Diabetes and Air Pollution during Pregnancy and Risk of Autism in Children

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NIEHS Partners of Environmental Public Health Webinar

April 24, 2019
Outline

- Brief background of autism
- Maternal conditions during pregnancy and risk of autism – *role of diabetic pregnancy*
- Air pollution during pregnancy and risk of autism
- Plans for future work
Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, Surveillance Summaries / April 27, 2018
https://www.cdc.gov/mmwr/volumes/67/ss/ss6706a1.htm

Autism affects an estimated 1 in 59 children in the U.S.

Boys vs girls: 4-5 times higher

ASD affects:
1 in 36 boys
1 in 164 girls
Why ASD Increased?

- A better definition/ascertainment
- Increasing public awareness and screening: CDC and AAP recommend screening starts
  - 9-months for development
  - 18-months for ASD
- Also great concerns of early life exposure
What Causes ASD?

- The etiology is largely unknown, likely multifactorial
  - Genetics likely play a major role (twin studies), but few specific genes identified
  - Environmental exposure in utero and early life is increasingly recognized
  - GxE, ExE interactions
Review of Prenatal Risk Factors

- Environmental toxics (toxic metals, air pollution)
- Alcohol and Drugs (SSRI, cocaine)
- Maternal infections (rubella, CMV)
- Maternal obesity and diabetes

Biological Plausibility of Maternal Diabetes and ASD

Hyperglycemia

- Maternal diabetes
- Maternal obesity

Prenatal

- Inflammation
- Oxidative stress
- Epigenetic programming
- Other

Early Life

- Adverse neuro-behavioral outcomes:
  - e.g. ASD
Maternal Diabetes and Risk of ASD

12 Studies: 3 cohort, 9 case-control

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Burstyn et al (1)</td>
<td>2010</td>
<td>1.65 (1.01, 2.70)</td>
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<tr>
<td>Burstyn et al (2)</td>
<td>2010</td>
<td>1.24 (0.94, 1.64)</td>
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<tr>
<td>Dodds et al (1)</td>
<td>2011</td>
<td>1.98 (0.94, 4.17)</td>
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<tr>
<td>Dodds et al (2)</td>
<td>2011</td>
<td>1.29 (0.90, 1.84)</td>
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<tr>
<td>Lyall et al</td>
<td>2011</td>
<td>1.76 (1.34, 2.32)</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td>1.48 (1.25, 1.75)</td>
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<tr>
<th>Author</th>
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<tr>
<td>Piven et al</td>
<td>1993</td>
<td>3.08 (0.12, 78.48)</td>
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<tr>
<td>Juul-Dam et al</td>
<td>2001</td>
<td>3.28 (1.32, 8.16)</td>
</tr>
<tr>
<td>Hultman et al</td>
<td>2002</td>
<td>1.20 (0.28, 5.23)</td>
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<tr>
<td>Croen et al</td>
<td>2005</td>
<td>2.60 (0.83, 8.17)</td>
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<tr>
<td>Leonard et al</td>
<td>2006</td>
<td>2.95 (1.30, 6.71)</td>
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<tr>
<td>Brimacombe et al</td>
<td>2007</td>
<td>1.61 (0.82, 3.17)</td>
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<tr>
<td>Buchmayer et al</td>
<td>2009</td>
<td>0.90 (0.49, 1.66)</td>
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<tr>
<td>Elhameed et al</td>
<td>2011</td>
<td>6.33 (0.24, 166.42)</td>
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<tr>
<td>Krakowiak et al</td>
<td>2012</td>
<td>1.52 (0.82, 2.82)</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td>1.73 (1.24, 2.42)</td>
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</tbody>
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Fig. 2.
Association of maternal diabetes and ASD in the offspring in the included studies, according to study design.

Limitations of These Studies

- Diabetes by ICD or unspecified
- GDM was combined with Pre-DM in many studies
- Small sample size
- Limited or no confounder adjustment
Maternal Diabetes During Pregnancy

- Three main types of diabetes:
  - T1D - type 1 diabetes (pre-existing, ~<0.5% in US)
  - T2D - type 2 diabetes (pre-existing, ~2% in US)
  - GDM - gestational diabetes identified during pregnancy (~6-9% in US)

- GDM is not a disease of pregnancy, it detects pre-existing β-cell defects

We Launched a Large Birth Cohort Study

- To assess the impact of maternal diabetes on a series of neurodevelopmental disorders in offspring
  - **Timing of exposure** (using gestational weeks of GDM diagnosis as a surrogate)
  - **Degree of hyperglycemia** (using pre-existing T1D, T2D, and GDM with and without medication treatment as surrogates)

- Data were derived from EMR from Kaiser Permanente Southern California (KPSC)
ASD: KPSC Birth Cohort

Singleton births at 28-44 weeks gestation in KPSC hospitals between 1995 - 2012
N=533,303

- Not enrolled as KPSC health plan member at age 1 (n=113,167)
- Missing/invalid data (n=711)

419,425 mother-child pairs included in primary analysis

Xiang et al. JAMA 2018;320:89-91; Xiang et al. JAMA 2015;313:1425-1434
ASD: KPSC Birth Cohort

- Follow-up ended on the first date of:
  - A clinical diagnosis of ASD (≥ 2 ICD codes)
  - A gap of ≥ 4 months of inactive KPSC health plan
  - Death from any cause
  - December 31, 2017

