Developmental origins of pediatric obesity and diabetes- what we know and don't know

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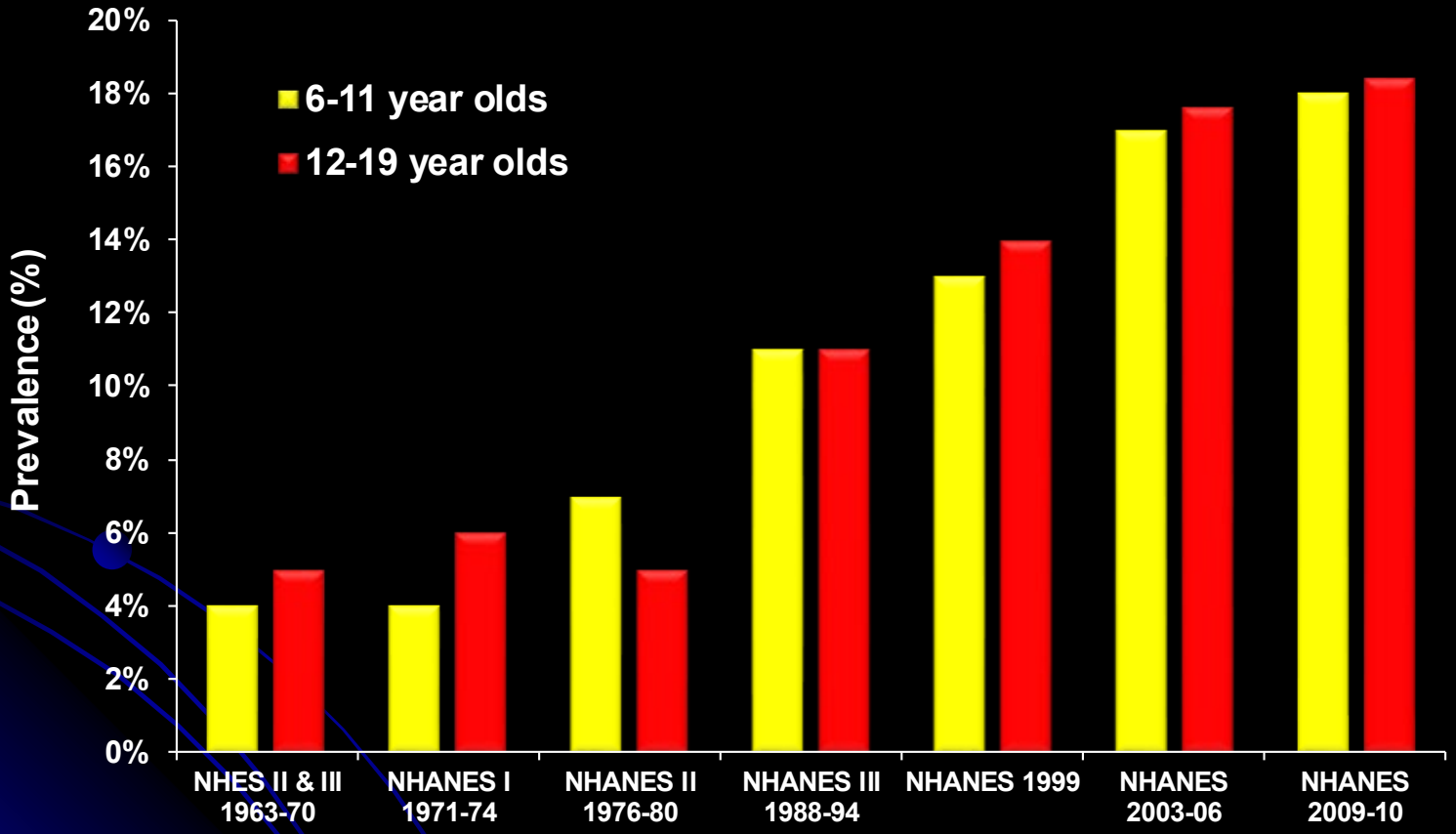
Outline

- Burden of obesity and type 2 diabetes in youth
- Developmental origins of pediatric obesity and type 2 diabetes
- Prevention throughout the lifecourse

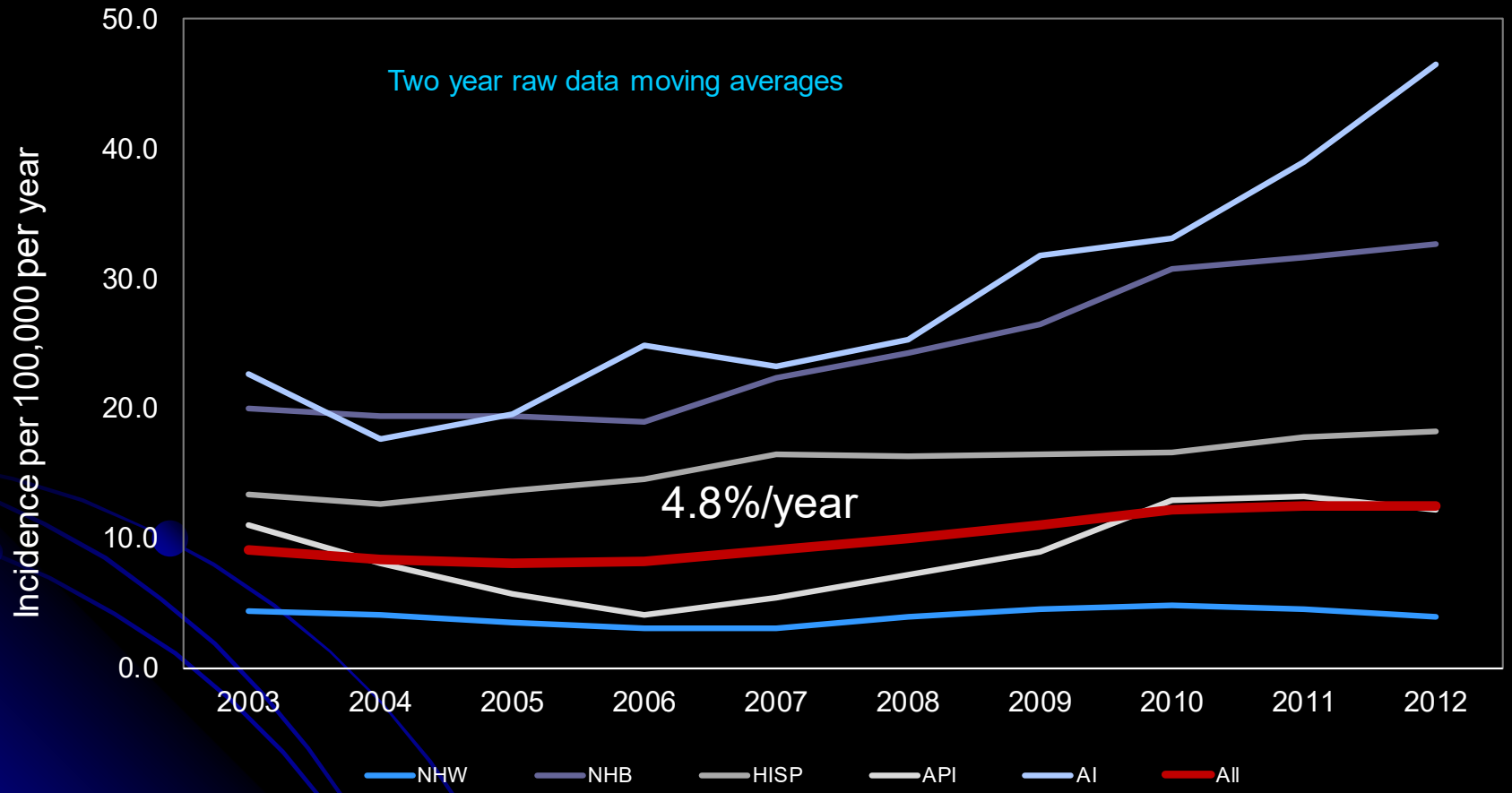
Burden of Obesity and Type 2 Diabetes in Youth

Rising Prevalence of Obesity Among US Children and Adolescents



Source: Centers for Disease Control and Prevention , National Center for Health Statistics, National Health and Nutrition Examination Survey

