Developmental Programming and Metabolic Health: Obesity and Diabetes

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PRESENTED BY:

Jonathan Q. Purnell, MD,

Professor of Medicine,

Knight Cardiovascular Institute,

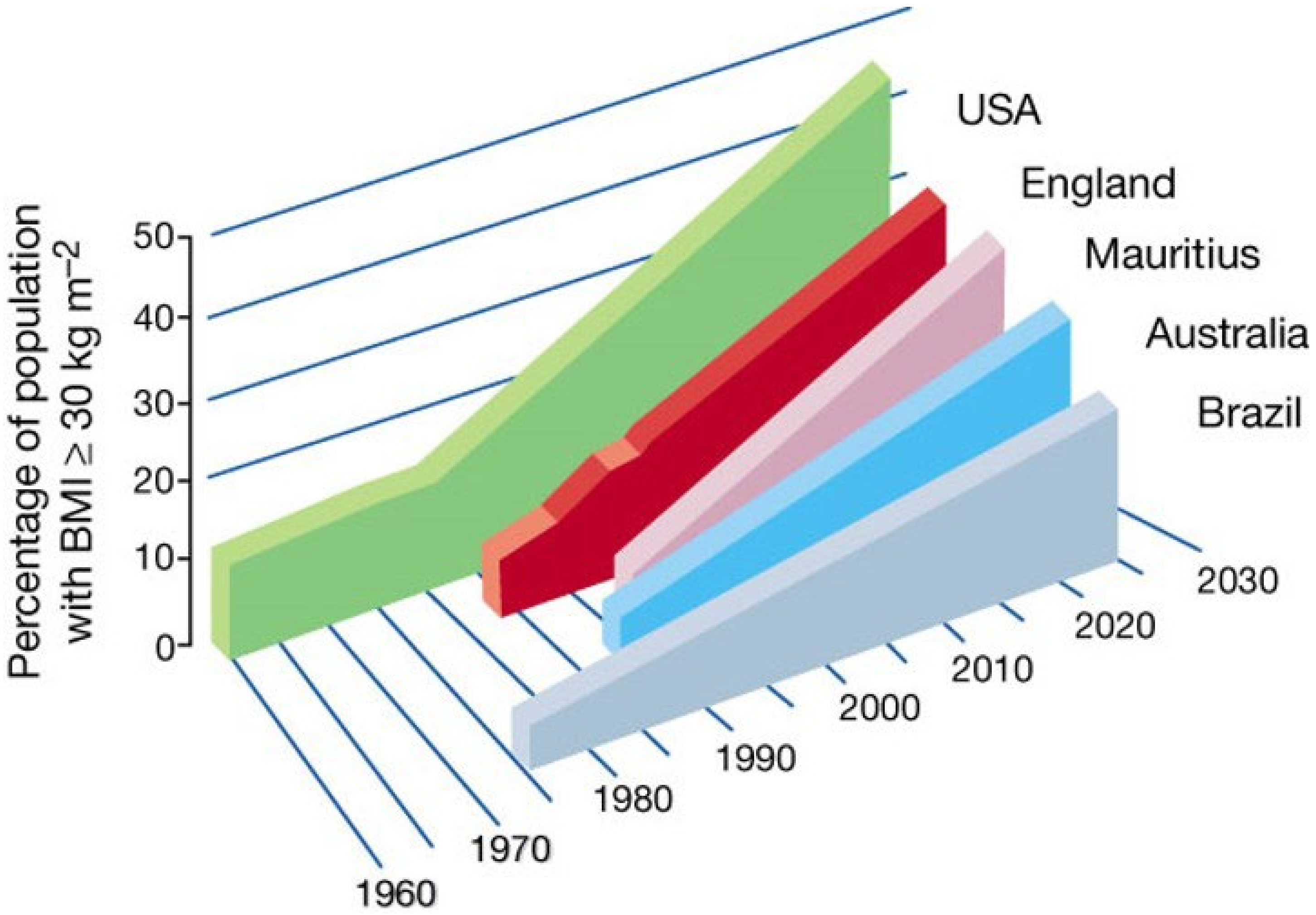
Division of Endocrinology, Diabetes, and Clinical Nutrition,

Oregon Health & Science University

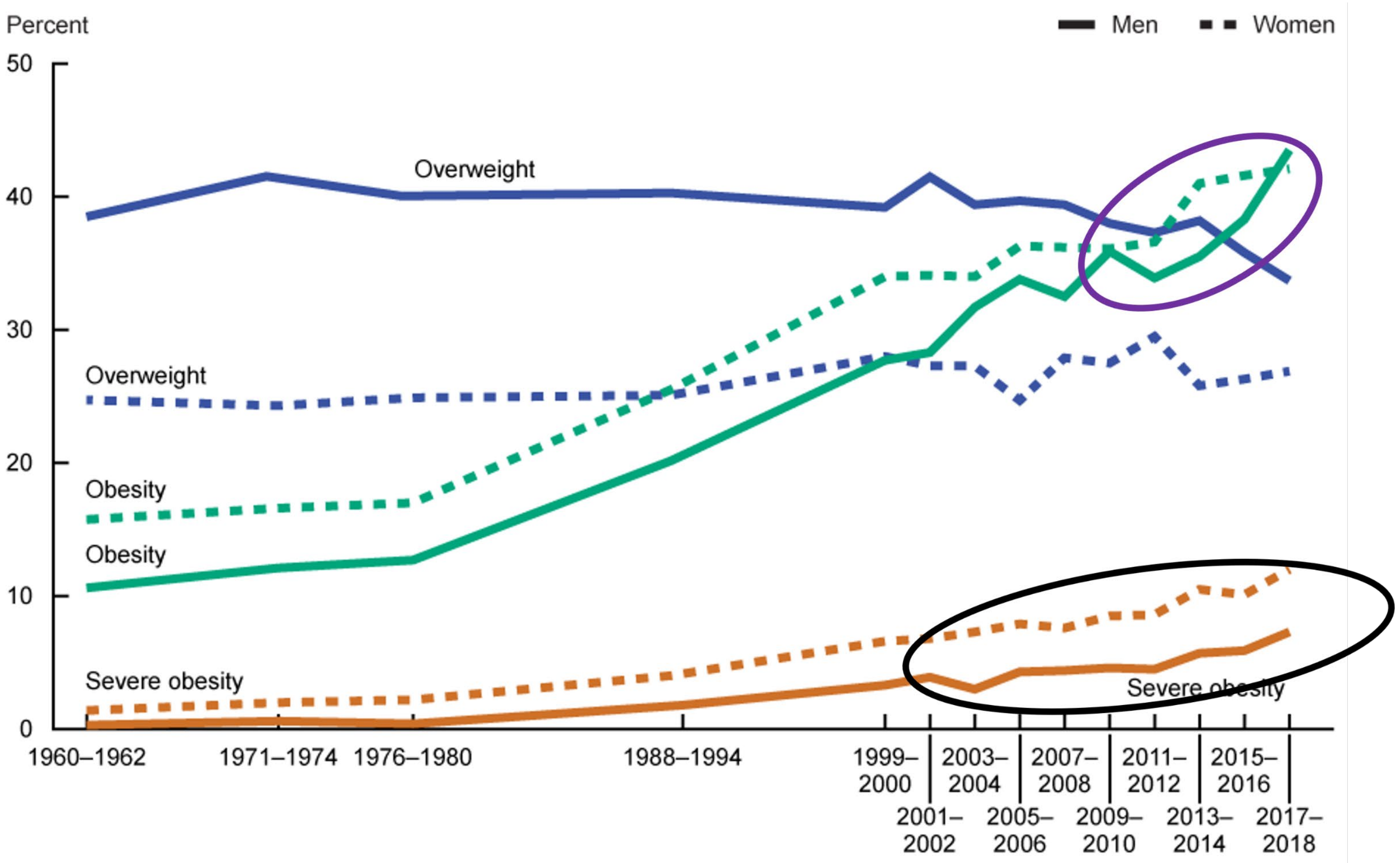
OHSU

Current and Projected Obesity Prevalence Rates from 1960 to 2025

Kopelman. Nature 404, 635 - 643 (2000)

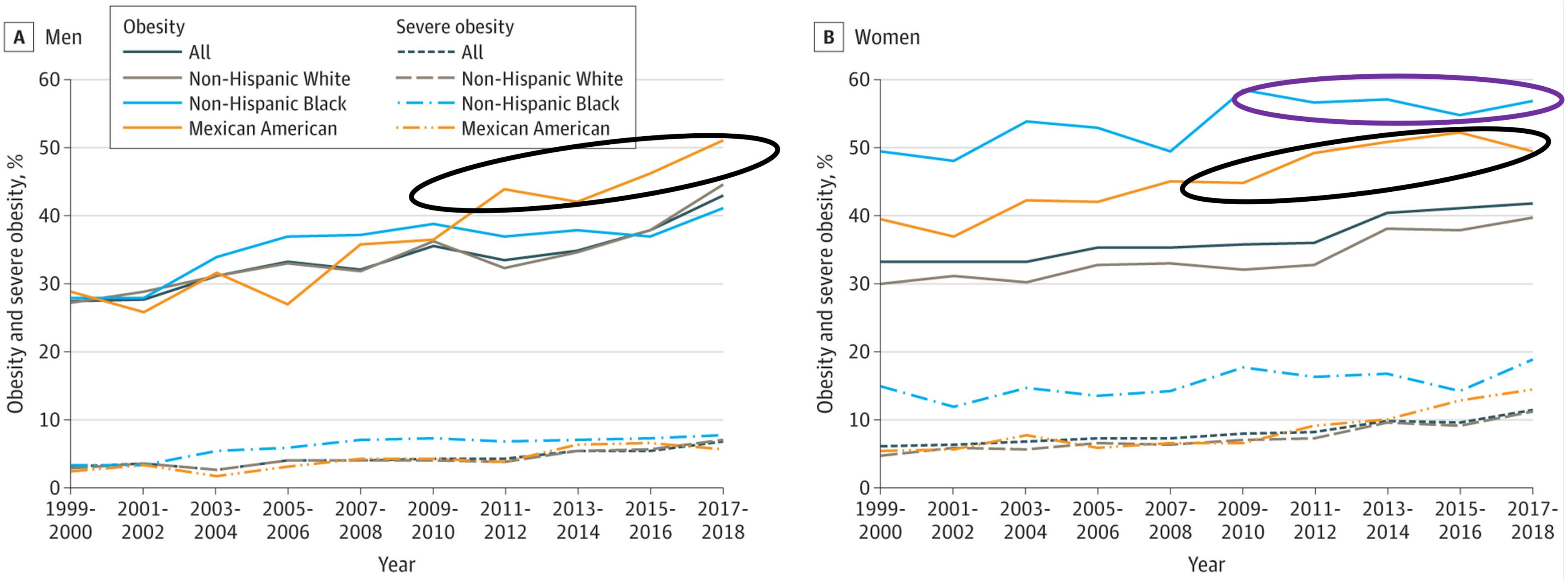


Prevalence of Overweight, Obesity, and Severe Obesity in US Adults: 1960-2018



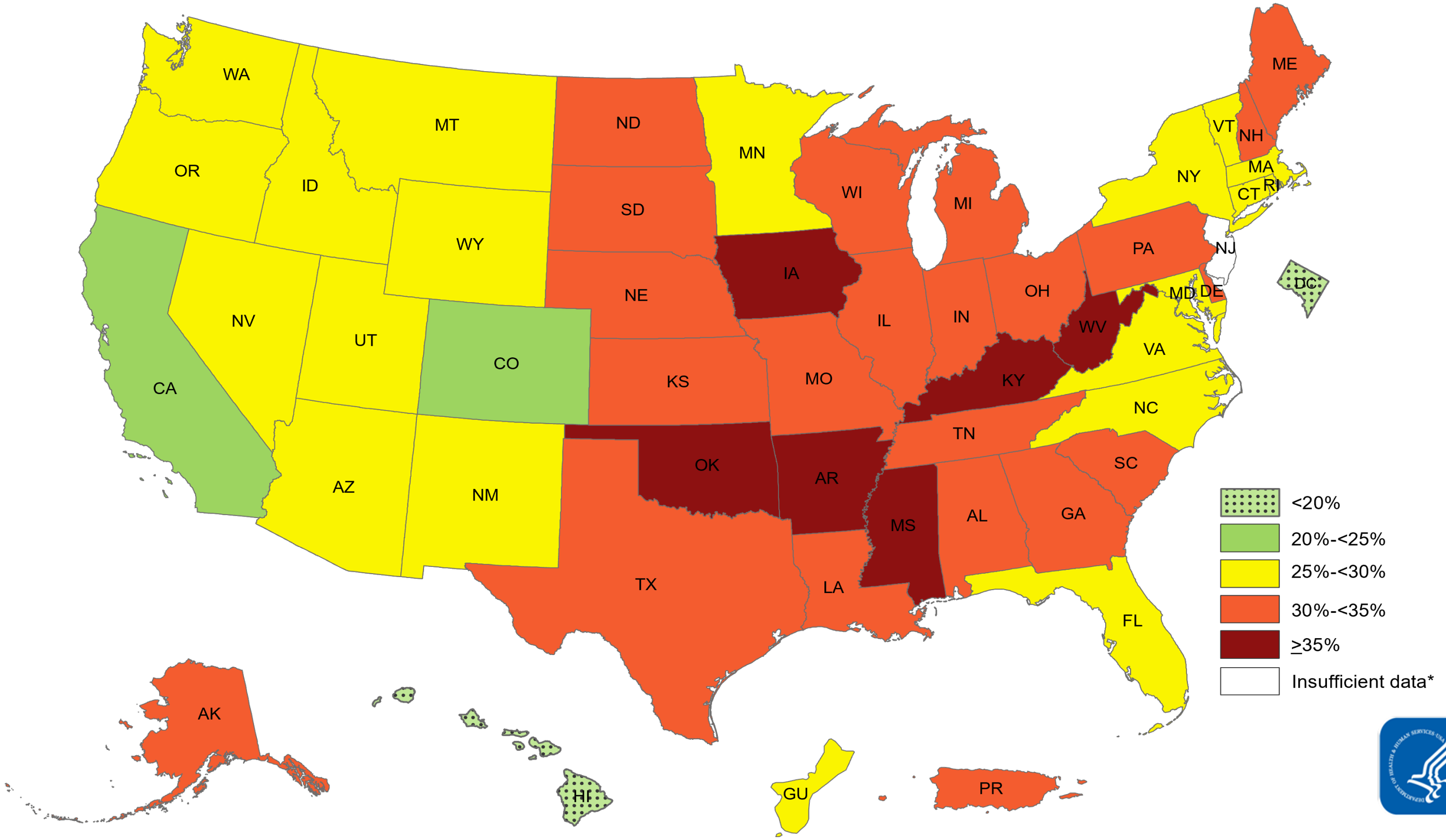
Fryar CD, Carroll MD, Afful J. NCHS Health E-Stats. 2020.

