Diabetes and Persistent Organic Pollutants

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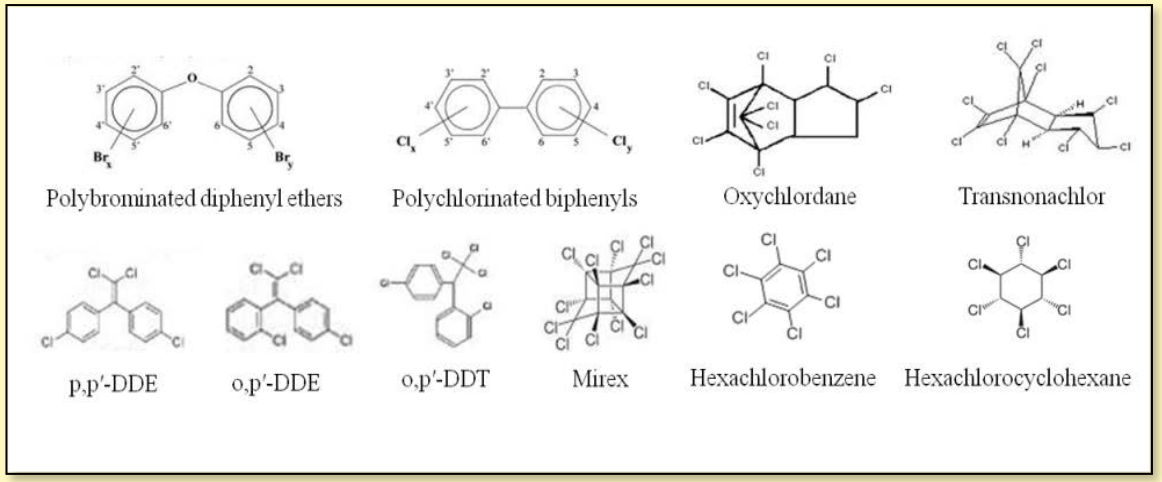
POPs



- Halogenated → stability, inflammability
- PCBs, dioxins, OC pesticides (DDT, HCB, chlordane), PBDEs
- Long half-lives, reflects long-term exposure
- Stored in adipose tissues
- Predominant exposure from food: fish, meat, dairy
- Some environmental exposure: consumer products, building materials (PBDEs)
- All human exposures are mixtures
- No humans are unexposed to POPs mixtures
- Multiple health impacts including endocrine disruption

Type 2 Diabetes

- **Risk factors**
  - Age
  - Ethnicity
  - Family history
  - Adiposity (unhealthy diet and physical inactivity)
  - Inflammation
  - Hormones
  - Environmental Chemicals
- **Clinical diagnosis:**
  - Prediabetes: FPG 100-125 mg/dL or HA1c 5.7-6.4%
  - Diabetes: FPG ≥ 126 mg/dL or HA1c ≥ 6.5%
- **Insulin sensitivity:**
  - HOMA-IR: calculated from fasting insulin & glucose
- **Diabetes transition:**
  - Early stage development of insulin resistance
  - Late stage development of insulin secretory defects (β cells)

