

Understanding Obesity Pathophysiology to Improve Clinical Care

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Pediatric Obesity:

CDC Growth Charts for age & gender

- Underweight: < 5%ile
- Healthy Weight: 5-84%ile
- Overweight: 85-94%ile
- Obesity: 95-98%ile
- **Severe Obesity:** ≥ 99%ile

Ogden et al. 2014; Flegal et al 2009; Gulati et al. 2012; Kelly et al. 2013; Skinner & Skelton 2014

Obesity further defined:

- Class I obesity
 - (≥95th percentile to <120% of the 95th percentile)
- Class II obesity (Severe obesity)
 - (≥120% to <140% of the 95th percentile) or a BMI ≥ 35 to ≤ 39, whichever was lower
- Class III obesity (Severe obesity)
 - (≥140% of the 95th percentile) or BMI ≥40, whichever lower.

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23 Million children in US have Overweight or Obesity

1 in 3 ME Kindergarteners - overweight or obesity
27.6% of ME high school students - overweight or obesity
4.5 million children in US with Severe Obesity

Severe obesity (Class II & III) is the fastest-growing subcategory of obesity in youth³

• **Demands Treatment**

Ogden, Carroll, Kit, et al. (2014)¹; Skinner, Perrin, Skelton (2016)²; Kelly et al. (2013)³; Ogden, Carroll, Fryar, et al. (2015)⁴

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It's a new world



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Obesity: a Disease

- Is it a Disease?
- Is it solely a Behavioral Disease or a Disease of Energy Management Dysregulation?
- Understanding the pathophysiology is the path to developing and implementing meaningful and effective therapies.
- Significant research illustrates 85% of Energy regulation is at the subconscious level (munzberg et al)

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Other examples of "behavioral" diseases..

Depression: "pull yourself up by your bootstraps" now replaced with scientifically based pharmacotherapy to treat this diverse disorder. Not all patients respond to the same medication – however, for many, medication is life-saving.

Addiction: personality flaw, weakness – now we understand the genetic underpinnings and the neuro-regulatory hormones that impact addiction – hedonic centers of the brain. Medications now used to target these areas are often needed.

ADHD: "just focus", redirection --- for some these interventions may be effective; most require medication to achieve their academic potential.

Bariatric Surgery: Currently the BEST durable treatment for Severe Obesity:

- this is NOT a behavioral intervention
- has provided invaluable information re: the pathophysiology of obesity.
- will guide development of non-surgical therapies.

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Medical Complications of Obesity

Metabolic
Structural
Inflammatory
Degenerative
Neoplastic
Psychological

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comorbidities
affecting EVERY
organ system and
medical specialty

Yuen M ... Kaplan LM, Obesity Week 2016



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The Normal Physiology of Energy Balance

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- Average adults **require** approximately 1300 kcal/day*
- Average adults **consume** 2000-2500 kcal/day
 - Average adults thus consume 1.5-2 times as much food as needed
 - Excess intake is available for physiological emergencies
- Maintenance of normal fat stores (and body weight) **requires precise disposal** of 40-50% of ingested calories daily
- Maintaining weight within 20 lbs. between ages 21 and 65 requires **matching of intake and expenditure within 0.2%**
 - Corresponds to accuracy of 4-5 kcal/day
 - Less than one-half potato chip



Thus, daily **energy balance** must be a tightly regulated physiological trait



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Nutrients can alter energy regulation

- Diet quality
- Pattern
- Portion



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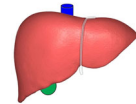
Obesity: Basic Physiology & Homeostasis

The body seeks a stable fat mass

Just as other regulated tissues do
At the subconscious level via
homeostatic physiologic mechanisms



Adipocyte: Fat Cell



Liver

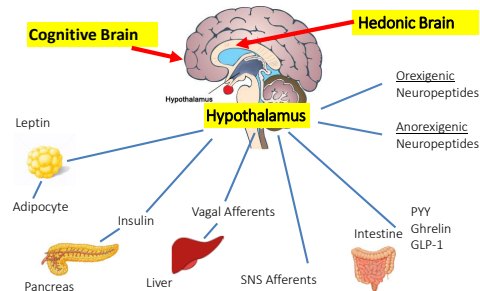


Red Blood Cells

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ERS Physiology Drives Behavior



