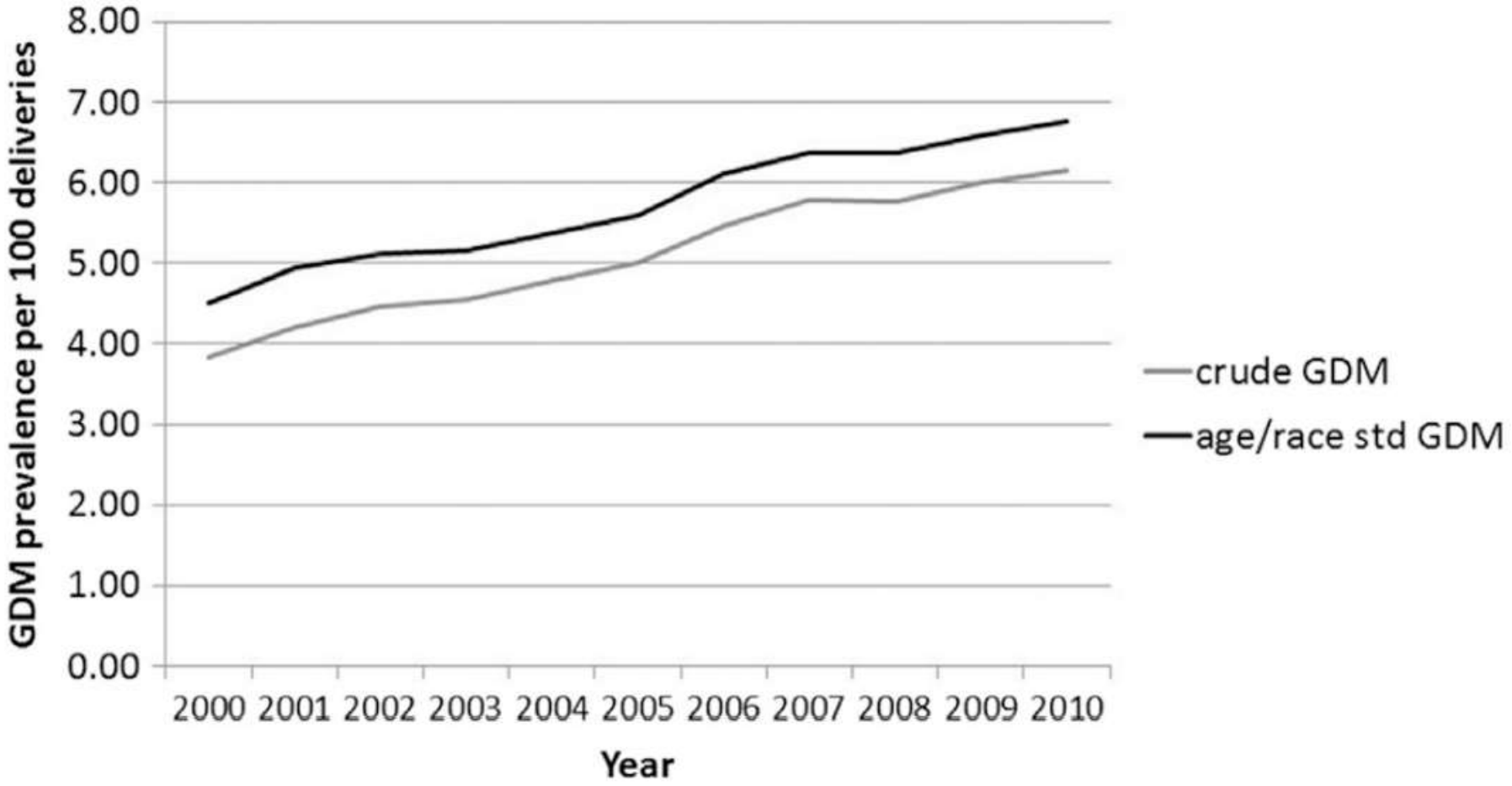




PHTHALATES AND GESTATIONAL DIABETES:

EXAMPLES FROM AVERAGE AND HIGH RISK POPULATIONS

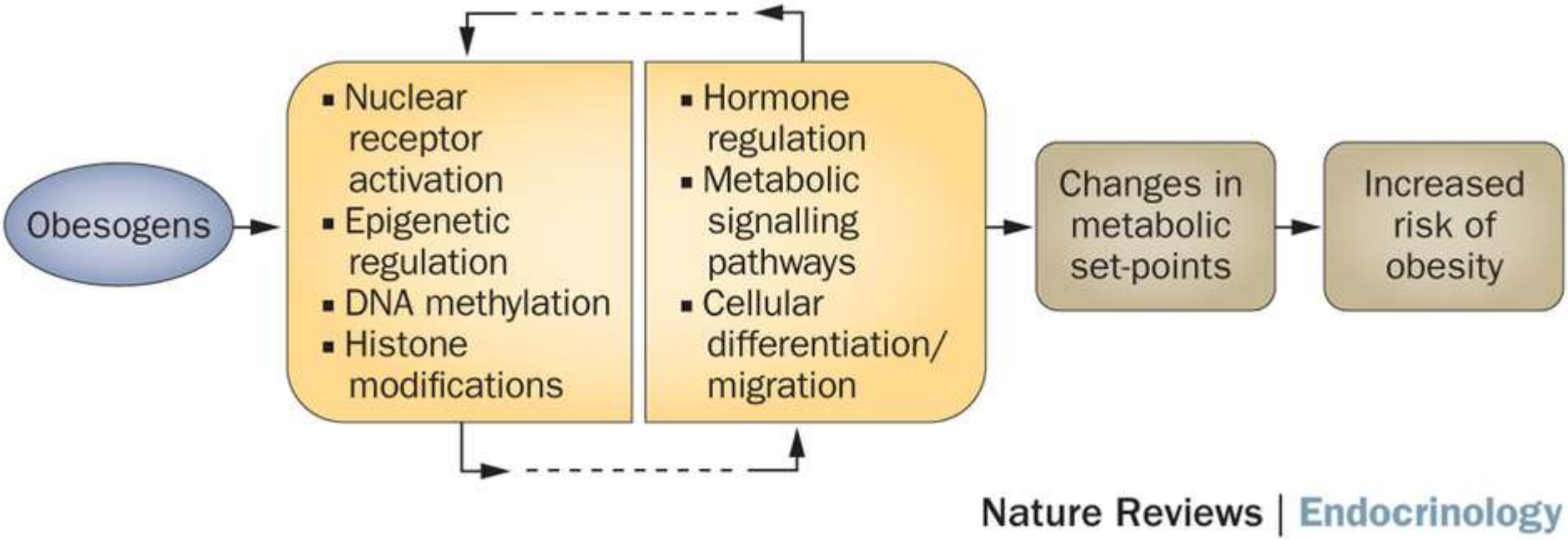
Prevalence of GDM



Bardenheier, Am J Prev Med, 2015

GDM Risk Factors

An example: Obesogens as EDCs



Heindel et al, Nature Reviews Endocrinology 2015

Phthalates, Obesity, Insulin Resistance & Diabetes

Research

2007

Concentrations of Urinary Phthalate Metabolites Are Associated with Increased Waist Circumference and Insulin Resistance in Adult U.S. Males

Richard W. Stahlhut,[1] Edwin van Wijngaarden,[1] Timothy D. Dye,[1,2] Stephen Cook,[3] and Shanna H. Swan[4]

[1]Department of Community and Preventive Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA; [2]Department of Research and Evaluation, Axios International, Paris, France; [3]Department of Pediatrics, and [4]Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA

Environmental Health

BioMed Central

2008

Research

Open Access

Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999–2002

Elizabeth E Hatch*[1], Jessica W Nelson[2], M Mustafa Qureshi[3], Janice Weinberg[4], Lynn L Moore[3], Martha Singer[3] and Thomas F Webster[2]