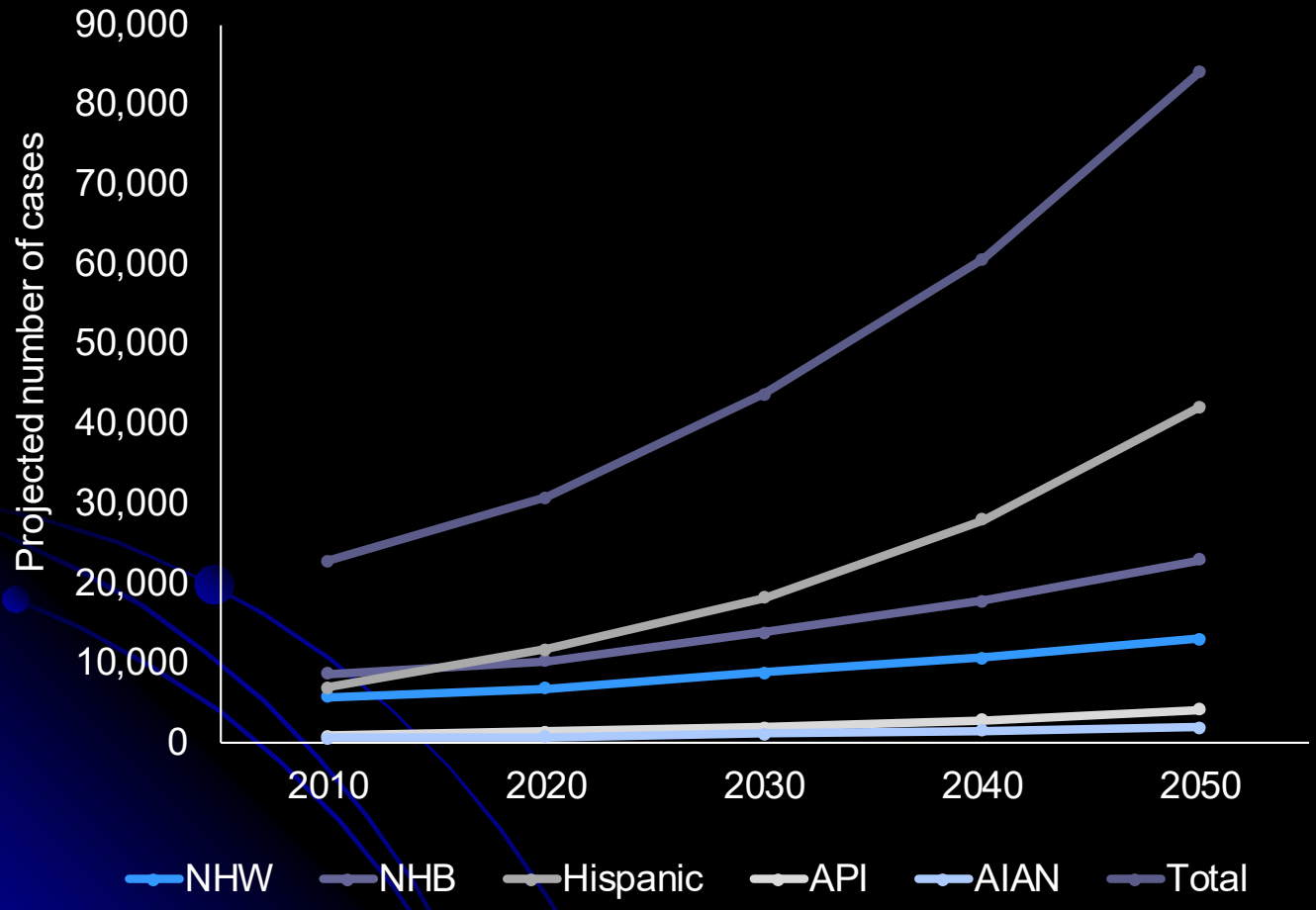
Trends in Incidence of Youth-onset T2D by Race/Ethnicity: SEARCH Study



% Annual Increase:	0.6%	8.5%	3.1%	8.5%	8.9%	4.8%
P value$_{adj}$:	0.65	0.009	<0.001	0.009	<0.001	

Mayer-Davis EJ, Dabelea D, et al., NEJM, 2017

Projected Number of Youth < 20 Years of age with T2D



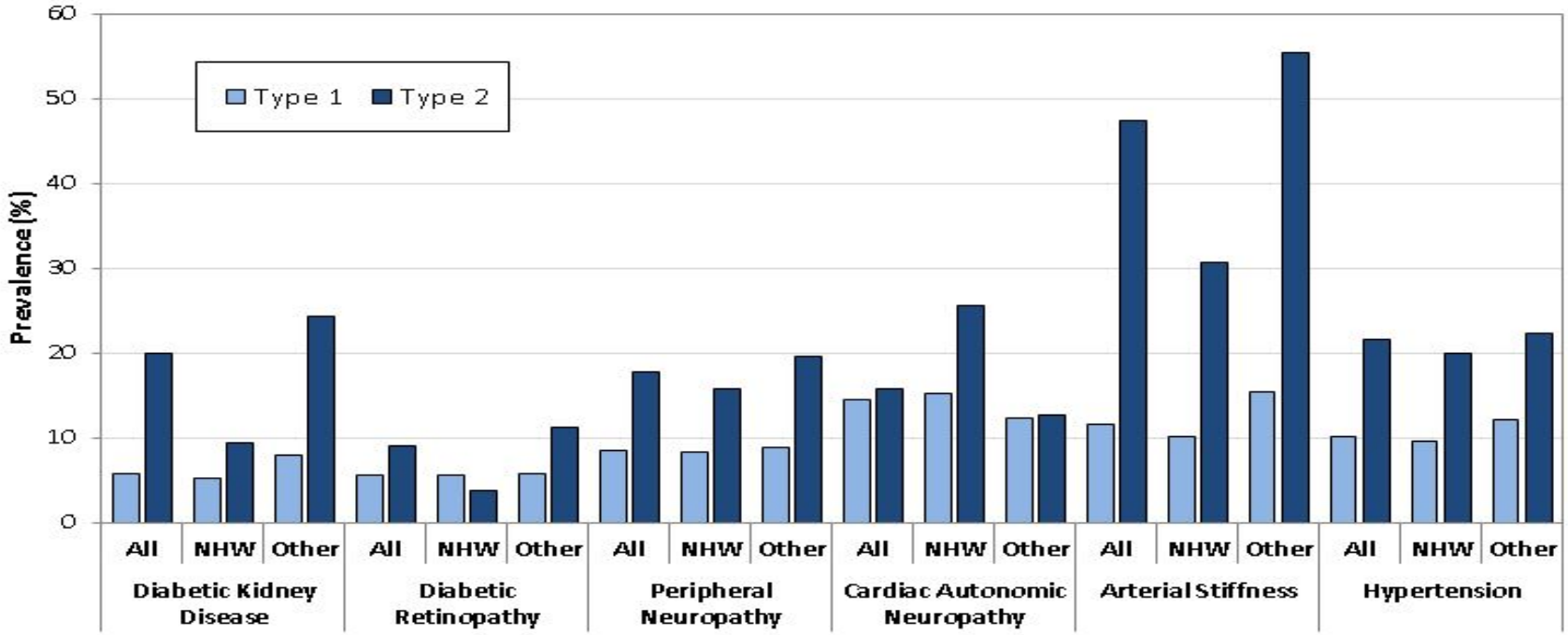
Number of US youth with T2D projected to increase 3.7-fold by 2050 from 22,000 to 84,000 youth

Highest among Hispanic youth (6.0 fold increase by 2050)

US health care systems need to be prepared

Imperatore, et al. *Diabetes Care,* 2012

Prevalence of Complications and Comorbidities is Higher in Youth Onset T2D vs T1D and non-white Youth



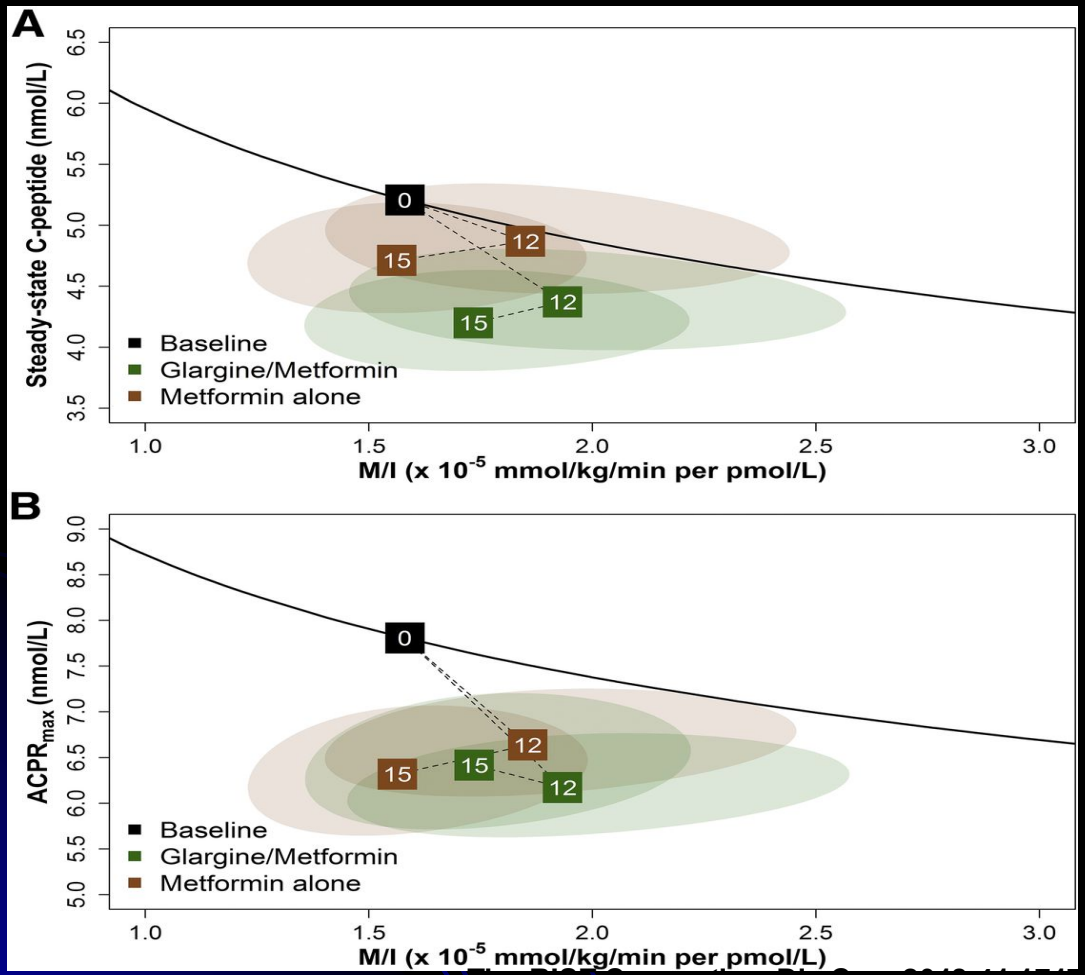
P values for Type 1 vs. Type 2 diabetes, overall and by race/ethnicity