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Arcuate Nucleus- 1st Order Neurons

POMC/CART neurons

- **Anorexigenic**
 - decreases food intake
 - increases energy expenditure via (-) AgRP/NPY & (+) neurons in PVN via MC3R
 - Insulin and leptin receptors

Serotonin receptors

- decrease appetite and increase EE

AgRP, NPY neurons

- **Orexigenic**
 - increases food intake
 - decreases energy expenditure via
 - (-) anorexigenic neurons in LH & PVN (POMC/CART) via MC3R and MC4R
 - (+) orexigenic neurons in LH and PVN via NPY and Ghrelin receptors

POMC: Proopiomelanocortin
CART: Cocaine- amphetamine regulated transcript
AgRP: Agouti-related Peptide
NPY: Neuropeptide Y

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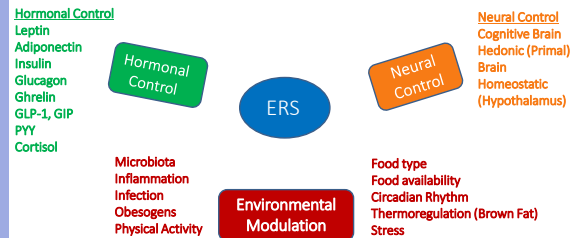
Paraventricular Hypothalamus: Second order neuron

- MC4R
deficiency or mutation leads to obesity
- Decreases appetite
- Increases energy expenditure via SNS stimulation

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The Energy Regulatory System (ERS): Hormonal and Neural control, modulated by Environmental factors



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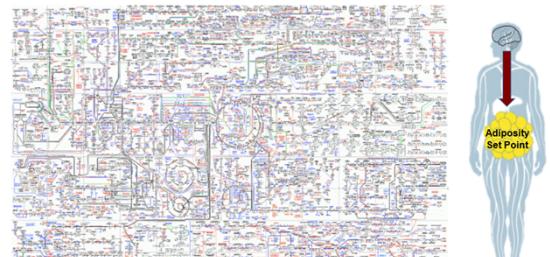
Obesity results from a failure of normal weight and energy regulatory mechanisms...

...leading to an elevated body fat set point



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Complex Biology of Obesity



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Critical Periods of Development and Obesity

- Prenatal and Infancy**
 - SGA/LGA
 - GDM
 - Maternal HTN, Obesity
 - Rapid growth/weight gain during infancy
- Early Childhood**
 - Adiposity Rebound
 - Consider syndromic & monogenic etiologies (Prader-Willi Syndrome, Bardet Biedl Syndrome, Alstrom Syndrome, POMC, MC4R def)
- Adolescence**
 - Impact on puberty
 - High risk to persist into adulthood

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International Journal of Paediatric and Child Health and AIDS (2020) Volume 9 Issue 1, 23-33

Available online at www.ijpaediatrics.com

ORIGINAL ARTICLE
Social Determinants of Overweight and Obesity Among Children in the United States
Zorah A. Fouad, PhD, MPH¹, Daniel D. Thompson, PhD², Rakib A. Fouad, PhD, MPH, FRCPC³, Michaela B. B. F. de Souza, PhD⁴, Thomas R. Bailey, PhD, FRCPC⁵

Abstract
Background: Childhood obesity is one of the fastest growing public health problems in the United States (US), leading to the emergence of comorbidities and increased healthcare costs. We explore the influence of selected social determinants of health (SDOH) on overweight and obesity among US children. Methods: We utilized the National Survey of Children's Health (NSCH) 2016-17 dataset for this analysis. Overweight was defined as Body Mass Index (BMI) ≥ 85th percentile, while obesity was defined as BMI ≥ 95th percentile. We used multivariate logistic regression to examine the association between SDOH and overweight and obesity. Results: About 35.5 million children were surveyed of which 9.5 million (26.8%) were either overweight or obese. The likelihood of obesity was elevated among Hispanic, Black, and Native American (P < 0.001, 0.001, and 0.001, respectively). Overweight was more frequent in younger children, children of single parents, and children who lived in a neighborhood with no amenities. Parental education, health insurance coverage, family structure, and language spoken at home were also associated with overweight and obesity. Conclusions and Global Health Implications: SDOH represent markers of socioeconomic or lifestyle factors that are associated with the development of overweight and obesity among US children. Key words: Social determinants • Obesity • Overweight • SDOH • Children • United States