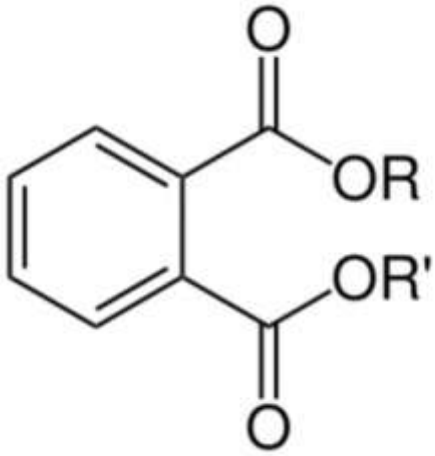
Phthalates





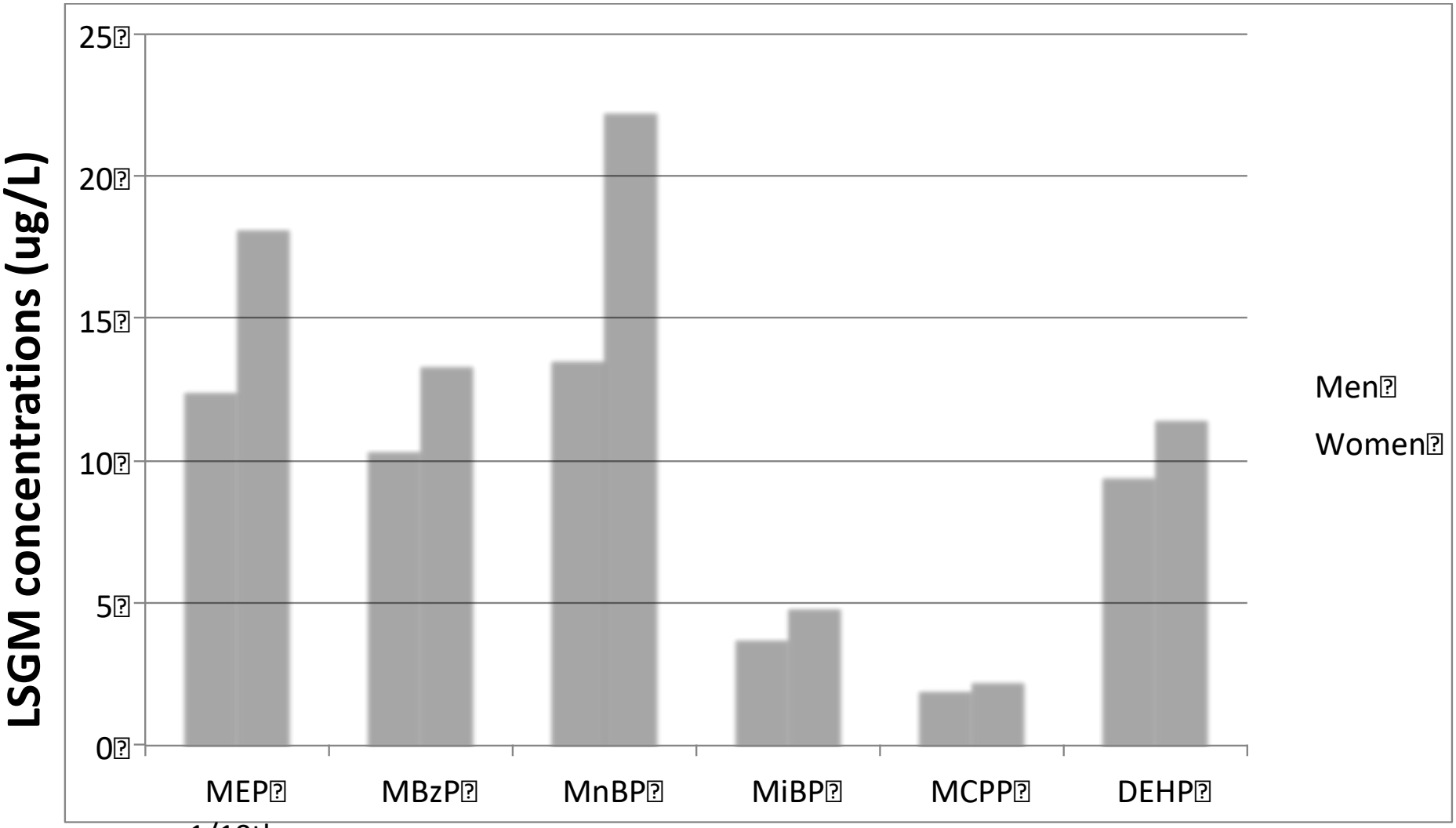
- Ubiquitous—75% of U.S. population has detectable levels
- Plasticizers, solvents, and lubricants
- Ingested, inhaled, and absorbed through skin

Phthalate metabolites of Interests:



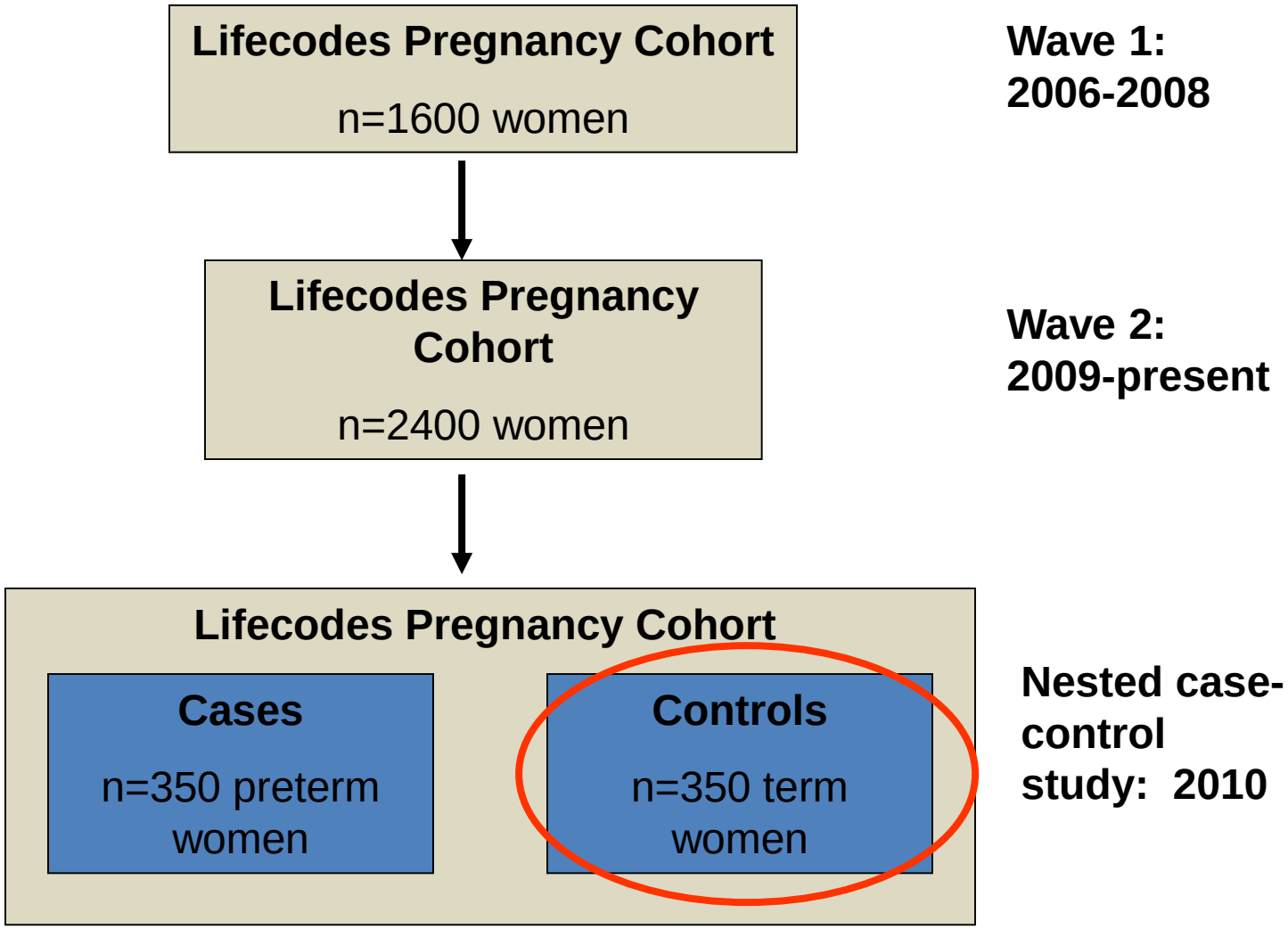
- Mono-ethyl phthalate (MEP)
- Mono-n-butyl phthalate (MBP)
- Mono-isobutyl phthalate (MiBP)
- Mono-benzyl phthalate (MZP)
- Mono-(3-carboxypropyl) phthalate (MCPP)
- Monomethyl phthalate (MMP)
- Mono-(2-ethyl)-3-hexyl phthalate (MEHP)
- Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP)
- Mono-2-ethyl-5-oxohexyl phthalate (MEOHP)

Phthalate Exposure by Sex (NHANES 1999-2010)



James-Todd et al, Environ Health, 2014

Average risk population: Lifecodes Pregnancy Cohort (BWH)



Lifecodes study data collection

Visit 1 (8-10 wks)	***Visit 2 (16-18 wks)***	***Visit 3 (22-26 wks)***	***Standard clinical care (24-28 wks)***	***Visit 4 (33-35 wks)***	***Delivery***
Blood, **Urine**, Survey, Diagnoses, Weight, and Height			**50 gram glucose load testing** and/or 100-gram oral glucose tolerance test for diagnosis of GDM	Blood, Urine, Survey, Diagnoses, Weight, Height	Labor and delivery records

