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**Scientific Statement**

# Obesity science, research gaps, and opportunities in the new era of obesity medicines: an Endocrine Society scientific statement

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## Abstract

**The medical management of obesity has been transformed by the introduction of obesity medicines (OMs), based on the actions of glucagon-like peptide-1 and other nutrient-stimulated hormones, enabling the achievement of unprecedented weight reduction through pharmacotherapy. Here we review our current understanding of key issues surrounding obesity treatment, weight reduction, and improving health for people living with obesity. Key gaps in our knowledge of fundamental aspects of energy homeostasis are identified with a focus on their translational importance for improving outcomes. We discuss the utility of weight and health metrics, heterogeneity in achievement of clinical outcomes, individualization of treatment targets and goals, strengths and limitations of clinical trial, observational and real-world data (RWD), opportunities for improving the joint use of lifestyle management and OMs, gaps in our understanding of the long-term safety and side effects of current and emerging medicines, and the potential negative effects of losing weight. Collectively, while not intended as guidance for treatment, this document highlights the considerable progress and new research opportunities for interrogating basic and clinical science with the goal of translating advances in endocrine science into optimized outcomes for a broad range of individuals along the continuum of the weight journey.**

## Essential points

- The pathophysiology of obesity with a focus on body fat regulation/defended fat mass
- The heterogeneity of obesity with a focus on treatment response
- Redefining treatment targets beyond percent total body weight loss
- The physiology of phases of treatment response to pharmacotherapy
- Health outcomes with pharmacotherapy
- Safety of pharmacotherapy

Obesity is the most prevalent chronic disease of our time (1), significantly impacting the health of most of the world. In 2017, the Endocrine Society brought together experts charged with assessing current knowledge regarding mechanisms underlying obesity (2). At that time, pharmacologic interventions were at a tipping point, emerging from efficacious (3) to highly efficacious monotherapies, with the Food and Drug Administration's (FDA) approval of semaglutide and tirzepatide for a "chronic weight management" indication in 2021 and 2023, respectively (4, 5). With the introduction of these and other novel nutrient-stimulated hormone (NuSH) receptor modulators (6, 7), the understanding of obesity pathophysiology, treatment, and disease state and life cycle is rapidly expanding. These powerful agents can be used as probes to help elucidate the complexities of this disease as well as its impact on overall health. Notably, over a brief period of just 3 years, numerous studies have emerged underscoring the clear impact of treating obesity on

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improving health (8, 9). These studies have led to a series of expanded indications for semaglutide and tirzepatide in the treatment of various obesity-related complications. In 2024, the FDA approved semaglutide for reduction of major adverse cardiovascular events (MACEs) in adults with cardiovascular disease (CVD) and overweight or obesity and approved tirzepatide for moderate to severe obstructive sleep apnea (OSA). In 2025, semaglutide was FDA-approved for metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver scarring (fibrosis) (10) without an overweight or obesity requirement (though 80-90% of people with MASH have overweight or obesity, by body mass index [BMI]). Clearly there is now a focus on utilizing these agents not only for treatment of overweight and obesity but also for obesity-related disease modification and potentially for other diseases (11, 12).

As much as we have learned over the last five decades about obesity, our understanding of obesity is relatively nascent. Indeed, the environmental and physiologic drivers of increasing obesity prevalence are still being debated (13). Furthermore, the recent ability to produce a reduction of body weight by 25% or more in many individuals demands a better understanding of the physiology of weight loss and how best to achieve optimal body composition and body health in the weight-reduced state. Similarly, understanding the mechanisms of action of these agents beyond weight reduction is equally important (14). Here we highlight key gaps in our understanding of obesity with a focus on pharmacological interventions and propose studies that may help clarify fundamental aspects of our understanding of obesity.

There are transformational discoveries in medicine, such as the discovery of penicillin, insulin, and vaccines; these discoveries not only saved lives but also reshaped how we understand the diseases they prevent and treat. Current and emerging pharmacotherapeutics for the treatment of obesity enable us to do just that, but we must seize the moment with intentionality, thoughtfully designing a research roadmap to better understand the disease, enabling optimal treatment and improving health outcomes for people living with obesity.

# The pathophysiology of obesity

We discuss key concepts underlying the pathophysiology, highlighting key unanswered questions meriting additional attention, as outlined below.

1. How does the brain regulate energy storage across the life cycle, including both the quantity and location of body fat?
   (A) What are the cellular and molecular mechanisms by which the body determines appropriate fat mass for each phase of the life cycle?
   (B) Are there distinct mechanisms to determine the size of different fat depots?
   (C) What are the cellular and molecular mechanisms by which the body defends total (and/or regional) fat mass?
   (D) What circuits in the brain are responsible for these regulatory mechanisms and how do they interact?
2. What are the pathophysiologic mechanisms by which "normal" fat mass and regional distribution are disrupted in obesity?
   (A) What are cellular and molecular mechanisms whose disturbance or disruption can lead to obesity?
   (B) Which mechanisms are common to most forms of obesity? Which are variable and likely to lead to clinically relevant obesity subtypes?
   (C) What are the cellular and molecular mechanisms by which effective obesity medications improve fat mass physiology?
   (D) To what degree are they distinct from or overlap with the mechanisms underlying the pathophysiology of obesity?
   (E) To what degree are the mechanisms in common to different classes of obesity medications? To what degree do they vary based on the molecular mechanism(s) of the medication?
   (F) How can genetic evaluation shed light on these various mechanisms?
   (G) To what degree do genetic contributors to obesity vary among types of obesity that express different phenotypes?
3. What are the primary environmental contributors to obesity?
   (A) Are there environmental contributors common to all people with obesity?
   (B) Are there phenotypic differences among patients who exhibit different responses to specific environmental contributors?
   (C) What are the similarities and differences in the phenotypes, cellular and molecular mechanisms, and genetic contributions to obesity induced by different classes of environmental obesogens?

## How does the brain regulate energy storage across the life cycle, including both the quantity and location of body fat?

Nearly all of the energy stored by animals is in the form of fat, most commonly triglycerides, and there is strong clinical and observational evidence that body fat mass and distribution are tightly but variably regulated across the life course. Decreases in baby fat, changes in fat mass associated with puberty, and fluctuations in body fat during and after pregnancy occur without deliberate management in both humans and animals, strongly suggesting that they are physiologically regulated. The anatomic distributions of baby fat, pregnancy-associated fat, and aging-associated fat (including increased fat and changes in fat distribution associated with menopause) are distinct. There are also wide interindividual variations in body fat distribution and the magnitude of inflammation-associated visceral adipose tissue that appear to reflect both familial and population-based differences (15). Despite these observations, the cellular and molecular mechanisms underlying these regulatory processes remain unclear.

Opinions vary as to the primary target of the regulation of adipose tissue mass and body weight, with possibilities including fat mass and body weight itself, energy balance, appetitive drives (eg, food-driven reward, hunger, satiation, satiety), energy intake (EI), taste attraction and aversion, energy partitioning, energy expenditure (EE), and a combination of all of these mechanisms. Underfeeding and overfeeding studies in animals and people

have demonstrated that these manipulations often lead to compensatory changes (counterregulatory forces) in both food intake and EE, promoting restoration of the preperturbation state (16–18). Most well-controlled studies have been conducted in rodent models, which have demonstrated that this compensatory response is mediated primarily by changes in EE, leading to its description as "metabolic adaptation." While similar effects are seen in humans, the compensatory responses appear to be mediated more by changes in appetite than changes in EE (17, 19). Thus, we recommend the use of the more inclusive, expanded definition of the term "metabolic adaptation," allowing inclusivity of both of these counterregulatory response/forces (EE and appetite). There is accumulating evidence that effective pharmacological and surgical therapies for obesity mitigate these compensatory responses (20, 21). The suppression is most evident during acute treatment-induced weight loss and is mitigated as body weight and fat mass settle into a new plateau. Ongoing human studies are interrogating the importance of molecular, cellular, behavioral, physiologic, environmental, and psychosocial factors that are associated with the ability to maintain a reduced body weight after successful weight loss (22).

These observations are all consistent with body fat mass (total or depot-specific) being the primary target of physiologic regulation, with appetitive drives and autonomically regulated EE serving as the mechanisms by which the target fat mass is attained (Fig. 1A and 1B). Studies in hypothalamus-lesioned dogs by Keesey et al provided early evidence for fat mass-targeted regulation (23), and more recent studies of the weight loss effects of bariatric surgery and obesity pharmacotherapy provide additional support for this model, which has often been described variously as physiologic regulation to homeostatic energy balance resulting in a "defended" fat mass, a fat mass "set point," or "settling point" (20, 24, 25). This terminology can be misleading, however, as changes in fat mass and its location across the life course indicate that the target fat mass is not fixed but varies in response to environmental variables as well as normal developmental and energy needs.

Multiple lines of evidence strongly suggest that regulation of body fat mass is primarily mediated by the brain (26). Pathological or surgical damage to the medial hypothalamus is associated with obesity in both animals and humans, while similar damage to the lateral hypothalamus leads to a profound loss of body fat (23). Genome-wide association studies have revealed that more than 75% of genes whose allelic variations are associated with obesity are expressed exclusively or predominantly in the central nervous system (CNS) (27). Moreover, the therapeutic effects of bariatric surgery and highly effective OMs appear to result primarily from changes in CNS signaling.

Despite these observations, relatively little is known about either the cellular or molecular basis for normal body fat regulation. These are high-priority areas of investigation (22), since their elucidation has the potential to uncover novel treatment