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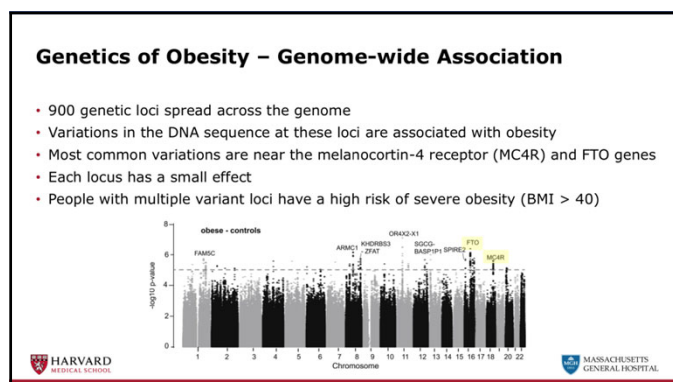
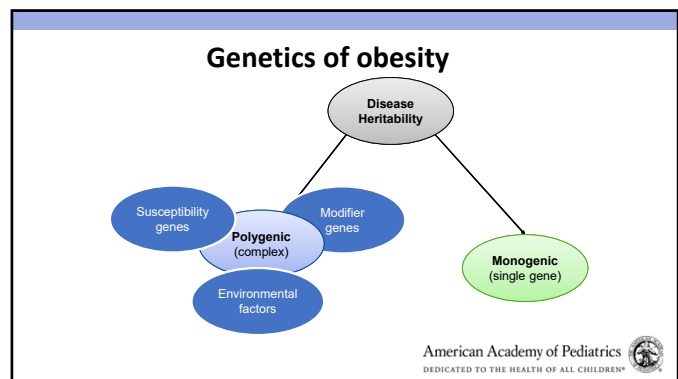
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Demographic and Placement Variables Associated with Overweight and Obesity in Long-Term Foster Care
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Abstract
Objectives—Overweight and obesity is a growing problem for children in foster care. This study examines the prevalence of overweight and obesity in an ethnic, ethnic minority population of children aged 12 to 19 in long-term foster care (LTFC) in Los Angeles, California. Methods—The prevalence of overweight and obesity among LTFC children was examined using data from the National Longitudinal Study of Adolescent Health (Add Health). Results—The prevalence of overweight and obesity among LTFC children was 12.1% and 11.4%, respectively. Conclusions—These findings suggest that older age and long-term foster care in general may be risk factors for obesity. LTFC children appear to have higher rates of overweight and obesity than their peers in the general population. Further research is needed to understand the complex interplay of factors contributing to these disparities.

Keywords: Childhood obesity, overweight, long-term foster care, aging foster

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Monogenic Obesity		
Disease	Characteristic Features	Comments
Congenital Leptin Deficiency	Early-onset severe obesity and hyperphagia, altered immune function, delayed puberty	<ul style="list-style-type: none"> • Mutations in the <i>ob</i> gene • Undetectable serum leptin levels • Treatment with leptin
Congenital leptin receptor deficiency	Early-onset severe obesity and hyperphagia, altered immune function, delayed puberty	Normal serum leptin levels
Melanocortin 4 receptor (MC4-R) Mutation	Tall stature and rapid growth	Normal mental status
Pro-opiomelanocortin (POMC) Mutation	Red hair, pale skin, low blood pressure or rapid pulse, and corticotropin deficiency, adrenal insufficiency	Hypopigmentation, and isolated ACTH deficiency