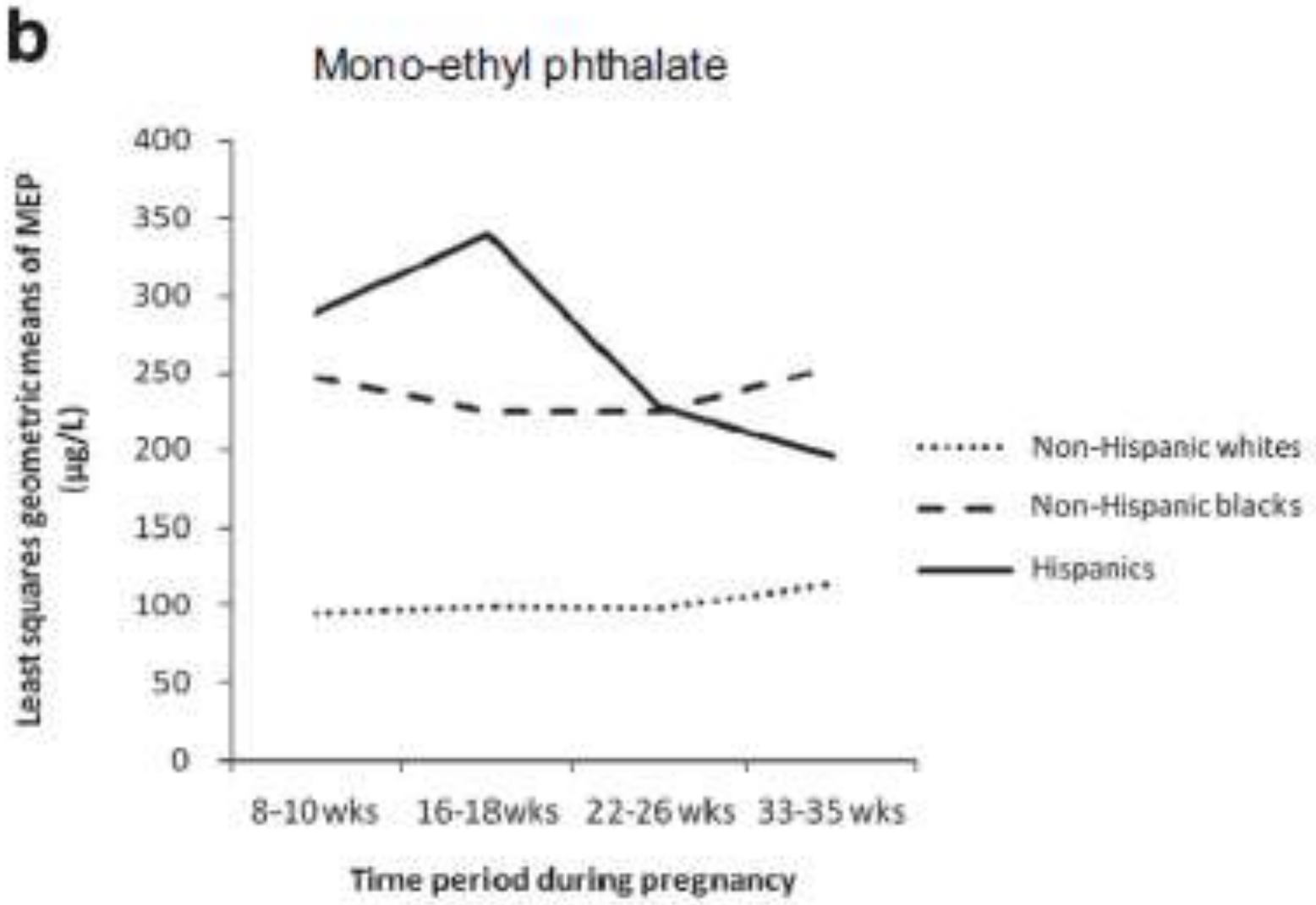
Statistical Analysis

- For continuous glucose levels, multivariable generalized linear models were used
- Multivariable logistic regression was used for categorical glucose outcomes
- Maternal age, race/ethnicity, education, and family history of diabetes as potential confounders
- All values are age and specific gravity adjusted

Lifecodes Pregnancy Cohort Study Population Characteristics (Controls-only, n=350)

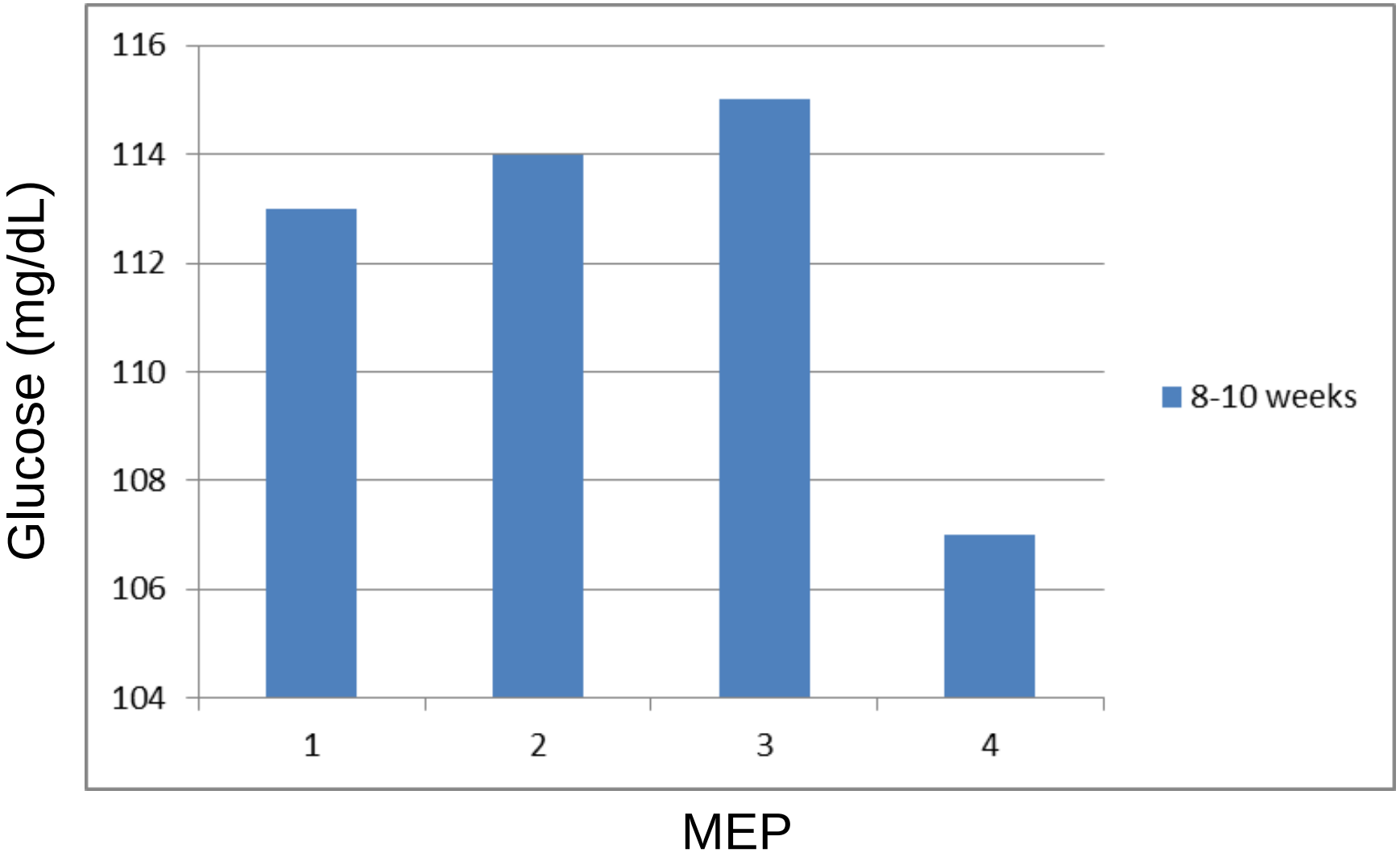
Maternal age (mean (SD))	31.9 (5.5)
Maternal BMI kg/m^2 (mean(SD))	25.9 (5.7)
Baseline weight in kg (mean(SD))	70.4 (15.7)
Education (%)	
<HS	13.4
Technical school/Some college	43.5
≥College	43.1
Ever smoking (%)	5.4
Current	23.1
Past	2.3
Family history of diabetes	45.1