	DKD	DR	PN	CAN	AS	HTN
All	<0.001	0.02	<0.001	0.62	<0.001	<0.001
NHW	0.18	0.46	0.03	0.03	<0.001	<0.01
Other	<0.001	0.03	<0.01	0.90	<0.001	<0.01

1 in 3 youth with T1D and 3 in 4 youth with T2D had at least one complication

Dabelea D, et al, *JAMA*, 317(8): 825-835, 2017

Pediatric T2D is an Aggressive Disease



Compared with adults , youth with IGT/new T2D:

- Are more insulin-resistant for same degree of obesity
- Have hyper-reactive b-cells- unclear why?
- Do not respond to approved therapies- Metformin, Insulin)

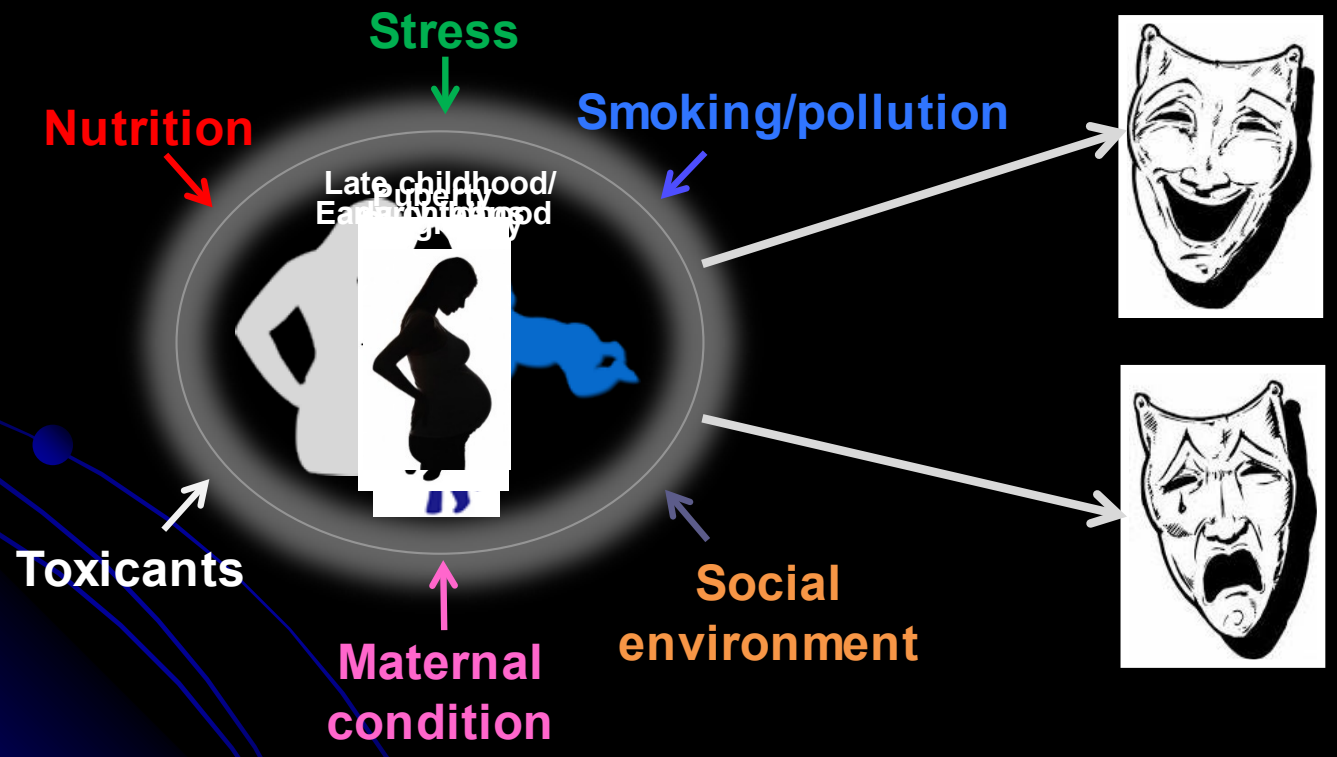
RISE study, Diabetes Care, 2018

Gaps in knowledge

- Interventions that target youth with frank dysglycemia/T2D are inadequate to prevent β-cell decline (RISE), T2D progression (TODAY)
  - Need for interventions that start before frank hyperglycemia is present, but unclear when
- Pathophysiology of T2D is different in youth vs adults
  - Need to understand the natural history and pathophysiology of combined processed leading to dysglycemia (obesity, insulin resistance, b-cell response) in youth
- Only a small subset of youth with obesity and other risk factors develop T2D during puberty
  - Need to determine subgroups at highest risk
  - Need to understand risk conferring pathways (likely before development of obesity)

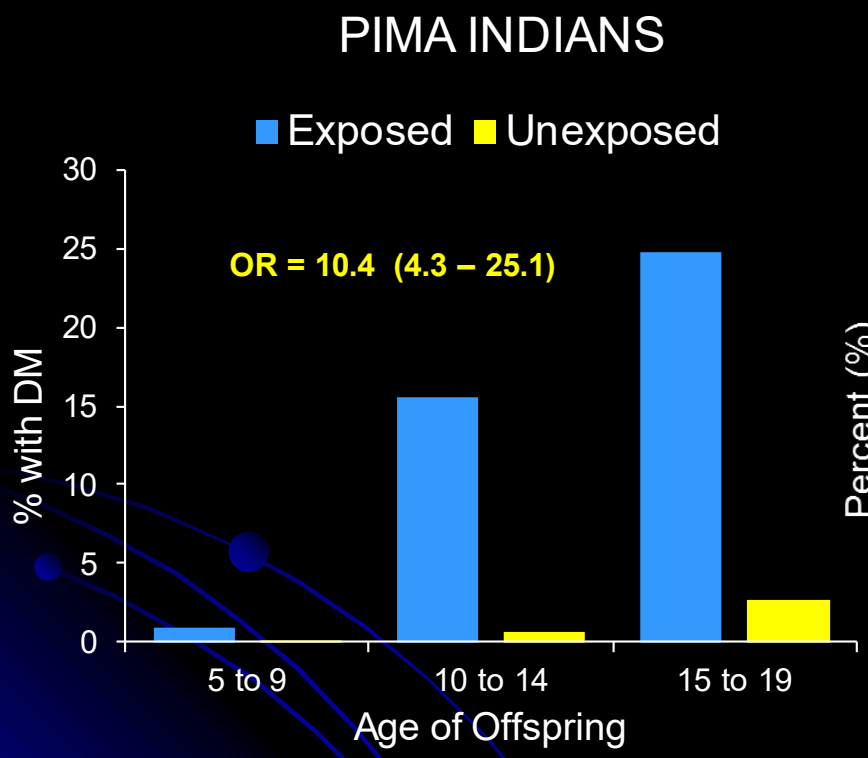
Developmental Origins of Pediatric Obesity and Type 2 Diabetes

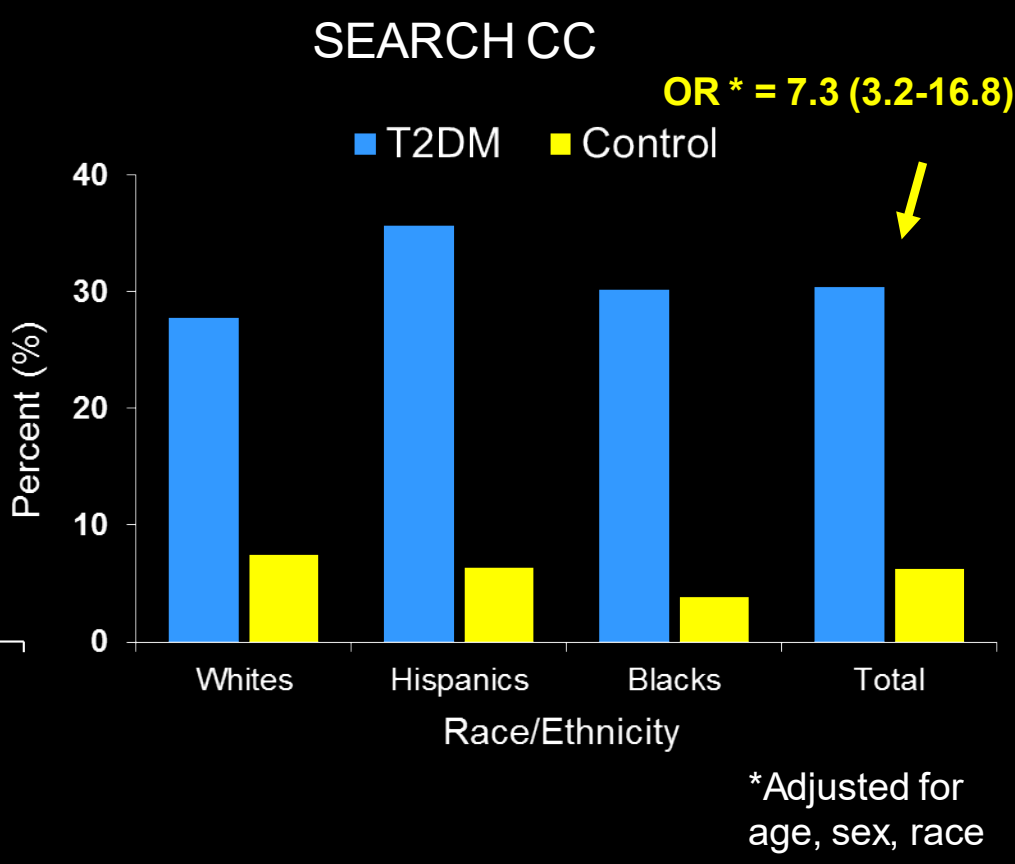
Developmental Origins of Health and Disease (DOHaD)