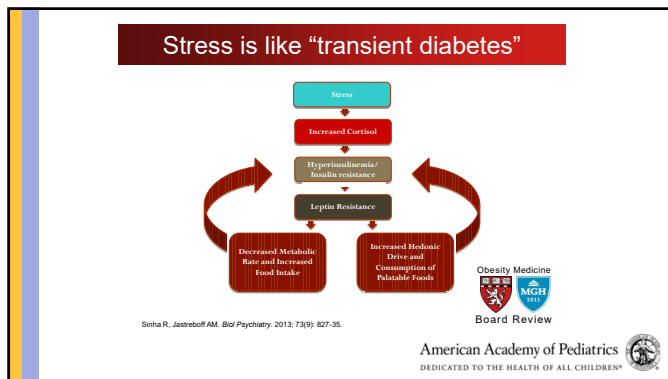
Syndromic Obesity		
Disease	Key Characteristics	Comments
Prader-Willi Syndrome	Short stature, hypotonia, developmental delay, hyperphagia	15q partial deletion on paternal chromosome; Increased ghrelin level
Bardet-Biedl Syndrome (Laurence-Moon)	Retinitis pigmentosa, polydactyly, hypogonadism, hypotonia, developmental delay	Autosomal recessive; Defect in cilia
Albright Hereditary Osteodystrophy	Developmental delay, short stature, and short fourth and fifth metacarpals, hypocalcemia	Maternal transmission via epigenetic methylation defect in adenylate cyclase-stimulating G alpha protein (GNAS) results in pseudohypoparathyroidism; Precocious puberty
Fragile X	Intellectual disability, large ears, large testes, CCG trinucleotide affecting <i>FMR-1</i> gene on X chromosome	FISH Hybridization
Cohen Syndrome	Obesity, hypotonia, microcephaly, prominent incisors	Chromosome 8 (8q22) Auto Recessive
Beckwith-Wiedemann Syndrome	Macroglossia, macrosomia, hypoglycemia, ear pits, midline abdominal wall defects	11p15.5, increased cancer incidence (Wilms tumor, hepatoblastoma)
Alström Syndrome	Sensorial hearing loss, blindness, IR and hyperinsulinemia, DM2,dilated cardiomyopathy, hypoglyc and renal failure	Mutation in <i>ALMS1</i> gene

Rare Genetic Disorders

- Likely underdiagnosed
- True prevalence of rare genetic disorders of obesity is unknown due to genetic testing is not routinely done in patients with obesity.
- Examples:
 - LEPR: 76 individuals detailed in case studies worldwide
3600 estimated prevalence in US
 - POMC: 31 individuals detailed in cases worldwide
650 estimated prevalence in US
 - PCSK1: 43 individuals in cases worldwide
8500 estimated in US

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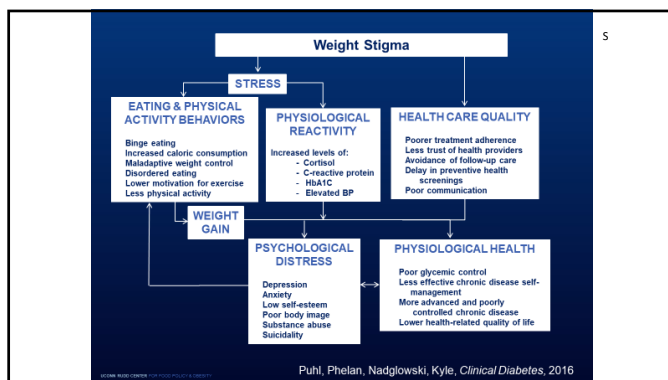