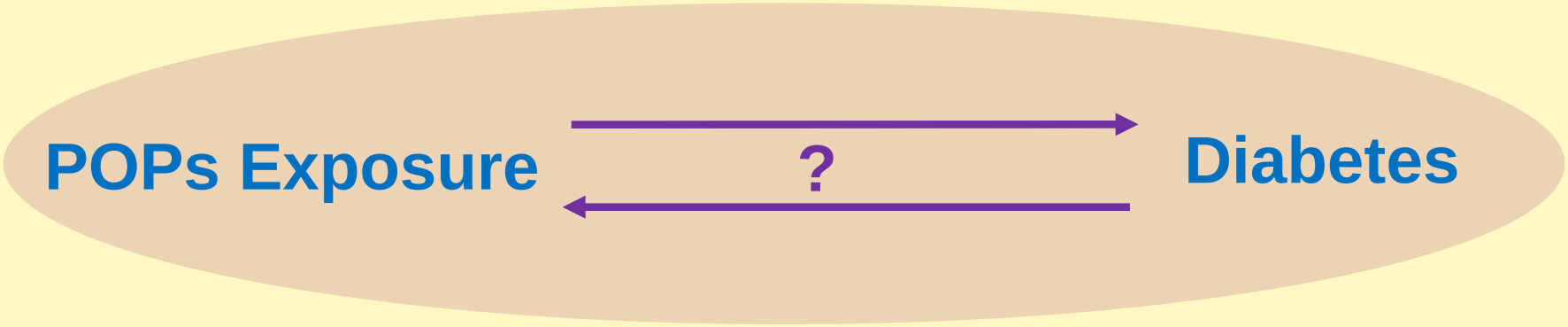
Prevalent Diabetes and POPs Exposures

Exposure	Exposure, ng/g	OR Diagnosed & Undiagnosed (HA1c>6.4)	OR Diagnosed, Undiagnosed & Prediabetes (HA1c>5.6)
DDE	<LOD-1.2	1	1
	1.3-2.0	1.9	0.9
	2.1-4.0	2.0	0.8
	4.1-24.0	4.1	0.8
	P trend	**0.003**	**0.25**
Dioxin-like PCBs	<LOD	1	1
	0.2-0.3	1.1	0.9
	0.3-1.6	1.8	1.9
	P trend	**0.11**	**0.06**

- N= 503 , diabetes prevalence =11%, Age mean=59 years, range=30-80 years, 71% males
- Adjusted for age, BMI, gender, triglycerides and cholesterol
- Diabetes was not associated with total PCBs or PBDEs, but was associated with PBDEs in persons with hypothyroidism
- Associations with dioxin-like PCBs were not independent of DDE
- Turyk et al, Chemosphere 75;674, 2009

Limitations of Diabetes Prevalence Study

- **Lack of data on temporality**
  - o Reverse causality
  - o Does diabetes result in changes in POP metabolism?

