Obesity in SMS:
Causes and Strategies for Treatment

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Disclosures

This presentation discusses the use of off-label medications

I have done speaking and consulting work for Rhythm Pharmaceuticals

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Overview

- What we know
- Where we are
- Where we might be going

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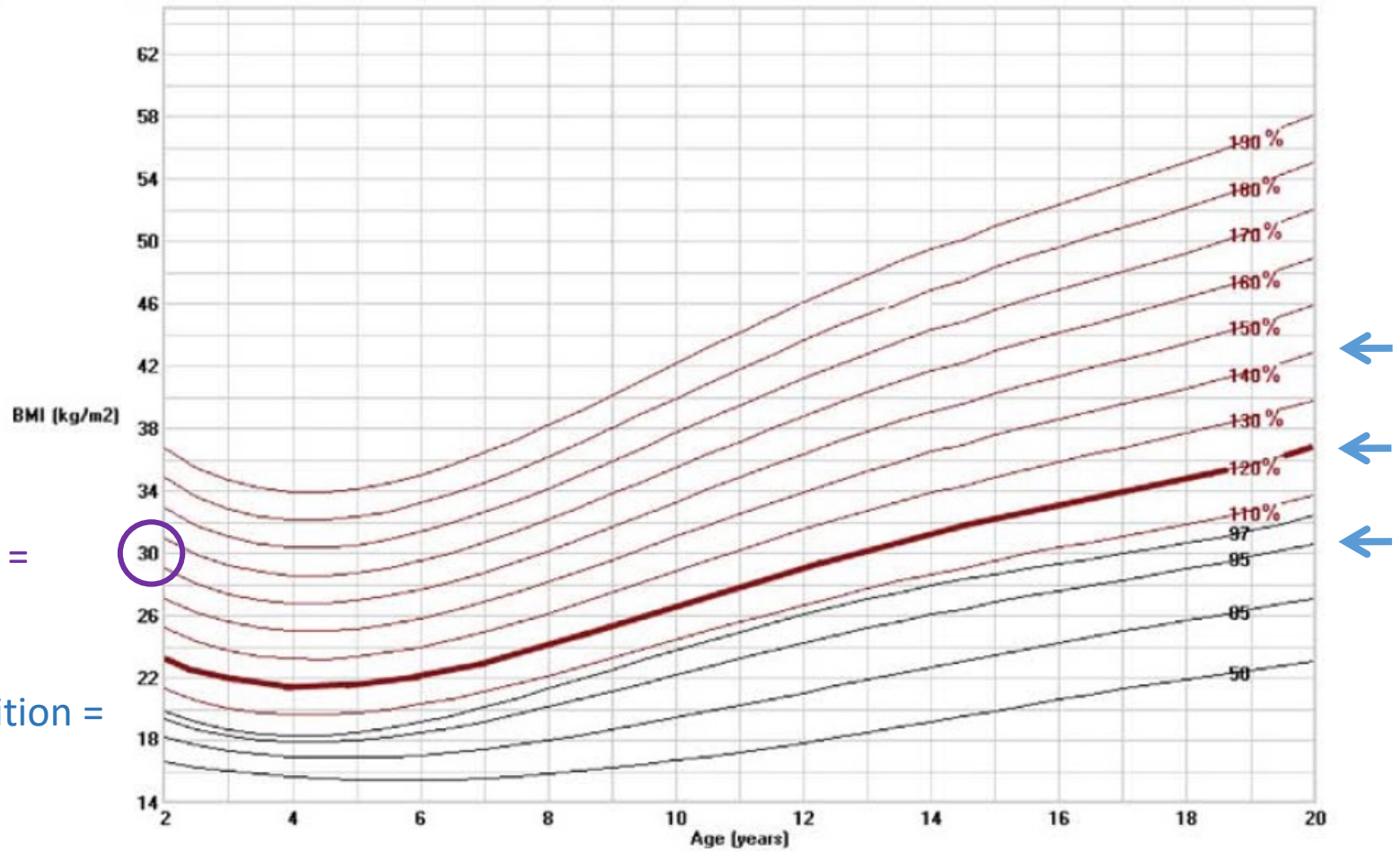
What We Know

The Definition of Obesity



Adult Definition =
BMI ≥ 30

Pediatrics Definition =
BMI ≥ 95%ile

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Why Do We Care?

Sanyaolu,A et al. *Global Health Pediatrics*. 2019

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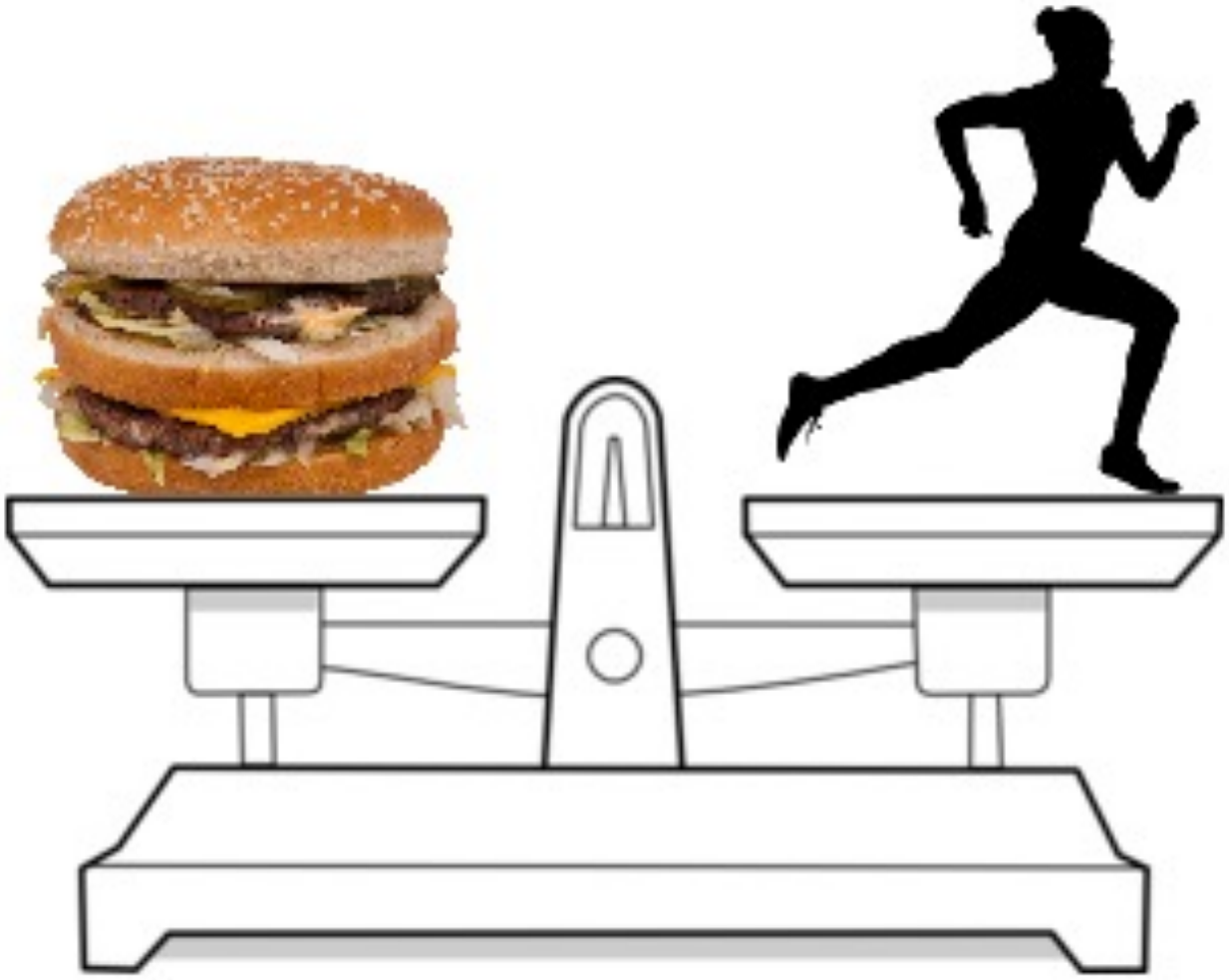
The Common Belief for Obesity Causes



https://conscienhealth.org/2016/08/unsubstantiated-nonsense-energy-balance/

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A Simplified View of Obesity Causes

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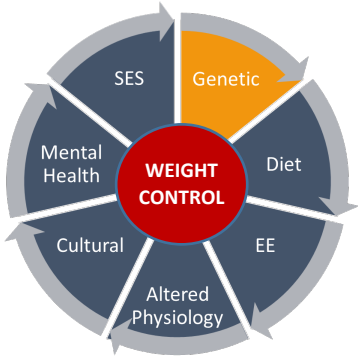
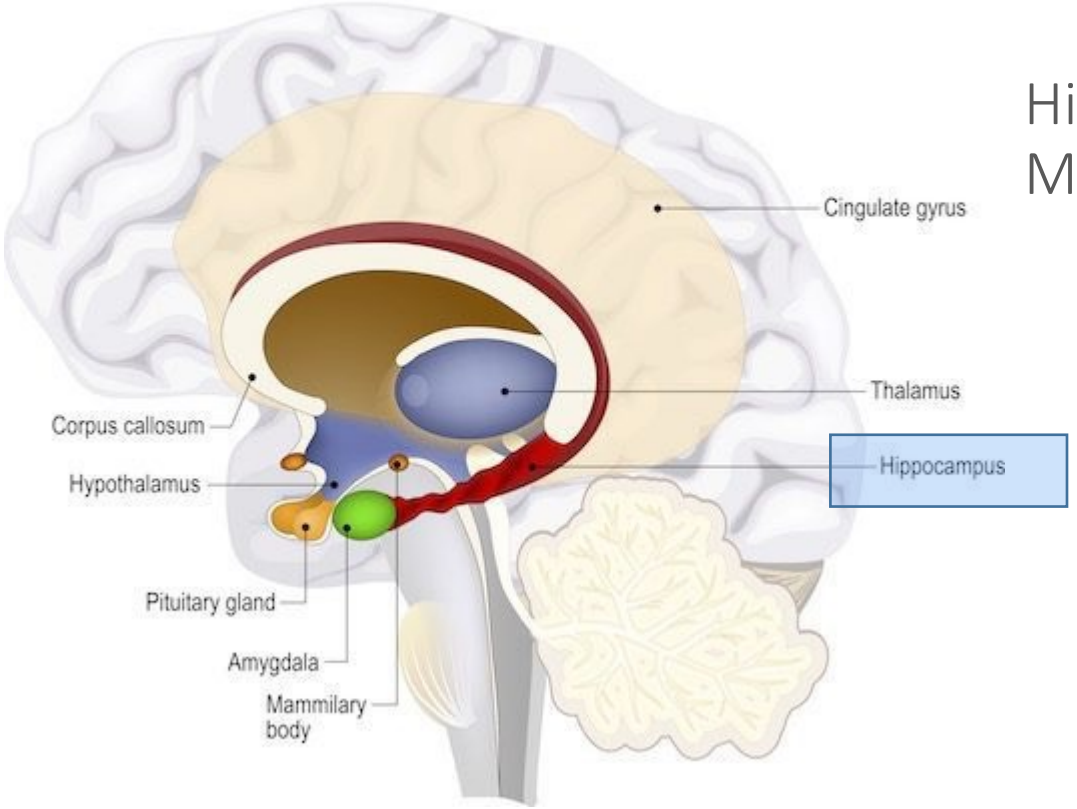
SMS, *RAI1*, and Obesity