Phthalates across pregnancy



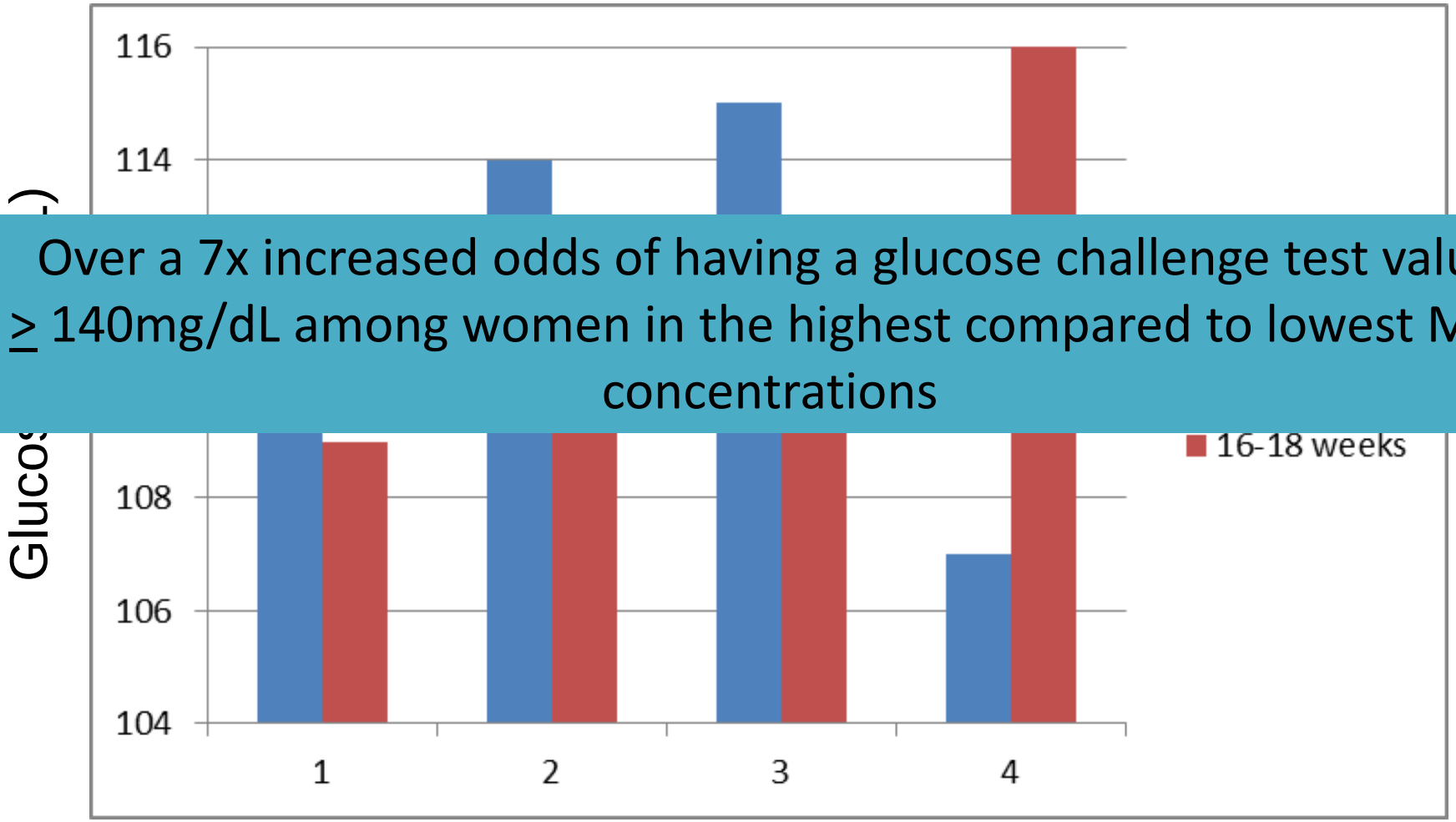
James-Todd et al, JESEE 2016

Phthalates and second trimester blood glucose



James-Todd et al, Env. Int. 2016

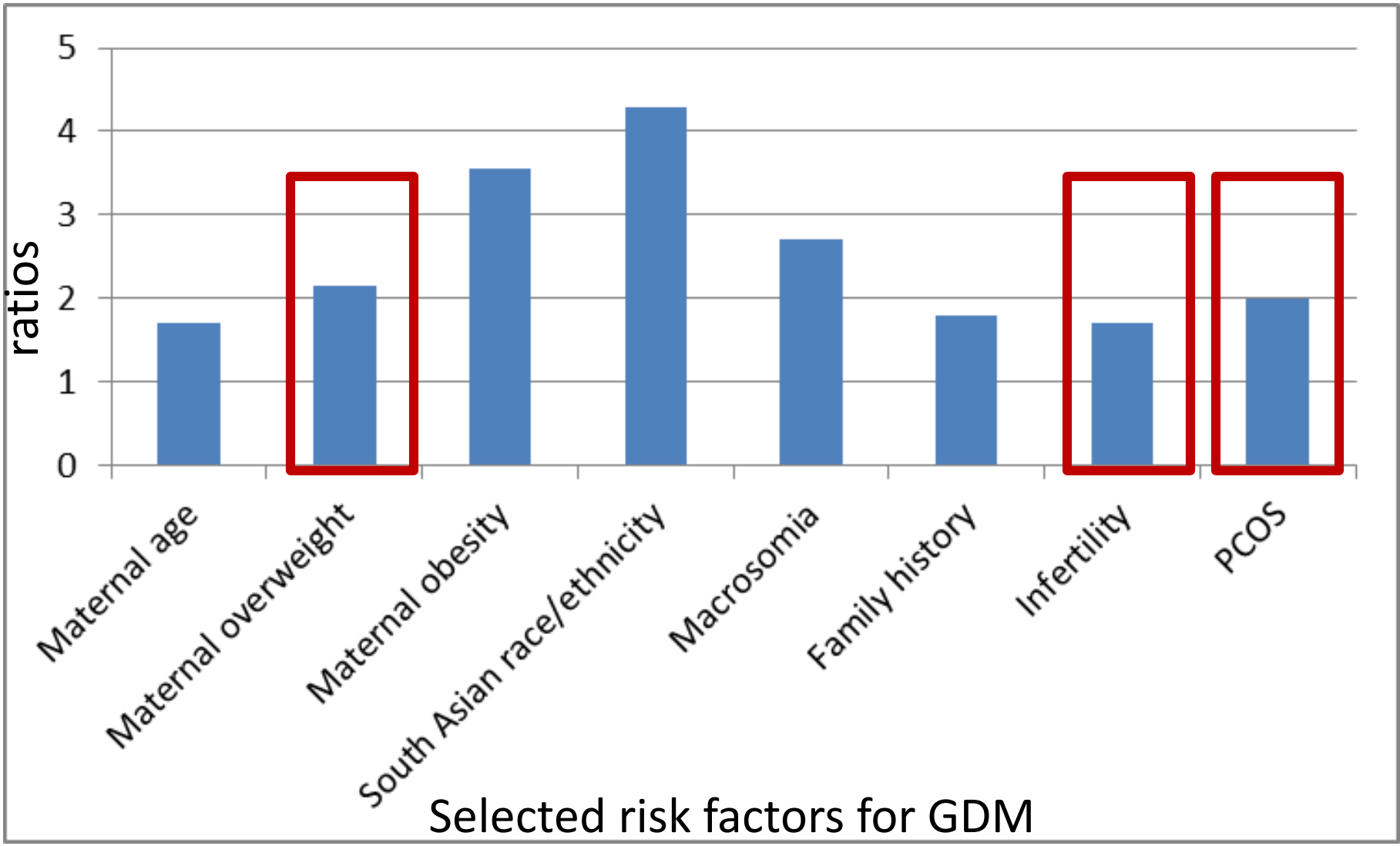
Phthalates and second trimester blood glucose



Over a 7x increased odds of having a glucose challenge test value ≥ 140mg/dL among women in the highest compared to lowest MEP concentrations

James-Todd et al, Env. Int. 2016

What about high-risk groups?



Environment and Reproductive Health (EARTH) study

- Prospective cohort study
- Women (and men) recruited since 2004 from Massachusetts General Hospital (MGH) Fertility Center (Boston, MA)
- A total of 246 women had available data on urinary phthalate metabolite concentrations from the 1st and 2nd trimesters (437 urine samples) and glucose data.

