Obesity and Glucose Dysregulation

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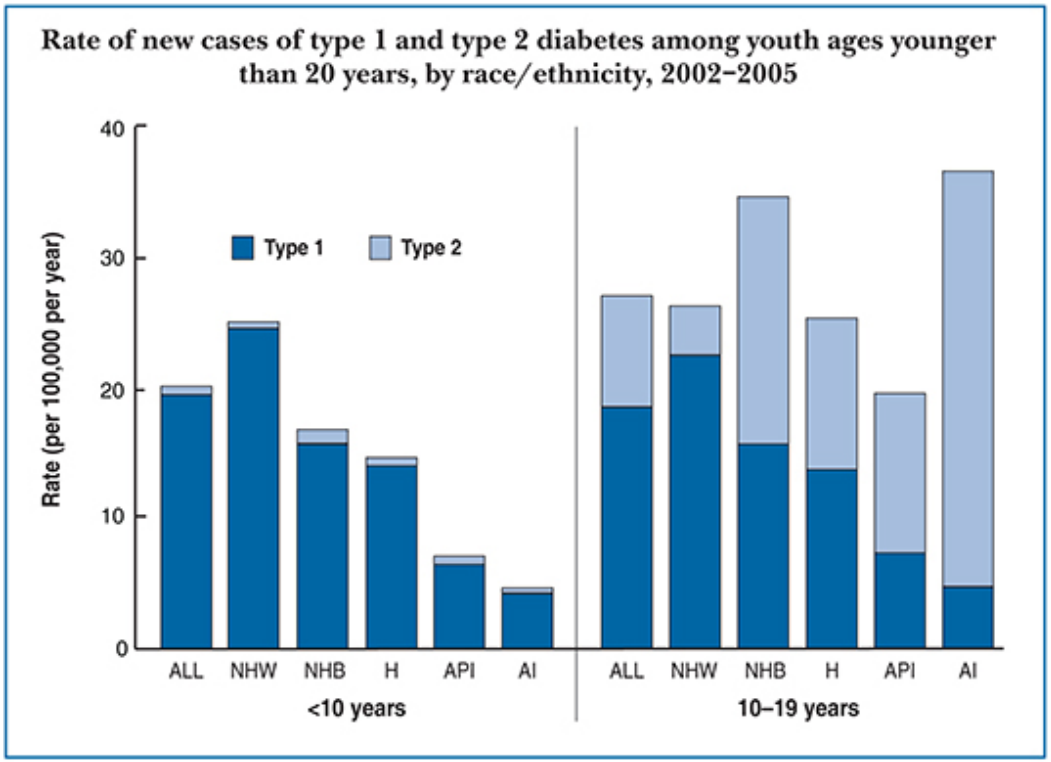
Epidemic of Diabetes in the U.S.

- ~25 million Americans are diabetic
- Diabetes in children is usually type 1, but rate of type 2 increasing, especially among non-whites