Hippocampus - Memory

https://brainmd.com/blog/what-is-the-hippocampus-and-how-to-protect-memory/; Henderson et al. *Hippocampus*. 2013

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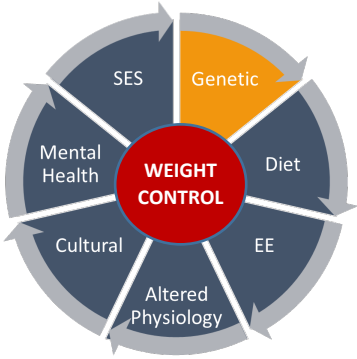
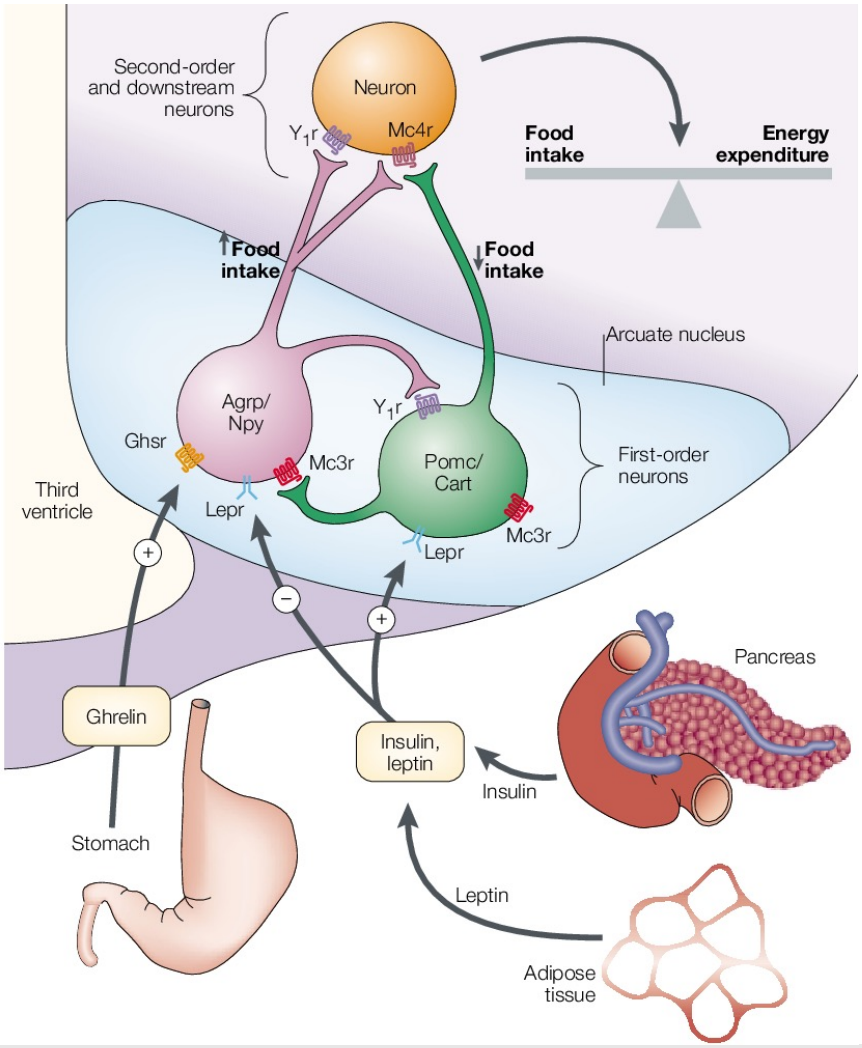
Influences on Satiety Hormones





Decreased production of *bdnf* leads to decreased *pomc*

Barsh, G & Schwartz, M. *Nature Reviews Genetics* 2002; Burns, B et. al. *Hum Mol Gen*. 2010

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Epigenetics Contributes to Obesity

Illustration by Bill Day http://www.urbanchildinstitute.org adapted from Waterland, RA *Moleculary and Cellular Biology* 2003

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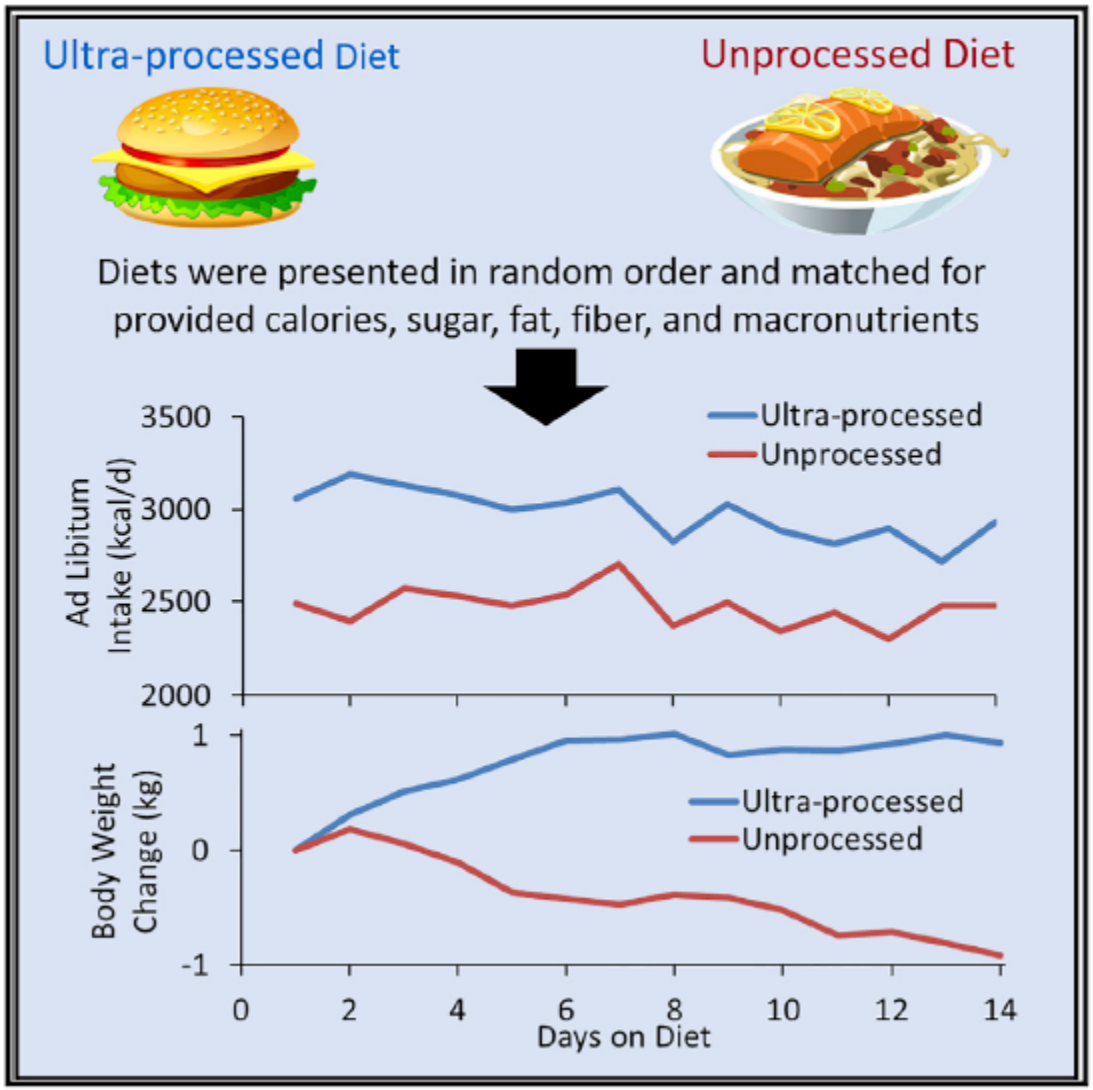
Processed Foods and Weight Gain



Hall *Cell Metab* 2019

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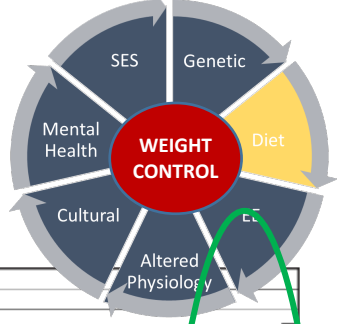
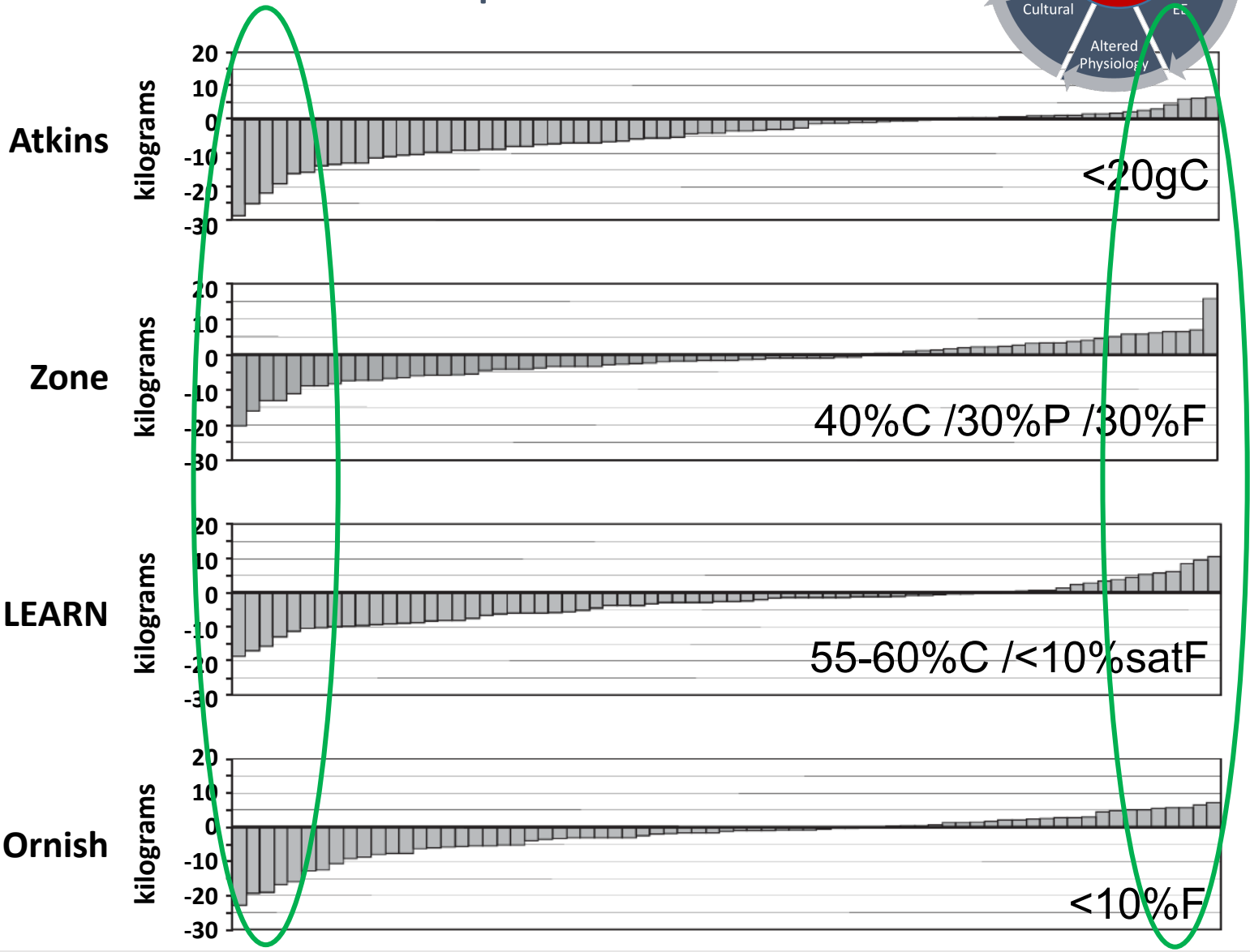
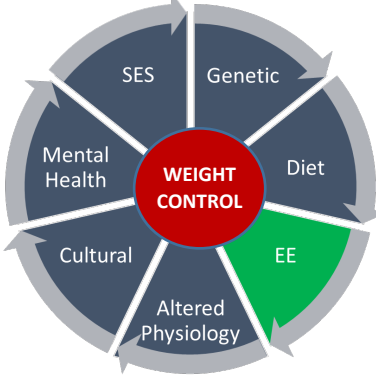
Variable Response to Diet

