CMHC
PEDIATRIC MASTERCLASS

Addressing Cardiometabolic Risk in Children and Adolescents:

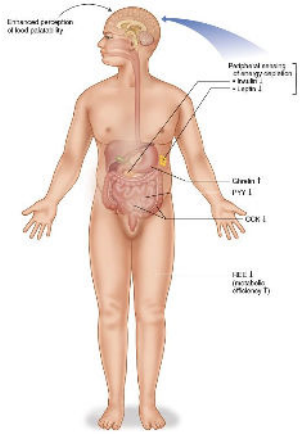
CHALLENGES AND SOLUTIONS

Educationally Partnered with FCAAP Florida Chapter of the American Academy of Pediatrics

CMHC PEDIATRIC MASTERCLASS

Tackling Pediatric Obesity

Utilizing the Spectrum of Available Tools to Optimize Treatment



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CENTER FOR PEDIATRIC OBESITY MEDICINE

Presented at the FCAAP FUTURE of PEDIATRIC PRACTICE 2022

Disclosures

- I engage in unpaid consulting and educational activities for Novo Nordisk, Vivus, Eli Lilly, and Boehringer Ingelheim
- I receive donated drug/placebo from Vivus and Novo Nordisk for NIH-funded clinical trials

Outline

- Limitations of lifestyle therapy as a singular treatment
- Rationale for the use of pharmacotherapy and/or bariatric surgery
- Metabolic/bariatric surgery outcomes
- Anti-obesity medications to treat adolescent obesity
- Pediatric anti-obesity medication pipeline: looking to the future

Lifestyle Modification Therapy

US Preventive Services Task Force

Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Obesity in Children and Adolescents
US Preventive Services Task Force
Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Based on year 2000 Centers for Disease Control and Prevention growth charts, approximately 17% of children and adolescents aged 2 to 19 years in the United States have obesity, and almost 32% of children and adolescents are overweight or have obesity. Obesity in children and adolescents is associated with morbidity such as mental health and psychological issues, asthma, obstructive sleep apnea, orthopedic problems, and adverse cardiovascular and metabolic outcomes (eg, high blood pressure, abnormal lipid levels, and insulin resistance). Children and adolescents may also experience teasing and bullying behaviors based on their weight. Obesity in childhood and adolescence may continue into adulthood and lead to adverse cardiovascular outcomes or other obesity-related morbidity, such as type 2 diabetes.

SUBPOPULATION CONSIDERATIONS Although the overall rate of child and adolescent obesity has stabilized over the last decade after increasing steadily for 3 decades, obesity rates continue to increase in certain populations, such as African American girls and Hispanic boys. These racial/ethnic differences in obesity prevalence are likely a result of both genetic and nongenetic factors (eg, socioeconomic status, intake of sugar-sweetened beverages and fast food, and having a television in the bedroom).

OBJECTIVE To update the 2010 US Preventive Services Task Force (USPSTF) recommendation on screening for obesity in children 6 years and older.

EVIDENCE REVIEW The USPSTF reviewed the evidence on screening for obesity in children and adolescents and the benefits and harms of weight management interventions.

FINDINGS Comprehensive, intensive behavioral interventions (≥26 contact hours) in children and adolescents 6 years and older who have obesity can result in improvements in weight status for up to 12 months; there is inadequate evidence regarding the effectiveness of less intensive interventions. The harms of behavioral interventions can be bounded as small to none, and the harms of screening are minimal. Therefore, the USPSTF concluded with moderate certainty that screening for obesity in children and adolescents 6 years and older is of moderate net benefit.

CONCLUSIONS AND RECOMMENDATION The USPSTF recommends that clinicians screen for obesity in children and adolescents 6 years and older and offer or refer them to comprehensive, intensive behavioral interventions to promote improvements in weight status. (B recommendation)

Editorial page 2378
Author Audio Interview
Related article page 2427 and JAMA Patient Page page 2460
CME Quiz at jamanetwork.com/learning
Related articles at jamapediatrics.com jamainternalmedicine.com

Author/Group Information: The US Preventive Services Task Force (USPSTF) members are listed at the end of this article.
Corresponding Author: David C. Grossman, MD, MPH (chair@uspstf.net).

JAMA. 2017;317(23):2417-2426. doi:10.1001/jama.2017.6803

"The USPSTF recommends that clinicians screen for obesity in children and adolescents 6 years and older and offer or refer them to comprehensive, intensive behavioral interventions to promote improvements in weight status."

"The USPSTF found that comprehensive, intensive behavioral interventions with a total of 26 contact hours or more over a period of 2 to 12 months resulted in weight loss. **Behavioral interventions with a total of 52 contact hours or more** demonstrated greater weight loss and some improvements in cardiovascular and metabolic risk factors."

O'Connor et al. *JAMA* 2017.

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Lifestyle Modification Therapy

US Preventive Services Task Force

Table 2. Summary of Change in BMI *z* Score in 28 Trials for Treatment of Obesity in Children and Adolescents[a]

Intervention Intensity, h[b]	No. of Trials	No. of Participants	Mean Change in BMI *z* Score		Difference in Change in BMI *z* Score From Baseline (95% CI)	Mean Change in Weight, lb[c]	
			Intervention	Control		Intervention	Control
≥52	5	875	−0.05 to −0.34	0.00 to 0.26	−0.31 (−0.16 to −0.46)	−7 to 3	8 to 17
26-51	7	489	−0.11 to −0.59	−0.20 to 0.40	−0.17 (−0.30 to −0.04)	Preschool: 1 to 5 Elementary: −6 to 15 Adolescent: 5	Preschool: 11 to 12 Elementary: 3 to 20 Adolescent: 7
6-25	7	513	0.05 to −0.24	0.09 to −0.13	0.01 (−0.06 to 0.08)	Elementary: 6 to 10 Adolescent: −3 to 7	Elementary: 6 to 10 Adolescent: −2 to 18
1-5	9	1315	0 to −0.20	0.10 to −0.10	−0.09 (−0.14 to −0.05)	Preschool: 1 to 4 Elementary: 1 to 12 Adolescent: 4	Preschool: 1 to 4 Elementary: 2 to 18 Adolescent: 6 to 12

Abbreviation: BMI, body mass index.

[a] Data presented in this table are limited to trials that reported BMI *z* score.

[b] Estimated.

