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Cadmium body burden and gestational diabetes mellitus in American women

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Information & Disclosures

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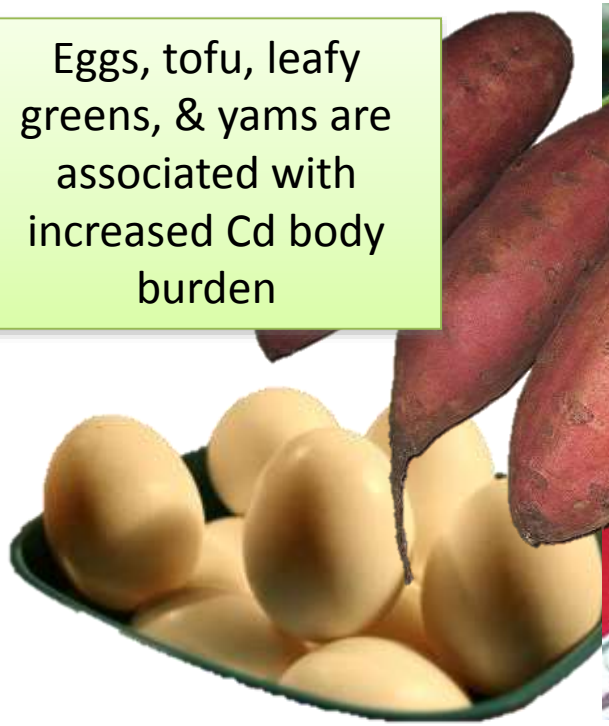
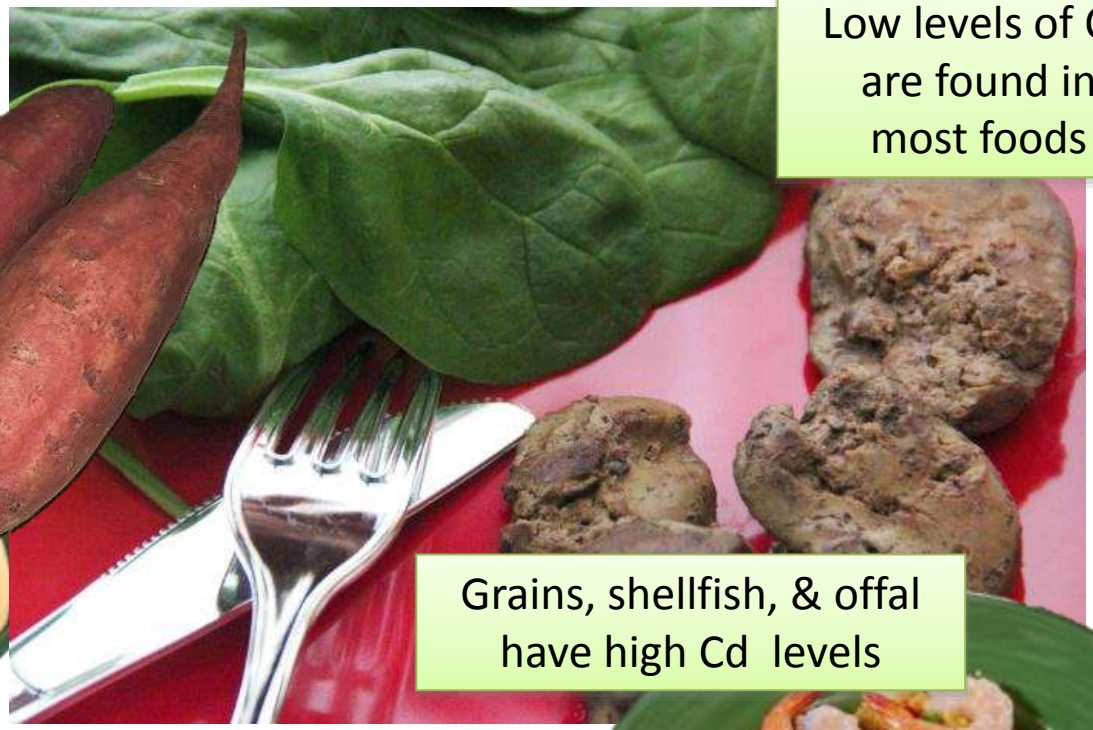
Cadmium