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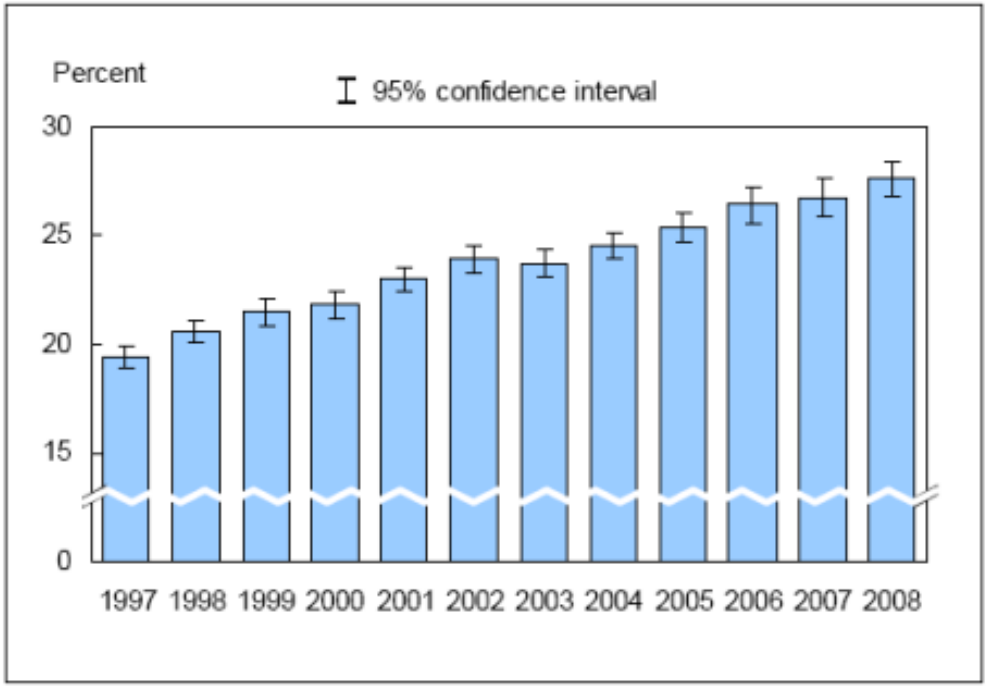
Epidemic of Obesity in U.S.

- 34% of Americans are overweight (BMI 25-29.9) and 34% are obese (BMI≥30)
- Percent of children who are obese
  - age 12-19 years: 18.1
  - age 6-11 years: 19.6
  - age 2-5 years: 10.4



Obesity Epidemic

- Thought to be due primarily to
  - increased caloric intake from high consumption of sugar-containing drinks and high-caloric-density fast food
  - decreased energy expenditure from a sedentary lifestyle
- Animal evidence suggests that chemicals in the environment may be “obesogens”
  - ? ambient air pollutants

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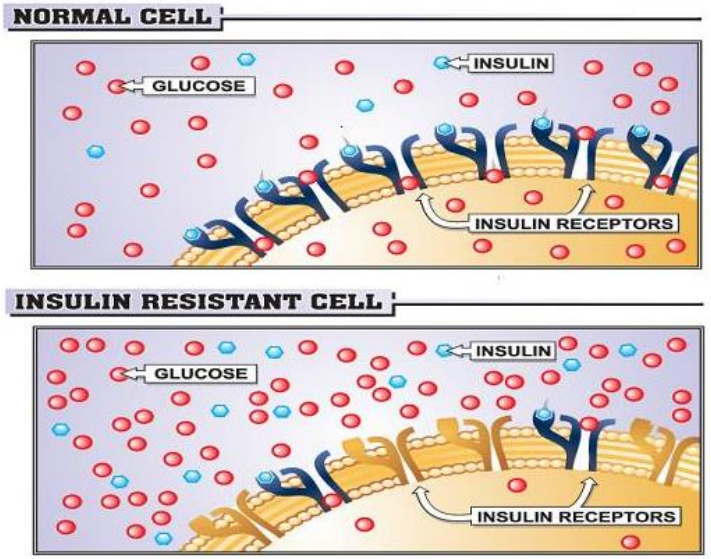
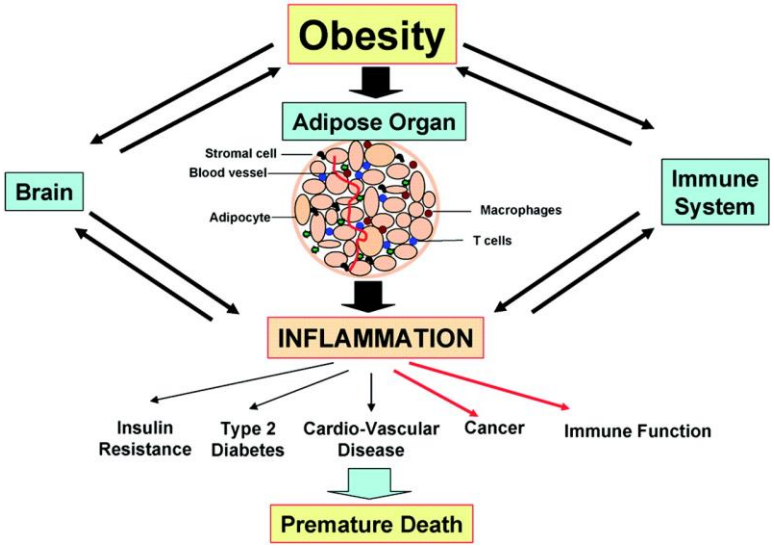
Linkage of Diabetes and Obesity