[c] Age-specific results were available from trials that limited enrollment to only 1 of the 3 age categories (preschool, elementary, or adolescent). Trials with 52 or more hours of contact enrolled participants across the 3 age categories and both sexes, so age- and sex-specific results were not available.

O'Connor et al. *JAMA* 2017.

Is the USPSTF Recommendation Practical?

- Fewer than 50% of pediatric patients referred for weight management services enroll in treatment
- Attrition rates >50% have been reported in behavioral-based clinical trials and in the clinical setting
- Adolescent adherence to behavioral counseling significantly diminishes over time

Danielsson et al. *JAMA Pediatr* 2012; Kumar et al. *J Pediatr* 2019; Savoye et al. *JAMA* 2007; Shaffer et al. *J Pediatr* 2016; Skelton et al. *Obes Rev* 2011; Smith et al. *Nutrients* 2015.

Real World Clinical Outcomes POWER (U.S. Clinical Registry)

Lifestyle Intervention

Age groups (y)	Percent change BMI, median (IQR) 4-6 mo	7-9 mo	10-12 mo
2-5	N/A	N/A	N/A
6-11	N/A	N/A	N/A
12-14	−0.32 (−3.2 to 2.2) n = 534	−0.21 (−4.2 to 3.1) n = 319	0.02 (−5.0 to 4.0) n = 207
15-18	−0.77 (−4.1 to 1.6) n = 451	−1.03 (−5.4 to 2.4) n = 230	−0.66 (−5.6 to 3.8) n = 127
P value: age group comparisons (6-18 years only)	§	§	NS

Kumar et al. *J Pediatrc* 2019.

Appetite/Satiety Hormone Dysregulation

Reduced Metabolic Rate

Stigma/Body Image

Iatrogenesis

Binge Eating Disorder

Genetic Predisposition

Television

Moving Walkways

Pre-pregnancy BMI

Antibiotic Use

Developmental Programming

Microbiota

Anxiety

Large Portions

Gestational Weight Gain

Sedentary Lifestyle

Depression

Reduced Executive Functioning

Stress

Leptin Resistance

Less Gym Class

Race/Ethnicity

Poverty

Dysregulated Reward Pathways

Weight Cycling

Poor Sleep Hygiene

Devices

Escalators

Impulsivity

Less Recess

Adverse Life Experiences

Economics

Catch-up Growth

Elevators

Epigenetics

Calorie-Dense Foods

Video Games

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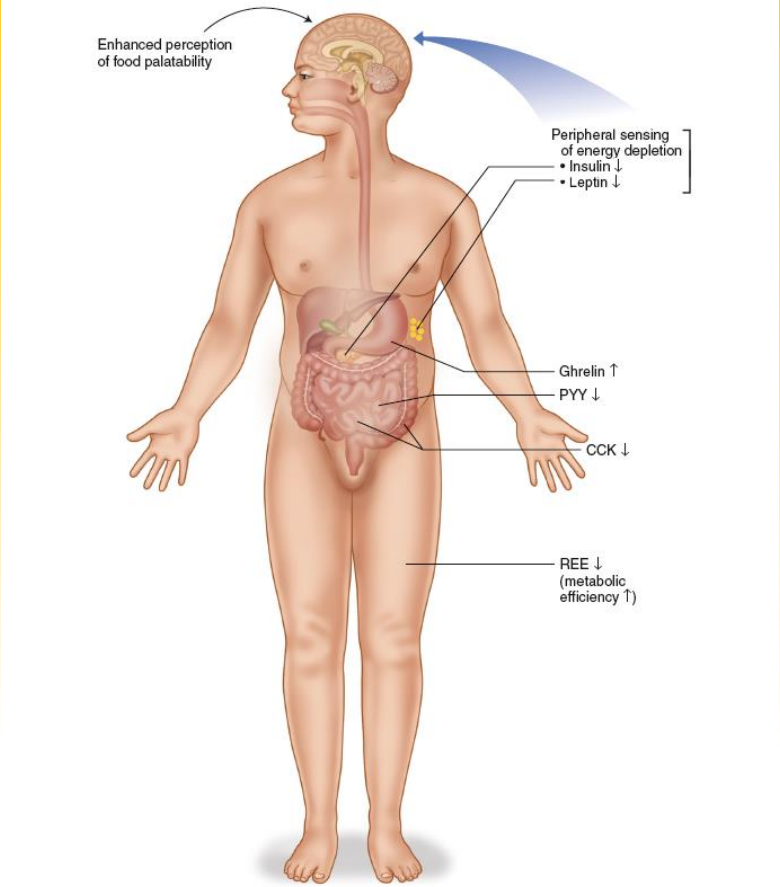
Biology of Obesity