EARTH STUDY

EARTH study: overview of data collection

Preconception	***1st Trimester***	***2nd Trimester***	***3rd Trimester***	***Standard clinical care (24-28 wks)***
Blood, **Urine**, Questionnaires, Diagnoses, Weight, and Height				**50 gram glucose load testing** and/or 100-gram oral glucose tolerance test for diagnosis of GDM

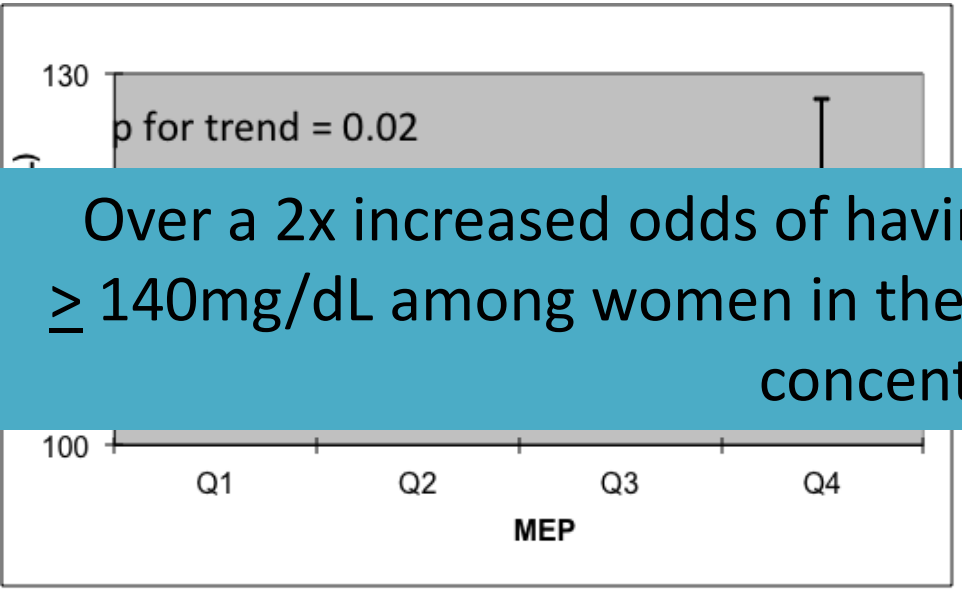
EARTH STUDY

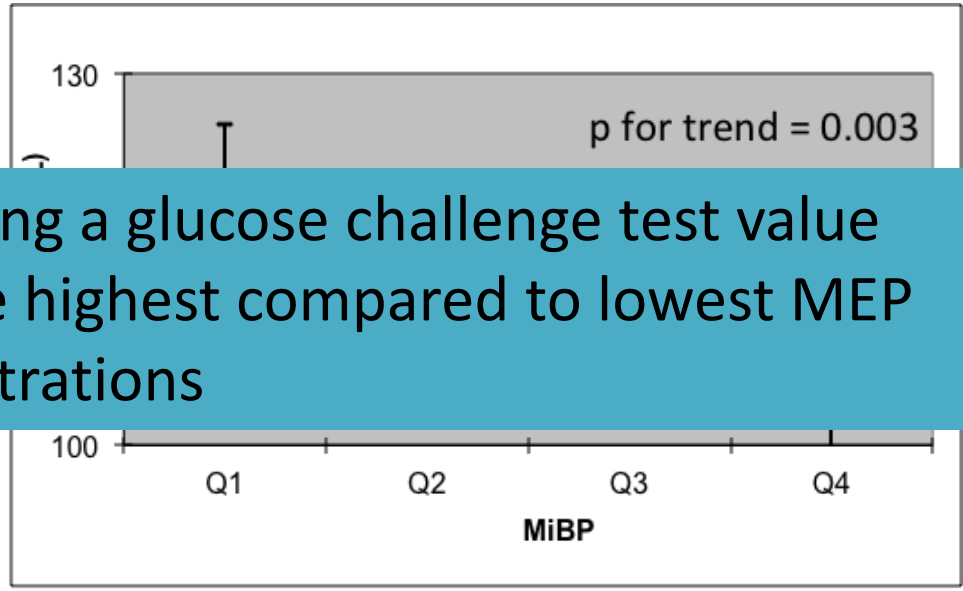
EARTH study population characteristics

Maternal characteristics	N=246
Mean maternal age	35 (3.8)
BMI >25kg/m²	74%
White	87%
>College graduate	88%
Family history of diabetes	12%
Infertility diagnosis	
IVF	56%
IUI	22%
Natural	22%
Multiples	19%
Glucose >140mg/dL	18%

EARTH STUDY

Phthalate metabolite concentrations in 2nd trimester and glucose levels





Over a 2x increased odds of having a glucose challenge test value ≥ 140mg/dL among women in the highest compared to lowest MEP concentrations

Adjusted for maternal age, race/ethnicity, education, BMI, smoking status, infertility diagnosis, family history of diabetes, and number of fetuses

EARTH STUDY

Strengths and limitations

Strengths:

- Prospective cohort design
- Assessed phthalate exposure at two time points
- Assessed in average and higher risk populations

Limitations:

- Urinary phthalate metabolites were evaluated in spot urines
- We did not assess overt GDM
- Higher risk women were those with a history of infertility for a variety of reasons

Conclusions and implications

- 2nd trimester exposure to diethyl phthalate, the parent compound of MEP--commonly used in personal care products, associated with increased glucose levels during pregnancy

- On the other hand, 2nd trimester exposure to MiBP was associated lower glucose levels during pregnancy

- 2nd trimester may be a more sensitive period for phthalate exposure as it relates to glucose dysregulation in pregnancy

Search engine for environmental exposures in epidemiological research

Examples of social factors:

- Sociodemographics
- Behavioral
- Residential
- Gender
- Stress
- Occupation

Examples of biological data:

- Blood
- Urine
- Semen
- Follicular fluid
- Placenta
- Cord blood
- Breast milk

Examples of health outcomes:

- Medical history
- Anthropometry
- Pregnancy complications
- Delivery outcomes
- Postpartum health
- Chronic disease

Data linkage issues are important to consider!

Next steps: Building a search engine for environmental exposures

Research

Clinical care

Education

Policy

Acknowledgements

Lifecodes Study Team:

- Tom McElrath, MD, PhD
- Ellen Seely, MD
- Janet Rich-Edwards, ScD, MPH
- John Meeker, PhD
- Kelly Ferguson, PhD
- Tianyi Huang, ScD, MPH
- David Cantonwine, PhD

EARTH Study Team:

- Russ Hauser, MD, ScD
- John Petrozza, MD
- Yu-Han Chiu, MD, MPH
- Carmen Messerlian, PhD
- Lidia Mínguez-Alarcón
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- Myra Keller, RN
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- Antonia Calafat, PhD
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- American Diabetes Association

Questions?