- Diabetes is a disorder of glucose metabolism
  - the body's cells fail to take up glucose from the blood due to insulin resistance
- 80% of those who develop type 2 diabetes are obese
  - obesity is associated with insulin resistance
- Both diabetes and obesity are associated with increased systemic inflammation





Air Pollution and Obesity

- Jerrett et al. found that higher levels of traffic were associated with higher attained BMI in children aged 10–18 (*Prev Med* 2010)
- This team later showed that traffic-related air pollution was positively associated with growth in BMI (*Environ Health* 2014)
- Rundle et al. found that early-life exposure to PAHs was associated with increased BMI and obesity at age 7 (*Am J Epidemiol* 2012)
- Calderón-Garcidueñas reported that children exposed to high concentrations of ambient $PM_{2.5}$ in Mexico City had high blood leptin levels (*Environ Res* 2015)

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Air Pollution and Diabetes

- Several studies have shown associations between diabetes in adults and exposure to traffic-related air pollution (TRAP)
- Few studies in children
  - Two studies have shown associations between ozone and type 1 diabetes (Hathout et al., *Pediatr Diabetes* 2006; Malmquist et al., *Environ Res* 2015*)
    *also NO_2
  - Thiering et al. found an association with TRAP and insulin resistance (*Diabetologia* 2013)

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Potential Mechanism

- Air pollution can induce oxidative stress and systemic inflammation
- $PM_{2.5}$ induced adipose tissue inflammation and insulin resistance in a mouse model of diet-induced obesity (Sun et al. Circulation 2009)
- Hypotheses:
  - Exposure to air pollution *in utero* and in early childhood increases risk of abnormal glucose metabolism later in childhood
  - Exposure to air pollution *in utero* and in early childhood increases risk of obesity in later childhood

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Specific Aim 1

- To determine whether chronic exposure to ambient air pollution, especially PAHs, is associated with:
  - increased HbA1c
  - increased BMI (ponderal index for infants)
  - increased levels of 8-isoprostane (biomarker of oxidative stress), CRP (biomarker of systemic inflammation), leptin, adiponectin, and high-density lipoprotein (biomarkers of abnormal fat and glucose metabolism)