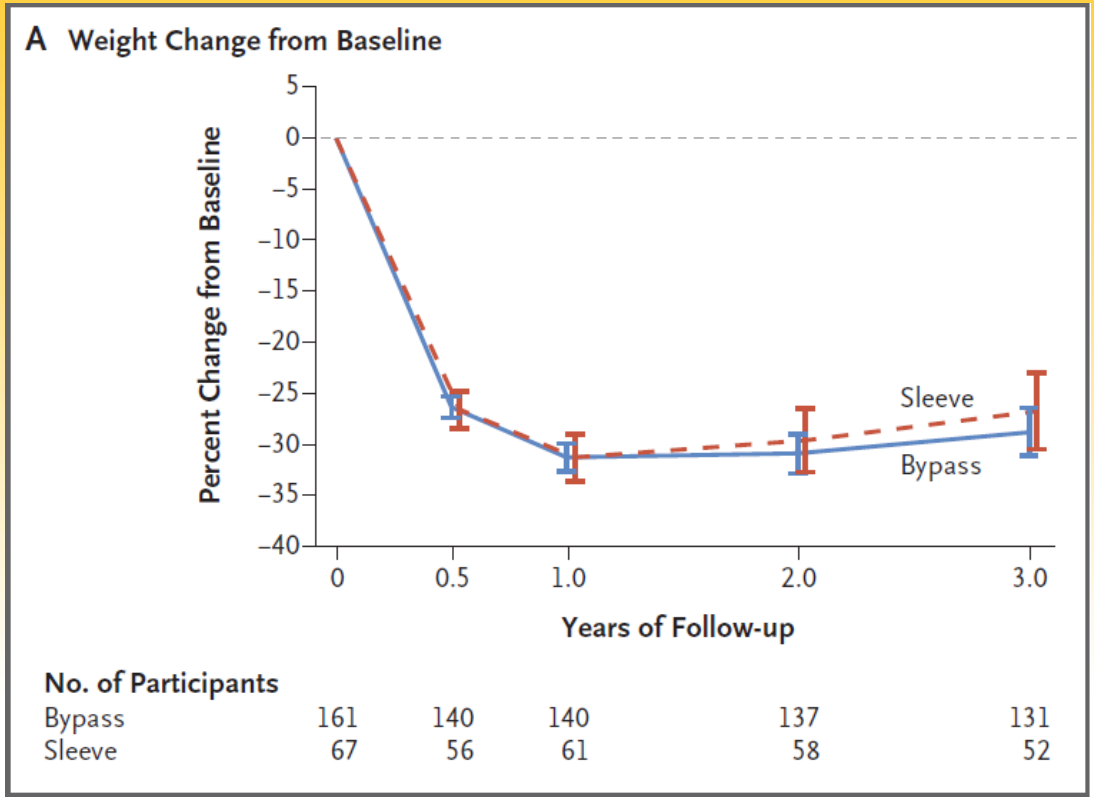


Kelly and Fox, from "Pediatric Obesity: Etiology, Pathogenesis, and Treatment" 2016.

Metabolic/Bariatric Surgery

Pratt et al. *Surg Obes Relat Dis* 2019.
Armstrong et al. *Pediatrics*. 2019.
Barlow et al. *Pediatrics* 2007.
Styne et al. JCEM 2017.

Metabolic/Bariatric Surgery



Inge et al. *NEJM* 2015.

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"Despite these findings, **less than 0.04%** of children and adolescents with severe obesity are treated with MBS each year."

Griggs et al. *JAMA Pediatr* 2018.

The Rationale for Anti-Obesity Pharmacotherapy

- Filling the treatment gap
- Ability to target underlying pathways regulating energy balance
- Potential for enhancement of weight loss maintenance
- Potential to scale up

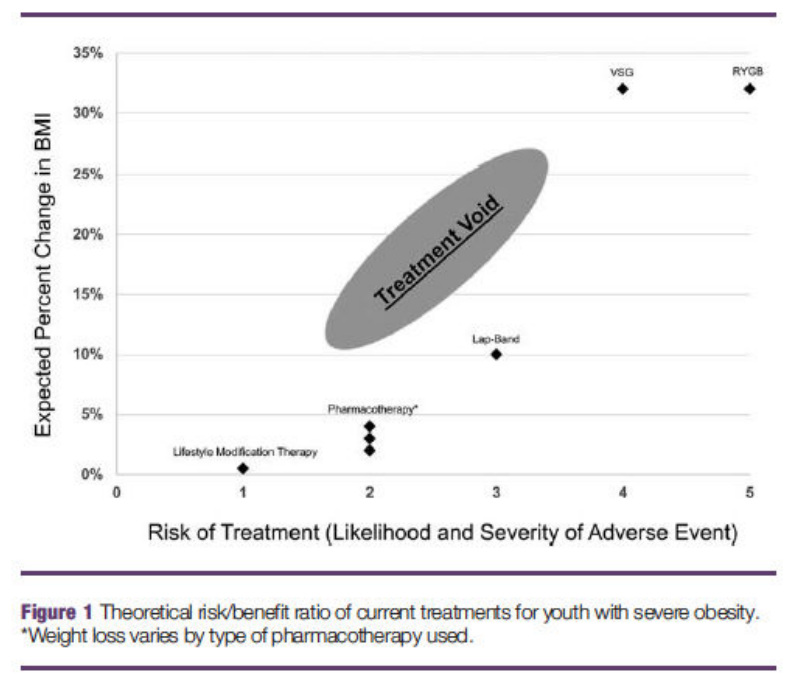

Figure 1 Theoretical risk/benefit ratio of current treatments for youth with severe obesity. *Weight loss varies by type of pharmacotherapy used.

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Current State of Pediatric Obesity Pharmacotherapy

- Orlistat approved for 12 years and older
- Phentermine approved for older than 16 years
- Liraglutide 3mg approved for 12 years and older
- Phentermine/topiramate approved for 12 years and older

- Liraglutide 3mg approved for 12 years and older

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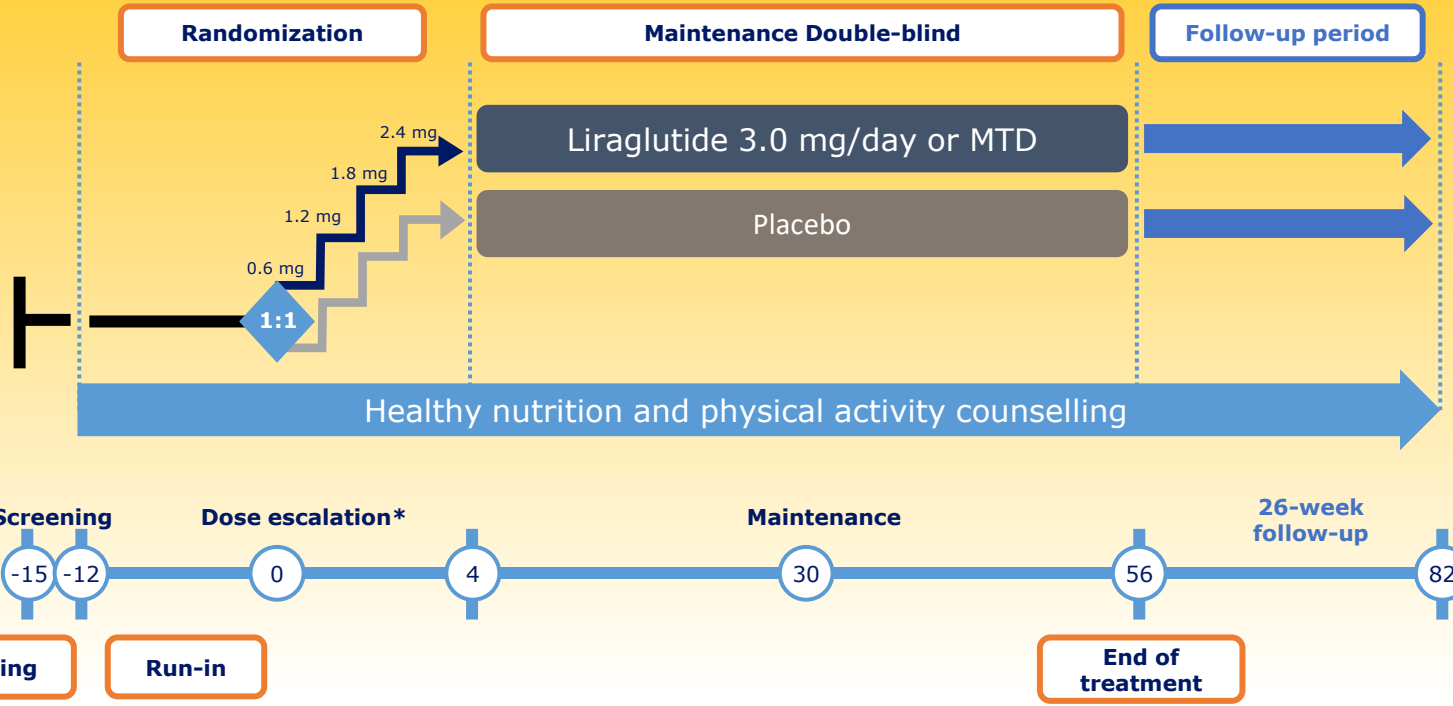
Liraglutide 3 mg Adolescent RCT