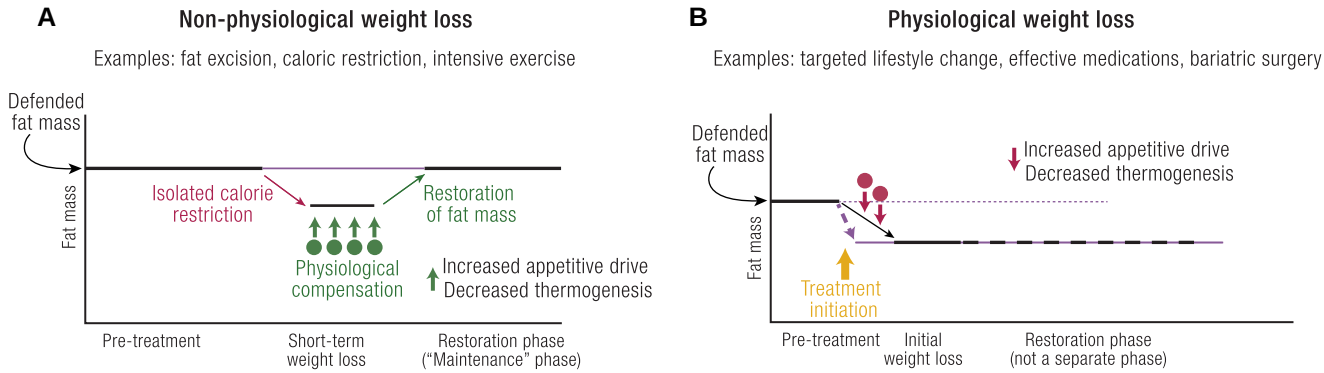


**Figure 1** Fat mass-targeted model of energy storage regulation. According to this model, the regulated parameter is body fat mass, either as a single entity or, more likely, as a group of targets for different adipose depots. Energy intake and utilization are regulated to achieve and maintain energy stores and fat distribution appropriate to developmental stage and energy needs. Energy balance, itself determined by appetitive drives and nonvolitional energy expenditure, is not the target of regulation. Rather, these parameters are mechanisms used by the body to regulate fat mass and distribution. In this model, durable changes in fat mass, whether normal or disrupted in obesity, are determined by changes in central regulation and then mediated by secondary alterations in appetite and energy expenditure. (A) Nonphysiologic weight loss is characterized by an illness- or injury-induced or purposeful decrease in food intake or an increase in energy expenditure (physical activity), without changing the underlying fat mass regulatory apparatus. While the initial effect is loss of fat and, consequently, body weight, it is followed by physiologic compensation (a combination of increased appetite and decreased energy expenditure) to return the body to the original target fat mass. This is commonly seen after acute illness and can account for the regain of lost weight as the body seeks to restore physiologically mandated energy stores. After nonphysiologic weight loss, the only way to maintain weight loss is to continually resist the physiologic drive for restoration of energy stores. (B) Physiologic weight loss is weight loss determined by normal developmental processes such as loss of baby fat, loss of body fat in males undergoing puberty, and loss of maternal fat after pregnancy and cessation of postpartum milk production. According to this model, it is also the mechanism that drives durably effective treatment of obesity, whether caused by changes in dietary composition (not calories), discontinuation of obesogenic medications, removal of environmental obesogens, obesity medications, or bariatric/metabolic surgery. With physiologic weight loss, the intervention rapidly alters physiologic regulation to decrease the target fat mass. Normal physiologic mechanisms then recognize the need to decrease fat mass, which is accomplished by a combination of decreased appetitive drives (decreased hunger, cravings, and food noise and enhanced satiation and satiety) and increased or preserved energy expenditure. Once fat mass falls to the new target, these physiologic forces normalize to maintain homeostasis at the new target by partially reversing the decreased appetite and increased energy expenditure. Under this model, maintenance of physiologically induced weight loss does not require purposeful resistance to enhanced appetitive drives.

targets, biomarkers of early treatment response, and more sensitive indicators of effective obesity prevention strategies. The regulation of body fat appears to be highly complex, suggesting the involvement of multiple brain regions. The medial hypothalamus, including the arcuate and adjacent nuclei, is key to leptin-mediated regulation (28). Despite the requirement for effective leptin signaling to maintain normal fat mass regulation, treatment with leptin receptor agonists provides minimal benefit for common forms of obesity (29, 30). In contrast, glucagon-like peptide-1 receptor (GLP-1R) signaling does not appear to be necessary for normal fat mass regulation, as evidenced by the lack of GLP-1R expression in major adipose tissue cell types, the absence of obesity in mice with genetic deficiency of the GLP-1R (31, 32) and the lack of compelling genetic data linking variation in the human GLP1R to control of adipose tissue mass or body weight (33, 34). Nonetheless, GLP-1R agonists (GLP-1 RAs) and other NuSH receptor modulators, such as glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RAs, have emerged as the most effective pharmacological means of treating obesity thus far identified. This apparent contradiction between the necessity and sufficiency of different signaling systems to regulate body fat mass underscores the complexity of the underlying physiology. It may also explain the observation that genetic variants that predispose to variation in body weight and obesity (determined by individual–locus associations or genome-wide polygenic scores) do not predict the weight loss response to bariatric surgery or obesity pharmacotherapy (35, 36). Perhaps the mechanisms by which these therapies work override the pathophysiologic changes causing obesity rather than simply undoing them.

After the initial discovery of the insulinotropic actions of native GLP-1 in the mid-1980s, observations that GLP-1 reduced food intake enabling weight reduction followed a decade later. As native GLP-1 is rapidly degraded by dipeptidyl peptidase-4 and cleared by the kidney, degradation-resistant molecules such as exendin-4 (exenatide) were pursued for type 2 diabetes (T2D), resulting in the first clinical approval of twice-daily exenatide in 2005. Nearly a decade later, once-daily liraglutide was approved for chronic weight management in 2014, followed by semaglutide in 2021 and tirzepatide in 2023. These 2 medicines are small acylated peptides, suitable for once-weekly administration, and have ushered in the modern era of the medical treatment of obesity. More recently, a daily oral formulation of semaglutide and the oral small molecule GLP-1 RA orforglipron have also been approved for the therapy of obesity. Many other molecules are in development, including additional small molecules and peptides suitable for oral administration, multihormone receptor modulators targeting new mechanisms, and monthly antibodies and peptides allowing for less frequent dosing (7).

Despite their powerful clinical benefit, we have limited knowledge of the regions, neural circuits, and cells within the human brain where GLP-1R activation promotes improvement in body fat mass regulation. We have even less knowledge of how that activation is translated into changes in defended fat mass. A striking example of the limitations of our understanding can be found in the comparison of liraglutide and semaglutide. Liraglutide, developed first, is a long-acting GLP-1 analog ($t_{½}$ of approximately 13 hours) (37) that induces significant weight loss. Semaglutide is a similar compound, with nearly identical receptor binding and activation properties in cell culture but was designed to have an even longer half-life (approximately 160 hours). That semaglutide has twice the weight loss efficacy of liraglutide in vivo in animals and people was unexpected. Brain distribution studies in rodents have suggested that peripherally administered semaglutide may penetrate the brain more effectively, perhaps generating a more effective stimulation of the medial hypothalamus, but careful assessment of the data suggests that higher concentrations of semaglutide are observed only in selected regions of the brain (20). Liraglutide concentrations are equal to or higher than semaglutide concentrations in relevant regions of the hypothalamus, suggesting that other regions of the brain may be the most relevant sites of action of GLP-1 RAs (20). A recent study provides strong support for the role of hindbrain nuclei, particularly neurons in the area postrema and nucleus of the solitary tract, and particularly those neurons that express the gene encoding pituitary adenylate cyclase-activating peptide (38). Studies to generate a more complete understanding of the cellular and molecular mechanisms by which regulators of the GLP-1, GIP, glucagon, amylin, and activin receptors influence body fat mass homeostasis could generate a variety of physiologic and therapeutic benefits. For example, one of the challenges of current and emerging obesity pharmacotherapy is the high incidence of gastrointestinal (GI) adverse effects (Fig. 2), requiring time-consuming dose escalation algorithms to allow tolerance of therapeutic drug levels. Although nausea and vomiting centers of the brain somewhat overlap with weight regulatory targets of these medications, several clinical studies have found little or no correlation between the presence or severity of adverse effects and the degree of weight loss induced by these medications (39, 40). If these beneficial and adverse effects of the medications are independent, perhaps they are mediated by different mechanisms and therefore different groups of cells within the same region (41, 42). If human GLP-1R + neurons have characteristics different enough to allow for selective activation of the cells that regulate fat mass without activation of the cells that generate the aversive side effects (42), there would be an increased potential for developing a drug that avoids the need for dose escalation.

In general, greater mechanistic understanding can lead to enhanced treatment specificity. Advances in neuroimaging linked to clinically relevant changes in appetite, body weight, and biomarkers gleaned from systems biology may provide greater insight into interindividual heterogeneity and responses to OMs. As we learn more about the differences among different clinical subtypes of obesity, greater mechanistic understanding may also be one of the most direct means of identifying novel biomarkers that could serve as effective predictors of treatment response and thereby facilitate more individualized and precise treatment strategies. Notably, this document does not attempt to address key issues related to the diagnosis and treatment of rare and monogenic forms of obesity, a related yet distinct set of disorders that is discussed elsewhere (43, 44).

## What are the pathophysiologic mechanisms by which “normal” fat mass and distribution are disrupted in obesity?

As described earlier, genetic evidence suggests that effective surgical and pharmacological treatment of obesity may be mediated through mechanisms distinct from those that cause

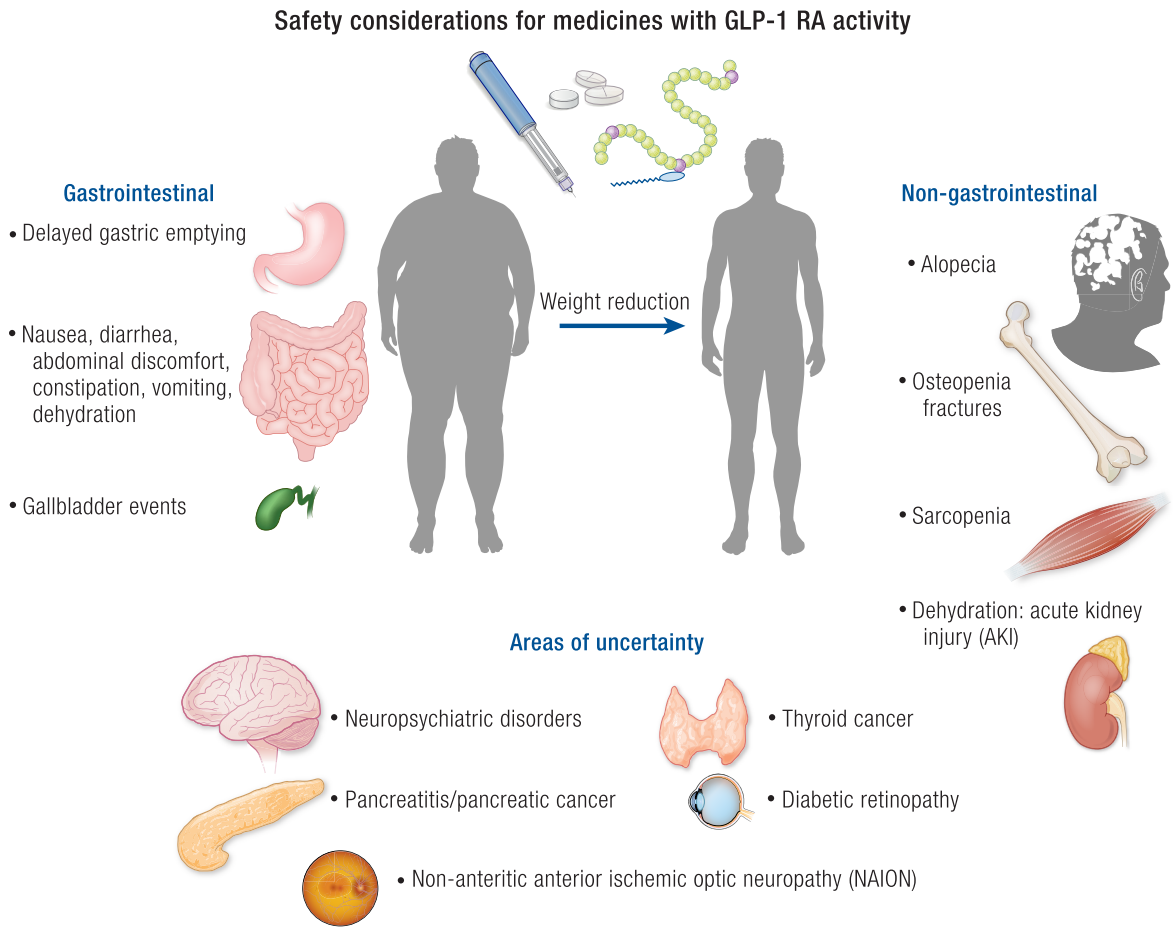


**Figure 2** Safety considerations associated with GLP-1 RA medicines. These considerations are classified as gastrointestinal or nongastrointestinal, together with areas of uncertainty.