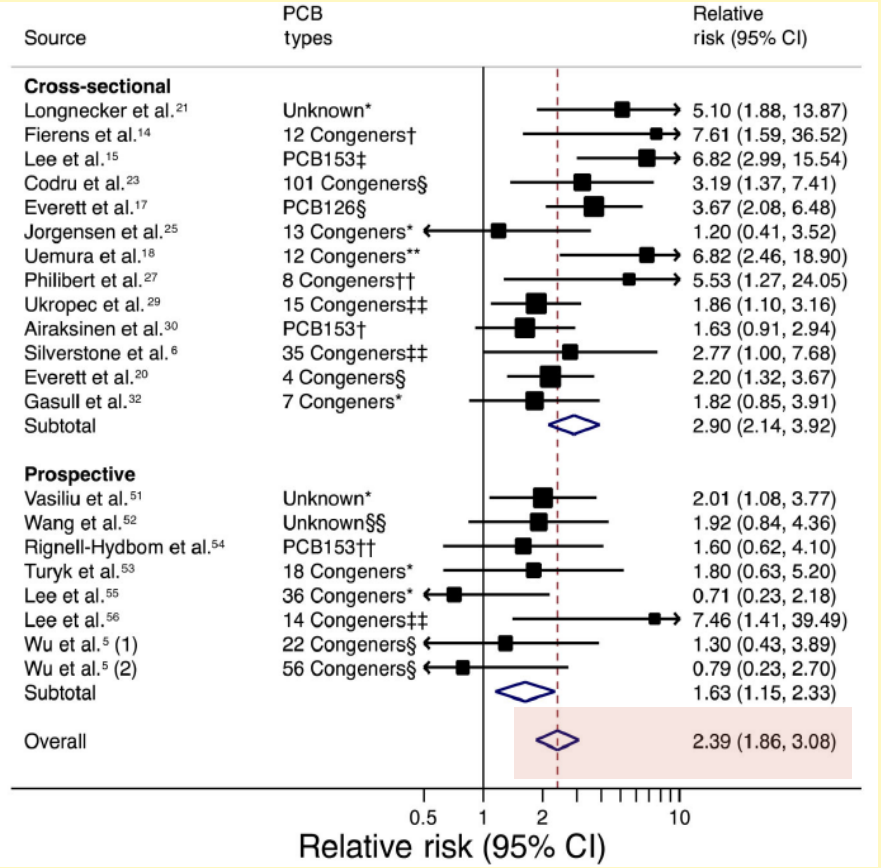


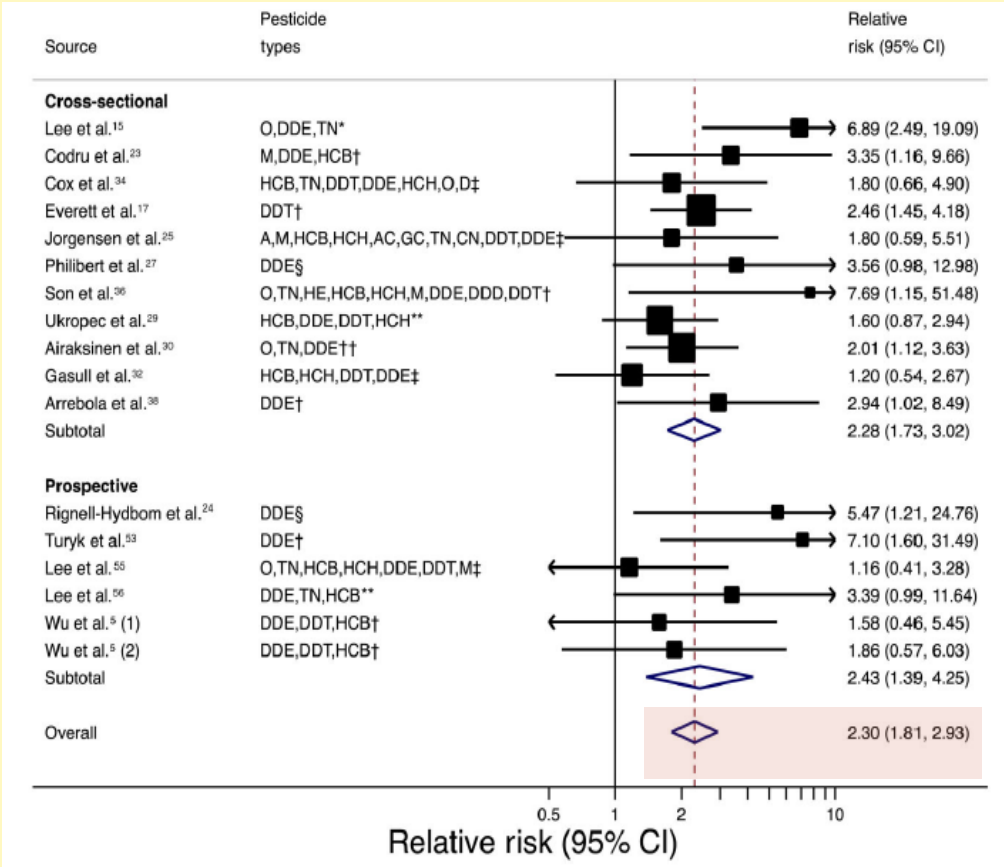
Diabetes Incidence and DDE Exposure

DDE Tertile	Tertile Range (ng/g)	New cases	Person years	Incidence/ 1000 person years	Incidence Rate Ratio		
					IRR	95% CI	P-value
1	<lod-2.2	2	1325	1.5	**1**		
2	2.2-5.3	12	1336	9.0	**5.5**	**1.2, 25.1**	**0.03**
3	5.4-49.2	22	1286	17.1	**7.1**	**1.6, 31.9**	**0.01**
						P trend	**0.008**

- N=471
- Adjusted for age, BMI, gender
- Association remained significant with further adjustment for smoking, alcohol use and lipids assessed during follow up.
- Total PCBs and individual congeners were not associated with diabetes incidence
- Turyk et al Environmental Health Perspectives 117;1076, 2009

Meta-Analysis Diabetes and POPs





- **Heterogeneity:**
  - PCBs: stronger associations cross sectional, females and non-white
  - DDE: stronger associations non-white
- **Song et al., J Diabetes 8:516, 2016**

LaSalle, IL Cross Sectional Study: Diabetes and PCBs

PCB Exposure	Females: OR (p-value)	Males: OR (95% CI)
Sum 38 congeners	4.4 (0.02)	3.0 (1.3, 7.0)
Dioxin-like (105, 118, 156, 157, 167, 189)	10.0 (0.004)	2.7 (1.3, 5.8)
Non-dioxin like (total – dioxin-like)	4.0 (0.03)	3.0 (1.3, 7.2)
Estrogenic (52, 99, 101, 110, 153)	3.4 (0.01)	3.0 (1.2, 7.5)
Anti-Estrogenic (105, 156)	12.3 (0.004)	2.4 (1.2, 4.9)