Key eligibility criteria

- 12–<18 years (pubertal)
- BMI corresponding to ≥30 kg/m^2 for adults[1]
- Insufficient weight loss in response to lifestyle therapy alone

Primary endpoint

- Change in BMI SDS from randomization to 56 weeks

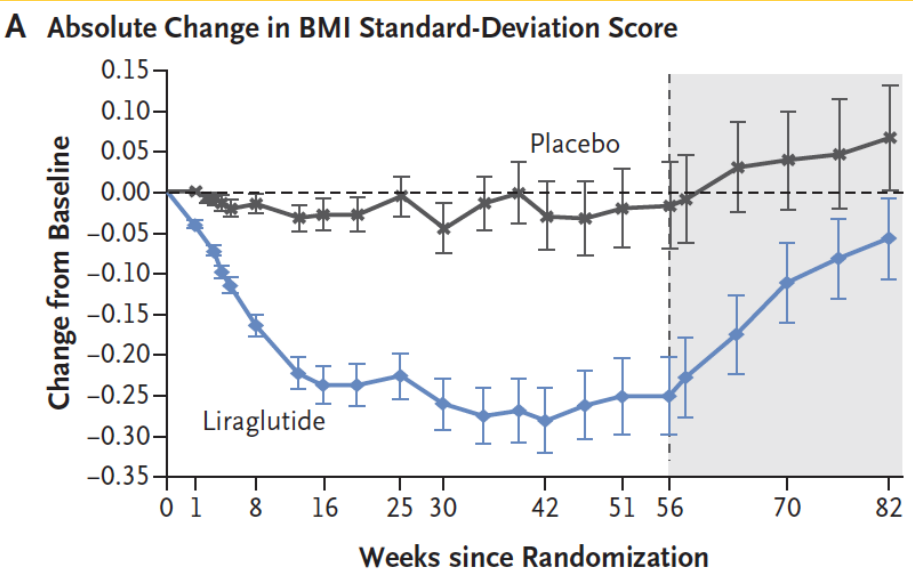


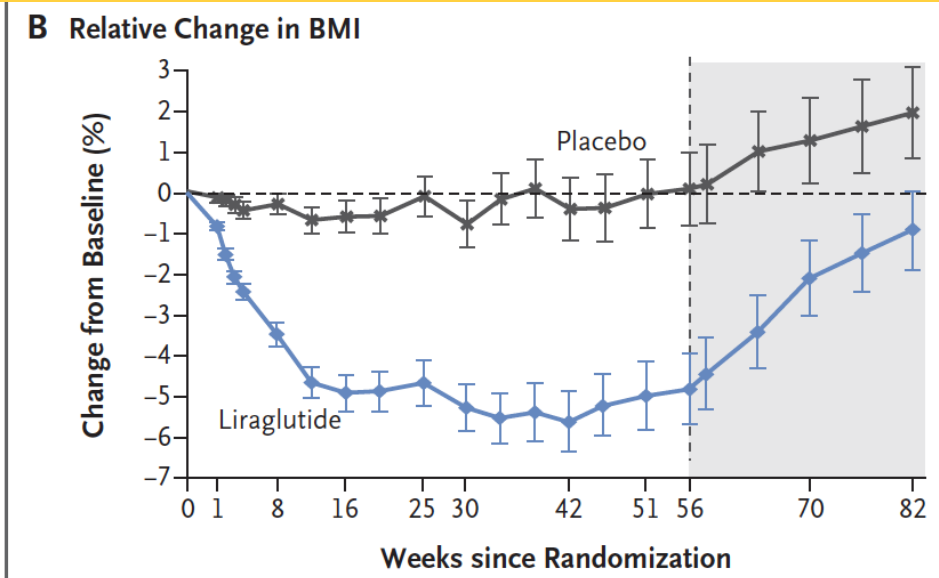
1. Cole TJ, et al. BMJ (Clinical research ed) 2000;320:1240–3.
Randomization was stratified by pubertal and glycemic status. Quality of life was assessed by Impact of Weight on Quality of Life [IWQOL]-Kids questionnaire.
BMI SDS, body mass index standard deviation score; MTD, maximum tolerated dose; QoL, quality of life.