Types of EDCs

Half-life=Amount of time it takes for 50% of the chemical to leave your body

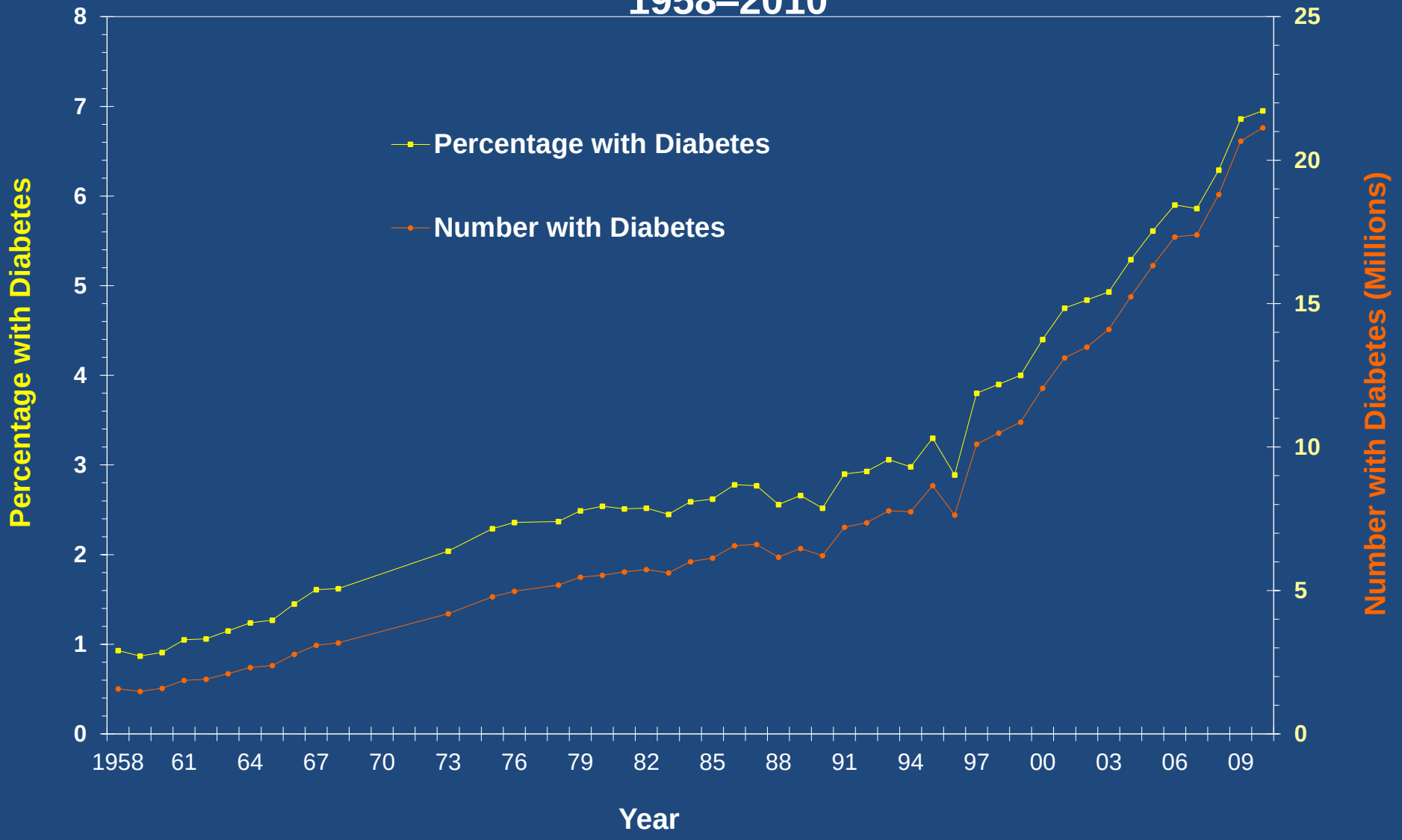
Persistent

- Persist in the environment, bioaccumulate through the food web over the course of years
- Examples:
  - PCBs
  - DDT
  - Dioxins

Non-persistent

- Rapidly excreted within hours or days
- Only recently considered to impact human health
- Examples:
  - Bisphenol A
  - Phthalates

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958–2010



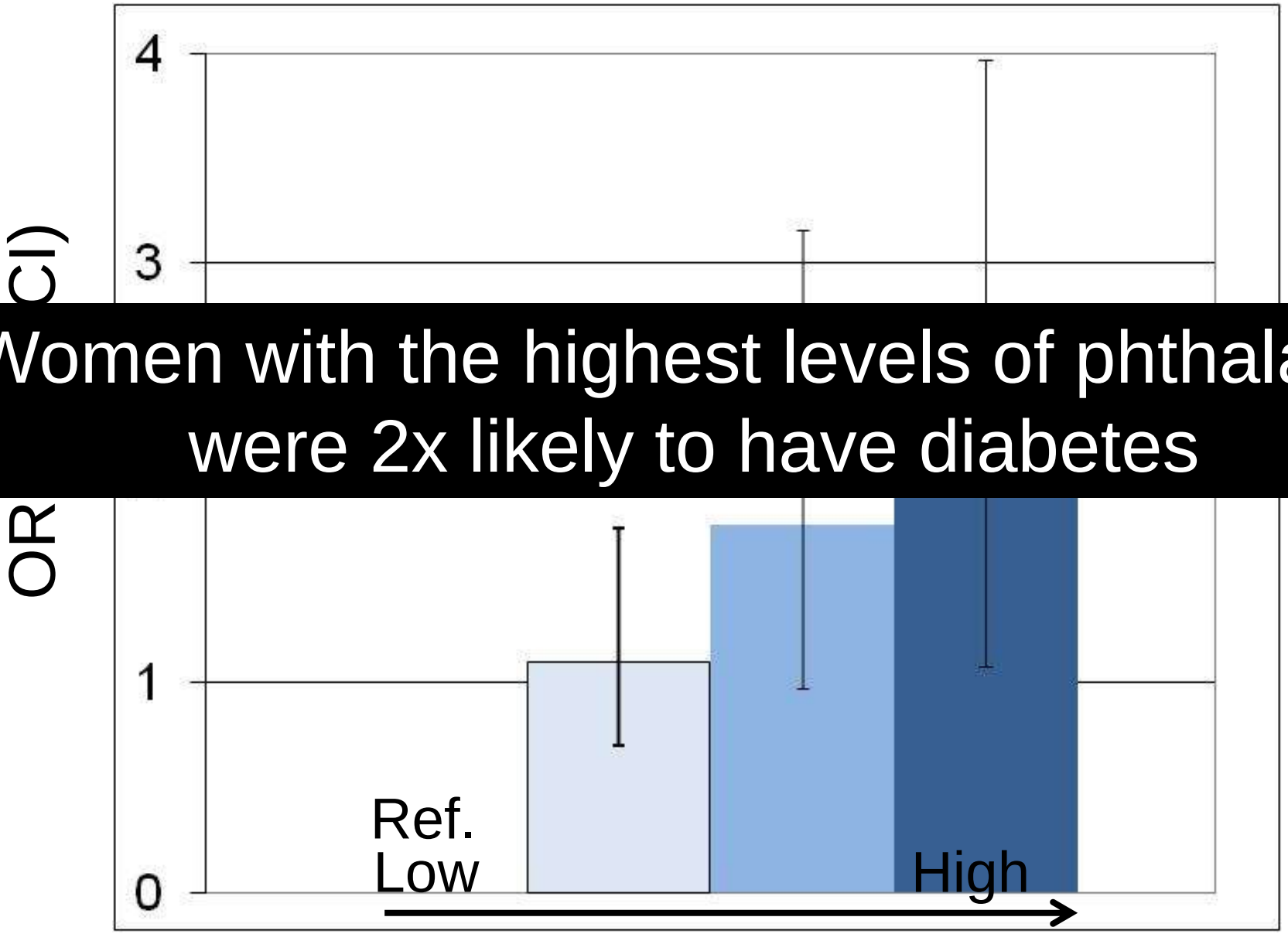
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Phthalates & Women's Health

Higher phthalate concentrations are associated with:

- Reproductive outcomes:
  - Premature breast development
  - Fibroids
  - Endometriosis
- Diabetes-related outcomes:
  - **Obesity**
  - **Insulin resistance**
  - **High blood sugar**

