Obesity and Type 2 Diabetes in Children

Health Effects of Early-Life Exposure to Air Pollution
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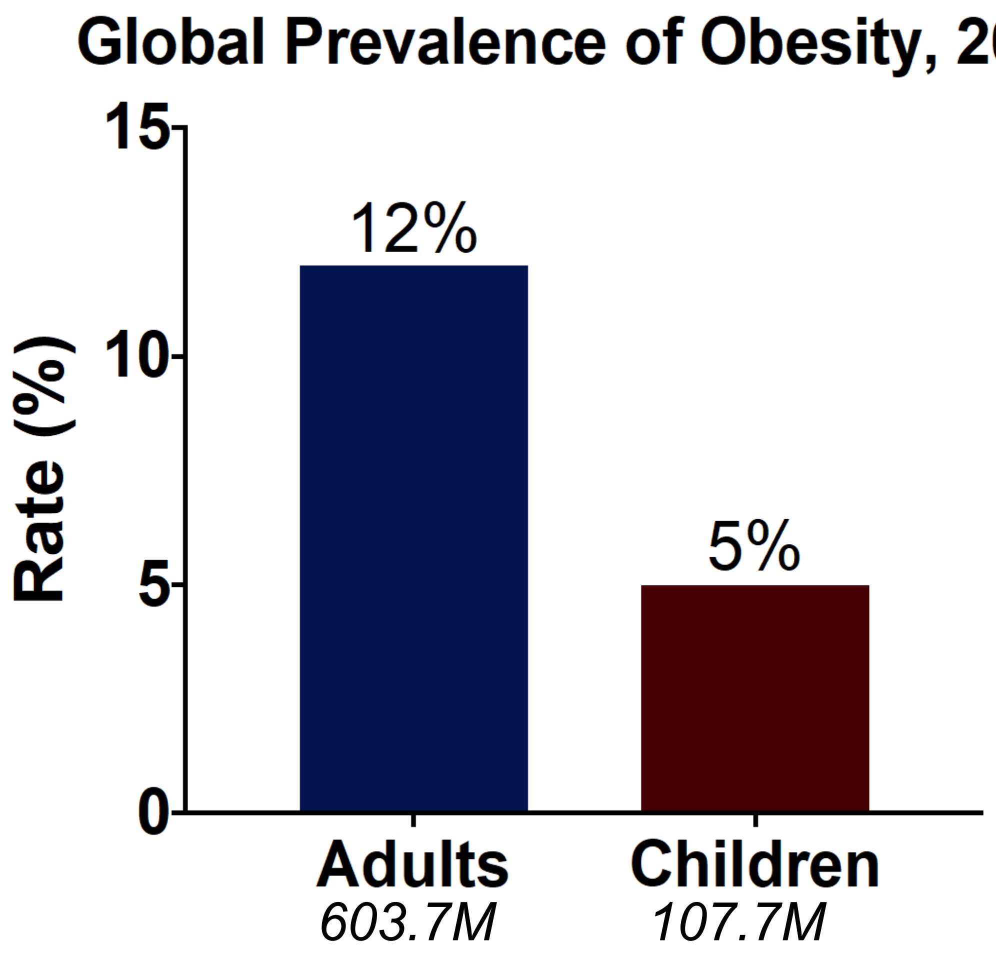
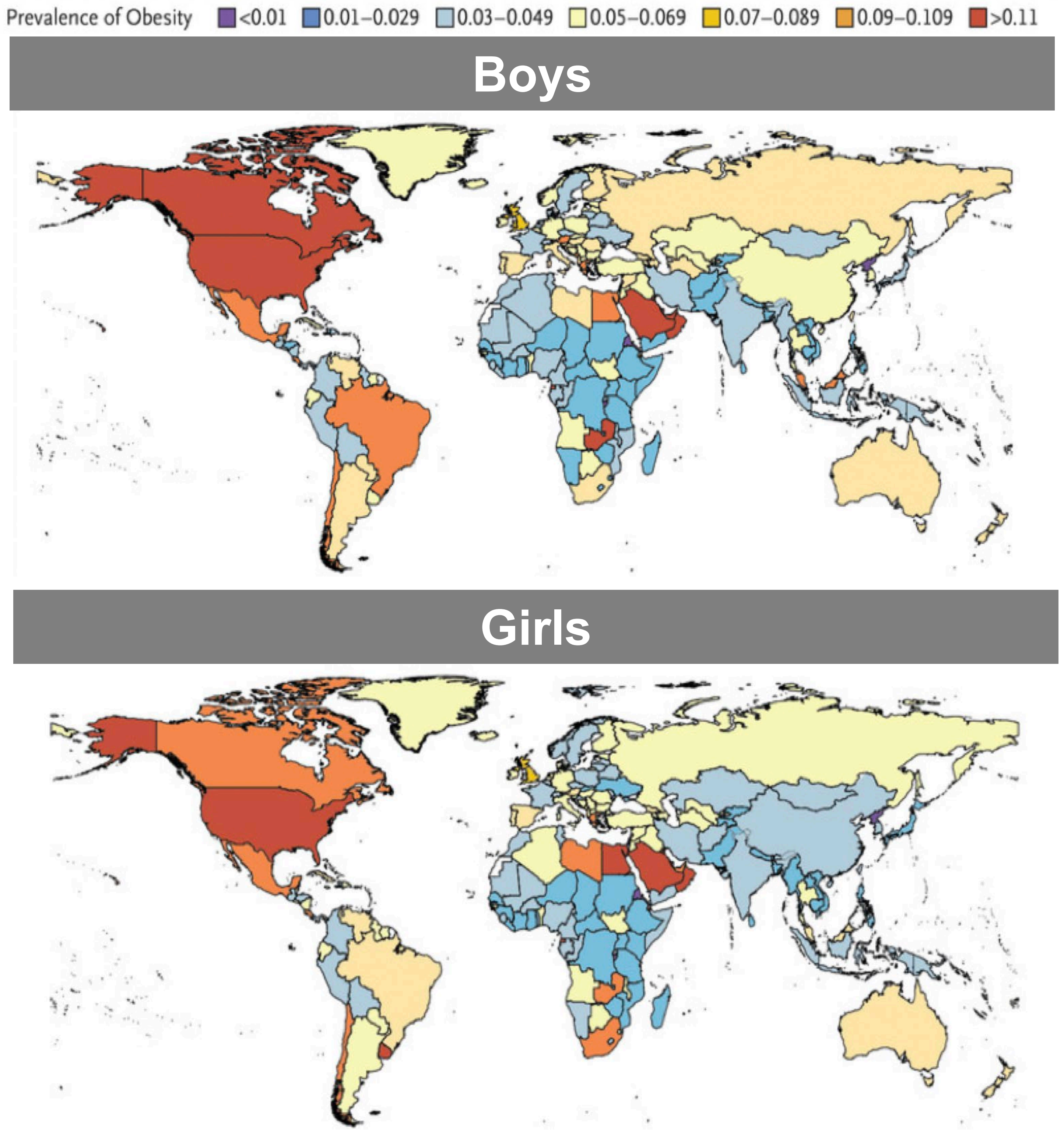
Global Rates of Obesity





High body mass index (BMI) contributed to 4M deaths and 120M disability-adjusted life-years.