5,827 (1.4%) children had ASD diagnosis
**Covariates: KPSC Birth Cohort**

- **Maternal social demographics**
  - Age at delivery, parity, education, household income, race/ethnicity

- **Maternal disease**
  - History of comorbidity, preeclampsia/eclampsia

- **Maternal obesity and smoking (collected in 2007)**
  - Pre-pregnancy BMI, gestational weight gain

- **Child characteristics**
  - Birth weight, gestational age at birth, sex, congenital anomaly

Xiang et al. *JAMA* 2015;313:1425-1434
ASD Risks – Timing of Exposure

Gestational age of GDM diagnosis is negatively associated with ASD risk

Compared to No Diabetes

- **GDM ≤ 26wks**: N=11,922
- **GDM 26-30wks**: N=14,726
- **GDM ≥ 30wks**: N=9,779

Relative Risk:
- **No diabetes**: N=372,924
ASD Risks – Cumulative Incidence of ASD

Xiang et al. JAMA 2018;320:89-91.
ASD Risks – Adjusted Relative Risk

Further adjusting for maternal obesity and smoking

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
<th>Adjusted Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>T1D</td>
<td>2.36</td>
<td>2.33</td>
</tr>
<tr>
<td>T2D</td>
<td>1.45</td>
<td>1.39</td>
</tr>
<tr>
<td>GDM at ≤ 26wks</td>
<td>1.30</td>
<td>1.26</td>
</tr>
<tr>
<td>GDM at &gt;26wks</td>
<td>0.99</td>
<td>0.98</td>
</tr>
</tbody>
</table>

\( ^a \) adjusted for sibship and birth year, maternal age, parity, education, household income, race/ethnicity, history of comorbidity, and sex of the child

Xiang et al. *JAMA* 2018;320:89-91.
Can we use this large birth cohort to study the multifactorial risk factors for ASD?

Answer – Yes
We have began to study air pollution exposure

In collaboration with Dr. Rob McConnell from USC, Fred Lurmann STI, Dr. William Funk from NWU, with support from NIEHS F31 (Heejoo Jo) and NIEHS R56 (Xiang)
Air Pollution vs ASD: - Gaps in Knowledge

- Which period of vulnerability during development?
  - Pregnancy? Early childhood?

- Differences by child sex?
  - Male-specific effect supported by animal studies

- Other potential effect modifiers?
  - e.g. maternal diabetes during pregnancy
  - Requires larger sample size
Preliminary Results using Birth Address

- KPSC birth cohort 1999-2009
- Monthly averages of regional pollutants ($PM_{2.5}$, $PM_{10}$, $NO_2$ and $O_3$) estimated by inverse distance-squared weighting
  - $PM_{2.5}$, $PM_{10}$ and $NO_2$ - average of daily 24-hr concentration
  - $O_3$ - average of daily maximum 8-hr concentration

- Exposure windows:
  - Entire pregnancy, trimester specific risk, 1st year of time

- Sex-specific interaction

Heejoo Jo et al Manuscript Under Review.
Crude Incidence Rate of ASD: 1999-2009 (KPSC Cohort)

Incidence rate per 1,000 Person-Years (up to age 5)

Heejoo Jo et al Manuscript Under Review.
Distribution of Pollutants (1999-2009)

PM$_{2.5}$ across birth year

PM$_{10}$ across birth year

NO$_2$ across birth year

O$_3$ across birth year
Where Do We Go from Here?

Prenatal

Pollutant exposures

Maternal immune activation related conditions, eg. diabetes, obesity

Increased inflammatory effects and oxidative stress

Early Life

Adverse neuro-behavioral effects, e.g. ASD
Plans for Future Work

- Using most updated spatial-temporal models to estimate PM (including PM$_{0.1}$) and chemical composition
  - e.g. secondary organic aerosols, elemental carbon, nitrates and ammonium, and primary PM emitted by on-road gasoline or diesel vehicles, and iron, chromium and nickel

- Incorporate changes in residential address and work address

- Extend the cohort to include recent births (larger sample size) and ASD with comorbidities (epilepsy, ADHD etc)

Take Home Messages

- ASD develops early in childhood and etiology remains largely unknown and multifactorial
- Strong evidence to support a link with diabetic pregnancy, especially diabetes in early pregnancy; maternal obesity exacerbates the risk
- However, the root cause is not known yet (e.g. glycemic control during pregnancy) – need more research including mechanistic studies
Take Home Messages

- Air pollution may play a role leading to increased ASD risk, but more research is needed
- Air pollution may interact with maternal conditions to affect the ASD risk – which we plan to assess
- Public health perspectives: exposures are modifiable through public health interventions and policy changes
- Women during pregnancy or planning for pregnancy should check and maintain normal blood sugar and avoid exposure to air pollution

https://airnow.gov
Acknowledgement

Kaiser Permanente Southern California
- Xinhui Wang
- Mayra P. Martinez
- Ting Chow
- Klara R Feldman
- Edward Curry
- Johanna C Walthall

Sonoma Technology, Inc.
- Fred Lurmann

University of Southern California
- Rob McConnell
- Heejoo Jo
- Jiu-Chiuan Chen
- Sandy Eckel
- Thomas A Buchanan
- Kathleen Page

Northwestern University
- William Funk

Funding Sources
- National Institute of Environmental Health Sciences (NIEHS): Ruth L. Kirschstein Predoctoral Individual National Research Service Award (F31 Jo); 1R56 ES028121-1 (Xiang)
- Kaiser Permanente Southern California Direct Community Benefit Funds