Obesity and Type 2 Diabetes in Children

Health Effects of Early-Life Exposure to Air Pollution
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Tanya L. Alderete, Ph.D.
Assistant Professor
Department of Integrative Physiology
University of Colorado at Boulder
Global Rates of Obesity

High body mass index (BMI) contributed to 4M deaths and 120M disability-adjusted life-years.
Obesity and Severe Obesity Continue to Increase in the United States

• 1 in 5 US children obese
• Highest prevalence in Hispanics & African Americans

Prevalence of Obesity and Severe Obesity Among US Children (2-19 years; 1999-2016)

Class I BMI ≥95th percentile; Class II BMI >120% of 95th percentile; Class III BMI ≥140% of 95th percentile

No Evidence of Decline in Obesity Prevalence in any Age Group
Type 2 Diabetes in Youth in the United States

- Increasingly, type 2 diabetes is diagnosed in youth
  - 20% to 50% of new-onset diabetes cases\(^1\)
  - Disproportionately affects specific racial/ethnic groups\(^2-4\)

- By 2050, number of youths with type 2 diabetes is projected to increase 4-fold\(^5\)

- Earlier age of diabetes onset, increases the future burden of disease

\(^1\)Bobo et al., 2004; \(^2\)Dabelea et al., 1998; \(^3\)Dean et al., 1998; \(^4\)Neufeld et al., 1998; \(^5\)Dabelea et al., 2014 (SEARCH Study)
Complex Relationships: Risk Factors, Obesity, and Type 2 Diabetes

These risk factors can relate to each other in various combinations.
Exposure to Air Pollutants at Home

- ~30 – 45% of urban population in North America lives near busy roads
- **2010 HEI Report**: traffic pollution causes asthma attacks and may cause onset of childhood asthma, impaired lung function, premature death, and cardiovascular disease
  - Those within 300 to 500 meters of highways most affected
- **2019 HEI and State of Global Air**: air pollution may contribute to low birth weight and pre-term birth
  - Included health burden related to type 2 diabetes

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Schools Located Near Busy Roadways in the United States

Nearly 8,000 public schools lie within 500 ft of highways / large roadways

https://publicintegrity.org/environment/the-invisible-hazard-afflicting-thousands-of-schools/
Exposure to Air Pollutants Occur During Critical Periods of Development

Maternal and Early Life Exposures to Air Pollutants: Implications for Childhood Obesity and Type 2 Diabetes

Developmental Origins of Health and Disease: Early life environment has widespread consequences for later health
Prenatal Air Pollution Exposure and Decreased Fetal Growth

Intrauterine growth restriction by ultrasound: catch-up growth and ↑adiposity in early/mid-childhood

- ↑NO₂ (0-12 wk): ↓fetal growth, birth size
- ↑PM₂.⁵ (prenatal): ↓birth weight, preterm birth, SGA
- ↑Traffic Density (3rd trimester): ↓fetal growth, ↑postnatal weight gain
- ↑PAH (1st/3rd trimester, prenatal): ↓fetal growth, ↓birth weight, SGA

Notably, these studies included personal exposure monitoring.

NO₂ = nitrogen dioxide  
PM₂.⁵ = particulate matter < 2.5 μm in diameter  
PAH = polycyclic aromatic hydrocarbons  
SGA = small for gestational age

Ong KK et al., 2000; Iñiguez C et al., 2018; Yuan et al, 2019; Fleisch AF et al., 2015; Choi et al., 2011; Choi et al., 2012; Image: Peleg D et al., 1990
# Prenatal Air Pollution Exposure and Childhood Obesity