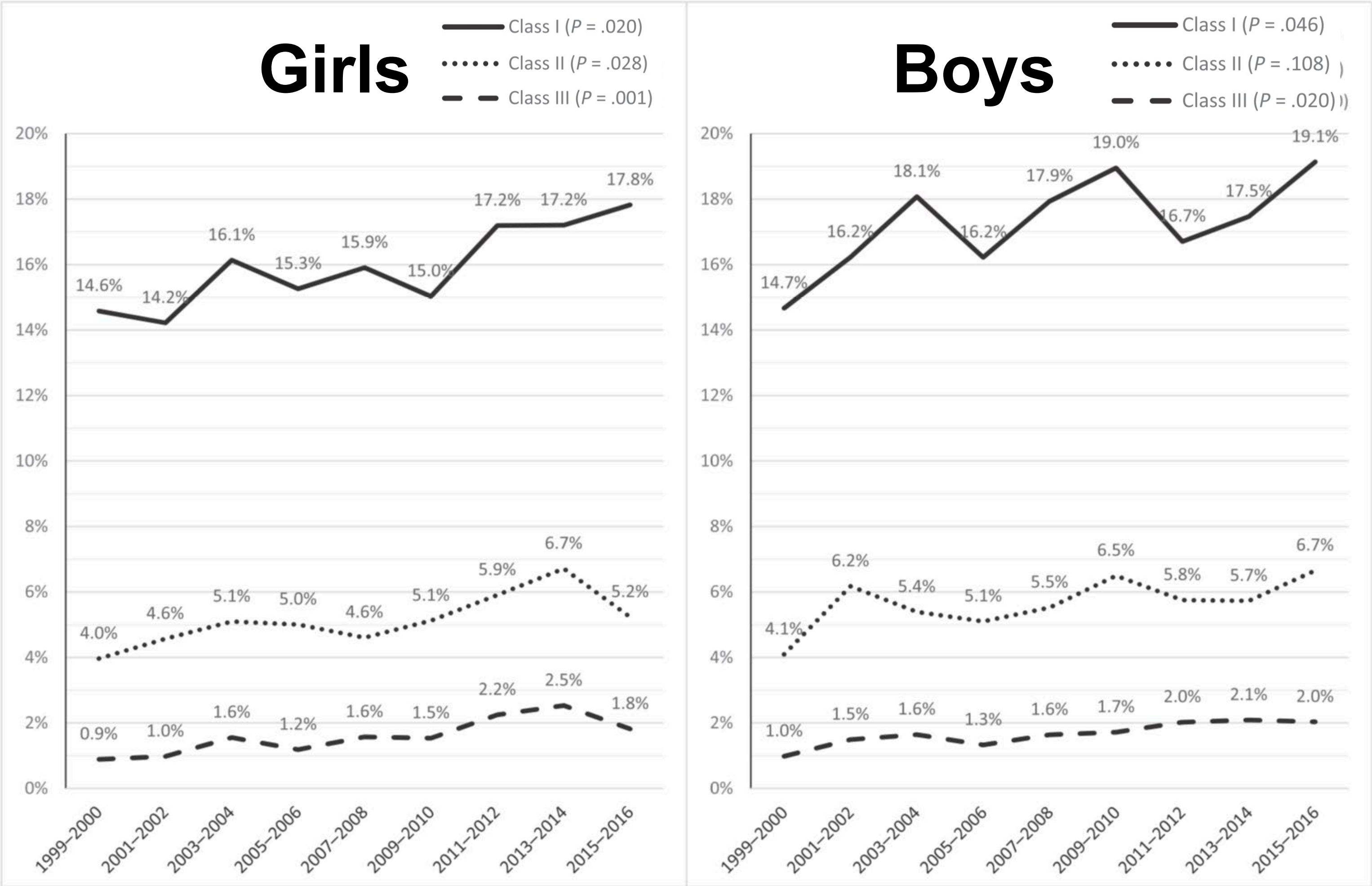
GBD 2015 Obesity Collaborators, NEJM, 2017;377:13-27

Obesity and Severe Obesity Continue to Increase in the United States

No Evidence of Decline in
Obesity Prevalence in any Age Group

- 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

Skinner et al., Pediatrics, 2018 and NEJM, 2015

Type 2 Diabetes in Youth in the United States

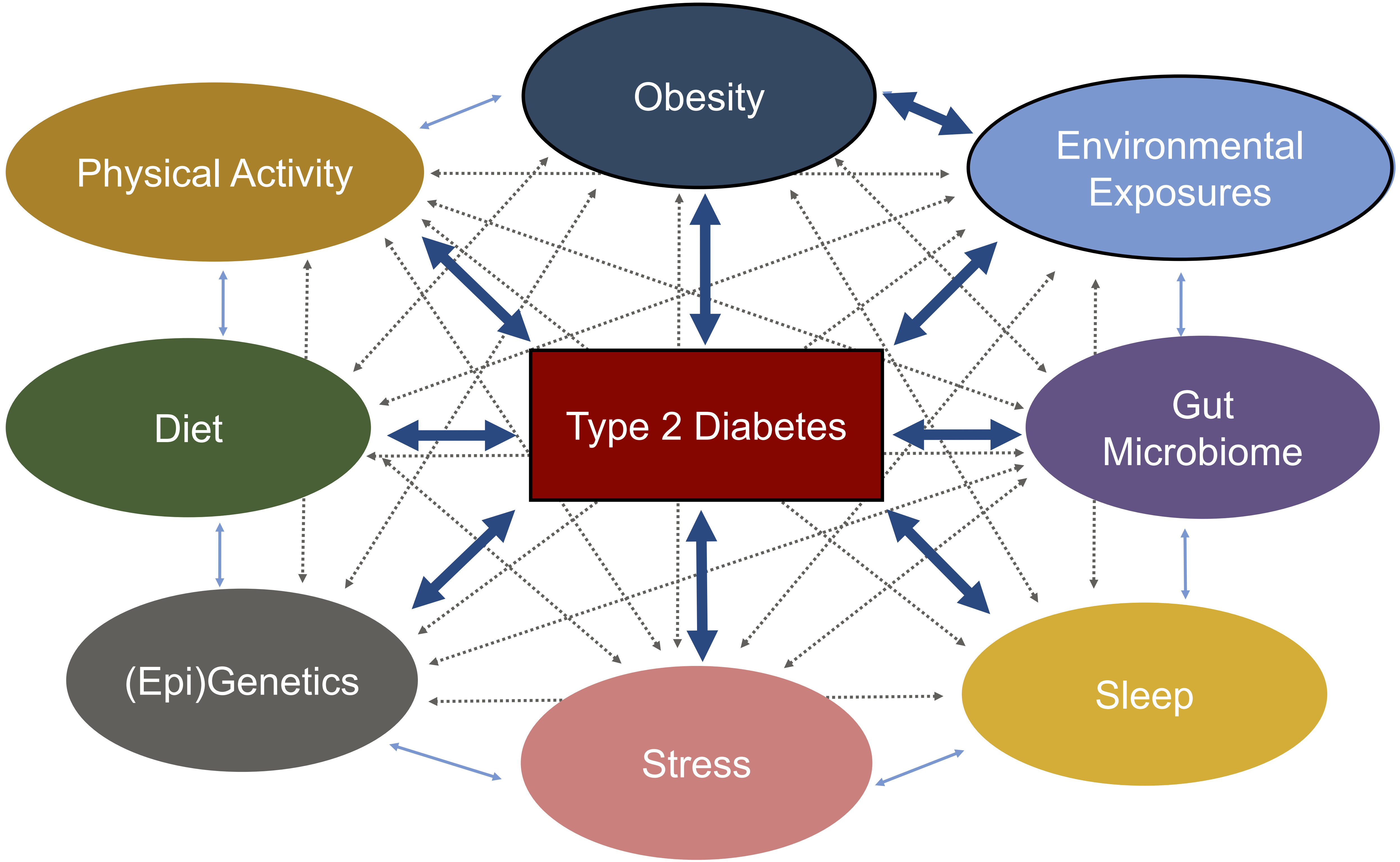
- Increasingly, type 2 diabetes is diagnosed in youth
  - 20% to 50% of new-onset diabetes cases[1]
  - Disproportionately affects specific racial/ethnic groups[2-4]