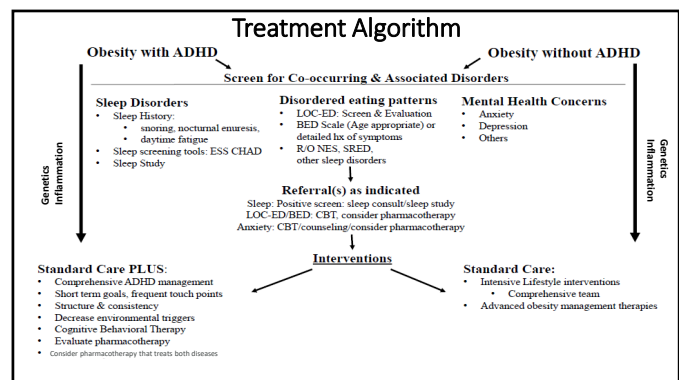
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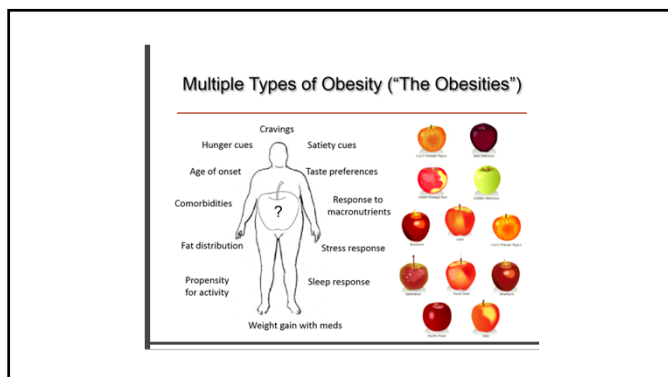
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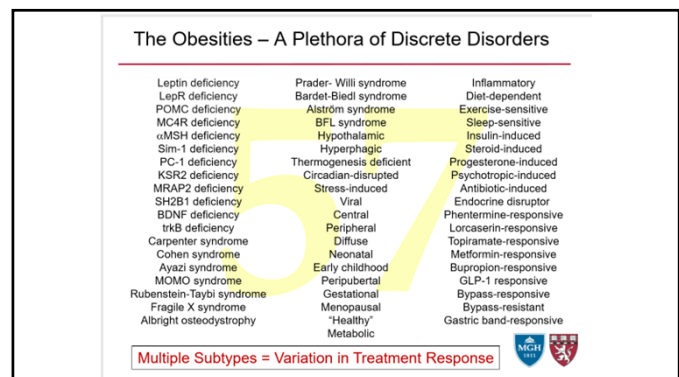
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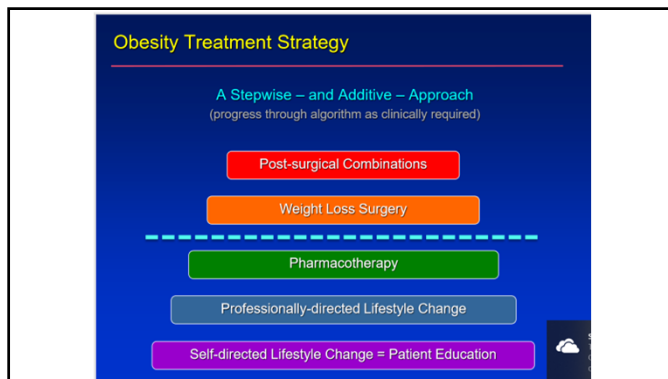
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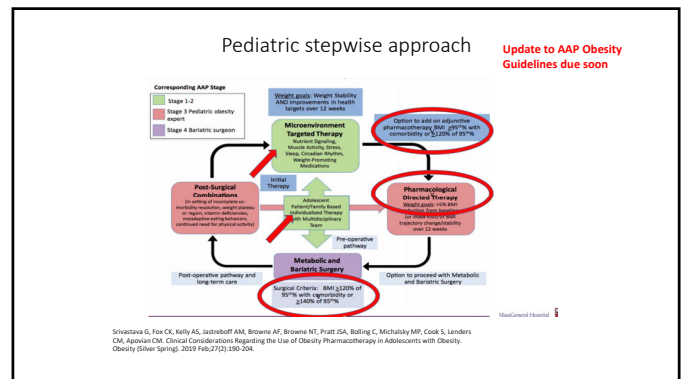
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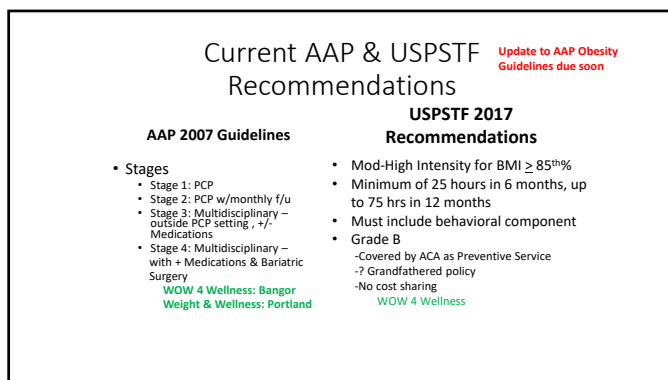
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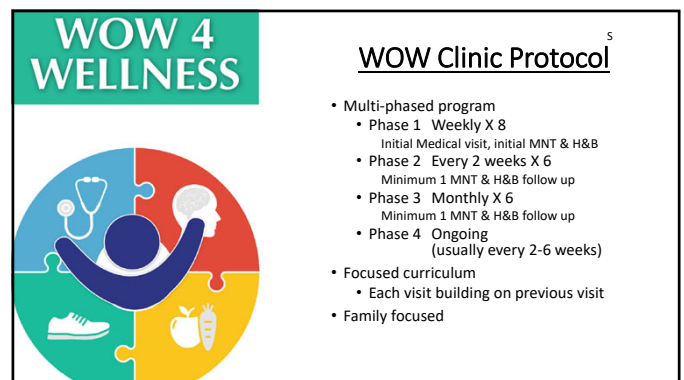
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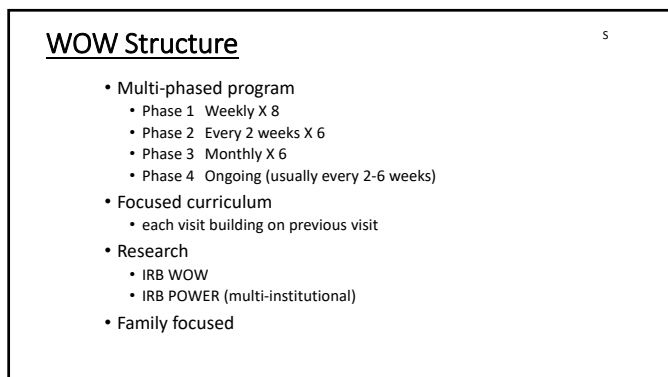
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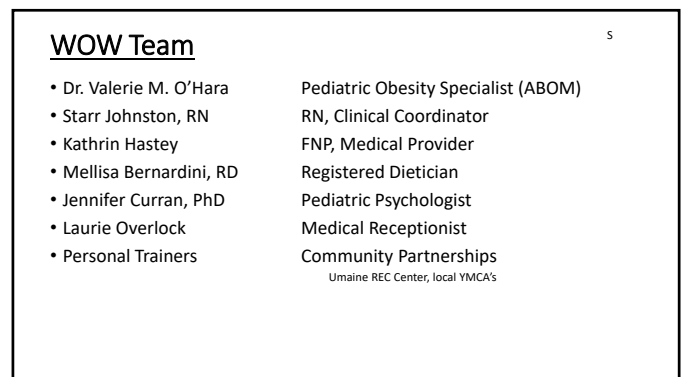
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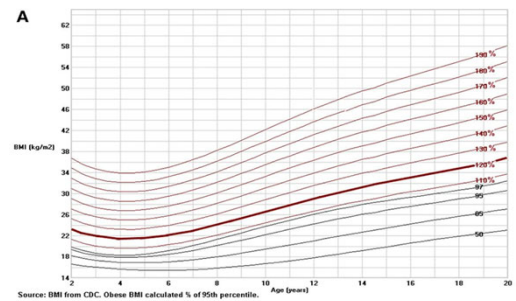