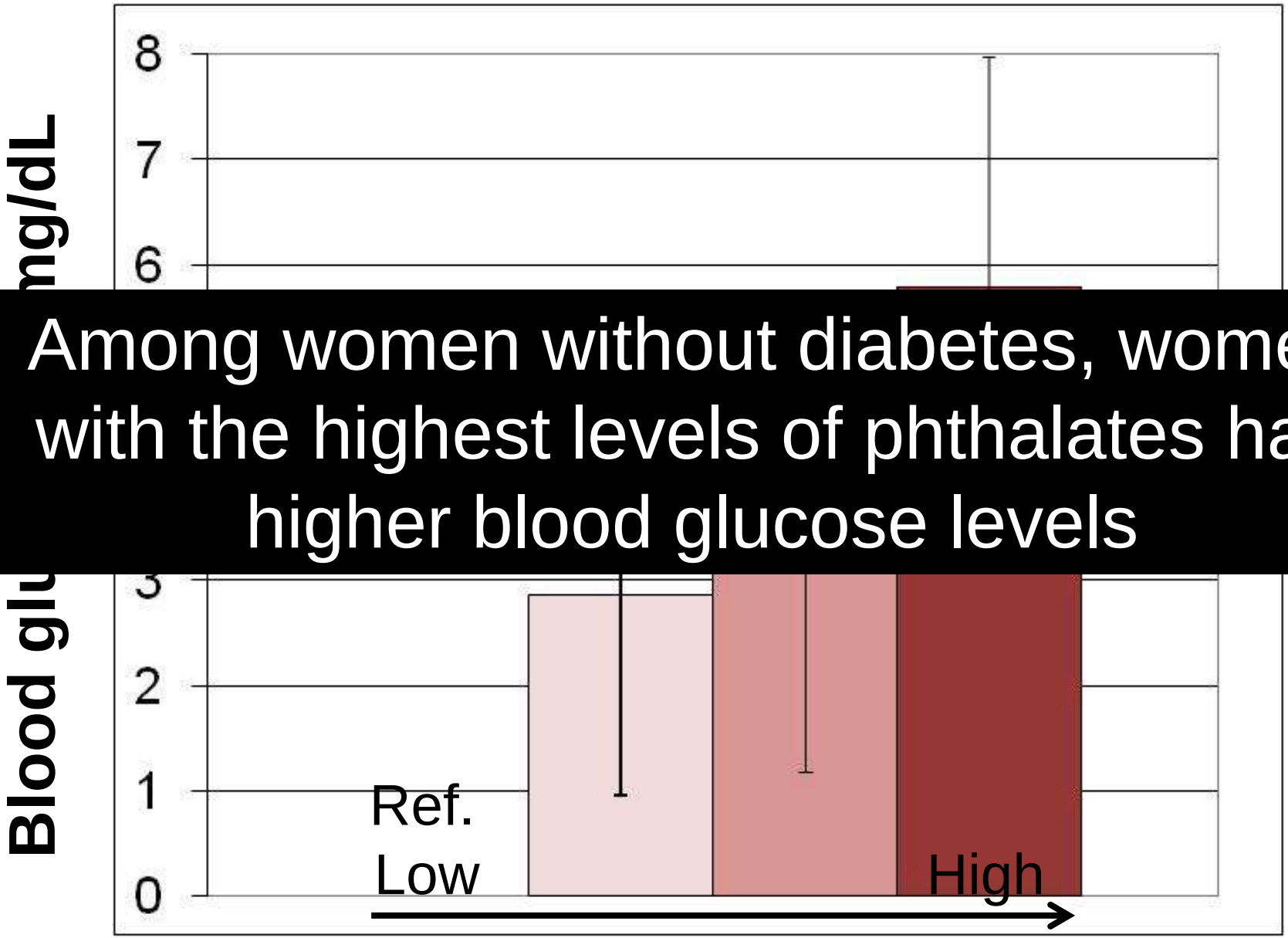
Phthalates and diabetes in women



Women with the highest levels of phthalates were 2x likely to have diabetes

James-Todd et al, 2012

Phthalates and blood glucose in women



Among women without diabetes, women with the highest levels of phthalates had higher blood glucose levels

James-Todd et al, 2012

Reproducibility of phthalate metabolite levels across pregnancy

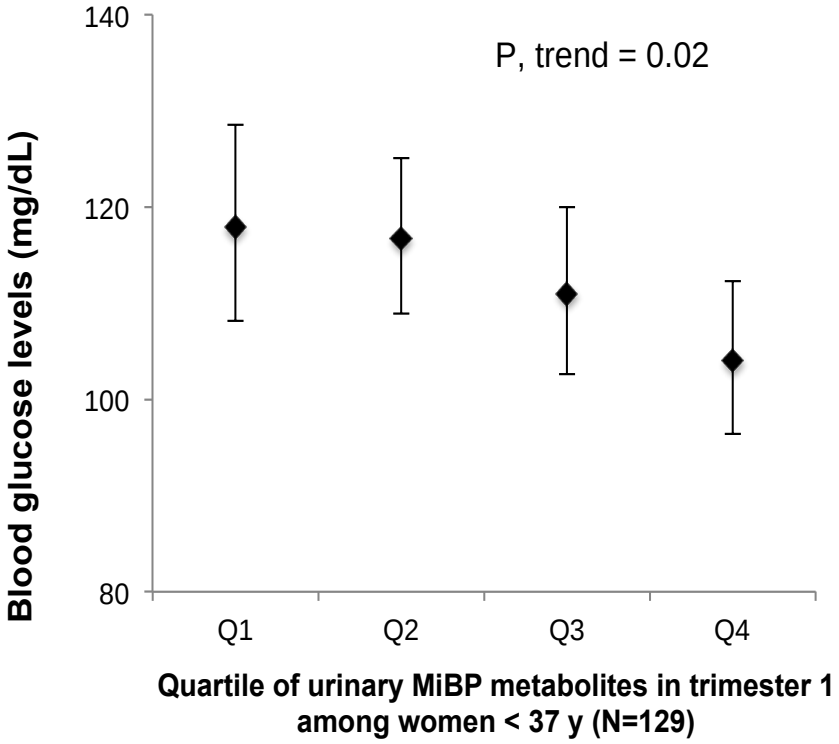
	Unadjusted	Adjusted for race
	ICC (95% CI)	
MBP	0.45 (0.40, 0.51)	0.43 (0.38, 0.49)
MEP	0.47 (0.41, 0.52)	0.45 (0.40, 0.51)
MiBP	0.57 (0.52, 0.62)	0.55 (0.49, 0.60)
MBzP	0.61 (0.56, 0.65)	0.58 (0.53, 0.63)
MCPP	0.35 (0.29, 0.41)	0.35 (0.29, 0.41)
MEHP	0.29 (0.23, 0.35)	0.29 (0.23, 0.35)
∑DEHP metabolites	0.21 (0.15, 0.27)	0.21 (0.15, 0.27)
∑DEHP oxidative metabolites	0.21 (0.16, 0.27)	0.21 (0.16, 0.27)

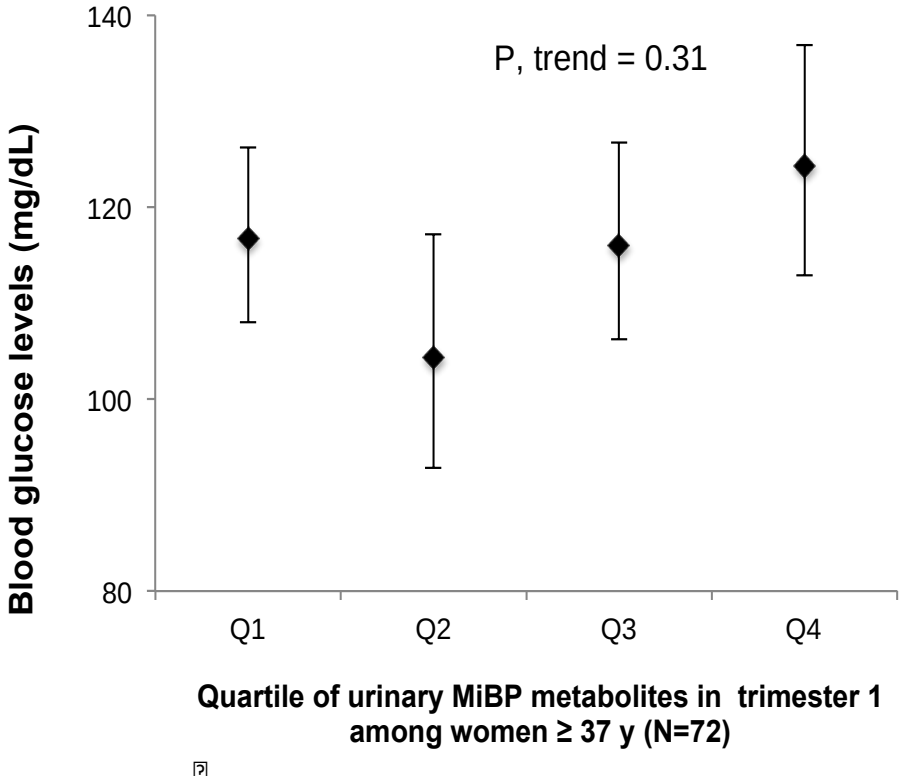
James-Todd et al, 2014

EARTH: Phthalate metabolite concentrations by trimester

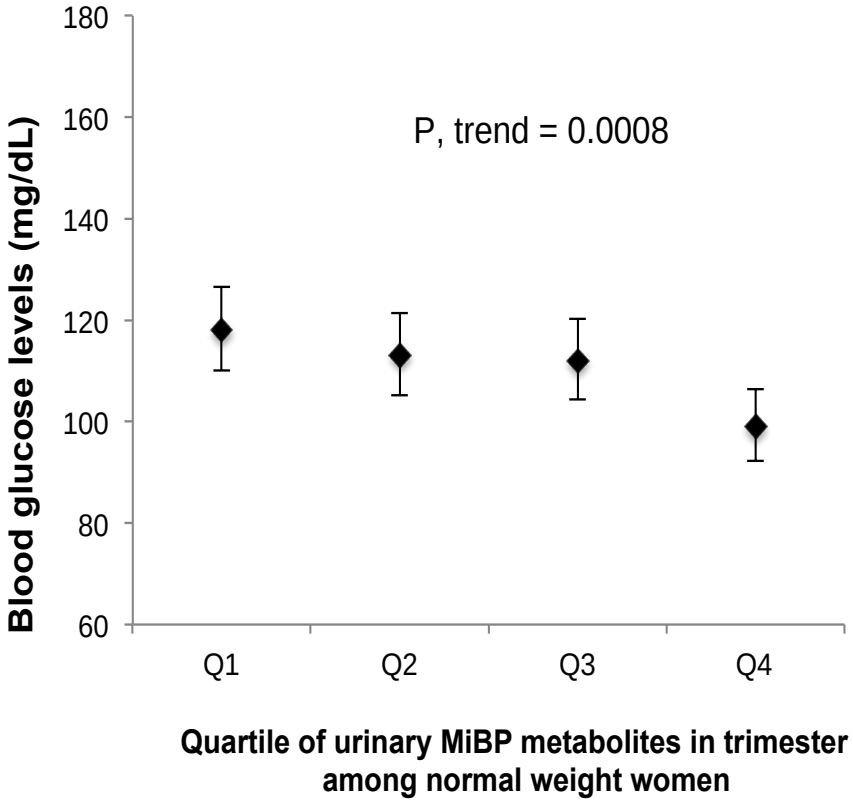
Phthalate metabolites	Trimester	N	Detection frequency[2]	SG-adjusted concentrations geometric (SD)
Mep (ng/mL)	**1**	208	100%	43.6 (4.4)
	2	209	100%	60.2 (6.1)
Mbp (ng/mL)	**1**	208	99.5%	10.9 (0.6)
	2	209	97.6%	11.8 (0.9)
Mibp (ng/mL)	**1**	208	96.6%	5.7 (0.3)
	2	209	97.6%	5.7 (0.4)
Mbzp (ng/mL)	**1**	208	95.7%	3.0 (0.2)
	2	209	91.9%	2.9 (0.2)
Mcpp (ng/mL)	**1**	208	98.1%	4.9 (0.5)
	2	209	96.7%	3.7 (0.3)
Mcop (ng/mL)	**1**	192	97.9%	28.2 (2.9)
	2	190	97.4%	21.9 (2.3)
Mcnp (ng/mL)	**1**	192	93.2%	4.2 (0.3)
	2	190	92.6%	3.5 (0.3)
Dehp(nmol/mL)	**1**	208	-	0.2 (0.02)
	2	209	-	0.1 (0.01)