Trends in US Obesity Prevalence by Race and Hispanic Origin—1999-2000 to 2017-2018

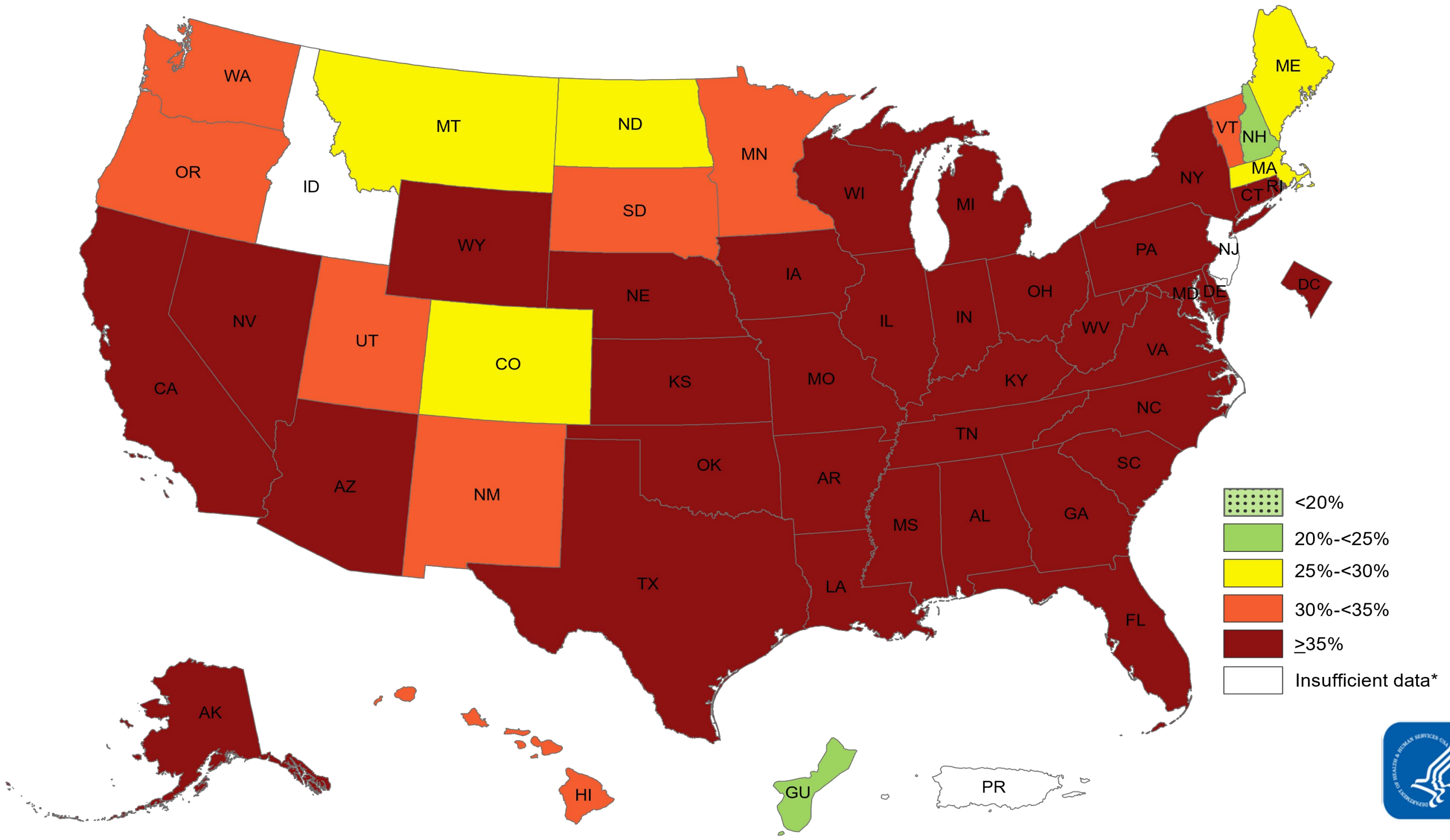


Ogden CL, et al. JAMA. 2020;324(12):1208-1210.

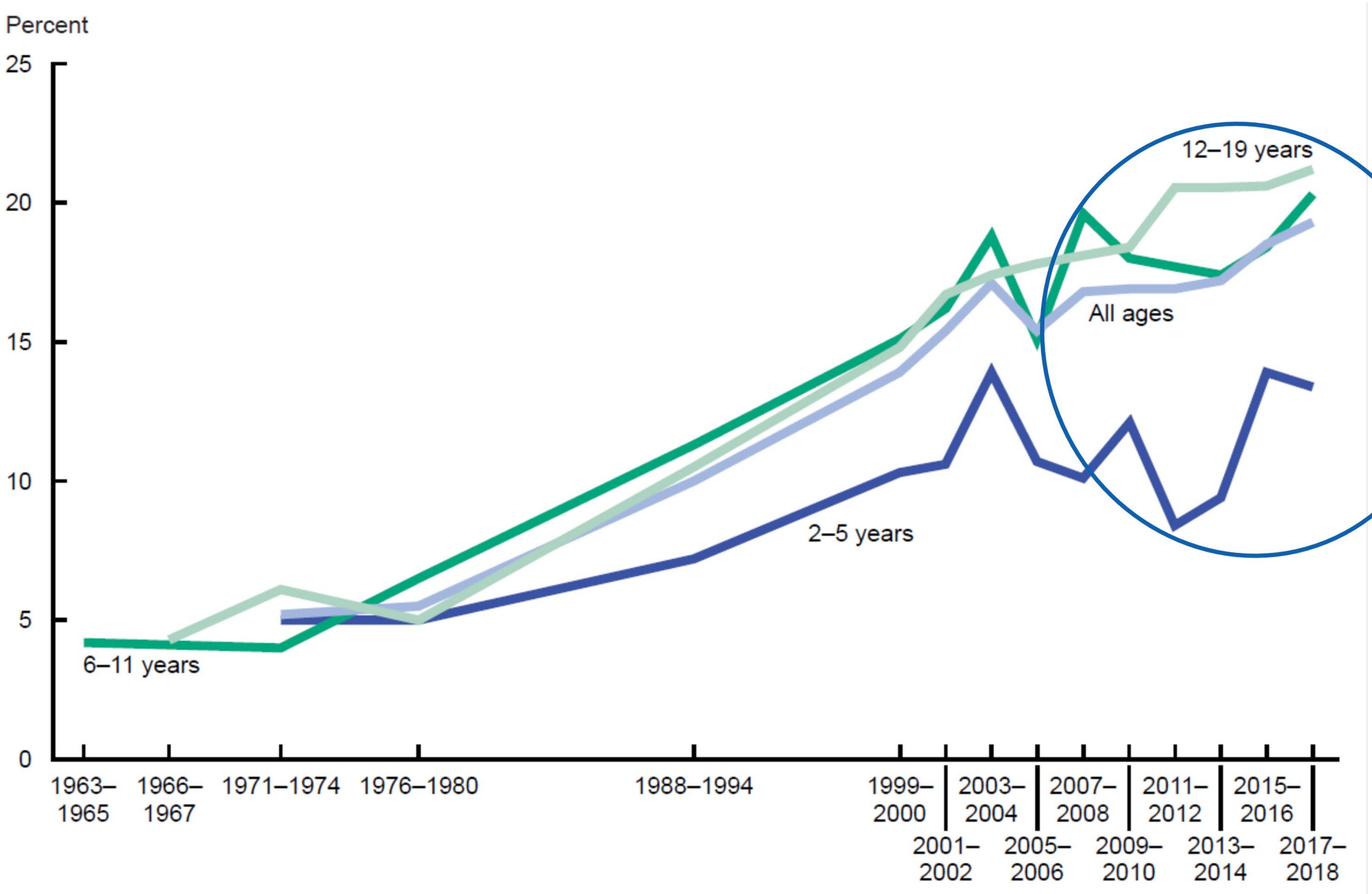
Prevalence of Obesity Among Non-Hispanic White Adults, by State and Territory, BRFSS, 2017-2019



Prevalence of Obesity Among Non-Hispanic Black Adults, by State and Territory, BRFSS, 2017-2019



Trends in Obesity in US Children: 1963-2018

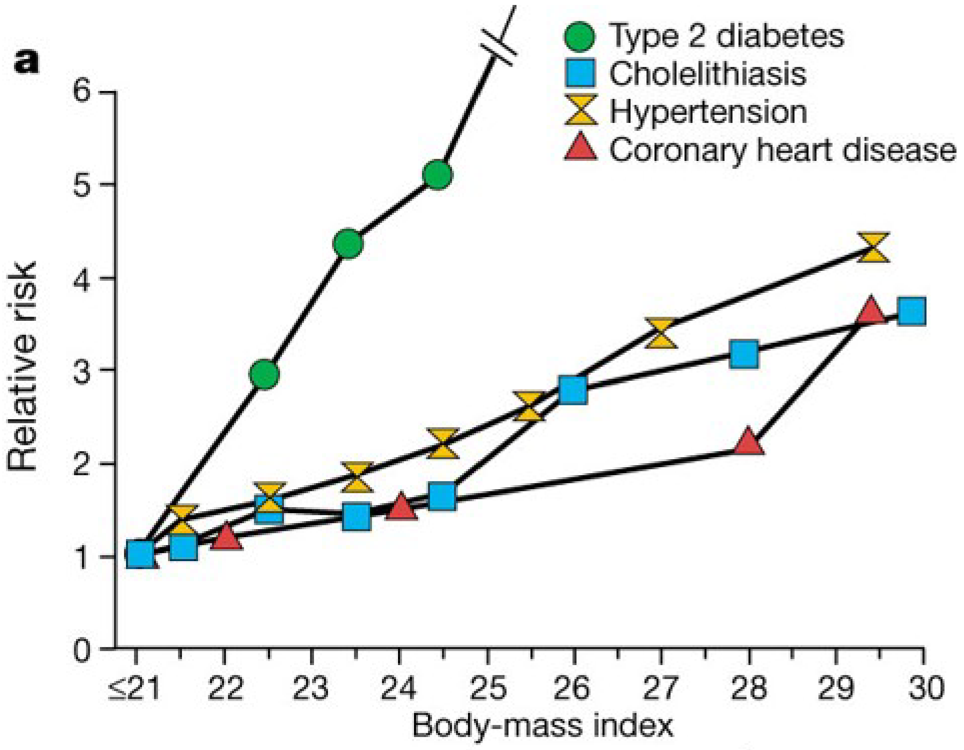


https://www.cdc.gov/nchs/data/hestat/obesity-child-17-18/obesity-child.htm

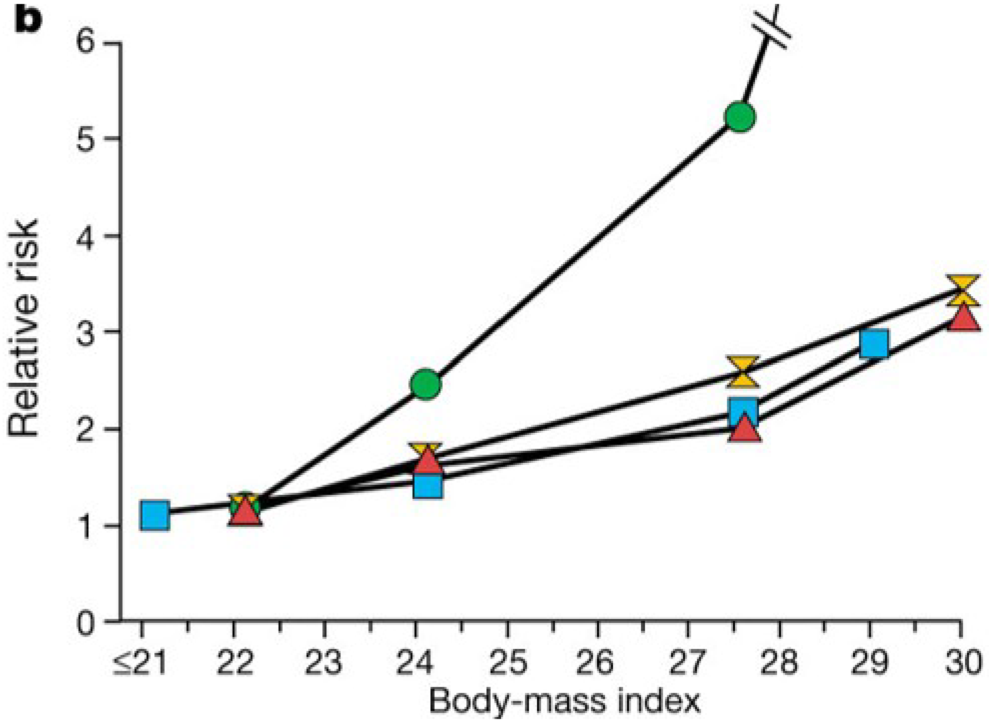
Relationship of Obesity to Co-Morbid Diseases