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Baseline Evaluations

- Key History: +FHx of obesity, HTN, T2DM, Sleep-nocturnal enuresis, medications – wt promoting, co-occurring dxs,
- Lab Screening: lipids, LFTs, FBS, HgBA1c
(at least by age 10yrs for pts with OV/obesity, younger if severe obesity & FHx of hyperlipidemia, T2DM, etc)
- Request adding updated BMI curve to include % of the 95th% to EMR

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Current and Emerging Treatments of Obesity

Lifestyle	Pharmacological	Medical Devices
Low-calorie diet	Remove weight-promoting	Adjustable gastric band
Low-carbohydrate diet	Phentermine	Vagal nerve block
Low-fat diet	Topiramate	Gastric balloon
Low-glycemic index diet	Zonisamide	Duodenal liner
Paleo diet	Metformin	Gastric aspiration
Mediterranean diet	Lorcaserin	Expandable gel capsule
Very low-calorie diet	Bupropion	
Aerobic exercise	Naltrexone	
Resistance training	Exenatide	
Sleep enhancement	Liraglutide	
Circadian enhancement	Dulaglutide	
Motivational interviewing	Pramlintide	
Stress reduction	Orlistat	
Cognitive-behavioral therapy	Diethylpropion	
	Leptin	
	Canagliflozin	
	Empagliflozin	
	Setmelanotide	
		Surgical
		Sleeve gastrectomy
		Gastric bypass
		Biliopancreatic diversion
		Duodenal bypass