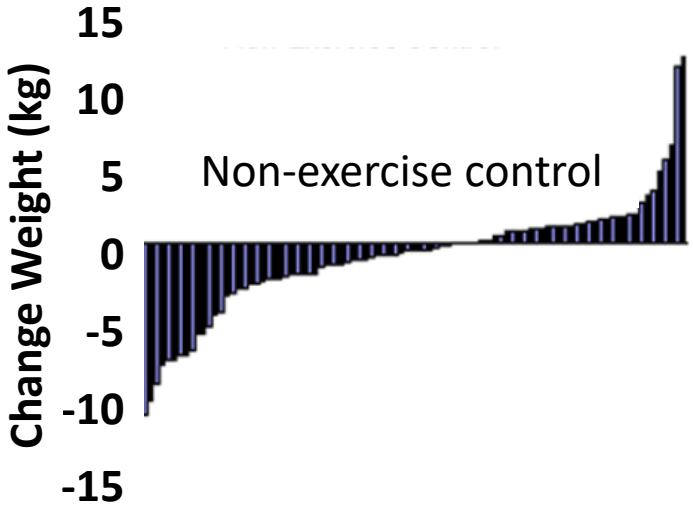


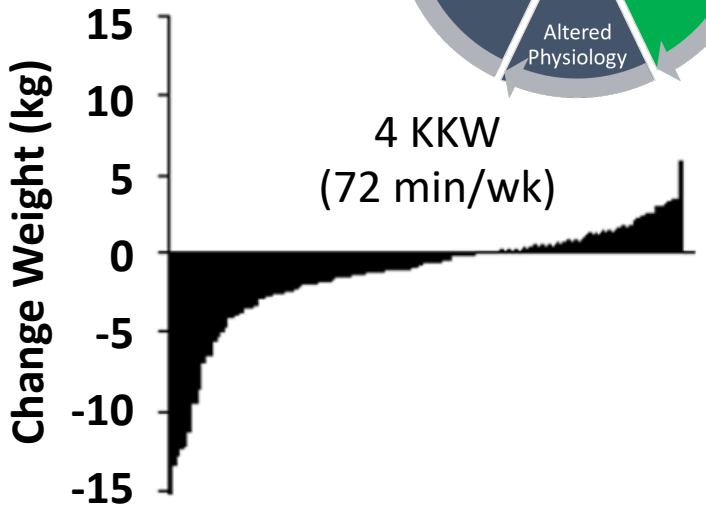


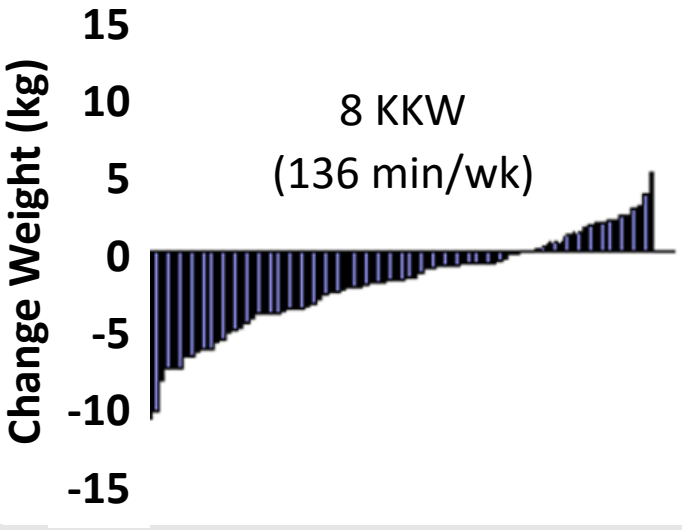
Gardner, CD. IJO. 2012

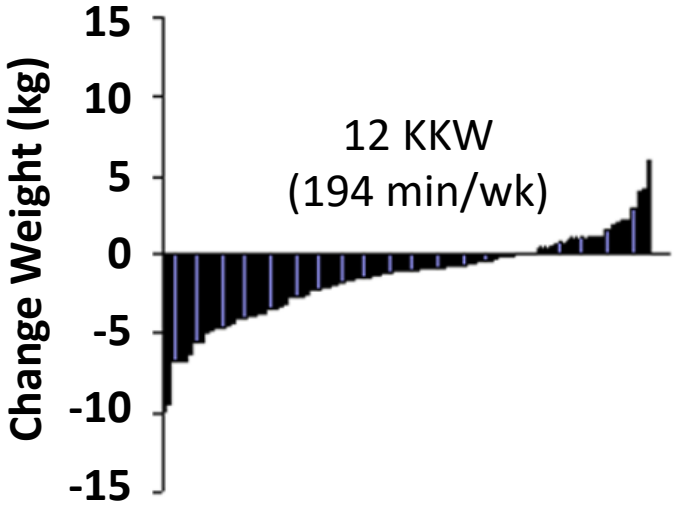
Variable Response to Exercise











Church, TS. PLoS One 2009

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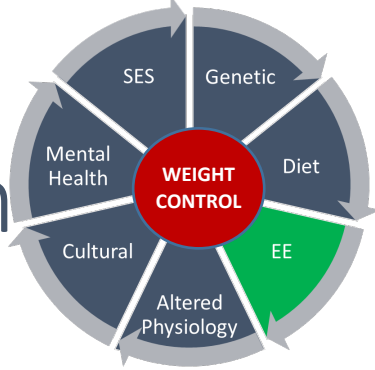
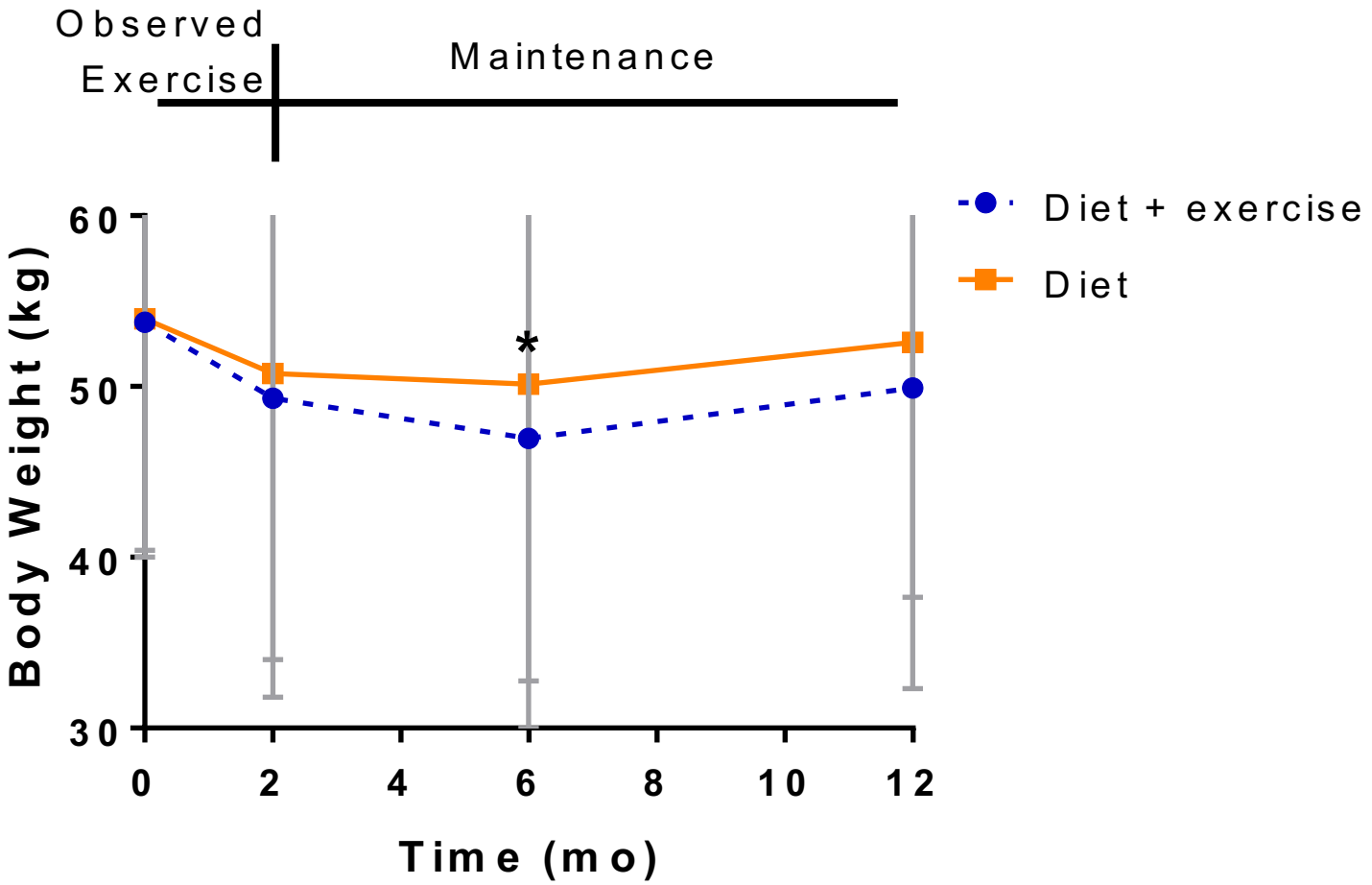
Exercise Effects in Children