Abbreviations: GLP-1, glucagon-like peptide-1; NAION, nonarteritic anterior ischemic optic neuropathy.

obesity in the first place. If so, these therapies have the capacity to reregulate the fat mass control system (Fig. 1) without directly "fixing" the dysregulation that causes obesity. This approach to therapy has been obviously effective but is fundamentally different from directly addressing the underlying problem. For obesity, the best examples of addressing the underlying problem are seen with metreleptin treatment for people with genetic leptin deficiency and setmelanotide treatment currently approved for those with proopiomelanocortin deficiency, acquired hypothalamic obesity, Bardet–Biedl syndrome, and monogenic/syndromic obesity for patients 2 years and older with confirmed proopiomelanocortin, proprotein convertase subtilisin/kexin type 1, or leptin receptor deficiency (https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213793s007lbl.pdf) (45). As effective as the current and emerging therapies are for the most common types of obesity, we may be missing opportunities for directly ameliorating the pathophysiologic causes of obesity, which may differ across individuals. Doing so will likely require a more detailed understanding of the regulatory circuitry that is disrupted in obesity generally or is dysfunctional in specific, identifiable subtypes of obesity.

Obesity appears to reflect a disturbance in the body's ability to determine or establish a physiologically appropriate amount and a balanced anatomic distribution of energy stores (body fat). Fully understanding the mechanisms underlying obesity is therefore likely to require a more complete understanding of the normal internal and external signals influencing the determination of body defended fat mass regulation and how the CNS regulatory circuits drive attainment of those dynamically regulated targets over time. There is far less evidence that obesity results from a disturbance in the physiologic defense of the target fat mass against acute insults such as acute or chronic illness, injury, or episodic overeating. Nonetheless, a better understanding of these 2 components of body fat mass regulation could provide new avenues of obesity prevention and treatment. The degree to which the cellular and molecular mechanisms of these 2 regulatory functions are distinct, overlapping, or fully integrated could have important implications for development of more effective, targeted prevention and treatment strategies. Emerging evidence also supports a role for epigenetic memory in modifying the cellular response to obesity, with implications for long-term control of body weight (46, 47). Whether approved or investigational OMs have the potential to reverse a subset of these epigenetic changes, thereby enabling restoration of the physiologic control of hunger and body weight, is not known.

A more immediate benefit of a greater understanding of the underlying pathophysiology of obesity and how it varies across its subtypes is likely to be seen in the development of personalized strategies for obesity management. As more OMs are developed with potentially distinct mechanisms of action, there will be a

rapidly growing opportunity to assess patient responses to different treatments or treatment combinations. At present, we can make educated guesses about the independence and complementarity of different classes of OMs. A better understanding of the mechanisms by which these medications influence the physiology of body fat mass regulation will provide important information on the most effective strategies for substituting or combining them.

Response to obesity therapy (or discontinuance of therapy) often occurs over long periods of time, and the underlying neurobiology and environmental food- and drug-related cues that shape interindividual heterogeneity in energy homeostasis and ultimately control of body weight are being explored in preclinical studies (48) but are not well understood in humans. It remains impractical to rely exclusively on trial-and-error testing of different approaches in individual patients with weight loss as the primary outcome. Clinical trials to test the effectiveness of different strategies for selecting and combining medications (or lifestyle-based treatments or surgery) will benefit from rescue and crossover studies that will be made less cumbersome by the availability of early markers of response. Development of clinical (eg, symptom-based), chemical, imaging-based, and genetic predictors or early indicators of clinical response will be essential, and increased pathophysiologic understanding will facilitate the identification and optimization of those early measures of therapeutic benefit and safety (Fig. 2).

Early indicators of response could also be helpful in individualizing appropriate doses of available medications. Currently, prescribing information accurately describes dose characteristics and regulatory guidance for forced dose escalation to maximally or near-maximally tolerated doses, reflecting the trial design, sometimes resulting in intolerance to the medications and excessive weight loss (49). This recommended dosing strategy is relatively unique to obesity among chronic metabolic and inflammatory diseases, perhaps a holdover from a time when anything less than maximal dosing was ineffective. Clinical trials and real-world evidence have demonstrated a wide interindividual variation in the effectiveness of every type of obesity treatment, and clinical experience suggests that there is a similar wide variation in the dose–response relationship of individual drugs (50). With the emergence of medications such as retatrutide that can mimic bariatric surgery in their effectiveness, some individuals may experience very rapid and excessive weight loss, necessitating individualized dosing to optimize both benefit and safety.

## What are the primary environmental contributors to obesity?

Most of our current understanding of the environmental contributors to the development of obesity is based on epidemiological studies. As genetics cannot fully explain the epidemiological trends and population-wide upward shifts in BMI over the last several decades (51), it is important to identify the multiple environmental factors that can promote obesity. For example, experimental changes in food environments can result in substantial changes in ad libitum EI and an apparent shift in the regulated fat mass (52, 53) through biological mechanisms that remain unclear but appear to involve interactions between brain regions classically thought to mediate reward, motivation, and homeostatic appetite control (48, 54). The specific environmental factors influencing body fat regulation include several classes of therapeutic drugs, certain foods (eg, highly processed, high-fat, high-carbohydrate, or high-glycemic-index), food additives (eg, emulsifiers), stress, sleep deprivation, circadian rhythm disruption, and pollutants (13, 22, 48). Clinical experience suggests that relatively few patients experience major obesogenic effects from any individual environmental influence and that there is wide interindividual variability in their contributions. Studies to determine the prevalence, exposure, and intensity of susceptibility to each of these influences would be helpful to our understanding of the degree to which they share similar pathophysiologic mechanisms or are complementary and additive. As with similar studies of the effectiveness and optimization of pharmacotherapies described earlier, understanding the role of different environmental obesogens would strongly benefit from identification of genetic and other predictors of susceptibility to each of them, determination of early markers of obesogenicity to help identify disease subtypes and guide individualized obesity prevention and treatment strategies. Greater understanding of the pathophysiology of obesity would allow more sensitive and specific assessment of how these obesogens disrupt the normal physiology.

# Heterogeneity

1. Can we determine a priori who is susceptible to developing obesity, and if so, how?
2. Can we determine who will or will not respond to treatment and to what type of treatment, and if so, how?
3. Can we predict weight regain (ie, degree, rate, composition), and if so, how?
4. Can we know who will develop obesity-related disease and which ones, and if so, how?

## Heterogeneity in obesity and its treatment

The development of obesity and the response to therapy reveal marked heterogeneity in biology that is poorly understood. It is fundamentally important to understand how the underlying biology in different individuals interacts with the environment and contributes to weight gain, and how and why these interactions differ across individuals. Similarly, there exists tremendous heterogeneity in (*a*) the response to treatment (Fig. 3), (*b*) the durability of response, (*c*) the development of side effects, and (*d*) the rapidity and extent of weight regain on or after discontinuation of treatment.

### Can we determine a priori who is susceptible to developing obesity, and if so, how?

Much of the interindividual variation in BMI within a given environment appears to be genetically determined (57, 58). Skewing of the population BMI distribution over time indicates a genetic interaction with environmental changes that promote obesity (59). Genome-wide association studies have identified more than 1000 genetic loci associated with common obesity (60), and clinically meaningful polygenic risk scores for obesity have been developed (35, 58, 61). However, the majority of BMI heritability remains unexplained. Various physiologic characteristics have been hypothesized to be determinants of individual

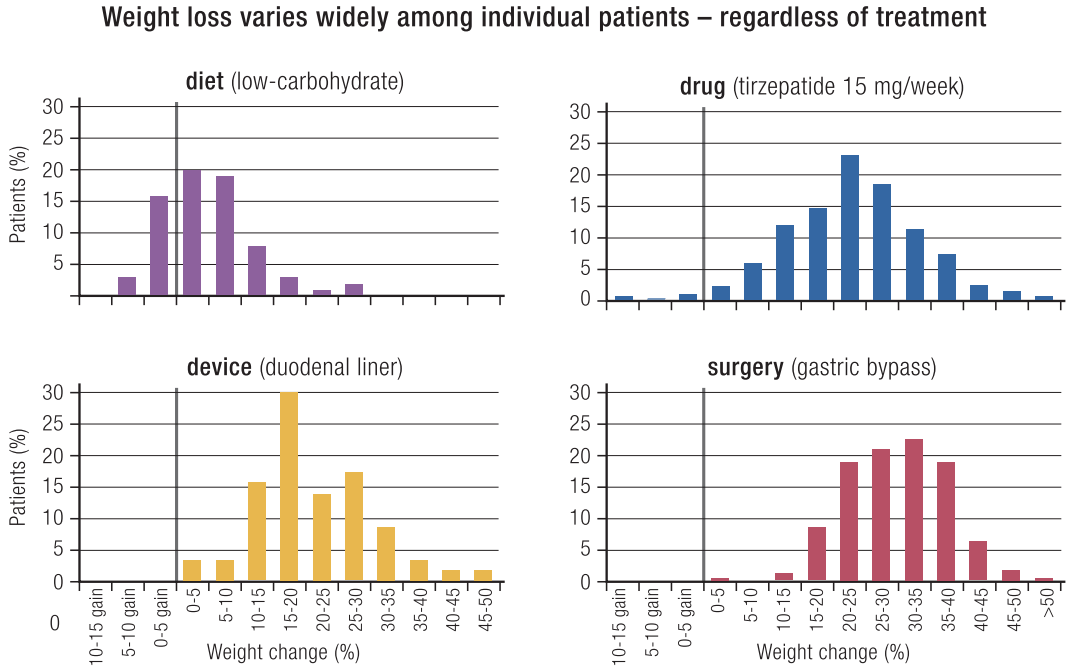


**Figure 3** Heterogeneity of response to obesity treatment. There is a wide variation in the weight loss response to all categories of obesity treatment. This figure shows the distribution for a low-carbohydrate diet, tirzepatide 15 mg/week in people without type 2 diabetes, treatment with the Endobarrier® duodenojejunal liner device, and Roux-en-Y gastric bypass. Despite the large differences in average weight loss among these treatment modalities, the interindividual variation is similar in each, with an SD of 10% to 12% total body weight loss. The distributions are unimodal, approaching a normal distribution, which suggests that biological factors are more likely responsible for the variation than differences in behavioral compliance, which would be predicted to produce evidence of a bimodal distribution. Adapted from previous studies (5, 55, 56).

weight changes, including aspects of gut function (62–64), energy metabolism (65–67), fuel selection (68, 69), and neural responses to food stimuli (70, 71).