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FDA- Approved Anti-Obesity Pharmacotherapy

Medication	MOA	Age
Phentermine	NE releasing agent	16yrs and older
Orlistat	Lipase inhibitor	12 yrs and older
Liraglutide (Saxenda)	GLP-1 agonist	12 yrs and older
Setmelanotide	MC4R agonist	6 yrs and older
*semaglutide (Wegovy)	GLP-1 agonist	Trials underway

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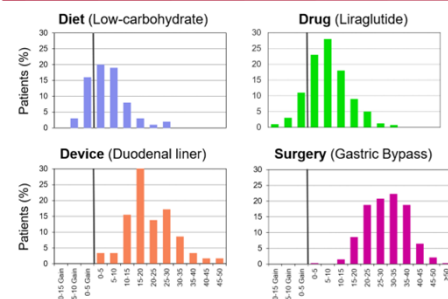
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Anti-Obesity Medications and Pediatrics

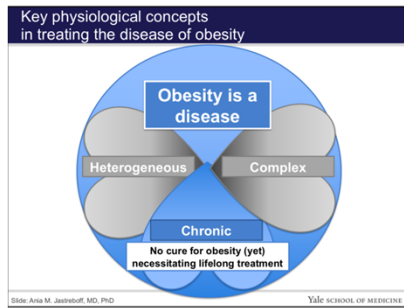
- Medications FDA-approved for indications of obesity in children exist
 - many Medicaid & private insurers do not cover currently
- Medications FDA-approved for indications of obesity in children:
 - Phentermine 16 years and older
 - Orlistat 12 years and older
 - Liraglutide 12 years and older at 3.0mg dose
 - Setmelanotide 6 years and older
- Alternatives
 - Phentermine (\$) + topiramate (\$) = *Qsymia* (\$\$\$)
 - Wellbutrin (\$) + naltrexone (\$) = *Contrave* (\$\$\$)
 - off label or if patient on Wellbutrin for depression
- For Binge Eating Disorder/Loss of Control eating + ADHD
 - 1st line Lisdexamfetamine
- For Pre-Diabetes, Type 2 diabetes, Insulin resistance
 - GLP-1 at 1.8mg dose

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Weight Loss Varies Widely Among Patients

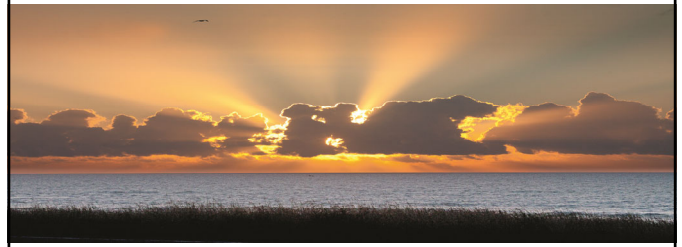


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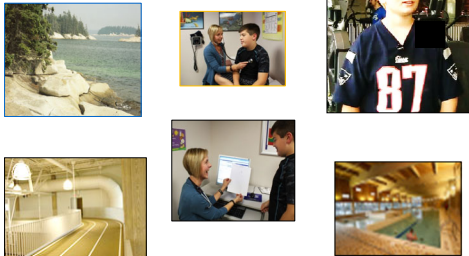
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Hopeful Thoughts



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WOW Thanks You!



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Current Obesity Reports
https://doi.org/10.1007/s13679-020-00410-0

CHILDHOOD OBESITY (A KELLY AND C FOX, SECTION EDITOR)

The Co-occurrence of Pediatric Obesity and ADHD: an Understanding of Shared Pathophysiology and Implications for Collaborative Management

Valerie M. O'Hara¹ · Jennifer L. Curran² · Nancy T. Browne³

Accepted: 5 October 2020
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Abstract
Purpose of Review To describe what is known about the association between obesity and attention-deficit hyperactivity disorder (ADHD) in children along with the co-occurring conditions of sleep dysfunction, loss of control/binge eating disorder (LOC-ED/ BED), and anxiety.

