Diabetes and Persistent Organic Pollutants in the Great Lakes Fish Consumption Study

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What’s in the fish?
Fish: Benefits

- **Nutrients**
  - Protein source low in saturated fats
  - Omega 3 fatty acids
  - Selenium and other micronutrients

- **Cultural traditions**

- **Recreation: sport fishing**

- **Maternal consumption:**
  - Higher scores on neurodevelopment testing (Daniels 2004)
  - Reduction in preterm birth (Nesheim 2007)

- **Cardioprotection:**
  - Decreased CHD mortality, stroke (Kris-Etherton 2002, Iso 2001)
Omega 3 Fatty Acids in Great Lakes and Fatty Marine Fish

Pantazopoulos et al, J GL Res 2013
Fish: Risks

- **Contaminants**
  - Legacy POPs
    - PCBs
    - Dioxins
    - DDT (pesticides)
  - Emerging Persistents
    - PBDEs
    - PFOS
  - Methyl Mercury

- **Selected health risks of contaminants**
  - Neurodevelopment
  - Cardiovascular
  - Diabetes
  - Cancer
PCB Production and Use

2 million tons produced from 1920’s to 1970’s

- Cooling & insulating fluid for transformers & capacitors
- Housing materials: caulk, paint, insulation, floor finish, fluorescent light ballasts
- Carbonless copy paper
- Banned in 1977 in US

Exposure

- Persistent in the environment
- Exposure from fish, other animal products, indoor environment
- Long half life in body, up to 10 years
PCBs in Great Lakes Top Predator Fish Basin wide status: fair, improving State of the Great Lakes 2011
DDE/DDT

- DDT use began in the 1940’s
- DDT banned in US in 1972
- DDE is a persistent metabolite of DDT
- Food chain contaminant

Total DDE in GL Fish

Basin wide status: Good, Improving

State of the Great Lakes 2009
PBDEs

Flame retardants for consumer goods

- Use began in 1980
- PentaBDE used in foam and fabrics (phased out 2004)
- DecaBDE used in electronics (phased out 2013)

Exposure

- Can migrate out of products into house dust
- Contaminated foods, including fish

PFOS (Perfluorooctane sulfonate)

Lake Superior PFOS

Concentration (ng/g)

0.1 1 10 100


Lake Trout

PFOS in Lake Ontario Fish

Bernard Crimmins, Clarkson University

State of the Great Lakes, 2011
Mercury (Hg)

- Organic Mercury (methyl mercury)
  - Most human exposure from fish consumption
  - Half-life 50-70 days in humans
  - Levels similar across fish in all GLs suggest atmospherically driven

Data from State of the Great Lakes, 2011
Basin wide status: Good, deteriorating
Great Lakes Fish Consumption Study

In the early 1990s, ATSDR established cooperative agreements to study human health effects of Great Lakes critical pollutants.

Five State Health Departments (WI, IL, IN, OH, MI), led by Dr. Henry Anderson, formed the Great Lakes Consortium to look at critical pollutants in anglers.

Recruited licensed GL charter boat captains and their spouses.

Referent group with low GL fish intake selected by random digit dialing.
Great Lakes Fish Consumption Study Timeline

- **1993**: Fish consumption survey: N=2,543 Captains, 1,664 Referents
- **1994**: PCB/DDE Biomarkers: N=619  PBDE Biomarkers: N=118
- **1996**: Health survey and hormone levels: N=255
- **2001**: Health survey, PCB/DDE/PBDE, hormone levels: N=207
- **2003**: Health survey sent to all original cohort members: N=1,788
- **2004**: Health survey, PCB/DDE/PBDE, hormone levels: N=515
- **2010**: Health survey to all with PCB/DDE/PBDE measures: N=594
POP Exposures in GL Cohort and NHANES

Geometric Mean, 95% CI (ng/g)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCBs</td>
<td>GL Study 1994-5</td>
<td>GL Study 2004-5</td>
<td>NHANES 2003-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDE</td>
<td></td>
<td></td>
<td>GL Study 1994-5</td>
<td>GL Study 2004-5</td>
<td>NHANES 2003-4</td>
<td></td>
</tr>
<tr>
<td>PBDEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Determinants of PCBs

- Serum PCBs were positively associated with:
  - Years eating sport caught fish
  - Male sex
  - Lived near Lake Michigan (versus Erie or Huron)
  - Age
  - GL Rainbow trout, chinook and salmon past year

- 42% of variation in serum PCBs explained by these factors

- Hanrahan et al., 1999
Determinants of PBDEs

- **PBDE level was positively associated with**
  - Age
  - Computer use, hours/day
  - Shellfish meals
  - Years consuming sport fish
  - Decreased with weight loss in last year

- **Explained 7% of variation serum PBDEs**

Anderson et al., Chemosphere 73:187, 2008
Fluorinated Chemicals and Fish Consumption in NHANES Participants

Fig. 2. Associations between any seafood consumption in the last 30 days and PFAS concentrations, after adjusting for age, BMI, sex, race/ethnicity and survey cycle.