Maternal Diabetes and Youth-Onset T2D

Exposure to Diabetes In Utero- Strongest Risk Factor for T2D in Youth

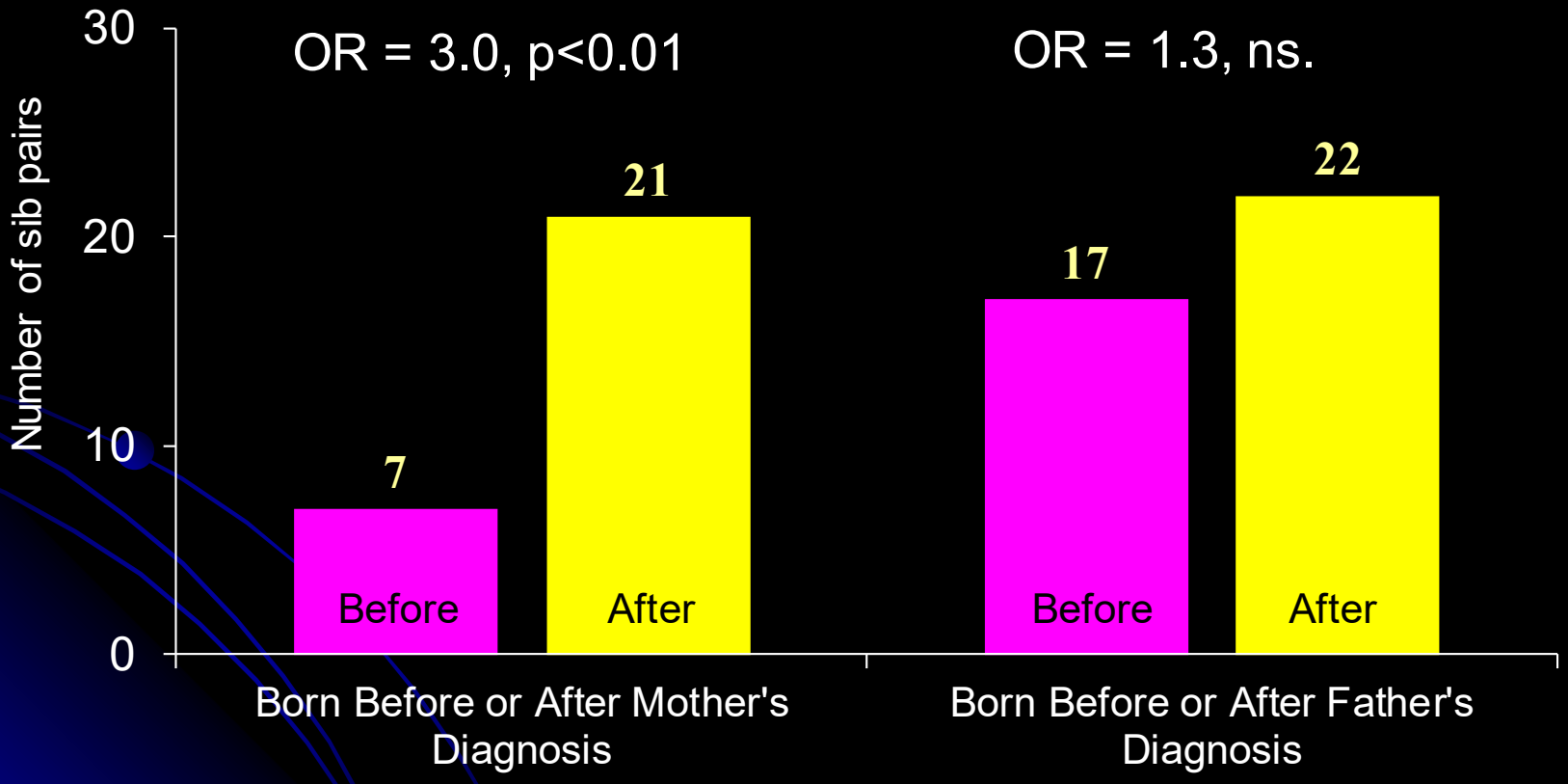




Dabelea D, *Diabetologia.*, 1998

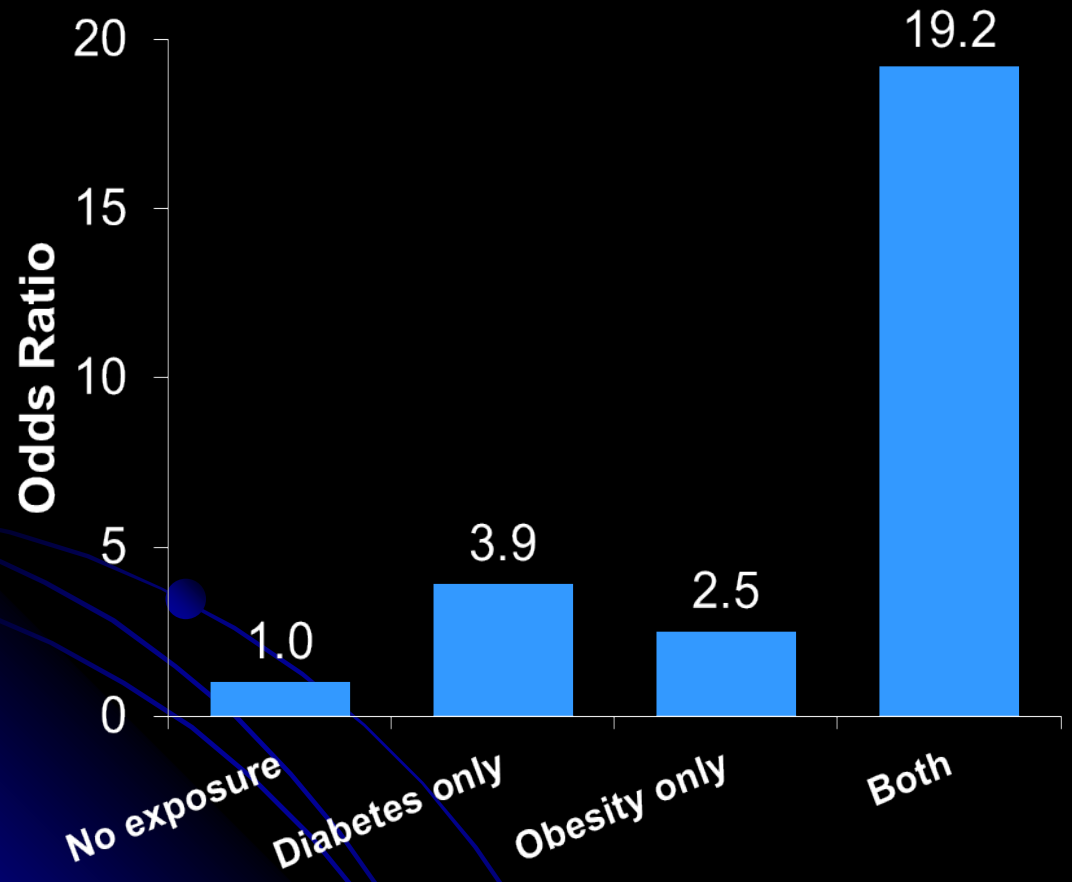
Dabelea D, *Diabetes Care*, 2008

Beyond Genetics: Pima Indian Sib Pairs Discordant for Diabetes and Exposure to Diabetes in Utero



Dabelea D, *Diabetes*, 2000

Public Health Impact: Population Attributable Risk



Population Attributable %	
No exposure	---
Diabetes only	4.7%
Obesity only	19.7%
Both	22.8%
Overall	47.2%