Epstein J Pediatrics 1985

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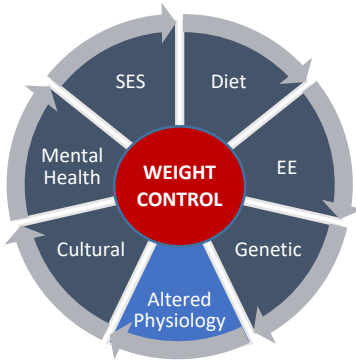
Altered Physiology and Obesity



- Disease Processes: Cushing's, Hypothyroidism, Puberty
- Environmental causes
- Iatrogenic: Insulin, steroids, anticonvulsants, antipsychotics

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Relationship Between Medications and Weight in SMS

↑ Maladaptive food behaviors in

- Individuals with overweight/obesity
- Individuals on anti-anxiety/depressant medications

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Resource for Medications

https://www.obesityaction.org/resources/prescription-medications-weight-gain/

Drug Class/Type (and Potential Related Weight Gain)	Common Name	Proprietary or Brand Name	Alternative Drugs (Weight neutral or may promote weight-loss)
Diabetes Therapies (may cause up to 8 kg weight gain in an intensive 3-month treatment course)			
Insulin	insulin lispro insulin aspart insulin glulisine	Humalog® Novolog® Apidra®	metformin (Glucophage®, Glucophage® XR, Fortamet®, Glumetza®, Riomet®, generics)
Thiazolidinediones (TZDs)	pioglitazone	Actos®	Linagliptin (Tradjenta®) saxagliptin (Onglyza®) sitagliptin (Januvia®) exenatide(Byetta®) Liraglutide (Victoza®) acarbose (Prandase®, Precose®) miglitol (Glyset®) *These combination products tend to have fewer side-effects and less weight gain:* metformin/pioglitazone (Actoplus Met®) glipizide/metformin (Metaglip®) glyburide/metformin (Glucovance®) glimepiride
Sulfonylureas (SUs) *usually ≤5 kg gain during 3-12 months of treatment*	glipizide glyburide glimepiride chlorpropamide tolbutamide	Glucotrol® Glucotrol® XL Diabeta® Micronase® Glynase® Amaryl®` Diabinese® generics	

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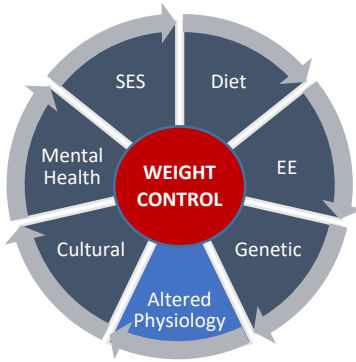
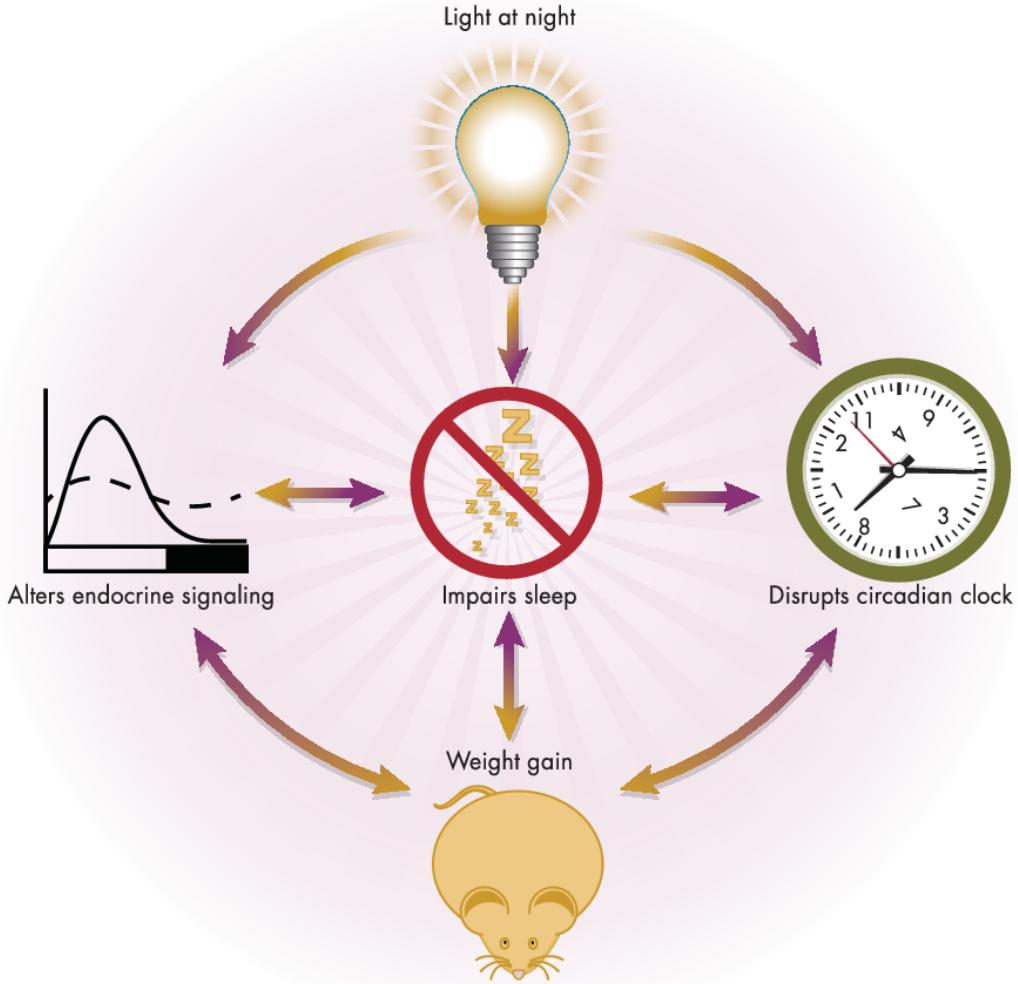
Circadian Rhythm Disruption and Weight





Fonken & Nelson. *End Rev*. 2014

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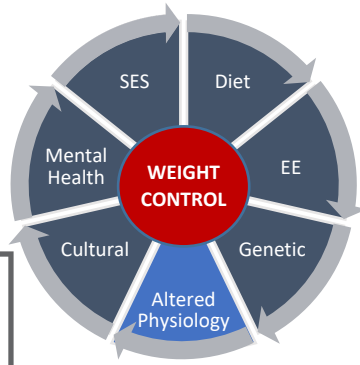
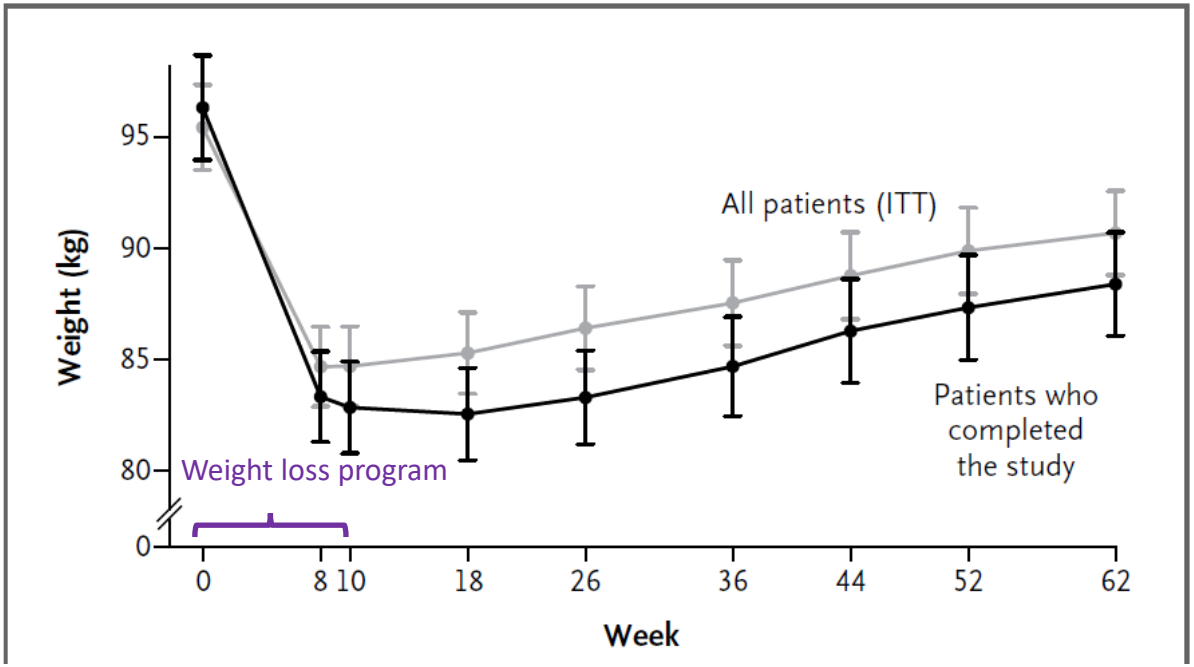
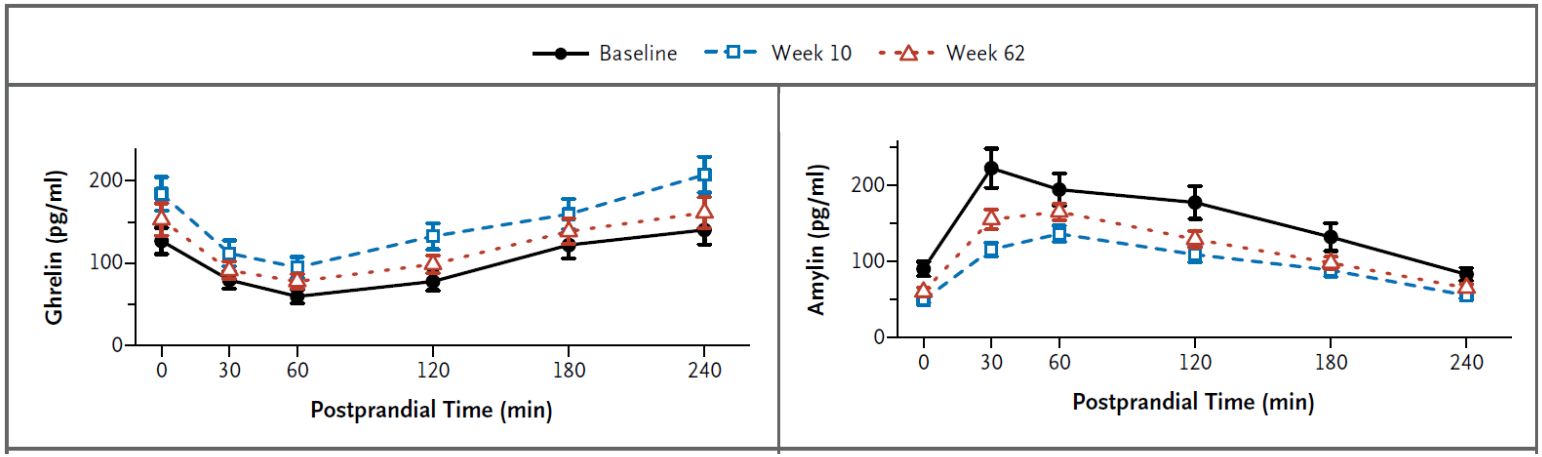
The Body Fights Back