Christensen et al., 2017
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 resistance:**
  - HOMA-IR: calculated from fasting insulin & glucose

• **Diabetes transition:**
  - Early stage development of insulin resistance
  - Late stage development of insulin secretory defects (β cells)
Diabetes and POPs Exposures: Cross sectional Study

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

- For DDE, we found stronger association with diabetes than with prediabetes and diabetes grouped together, suggesting that the effect of DDE may be at later state of diabetes development.
- **Diabetes was not associated with total PCBs or PBDEs, but was associated with PBDEs in persons with hypothyroidism**
- N= 503, diabetes prevalence =11%, Age mean=59 years, range=30-80 years, 71% males, adjusted for age, BMI, gender, triglycerides and cholesterol
- Turyk et al, Chemosphere 75;674, 2009
## LaSalle, IL Cross Sectional Study: Diabetes and PCBs

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

- Associations were seen with diabetes in PCBs grouped by different biological mechanism of action, including dioxin-like, non-dioxin like, estrogenic and non-estrogenic.
- Groupings may inadequately categorize biological mechanisms.
  
  - Females: adjusted for age, BMI, triglycerides, cholesterol, DHEA, FSH, T3-uptake, n=93, diabetes prevalence=16%; Persky et al., Environmental Research 111:817, 2011
LaSalle, IL Cross Sectional Study: HOMA-IR and PCBs

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

- We did not find any significant associations of PCBs with HOMA-IR.
- This suggests that PCBs may be affecting a later stage of diabetes development.
- **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
Limitations of Cross Sectional Diabetes Studies

• Lack of data on temporality
  o Reverse causality
  o Does diabetes result in changes in POP metabolism?
Diabetes Incidence: Cohort Study

- Illness: 2
- Person-year at risk: 41
- Incidence density: 4.9 / person-year

One year
Development of illness
Censored
Diabetes Incidence and DDE Exposure

<table>
<thead>
<tr>
<th>DDE Tertile</th>
<th>Tertile Range (ng/g)</th>
<th>New cases</th>
<th>Person years</th>
<th>Incidence/1000 person years</th>
<th>Incidence Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;lod-2.2</td>
<td>2</td>
<td>1325</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2.2-5.3</td>
<td>12</td>
<td>1336</td>
<td>9.0</td>
<td>5.5  1.2, 25.1  0.03</td>
</tr>
<tr>
<td>3</td>
<td>5.4-49.2</td>
<td>22</td>
<td>1286</td>
<td>17.1</td>
<td>7.1  1.6, 31.9  0.01</td>
</tr>
</tbody>
</table>

P trend 0.008

- Total PCBs and individual congeners were not associated with diabetes incidence
- N=471, about 4,000 years of follow up
- Adjusted for age, BMI, gender
- Association remained significant with further adjustment for smoking, alcohol use and lipids assessed during follow up.
- Turyk et al Environmental Health Perspectives 117;1076, 2009
Summary of Epidemiology Findings

- POPs have been associated with type 2 diabetes in many epidemiological studies.
- No single POP predicts diabetes in all studies.
- POPs have diverse biologic mechanisms. Thus, detection of associations with many different POPs is not useful in hypothesizing potential mechanisms of action.
- POPs are often strongly correlated in human populations, so the detected associations may be confounded by other unmeasured POPs.
- Our studies suggest that POPs may have a stronger impact on the later rather than earlier stages of diabetes development.
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?

Mediation

Factor is an intermediate in the causal pathway between exposure and disease.

Effect of exposure on disease is attenuated by mediator.

Identify plausible biological mechanisms.
Modification

Association of Exposure with Disease differs by level of modifier

Identifies high risk groups

Identifies factors that could be targeted for intervention
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

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HA1c % (β, p-value)</th>
<th>Incident Diabetes (OR, p-value)</th>
<th>DDE</th>
<th>Sum PCBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>-0.16, 0.0004</td>
<td>0.20, 0.002</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>CRP</td>
<td>0.01, 0.70</td>
<td>3.22, 0.02</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>GGT</td>
<td>0.08, 0.15</td>
<td>1.70, 0.08</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

- **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
- n=413, females and males for HA1c
- n= 287, females and males for incident diabetes (16 cases)
Modification of associations of LnDDE with HA1C by level of BMI, CRP, GGT and adiponectin (n=413 males and females)
Key Findings

• Adiponectin, CRP and GGT were not associated with POPs and did not mediate associations of POPs with HA1c.