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Location</th>
<th>Exposure</th>
<th>Prenatal</th>
<th>Direction of Outcome in Early Life &amp; Childhood¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rundal (2011)</td>
<td>422</td>
<td>United States</td>
<td>PAH</td>
<td>3rd Trimester</td>
<td>+ BMI-z, Obesity, Fat Mass</td>
</tr>
<tr>
<td>Chiu (2017)</td>
<td>239</td>
<td>United States</td>
<td>PM$_{2.5}$</td>
<td>2-22 wks 8-17 wks Pregnancy</td>
<td>+ Waist-to-Hip Ratio + BMI-z, Fat Mass (males) + BMI-z, Fat Mass (males) + Waist-to-Hip Ratio (females)</td>
</tr>
<tr>
<td>Fleisch (2017)</td>
<td>1418</td>
<td>United States</td>
<td>&lt;50 m vs. ≥200m</td>
<td>Delivery</td>
<td>+ Fat Mass</td>
</tr>
<tr>
<td>Kim (2018)*</td>
<td>2318</td>
<td>United States</td>
<td>Near-Roadway</td>
<td>In Utero</td>
<td>BMI Growth</td>
</tr>
<tr>
<td>Frondelius (2018)*</td>
<td>5815</td>
<td>Sweden</td>
<td>Near-Roadway</td>
<td>Pregnancy</td>
<td>Obesity</td>
</tr>
<tr>
<td>Fleisch (2019)*</td>
<td>1649</td>
<td>United States</td>
<td>PM$_{2.5}$, BC</td>
<td>3rd Trimester</td>
<td>BMI Growth</td>
</tr>
<tr>
<td>Huang (2019)</td>
<td>8327</td>
<td>Hong Kong</td>
<td>SO2</td>
<td>In Utero</td>
<td>(males) BMI-z (males) Fat Mass</td>
</tr>
</tbody>
</table>

Results largely mixed and may differ by sex and pollutants examined…

BMI = Body mass index  
PM$_{2.5}$ = particulate matter < 2.5 μm in diameter  
PAH = Polycyclic aromatic hydrocarbons  
¹6 months, 3-15 years; *Longitudinal study; PAH (polycyclic aromatic hydrocarbon); near-roadway (modeled with NOx)
## Early Life Exposure to Air Pollution and Childhood Obesity

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Location</th>
<th>Age (yr.)</th>
<th>Pollutant</th>
<th>Direction of Outcome in Childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerrett (2010)*</td>
<td>3318</td>
<td>United States</td>
<td>9-10</td>
<td>Traffic by home</td>
<td>+ BMI (150m) + BMI (300m, females)</td>
</tr>
<tr>
<td>Dong (2014)</td>
<td>30056</td>
<td>China</td>
<td>2-14</td>
<td>PM\textsubscript{10}, O\textsubscript{3}, NO\textsubscript{2}, SO\textsubscript{2}</td>
<td>+ Obesity + Overweight (O\textsubscript{3} only)</td>
</tr>
<tr>
<td>Nikolic (2014)</td>
<td>1059</td>
<td>Serbia</td>
<td>7-11</td>
<td>High vs. Low Exposed (SO\textsubscript{2}, NO\textsubscript{2}, Black Smoke)</td>
<td>+ Weight, BMI</td>
</tr>
<tr>
<td>Jerrett (2014)*</td>
<td>4550</td>
<td>United States</td>
<td>5-7</td>
<td>Near-Roadway</td>
<td>+ BMI</td>
</tr>
<tr>
<td>McConnell (2015)*</td>
<td>3318</td>
<td>United States</td>
<td>10</td>
<td>(Near-Roadway modeled NO\textsubscript{x}) * SHS</td>
<td>+ BMI</td>
</tr>
<tr>
<td>Alderete (2017)*</td>
<td>314</td>
<td>United States</td>
<td>8-15</td>
<td>PM\textsubscript{2.5}, NO\textsubscript{2}</td>
<td>+ BMI &amp; SAAT Growth</td>
</tr>
<tr>
<td>Kim (2018)*</td>
<td>2318</td>
<td>United States</td>
<td>1-4</td>
<td>Near-Roadway</td>
<td>+ BMI Growth</td>
</tr>
<tr>
<td>de Bont (2019)</td>
<td>2660</td>
<td>Spain</td>
<td>7-10</td>
<td>PM\textsubscript{10}-home, UFP-school, NO\textsubscript{2}, EC</td>
<td>+ Obesity + Overweight</td>
</tr>
<tr>
<td>Huang (2019)</td>
<td>8327</td>
<td>Hong Kong</td>
<td>9-15</td>
<td>NO\textsubscript{2}</td>
<td>+ BMI (males)</td>
</tr>
</tbody>
</table>