Sumithran *NEJM* 2011

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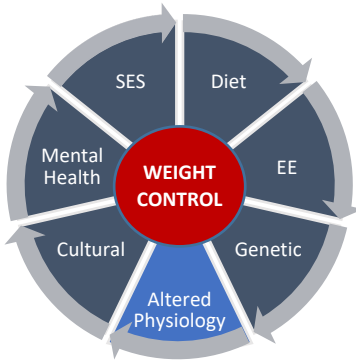
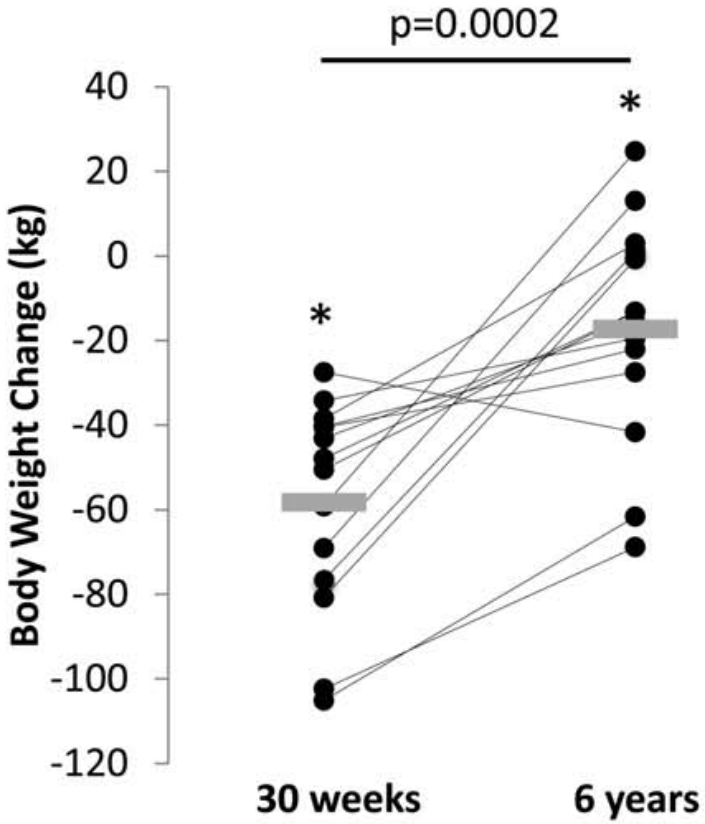
Adaptation to Weight Loss





Fothergill, E et al. *Obesity* 2016

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Other Influences

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Where We Are

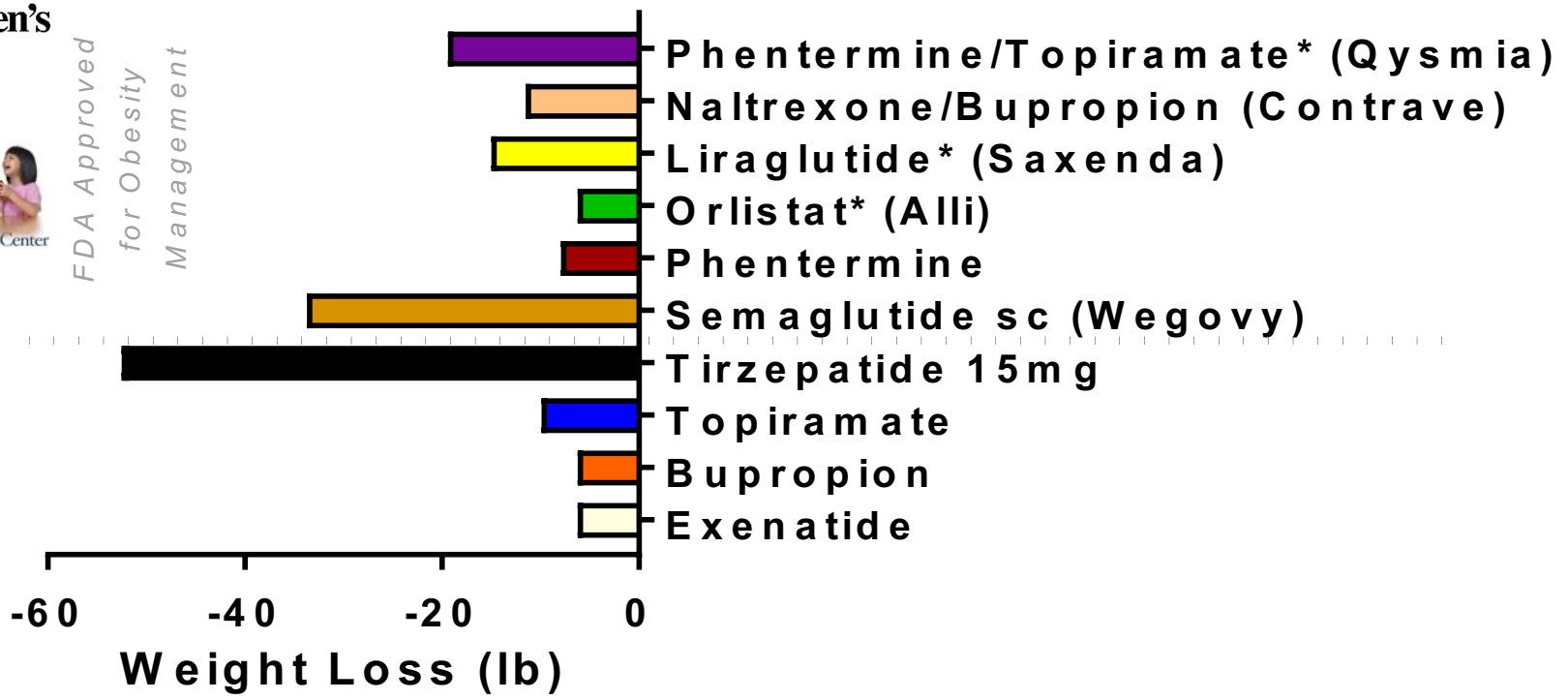
When to Use Pharmacotherapy

	Adult	Pediatric
No comorbidity	BMI ≥ 30	BMI ≥ 120% of 95th%ile or BMI ≥ 35
With comorbidity	BMI ≥ 27	BMI ≥ 95th %ile or BMI ≥ 30

- Failure of lifestyle therapies
- Long term use if ≥ 5% BMI reduction after 12 weeks

Srivastava *Obesity* 2019

Effects of Pharmacotherapy



Adapted from Jastrebof, A. *NEJM* 2022; Wilding J. et al. NEJM 2021; Butch, S ABOM course 2016

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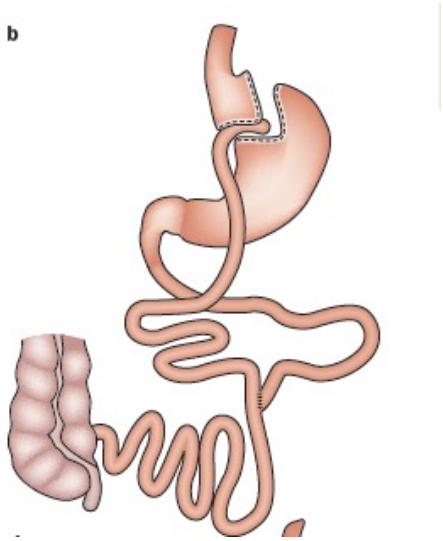
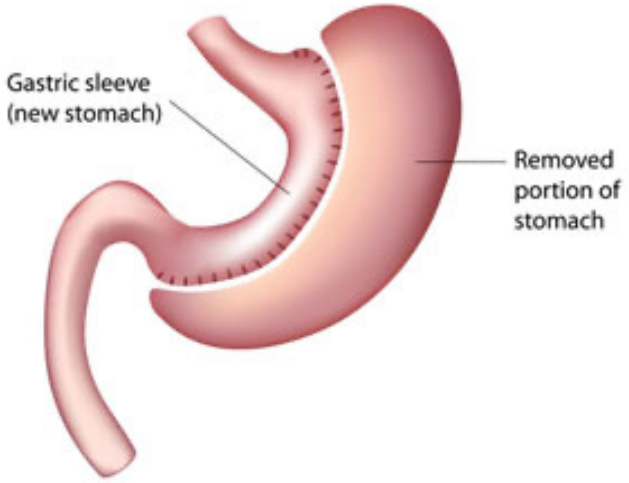
Metabolic Surgery

Roux-en Y (RYGB or "Gastric bypass")



Vertical Sleeve Gastrectomy (VSG or "sleeve")



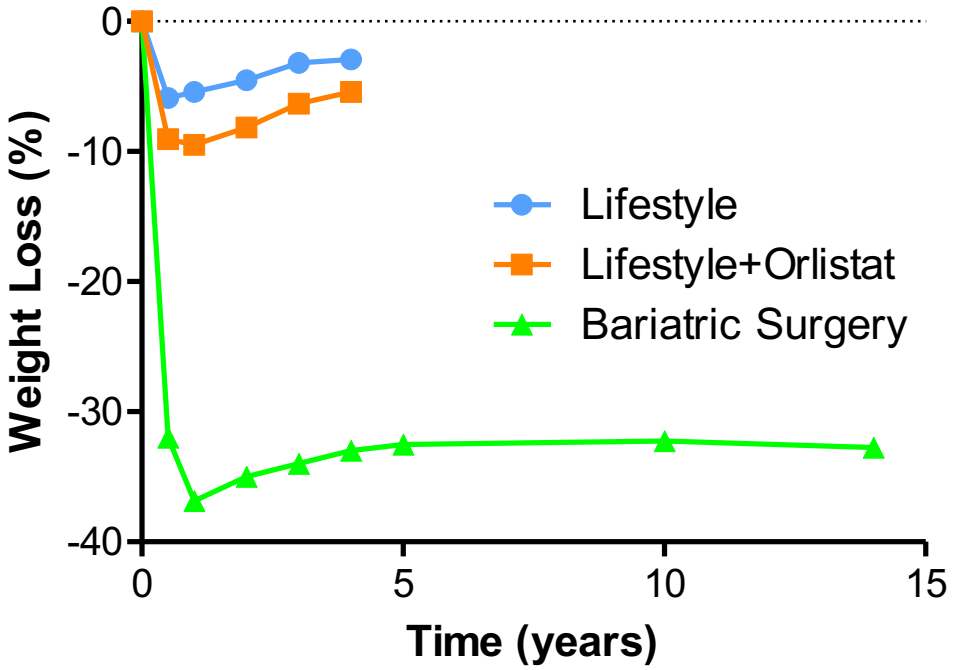
Brandt M. *Nat Rev Endocrinol* 2010;6:637