Kelly *et al. N Engl J Med* 2020; doi:10.1056/NEJMoa1916038

Liraglutide 3 mg Adolescent RCT

Mean BMI Change by Group





Kelly et al. NEJM 2020

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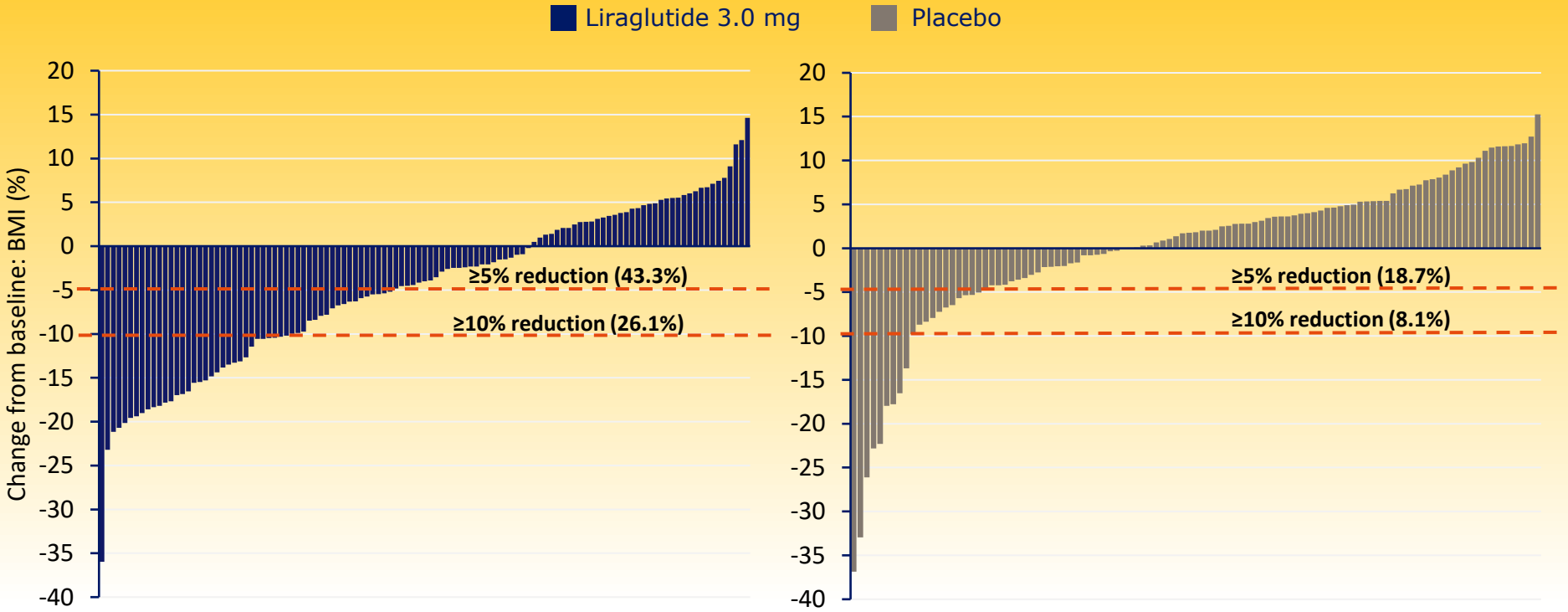
Liraglutide 3 mg Adolescent RCT

Participant-Level BMI Change

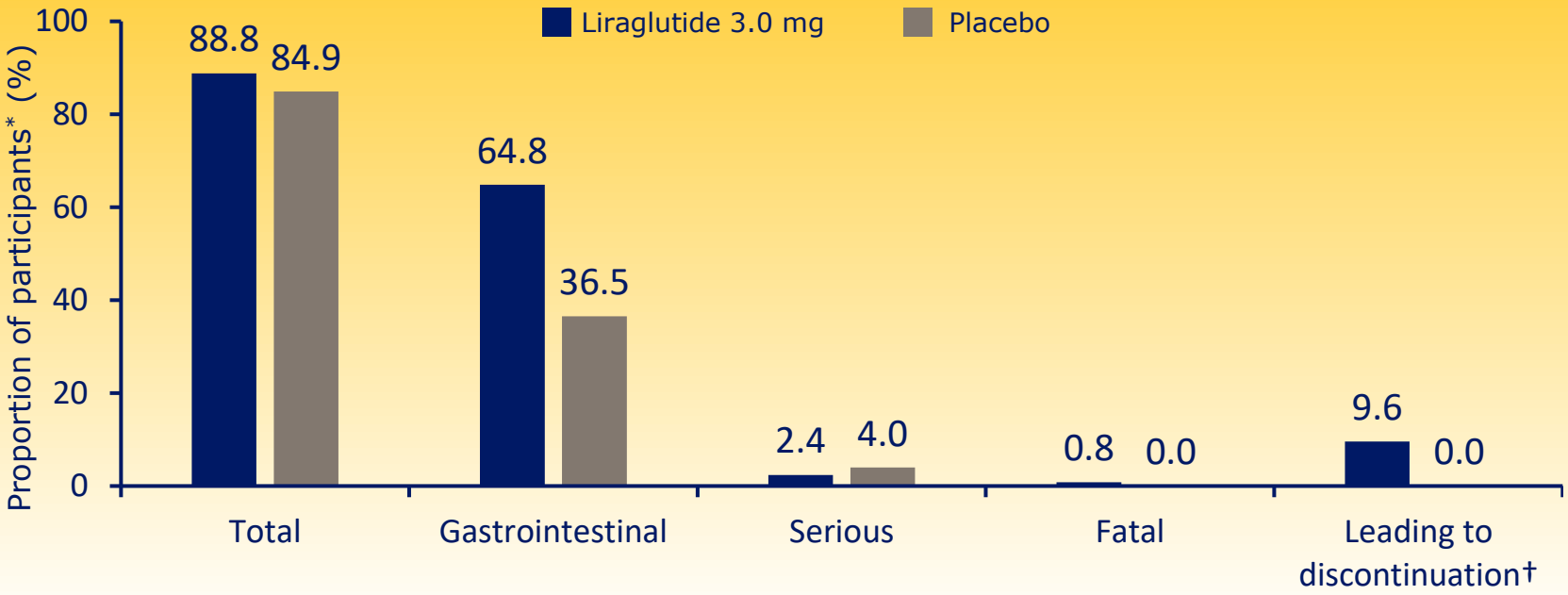


Full analysis set. Statistical analysis is logistic regression with jump-to-reference missing data imputation.
*post-hoc analysis