- 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

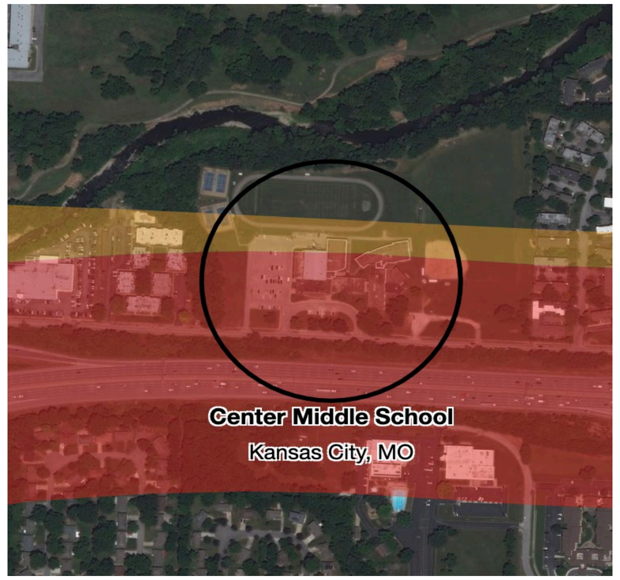
Exposure to Air Pollutants at Home

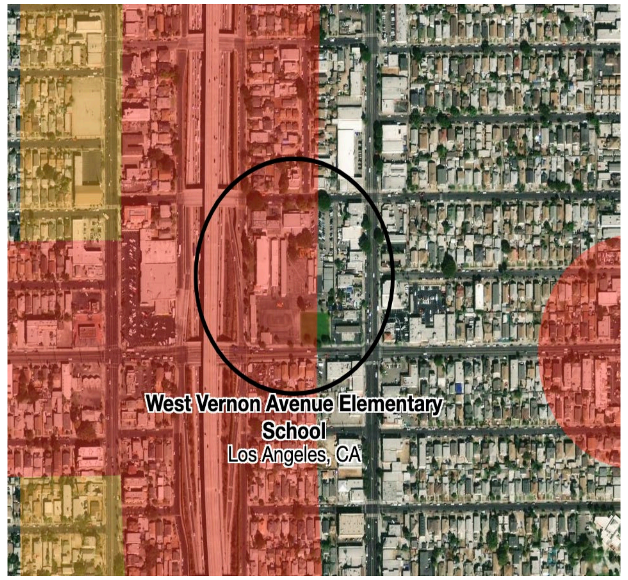
- **~30 – 45%** of urban population in North America lives near busy roads
- **2010 HEI Report:** traffic pollution causes asthma attacks and may cause onset of childhood asthma, impaired lung function, premature death, and cardiovascular disease[1]
  - Those within 300 to 500 meters of highways most affected[1]
- **2019 HEI and State of Global Air:** air pollution may contribute to low birth weight and pre-term birth[2]
  - Included health burden related to type 2 diabetes[2]

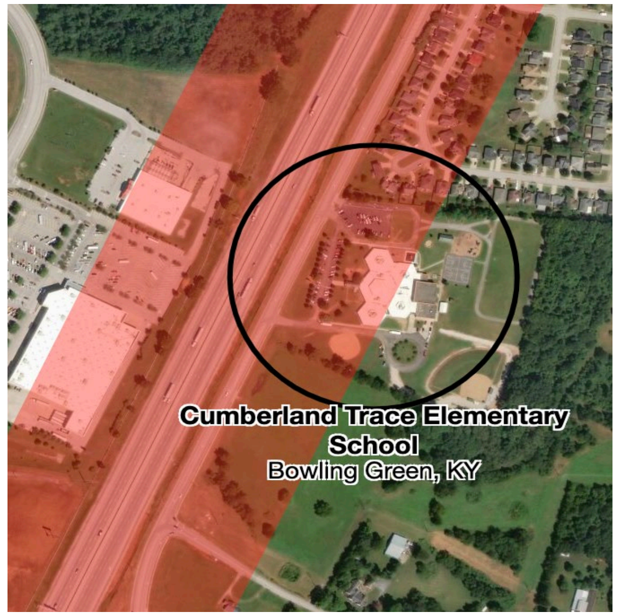
[1]HEI Panel on the Health Effects of Traffic-Related Air Pollution, *Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects.* 2010. [2]HEI. 2019. State of Global Air 2019, www.stateofglobalair.org. Images: *Los Angeles Times*

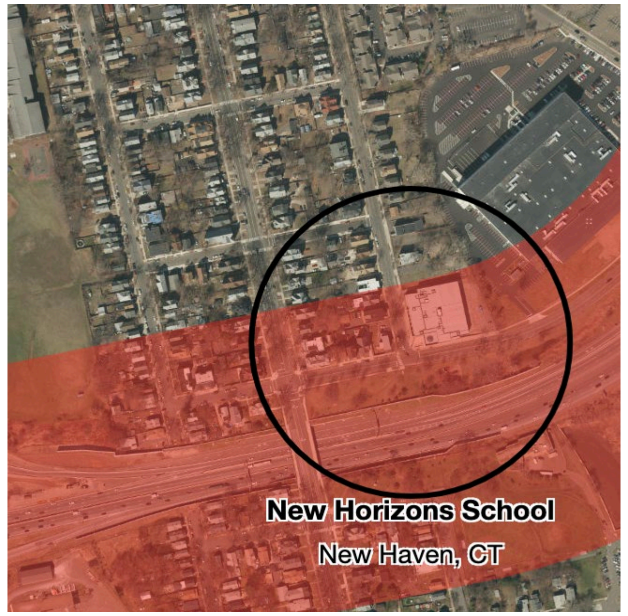
Schools Located Near Busy Roadways in the United States