Given the wide variety of genes and physiologic variables potentially contributing to the propensity for weight gain, obesity is increasingly conceptualized as a heterogeneous condition with different etiologies, pathophysiologic consequences, and clinical trajectories, thus underscoring the potential for different treatment strategies. Several approaches have been used to characterize obesity heterogeneity and partition individuals into more homogeneous subgroups (33, 72–74).

## Can we determine who will or will not respond to treatment and to what type of treatment, and if so, how?

The hope is that identification of more homogeneous obesity subgroups based on biological differences will result in more predictable clinical trajectories and responses to interventions (75, 76). If we could prospectively identify patients who are more likely to successfully respond to one intervention over another, it would be possible to personalize obesity prescriptions. The ability to target the best medication to the right patient would be especially advantageous given that the number of approved obesity pharmacotherapies is growing substantially and will continue to expand in the coming years. However, precision medicine for obesity remains largely aspirational, as most studies identifying distinct obesity clusters have not yet conclusively demonstrated that these subgroups predict meaningfully different treatment responses in prospective trials. Indeed, we are still unable to explain much of the substantial variability of interindividual weight loss to lifestyle modification, pharmacotherapy, or bariatric surgery interventions (Fig. 3) (36). For example, obesity polygenic risk scores do not predict clinically meaningful differences in weight loss in response to intensive lifestyle interventions (58, 77). Similarly, a combination of genome-wide association studies and targeted analysis of genetic variation in genes important for GLP-1R signaling did not yield identification of interindividual genetic variation that would explain important differences in weight loss responses after bariatric surgery or following treatment with GLP-1 RA or GIP/GLP-1 RA medicines (36).

Although progress continues to be made in the identification of genetic variation associated with individual responses to GLP-1 RA and GIP RA / GLP-1 RA medicines, the relatively small effect size observed in many genetic studies currently precludes their utility as useful tools for precision obesity therapy (78).

Responsiveness to GLP-1 RA and GIP RA / GLP-1 RA treatment appears to partly depend on average circulating concentrations of the GLP-1 RA medicine, which can vary substantially between individuals even given the same dose and route of administration (79). Interestingly, in many studies, female participants tend to lose more weight with modern GLP-1 RA and GIP RA / GLP-1 RA medicines relative to males (80, 81), (as well as medications in development) (6) and hormone replacement therapy has been associated with greater tirzepatide-induced weight reduction in postmenopausal women (82). The molecular mechanisms linking hormone replacement therapy to enhanced weight loss have not been determined; however, targeting of estrogen to GLP-1R+ neurons in mice enhances the weight loss efficacy of GLP-1 medicines (83). Additionally, individuals with obesity who do not have

T2D lose more weight than people with T2D, the reason for this has yet to be elucidated.

Even under highly controlled experimental conditions, the measurement imprecision of energy balance variables at the individual level introduces a substantial expected variation in weight change trajectories entirely due to the uncertainty in the magnitude of the intervention (84). This suggests that identifying physiologic mechanisms underlying individual weight loss variability will be technically difficult. There are also major challenges in prospectively validating intervention responders vs nonresponders. Retrospective subgroup analyses are prone to error and may not translate into predictable prospective responses (85). This may be because much of the treatment response variability is not repeatable or truly driven by biological differences (86). These limitations challenge an implicit presumption of the precision OM paradigm because variable intervention responses could also in part be explained by environmental variables interacting with the biological system regulating adiposity. For example, does the patient have a supportive social environment, stable employment, and have the resources and support to access and maintain pharmacotherapy with lifestyle change? More research is needed to assess individual reproducibility of treatment responses that could form the basis for identifying more robust obesity subgroups for precision medicine. For example, N-of-1 trials expose the same individual successively to various interventions that sometimes repeat to evaluate the reproducibility of their response (87). Unlike surrogate outcomes such as blood pressure or lipid profiles where interventions often exert their effects within weeks and washout quickly, N-of-1 trials for obesity treatment are challenged by the long time course to achieve maximal weight loss, which also results in a different physiologic state. However, early weight loss may be predictive of long-term weight loss in many individuals (88), and future research could examine how changes in individual weight loss trajectories or short-term assays of eating behavior or EE might be predictive of longer-term weight loss responses as various treatments are applied. Such N-of-1 trials have the potential to more reliably identify responder groups to specific interventions. Subsequent identification of biological differences between responder groups to different treatments might thereby provide a more reliable path toward precision OM.

### Can we predict weight regain (ie, degree, rate, composition), and if so, how?

Obesity is a chronic disease; hence, weight regain is expected once its treatment ends unless the environment or underlying biology has changed in a way that no longer promotes excess adiposity. This has been demonstrated in several trials in participants who stopped semaglutide or tirzepatide treatment (89–91). However, there is wide interindividual variation in weight regained after cessation of obesity treatment and it is presently unclear what factors predict this variability. In the context of lifestyle interventions for weight loss, greater self-monitoring behaviors, physical activity, and dietary protein have been associated with improved maintenance of lost weight (92, 93). Contrary to expectations, an increased rate of weight loss does not appear to increase the propensity for weight regain in clinical trials (94). A recently completed study was designed to elucidate the determinants of weight regain after a lifestyle intervention (22). However, it is unclear whether the same factors will be at play during weight regain after pharmacological obesity treatment.

Just as there has been much discussion about the composition of body weight loss during obesity interventions (95–97), the composition of regained weight is important to consider, especially since weight regain is so common in lifestyle interventions and obesity pharmacotherapies are often curtailed for a variety of reasons. The prospect of disproportionate body fat regain, reduced strength, and the potential for development of sarcopenic obesity with repeated weight loss and regain cycles has been suggested by cross-sectional analyses examining patients with varying histories of weight cycling (98). Longitudinal body composition and strength assessments are needed to help determine the direction of causality in these relationships.

### Can we determine who will develop obesity-related disease and which ones, and if so, how?

Recent definitions of obesity as a disease have attempted to dissociate pathophysiology from overall adiposity per se (99, 100). In support of this concept, recent genetic studies have shown that BMI can be dissociated to some extent from the risk of T2D and cardiometabolic disease (73, 74). For example, individuals with a genetic predisposition to accumulate body fat preferentially in the gluteofemoral region are relatively protected from the pathophysiologic consequences of excess adiposity as compared with those who are predisposed to gain fat in the abdomen (101). A potentially related concept involves the identification of a subset of individuals with high levels of adiposity who are deemed to have “metabolically healthy obesity” based on a collection of cardiometabolic biomarkers in the normal range and often associated with low amounts of visceral and ectopic fat (100, 102, 103). The degree to which weight loss interventions help resolve T2D may depend on reducing fat that has accumulated in metabolically sensitive ectopic regions such as the liver and the pancreas (104). To accomplish this, individuals may likely require differing amounts of weight loss to reduce overall adiposity below their own personal threshold. Overall reductions in body fat mass result in reduced visceral adipose tissue in an allometric relationship whereby visceral adiposity preferentially decreases as compared to subcutaneous adipose tissue (105). More research is needed to determine whether interventions can preferentially target visceral and ectopic fat depots and thereby have cardiometabolic benefits beyond overall weight loss, especially in individuals with greater visceral adiposity. Notably, with mechanical complications of obesity, such as knee osteoarthritis and obstructive sleep apnea (OSA), there is a relationship with BMI, with higher BMI being more predictive of disease occurrence. The psychosocial or mental health impacts on health and well-being are also critical to consider including ways to identify who most likely will have occurrence of these conditions in the setting of obesity. Ongoing research continues to refine our understanding of the factors determining the susceptibility to developing various obesity-associated complications, potentially enabling the prioritization of high-risk individuals for treatment (106).

## Treatment targets

1. How do we determine what treatment targets should be? What is clinically meaningful?

2. What should we consistently be measuring or assessing in studies and trials?
3. How should these targets be different for varied populations (eg, older individuals, pediatric populations)?
4. What is needed to develop a composite score? Is there a potential for a biomarker?

## Treatment targets

### How do we determine what treatment targets should be? What is clinically meaningful?

In the 19th century, Adolphe Quetelet introduced what has become known as the BMI, which is the mathematical relationship between body weight and height that exhibited minimal interindividual variation and had the expected normal distribution for the population (107). This index was forgotten until 1972, when experiments by Keys et al showed it to be the best index for correlating body fat with densitometric and 2-skinfold determinations (108). Today, BMI is the most widely used anthropometric measure for estimating overall adiposity, and its population mean and variation have both markedly increased in recent decades, thereby indicating a substantial increase in overall adiposity and its interindividual variability (51). Nevertheless, BMI is not a direct measure of body fat or its distribution.

These limitations of BMI have prompted ongoing discussion and revision of the definition and diagnostic criteria for obesity, and any modifications will influence treatment targets. A group of international experts proposed a disease-oriented redefinition of obesity, using terms clinical and preclinical to distinguish whether excess adiposity was causing organ dysfunction or functional impairment (100). This shift has important implications for diagnosis, epidemiology, and health policy but also has limitations, accounting for functional and some metabolic implications (T2D excluded) but does not account for psychological and mental health impacts and still relies largely on BMI. Therefore, their findings highlight the limitations of universal BMI thresholds, particularly in Asian populations with a predisposition to visceral adiposity at lower BMI levels (100). The findings also highlight important gaps in the validated anthropometric measures and their relationship to health complications across the lifespan, especially across childhood and adolescence, and for different races (109). Thus, while there is intense debate about a research agenda to better diagnose obesity, research to identify targets for obesity treatment and weight-reduction efforts must account for heterogeneity across populations and along the lifespan. For a better obesity definition, more research is needed to identify (*a*) readily available clinical criteria to identify unhealthy body function and disease and (*b*) population-based studies identifying and validating anthropometric indices across the lifespan in all races reflecting healthy body composition.

## What we already know about the search for anthropometric targets of weight reduction as a reflection of obesity complication risk

Percentage weight reduction from baseline (relative change in weight) is the current primary endpoint used to measure effectiveness for regulatory approval. Medications currently on the market for obesity treatment were approved under guidance from 2007, the first modern standard utilized in determining regulatory approval for medications for treatment of overweight and obesity (110). Based on that guidance, the current clinical trial standard measure of weight reduction efficacy in adults is mean percentage body weight loss from baseline, usually in response to 52 weeks on a given dose or treatment or a point at which weight is maintained at a steady state while on treatment.

A new document circulated January 7, 2025, by the US Food and Drug Administration (FDA) *Obesity and Overweight: Developing Drugs and Biological Products for Weight Reduction Guidance for Industry* (111) is out for comment. It states, "The efficacy of a weight-reduction drug in adults should be assessed by analyses of mean percentage change from baseline body weight in the investigational drug group vs the control group. Note that in subjects with stable height (ie, adults who have achieved terminal height), percentage change in body weight equals percentage change in BMI." In pediatrics, it specifies that efficacy should be defined as "a function of change in BMI." This is essentially unchanged from the earlier guidance, and thus, percentage weight loss (or change in BMI) is the primary endpoint for phase 3 studies. These measures are not targets, per se, nor are they an overall satisfactory measure of success in all individuals.