- Capacitor manufacturing plant employees

- Females: adjusted for age, BMI, triglycerides, cholesterol, DHEA, FSH, T3-uptake, n=93, diabetes prevalence=16%
- Persky et al., Environmental Research 111:817, 2011

- Males: adjusted for age, BMI, lipids, n=63, diabetes prevalence =11%
- Persky et al, Environmental Health 11:57, 2012

LaSalle, IL Cross Sectional Study: HOMA-IR and PCBs

PCB Exposure	Females: Beta (p-value)	Males: Beta (95% CI)
Sum 38 congeners	-0.16 (0.08)	-0.02 (-0.13, 0.10)
Dioxin-like (105, 118, 156, 157, 167, 189)	-0.08 (0.24)	-0.02 (-0.11, 0.07)
Non-dioxin like (total – dioxin-like)	-0.17 (0.07)	-0.02 (-0.14, 0.10)
Estrogenic (52, 99, 101, 110, 153)	-0.19 (0.04)	-0.03 (-0.14, 0.09)
Anti-Estrogenic (105, 156)	-0.07 (0.04)	-0.03 (-0.11, 0.06)

- Capacitor manufacturing plant employees

- Females: adjusted for age, BMI, triglycerides, cholesterol, SHBG, CRP, T3-uptake, n=72, only participants without diabetes
- Persky et al., Environmental Research 111:817, 2011

- Males: adjusted for age, BMI, lipids, n=52, only participants without diabetes
- Persky et al, Environmental Health 11:57, 2012

Meta-Analysis Fasting Glucose and HOMA-IR with POPs

Exposure	Fasting Glucose (mg/dL)		HOMA-IR	
	No. Subjects (No. Studies)	Mean Difference (95% CI)	No. Subjects (No. Studies)	Mean Difference (95% CI)
Dioxin	4075 (5)	3.96 (1.23, 6.70)	2023 (3)	0.46 (-0.16, 1.09)
PCB	2882 (3)	3.27 (1.87, 4.67)	933 (3)	-2.05 (-4.65, 0.56)
Chlorinated pesticides	836 (2)	0.81 (-3.31, 4.93)	933 (3)	0.73 (-0.17, 1.63)

- Random-effect pooled mean differences of metabolic traits comparing the highest with the lowest chemical concentration categories

- Song et al., J Diabetes 8:516, 2016

Hypothesized mechanisms through which POPs could impact diabetes development

- Adiposity
- Dyslipidemia
- Inflammation
- Oxidative stress
- Perturbation of endogenous hormones (steroid or thyroid)

Biomarkers of Diabetes Risk and POPs

- Are POPs associated with biomarkers of diabetes risk?
- Do biomarkers of diabetes risk mediate associations of POPs with diabetes?
- Do biomarkers of diabetes risk modify associations of POPs with diabetes?
- Turyk et al. Environmental Research140:355, 2015