Willet, et al. NEJM. 341:427-34, 1999

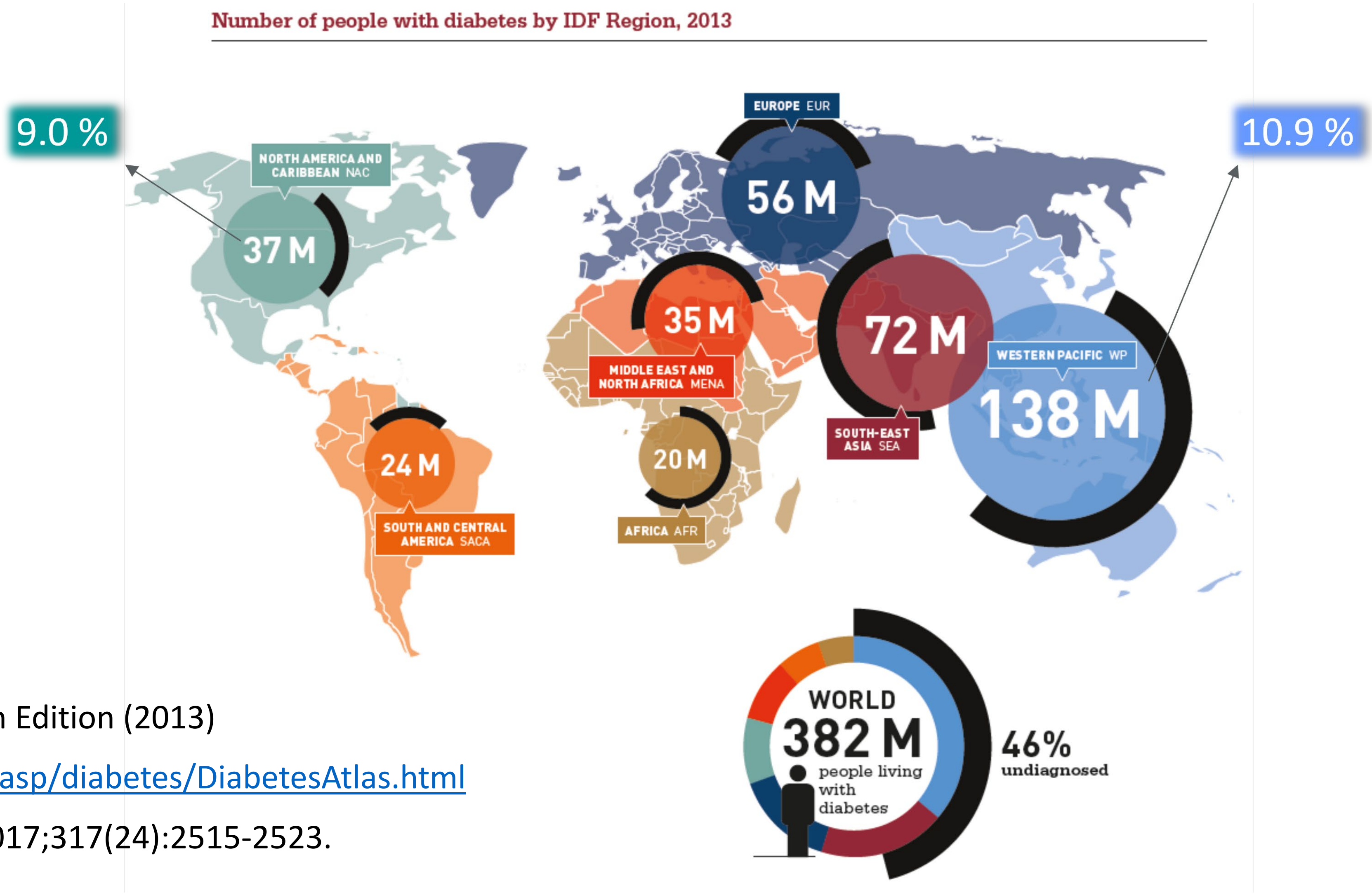
Women



Men



Worldwide Diabetes Prevalence: 2013



IDF Diabetes Atlas 6th Edition (2013)

https://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html

Wang, et al. *JAMA*. 2017;317(24):2515-2523.

Epidemiology: Summary

- Trends for obesity, diabetes continue to rise
- Communities of color are disproportionately affected
- Number of “healthy weight” Americans is now < 30%

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Causes of Obesity

<u>Primary:</u>

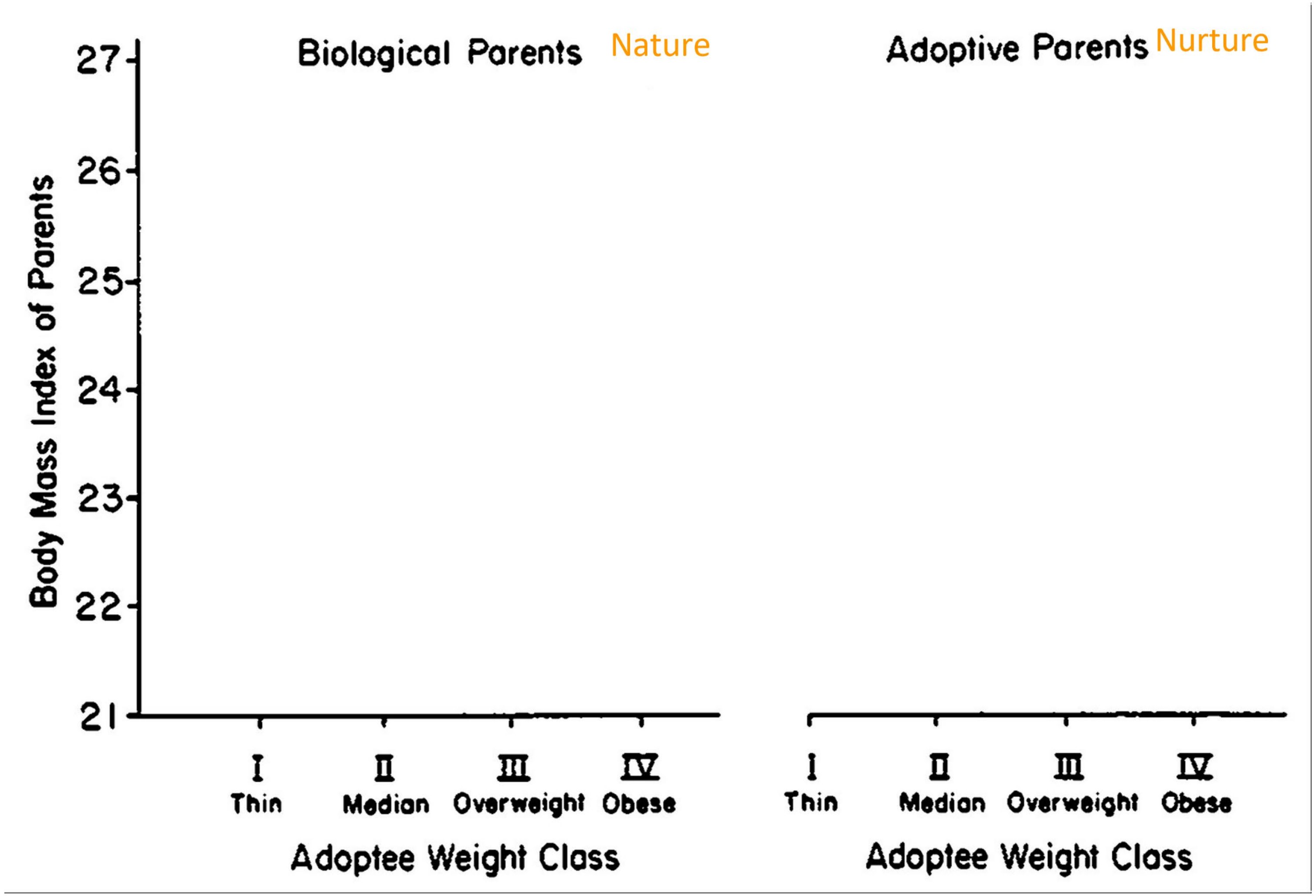
- Genetics: 40 - 70%
- Environment

<u>Secondary:</u>

- Hypercortisolemia
- Drugs

Danish Adoptees Study

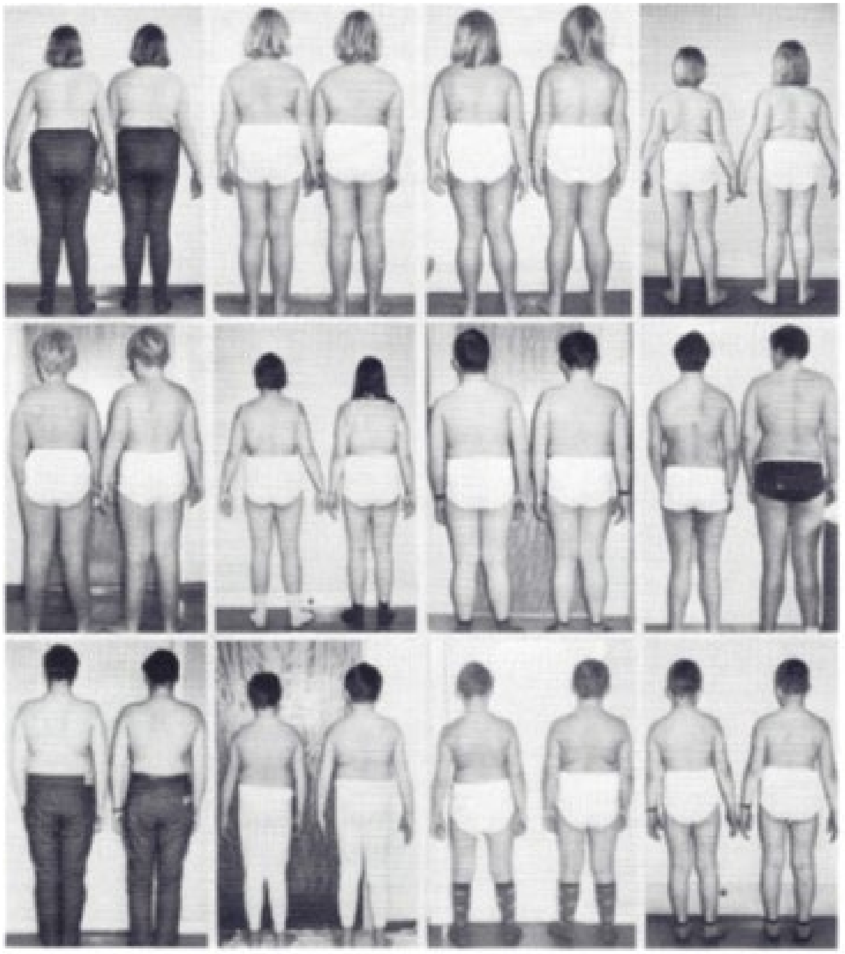
Stunkard AJ et al. N Engl J Med 1986;314:193-198.



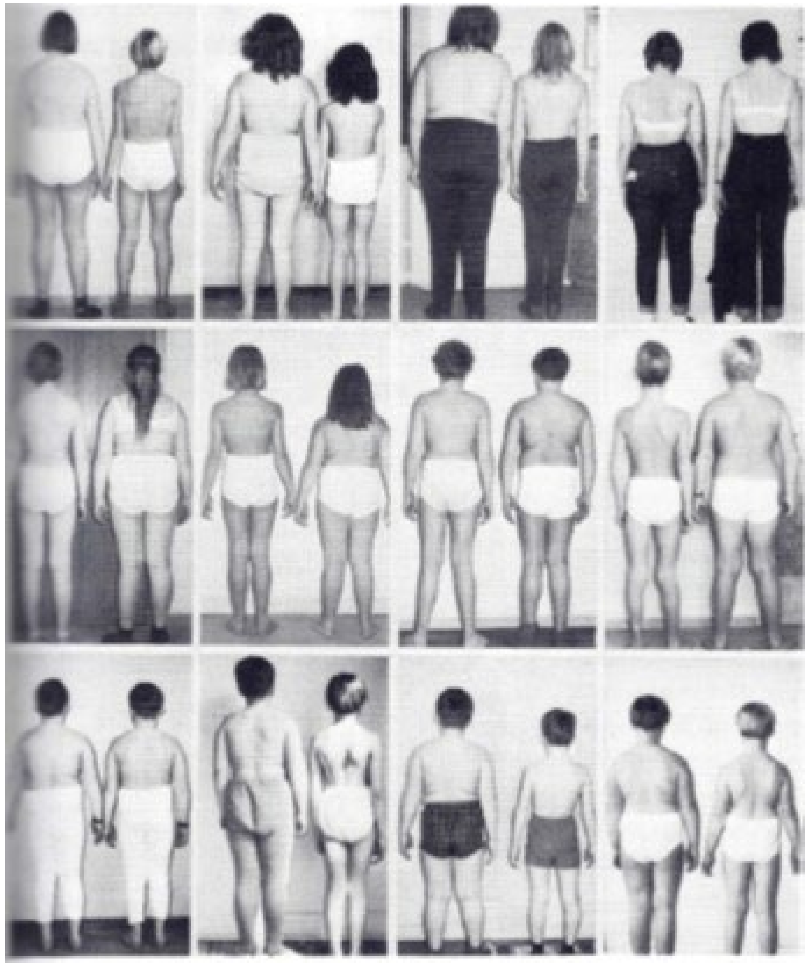
Twins Studies

Acta Ptediatr Scand 65: 279-287, 1976

Monozygous (Identical) Twins



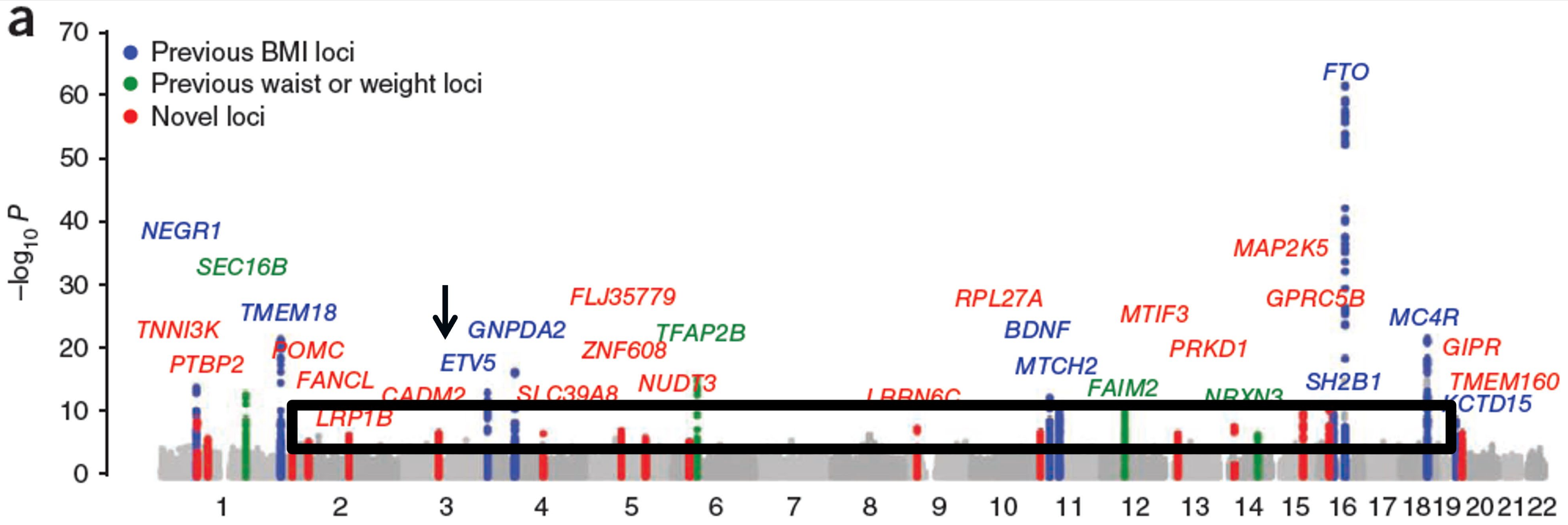
Dizygous (Fraternal) Twins



Genetic Mutations Associated With BMI and Obesity Measures

Nature Genetics 45, 501–512 (2013)
Buniello, A. et al. Nucleic Acids Res. 2019. 47, D1005–D1012.

n = 250,000. 165 *Loci associated with BMI* or waist circumference.