Kelly *et al. N Engl J Med* 2020; doi:10.1056/NEJMoa1916038

Liraglutide 3 mg Adolescent RCT

Adverse Events

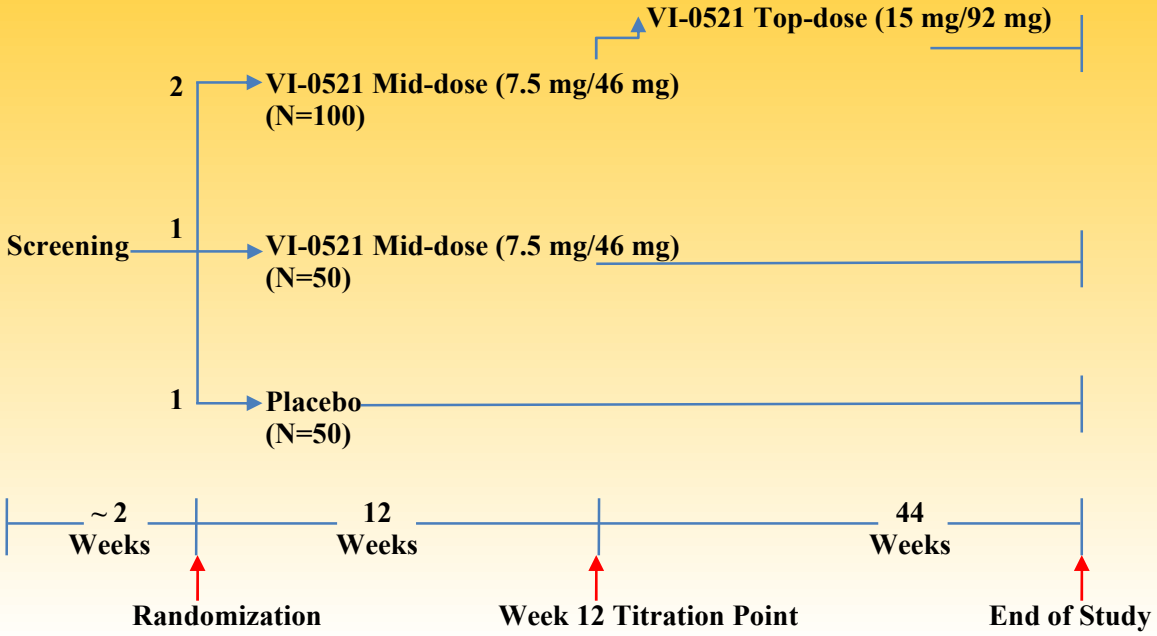


Safety analysis set (n=125 for liraglutide and n=126 for placebo). Data are from participants on-treatment (including events occurring up to 14 days after the last day on trial product).
*Participants experiencing at least one event.
†Leading to discontinuation of trial product

Kelly *et al. N Engl J Med* 2020; doi:10.1056/NEJMoa1916038

Phentermine/Topiramate Adolescent RCT

- Key Eligibility Criteria
  - Age 12 to <17 years old
  - BMI ≥95th percentile
  - Tanner stage >1
- Primary Endpoint
  - Mean percent change in BMI
- Key Secondary Endpoints
  - Categorical BMI reduction
  - Waist circumference
  - Cardiometabolic risk factors
- All received lifestyle therapy
- 20 study sites in the U.S.



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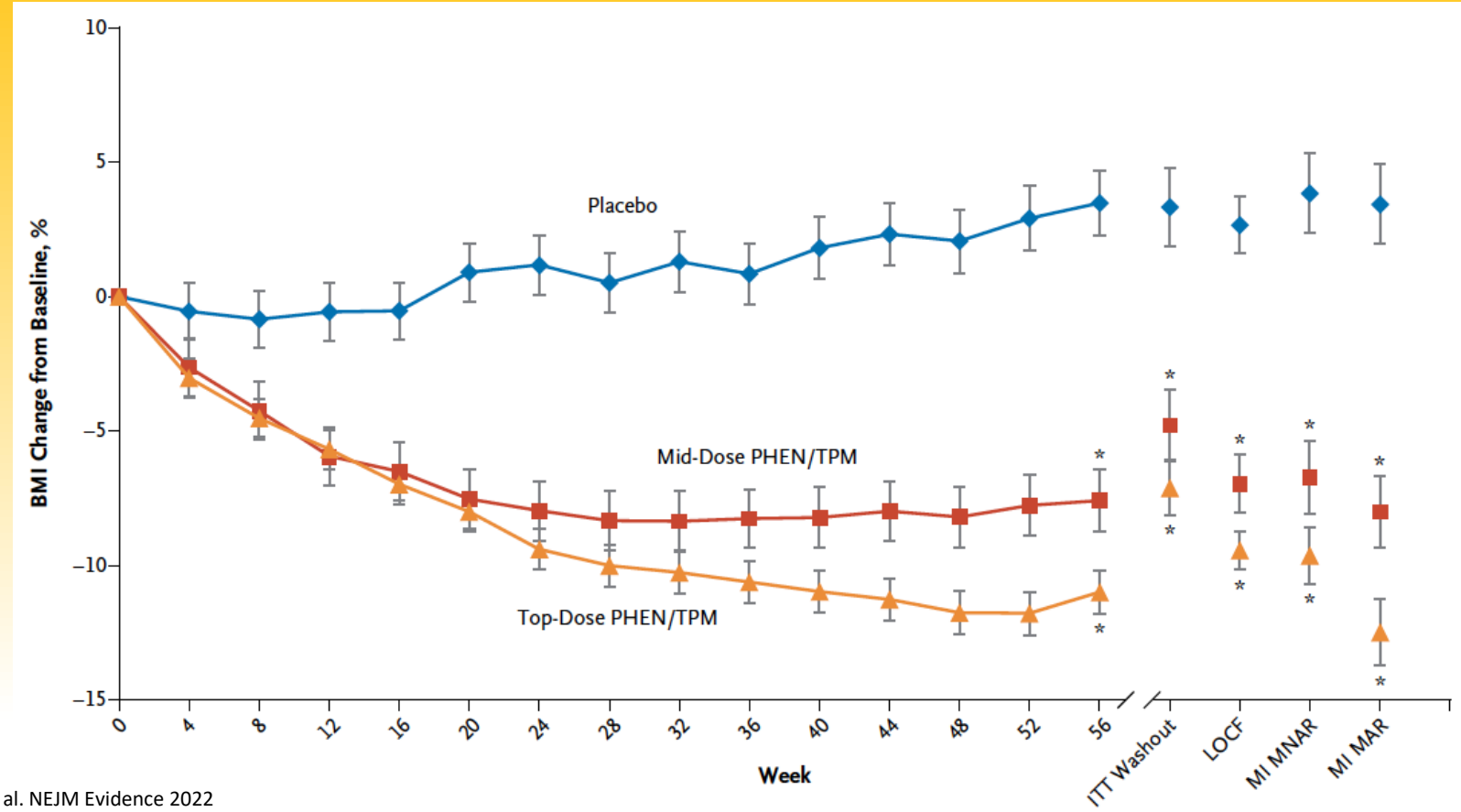
Percent Change in BMI