## Why is percentage weight loss not ideal as a measure of efficacy?

With lifestyle intervention and earlier medications that produced only modest weight loss, percentage weight reduction served well as a surrogate associated with measures of health improvement. However, since robust weight reduction became a reality with newer medications, a shift from emphasizing percentage weight loss as an efficacy marker to an anthropometric target is warranted.

Mean percentage weight reduction from baseline ignores the huge variation in weight loss response, commonly observed in a population. It also ignores that compared with individuals with BMI categorized as more severe in the obesity range, those with lower BMI will reach BMI categorized as "healthy" with a smaller percentage weight loss, magnifying the physiologic impact of weight loss for those starting at lower BMI levels. For those with BMI <30 $kg/m^2$, exceeding 20% weight loss can result in undesirable and unhealthy BMI levels, and for many, health goals may be met with less weight reduction.

A somewhat different measure of efficacy has been used in metabolic and bariatric surgery, percent excess weight loss. This is usually defined as the proportion of weight loss beyond that needed to achieve a BMI of 25 $kg/m^2$ or an ideal weight (from life insurance charts) (112). However, using BMI alone as an anthropometric target is problematic in that BMI does not directly measure body fat or changes in body composition or adipose tissue distribution.

Changes in waist circumference (WC) and waist-to-height ratio (WHtR) are frequently recommended as surrogates for change in visceral adiposity, but WC measurement has not been widely adopted in clinical practice. Waist circumference change is a surrogate for visceral adiposity change, which is, in turn, a surrogate

for ectopic adiposity change. While targeting a WC cutoff point has some appeal, the WC cutoff points must be adjusted for sex, race, and BMI (113, 114). The WHtR is not typically adjusted for sex, age, or race.

Robust statistical evidence involving more than 300 000 adults in several ethnic groups has shown the superiority of WHtR over WC and BMI for detecting cardiometabolic risk factors in both sexes (115). According to the British data, healthy central adiposity is a WHtR of 0.4 to 0.49, indicating no increased health risks from abnormal fat distribution. A WHtR between 0.5 and 0.59 indicates increased health risks from high central adiposity. An even higher value of a WHtR ≥0.6 indicates the highest risk from centrally located fat (115). However, drawbacks to using this index as a treatment target are limited evidence supporting its validity in ethnically diverse populations outside the United Kingdom, and widespread implementation is challenged in that WC measurement is difficult to do accurately, has few trained measurers in clinical practice and thus has not been embraced in primary care.

## Body composition assessments are needed to better define health impacts of obesity treatment

Measuring overall weight reduction does not reveal the key organs contributing to loss of tissue mass or location of fat mass loss. The goal of obesity intervention is the reduction of excess abnormal body fat (not body mass or body size) to improve organ function and mitigate disease symptoms. Reduction of excess abnormal or ectopic fat mass is a surrogate for health improvement with obesity treatment—that is, reduction of excess, abnormal body fat to levels that support optimal organ function and optimal body composition. However, there is no agreed-upon standard technique for measuring body composition effects of weight reduction, such as fat mass, fat-free mass, lean mass, or muscle mass, much less consensus for the optimal methodology for the generalized assessment of these parameters.

Body composition is further complicated as an outcome as it is a moving target across the lifespan, and characterization of these changes is limited for some of the measurement techniques. Body composition changes dramatically with sexual maturation and among adults, body composition differs by sex, age, race, and menopausal status. While there are multiple strategies to measure body composition (116, 117), there is no consensus on how best to measure body composition changes with weight loss in clinical practice. Impedance can measure percentage body fat and is used in obesity clinics but is criticized for inaccuracy (118). Digital anthropometry (3D optical systems) has been validated against dual-energy X-ray absorptiometry (DXA) for measuring percentage body fat and can also give an accurate measure of WC but has not penetrated clinical use (119). DXA assessment of body composition measures fat mass, fat-free mass (removing bone mass), and lean mass (120) but does not give an accurate assessment of muscle mass. Magnetic resonance imaging (MRI) gives the best measurement of bone, muscle, fat, and distribution of fat, but it is expensive, limiting its use in the clinic (121). Muscle mass is accurately measured by MRI and $D^3Cr$ dilution (122), but these are not commonly available in the clinical setting. DXA is the gold standard for precision measurement of bone; however, body fat changes can introduce artifacts into accurate measurement of skeletal changes with weight loss (123). Thus, there is no current consensus on which body composition measures to use and no universal agreement on how changes in body composition should be assessed.

Bone changes with weight loss deserve special attention, since osteopenia and osteoporosis is common, especially for older women. With more accurate measures of body composition, changes in the skeleton may be better understood and managed. While individuals with obesity tend to have higher bone density and healthier microarchitecture, meta-analyses have identified a higher risk of humeral and distal lower extremity fractures, likely due to multiple factors (124, 125). Weight reduction by any method reduces the mechanical load on the skeleton, resulting in myriad physiologic changes to increase bone resorption and lower bone density (126).

This has been studied to a greater and longer extent in the setting of bariatric surgery, with findings differing in terms of fracture risk by type of surgery (126) and leading to specific American Society for Metabolic and Bariatric Surgery recommendations for bone health monitoring, physical activity goals, and targets for calcium and vitamin D intake (127). With medical weight reduction, based on data from the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial in older individuals with atherosclerotic CVD followed for a mean of >3 years, more hip and pelvic fractures were seen in the subset of women >75 years who received active treatment (128). Systematic studies are needed to identify the most scalable measurement techniques, describe changes in bone health and fracture risk in the context of obesity medications, and identify interventions to limit the skeletal effects of mechanical offloading. Carefully designed studies can help to understand why some individuals develop bone fragility, and others do not, and whether there is a threshold or quantity by which bone density decreases with varied degrees of medical weight loss.

Some guidance may emerge in the near future regarding better measures of body composition that are affordable and scalable, thus useful in the clinic. Redefining Evaluation of Adiposity and Leanness: Broadening Objective Diagnostics for Obesity (REAL BODY https://fnih.org/our-programs/redefining-evaluation-of-adiposity-and-leanness-broadening-objective-diagnostics-for-obesity-real-body/) is planned as an 18-month collaborative effort designed to advance the development of a diagnostic body composition biomarker to support the following:

- Aim 1: To determine whether body composition measurements of total fat mass and total fat-free mass from [bioelectrical impedance analysis (BIA)] and 3D optical systems are valid and reliable alternates for DXA as the reference method.
- Aim 2: To determine if body composition measurements of visceral fat from BIA and 3D optical systems are valid and reliable alternates for MRI as the reference method.
- Aim 3: To determine if body composition predictions of total fat, fat-free mass, and visceral fat from a blood-based multiomics are a valid alternate for DXA and MRI as reference methods. If the results of this work are promising, similar studies can be expanded across the lifespan and in different populations.

Anthropometric targets need to be validated to serve as surrogates for obesity-related cardio-renal-metabolic risk and improvements and for obesity-related mechanical complications to define weight loss efficacy linked to these health outcomes. Moreover, depending on what complication one is seeking to address, the anthropometric targets may vary since tissues respond differently by degree of weight reduction. For example, complications of obesity may be due to the mechanical burden of excess adiposity or to the cardio-renal-metabolic lipotoxic complications of excess abnormal body fat (129). For cardiometabolic complications of obesity, the extent of weight reduction required to improve individual cardiometabolic risk factors will reflect differences in the sensitivity of these complications to degrees of weight loss (130). Weight reduction of only 2% to 5% of body weight can improve glycemia and lower triglycerides, with greater weight loss producing even greater improvements. For some obesity-related complications and conditions, more weight reduction is needed (10-15%) to translate into clinically meaningful improvement. This is true when considering the importance of weight reduction for improvement in OSA, knee osteoarthritis, and, to a lesser extent, MASH. Nevertheless, preclinical studies and post hoc analysis of the Effect of Semaglutide in Subjects with Non-cirrhotic Non-alcoholic Steatohepatitis (ESSENCE) trial reveal important weight loss-independent benefits of semaglutide for the reduction of hepatic inflammation and fibrosis (131, 132).

There is a graded improvement in measures of quality of life, depression, mobility, sexual dysfunction, and urinary stress incontinence, with benefits demonstrable with modest weight loss (5-10%), and further weight reduction leading to even greater improvements. For polyendocrine metabolic ovarian syndrome and infertility, modest weight reduction (beginning at 2-5%) can bring restoration of menstrual cycles, ovulation, and fertility. Moderate weight reduction (5-10%) has been shown to be associated with reduced health care costs (130). Effects of weight reduction on inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) are generally larger with greater degrees of weight loss, but there may be a threshold effect where >11% weight loss is required for meaningful hsCRP reduction (130). Nevertheless, GLP-1 RA and GIP RA/GLP-1 RA medicines such as semaglutide and tirzepatide (133,134,135) reduce circulating hsCRP levels in clinical trials and mitigate cardiovascular, kidney, and liver disease through mechanisms that are only partially related to the extent of weight loss (12, 14, 136). For conditions like knee arthritis, OSA, and gastroesophageal reflux disease, which are associated with the mechanical burden of excess fat mass, substantial weight reduction may be required to improve symptoms. Hence, attaining specific BMI thresholds (defined target) may be a good strategy for reducing mechanical complications of obesity rather than striving for a percentage weight or body fat reduction (relative change).

## Relationship of anthropometric targets to 10-year risk of obesity complications in electronic health record datasets

A promising approach to identifying anthropometric targets was reported at the European Obesity Congress in 2024 by Busetto et al (137). Using a UK primary care electronic health record database, the relationship of BMI and WHtR to 10-year risk of developing 4 obesity related complications (T2D, hypertension, hip or knee osteoarthritis, and ASCVD) was interrogated to identify anthropometric cutoff points. BMI of 27 kg/m$^2$ and/or WHtR of $\leq$0.53 after weight reduction were good indicators of low absolute risk of incident T2D, hypertension, hip or knee osteoarthritis, and ASCVD. Subsequently, this group evaluated the magnitude of BMI and WHtR changes needed to reach a low reference risk of the obesity-related complications and to identify biomarkers that might be used to identify risk. In a population of >280 000 primary care patients, the risk for T2D and atherosclerotic CVD (ASCVD) was inferred to be modulated by different combinations of BMI, WHtR, and biomarker (systolic blood pressure, diastolic blood pressure, lipid) levels, thus suggesting that personalizing targets using both anthropometric and biomarker input could be valuable.