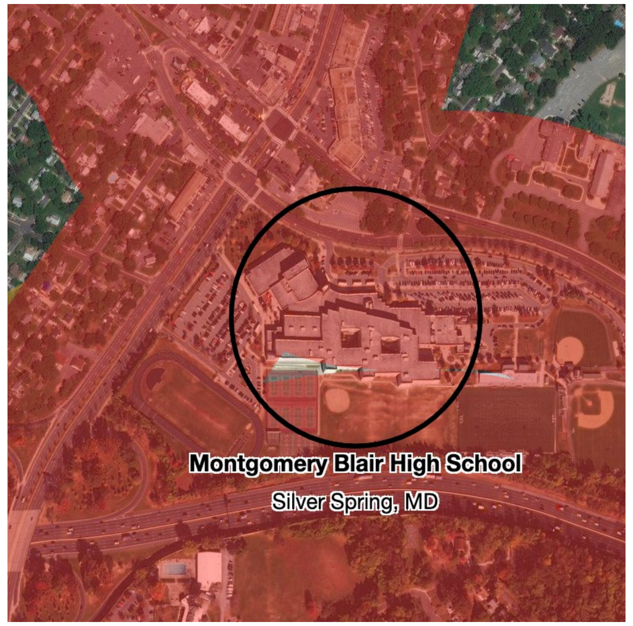
Nearly 8,000 public schools lie within 500 ft of highways / large roadways









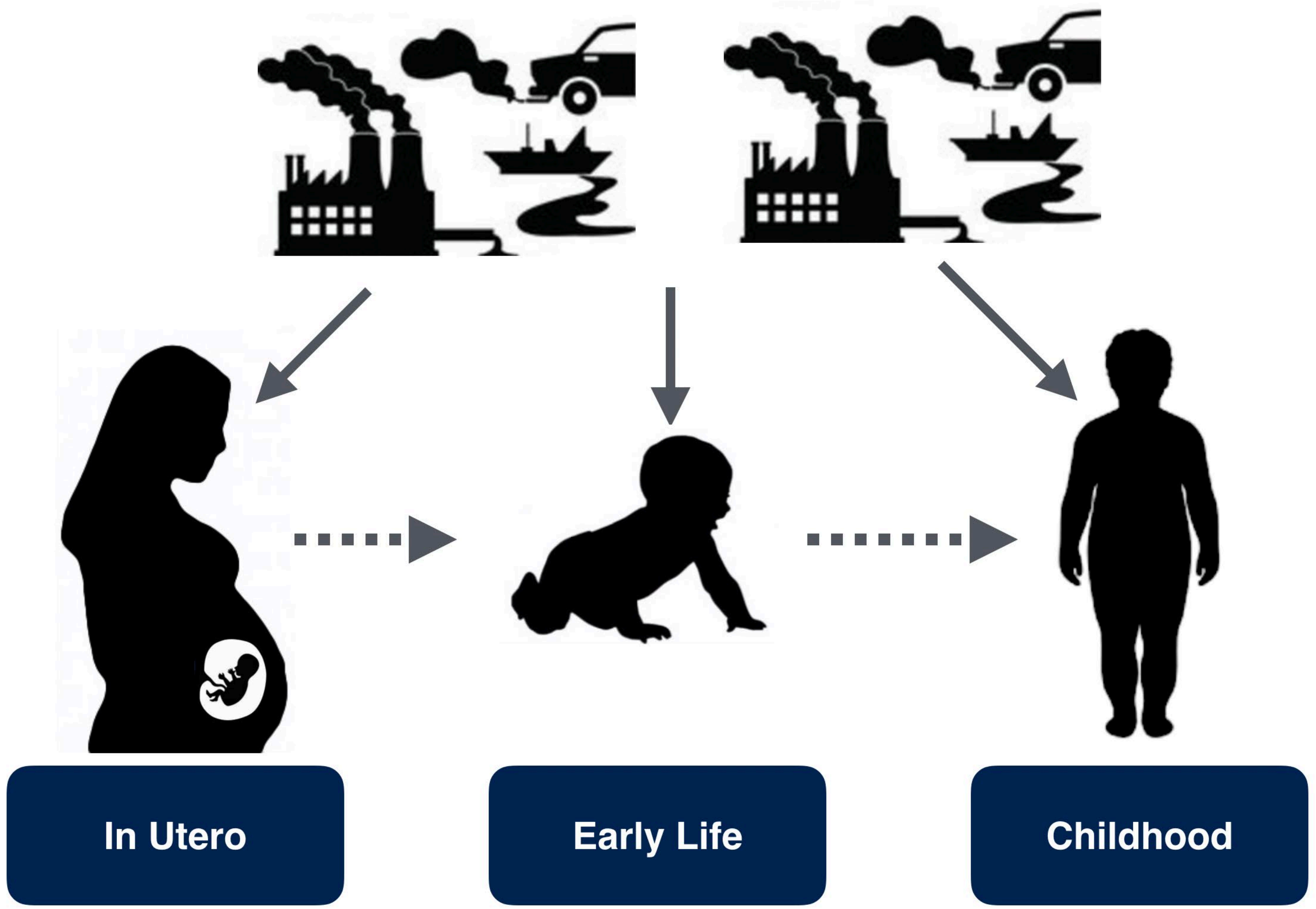


w/in 500 ft. of road w/30,000+ vehicles on an average day   w/in 500 ft. of road w/10,000+ vehicles & 500+ trucks on an average day

https://publicintegrity.org/environment/the-invisible-hazard-afflicting-thousands-of-schools/

Exposure to Air Pollutants Occur During Critical Periods of Development

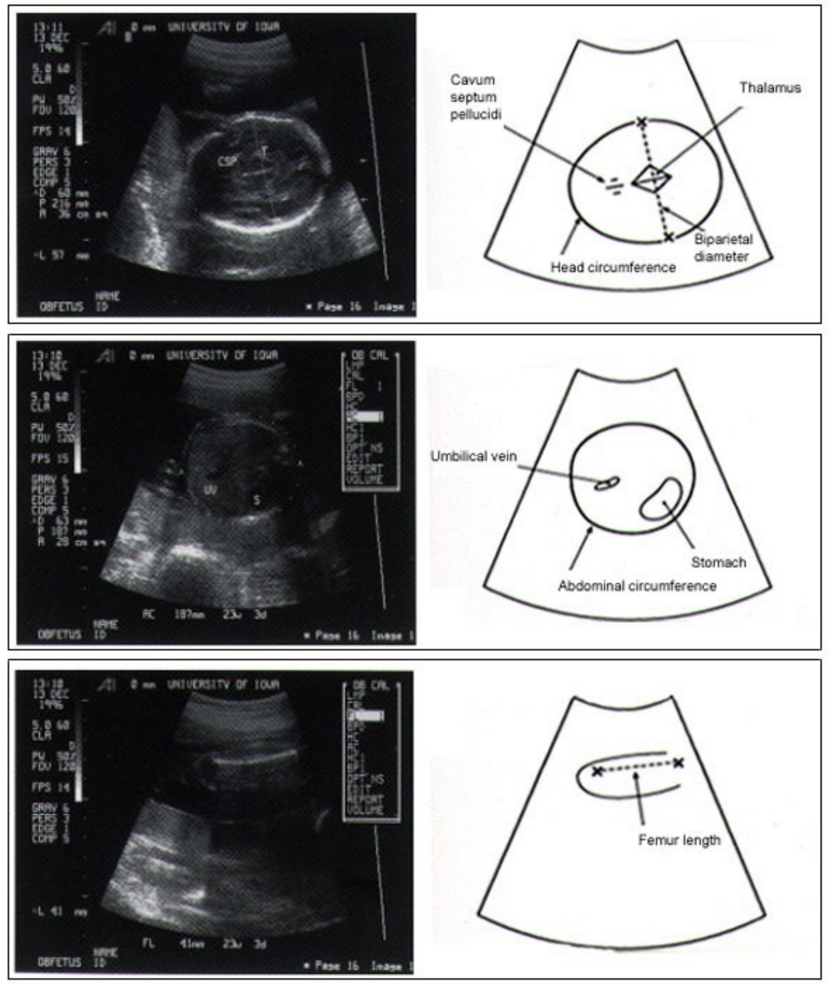
Maternal and Early Life Exposures to Air Pollutants: Implications for Childhood Obesity and Type 2 Diabetes