Effect of Metabolic Surgery

Diet and exercise

Drug therapy

Bariatric surgery



Adapted from Pories et al., *Ann Surg* 1995; and Torgerson et al., *Diabetes Care* 2004; Slide courtesy of Hiliary Wilson-Perez

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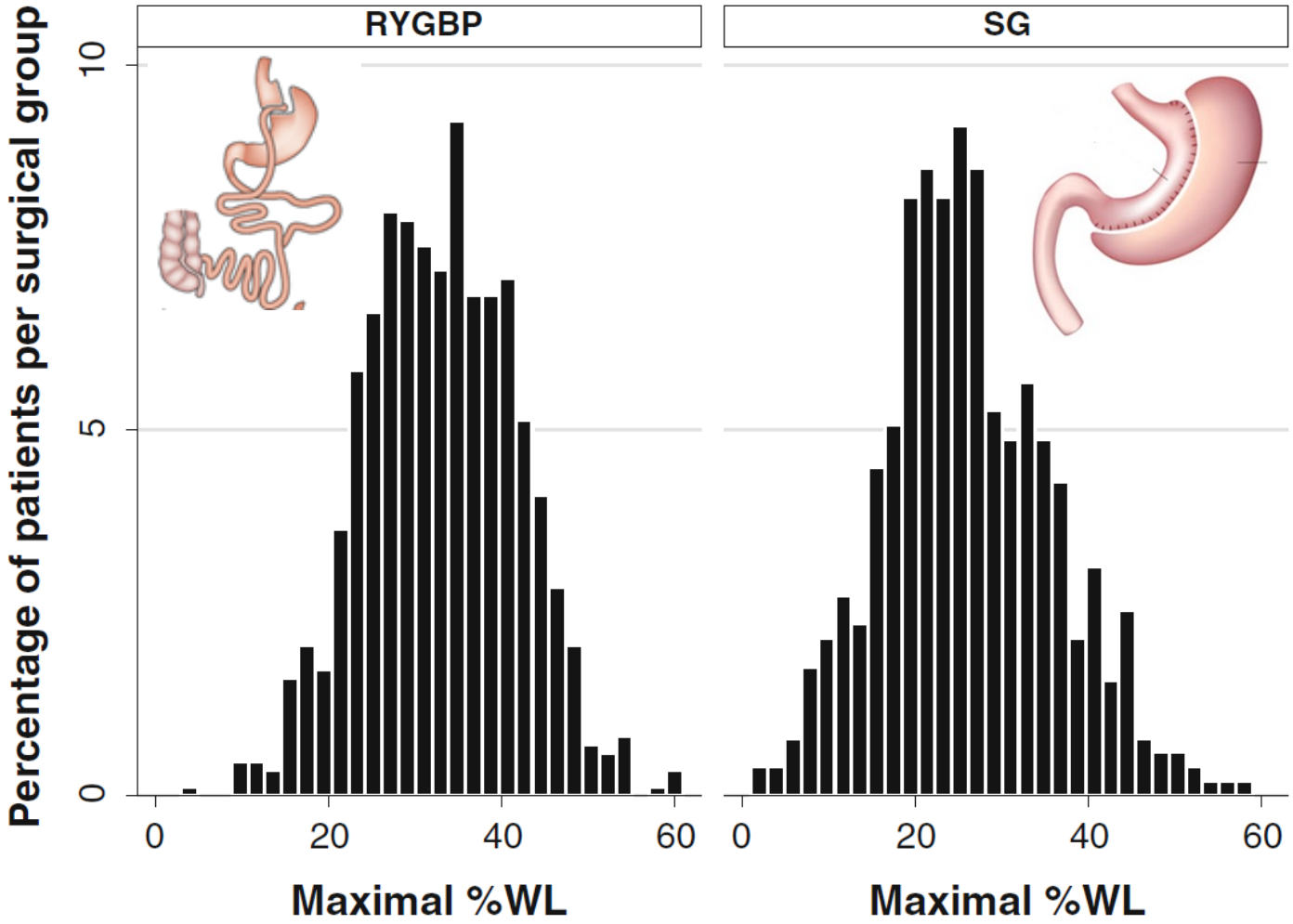
Variable Response in Bariatric Surgery



Brandt M. *Nat Rev Endocrinol* 2010;6:637 Manning, S. Surg Endosc 2015

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Want to Off-Road?

https://www.borntowin.net/audio/the-end-of-the-road/

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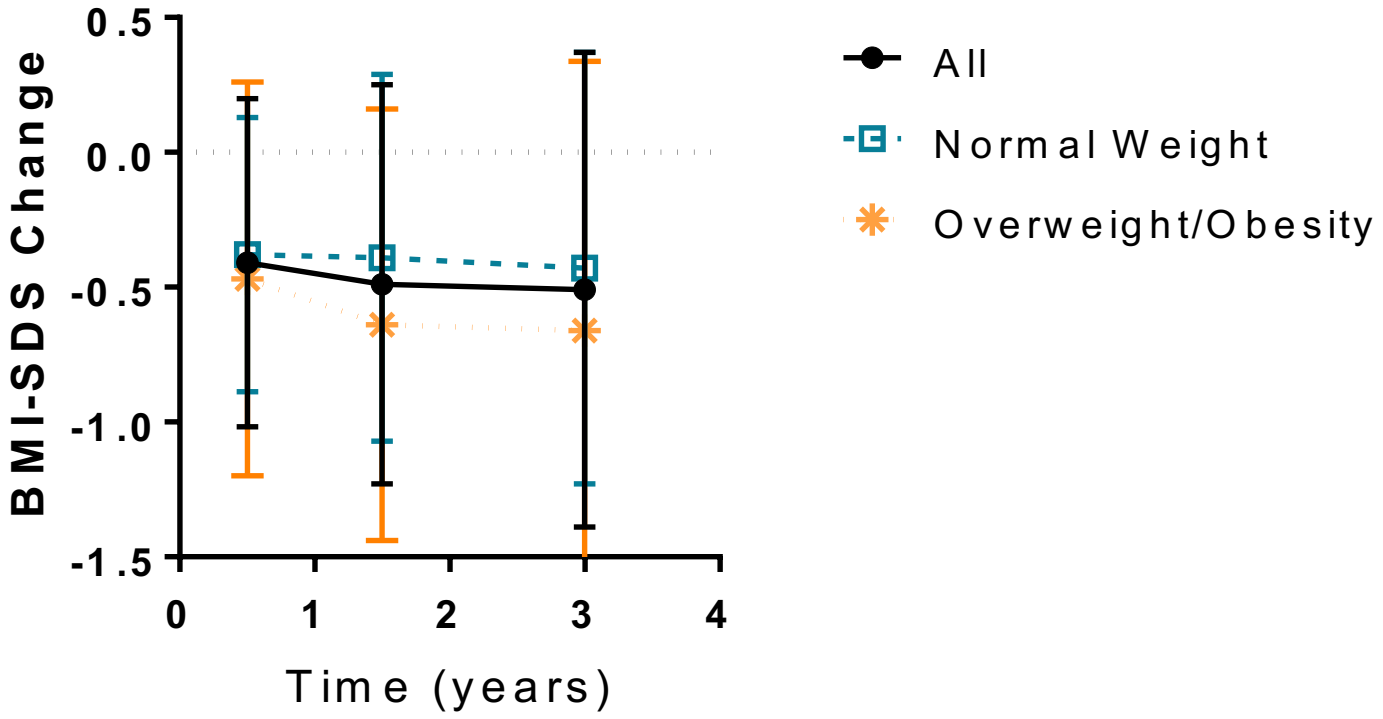
Thinking Outside the Box…

- Diabetes medications with weight reducing effects: SGLT2, exenatide, tirzepatide
- Pediatrics: topiramate, naltrexone, bupropion
- Stimulants

- There are no approved drugs in pediatrics under age 12 for weight management

Methylphenidate Weight Outcomes



Adapted from Mellstrom, E et al. *J of Attention Disorders* 2020

Comparison of Stimulants on Weight in Adolescents

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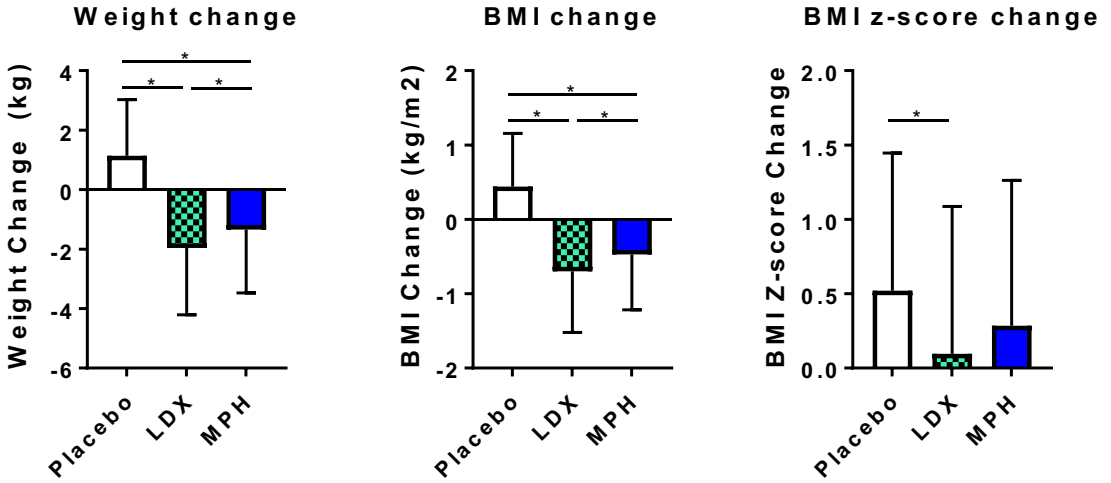
Flexible