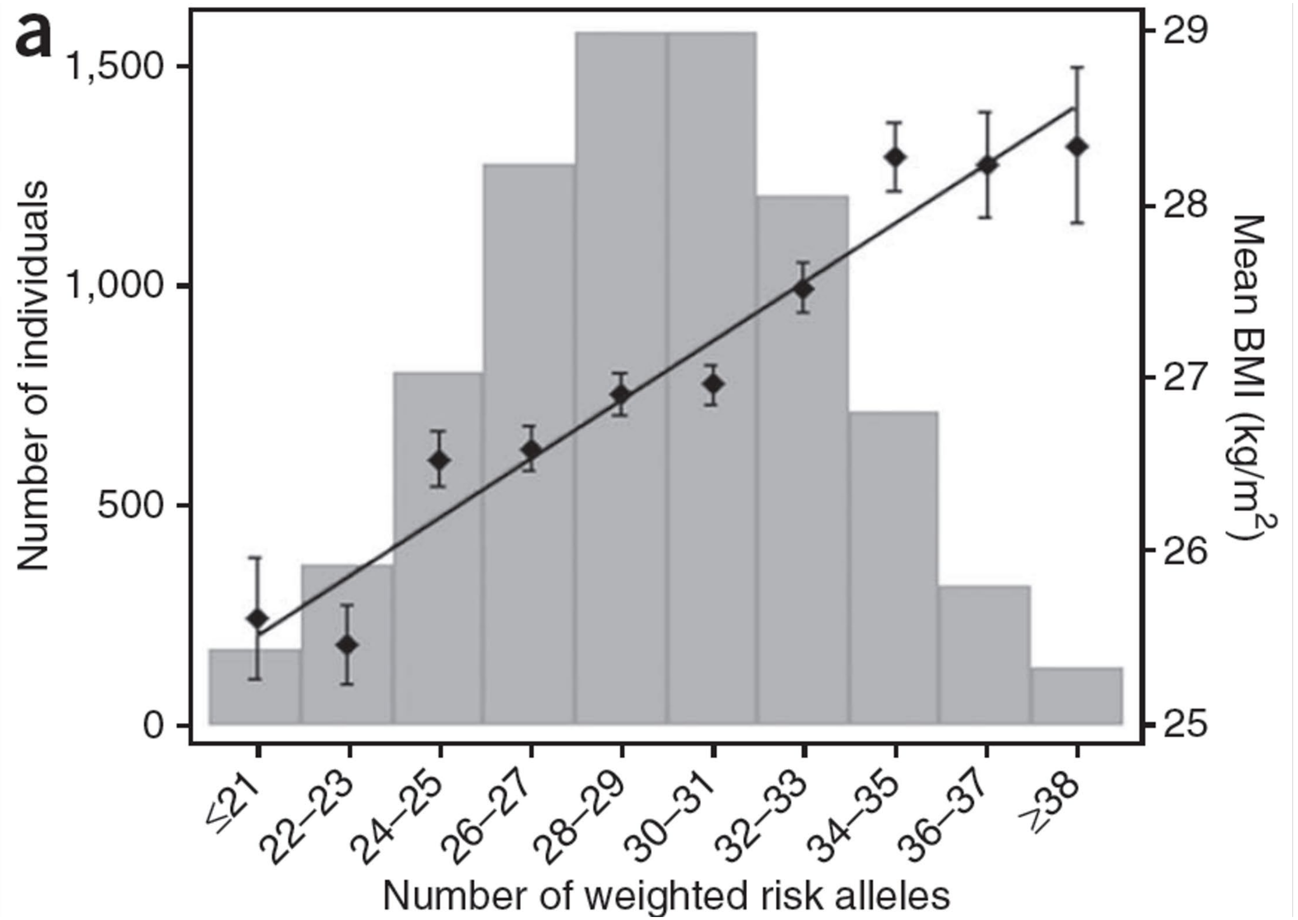


All alleles accounted for 6-11% of genetic variation in BMI.

Up to 1,100 undetected loci…

Genetic Mutations Associated With BMI

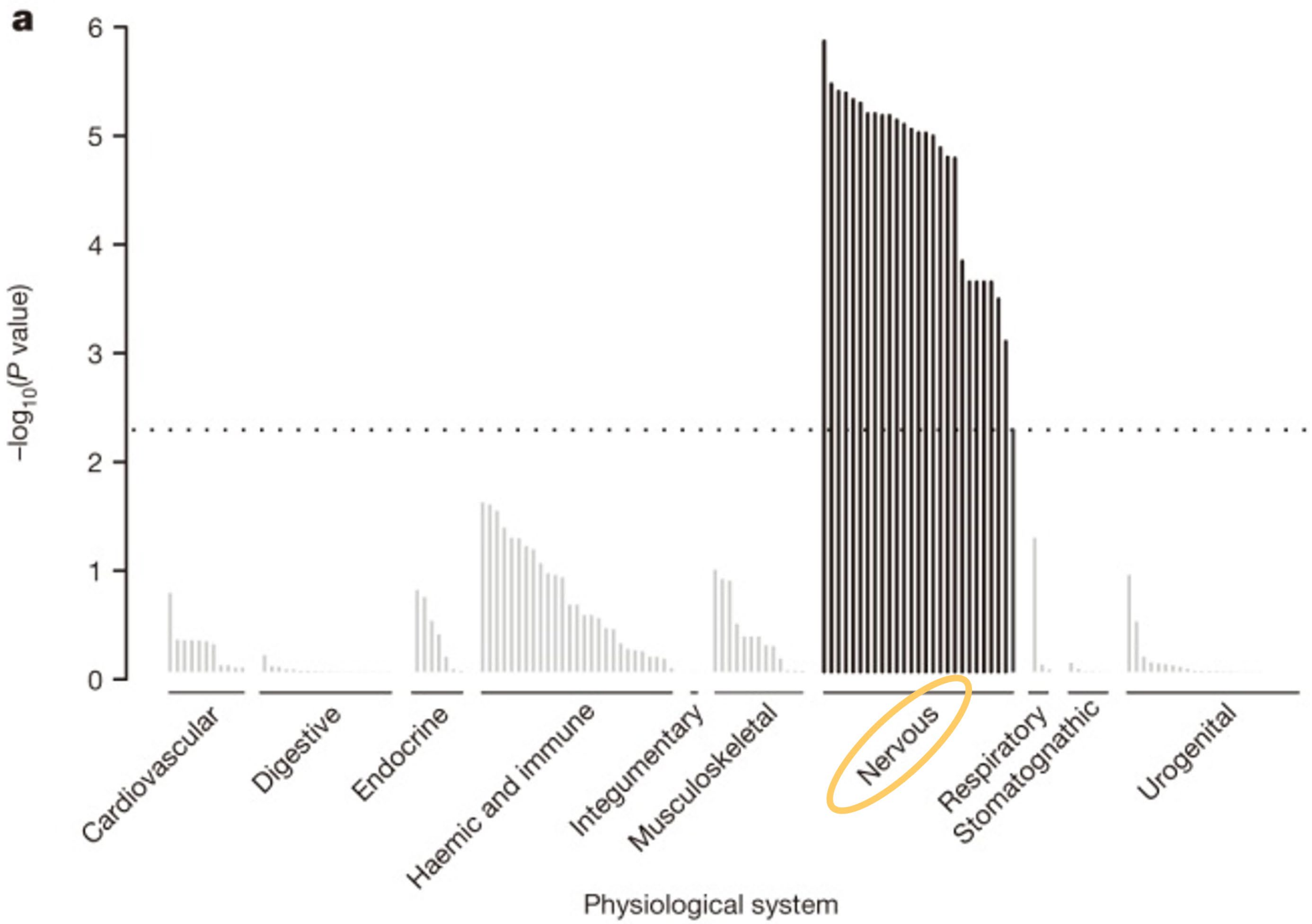
Nat Genetics. 2010. 42:937-48.



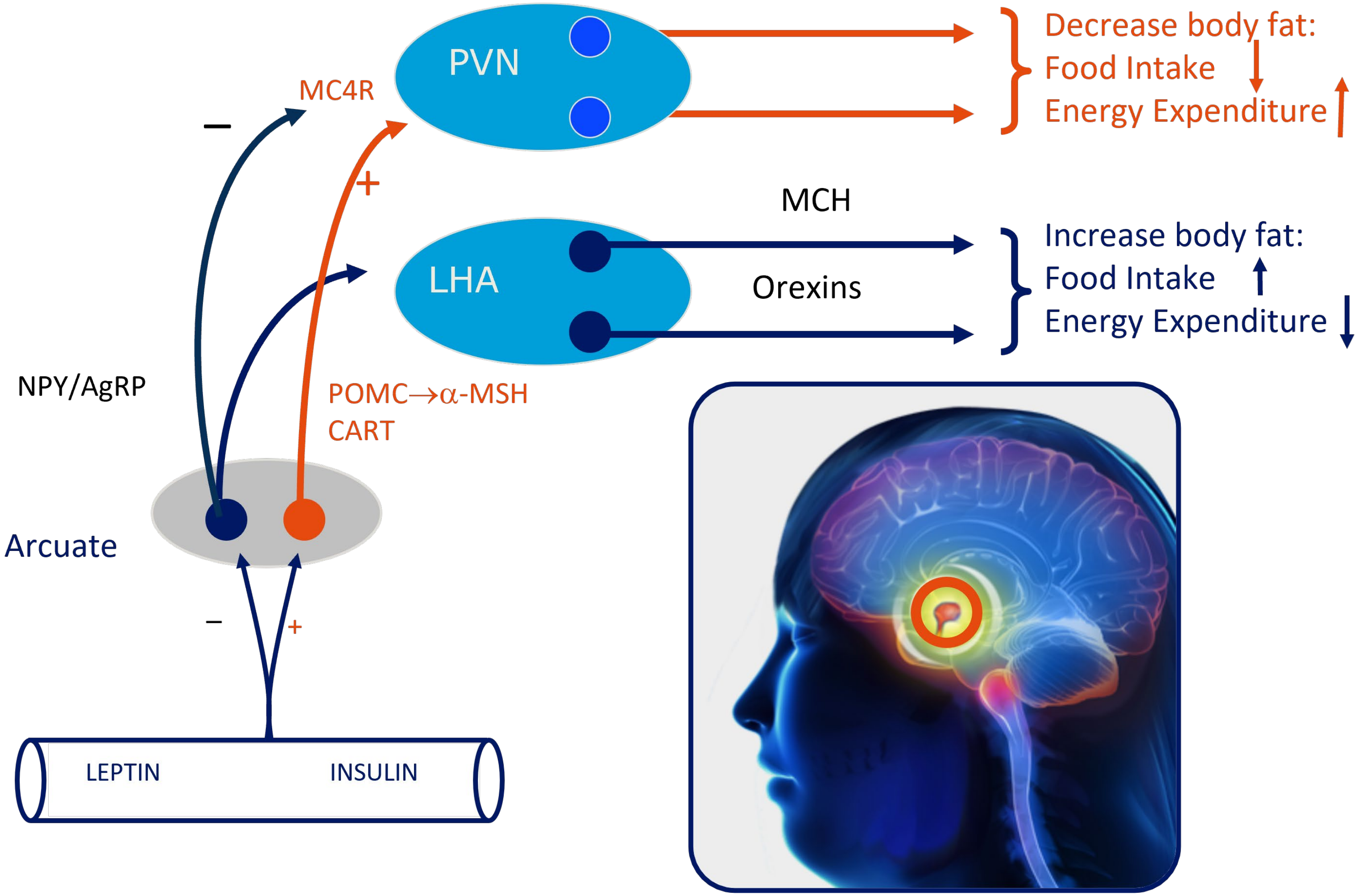
n = 250,000

BMI-associated Genetic Loci: Tissue Specificity

AE Locke et al. Nature. 2015. 518, 197-206.