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[1]



- **↑NO_2 (0-12 wk):** ↓fetal growth, birth size[2]
- **↑$PM_{2.5}$ (prenatal):** ↓birth weight, preterm birth, SGA[3]
- **↑Traffic Density (3rd trimester):** ↓fetal growth, ↑postnatal weight gain[4]
- **↑PAH (1st/3rd trimester, prenatal):** ↓fetal growth[5], ↓birth weight, SGA[6]

Notably, these studies included personal exposure monitoring.

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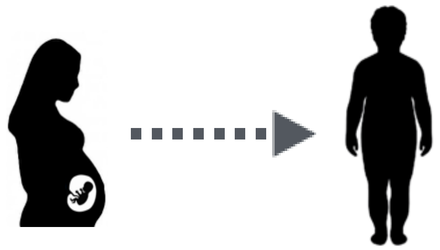
NO_2 = nitrogen dioxide
$PM_{2.5}$ = particulate matter < 2.5 μm in diameter
PAH = polycyclic aromatic hydrocarbons
SGA = small for gestational age

[1]Ong KK et al., 2000; [2]Iñiguez C et al., 2018; [3]Yuan et al, 2019; [4]Fleisch AF et al., 2015; [5]Choi et al., 2011; [6]Choi et al., 2012; **Image**: Peleg D et al., 1990



Prenatal Air Pollution Exposure and Childhood Obesity

Author	N	Location	Exposure	Prenatal	Direction of Outcome in Early Life & Childhood[1]
Rundal (2011)	422	United States	PAH	3rd Trimester	**+ BMI-z, Obesity, Fat Mass**
Chiu (2017)	239	United States	$PM_{2.5}$	2-22 wks 8-17 wks Pregnancy	**+ Waist-to-Hip Ratio** **+ BMI-z, Fat Mass** (*males*) **+ BMI-z, Fat Mass** (*males*) **+ Waist-to-Hip Ratio** (*females*)
Fleisch (2017)	1418	United States	<50 m vs. ≥200m	Delivery	**+ Fat Mass**

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

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BMI = Body mass index
$PM_{2.5}$ = particulate matter < 2.5 µm in diameter
PAH = Polycyclic aromatic hydrocarbons

[1]6 months, 3-15 years; *Longitudinal study; PAH (polycyclic aromatic hydrocarbon); near-roadway (modeled with NOx)

Early Life Exposure to Air Pollution and Childhood Obesity

Author	N	Location	Age (yr.)	Pollutant	Direction of Outcome in Childhood
Jerrett (2010)*	3318	United States	9-10	Traffic by home	**+ BMI** (150m) **+ BMI** (300m, *females*)
Dong (2014)	30056	China	2-14	PM_{10}, O_3, NO_2, SO_2	**+ Obesity** **+ Overweight** (*O_3 only*)
Nikolic (2014)	1059	Serbia	7-11	High vs. Low Exposed (SO_2, NO_2, Black Smoke)	**+ Weight, BMI**
Jerrett (2014)*	4550	United States	5-7	Near-Roadway	**+ BMI**
McConnell (2015)*	3318	United States	10	(Near-Roadway modeled NO_x) * SHS	**+ BMI**
Alderete (2017)*	314	United States	8-15	$PM_{2.5}$, NO_2	**+ BMI & SAAT Growth**
Kim (2018)*	2318	United States	1-4	Near-Roadway	**+ BMI Growth**
de Bont (2019)	2660	Spain	7-10	PM_{10}-home, UFP-school, NO_2, EC	**+ Obesity** **+ Overweight**
Huang (2019)	8327	Hong Kong	9-15	NO_2	**+ BMI** (*males*)

PM_{10} = particulate matter < 10 μm in diameter; O_3 = ozone;
NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; SO_2 = sulfur dioxide;
UFP = ultrafine particles; EC = elemental carbon;
SHS = second hand smoke; SAAT = subcutaneous abdominal adipose tissue