## What are the gaps and studies needed?

A more accurate characterization of what is “healthy” in terms of BMI, WHtR, and even other anthropometric targets such as quantity and percentage body fat and visceral fat is needed in both sexes, all races, according to menopausal status, and across the lifespan for all ages. We need a clear definition of what we mean by “health” with which to correlate anthropometric and/or biometric targets. While there is a good understanding of the correlates of cardiometabolic health with anthropometric measures such as BMI and WC, the relationships between mechanical and functional signs and symptoms and anthropometrics and biomarkers are less well characterized. Moreover, mental health is more challenging to ascertain and remains poorly defined as a target. The Innovative Medicines Initiative’s Stratification of Obesity Phenotypes to Optimize Future Therapy (SOPHIA) trial explored this relationship in a qualitative study but does not provide guidance for tracking (138). Ideally, we need to determine whether anthropomorphic targets are sufficient by themselves or whether they should be combined with biomarkers and patient-reported outcomes to develop a more comprehensive and clinically useful risk assessment and target goal index. Better (accurate, validated, and correlated with outcomes) characterization of healthy body composition measures (fat mass, fat-free mass, bone mass, muscle mass) in both sexes, all races, according to pubertal and menopausal status, across the lifespan is required, complemented by assessment of functional outcomes. An expanded scientific understanding of healthy body composition is required with emphasis on how this relates to meaningful health outcomes in people of different ages.

Additional studies are needed on the changes in physiology associated with varied degrees of relative weight reduction (5%, 10%, 15%, 20%, and 25%) with obesity medications to determine the corresponding physiologic responses to weight loss in different tissues in populations of persons with obesity and T2D and weight-associated complications and conditions. Implementation of new targets and measurements requires easier, less expensive, and more accurate assessment tools and more data generated from large studies to better understand the effects of weight loss and validate clinically useful measurements. For example, the clinical and predictive utility of digital

anthropometry (3D optical systems), a potentially easy, accurate, safe, and affordable solution versus tape-derived measurements, could be compared in large clinical trials. Technological advances to replace DXA as a component of weight loss evaluation in older individuals, ideally deploying less expensive, simpler machines to determine fat mass, lean mass, bone mass, and bone density, require evaluation. Similarly, assessing the utility of $D_3Cr$ dilution-based measurements in research settings is warranted, as is evaluating changes in muscle mass and function during weight loss, particularly in women aged >60 and men aged >70 years.

## What should we be measuring or assessing in studies and trials of obesity medications?

In addition to the usual primary endpoint required by regulatory guidance for medication approval (percent weight reduction from baseline), we should add secondary and exploratory endpoints such as percent excess weight loss (percent of weight loss ≥BMI 25 kg/m$^2$; for pediatrics, measures of BMI change). Other secondary endpoints in all medication studies should explore anthropometric cutoff points associated with health; these would be based on the usual taping measures (height, WC, WHtR) and digital anthropometry (3D optical systems) for WC and percent fat and fat mass and on bioimpedance-measured percent fat and fat mass. Beyond the usual relative change percent weight loss thresholds (≥5%, ≥10%, ≥15%, ≥20%), we should expand to ≥25%, ≥30%, and ≥35% to characterize more powerful medications. For all of these, we should evaluate BMI subgroup response rates. In addition to the usual BMI targets of percent achieving <40, <30, and <25 kg/m$^2$, we should add <35, <27, <23, and <18.5 kg/m$^2$ (adapted for Asian populations). For pediatrics, we should assess the proportion of individuals achieving BMI <140th percentile and <120th percentile of the 95th percentile and BMI <95th and <85th percentiles. Other measures would be the proportion of individuals achieving BMI <27 kg/m$^2$ and WHtR <0.53 (or other predetermined composite score associated with reduced complication risk, such as percent change in 10-year complication risk score. Overall, a move toward defined treatment targets associated with improved outcomes (analogous to targets such as hemoglobin A1c (HbA1c) < 6.5% in diabetes) rather than relative change (such as percent change in weight from baseline) supports approaching and treating obesity as we treat any other chronic disease. Importantly, targets should be determined and defined by health outcomes, evolving as new data are accrued.

### How should these targets be different for varied populations (eg, older individuals, pediatrics populations)?

For children who have likely not reached their terminal height, the *z* score can reflect the degree of adiposity. However, at very high BMI, change in the *z* score may not recognize clinically relevant shifts in BMI (139). Therefore, in clinical practice, severe obesity in youth is measured using the BMI percentage above the 95th percentile (140). Consideration should be given to the utility of change in *z* score in the adult population, given the likelihood of robust weight loss and the broad range of starting BMI. For older individuals (above age 60), bone density and muscle mass and function are important outcomes to consider.

### What is needed to develop a composite score?

Large datasets with relevant and detailed electronic health records with >10 years of observation are needed to explore composite scores. These composites could consist of intermediate outcome measurements (risk factors), anthropometric measures, and relevant disease-related outcomes (osteoarthritis knee and hip, ASCVD, T2D, hypertension, OSA, MASH, others) (141).

## Is there a potential for a biomarker or biomarkers, separately or in combination, as composite scores?

Biomarkers are an important area for research as there are existing and emerging biomarkers that have potential when used in combination for usefulness in assessing targeted health improvement.

Core body composition biomarkers are typically derived from anthropometry, BIA, or medical imaging such as DXA and MRI. Visceral adipose tissue describes fat around internal organs. Subcutaneous adipose tissue describes fat stored directly under the skin. Intramuscular adipose tissue describes fat within muscle tissue (myosteatosis). WC, waist-to-hip ratio, and WHtR are all proxies for central adiposity and stronger predictors of cardiovascular risk than BMI. The skeletal muscle index describes muscle mass normalized for height and is used to diagnose sarcopenia. Bone mineral density indicates bone strength and risk of osteoporosis. Fat-free mass is the combined weight of muscle, bone, and organs (142).

### Circulating and metabolic correlates

While not direct measures of composition, these blood-based biomarkers often reflect an individual's body composition and health status. Adipokines such as leptin and adiponectin correlate with total and visceral fat mass. Inflammatory markers such as hsCRP, IL-6, and ferritin are often elevated in cases of high visceral adiposity. Myokines like myostatin or myoglobin can reflect muscle health and turnover. Other measures or a combination with existing biomarkers may be beneficial in understanding disease severity as well as response to treatment.

### Omics markers of obesity

Obesity's metabolic heterogeneity is not fully captured by BMI. Deep multiomics phenotyping is showing promise in identifying biomarkers that could be used to more accurately detect obesity and thus serve as targets for response. This includes adipose tissue-microbiome interactions (143), lipidomic-based models for BMI (144), and other multiomics-based strategies (145).

### Emerging radiomic biomarkers

New automated tools extract advanced "radiomic" features from routine computed tomography or MRI scans, such as the sarcopenia marker, which is calculated as muscle volume relative to bone and fat, and the cardiac marker, which normalizes

epicardial fat to muscle volume to predict heart health. Muscle density, which reflects fatty infiltration into muscle, may also be useful. There could be efforts to explore the utility of developing a risk score based on a combination of anthropometrics, biochemical intermediates, omics, and even patient-reported outcomes.

### Research priority areas

- Large-scale population-based representative samples for validation of anthropometric indices across the lifespan in all races reflecting healthy body composition.
- Scalable assessments to define excess adiposity impacting health and organ function
- Validated, accessible measures of bone and muscle health in vulnerable populations with accuracy across a spectrum of weight reduction thresholds
- Defined domains of health impacted by obesity treatment and standardized indices to evaluate change in these domains, including mental health

## Understanding fat mass dynamics through treatment: what can we learn from phases of treatment with obesity medications?

1. What is known about the physiology of weight loss/weight reduction, weight plateau and longer-term weight maintenance achieved with medicines?
2. How do we optimize health by incorporating lifestyle during the weight reduction and maintenance phases of treatment with phramacotherapy?
3. What is the optimal rate of weight reduction with pharmacotherapeutic intervention?
4. How do we determine whether there is a role for changing medications/therapies or dose changes, during the weight maintenance phase?

## What do we know about the physiology of fat mass dynamics with pharmacotherapy, and what can it teach us about the physiology of obesity?

The emergence of highly efficacious obesity pharmacotherapeutics enables the investigation of fat mass dynamics in the setting of weight reduction (described previously). Prior to these pharmacotherapies, we were limited to studying nonphysiologic weight loss (weight loss induced by diet/exercise, a consequence of which is metabolic adaptation). To break fat mass dynamics into phases is a somewhat artificial construct, but it is brought out in part due to the inherent prolonged initial weight loss/reduction phase (ie, fat loss and other associated changes take time versus, for example, blood pressure control, which can be near immediate), which can be continuously monitored by the individual experiencing the weight reduction [Fig. 4]. Nevertheless, a clearer understanding of what occurs at various stages of treatment may provide critical insights into disease physiology and help communicate expectations for treatment response to patients.

In this section, we will describe how we may approach describing fat mass dynamics and what pharmacologic treatment can teach us about obesity physiology, treatment, what people with obesity may experience as a result of changes associated with weight loss, and how a better understanding of what occurs physiologically during treatment may help us better understand the disease itself.

We can consider these “phases” as fat mass dynamics inasmuch as in the phase when weight loss is actively occurring, the body is in a negative energy balance state ("chasing" the reduced defended fat mass), and when weight is stable, it is in a homeostatic energy balance state (existing at the defended fat mass). We know very little about the distinct physiology of these states or phases in the setting of pharmacotherapy, with information being extrapolated from lifestyle intervention studies. Yet, treatment with pharmacotherapeutic interventions is distinct from that of lifestyle interventions. Fat mass changes with pharmacotherapy can be described as physiologic, whereas fat loss from diet/exercise can be described as nonphysiologic. This means that when pharmacotherapy is used, the regulated level of fat mass (defended fat mass) is reduced and the weight (fat mass) follows. But when diet/exercise are used, the regulated level of fat mass (defended fat mass) is not reduced; hence, the body’s constant pull (global metabolic adaptation) backs up to regain the weight to the higher regulated level of fat mass. Stated yet another way, nonphysiologic weight loss can be defined as inducing a counterregulatory response, whereas physiologic weight loss does not.

We can consider the approach in other diseases where treatment is considered in phases. In cancer, phases of treatment can be broken down into induction (with the goal of achieving remission), consolidation/intensification (adjusting treatment based on response), and maintenance (maintaining a state where the body is cancer-free [remission]). For diabetes or hypertension, phases of treatment are not broken down explicitly; rather, the disease is described as uncontrolled versus controlled (once goal glycemic or blood pressure parameters are reached), and this often occurs much more quickly than with these other diseases. These changes are not often observed by the patient, albeit with some opportunities (eg, a continuous glucose monitor allows for moment-to-moment monitoring of interstitial glucose levels). In some settings, the term *remission* has been used to connote a patient who has reverted to normoglycemia, at least temporarily. In obesity, the goal is improving health in part through achieving a level and distribution of fat that optimizes body functions. Perhaps describing treatment response falls somewhere between the prior examples, given that the goal is to reach a target (though not yet defined as described previously) of healthier measured and actual fat mass that is in equilibrium with the regulated level of fat mass (defended fat mass). Of course, the goal is not to rid the body of fat (as is the case with cancer) but to achieve and maintain a level and distribution which optimizes health.