LDX 30->70
Mean~50

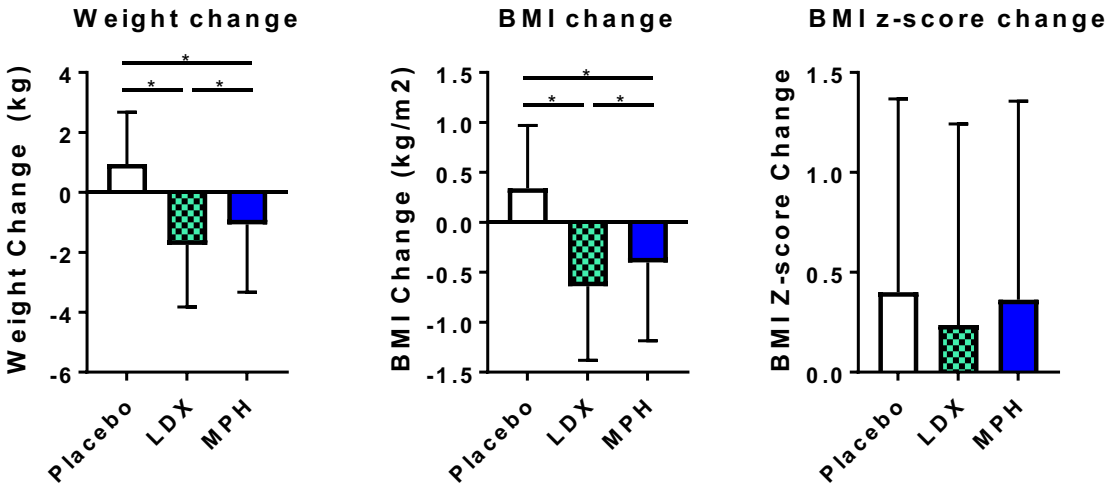
MPH 18->72
Mean ~45



Forced

LDX 30->70

MPH 18->72



LDX=lisdexamfetamine
MPH=osmotic-release methylphenidate

Adapted from Newcorn, JH et al. *CNS Drugs* 2017; stats not presented in paper

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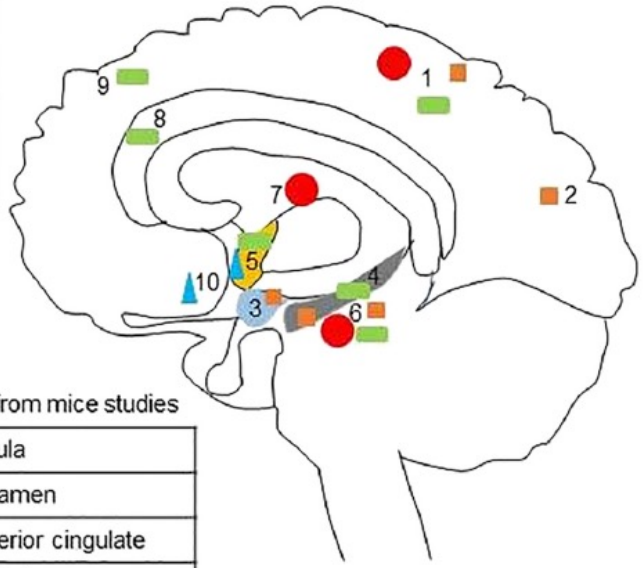
Combination Therapy

Liraglutide	1, 6, 7
Lorcaserin	1, 2, 3, 4, 6
Nal-Bup	1, 4, 5, 6, 8, 9
Phen-Top*	5, 10 *

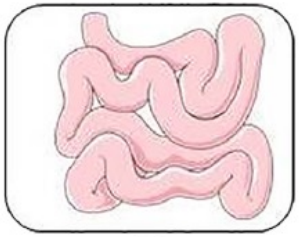
Appetite suppresion
↓ caloric intake
↓ food reward



* from mice studies

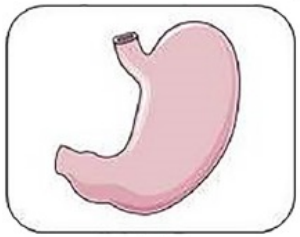
1	parietal cortex	6	insula
2	visual cortex	7	putamen
3	amygdala	8	anterior cingulate
4	hippocampus	9	frontal gyrus
5	hypothalamus	10	nucleus accumbens

Orlistat

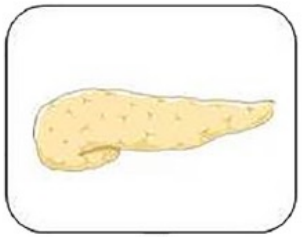


↓ lipid absorption

Liraglutide



Slows gastric emptying
↓gastric motility & HCl secretion



↑ insulin secretion

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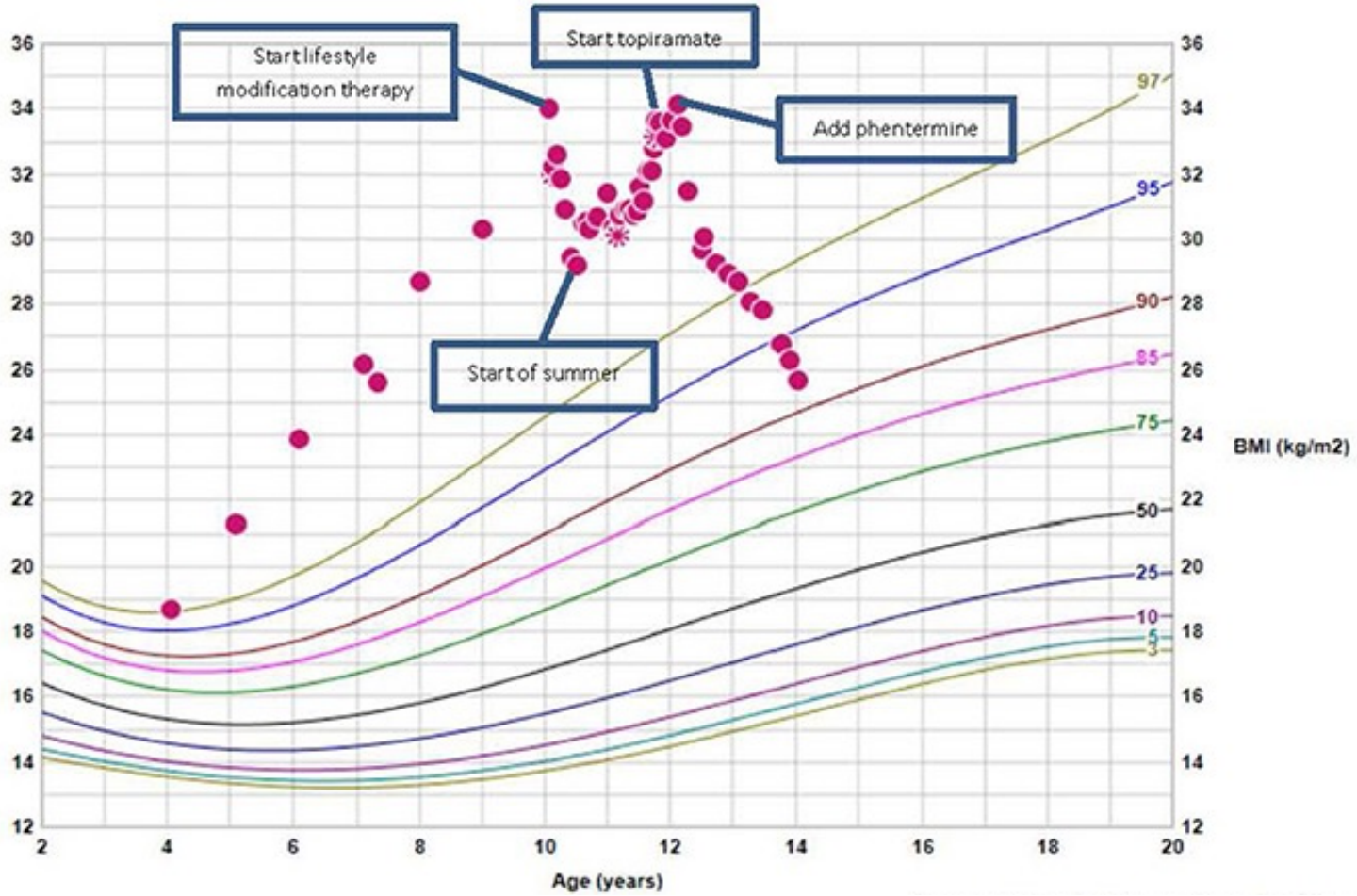
Combination Therapy – Topiramate+Phentermine



Fox, CK & Kelly, AS. *Front Pediatr* 2018

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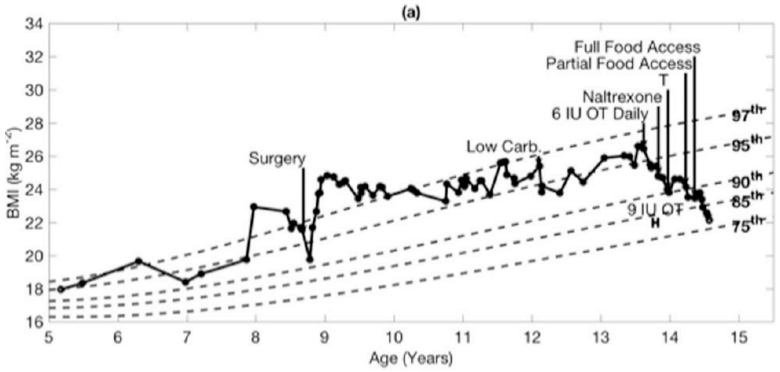
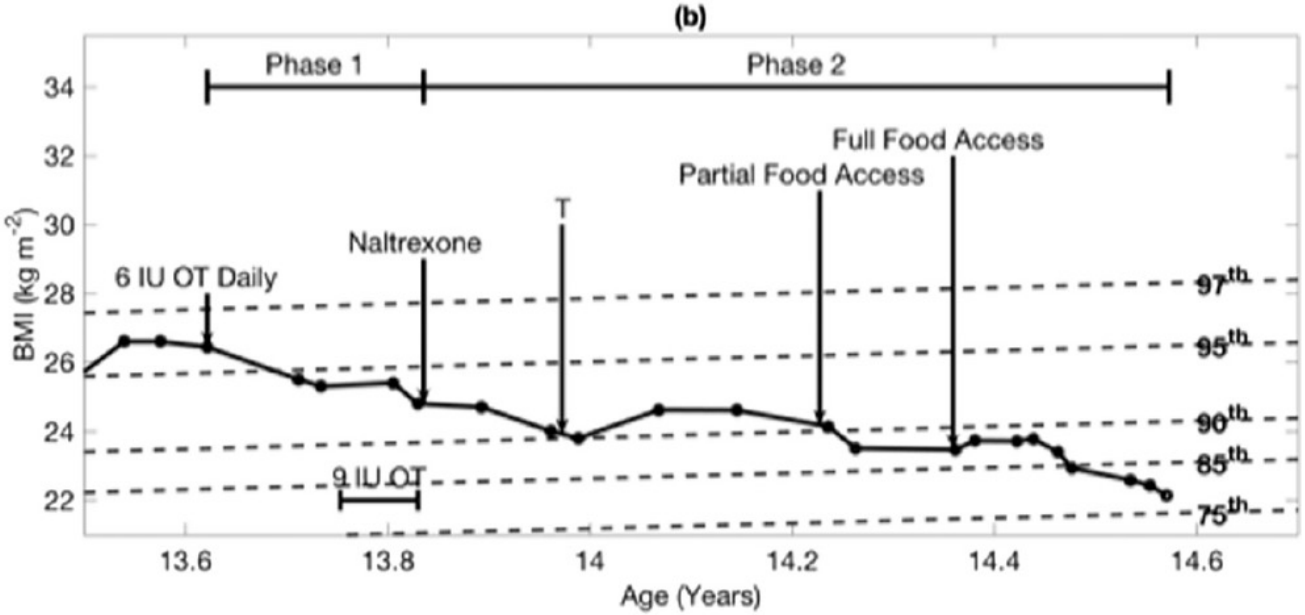
Combination Therapy- Oxytocin+Naltrexone