9 Recent Studies: *Longitudinal study

Early Life Exposure to Air Pollution and Childhood Obesity

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

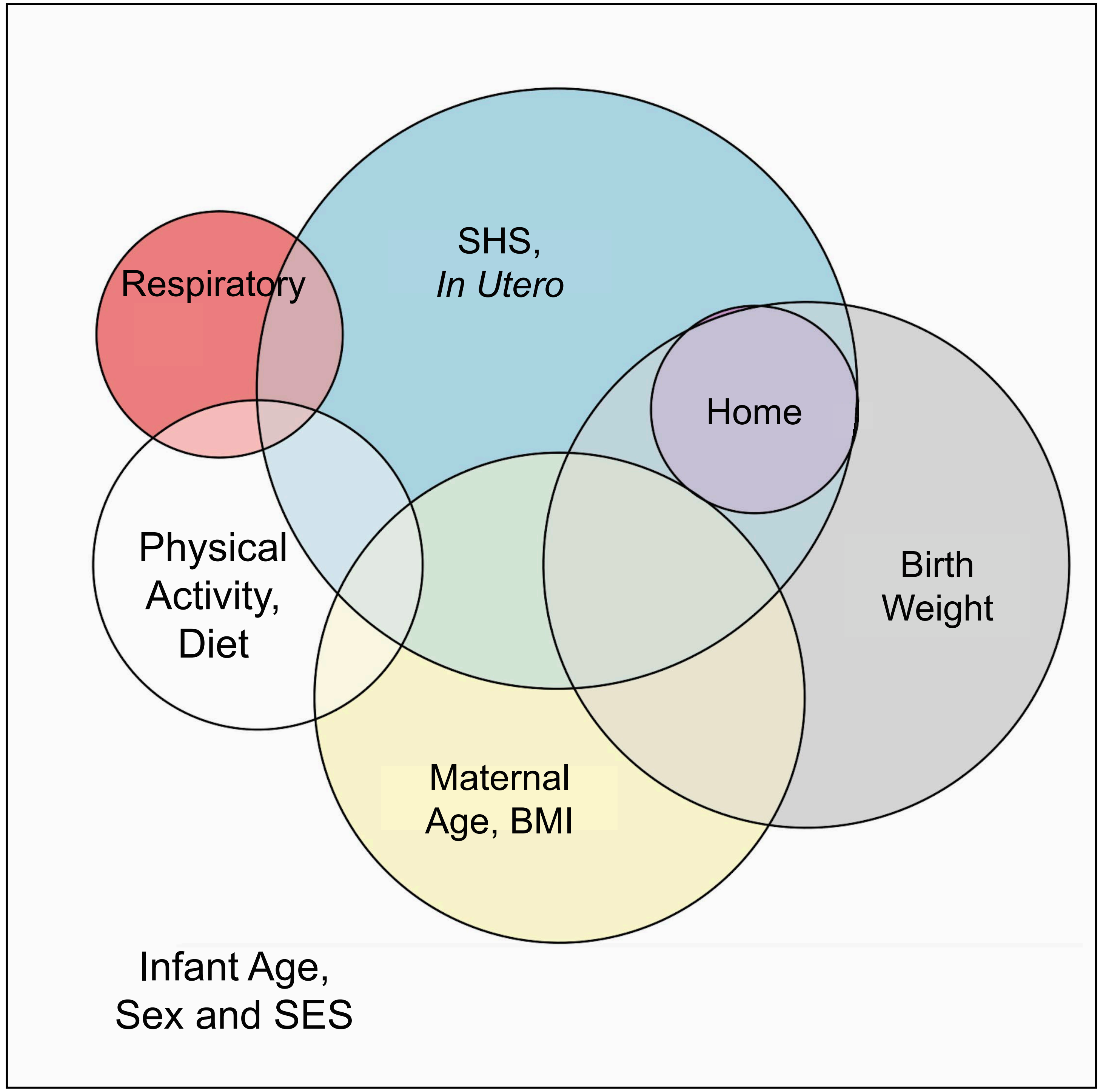
Author	N	Location	Age (yr.)	Pollutant	Direction of Outcome
Toledo-Corral & Alderete (2018)	429	United States	8-18	$PM_{2.5}$, NO_2, O_3, Near-Roadway	0 BMI-z, BF%, SAAT & IAAT
Fioravanti (2018)*	719	Italy	4, 8	NO_x, PM_{10}, $PM_{2.5}$, NO_2	0 BMI-z, Waist Circumference & WHR
Kim (2016)*	1129	South Korea	0-5	PM_{10}	**- Weight**
Huang (2019)	8327	Hong Kong	9-15	SO_2	**- BMI** (*males*)

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

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)

<u>Covariates</u>: 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

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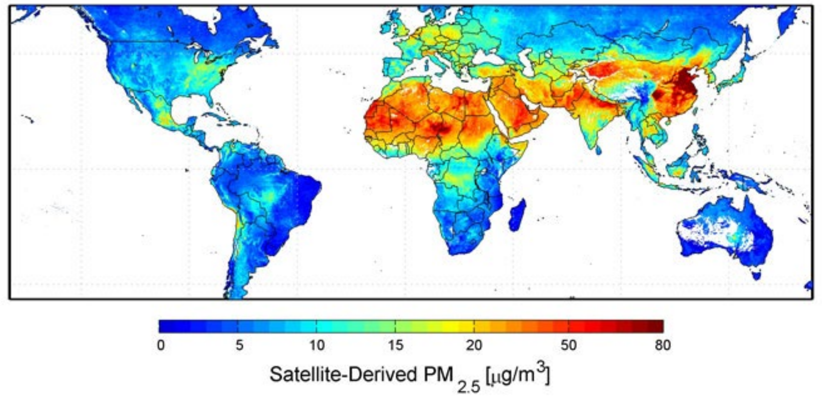
17 Recent Studies: Jerrett (2010); Dong (2014); Jerrett (2014); McConnell (2015); Alderete (2017); Kim (2018); Nikolic (2013); Kim (2016); Toledo-Corral & Alderete (2018); Fioravantia (2018); Rundal (2011); Chiu (2017); Fleisch (2017); Frondelius (2018); Fleisch (2019); de Bont (2019); Huang (2019)

Exposure Assessment and Multi-Pollutant Models





Exposure Assessment Methods:

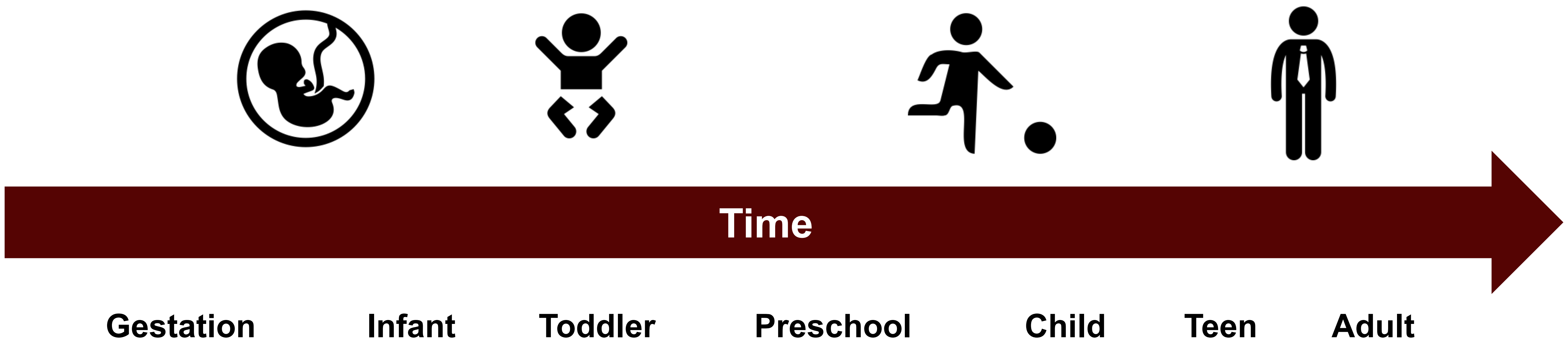
- Traffic Density / Distance to Roadways
- Modeled NO_x (e.g., CALINE, Dispersion)
- Ambient Monitoring Stations (e.g., LUR, IDW)
- Satellite, Hybrid Satellite with LUR
- Personal Monitors (*rare*)
- School & Home Monitors (*rare*)

NO_x = nitrogen oxides
CALINE = California Line Source Dispersion Model
LUR = land use regression
IDW = inverse distance weighted

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)

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)

Westergaard et al., 2017; Mao et al., 2017; BW (birth weight); NHB (non-Hispanic Black); NHW (non-Hispanic White); SES (socioeconomic status)

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

Childhood Exposure to Air Pollutants and Risk Factors for Type 2 Diabetes

Type 2 Diabetes Characterized:

- High peripheral **glucose** concentrations caused by **insulin resistance**
- Relative **deficiency** of **insulin** from pancreatic β-cells