9 Recent Studies: *Longitudinal study

PM\textsubscript{10} = particulate matter < 10 μm in diameter; O\textsubscript{3} = ozone; NO\textsubscript{2} = nitrogen dioxide; NO\textsubscript{x} = nitrogen oxides; SO\textsubscript{2} = sulfur dioxide; UFP = ultrafine particles; EC = elemental carbon; SHS = second hand smoke; SAAT = subcutaneous abdominal adipose tissue
## Early Life Exposure to Air Pollution and Childhood Obesity

2 found no association and 2 had protective association when examining obesity

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<tr>
<th>Author</th>
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<th>Age (yr.)</th>
<th>Pollutant</th>
<th>Direction of Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toledo-Corral &amp; Alderete (2018)</td>
<td>429</td>
<td>United States</td>
<td>8-18</td>
<td>PM$_{2.5}$, NO$_2$, O$_3$, Near-Roadway</td>
<td>0 BMI-z, BF%, SAAT &amp; IAAT</td>
</tr>
<tr>
<td>Fioravanti (2018)*</td>
<td>719</td>
<td>Italy</td>
<td>4, 8</td>
<td>NO$<em>x$, PM$</em>{10}$, PM$_{2.5}$, NO$_2$</td>
<td>0 BMI-z, Waist Circumference &amp; WHR</td>
</tr>
<tr>
<td>Kim (2016)*</td>
<td>1129</td>
<td>South Korea</td>
<td>0-5</td>
<td>PM$_{10}$</td>
<td>- Weight</td>
</tr>
<tr>
<td>Huang (2019)</td>
<td>8327</td>
<td>Hong Kong</td>
<td>9-15</td>
<td>SO$_2$</td>
<td>- BMI (males)</td>
</tr>
</tbody>
</table>

Mixed results may be due to differences in sex, age group, and pollutant...

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**BMI** = Body mass index; **PM$_{2.5}$** = particulate matter < 2.5 μm in aerodynamic diameter; **PM$_{10}$** = particulate matter < 10 μm in aerodynamic diameter; **SO$_2$** = sulfur dioxide; **EC** = elemental carbon; **NO$_2$** = nitrogen dioxide; **NO$_x$** = oxides of nitrogen

*Longitudinal Study; Near-Roadway (modeled with NO$_x$); SAAT (subcutaneous abdominal adipose tissue); IAAT (intraabdominal adipose tissue); WHR (waist-to-hip ratio)
Covariates: Early Life Exposure to Air Pollution and Childhood Obesity

- Infant Age, Sex, Socioeconomic status: 100%
- Secondhand smoke/In Utero: 72%
- Birth Weight: 56%
- Maternal Factors: 44%
- Physical Activity/Diet: 28%
- Respiratory Health: 17%
- Home Characteristics: 11%

SHS = secondhand smoke; BMI = body mass index

17 Recent Studies: Jerrett (2010); Dong (2014); Jerrett (2014); McConnell (2015); Alderete (2017); Kim (2018); Nikolic (2013); Kim (2016); Toledo-Corral & Alderete (2018); Fioravantia (2018); Rundal (2011); Chiu (2017); Fleisch (2017); Frondelius (2018); Fleisch (2019); de Bont (2019); Huang (2019)
Exposure Assessment and Multi-Pollutant Models

Exposure Assessment Methods:

- Traffic Density / Distance to Roadways
- Modeled NO\textsubscript{x} (e.g., CALINE, Dispersion)
- Ambient Monitoring Stations (e.g., LUR, IDW)
- Satellite, Hybrid Satellite with LUR
- Personal Monitors (*rare*)
- School & Home Monitors (*rare*)