Diabetes Risk Biomarkers

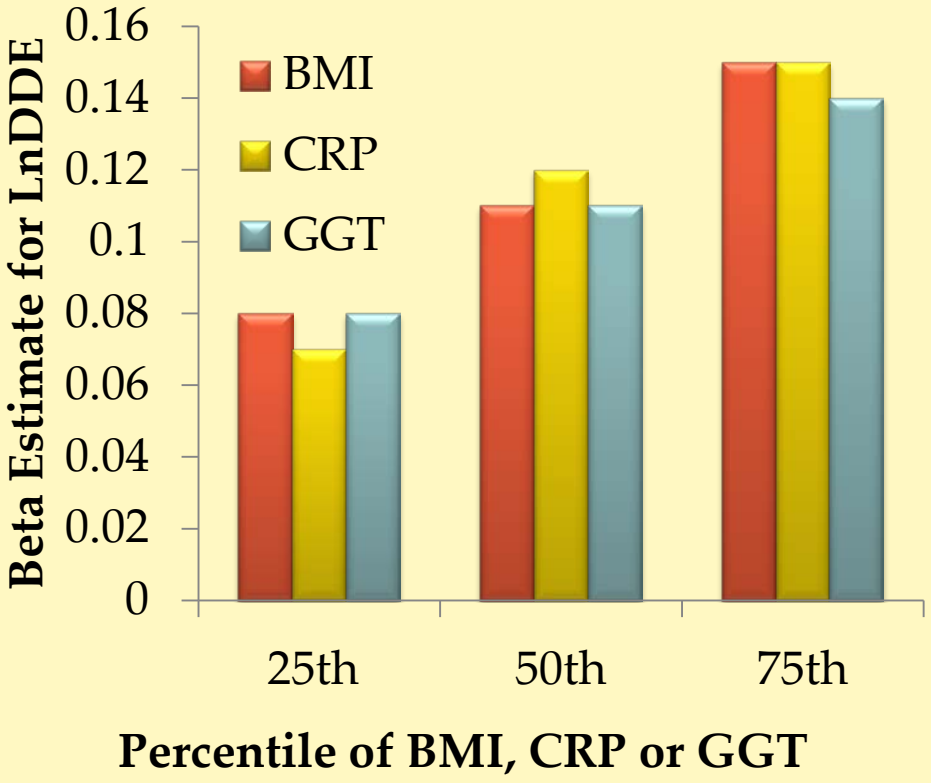
- **C reactive protein (CRP)**
  - Marker of systemic inflammation
  - ↑ diabetes risk
- **Adiponectin**
  - Adipocyte cytokine with anti-inflammatory properties
  - ↓ diabetes risk, ↑ insulin sensitivity
- **Gamma-glutamyl transferase (GGT)**
  - Liver enzyme induced by oxidative stress and involved in the metabolism of xenobiotics, such as POPs
  - ↑ diabetes risk

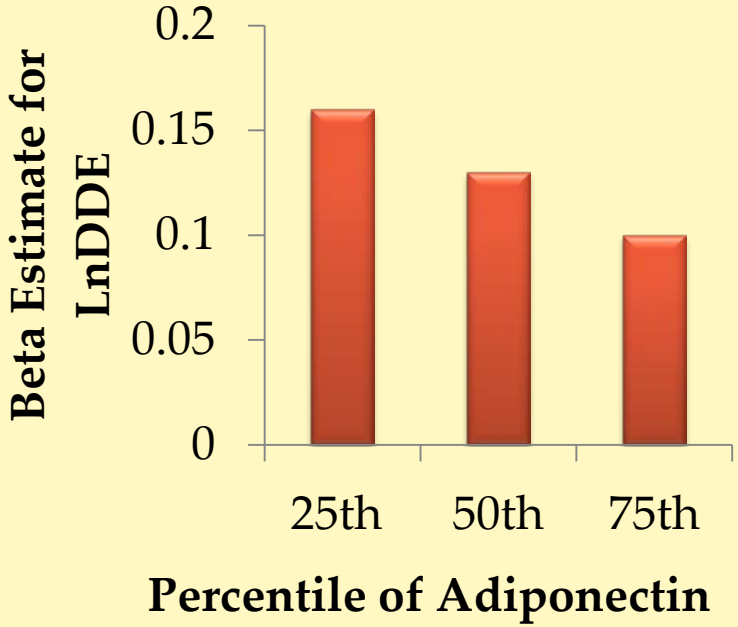
Adjusted Associations of Diabetes Risk Biomarkers with HA1c, Incident Diabetes, and POPs

Biomarker	HA1c % (β, p-value)	Incident Diabetes (OR, p-value)	DDE	Sum PCBs
Adiponectin	-0.16, 0.0004	0.20, 0.002	ns	ns
CRP	0.01, 0.70	3.22, 0.02	ns	ns
GGT	0.08, 0.15	1.70, 0.08	ns	ns

- n=413, females and males for HA1c
- n= 287, females and males for incident diabetes (16 cases)
- Biomarkers did not mediate associations of POPs with HA1c or incident diabetes
- DDE and PCB-118 were associated with HA1c
- DDE and PCB congeners were associated with incident diabetes

Modification of associations of LnDDE with HA1C by level of BMI, CRP, GGT and adiponectin (n=413 males and females)