To break it down simply, fat mass dynamics with treatment with obesity pharmacotherapy can be described as follows: the weight/fat mass reduction phase (induction, when the regulated level of body fat [defended fat mass] is lower than the body’s current fat mass, thus not at homeostasis), weight plateau (reaching

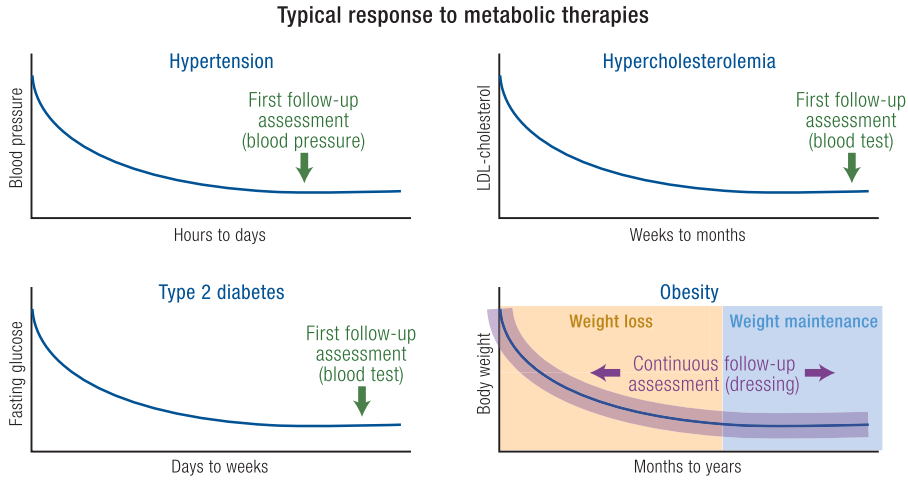


**Figure 4** Dynamic changes in markers of health after treatment of metabolic disease. Effective, physiologic treatment of metabolic disease leads to a change in measurable physiologic markers. Changes in those markers, including blood pressure for hypertension, fasting glucose for type 2 diabetes, low-density lipoprotein cholesterol for hypercholesterolemia, and body weight for obesity, follow an initial pattern of improvement followed by a longer period of homeostasis marked by maintenance of the improved physiologic state. For most metabolic diseases, the distinction between the initial correction and maintenance is generally inapparent to the patient because the biological marker is generally tested after the new steady state is reached. Several characteristics of obesity and its treatment highlight the differences between the initial correction and steady state. Unlike other metabolic diseases, whose improvement can be completed in days or weeks, improvement in obesity typically occurs over a much longer period. During this period, patients perceive the improvement continuously through changes in body shape and the fit of clothing, as well as dynamic changes in appetitive drives. Weight loss is sensed over an extended period, and it is easy to discern when a new steady state has been reached. Appetitive drives that are often diminished during the period of fat mobilization and weight loss commonly increase as the body reaches a new plateau. These features of obesity provide a perception of two distinct phases in the response to treatment. As described in Fig. 1, those 2 phases (weight loss and then weight restoration in response to metabolic adaptation) are more distinguishable with nonphysiologic weight loss, but with physiologic weight loss, as with effective treatment of other metabolic disorders, clinical observation suggests a single phase, with a steady progress toward a new, healthier steady state.

nadir weight with no further weight reduction on a given treatment regimen/dose; the body reaches homeostasis), and weight maintenance (long-term maintenance, disease control in the setting of potential disease progression, with the goal to maintain homeostasis). During the weight plateau and maintenance, the body is at homeostasis, with the caveat that during maintenance, disease progression may occur over time. For the purposes of this discussion, we separate out weight plateau and maintenance with the consideration that if obesity progresses, dose adjustment or additional therapies would be implemented to maintain disease control. It is also important to understand what is occurring at baseline prior to initiation of pharmacotherapy. The assumption may be that most are living below their defended fat mass, though for some individuals this may not be the case and they may be in equilibrium at the elevated defended fat mass. In sum, a deeper understanding of the physiology of the following is needed:

- Untreated/pretreatment: The body is not at homeostasis where the regulated level of fat mass (defended fat mass) is higher than current measured/actual fat mass.
- Initiation of therapy, induction, and active weight loss: The body is not at homeostasis where the regulated level of fat mass (defended fat mass) is lower than current measured/actual fat mass, this can be termed “chasing” the new defended fat mass.
- Reaching plateau: The body is at homeostasis; the regulated level of fat mass (defended fat mass) and current measured/actual fat mass are aligned.
- Maintenance: Pharmacotherapy keeps the state in homeostasis over time (defended fat mass and actual fat mass aligned) in a setting where the defended level of body fat may potentially be increasing (disease progression) and while actual body fat mass may again be below the defended fat mass.

Defining the threshold weight loss required to improve key health outcomes will continue to underlie the definition of treatment goals and the individualization of weight reduction and health goals in the clinic (147).

Prior to the OMs, the phases of treatment were investigated in studies of weight reduction using nonpharmacological interventions that led to nonphysiologic weight loss. Caloric restriction, leading to 10% body weight reduction, results in a decrease in EE, with the body compensating by becoming more efficient (17), with the decrease in EE appearing to persist over time (148). Acute caloric restriction (10 weeks) also results in NuSH changes and an increase in hunger (18). The hormonal changes persist beyond the acute weight-reduction phase over the subsequent year, even after the onset of weight regain (18). These changes are collectively referred to as *metabolic adaptation*. Longer-term studies of intensive lifestyle interventions, assessing the maintenance phase, demonstrated the challenge of maintaining a clinically meaningful amount of weight loss over time (149, 150). We are in the early stages of understanding the long-term physiology of weight change in the context of nonpharmacological interventions, yet even less is known in the context of OMs (physiologic weight loss).

### The weight reduction/weight loss phase

Most of the studies of obesity treatment with the novel OMs examine the initial weight reduction (weight loss) phase. Given the FDA's regulatory requirement (111) of 52 weeks on treatment for a given agent at a specific dose, the average duration of the trials has been 1 year to 1½ years, allowing for a period of dose escalation, followed by time on target dose, resulting in limited longer-term data. As a result, most of what we know thus far is what occurs as individuals lose weight but not thereafter. The latter 2 stages are largely unstudied, leaving a significant gap in our understanding of the physiology of the plateau phase and maintenance of weight reduction. Additionally, most human studies of the weight loss phase in general have not assessed physiologic changes (EE, EI, etc), though there are a few that have begun to tackle these questions (146, 151, 152). These studies have provided insight into the acute changes in appetite that occur during the weight reduction phase (ie, decreases in hunger, craving, and food intake with receptor modulators) (152). Studies of EE in humans treated with an OM thus far have not demonstrated a key role for changes in EE as contributing to weight loss (146), though there may be a dampening of the decrease in EE observed with nonphysiologic weight loss (with diet/exercise) that may be more subtle and thus more challenging to detect.

During the weight-reduction phase of treatment, as an OM is initiated, the hypothesis is that the regulated fat mass (the defended fat mass) level is recalibrated and decreased by the pharmacotherapeutic. This acute decrease in the regulated level of body fat mutes hunger, craving, and food noise (defined as persistent, intrusive, disruptive thoughts of food) (153), while potentially also blunting the expected decrease in EE, all in an effort to allow the body's fat stores to equilibrate with the recalibrated body fat level commensurate with biological regulation. In a sense, the body "chases" its new (lower) defended fat mass, which is why during this phase individuals report lower appetite.

Evidence for this can be found in several pivotal studies. Treatment with semaglutide (12 weeks) or tirzepatide (3 weeks) both demonstrate decreases in observed food intake, hunger, and craving and impacted food preference, but the impact on EE is less clear (146, 151, 154, 155). Notably, it is challenging to match weight loss in the OM treatment group with the lifestyle intervention group owing to the efficacy of the OMs making studies of EE particularly challenging. Using a lower effective dose of an OM may allow for weight loss matching with the caveat that the overall treatment effect will be dampened and thus potentially more difficult to detect. To better understand the physiology of the acute weight reduction phase, studies are needed that match weight loss with OMs alone vs OMs paired with lifestyle vs lifestyle alone during which EI and expenditure are assessed. Additional critical measures include changes in hormonal response, body composition, patient-reported outcomes, and adverse events.

## What is the optimal rate of weight reduction in the weight reduction phase?

Until recently, there was little consideration of the rate of weight reduction given the paucity of tools that would enable a significant amount of weight loss. In the setting of bariatric surgery, we do not have the means of slowing down weight loss. In the setting of medications, the rate of weight reduction can be finely tuned by thoughtful dose titration. A majority of current trials have implemented rapid, timed dose titration to minimize the dose escalation period while ensuring 52 weeks on a specific target dose, per the FDA regulatory requirement. This has provided information on more rapid weight loss but has not informed or directly compared whether different rates of weight reduction impact health outcomes, including impact on muscle function, bone mass, energy levels, adverse events, and other health outcomes.

It is well known that rapid dose escalation increases the potential and severity of GI side effects and that slowing dose titration can prevent or mitigate them. It is also known that rapid weight reduction with bariatric surgery, medications, or caloric restriction can increase incidence/prevenance of cholelithiasis. Rapid weight loss, albeit in the setting of bariatric surgery (which also has a restrictive component) and a very low-calorie diet, has also been associated with nutrient deficiencies (micronutrient), electrolyte imbalance, and fatigue in the setting of markedly reduced food intake (156, 157). Given that OMs are now near or approaching the efficacy of bariatric surgery, it is critical to monitor for markedly decreased food intake and closely monitor the rate of weight reduction to prevent potential negative outcomes. Studies implementing the lowest effective dose with dose titration targeting a set goal or target, rather than maximum treatment dose, which is what has been done to date, are critical. With few exceptions, most therapies treat to target (see the previous discussion) rather than use a specific dose. The critical questions that need to be answered are at which point the rate of weight reduction has detrimental impacts on health, and beyond mitigating potential side effects, what are the potential benefits of targeting a specific, more gradual rate of weight reduction. For example, studies examining weight reduction of up to 1% body weight per week versus >1% per week should examine changes in body composition, physical function, metabolic measures, and mental health and well-being (energy level, mood, and quality of life).

### The weight plateau phase and maintenance of lower weight

What is known about reaching and maintaining a weight plateau with OMs is from a handful of longer trials of at least 3 years that were designed with measured outcomes disparate from studying physiology. The SELECT semaglutide cardiovascular outcomes trial (5 years) (8), the SURMOUNT-1 tirzepatide 3-year trial (3 years) (158), and the SCALE liraglutide obesity and diabetes trial (3 years) (159) are some of the longest trials to date. These trials were not designed to examine details of EI, EE, or any other accompanying physiologic changes. Nevertheless, they have each demonstrated that if the therapeutic agent is continued, the weight loss is maintained. A limitation of these studies is that there are no data on participants who drop out of the trials.