Dabelea D, *Diabetes Care*, 2008

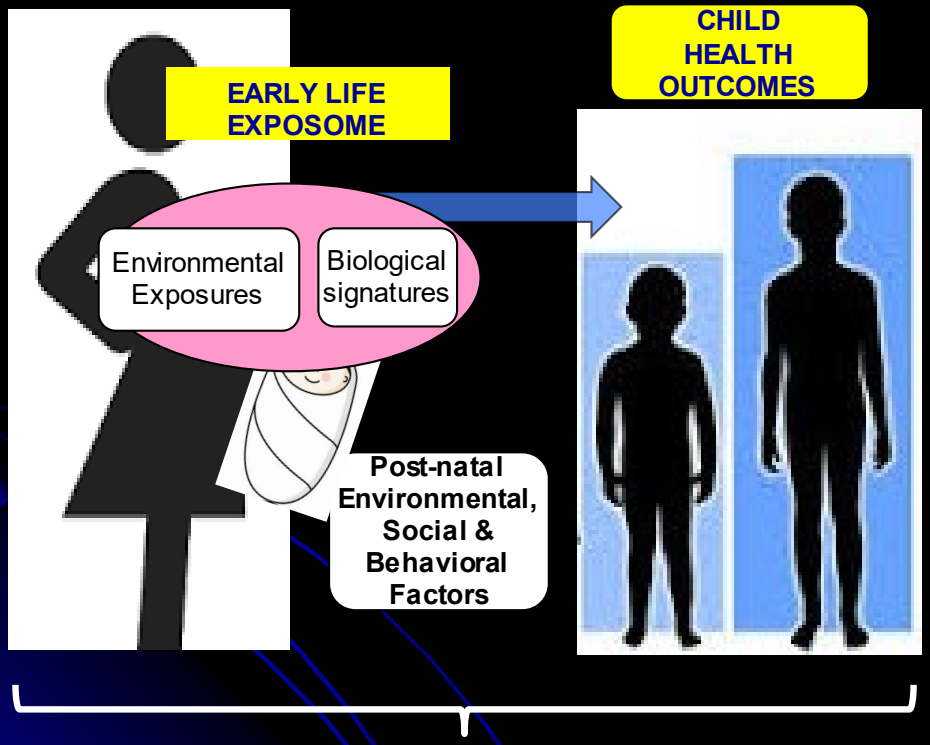
Gaps in knowledge

- What other prenatal and postnatal exposures contribute to pediatric T2D/dysglycemia and obesity and what are the respective attributable risks
  - Need for large observational cohorts/consortia of cohorts
- What are the specific intrauterine effects (programming mechanisms) responsible for the long term consequences of such exposures?
  - Need mechanistic studies nested in observational cohorts/consortia of cohorts
  - Include study of epigenetic effects
- How does genetic susceptibility influence the effect of these exposures?
  - Need G*E studies on pediatric T2D/dysglycemia/obesity –related traits
- Develop framework to Inform on timing, type and focus of future interventions
  - Need a DPP study for kids

Beyond Maternal Diabetes

Focusing on Offspring Adiposity

Colorado Healthy Start Study



Pre-birth cohort study of 1410 mothers and offspring in Colorado

Followed from early pregnancy through delivery and into childhood (8-10 years)

Main exposures: the early life exposome

Maternal obesity, diet, physical activity, environmental chemicals, depression

Air Pollution, built environment

Biological signatures

Main outcomes: offspring adiposity & growth; cardiovascular and metabolic, brain development, neuro-cognitive, behavioral

Now part of the ECHO consortium

ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

Assessment of Offspring Adiposity in Healthy Start

- Adiposity markers (birth, 4-6mo, 4-6yr; 8-10 yr)
  - Weight and height/length, skinfolds, circumferences
  - Body composition via air displacement plethysmography FM, FFM, FM%)
  - Abdominal MRI (visceral, subcutaneous fat, fatty liver) (4-6yr; 8-10 yr)




Neonatal Adiposity Predicts Child Obesity

Birth – 9% adiposity

5 months – 24% adiposity

5 years – 20% adiposity

Each 1 SD increment in neonatal adiposity → 0.12 units higher BMI and ~20% higher prevalence of overweight/obesity between 2 to 6 years of age

Sauder et al, J Pediatr 2017
Moore et al, Pediatrics 2020

ECHO: What are optimal levels of neonatal/childhood adiposity?

The Prenatal Environment

Maternal Obesity and Gestational Weight Gain are Associated with Infant Adiposity

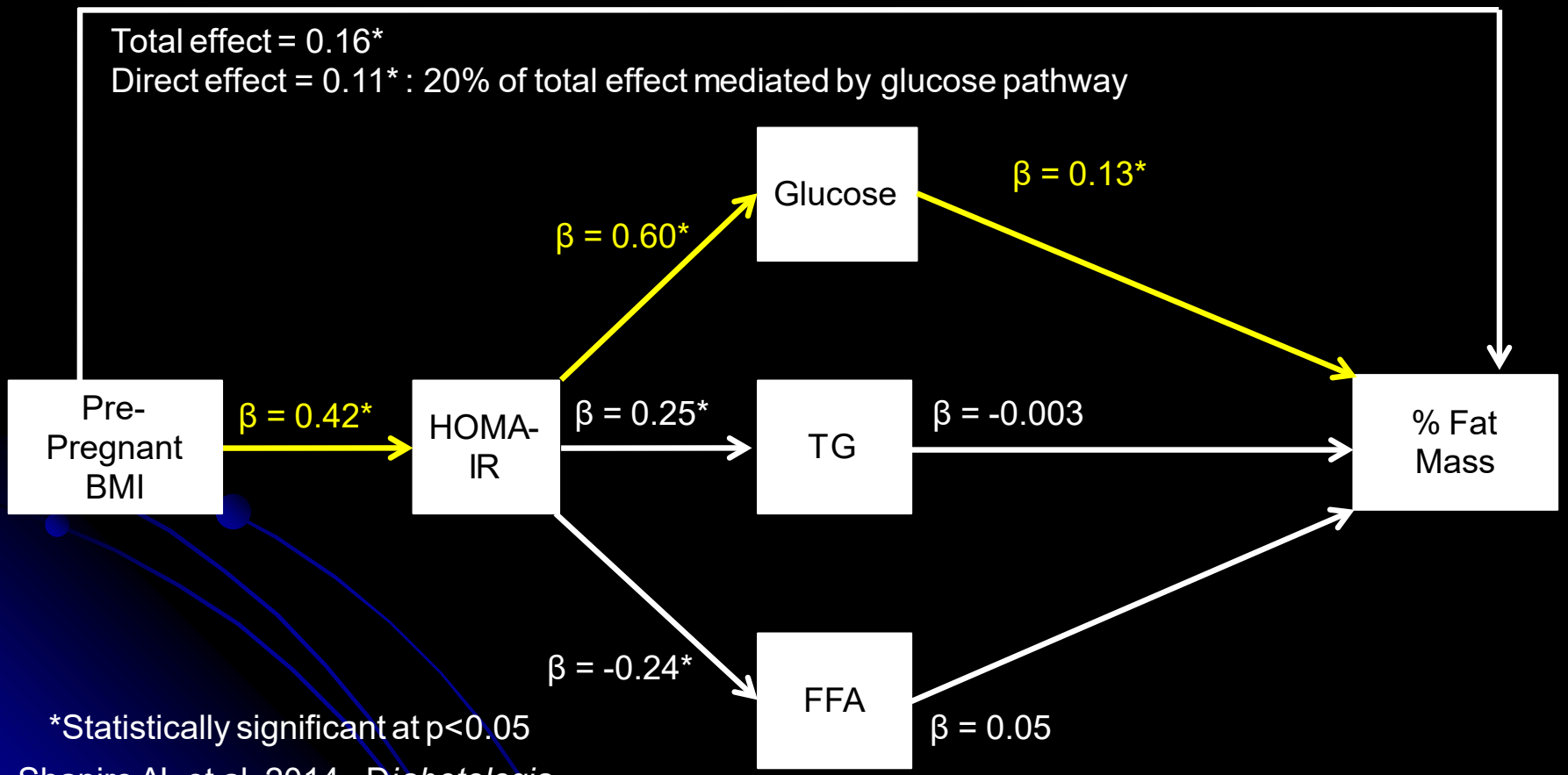
- Higher maternal pre-pregnancy BMI associated with increased neonatal percent body fat (↑0.12 % FM)
- Increased gestational weight gain (GWG=+0.1 kg/week) associated with %body fat (↑ 0.55% FM) in all 3 trimesters, independent of pre-pregnant BMI

- **Supports hypothesis that greater maternal weight gain during pregnancy, regardless of pre-pregnancy BMI, is directly related to offspring adiposity at birth.**

Starling A, et al., *Amer J Clin Nutr*, 2015

ECHO: What are optimal levels of maternal GWG?