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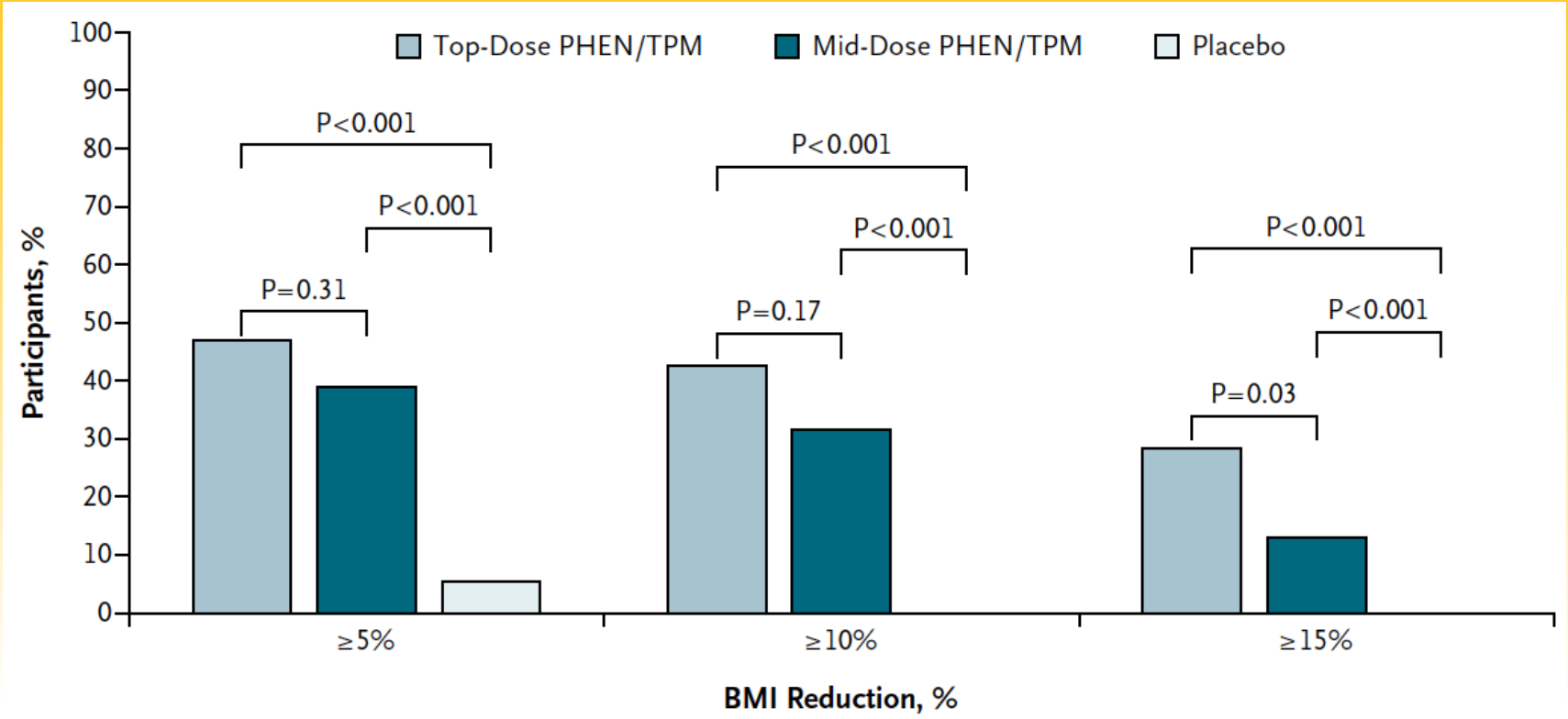
Categorical BMI



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Primary and Secondary Outcomes

Endpoint	Placebo (N = 56)	Mid-dose (N = 54)	Top-dose (N = 113)	Mid-dose vs. Placebo (95% CI)	Top-dose vs Placebo (95% CI)
Percent body mass index (percentage point difference)	3.34 (1.44)	-4.78 (1.30)	-7.11 (1.01)	-8.11% (-11.92, -4.31)	-10.44 (-13.89, -6.99)
Body mass index (kg/m^2)	1.20 (0.46)	-2.53 (0.44)	-4.15 (0.31)	-3.73 (-4.97, -2.50)	-5.35 (-6.44, -4.27)
Weight (kg)	6.57 (1.28)	-5.49 (1.23)	-9.23 (0.86)	-12.06 (-15.55, -8.58)	-15.80 (-18.82, -12.77)
Waist circumference (cm)	0.31 (1.39)	-7.42 (1.29)	-9.27 (0.91)	-7.72 (-11.43, -4.02)	-9.58 (-12.83, -6.33)
HDL-C (percentage point difference)	-3.65 (2.85)	6.65 (2.45)	5.10 (1.76)	10.30 (2.91, 17.70)	8.75 (2.15, 15.35)
Triglycerides (percentage point difference)	8.35 (7.37)	-12.79 (6.30)	-12.37 (4.49)	-21.14 (-40.24, -2.05)	-20.72 (-37.71, -3.72)
Systolic blood pressure (mmHg)	2.80 (1.62)	-0.97 (1.50)	1.00 (1.04)	-3.76 (-8.09, 0.56)	-1.80 (-5.58, 1.97)
Diastolic blood pressure (mmHg)	3.11 (1.33)	-0.87 (1.22)	0.14 (0.85)	-3.99 (-7.53, -0.45)	-2.97 (-6.07, 0.12)

Kelly et al. NEJM Evidence 2022

Adverse Events

- Incidence of at least one adverse event was 51.8%, 37.0%, and 52.2% in the placebo, mid-dose, and top-dose groups, respectively
- Three serious adverse events (bile duct stone, depression, suicidal ideation) were reported in two participants in the top-dose group
  - One participant was hospitalized for a bile duct stone within one week of completing the study
  - One participant experienced depression and suicidal ideation and study drug was discontinued; subsequently experienced several recurrences thereafter; events occurred during the first month of treatment, before dose escalation

Kelly et al. NEJM Evidence 2022

Mental Health and Bone Outcomes

- Psychiatric disorders occurred in 7.4% in the mid-dose group, 8.8% in the top-dose group, and 1.8% in the placebo group
- No clinically relevant differences across groups for PHQ-9 and C-SSRS
- CANTAB (cognition) demonstrated no differences among groups
- No adverse events related to drug abuse, dependence, or withdrawal
- No differences among groups in bone age or bone health