**Very few studies examined multi-pollutant models (complex mixtures)**

**17 Recent Studies:** Jerrett (2010); Dong (2014); Jerrett (2014); McConnell (2015); Alderete (2017); Kim (2018); Nikolic (2013); Kim (2016); Toledo-Corral & Alderete (2018); Fioravantia (2018); Rundal (2011); Chiu (2017); Fleisch (2017); Frondelius (2018); Fleisch (2019); de Bont (2019); Huang (2019)

NO\textsubscript{x} = nitrogen oxides
CALINE = California Line Source Dispersion Model
LUR = land use regression
IDW = inverse distance weighted
Life Course Perspective of Obesity

- Prenatal and early-life factors are involved in development of obesity
- Causes of obesity are multifactorial
- Overweight / Obesity appear at different ages by race/ethnicity
- BMI has limitations as a measure of obesity (not capturing body composition)
Maternal Susceptibility to Air Pollution: Low Birth Weight and Childhood Obesity

7 studies examined effect modification of the association between ambient air pollution and low birth weight with maternal factors:

- **Smoking**
  - Smoke, ↑BW
  - Smoke, ↓BW

- **BMI**
  - ↑BMI, ↓BW
  - ↑BMI, ↑Child Obesity

- **SES**
  - ↓SES, ↓BW

- **Asthma**
  - No effect modification

- **Race/Ethnicity**
  - ↓BW: ↑NHB & ↑Hispanic vs. NHW

"The current epidemiologic evidence is scarce, but suggests that pregnant women who are smoking, being underweight, overweight/obese or having lower SES are a vulnerable subpopulation when exposed to ambient air pollution." (Westergaard et al., 2017)
Summary: Exposure to Air Pollutants and Childhood Obesity

- Influence of air pollution on body weight/obesity is mixed and may differ by sex, age group, race/ethnicity, and air pollutant

- **Future studies should examine:**
  - Multi-pollutant models
  - Personal monitoring
  - Important confounders and effect modifiers
  - Vulnerable populations
  - Mechanisms underlying associations
Type 2 Diabetes Characterized:
• High peripheral glucose concentrations caused by insulin resistance
• Relative deficiency of insulin from pancreatic β-cells

Risk for Developing Type 2 Diabetes (Early Indicators):
• Blood markers of glucose metabolism
  • Fasting glucose, post-prandial glucose, HbA1c
• Insulin resistance / insulin sensitivity, acute insulin response, β-cell function
Air Pollution Exposure in Childhood and Risk Factors for Type 2 Diabetes

- Compared to control children, those living in a ↑exposure metropolitan region of Mexico had ↑fasting glucose levels¹
- ↑Air Quality Index (AQI) associated with ~2x higher odds of ↑fasting glucose in children and adolescents²
- ↑NO₂ associated with ↓metabolic benefits (e.g., HbA1c) of laparoscopic adjustable gastric banding in adolescents³
- ↑NO₂ and PM₂.₅ as well as proximity to roadways was associated with greater insulin resistance (HOMA-IR)⁴-⁶

¹Calderón-Garcidueñas et al. 2015; ²Poursafa et al., 2014; ³Ghosh et al. 2017; ⁴Kelishadi et al., 2009; ⁵Thiering et al., 2013 and ⁶2016 as reviewed in Alderete, Chen, & Toledo-Corral et al., 2018
Air Pollution Exposure has a Stronger Effect on Insulin Resistance in Adolescents with a Lower SES