• Adiponectin, CRP, GGT and BMI modified the associations of POPs with HA1c, with stronger associations in persons with higher levels of the diabetes risk factor.
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
Modeling Risks and Benefits: Negative Confounding

- True benefit in the absence of risk
- MeHg masking benefit
- Observed benefit
- True risk in the absence of benefit
- PUFA masking risk
- Observed risk

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

- **UIC**: Victoria Persky, Sally Freels, Giamila Fantuzzi
- **Wisconsin Department of Health and Family Services**: Henry A. Anderson, Lynda Knobeloch & Pamela Imm
- **Northwestern University**: Robert Chatterton, Jr.
- **ATSDR 75/ATH598322, US EPA STAR Program Grant RD-83025401-1 & NIEHS 1R21ES017121-01A1**

- LaSalle Study funded by Illinois Department of Public Health under cooperative agreement U50/ATU502923 from the ATSDR
  - Victoria Persky, Julie Piorkowski, Sally Freels, John Dimos, Lin Kaatz Chary, Terry Unterman (UIC), Robert Chatterton, Jr (Northwestern), H. Leon Bradlow, Daniel W. Sepkovic (Hackensack University Medical Center), Virlyn Burse (Battelle Memorial Institute), Kenneth McCann (Illinois Department of Public Health)

- **Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos, NIEHS R01 ES025159-01A1**
  - Victoria Persky, Martha Daviglus, Sally Freels, Noel Chavez, Terry Unterman, Robert Sargis (UIC), Jianwen Cai, (University of North Carolina at Chapel Hill), Robert Kaplan (Einstein College of Medicine), Neil Schneiderman (University of Miami), Gregory Talavera (San Diego State University), Andreas Sjodin (CDC)
  - The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) was carried out as a collaborative study supported by contracts from the National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute to the University of North Carolina (N01- HC65233), University of Miami (N01-HC65234), Albert Einstein College of Medicine (N01-HC65235), Northwestern University (N01- HC65236), and San Diego State University (N01-HC65237). The following institutes/centers/offices contribute to the HCHS/SOL through a transfer of funds to the National Heart, Lung, and Blood Institute: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, and NIH Institution-Office of Dietary Supplements.
Promoting Healthy Seafood Choices in Asian Communities
Study Objectives

- Characterize exposure to Hg and PCBs from fish consumption among Asians in Chicago

- Develop public health messages to decrease exposure to contaminants while maintaining consumption of healthy nutrients in fish
Exposure Characterization: Hair Mercury Testing

- Reflects Hg exposure in past 4-6 weeks
Exposure Survey

- Demographics and cultural and dietary acculturation
- Attitudes/knowledge of risks and benefits of eating seafood
  - Fish and shellfish consumption
    - Detailed info last 30 days: meals, size, parts, cooking (not pre-specified list)
    - Sources: purchased or locally caught
    - Who in household chooses fish, shops, prepares
    - Changes in fish consumption: seasonal, holiday, travel
    - Fish consumption during pregnancy and lactation
Exposure Characterization: Fish Contaminant Assessment

- Hg, PCB, and omega 3 fatty acid levels in fish from literature and IL DNR for sport fish

- Hg and PCB measurements in commonly eaten commercial fish
  - Fillet with skin, whole fish, fish preparations

- Hg: 100-200 tests (Nagy Lab)
- PCBs: 100 tests (Li Lab)
## Demographics and Fish Consumption

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chinese</th>
<th>Korean</th>
<th>Vietnamese</th>
</tr>
</thead>
<tbody>
<tr>
<td>N enrolled</td>
<td>125</td>
<td>114</td>
<td>75</td>
</tr>
<tr>
<td>Female</td>
<td>89%</td>
<td>86%</td>
<td>73%</td>
</tr>
<tr>
<td>US Born</td>
<td>2%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Income &lt;$20,000</td>
<td>49%</td>
<td>38%</td>
<td>72%</td>
</tr>
<tr>
<td>Income $20,000-55,000</td>
<td>38%</td>
<td>38%</td>
<td>19%</td>
</tr>
<tr>
<td>Income &gt;55,000</td>
<td>13%</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Eat Fish 3 or more times/week</td>
<td>37%</td>
<td>66%</td>
<td>43%</td>
</tr>
<tr>
<td>Eat Fish 1-2 times/week</td>
<td>52%</td>
<td>34%</td>
<td>47%</td>
</tr>
<tr>
<td>Eat Fish 1-3 times/month</td>
<td>11%</td>
<td>1%</td>
<td>11%</td>
</tr>
<tr>
<td>Eats any locally caught fish</td>
<td>44%</td>
<td>4%</td>
<td>41%</td>
</tr>
</tbody>
</table>
Next Step: Intervention

- Target Asian women of reproductive age with frequent fish consumption
- Text messages to promote healthy fish consumption
- Messages tailored to the individuals’ dietary patterns and culturally-specific dietary practices
- 6 month, randomized, controlled trial
- Outcome: Hair Hg, fish intake

http://creditcardforum.com/blog/warning-credit-card-numbers-are-being-stolen-via-text-message/