- Natural toxic metal
- Widely used in commercial products
- Enters the environment through:
  - Mining
  - Industrial processing
  - Burning of coal
  - Household wastes
- Long recognized as occupational hazard
- Accumulates in tissues throughout the body:
  - Liver & kidneys (primary)
  - Pancreas
  - Placenta
- Excreted at a steady but extremely low rate: 10-30 year half-life
- Known carcinogen
- Causes renal damage, cardiovascular diseases, & osteoporosis

How is the general population exposed to cadmium?

Eggs, tofu, leafy greens, & yams are associated with increased Cd body burden





Low levels of Cd are found in most foods

Grains, shellfish, & offal have high Cd levels

Tobacco has high Cd content

Mechanism for Cd induced gestational diabetes mellitus (GDM)

- Elevated blood glucose discovered during pregnancy among women who were not previously diabetic

- Rodent studies suggest that cadmium is diabetogenic
  - Accumulates in pancreatic tissue
  - Damages the islets of Langerhans, reducing insulin secretion

- Epidemiological studies to suggest Cd-diabetes association
  - Mostly cross-sectional
  - Examine type 2 diabetes

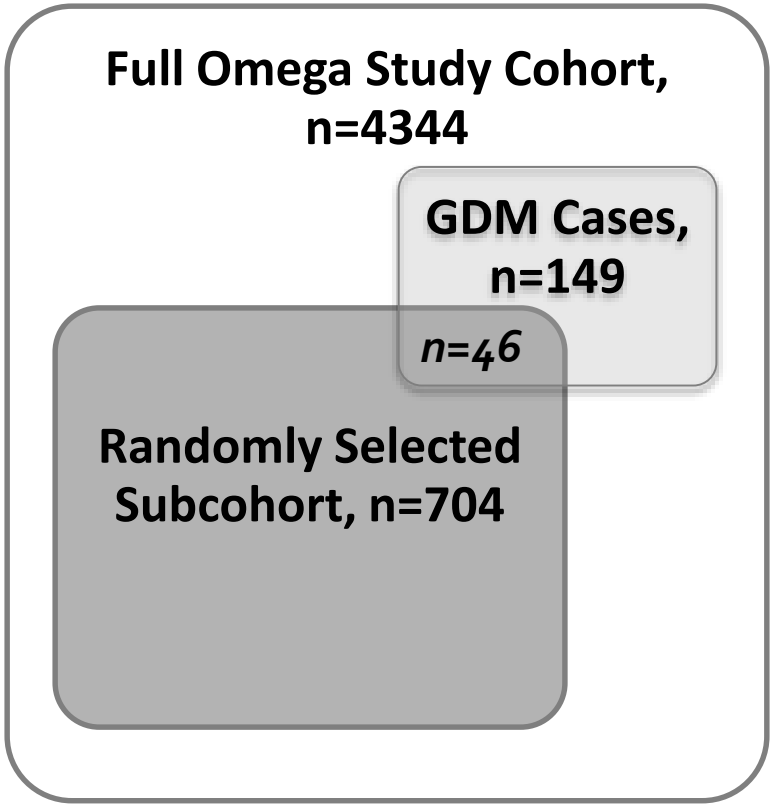
Objective: To determine the effect of body burden of cadmium on women's risk of developing gestational diabetes mellitus during pregnancy

Nested within the larger Omega Study

Early pregnancy urine samples used to assess maternal body burden of Cd

Case-cohort design

- Randomly selected subcohort (n=750)
- All GDM cases from full cohort (n=195)