↑ Blood Glucose

→ ↓ Insulin

Pancreas
(β-cells secrete insulin)

Risk for Developing Type 2 Diabetes (Early Indicators):

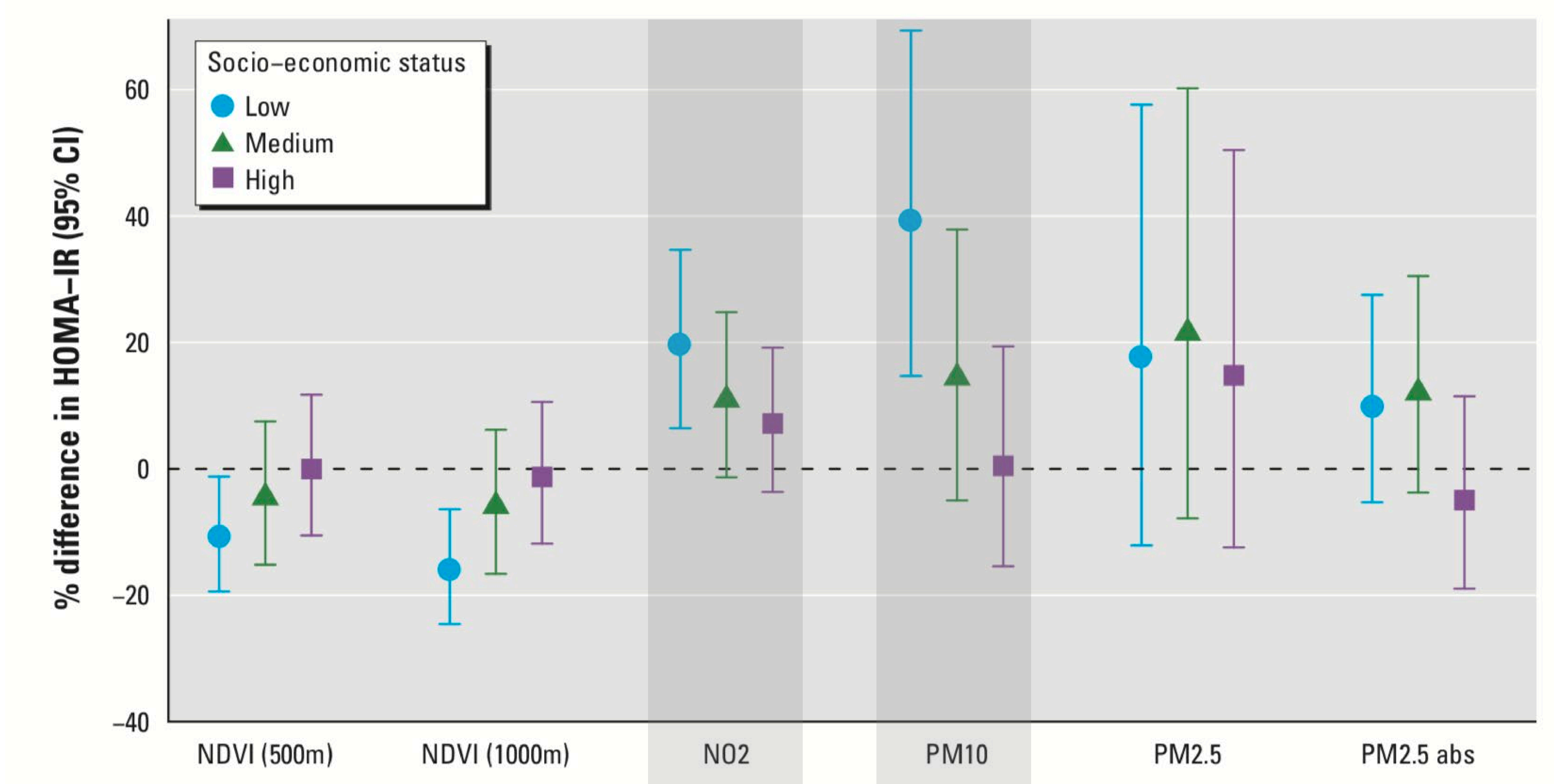
- Blood markers of glucose metabolism
    - Fasting glucose, post-prandial glucose, HbA1c
- Insulin resistance / insulin sensitivity, acute insulin response, β-cell function

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 levels[1]
- ↑Air Quality Index (AQI) associated with ~2x higher odds of ↑fasting glucose in children and adolescents[2]
- ↑NO_2 associated with ↓metabolic benefits (e.g., HbA1c) of laparoscopic adjustable gastric banding in adolescents[3]
- ↑NO_2 and $PM_{2.5}$ as well as proximity to roadways was associated with greater **insulin resistance** (HOMA-IR)[4-6]

[1]Calderón-Garcidueñas et al. 2015; [2]Poursafa et al., 2014; [3]Ghosh et al. 2017; [4]Kelishadi et al., 2009; [5]Thiering et al., 2013 and [6]2016 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): $p = 0.126$.

Thiering et al., Environ Health Perspect, 2016

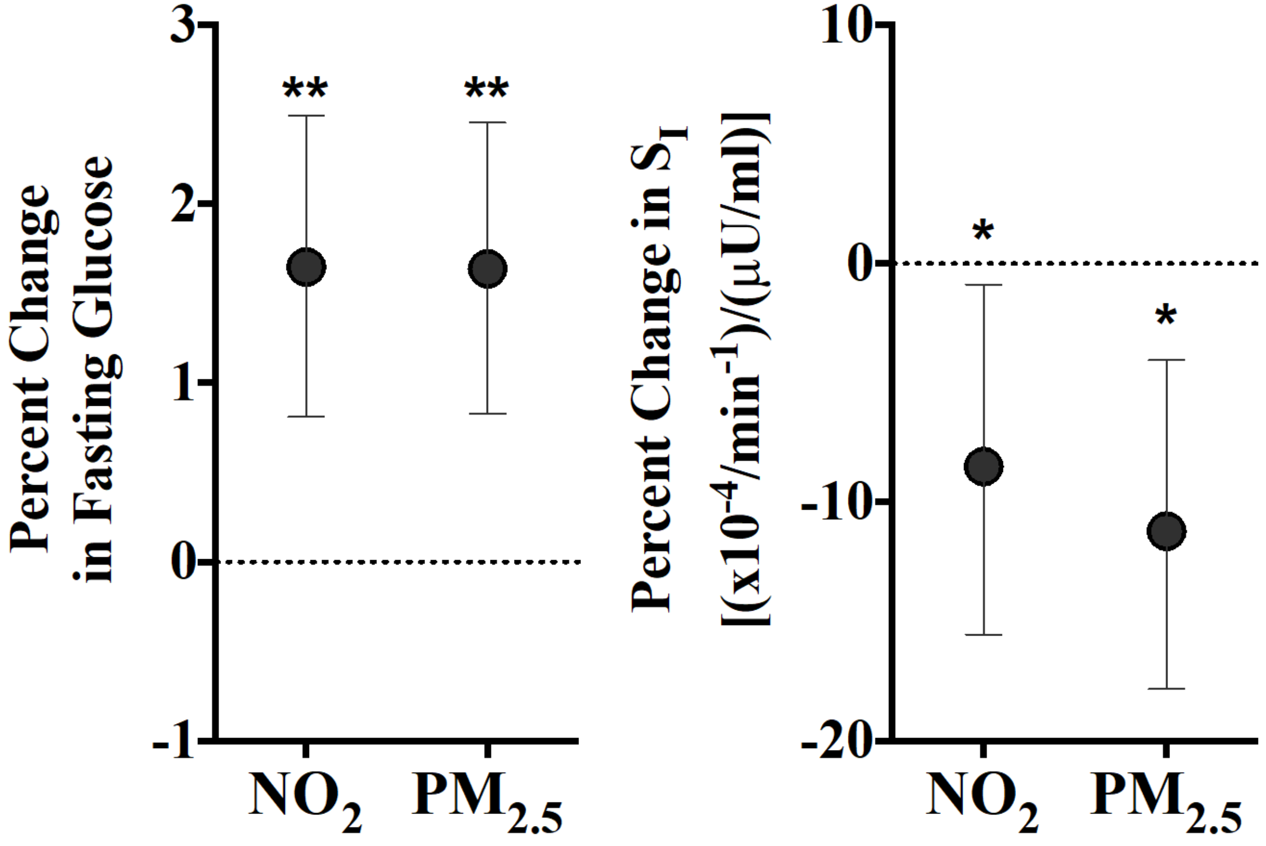
Cross-Sectional Findings From Minority Youth Living in Los Angeles, CA