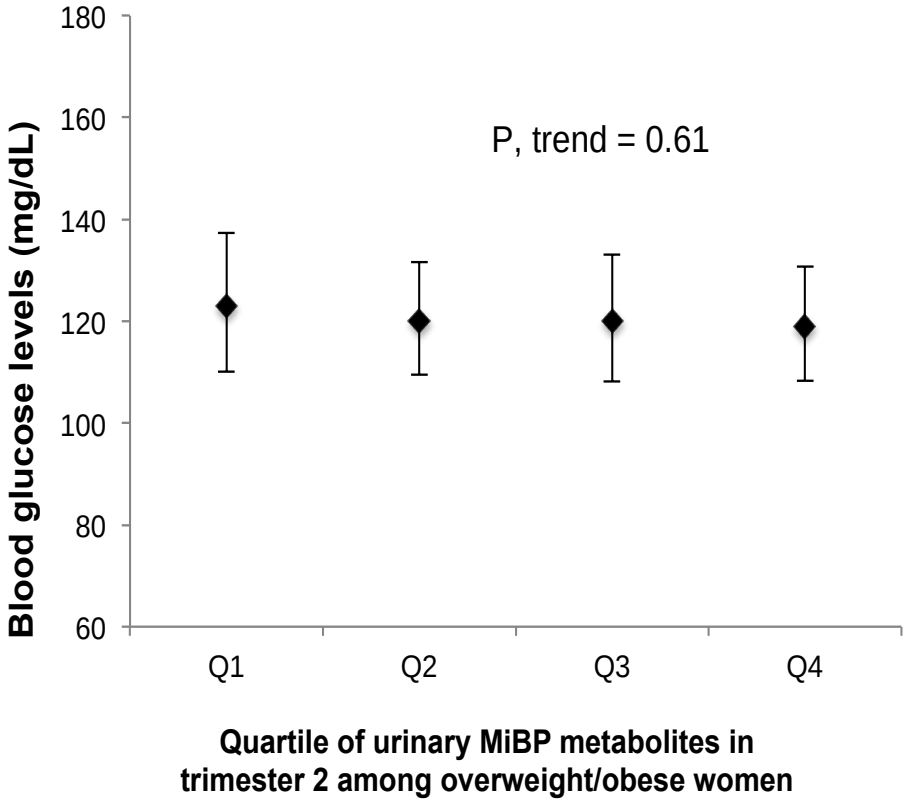
Phthalate metabolite concentrations and 2nd trimester glucose levels





2nd trimester MiBP and glucose levels by BMI status

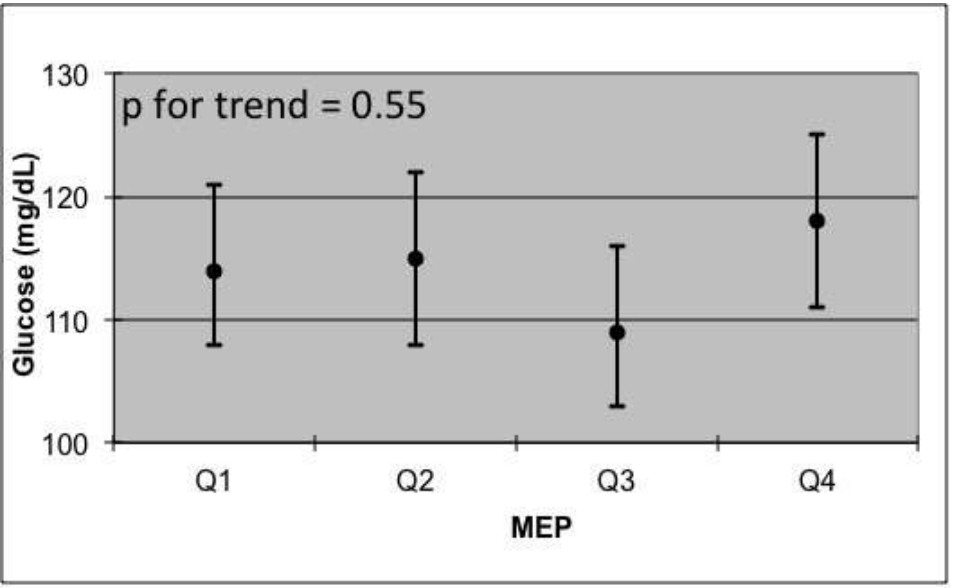


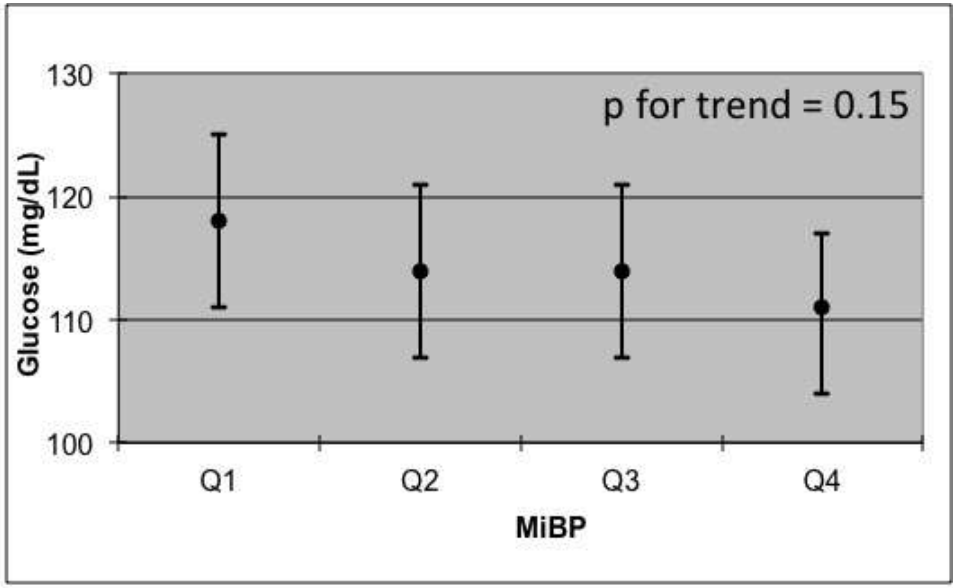


Considerations for EDC exposure during pregnancy and beyond

- Timing
  - Pre-pregnancy
  - During pregnancy
  - Post-pregnancy
- Dose
  - Linear v. non-linear
- Biology
  - Temporary or permanent alterations to “normal” pancreatic function

Phthalate metabolite concentrations in 1st trimester and glucose levels





Adjusted for maternal age, race/ethnicity, education, BMI, smoking status, infertility diagnosis, family history of diabetes, and number of fetuses

EARTH STUDY

Next steps: Building a search engine for environmental exposures

- **<u>What should we collect?</u>**
  - Environmental exposure data in the clinical setting
  - Biological samples and biorepositories
  - Behavioral and social environment matter
  - Maternal *and* paternal data

- **<u>How should we collect?</u>**
  - Checklist or other simplified tool
  - Linkage and long-term considerations

<u>Who should collect this data?</u>

- Training of medical workforce
- Patient education and reporting back

Reducing exposures to decrease risk?