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Omega Study

- Large prospective cohort study assessing risk factors of pregnancy complications (1996-2008)
- Based at the Center for Perinatal Studies at Swedish Medical, Seattle WA, & Tacoma General Hospital, Tacoma, WA

Eligibility:

- Initiated prenatal care <20 gestational weeks
- ≥18 years of age
- English speaker
- Intended to carry pregnancy to term & deliver at a study institution

Exclusions :

- No urine sample (n=18)
- Pre-existing diabetes/ missing GDM status (n=18)
- Renal disease (n=10)
- Multiple fetal pregnancy (n=37)
- Delivery <24 gw (n=9)
- Urinary Cd >2µg/g Cr (n=8)
- Urinary Cr <30 or >300 mg/dL (n=174)
- 140 GDM & 516 subcohort

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Omega Study data collection

Method	Time	Data Collected
Interviewer administered questionnaire	Enrollment	Demographics Behavioral/lifestyle factors Medical history Reproductive history
Semi-quantitative FFQ	Enrollment	Dietary habits for ~3 months prior to and first 3 months of pregnancy
Spot urine collection	~15 weeks	Metals by ICP-MS Creatinine
Blood draw	Enrollment 24-28 weeks	Non-fasting blood draw Glucose tolerance test
Medical record abstraction	After delivery	Pregnancy course and outcome Infant anthropometrics Antepartum & postpartum complications Prenatal care

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Cadmium measurement

- Clean-catch spot urine samples (~15 gestational weeks)
- Urinary Cd & total arsenic (As) quantified by ICP-MS
- Urinary creatinine (Cr) was assessed with improved Jaffe Reaction
- Categorized urinary Cd tertiles using the distribution in the subcohort

GDM diagnosis

- American Diabetes Association recommended screening (2003)
- All women: 50g 1-hour oral glucose test (24-28 weeks gestation)
- Women with glucose ≥140 mg/dl: 100g 3-hour oral glucose test

GDM diagnosed if ≥2 test levels exceed ADA criteria:

- fasting ≥ 95 mg/dl
- 1-hour ≥180 mg/dl
- 2-hour ≥155 mg/dl
- 3-hour ≥140 mg/dl

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Statistical Analysis

Multivariable unconditional logistic regression was used to estimate ORs & 95% CIs and all estimates were adjusted for:

- Age
- Pre-pregnancy BMI
- Race/ethnicity
- Parity
- Preeclampsia
- Chronic hypertension
- Family history of diabetes
- Family history of hypertension
- Total urinary As (& fish consumption)

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Table 1: Characteristics of the study population

	Non-cases in Subcohort n=481	**GDM Cases n=140**	
	mean ± sd	mean ± sd)	
Maternal Age (years)	32.8 ± 4.5	33.6 ± 4.7	*
Pre-pregnancy BMI (kg/m^2)	23.7 ± 5.0	23.7 ± 5.0	*
Spot urine collection (gw)	15.2 ± 2.9	15.0 ± 2.9	
	%	%	
Nulliparous	59	55	
Non-Hispanic White Race/Ethnicity	84	69	*
Post high school education	90	94	
Married	85	83	
Preeclampsia	2	8	*
Iron deficiency anemia	2	4	
Chronic hypertension	4	9	*
Family history of diabetes	15	34	*
Family history of hypertension	45	63	
Never smoker	66	67	