Hypothalamic control of energy homeostasis by adiposity signals: The Set Point



Causes of Obesity – Environmental Factors

<u>Primary:</u>

- Genetics: 40 - 70%
- Environment
  - Low activity
  - Calorie dense foods (high fat, refined sugar)
  - Microbiome
  - Environmental toxins
  - In-utero

<u>Secondary:</u>

- Hypercortisolemia
- Drugs

Causes of Obesity – In-Utero Environment

<u>Primary:</u>

- Genetics: 40 - 70%
- **Environment**
    - Low activity
    - Calorie dense foods (high fat, refined sugar)
    - Microbiome
    - Environmental toxins
    - **In-utero**

<u>Secondary:</u>

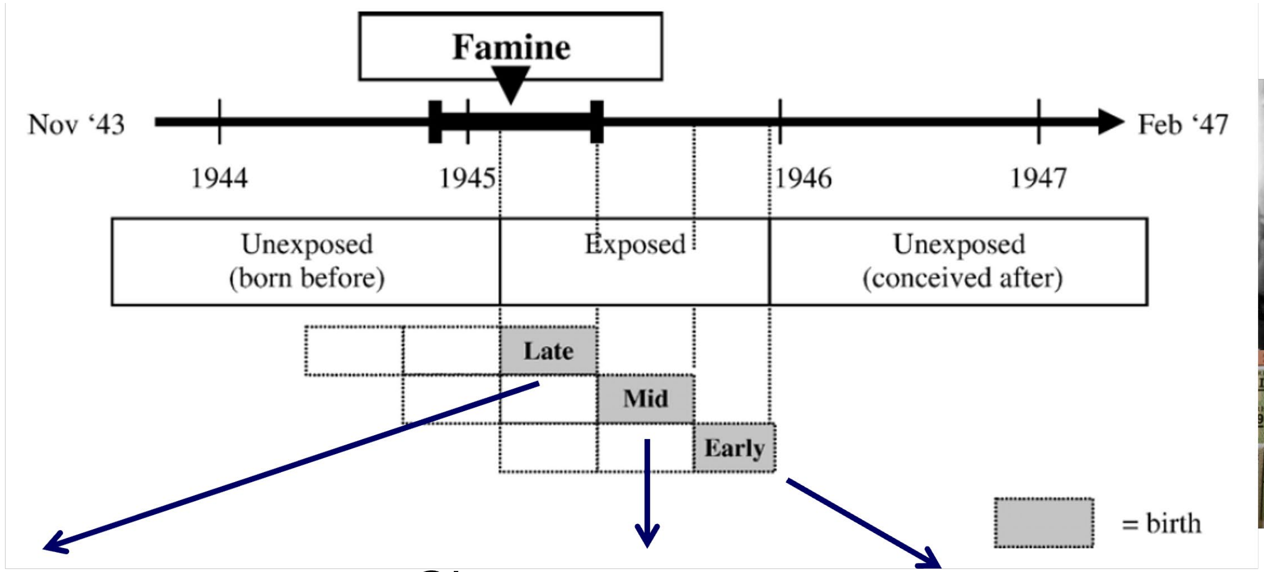
- Hypercortisolemia
- Drugs

Early Life Programming of Diabetes and Obesity:

Undernutrition

Dutch Famine (“Hongerwinter”) Study

Roseboom, et al. Early Human Development (2006) 82, 485—491



Glucose
Intolerance

- Glucose Intolerance
- Microalbuminuria
- Obstructive airway disease

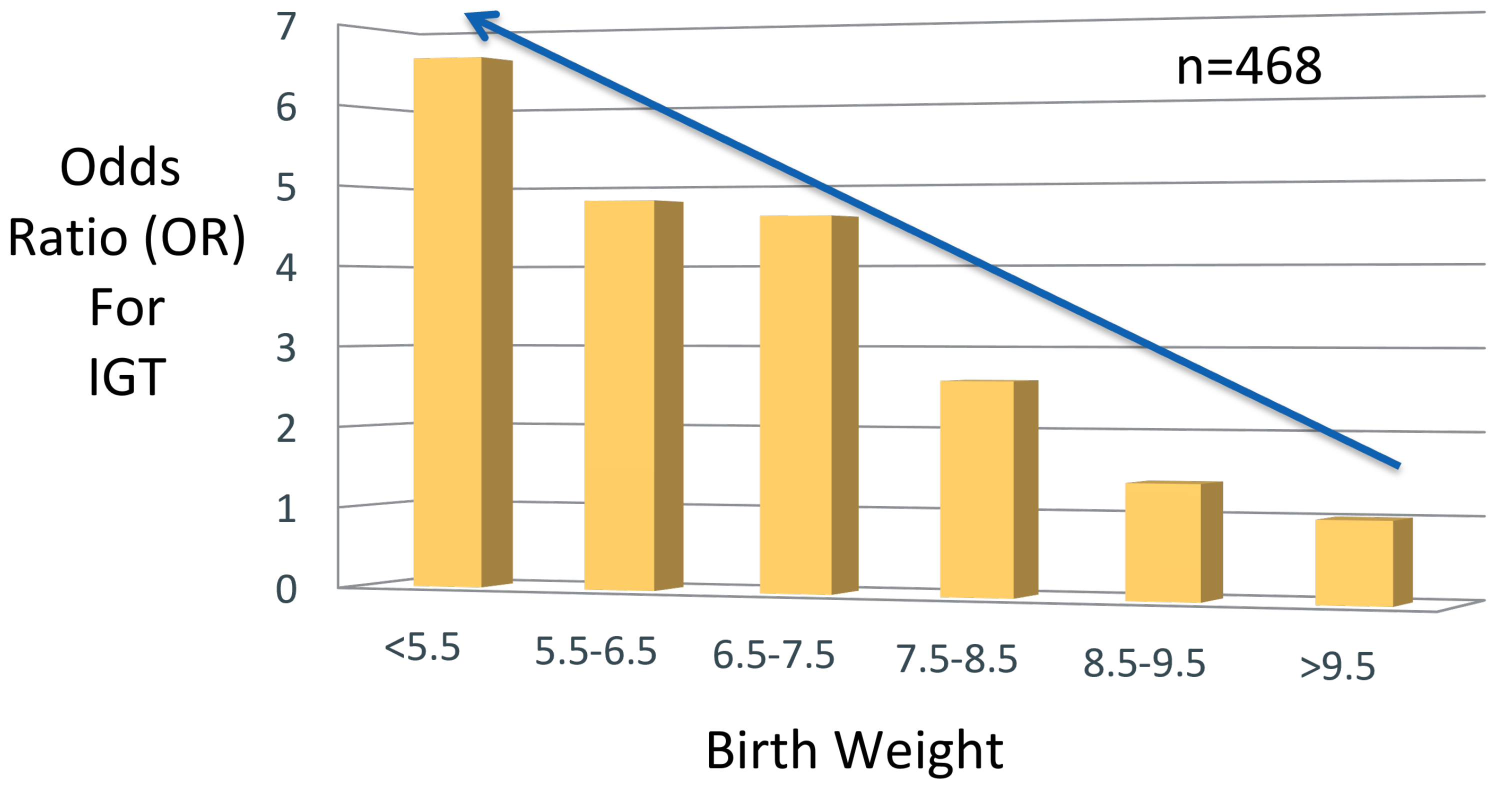
- Glucose Intolerance
- Obesity
- Dyslipidemia
- Hypercoagulable state
- CVD
- Breast CA

Fetal Undernutrition & Later Obesity

SPECIES	TIMING	TYPE	OUTCOME
Human: Dutch Famine	Early-mid gestation	Decrease Global Calories	Increase Obesity
Human: Birth-to-10 (S Afr)	Throughout gestation	Decrease Global Calories	Increase Visceral fat IF increase postnatal nutrients
Sheep	Early-mid gestation	Decrease Global Calories	Increase Visceral fat
Rats	Throughout gestation	Decrease Global Calories	Increase Visceral fat

Adult Offspring Impaired Glucose Tolerance (IGT) Risk by Birthweight

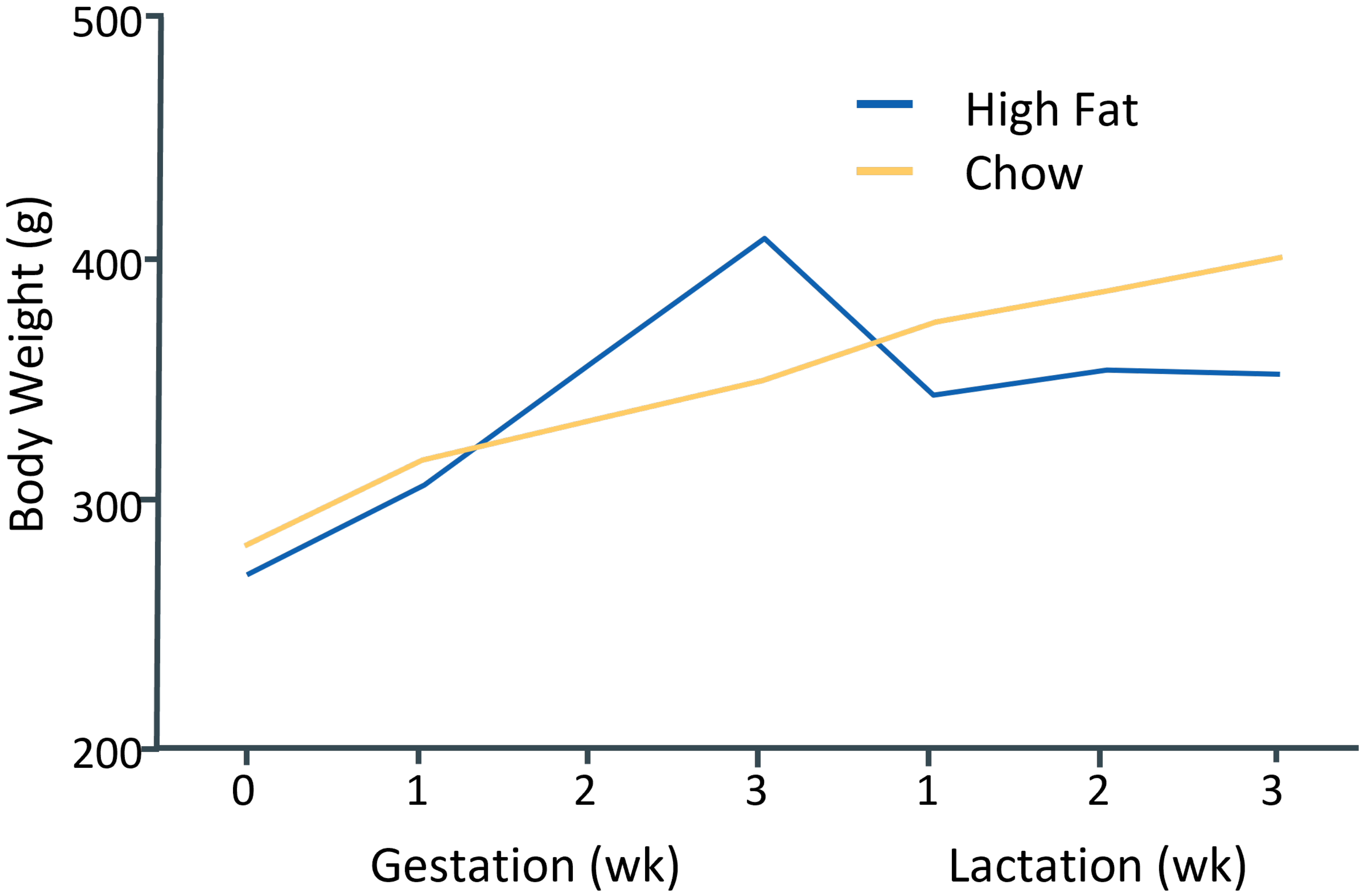
Hales, et al. BMJ. 1991. 303:2019-22.

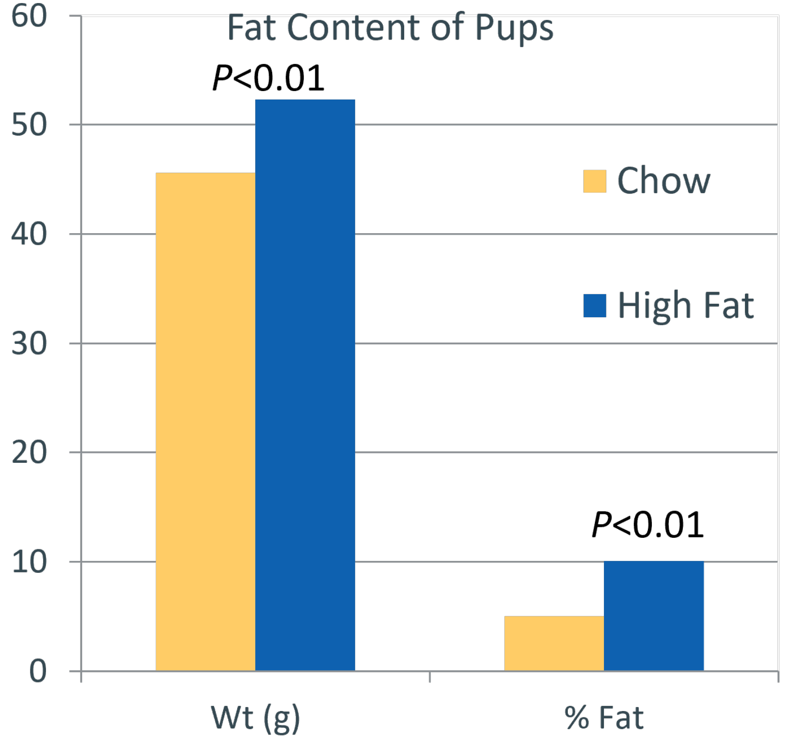


Early Life Programming of Diabetes and Obesity:

Over (mal) nutrition

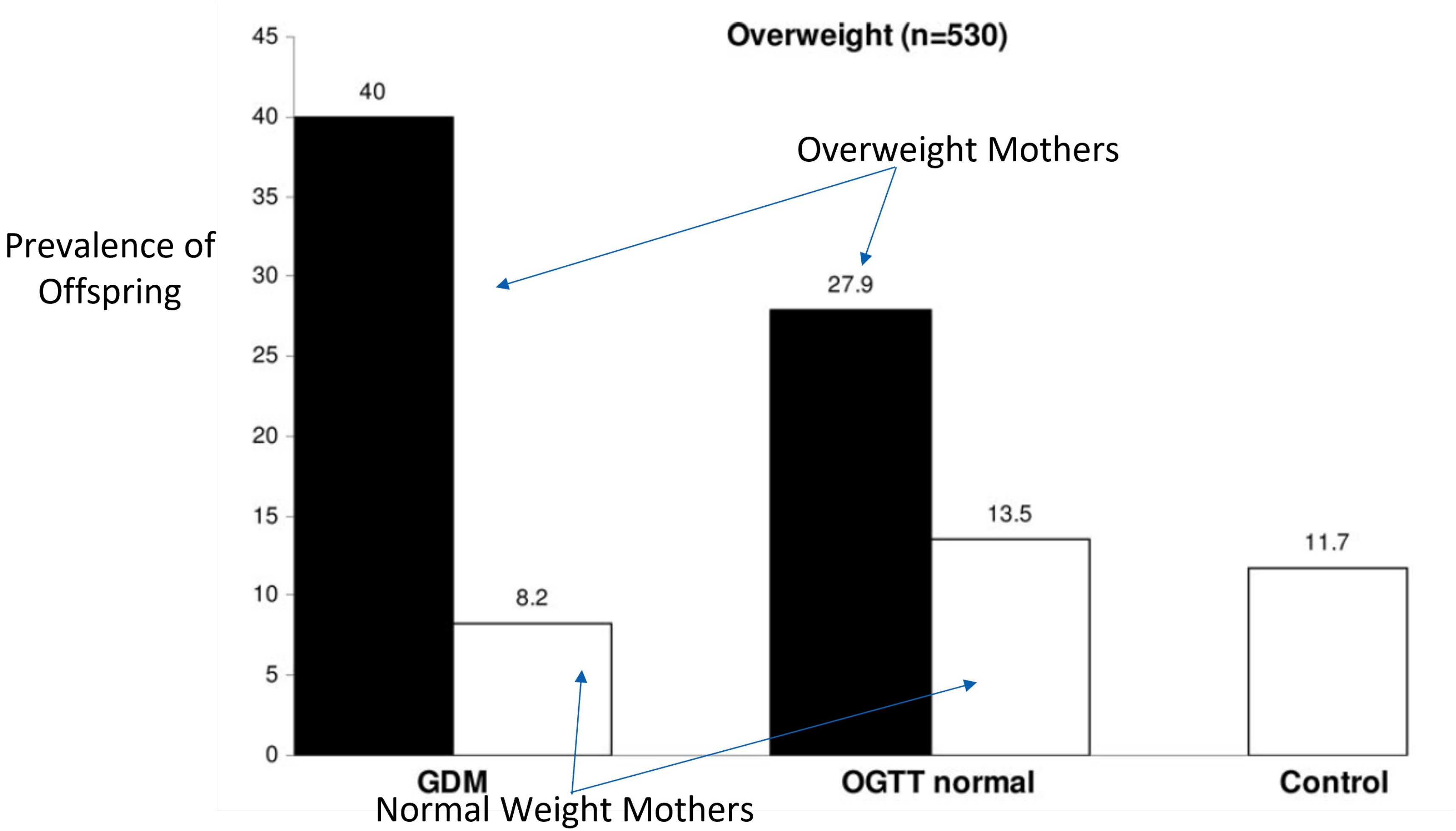
Progeny Wt Gain of Wistar Rat Moms Fed a High Fat Diet
Guo and Jen. Physiol Behav. 1995;681-6.





Increased Prevalence of Offspring Overweight at Age 16 From Overweight Women and GDM

Pirkola, et al. Diabetes Care. 2010. 33: 1115-21.



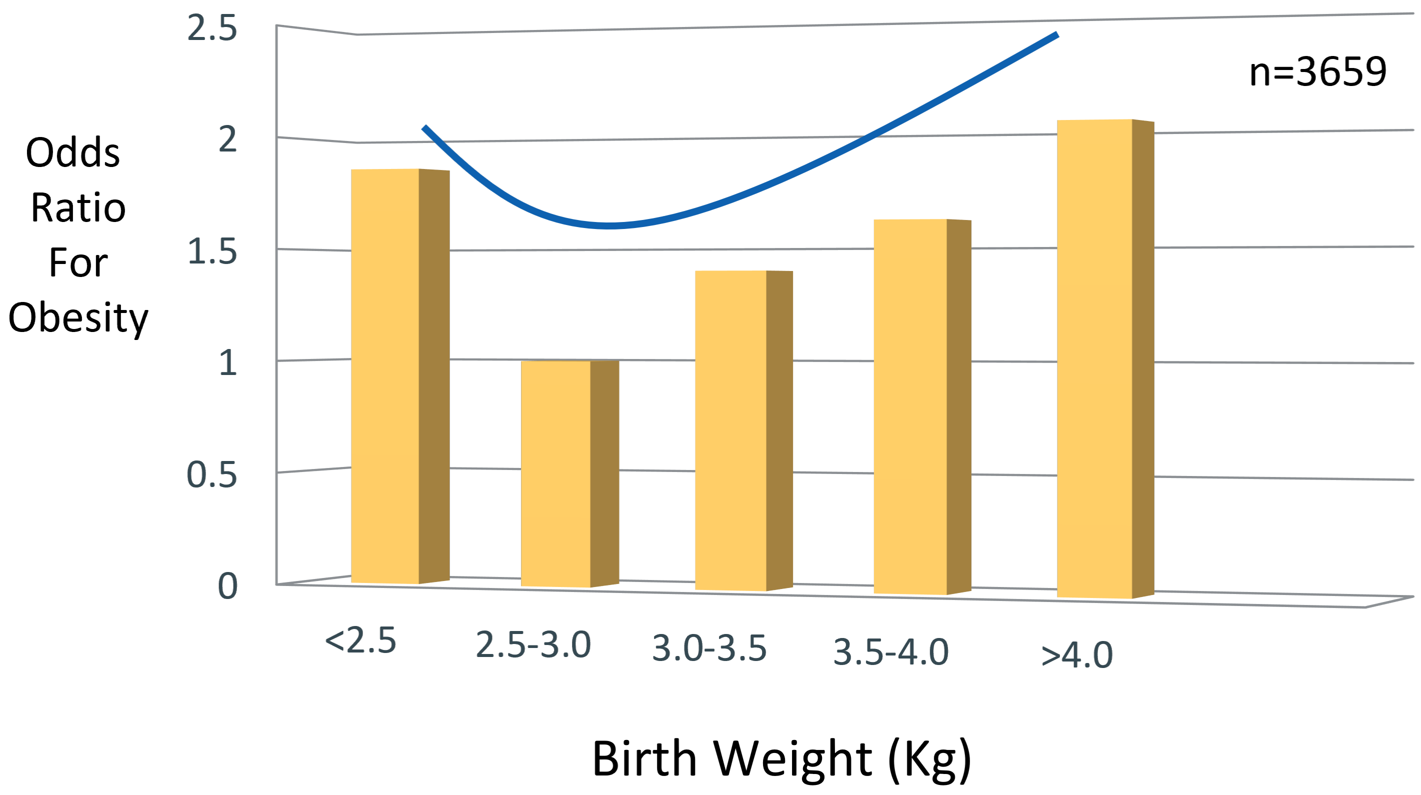
Maternal Glycemia and Offspring Obesity At Age 5 – 7 Years

Hillier, et al. Diabetes Care. 30:2287–2292, 2007.

Maternal glucose scale with screening for GDM by GCT and OGTT	*n*	Child's weight >95th percentile*	
		Prevalence (%)†	OR (95% CI)‡§
Women with normal GCT (quartiles)	7,609		
43–94 mg/dl	1,987	10.3	Reference
95–108 mg/dl	1,953	12.0	1.15 (0.92–1.44)
109–121 mg/dl	1,801	13.4	1.20 (0.96–1.50)
122–140 mg/dl	1,868	13.2	**1.28 (1.02–1.60)**
Women with GCT/OGTT	9,439		

Birth Size and Obesity in Adult Life: Trouble at Both Ends of the Birth Weight Spectrum

Eriksson, et al. IJO. 2001. 25:735-740.

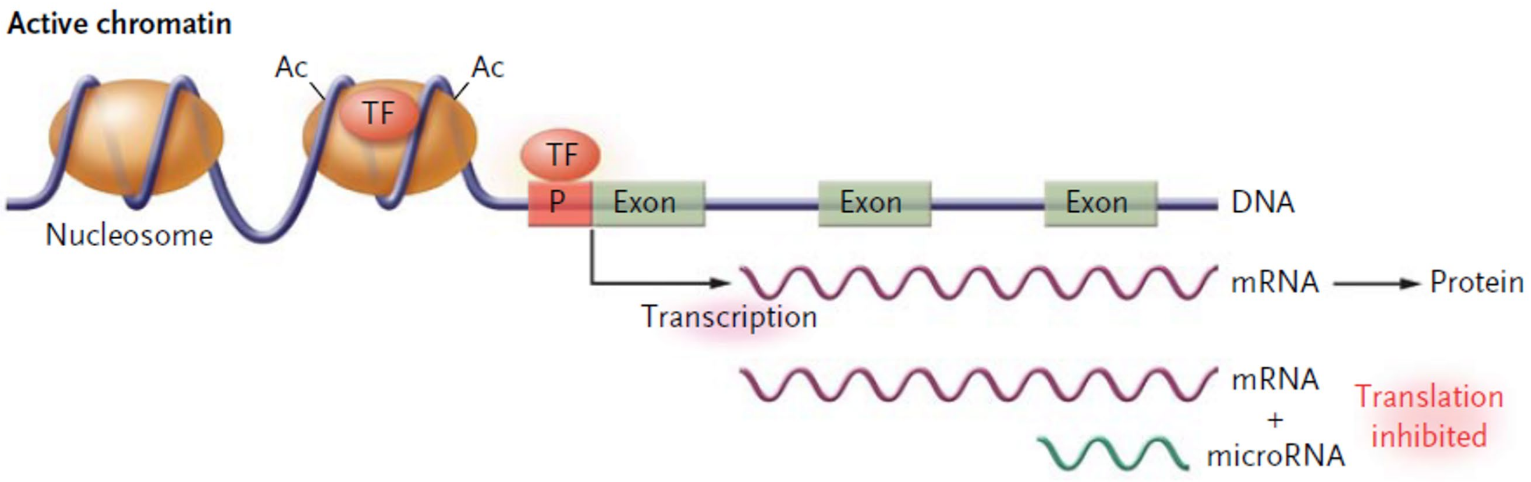


Early Life Programming of Diabetes and Obesity:

Mechanisms

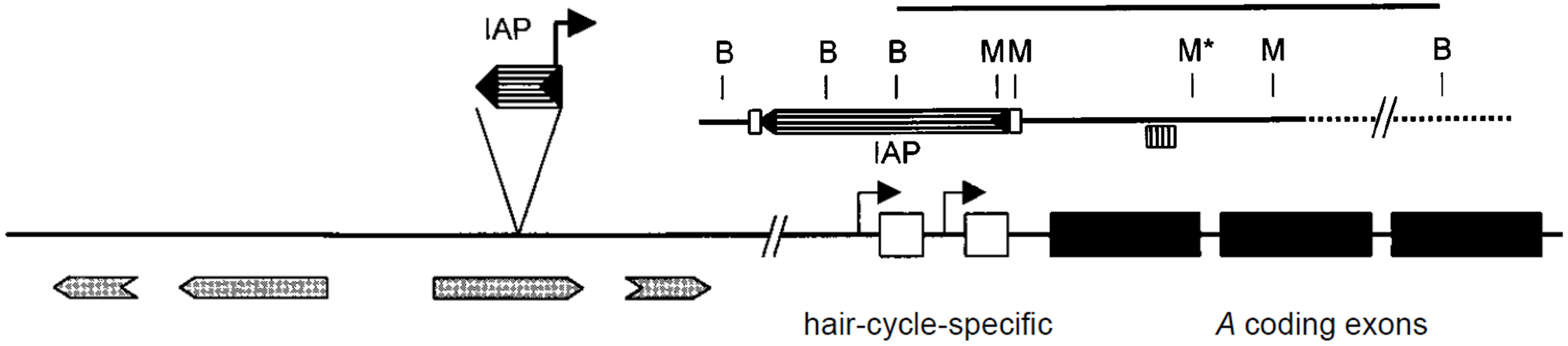
Effect of In Utero and Early-Life Conditions on Adult Health and Disease: Epigenetics

Gluckman, et al. NEJM. 2008;359:61-73.



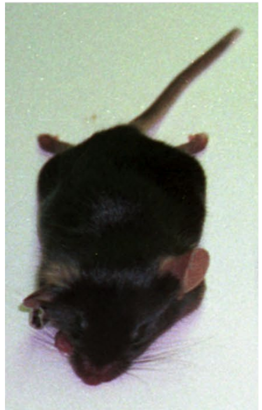
Epigenetic inheritance at the agouti locus in mice.

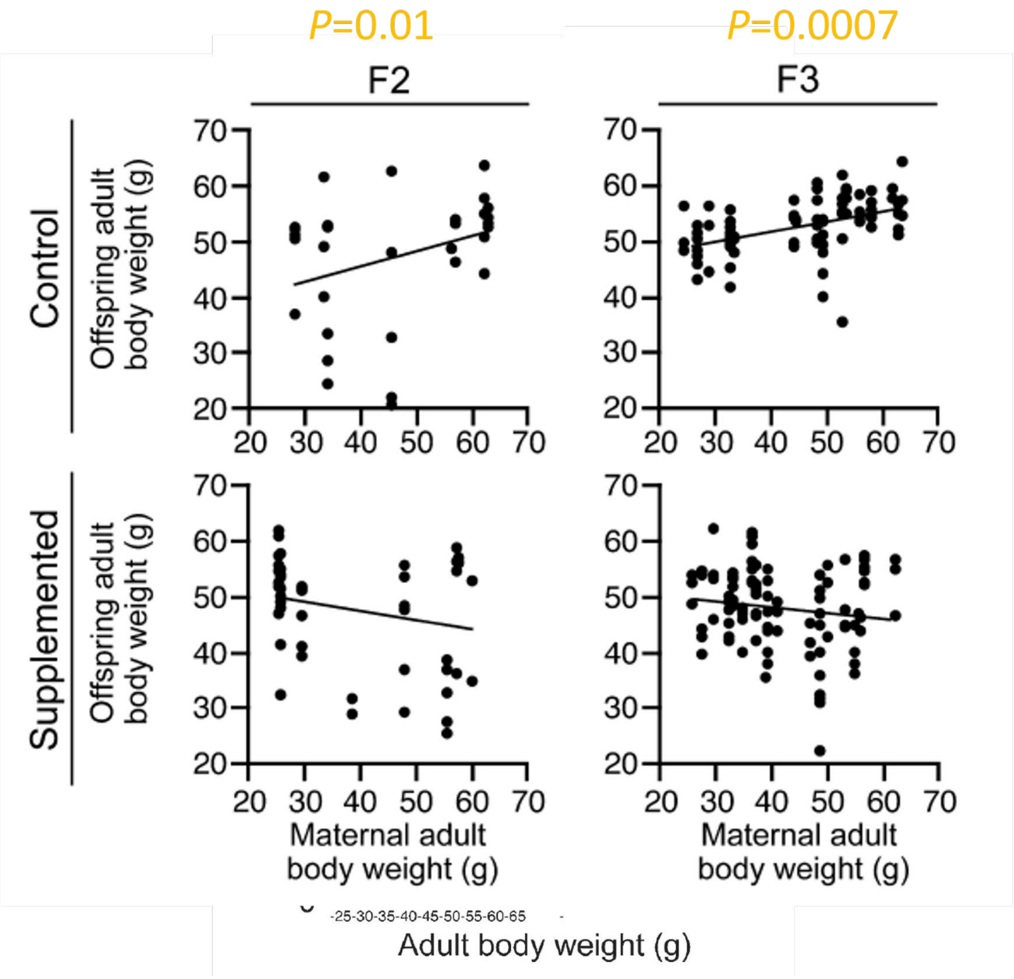
Morgan, et al. Nat Genetics. 1999.