Maternal Glucose Mediates Associations between Maternal BMI and Neonatal Adiposity



*Statistically significant at p<0.05

Shapiro AL et al. 2014., D*iabetologia.*

ECHO: Needs replication in larger, more divers cohorts

Increased Physical Activity in Late Pregnancy is Associated with Less Infant Adiposity

- Neonates of mothers in the highest compared with the lowest quartile of total energy expenditure during late pregnancy had 41.1 g less neonatal fat mass (249.4 g compared with 290.5 g; p=.03)

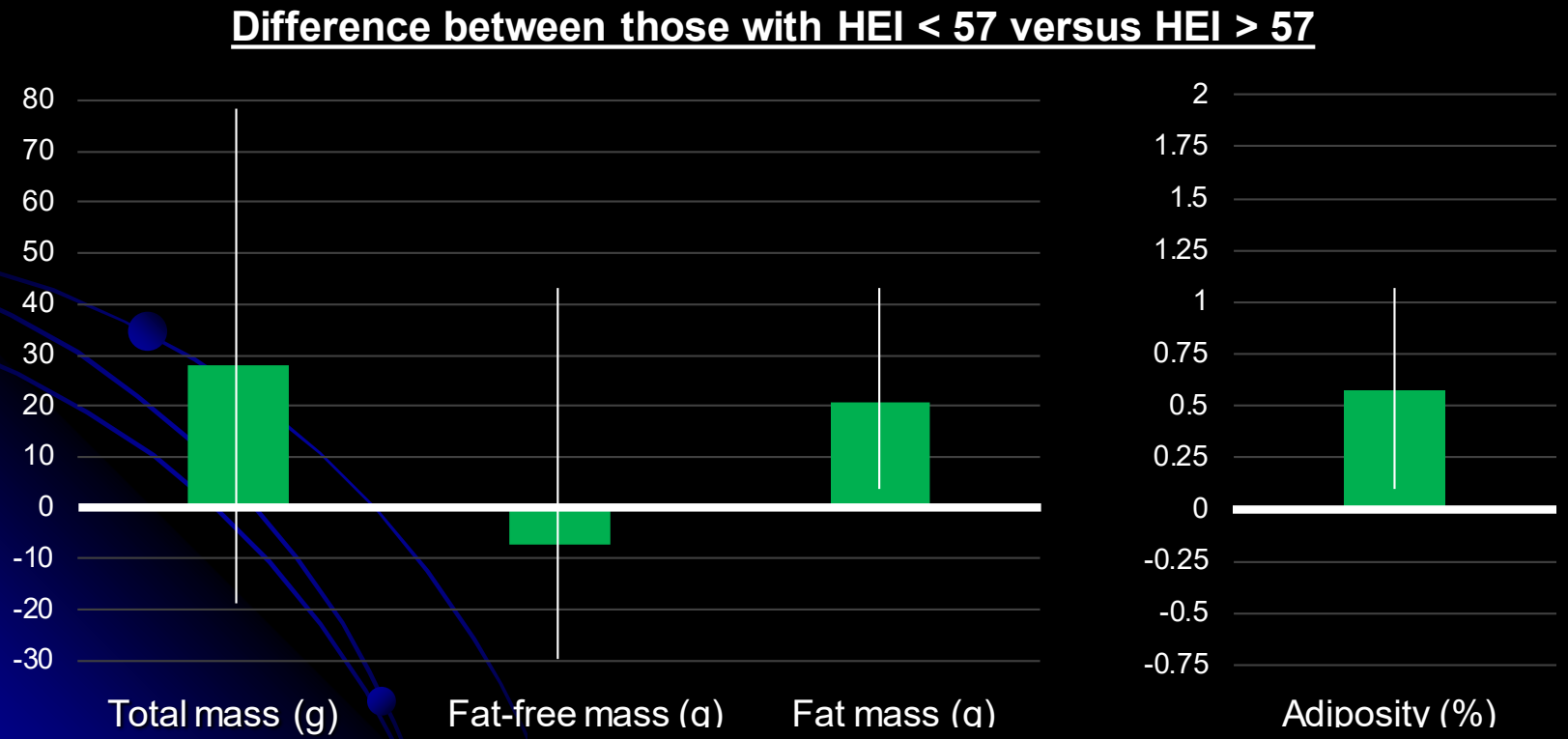
- **Increasing levels of late-pregnancy total energy expenditure are associated with decreased neonatal adiposity without significantly reduced neonatal lean mass**

Harrod C, et al., *Amer J OB GYN*, 124 (2 part 1), 257, 2014

ECHO: Needs replication in larger, more divers cohorts

Maternal diet quality is associated with increased infant adiposity

- Lower diet quality (HEI < 57) associated with ↑ fat mass & adiposity, but not total or fat-free mass
- Effects independent of maternal BMI and total energy intake



Shapiro et al, Int J Obesity 2016

ECHO: Needs replication in larger, more divers cohorts

Smoking during pregnancy is associated with smaller babies but rapid post-natal growth

- Exposure to prenatal smoking was significantly associated with reduced neonatal fat mass (FM) and fat-free mass (FFM)
- At 5 months of age, exposed offspring had greater FM and FFM after adjustment for birth weight.

- Exposure to prenatal smoking resulted in growth restricted babies that exhibited rapid early postnatal growth, which may increase the offspring's risk of obesity and metabolic diseases.

Harrod C, et al., *Obesity*, 23, 234, 2015

Environmental exposures & Neonatal adiposity

- ↑ mid-pregnancy urinary PFAS
  - ↓ adiposity at birth
  - ↑ adiposity at 5 months (♂)
  - Rapid growth in weight-for-age to 5 months
- Third trimester ozone exposure associated with greater adiposity at 5 months

Starling et al, Environ Health Perspect 2017
Starling et al, Environ Int 2019

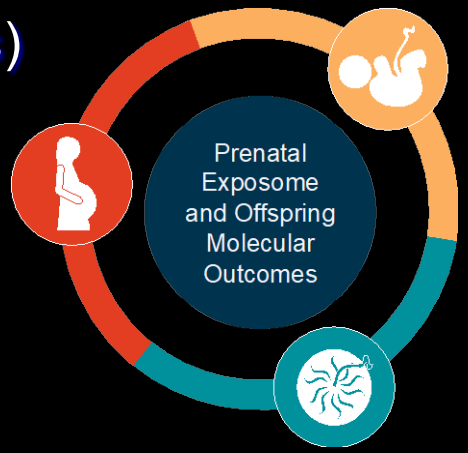
Starling et al, Environ Res 2020

ECHO: Needs replication in larger, more divers cohorts

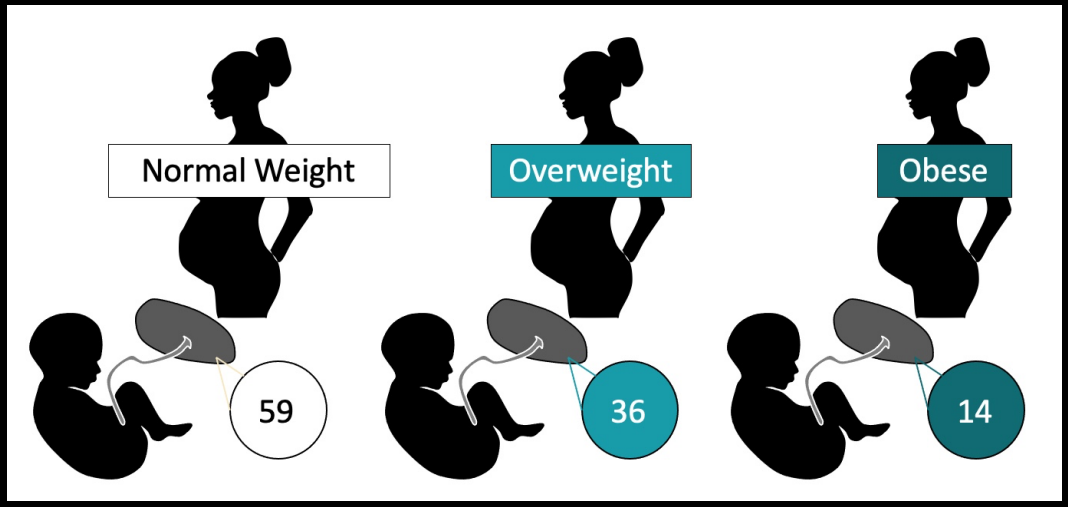
Programming Mechanisms
ECHO Site Specific Aim

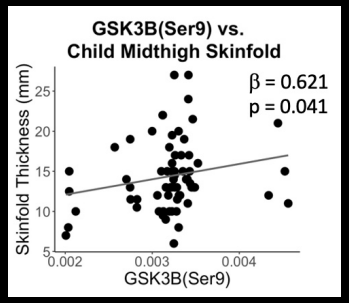
To measure molecular signatures associated with in utero metabolic/lifestyle/environmental exposures to determine biological pathways linking these exposures with child outcomes

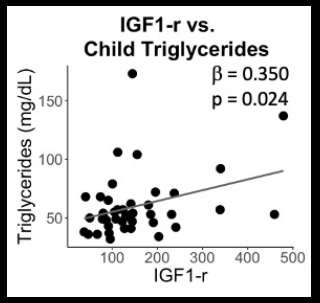
- Biological Samples
  - Placenta
  - Infant mesenchymal stem cells (MSCs)
  - Umbilical cord blood



Placenta Studies (Thomas Jensen lab)