*p<0.05

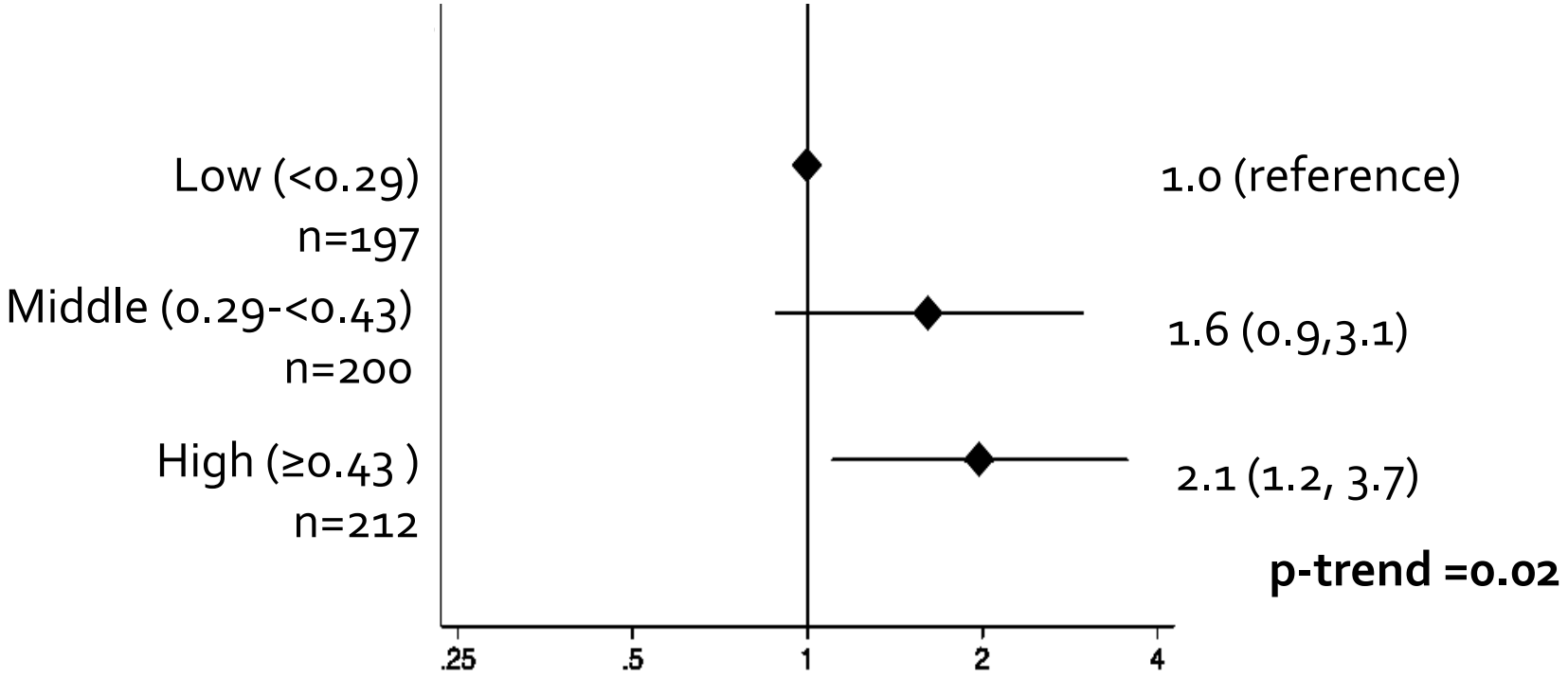

Figure 1: Adjusted odds ratios and 95% CI for urinary Cd (µg/g Cr) and GDM risk

Strengths

- Well-characterized cohort of pregnant women with rich covariate data
- Prospective study design
  - Early pregnancy biological samples
  - Outcome misclassification due to pre-gestational glucose intolerance unlikely
- ICP-MS is robust and well-validated
- Study addresses current knowledge gap

Limitations

- Residual confounding
- Limited generalizability due to lack of sociodemographic diversity

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Future directions & Implications

- Confirm findings in diverse populations
  - Arsenic, Cadmium, and Chromium measured in meconium are positively associated with GDM prevalence (Peng et al. Environ Health. 2015 Feb 28;14:19.)
  - Placental cadmium was lower among GDM cases in metallomics study (Roverso et al. Metallomics. 2015 Apr 28. [Epub ahead of print])

- Assess micronutrient (e.g. calcium, iron, zinc) & toxic metal interactions

- Improved understanding of environmental risk factors will assist in identifying women at high risk of GDM

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