Transgenerational Obesity Phenotype of Agouti Mouse is Modified by Methyl Supplemented Diet

Waterland, et al. IJO. 2008. 32:1373-79.





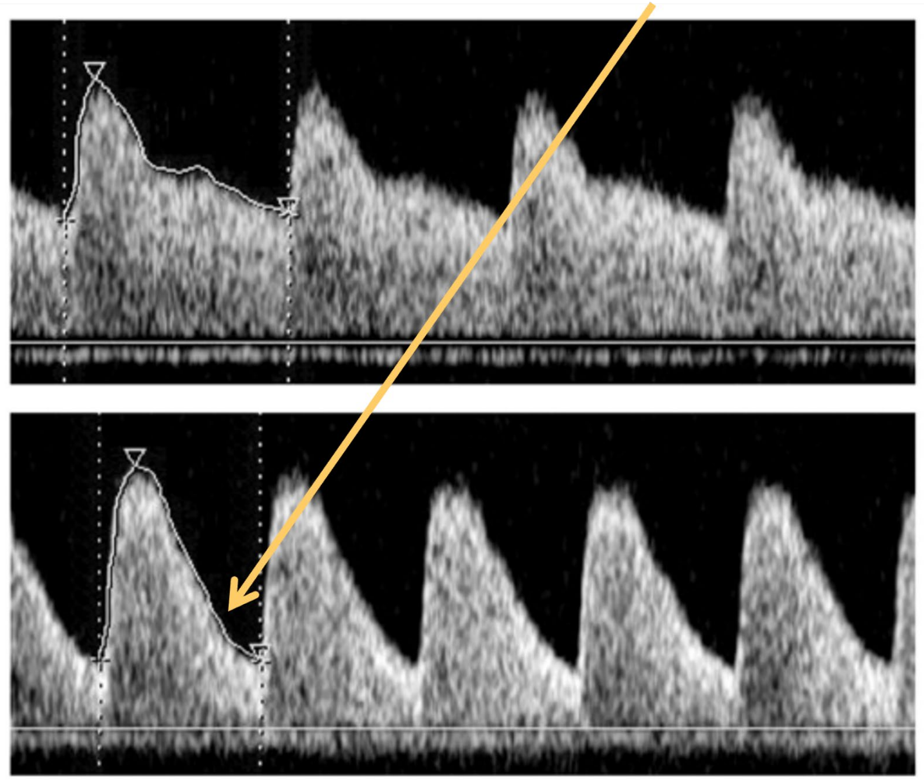
Early Life Programming of Diabetes and Obesity:

Placental Health

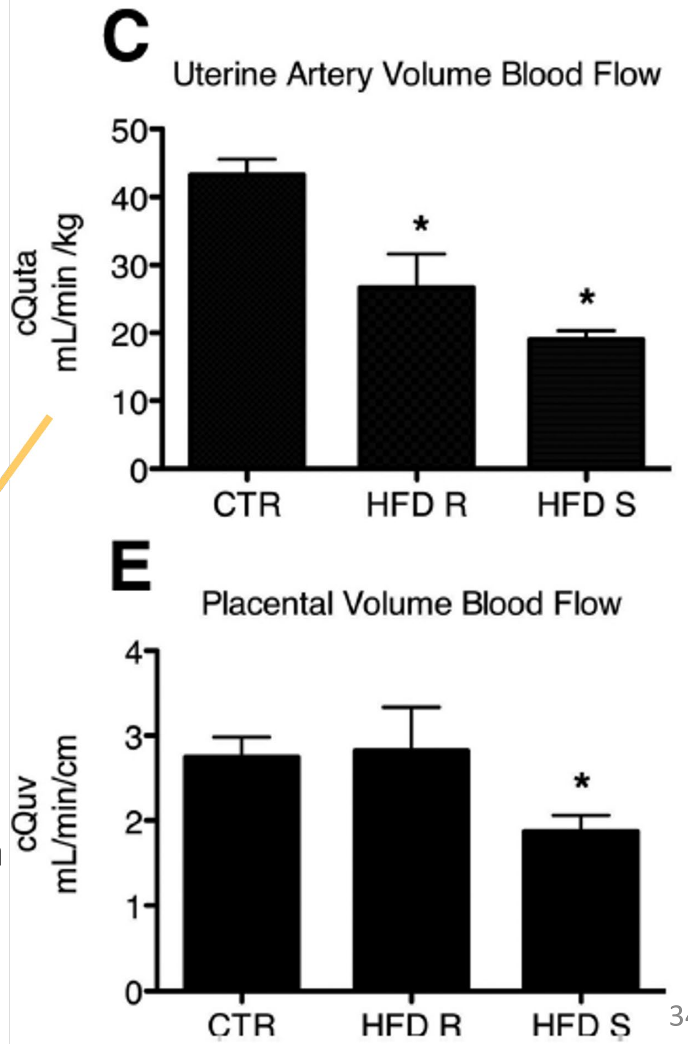
High Fat Diet Impairs Placental Health in Primates

Frias, et al. Endocrinology 152: 2456–2464, 2011

Increased Vascular Impedance.
Reduced Diastolic Flow



↑ Placental infarctions
↑ Placental inflammation



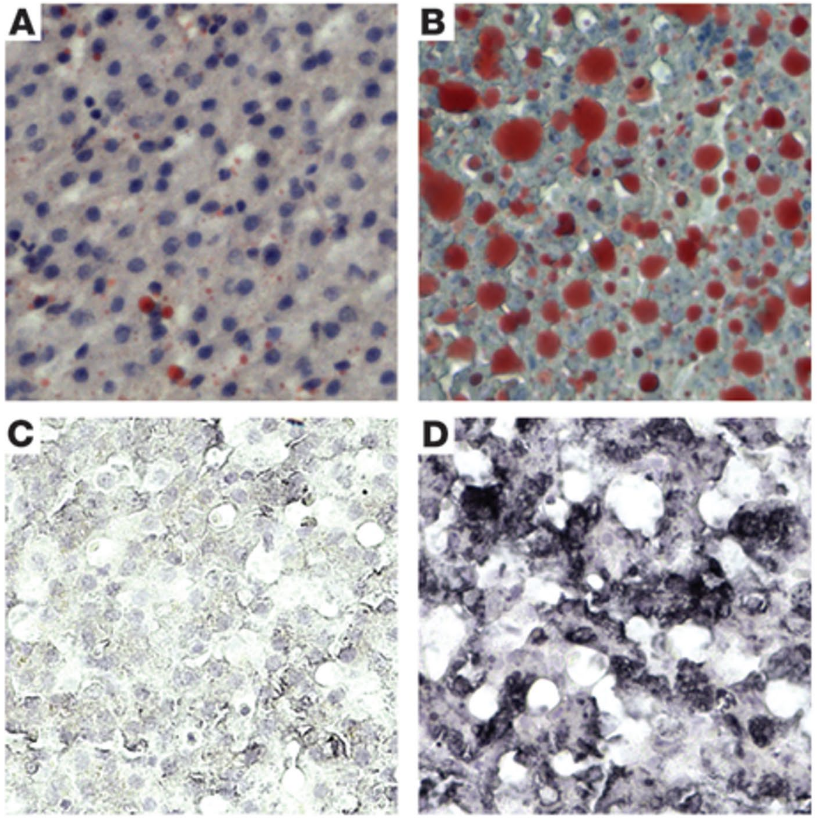
Early Life Programming of Diabetes and Obesity:

Inflammation

Fetal Liver Fat Accumulation/Lipotoxicity in Offspring of Monkey Mom’s on Chronic High Fat Diet