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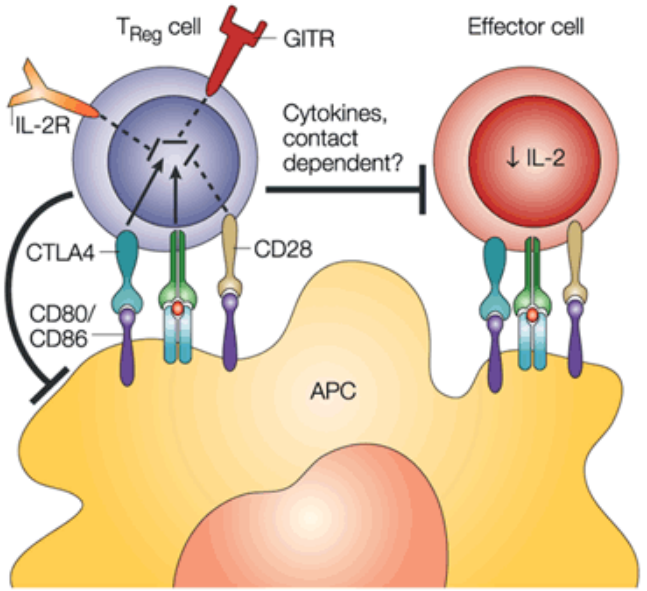
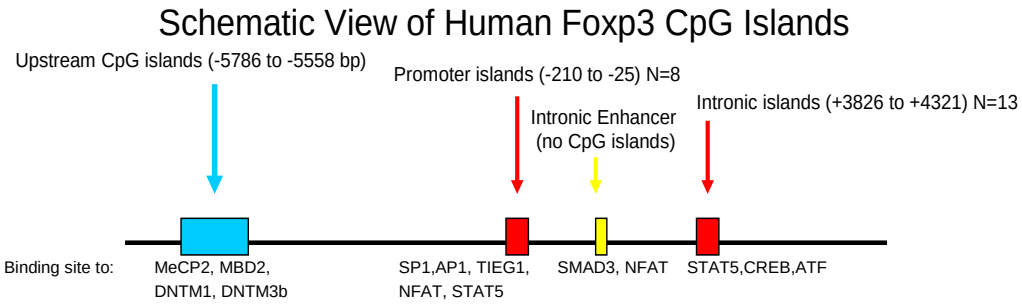
Specific Aims 2 and 3

- To determine whether chronic exposure to air pollution-induced Treg and Teff cell dysfunction is associated with:
  - increased HbA1c
  - increased BMI (ponderal index for infants)
- To determine whether epigenetic modification of FOXP3 underlies the associations between Treg dysfunction and abnormal glucose regulation/increased BMI





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CHAPS Study Design

- Follow birth cohort to be recruited (birth data, including cord blood; annual visit ages 1 and 2; n=200)
- Child cohort (age 7, follow-up visit at age 9; n=200)
- Adolescent cohort (mean age 16, had previous P20 visit for comparison; n=200)
- For all participants
  - HbA1c, adiponectin and leptin, 8-isoprostane, CRP, IL-6, immune biomarkers (CyTOF), anthropometry, dietary and physical activity data at each visit
  - Estimated air pollution exposure pre-natal to present

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Characteristics of first 100 adolescent participants

Characteristic	%
%Latino	48.9%
%White	40.6%
%African-American	7.3%
%Male	50.0%
%≥18	33.0%
%asthma	35.0%
%Rent	39.2%
%Income<$15000	27.5%
%Income>$50,000	39.6%
%Health Insurance	88.9%

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Distribution of Outcome Variables (first 100 adolescent participants)

Variable	25th percentile	Median	75th percentile	Mean	SD
Weight (kg)	55.2	64.4	79.5	69.2	20.3
Height (m)	1.58	1.66	1.74	1.66	0.2
BMI	20.7	22.5	27.3	25.8	10.1
% Body Fat	21.4	26.6	35.6	28.4	9.3
Waist Circumference (in)	29.3	31.3	35.2	33.2	5.7
Waist-Height-Ratio	0.45	0.48	0.55	0.52	0.11
Diastolic BP (avg of 3)	55.0	60.7	69.3	61.6	9.4
Systolic BP (avg of 3)	103.5	113.2	124.8	114.4	14.0
HbA1c	5.0	5.1	5.3	5.13	0.3

Median values (16 y/o)	Boys	Girls
BMI	22.3	22.1
% Body Fat	21.4	32.4
Waist Circumference	31.2	30.4
Waist-Height Ratio	0.45	0.48
HbA1c (15-19 y/o)	4.9	

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Summary

- The prevalence of both obesity and diabetes is high among Latino youth in the SJV
- Air pollution may increase the risk of both conditions by inducing oxidative stress and systemic inflammation
- PAH-induced immune dysfunction may be on the pathway
- The CHAPS design allows investigation of this potential pathway in multiple age cohorts (birth, child, and adolescent)

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