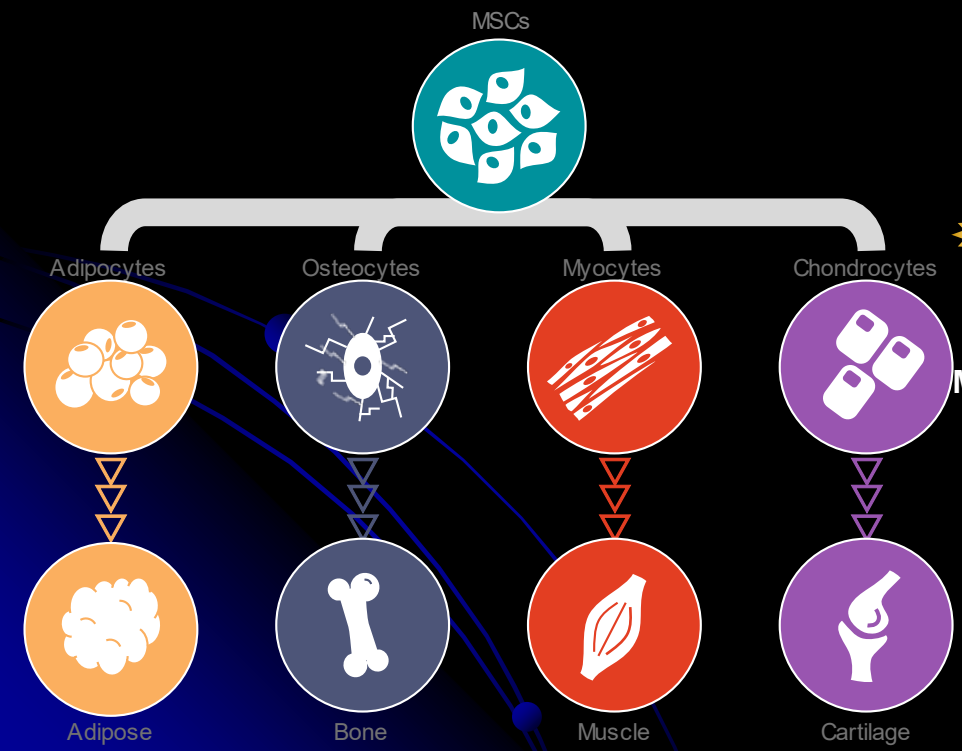


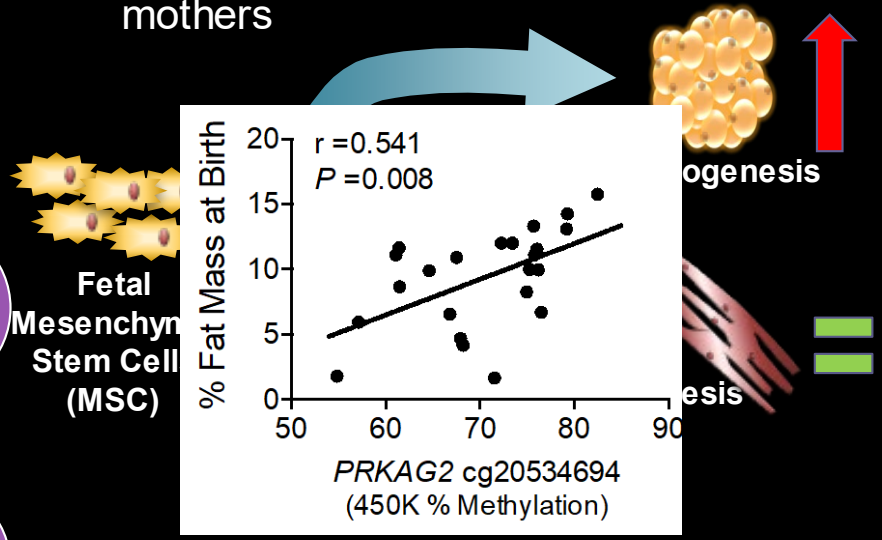
- Hypothesis: From diverse, healthy women across the BMI spectrum, placental proteins will be linked to child cardiometabolic traits
- Results: Proteins involved in mTOR, AMPK (Keleher et al. 2020), inflammation, and insulin signaling (Keleher et al. 2021) are linked to child cardiometabolic traits at 4-6 years of age
- Next Steps: Does maternal diet quality affect placental proteins?

MSC Studies: Healthy Start Baby Bump (Kristen Boyle Lab)

Biology of intra-Uterine Metabolic Programming - mechanistic arm of the Healthy Start study

- Fresh umbilical cord tissue collected at birth
- **165 MSCs** isolated, grown and stored
- Greater adipogenesis in MSCs from obese vs normal weight mothers
- DNA methylation in MSCs correlates with % FM at birth

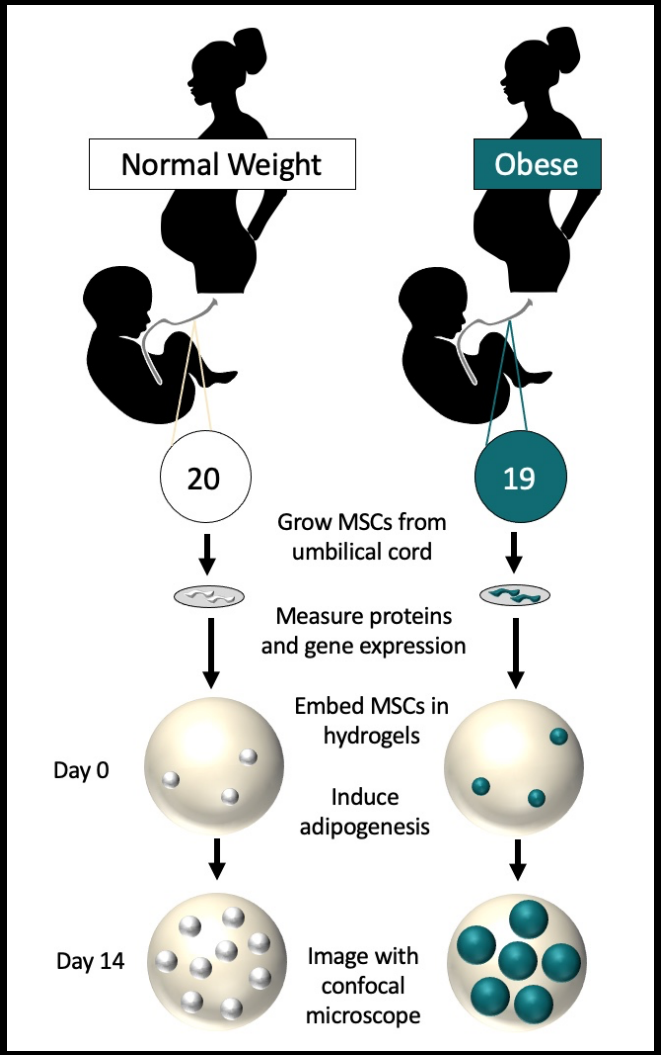




Boyle KE et al., *Diabetes* 2016
Shapiro AL, et al., *PLoS One* 2016
Baker PI, JCI Insight, 2017

MSC Studies: Adipocyte Hypertrophy

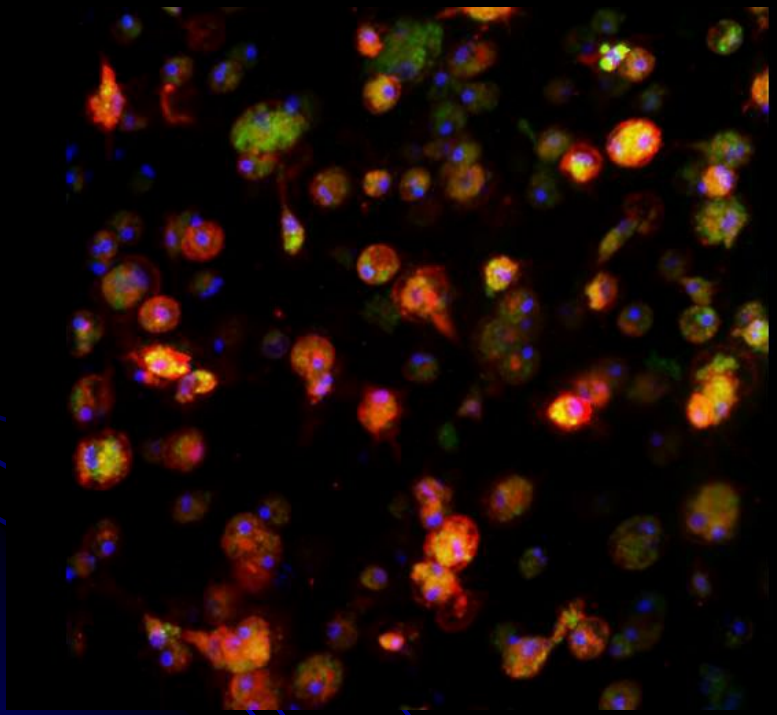
- Hypothesis: Maternal obesity primes MSCs for adipocyte hypertrophy
- Results: Maternal obesity is associated with MSCs that overexpress adipogenesis proteins such as Zfp423—associated with the expression of 500+ genes, enriched for cell cycle pathways—which then differentiate into larger adipocytes.
- Next Steps: How does this model respond if the MSC hydrogels are embedded in mouse fat tissue?