McCurdy et al, J Clin Investigation. 2009

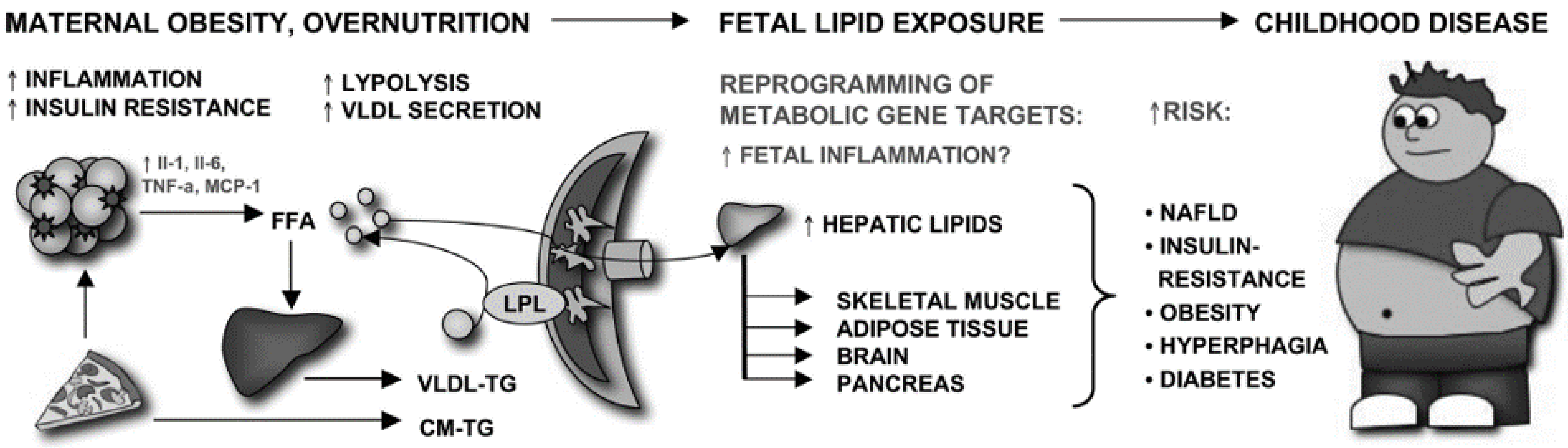
Control High Fat Diet



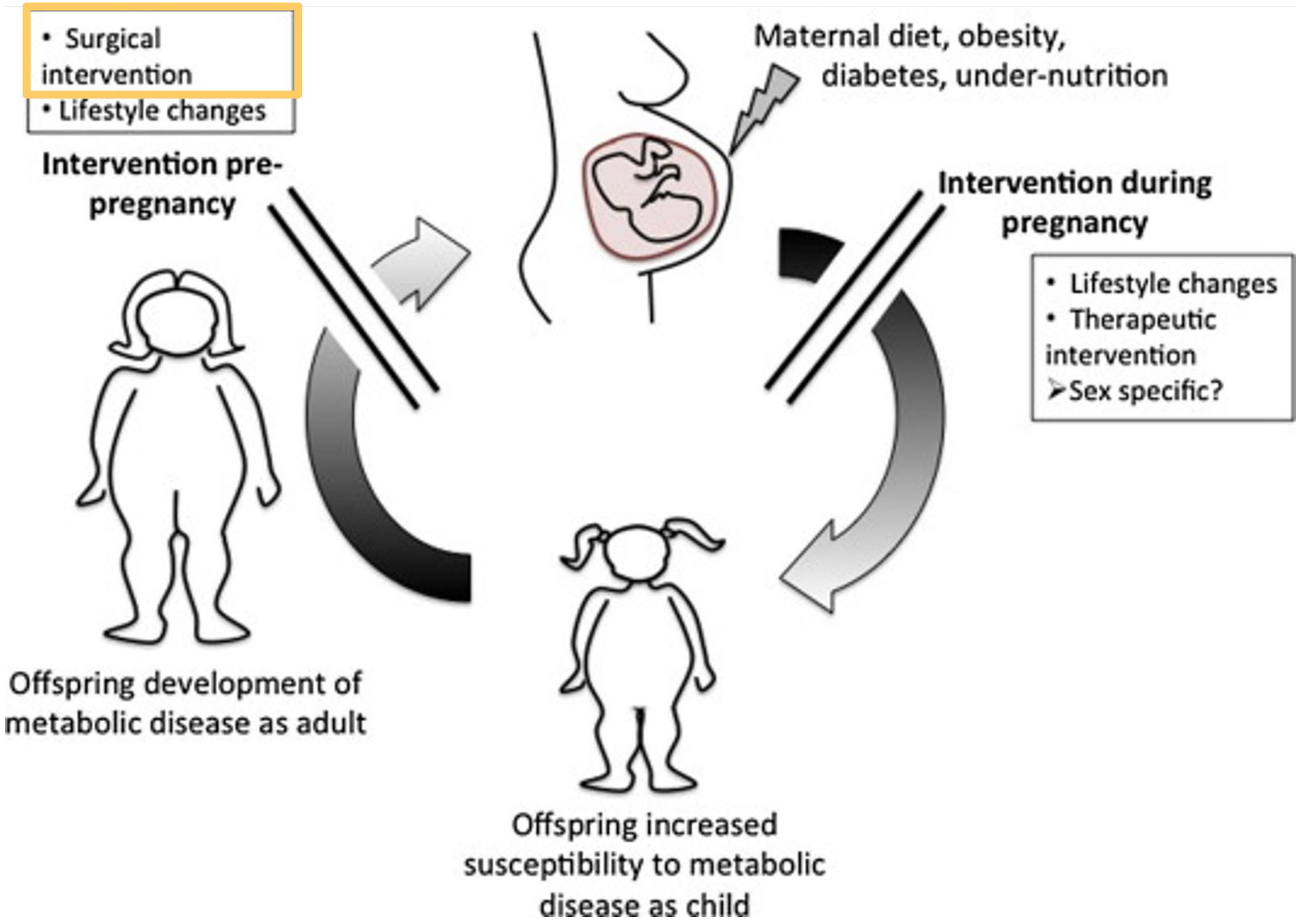
Triglyceride Staining

Oxidative Stress Staining

Maternal Obesity/Overnutrition leading to Childhood Disease



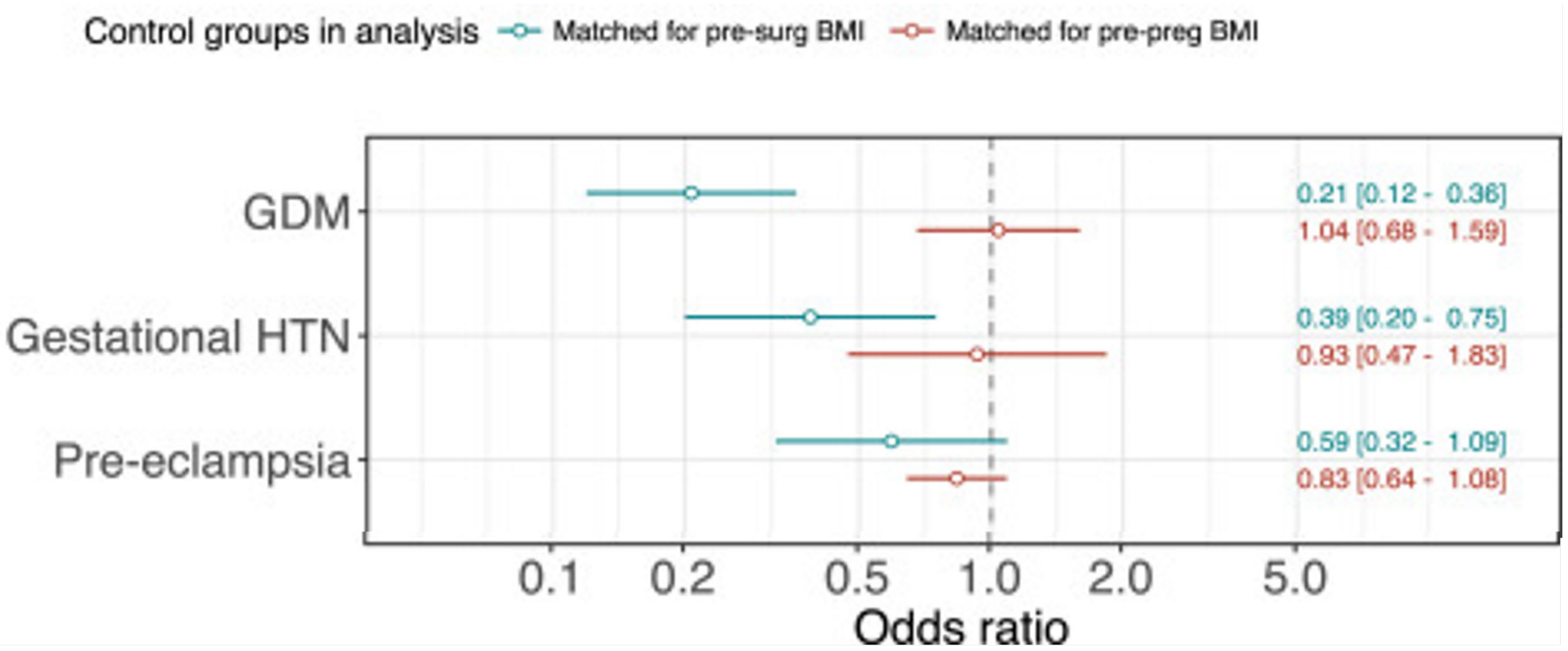
Early Life Programming of Diabetes and Obesity: Effect of Weight Loss



Maternal Fetal Outcomes after Bariatric Surgery – High Blood Pressure and Blood Sugar

Kwong W, et al. AJOG. 2018. 218:573-580

20 cohort studies, ~ 2.8 million subjects,
8364 of whom had bariatric surgery



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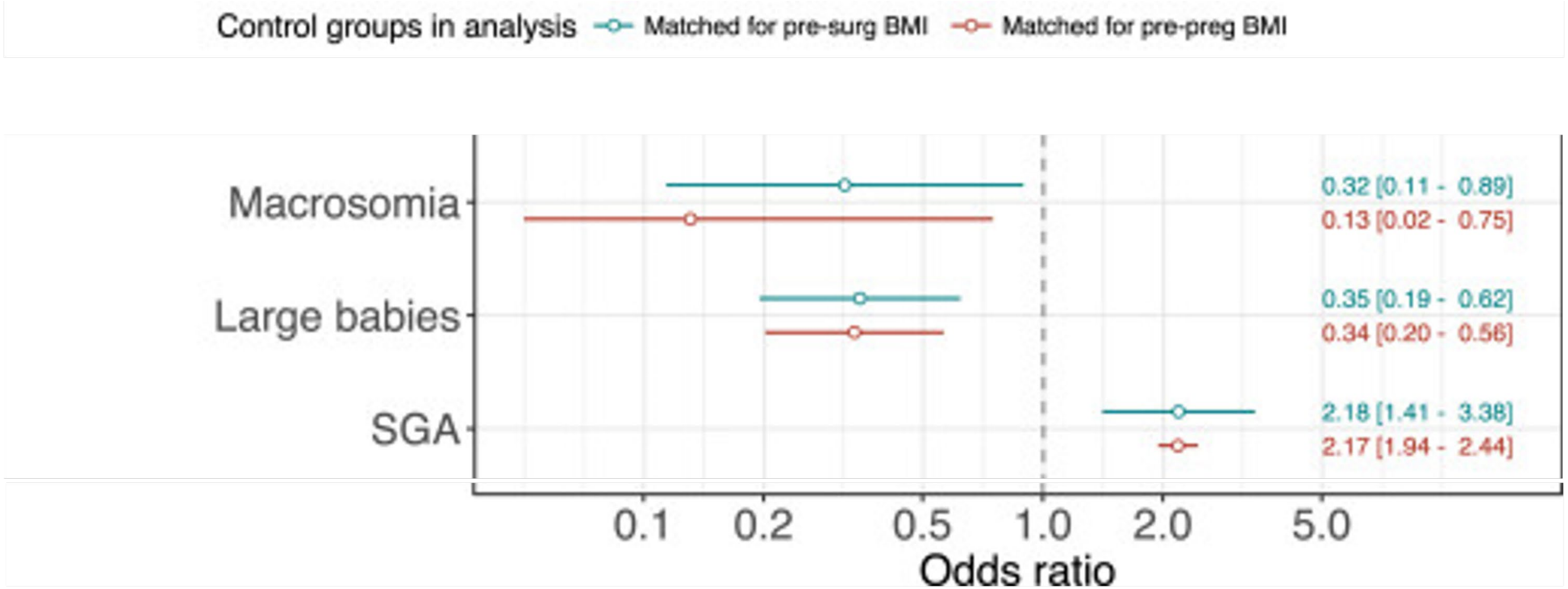
Maternal Fetal Outcomes after Bariatric Surgery – Larger Birth Weights

Kwong W, et al. AJOG. 2018. 218:573-580

20 cohort studies, ~ 2.8 million subjects, 8364 of whom had bariatric surgery



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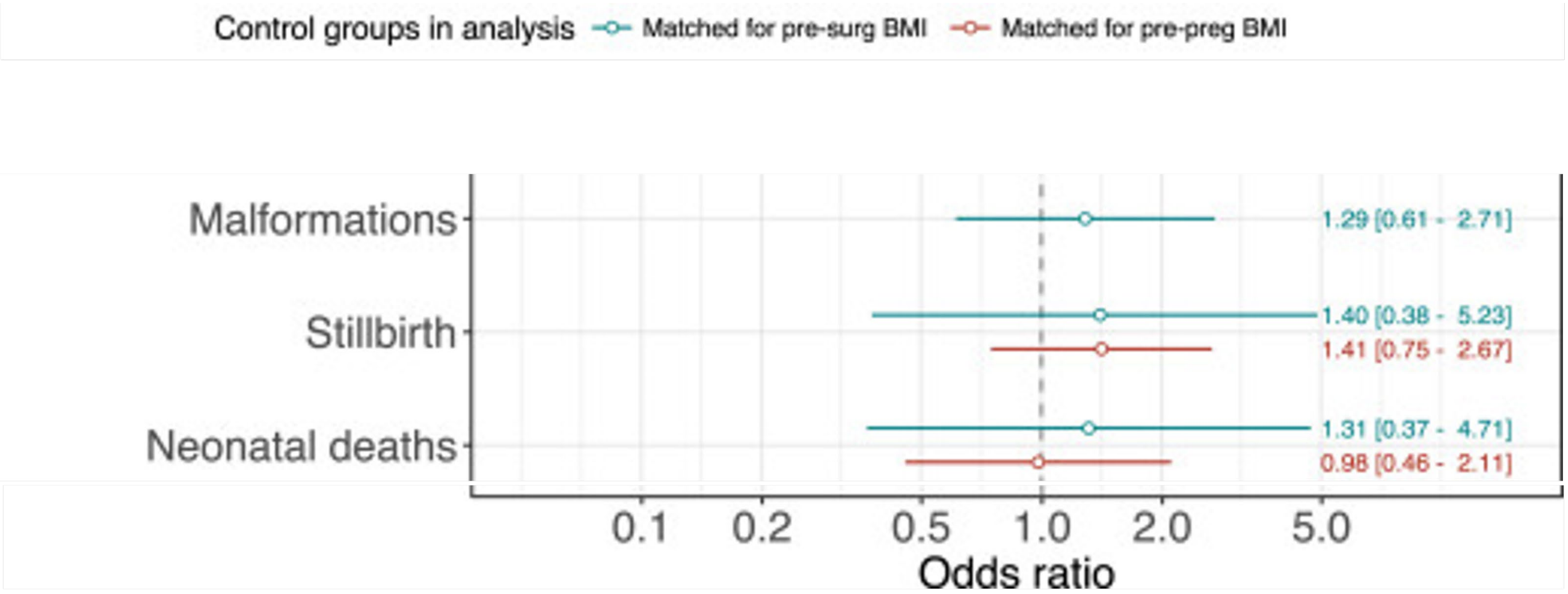
Maternal Fetal Outcomes after Bariatric Surgery – Birth Issues

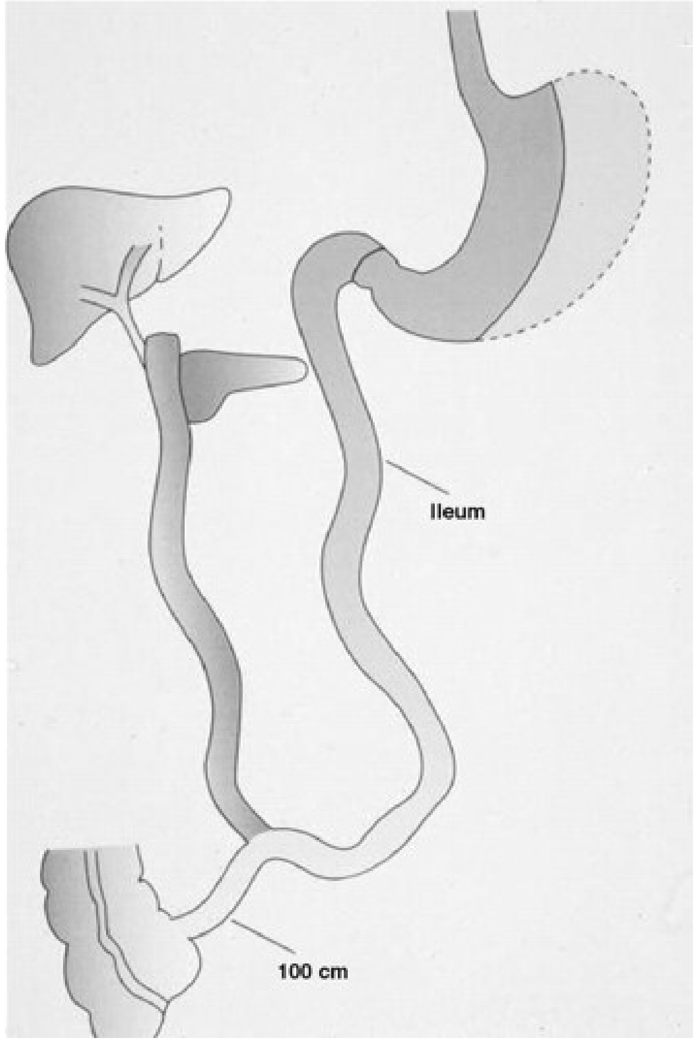
Kwong W, et al. AJOG. 2018. 218:573-580

20 cohort studies, ~ 2.8 million subjects,
8364 of whom had bariatric surgery



Maternal Weight Loss From Biliopancreatic Diversion Prevents Transmission of Obesity to Children

Kral, et al. Pediatrics. 118:e1644-49, 2006.



- N=113 women
- BPD with pylorus-preserving sleeve gastrectomy ("duodenal switch")
- Mean BMI decreased from 48 to 31 kg/m2

Maternal Weight Loss From Biliopancreatic Diversion Prevents Transmission of Obesity to Children (con't)

Kral, et al. Pediatrics. 118:e1644-49, 2006.

Weight Group	Before BPD (n = 45)	After BPD (n = 172)	Change
Normal weight, n (%)	16 (36)	98 (57*)	Increase
Overweight, n (%)[a]	9 (20)	28 (16)	Decrease
Obese, n (%)[b]	18 (40)	33 (19)	Decrease
Severe Obese, n (%)[c]	11 (24)	23 (13)	Decrease
Underweight, n (%)	2 (4.4)	13 (7.5)	Level

[a] Overweight + obese among BMS versus AMS: $P = 0.006$.
[b] Obese among BMS versus AMS: $P = 0.005$.
[c] Severe obese among BMS versus AMS: $P = 0.04$
* Same as general population.

Summary

- Both maternal undernutrition (low birth weight) and over (mal) nutrition (increased birth rate) contribute to increased risk for obesity and diabetes.
- Evidence supports independent effects of both body weight and maternal diet on offspring risk.
- Proposed mechanisms include
  - Metabolic programming
  - Epigenetics
  - Altered placental health
  - Inflammatory mediators
- Implications are for a “feed forward,” transgenerational potentiation of obesity and T2DM.
- Preliminary data support benefits of maternal weight loss.