Higher <u>prior year</u> 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 Percent Change for a 1-SD increase in Exposure



Estimated effects for a **1 standard deviation (SD) difference in prior year NO_2 (6.8 ppb) and $PM_{2.5}$ (5.2 μg/m³)** 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.

Toledo-Corral* and Alderete* et al., *Ped. Obesity,* 2018

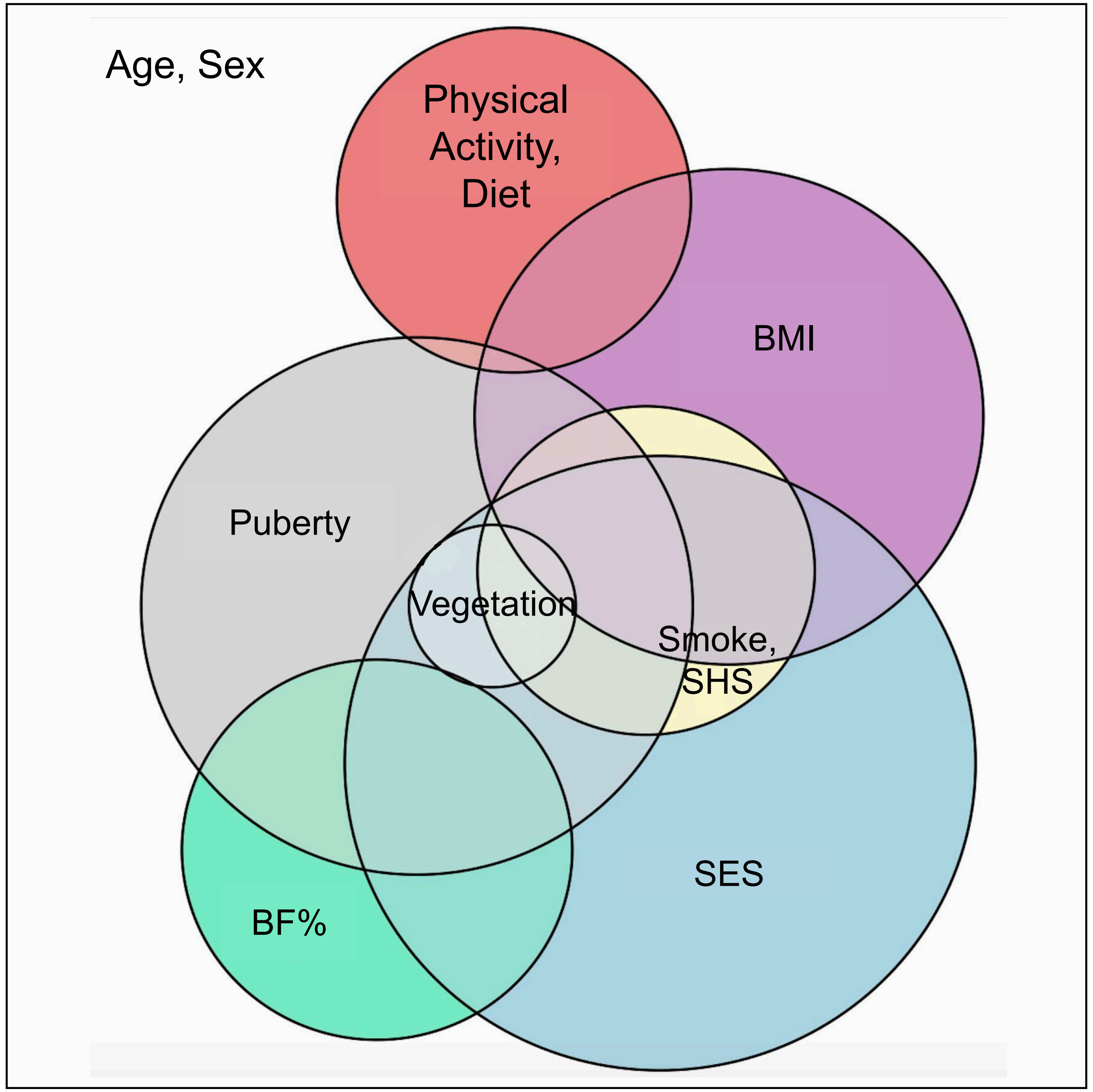
Longitudinal Study Among Overweight/Obese Hispanic Youth from Urban Los Angeles, CA

Exposures had Effects Comparable to a 5% Increase in Body Fat Percent at Age 18

	Long-Term NO_2 and $PM_{2.5}$	Body Fat % (+5%)
Insulin Sensitivity	**-13% to -21.6%**	**-16.7%**
Acute Insulin Response	**+28.5%**	**+10.2%**
β-cell function (DI)	**-13%**	**-6.9%**

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 μg/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.

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%

SHS = secondhand smoke

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

Exposure Assessment and Multi-Pollutant Models

Exposure Assessment Methods:
- Traffic Density / Distance to Roadways
- Modeled NO_x (e.g., CALINE, Dispersion)
- Ambient Monitoring Stations (e.g., LUR, IDW)

Very few studies examined multi-pollutant models…

NO_x = nitrogen oxides
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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

↑BMI:
↓SI, ↓DI

SES

↓SES:
↑HOMA-IR,
↓SI, ↓DI

Race/Ethnicity

↑Risk Factors:
NHB, Hispanic

BMI = body mass index; SI = insulin sensitivity; DI = β-cell function; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; NHB = non-Hispanic Black; SES = socioeconomic status

Thiering et al., 2016, Toledo-Corral & Alderete et al., 2018, Alderete et al., 2017

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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