Kelly et al. NEJM Evidence 2022

Pediatric Pipeline and Expected Timeline

- Liraglutide 3 mg approved by FDA and EMA
- Phentermine/topiramate approved by FDA
- Semaglutide adolescent trial completed with results expected soon
- Tirzepatide results from adult phase III trial recently published

The Need for Precision Medicine in Obesity Management

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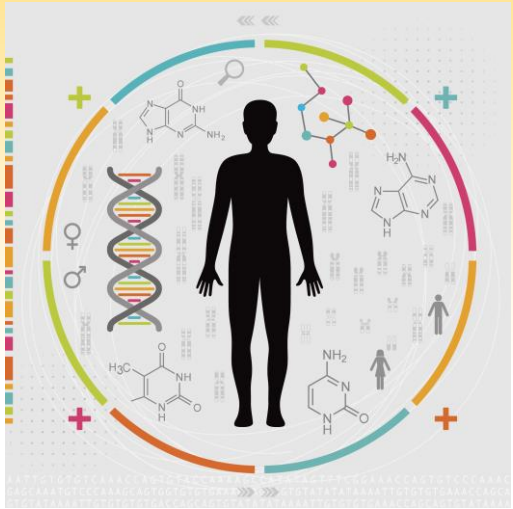
What is Precision Medicine?

- Identification and characterization of sources of heterogeneity
- Synthesis and application of this information to select appropriate treatment(s) with goal of maximizing benefit while minimizing risk
- In other words, getting the right treatment to the right patient at the right time



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On the Horizon – Areas Worthy of Investigation

VIEWPOINT

Toward Precision Approaches for the Prevention and Treatment of Obesity

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Obesity, defined as a body mass index of 30 or greater for adults and 95th percentile or more for age and sex among youths, affects almost 40% of adults and 19% of youths in the United States and has increased substantially over the past 40 years.[1] Easy availability of inexpensive, energy-dense, palatable foods; higher costs of, and insufficient access to, more healthful foods; reduced need for physical activity; and plentiful opportunities to engage in rewarding sedentary behaviors create an ideal environment for obesity to emerge. The significant differences in obesity prevalence among genetically similar Pima American Indians living in Arizona (>60%) and in Mexico (<20%)—groups with marked differences in access to food and obligate physical activity[2]—provide a clear example of how important environment can be for obesity.

Nevertheless, even under obesity-promoting conditions, not everyone develops obesity. There is variability in response to the environment. Important differences among individuals in obesity susceptibility may be due to psychosocial, cultural, and economic factors, but also can be caused by genetic sequence variations, epigenetic events, and other factors, including gene-environment interactions. There are, for example, an increasing number of identified single-gene defects sufficient to cause severe, childhood-onset obesity. Individuals with rare inactivating mutations of genes in the hypothalamic leptin-signaling pathway (such as those with complete deficiencies of leptin, its receptor, and several downstream effectors of leptin) develop obesity. Heterozygous mutations affecting some genes in the same pathway, including the melanocortin 4 receptor (*MC4R*), also lead to obesity. *MC4R* heterozygous inactivating mutations are reported to be found in as many as 1% to 4% of individuals with severe, early-onset obesity.[3]

Additionally, many single-nucleotide polymorphisms (SNPs) and copy number variations throughout the genome that are not directly linked to leptin are associated with BMI. In many cases, each change has a relatively minor contribution to body weight. The most well known of these are intronic SNPs of the *FTO* gene (a gene linked with common obesity), for which presence of 2 risk alleles increases adults' body weight by a mean of approximately 3 kg and increases odds for obesity 1.67-fold.[4] Some SNPs (including those of *FTO*) show evidence for gene-environment interactions, including interactions with physical activity and even socioeconomic status.[5]

> Even the most sophisticated individual approaches for obesity prevention and treatment are less likely to be effective in an environment that is obesity-promoting.

Concordant with the individual heterogeneity in circumstances that leads to variability in weight gain, when people with obesity try to lose weight, they also demonstrate substantial individual differences both in the amount of weight lost during intervention and in the amount of weight regained thereafter. Such variability is seen for behavioral,[6] pharmacotherapeutic,[7] and surgical[8] approaches. Although there have been myriad attempts to characterize predictors of response for behavioral and pharmacologic approaches for weight management, the only consistently identified predictors of later response appear to be early responses to the intervention (eg, weight lost during the first few weeks of intervention) and adherence to the weight loss program.[9] However, most studies attempting to predict weight loss involve relatively small cohorts. Furthermore, because similar measures of potential predictors are infrequently collected by different investigators, results are difficult to combine through meta-analysis. As a result, initial choices for obesity prevention or treatment usually do not consider predictors of variability in response. Instead, factors such as availability, cost, and patient or physician preferences take precedence over a more targeted approach.

Advances in the understanding of the genetics of obesity have begun to change this situation, and some patients with monogenic obesity can receive treatment specifically directed at their disorders. For the rare individual with leptin deficiency, treatment with leptin induces a remarkable and sustained improvement in adiposity. In 2 patients with proopiomelanocortin (*POMC*) deficiency, substantial weight losses in response to injections with an α-melanocyte-stimulating hormone analogue have been recently reported.[10] As the understanding of the most important genes regulating body weight increases and additional patients with monogenic disorders are identified, more treatments targeted to underlying mechanisms can be developed and deployed.

Because most people with obesity do not have a monogenic cause, but rather have multiple genetic risk variants (each with small effects), a solitary "magic bullet" seems unlikely to materialize. Nevertheless, it remains possible that identification of genetic, metabolic, behavioral, and environmental factors that make

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Box. Examples of Approaches to Investigate Targeted Strategies for Obesity Prevention and Treatment

- Patient-reported measures
- Measures of food preferences, hunger, and satiety
- Neurocognitive testing
- Physiological and psychological response to activity
- Functional neuroimaging
- Gastrointestinal physiology and microbiome
- Metabolomics
- Sequence and copy number variants
- Epigenetic modifications
- Nutrigenomics
- Pharmacogenomics

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Summary and Key Points

- Lifestyle therapy is critical but the dose needed is challenging
- The body fights back to resist weight loss and maintenance
- Anti-obesity medication has a key role but options are currently limited
- The anti-obesity medication pipeline is growing with approvals expected in the next few years
- Tailored treatments are needed

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