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Telemedicine as a tool

Received: 20 April 2020 | Revised: 4 June 2020 | Accepted: 3 June 2020
DOI: 10.1111/obes.12484

REVIEW ARTICLE

CHILDHOOD OBESITY WILEY

The paediatric weight management office visit via telemedicine: pre- to post-COVID-19 pandemic

Valerie M. O'Hara | Starr V. Johnston | Nancy T. Browne

Northern Light Health, Eastern Maine Medical Center, Department of Pediatrics, W206
Portland, & Adolescent Weight & Cardiovascular Clinic, Orono, Maine

Summary
Telemedicine is a powerful tool that eases many logistical barriers to care and may increase access. Due to the need for social distancing, the COVID-19 pandemic has

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Prevalence

- **Overweight & obesity** affected 32% of the U. S. youth aged 2 to 19 years in 2012 (NHANES).¹

- Preschool children (2-5 Years Old)

- 13.4% overweight
- 9.4% obesity

- 6 to 11 year olds

- 16.8% overweight
- 17.4% obesity

- adolescents 12 to 19 years of age

- 13.9% overweight
- 20.6% obesity

- **Prevalence by Obesity Class (2014 NHANES)²**

- 17.4% of children met criteria for class I obesity (12.7 million children*)
- 6.3% for class II (Severe obesity)
- 2.4% for class III (Severe obesity)

- A clear, statistically significant increase in all classes of obesity continued from 1999 through 2014. ²

- **Severe obesity (Class II & III) is the fastest-growing subcategory of obesity in youth³**

Ogden, Carroll, Kit, et al. (2014)¹; Skinner, Perrin, Skelton (2016)²; Kelly et al. (2013)³; Ogden, Carroll, Fryar, et al. (2015)⁴

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WOW Presentations

1. OMA Telemedicine Webinar: Oct 2018
2. POWER Presentation on Telemedicine for Pediatric Obesity: Feb 2019
3. Northeast Telehealth Conference: co-presented on Telemedicine for Obesity care. July 2018
4. Obesity Pathophysiology: Let's Go Webinar Series, Jan 2019
5. Obesity Pathophysiology for UNECOM medical students: April 2019 and ongoing.
6. AAP ECHO Webinar Pilot: Obesity Pathophysiology. April 2019
7. AAP Obesity Course. April 2021 Pathophysiology & Case Presenter
8. OMA Webinar :The Co-Occurrence of Pediatric Obesity & ADHD 2020
9. ME AAP Conference: The Co-Occurrence of Pediatric Obesity & ADHD
10. TOS Obesity Week: Lessons Learned in Pediatric Obesity Telemedicine Care. Nov 2021
11. Practical Implementation of Pediatric Obesity Care. UMN Advanced Therapies for Pediatric Obesity. Feb 2022

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WOW Publications:

- Jacobs, L. (2017). Probiotics, Prebiotics and Synbiotics: What are they and how do they affect obesity? *Journal of Pediatric Surgical Nursing*, 6 (3), 53-55.
- Johnston, S. V., & Browne, N. T. (2019). Pediatric obesity education educational components: an update of an elevator speech featuring food insecurity and sleep disorders. *Journal of Pediatric Surgical Nursing*, 8 (2), 3-8.
- Srivastava, G., O'Hara, V., & Browne, N. T. (2019). Case Report: Use of lisdexamfetamine to treat obesity in an adolescent with severe obesity and binge eating. *Children*, 6, 22. doi:10.3390/children6020222
- Srivastava, G., Fox, C., Kelly, A., Jastrzebski, A., Browne, A., Browne, N.,.....Apovian, C. (2019). Clinical Considerations Regarding the Use of Obesity Pharmacotherapy in Adolescents with Obesity. *Obesity*, 27, 190-204.
- Srivastava, G., O'Hara, V., & Browne, N. T. (2018). Case Report: Teen with Severe Obesity and Sleep Disturbance. *Journal of Sleep Medicine & Disorders*, 5, 1092.
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- Prent, J. S., Browne, A. F., Browne, N. T., Bruzoni, M., Cohen, M., Desai, A., Zisman, J. (2018). ASABMS pediatric metabolic and bariatric surgery guidelines, 2018. *SOAR*, 24, 182-193.
- Cuda S, Censari M, Joseph M, Browne N, O'Hara V. Pediatric Obesity Algorithm, presented by the Obesity Medicine Association 2018-2020.

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