Hsu, EA et al. *JCEM* 2018

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Where We Might Be Going

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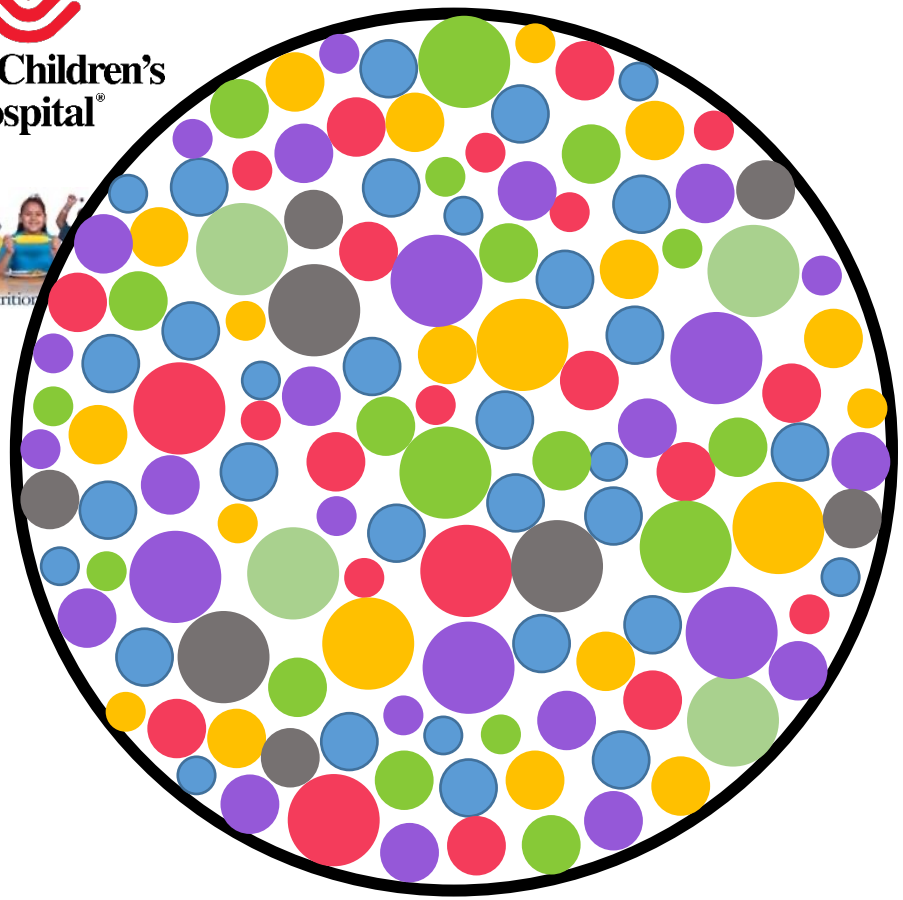
In the pipeline

- Tesomet: tesofensine+metoprolol for hypothalamic obesity and PWS (Phase 2b, 2023)
- Semaglutide: once weekly GLP-1R agonist
  - Diabetes: PIONEER TEENS NCT04596631
  - Obesity: NCT04102189
- Oxytocin: NCT04551482, NCT02849743 (Hypothalamic Obesity)

Examining All Causes of Obesity



- Monogenetic causes
- Syndrome related
- Timing differences
- Metabolic effects
- Body distribution
- Diet-responsive
- Drug-responsive
- Environmental causes

Genetic Disorders of Obesity Program

Referral

Age >1 yo
BMI > 97% prior to age 5

Evaluation

Endocrinologist

Geneticist

Outcomes

Genetic Testing

Pharmacologic Therapy

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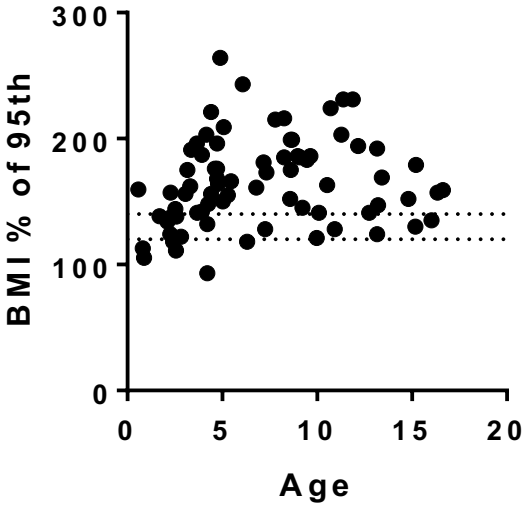
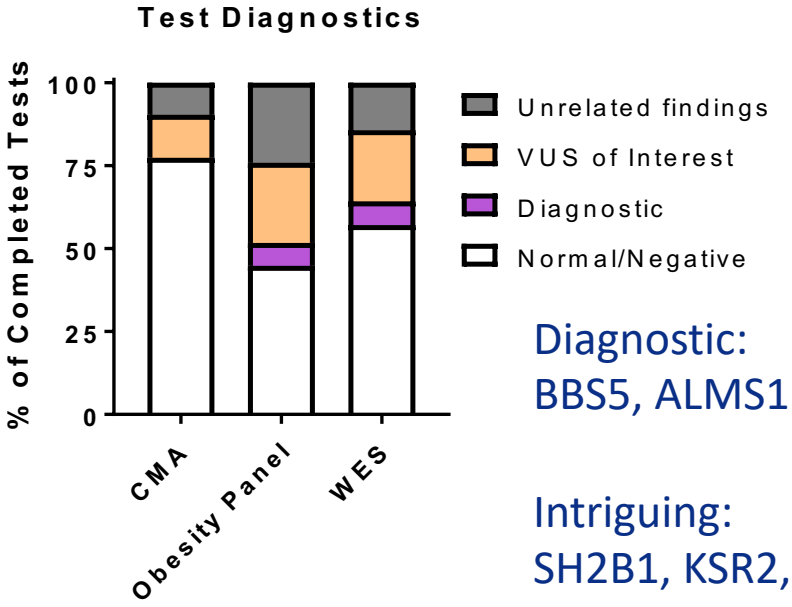
GDOP Patients
May 2019 - July 2022

Patient Characteristics (n=108)	Mean (Range) or Percent (n)
Age	6.7y (0.6-16.6)

Characteristics and Preliminary Outcomes





Diagnostic:
BBS5, ALMS1

Intriguing:
SH2B1, KSR2,
SIM1, RAI1

Unpublished data

Baylor College of Medicine

Texas Children's Hospital®

Isolation in a sea of "experts"

- Facing barriers at every turn
- Carrying all of the burdens
- Struggling to get their child seen as an individual

"I'm not a real easily shaken person, I'm not an easily offended person at all. And when we left I cried because [the pediatrician] was just so- Like [the pediatrician] just didn't listen, and it was just very frustrating."

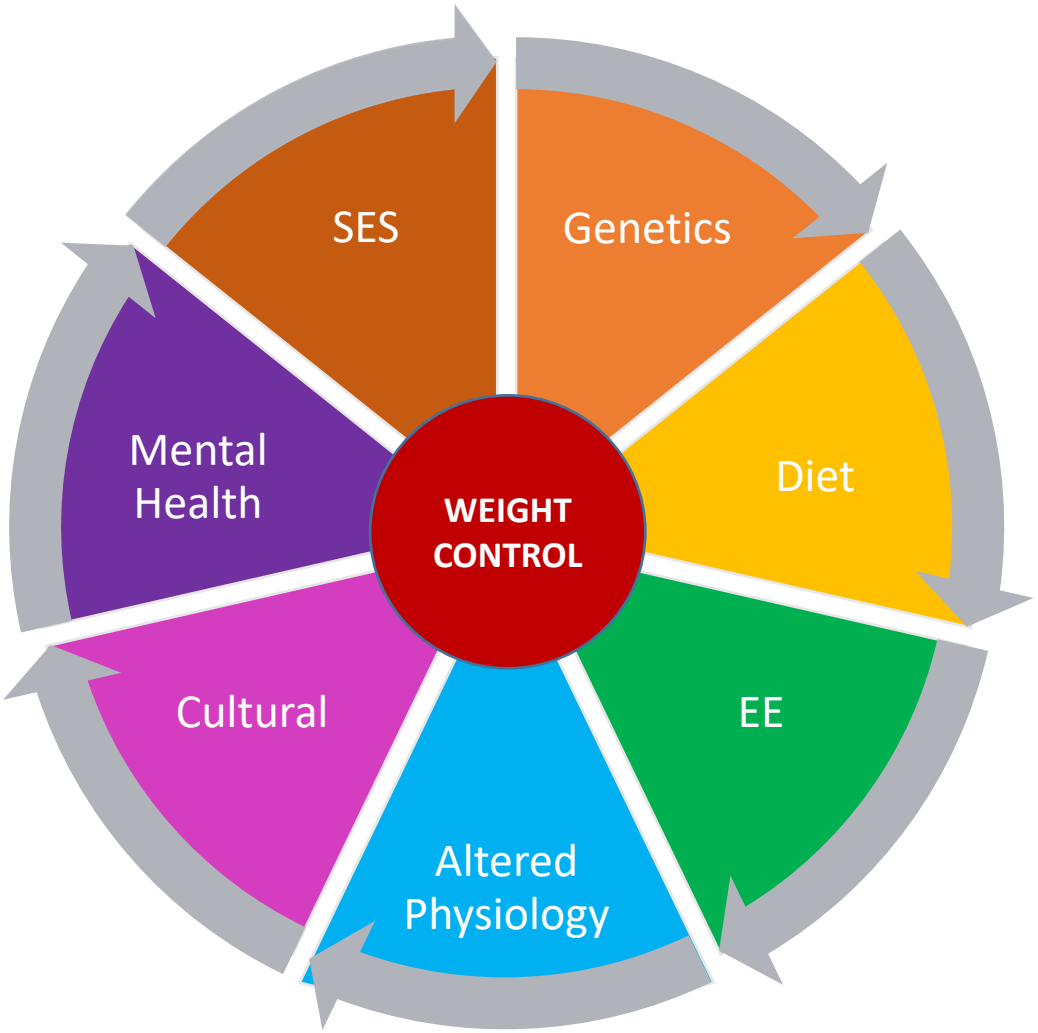
Unpublished data

Baylor College of Medicine

Texas Children's Hospital®

USDA/ARS Children's Nutrition Research Center

So What Can You Do?



Study to Better Characterize Food-Related Behaviors in SMS

- Drs. Elsea and Sisley are conducting focus groups this weekend to better understand food-related behaviors in the SMS population
- Goal is to create a better questionnaire for clinical trial use
- Need caregivers of SMS individuals who are at least 6 years old
- Focus groups will be audio recorded for accurate transcription
- Saturday at 12:30p in Beeman A and additional virtual sessions

For more information, contact Stephanie Sisley 513-465-8701 or email Sisley.lab@bcm.edu