Estimated effect for 2 standard deviation increase in exposure. For example, PM$_{10}$ (6.7 μg/m$^3$) and NO$_2$ (8.9 μg/m$^3$). Gam models adjusted for study area, cohort, sex, age, BMI, smoking by the adolescent, physical activity, pubertal state. $p$-Values for the interaction with time spent outside in summer: NDVI (500 m): $p = 0.317$, NDVI (1,000 m): $p = 0.251$, NO$_2$: $p = 0.122$, PM$_{10}$: $p = 0.029$, PM$_{2.5}$: $p = 0.186$, PM$_{2.5}$ absorbance (abs): $p = 0.126$. 
Higher prior year exposure to NO$_2$ and PM$_{2.5}$ associated with:

1. ↑ Higher fasting glucose
2. ↓ Lower insulin sensitivity ($S_I$) among overweight and obese minority youth

Estimated effects for a 1 standard deviation (SD) difference in prior year NO$_2$ (6.8 ppb) and PM$_{2.5}$ (5.2 μg/m$^3$) exposure with 95% CI. Adjusts for age, sex, pubertal stage, season of testing (warm/cold), body fat%, and social position. N=429 and 387, respectively.
### Estimated effects are shown as a % difference with 95% confidence interval (CI) for a 1-SD increase in NO$_2$ (5 ppb), 1-SD increase in PM$_{2.5}$ (4 $\mu$g/m$^3$), or a 5% increase in body fat% for insulin sensitivity, acute insulin response to glucose, and disposition index (DI). For body fat%, models adjusted for age, sex, Tanner stage, study wave, year, and social position. Average of 3 years of follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Long-Term NO$<em>2$ and PM$</em>{2.5}$</th>
<th>Body Fat % (+5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Sensitivity</td>
<td>-13% to -21.6%</td>
<td>-16.7%</td>
</tr>
<tr>
<td>Acute Insulin Response</td>
<td>+28.5%</td>
<td>+10.2%</td>
</tr>
<tr>
<td>$\beta$-cell function (DI)</td>
<td>-13%</td>
<td>-6.9%</td>
</tr>
</tbody>
</table>
Covariates: Early Life Exposure to Air Pollution and Risk Factors for Type 2 Diabetes

- **Age and Sex:** 100%
- **Socio-economic status (SES):** 75%
- **Puberty:** 50%
- **Body mass index (BMI):** 63%
- **Physical Activity/Diet:** 50%
- **Body Fat (BF) Percent:** 25%
- **Vegetation:** 13%

**8 Studies Included:** Calderón-Garcidueñas et al. 2015; Poursafa et al., 2014; Ghosh et al. 2017; Kelishadi et al., 2009; Thiering et al., 2013, Thiering et al., 2016, Toledo-Corral & Alderete et al., 2018, Alderete et al., 2017

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Child Susceptibility to Air Pollution: Risk Factors for Type 2 Diabetes

Studies suggest certain groups of youth are more susceptible:

**BMI**
- \(\uparrow\) BMI:
- \(\downarrow\) SI, \(\downarrow\) DI

**SES**
- \(\downarrow\) SES:
- \(\uparrow\) HOMA-IR,
- \(\downarrow\) SI, \(\downarrow\) DI

**Race/Ethnicity**
- \(\uparrow\) Risk Factors:
  - NHB, Hispanic

BMI = body mass index; SI = insulin sensitivity; DI = \(\beta\)-cell function; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; NHB = non-Hispanic Black; SES = socioeconomic status
Summary: Exposure to Air Pollutants and Type 2 Diabetes in Children

• Short- and long-term exposures to ambient and near-roadway pollution play a role in glucose metabolism and the pathogenesis of type 2 diabetes in youth.

• Emerging evidence indicates that exposure to air pollutants has stronger effects in susceptible populations (e.g., obesity, existing metabolic dysfunction).
Overall Conclusions

- A growing body of literature supports an independent role of exposure to air pollutants in:
  - Childhood obesity
  - Pathophysiology of type 2 diabetes

- Specific pollutant sources and chemical components of the urban air mixture responsible for the observed effects remain uncertain

- Exact mechanisms warrant further investigation
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Contact Information
✉️ tanya.alderete@colorado.edu
🌐 www.adorlab.com
🐦 @tanya24lynn