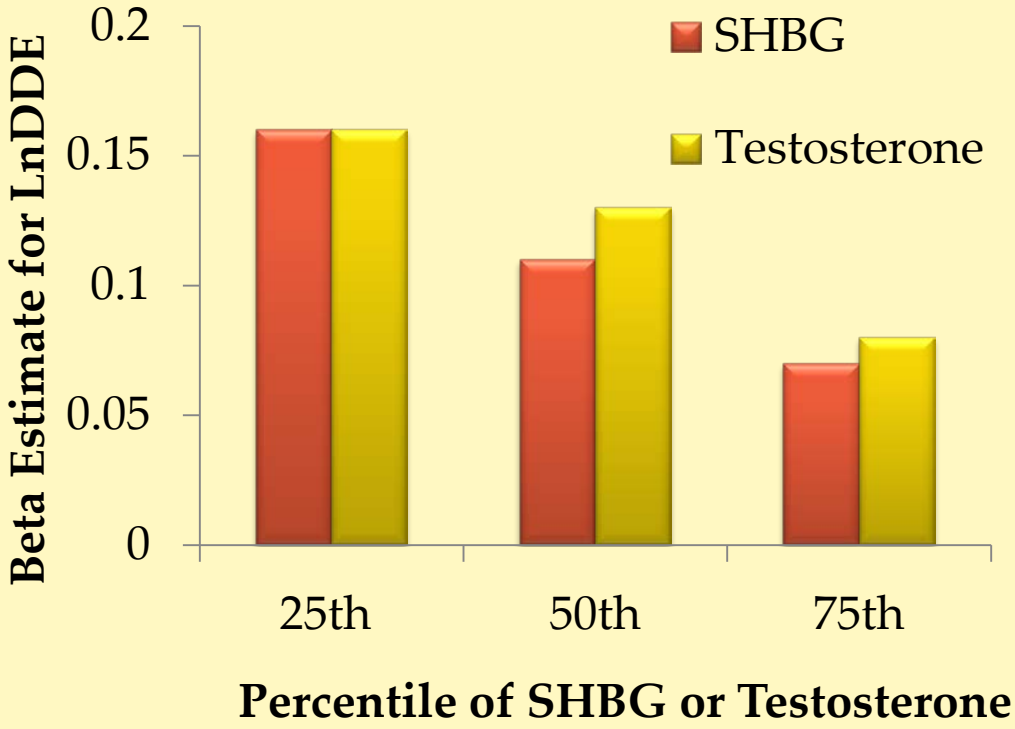




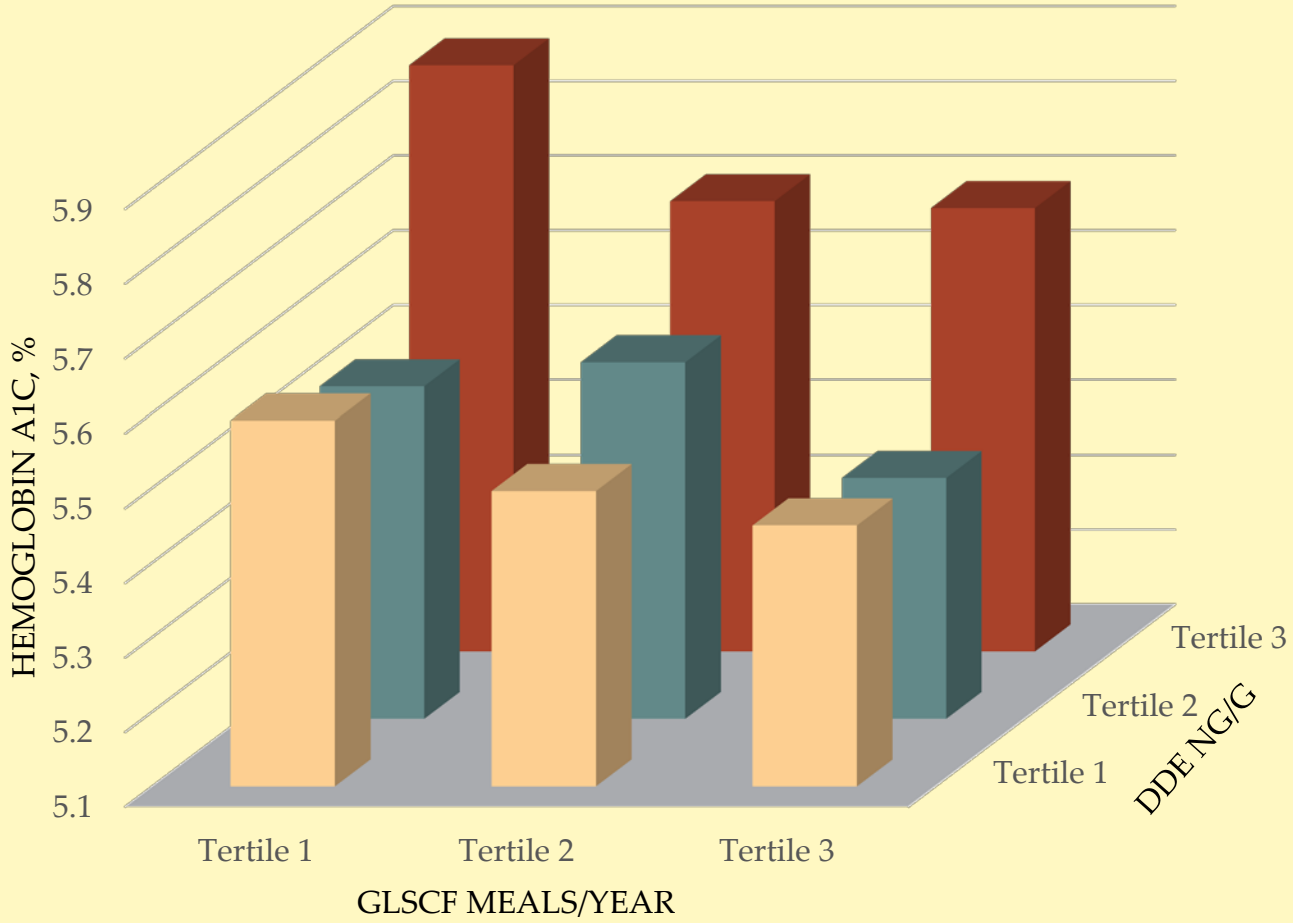
Associations of Hormones with HA1c & POPs

Biomarker	HA1c % (β, p-value)	DDE	Sum PCBs
SHBG	-0.13, 0.007	-0.05, 0.28	-0.05, 0.46
Testosterone	-0.04, 0.03	0.05, 0.56	0.14, 0.15

- n=313 males Hormones did not mediate associations
- of POPs with HA1c
- Turyk et al, unpublished



Joint Association of DDE Exposure and Great Lakes Fish Meals on HA1c Levels



Adjusted for age centered, BMI centered, sex, diabetes medication use and serum lipids, n=413

Key Points

- POPs have been associated with type 2 diabetes in many epidemiological studies.
- Our studies suggest that POPs may have a stronger impact on the later rather than earlier stages of diabetes development.
- Adiponectin, CRP, GGT and steroid hormones were not associated with POPs and did not mediate associations of POPs with HA1c.
- Adiponectin, CRP, GGT, BMI and steroid hormones modified the associations of POPs with HA1c, with stronger associations in persons with higher levels of the diabetes risk factor.

Current Work

- **Hispanic Community Health Study/Study of Latinos (HCHS/SOL)**
  - Cohort of multiethnic Hispanics from Chicago, San Diego, New York and Miami
  - Men and postmenopausal women ages 45-74 years
  - 1,175 prediabetes and 1,175 normal glucose at baseline
  - Measure POPs and sex steroid and thyroid hormones at baseline
  - Measure development of metabolic dysfunction at six year follow up
    - diabetes, prediabetes, insulin resistance and β cell dysfunction

Current Work

- **Examine the relationships of POPs and endogenous hormones with the subsequent development of diabetes, prediabetes, insulin resistance and β cell dysfunction.**

- **Explore effects of POPs at early (insulin resistance) and late (insulin secretory defects) stages of diabetes transition**

- **Explore effect modification and mediation by obesity, inflammation and hormonal status on associations of POPs with metabolic dysfunction.**

Study Partners/Funding

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