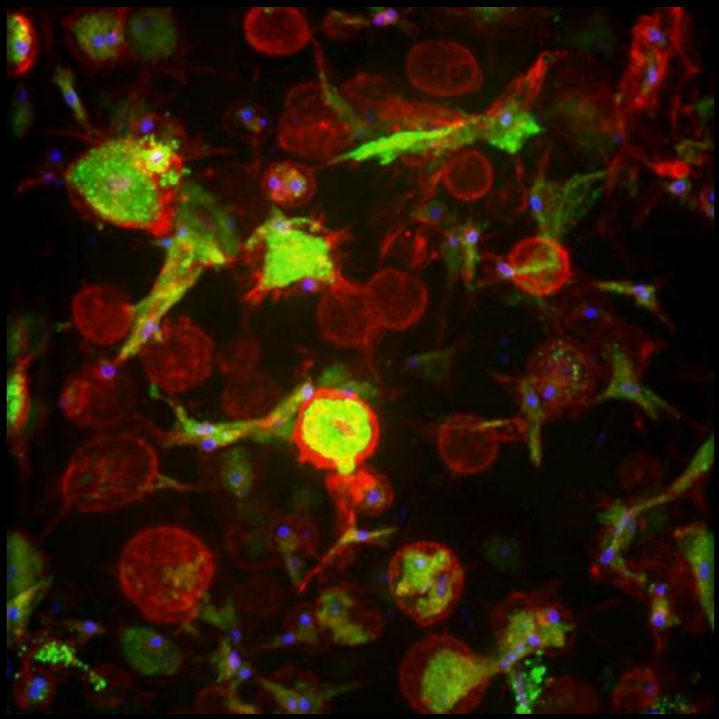
Keleher et al., submitted.

MSCs after 2 weeks adipogenesis

NW-MSCs



Ob-MSCs

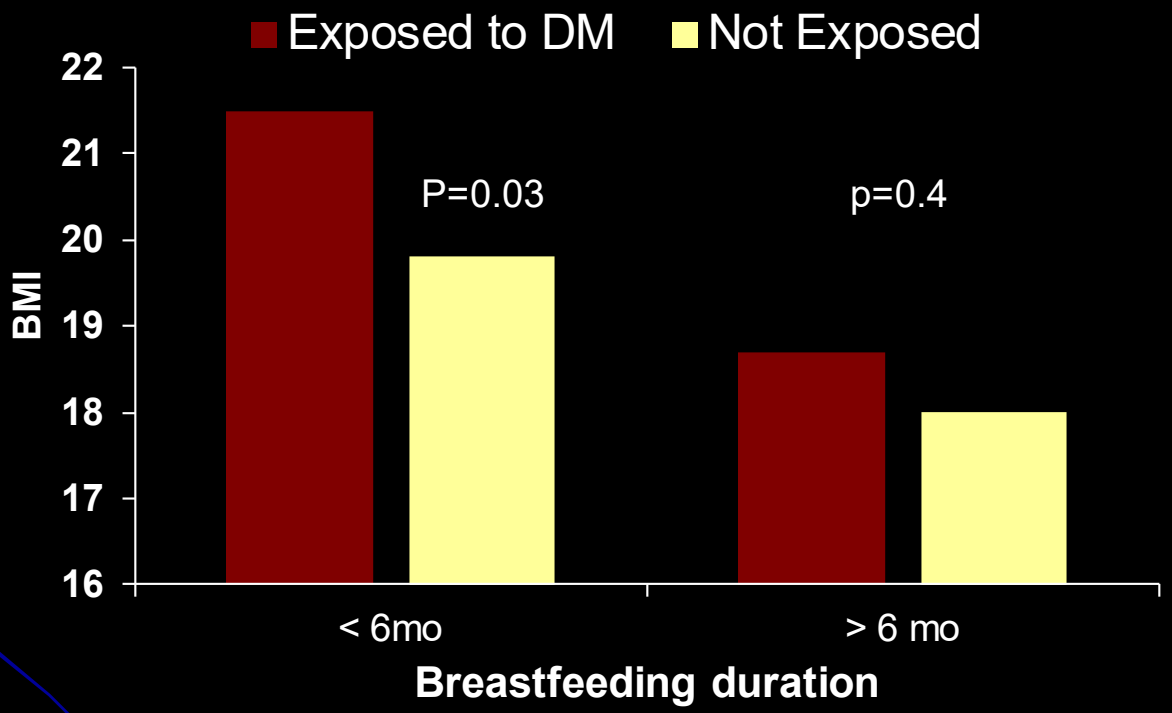


After 14 days of adipogenic induction in hydrogels, Ob-MSCs 73% larger and stored 72% more fat than NW-MSCs

The Postnatal Environment

Breastfeeding Modifies the Effect of Exposure to Diabetes *in Utero* : EPOCH Study

Body Mass Index (BMI) in 10 year-old offspring



Results were similar for visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and waist circumference

Crume T, et al., *Diabetes Care* 2011

Current Child Diet Modifies the Effect of Exposure to Diabetes *in Utero* : EPOCH Study

HEI below median (<60/100)

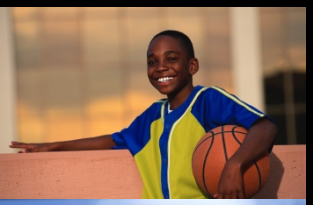
	Unexposed			Exposed			
	Mean	**(95% CI)**		**Mean**	**(95% CI)**		**p**
BMI (kg/m^2)	20.2	(19.7	20.7)	21.6	(20.6	22.7)	**0.006**
WtHR	0.46	(0.45	0.47)	0.49	(0.47	0.50)	**0.0006**
VAT (cm^2)	22.3	(20.2	24.5)	27.5	(23.4	32.4)	**0.004**
SAT (cm^2)	114.2	(102.2	127.5)	155.5	(128.7	187.9)	**0.001**

HEI above median (>60/100)

	Unexposed			Exposed			
	Mean	**(95% CI)**		**Mean**	**(95% CI)**		**p**
BMI (kg/m^2)	20.1	(19.4,	20.7)	20.8	(19.5,	22.2)	**0.24**
WtHR	0.46	(0.45,	0.47)	0.46	(0.44,	0.49)	**0.22**
VAT (cm^2)	22.0	(19.5,	24.7)	24.2	(19.6,	29.8)	**0.22**
SAT (cm^2)	113.9	(100.0	129.6)	136.3	(108.4	171.3)	**0.18**

Sauder KA, et al, Pediatr Obes, 2019

ECHO: Can postnatal diet/physical activity mitigate the increased risk conferred by prenatal exposures/?




……Most U.S. Youth

- Do not meet the recommendations for eating 2½ - 6½ cups of fruits and vegetables each day
- Do not eat the minimum recommended amounts of whole grains (2–3 ounces each day)
- Eat more than the recommended maximum daily intake of sodium (1,500–2,300 mg* each day)
- Have 40% of daily calories coming from “empty calories” (sugars and solid fats)
- In 2011, 29% percent of high school students had participated in at least 60 minutes per day of physical activity on each of the 7 days before the survey

http://www.cdc.gov/ccdphp/dash/nutfact.htm




What can we do?

"Remember when we used to have to fatten kids up first?"

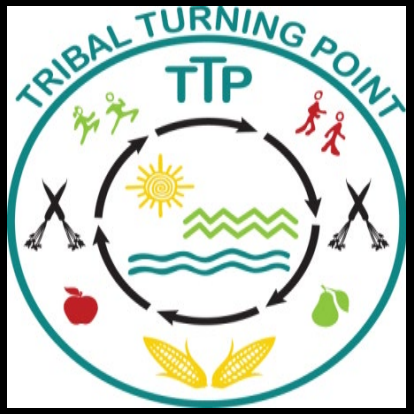
A COMPREHENSIVE APPROACH TO PREVENTION THROUGHOUT THE LIFE-COURSE

Primordial Prevention: "Tribal Turning Point"

Reducing Risk for Type 2 Diabetes in American Indian Youth

DPP-based intervention for American Indian children aged 7-10 years

- 12 group classes with physical activity, interactive learning, culture, group meal
- 4-7 individual MI sessions to build problem-solving skills to reach behavioral goals
- Toolbox with general and local resources



Randomized pilot study: 62 youth in Navajo & Eastern Band Cherokee

	Intervention			Control			Treatment effect	
	Final - Baseline			Final - Baseline			Unadjusted	Adjusted*
	Mean	(SE)	p	Mean	(SE)	p	p	p
BMI	0.3	(0.2)	0.13	1.0	(0.2)	0.0001	0.02	0.08
BMI z score	-0.17	(0.06)	0.001	0.01	(0.05)	0.82	0.02	0.049
Decrease in BMI z-score (n)	21	(72%)		14	(42%)		0.02	0.02
Waist circumference (cm)	1.2	(0.7)	0.09	3.7	(0.7)	0.0001	0.01	0.01

*Sauder K, *Pediatric Obesity*, 2017

Future Focus: Pre-conception health (Kate Sauder)

***E**xploring*
***P**erinatal*
***O**utcomes among*
***CH**ildren*

Pre-birth exposures influence obesity and diabetes risks across the lifecourse

Earlier intervention is needed

Prenatal interventions have little effect on gestational weight gain, diabetes

Future Research

- Systematic and sustainable surveillance of pediatric obesity and diabetes
  - To understand burden and risk, effects of prevention programs, development and burden of complications, mortality
- Longitudinal (pre-) birth cohort studies- consortia : ECHO
  - To comprehensively explore the role of environmental exposures (exposome) and their biologic signatures & pathways (omics)
  - To identify potentially causal associations
- Improved understanding of mechanisms:
  - Mechanistic studies nested in population cohorts
- Effective interventions: randomized clinical trials and translation studies
  - Increase focus on primordial prevention in youth
  - Focus on pre-conceptual health

Acknowledgments
LEAD Center