There is considerable interest in maintenance/durability of maintaining lower weight given that obesity is a chronic disease, necessitating long-term treatment. The SURMOUNT-MAINTAIN trial studied the efficacy of switching from maximally tolerated (either 10 or 15 mg once-weekly (qw) tirzepatide over the first

52 weeks) to 5 mg qw over an additional 52 weeks, demonstrating substantial maintenance (approximately two-thirds) of the initial weight loss with the lower dose of tirzepatide (160). The ATTAIN-MAINTAIN trial studied whether switching to a once-daily oral GLP-1 RA tablet (24 or 36 mg of orforglipron) after 72 weeks of maximally tolerated semaglutide (up to 2.4 mg qw) or tirzepatide (up to 15 mg qw) would be effective in maintaining weight loss (161). Orforglipron was effective in maintaining weight loss, with final weight loss (from the start of injectable therapy) of 16.8% in the initial tirzepatide group and 15.1% in the semaglutide cohort after an additional year of therapy. In the real world, people frequently stop OMs owing to many factors, with a main one being lack of access (162) or potentially due to misunderstanding that losing weight does not result in disease remission, but rather disease control (as is the case with T2D) (163). In trials stopping the therapy, weight regain (164) has been demonstrated with semaglutide in the STEP-4 trial (165) and the STEP-1 extension (89) and with tirzepatide in the SURMOUNT-4 trial (90). Weight regain after cessation of OMs has also been demonstrated in the real world (166). Furthermore, not only is the weight regained with cessation of the OMs, but there is also reversion of various cardiometabolic measures of health, including an increase in blood pressure, lipids, and glycemia (89, 90). Thus, a multitude of health gains (reached during the weight reduction phase) are lost with cessation of therapy, as would be the case if treatment were discontinued for any other chronic disease. Perhaps not surprisingly, interindividual variability in the rate of weight regain occurs (90) with a lack of long-term studies to assess whether weight returns to baseline or close to baseline over time. RWD may be able to best answer this question, given that discontinuation of therapy in a trial, without providing active comparator control, raises ethical concerns.

There are several additional considerations for maintenance that need to be addressed in studies. If the assumption is that obesity is a progressive disease, then maintaining a weight plateau may be different from reaching a weight nadir and initial weight plateau. Given that until recently there has been a lack of highly effective, durable treatments for obesity, with the exception of bariatric surgery, it is also important to consider that a given weight plateau may optimize health for an individual at a certain stage in life, whereas various factors may impact the treatment goal (as discussed previously). A parallel can be drawn from goals of treating T2D, where the HbA1c goal may change depending on factors such as age, overall health, and risks of side effects such as hypoglycemia. In the same way, the goals of obesity treatment may change over an individual's lifetime. Finally, longevity has been studied in the setting of nonphysiologic weight loss (167), with reduced temperature, blood pressure, pulse, insulin, and T3, all associated with longevity. Nevertheless, whether any long-term health risks, potentially related to alteration in immune function, are associated with sustained caloric restriction in individuals with weight loss has not been carefully studied (168). Furthermore, it is not known whether it is the energy state or these physiologic changes that contribute to the extended lifespan. This has yet to be studied in the setting of the OMs, as we have not yet characterized the physiologic status of the NuSH weight/fat mass-reduced state.

## How do we determine whether there is a role for dose deescalation or changing medications/therapies during the maintenance phase?

Perhaps in large part due to the initial lack of consistent access to treatment with OMs, the question has been raised whether medications need to or should be changed or switched, or doses lowered, during the maintenance phase. As an example, if a specific treatment works for a patient with T2D to lower a patient's glycated hemoglobin, for the most part, that treatment is continued and not lowered or switched (unless due to side effects, other health issues, or access). An inherent assumption within the question of maintenance is whether there is something different about the weight loss phase and maintenance phase of obesity that is distinct from other chronic diseases (169). If clinically, we do not think or find there is a meaningful difference, then the question returns to access, cost, and ease of chronic medical treatment to maximize adherence. If we do think or find there is something inherently different, then the focus should be on understanding the differences in maintenance physiology and designing treatments that best target those differences.

Ongoing studies are investigating various maintenance strategies, including maintaining dose versus lowering dose (NCT06780449; IRAS ID 1009583), spacing out the frequency of the dosing interval (170), and switching from an injectable agent to an oral medication [NCT06584916]. Retrospective RWD studies have provided initial information on switching from an OM to older medications, assessing whether weight reduction can be maintained with promising results (171). These studies will begin to inform about outcomes with additional studies needed to specifically understand the physiology.

## How do we optimize health with lifestyle during the weight loss, plateau, and maintenance phase?

The role of lifestyle intervention in the setting of OMs offers an opportunity to focus on the goal of obesity treatment, namely improving health. The role of lifestyle interventions in improving health is clear, despite the fact that these interventions do not lead to a high degree of sustained long-term weight reduction (149).

The FDA (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/obesity-and-overweight-developing-drugs-and-biological-products-weight-reduction) has revised the obesity medication indication language to "in combination with a reduced calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term," thus, appropriately shifting the onus away from relying strictly on lifestyle to treat this complex disease, paralleling treatments for other chronic diseases, such as diabetes, which pair pharmacologic interventions with healthful diet and physical activity, all with the goal of improving overall health.

A key question is how pairing pharmacologic interventions with physical activity, nutrition, diet quality, sleep, and stress management can work together to optimize health outcomes

in people with obesity. Pairing liraglutide with physical activity resulted in a greater decrease in percent body fat loss as well as improvements in glycated hemoglobin and insulin resistance (92). The STEP-3 trial (172), which combined semaglutide with intensive lifestyle interventions, demonstrated weight reduction within about 1% of STEP-1 (semaglutide without intensive lifestyle intervention, with standard-of-care lifestyle intervention). Though the data cannot be compared directly given that these were two distinct trials, they do provide insight that initially the rate of weight reduction was potentially slightly faster but that the outcome was nearly the same. The SURMOUNT-3 trial (173) demonstrated that individuals who had lost 5% to 10% body weight with intensive lifestyle intervention experienced additional weight reduction when tirzepatide was added. Studies are needed that directly examine medications with and without intensive lifestyle intervention and the impact on body composition, muscle function, quality of life, and other health measures.

### What studies are needed?

Understanding the physiology of fat mass dynamics in the setting of physiologic weight loss via treatment with pharmacotherapy will enable a deeper understanding of the disease and the discovery of increasingly targeted therapies. Studies are needed that examine EE, EI, hormonal changes, neural responses and changes, and resulting impact on eating behavior during the weight reduction (negative energy) phase and weight plateau (energy homeostasis) phase. As each phase of treatment is designed, studies will support a deeper understanding of physiologic changes centrally (neurobiological changes), peripherally (adipose tissue–specific), and systemically (other organs, cardiovascular-kidney-metabolic [CKM], systemic and localized inflammatory disorders), which will not only lead to the development of targeted, better tolerated, highly efficacious obesity treatment but also potentially obesity prevention.

### Research priorities

The research priorities are as follows:

- Human physiology studies investigating physiologic weight loss (in the setting of pharmacotherapy) versus nonphysiologic weight loss (in the setting of diet and exercise), assessing metabolic adaptation (counterregulatory response).
- Studies that enable a better understanding of the weight reduction phase versus the weight plateau phase in the setting of pharmacotherapy, including assessment of EE, EI, hormonal changes, neural responses/changes, and resulting impact on eating behavior.
- Studies that examine the physiology of weight maintenance in the setting of potentail disease progression.
- Studies that examine whether the rate of weight reduction has an impact on body composition (including function), bone health, nutritional status, adverse events (including gallbladder events, fatigue, and hair loss).
- Studies that pair pharmacotherapy with type and quality of diet, macronutrient composition, and type and amount of physical activity to determine the impact on health outcomes.
- Studies that assess the minimal effective dose versus maximum tolerated dose on weight, health outcomes, and incidence or prevalence of adverse events.
- Identification of new medicines with complementary actions.

## Health outcomes

1. What is the risk of not treating vs treating obesity?
2. What are the potential impacts on obesity-related disease (heart, kidney, OSA, etc)?
3. What are the weight-dependent vs weight-independent effects of the novel medications?
4. When should we be treating in the trajectory of obesity (early vs late; ie, initiate treatment to improve health outcomes)?

## Prioritizing health outcomes

As noted in earlier sections of this statement, obesity is a chronic, progressive disease that leads to a new energy balance state, with excess energy stored in various fat depots (ie, excess adiposity). The consequences of the excess adiposity are cumulative and likely a function of the duration of exposure (ie, chronicity), locations of excess fat deposits (ie, visceral vs subcutaneous), and amounts of excess adiposity (ie, total mass). This means that individuals may have varying disease burdens and health consequences resulting from the development of obesity.

This section of the statement will focus on those health outcomes associated with obesity in the context of new and emerging obesity medications. The key topics for consideration include the comparative risks of treating obesity verus not treating it, the impact on organ systems, weight-dependent versus drug-specific effects of treatment, and the ideal timing for intervention. Within these topic areas, the statement will assess what we already know, what the key gaps in our current understanding are, and what research is needed to address these gaps and improve clinical outcomes.

### What is the risk of not treating versus treating obesity?

#### *What do we already know? Risks of untreated versus treated obesity*

The risks of untreated obesity are often described in terms of impact on metabolic health. The phenotype of metabolically healthy obesity has been used to identify individuals who have obesity but do not exhibit a complex of abnormalities in related biomarkers of metabolic health (103). Putting aside the challenges with how metabolically healthy obesity is defined in the literature (eg, dichotomous cut points, differing cut points, threshold for cluster), there is clear evidence that this state is transient, and longer exposure to excess adiposity appears to be associated with eventual development of metabolic abnormalities in most individuals (174, 175). Therefore, left untreated, obesity is frequently associated with poor health outcomes over time, even when there may be little evidence of poor metabolic health early in life (174). Accordingly, most children with obesity continue to have obesity as adults (176, 177).

The harms of untreated obesity are not a simple function of fat mass but of adipose tissue that has become dysfunctional. As

adipocytes hypertrophy and storage capacity is exceeded, lipid spills into visceral and ectopic depots and the tissue shifts its secretory profile: adiponectin falls, leptin rises, and the release of proinflammatory cytokines and free fatty acids increases, producing chronic low-grade inflammation, insulin resistance, and neurohormonal activation that link excess adiposity to its cardiovascular, kidney, and metabolic consequences. This view may explain why visceral and ectopic fat carry disproportionate risk, why metabolically healthy obesity is typically transient, and why excess adiposity has been proposed as a unifying driver of specific syndromes such as obesity-related heart failure with preserved ejection fraction (178). Yet the cellular and molecular basis of adipose dysfunction, and how it varies across individuals and fat depots, remains incompletely understood, a gap directly relevant to treatment: adipokine and inflammatory signatures are candidate biomarkers of who is harmed by excess adiposity, who benefits most from weight reduction, and whether a given therapy confers benefit beyond fat loss.

The more recently developed CKM framework provides an alternative perspective on how obesity perpetuates a cycle of metabolic and organ dysfunction that progressively compounds over time (179). The CKM model emphasizes the interconnectedness of cardiovascular, kidney, and metabolic health, highlighting how excess and dysfunctional adipose tissue, particularly visceral fat, drives inflammation, insulin resistance, and metabolic risk factors, including hypertension, hypertriglyceridemia, and T2D. These metabolic disturbances contribute to chronic kidney disease and CVD, including heart failure, coronary artery disease, and stroke. The CKM framework stages the progression from excess adiposity (stage 1) to metabolic risk factors and moderate-to-high risk CKD (stage 2), subclinical CVD (stage 3), and clinical CVD (stage 4), underscoring the importance of early intervention to prevent the escalation of CKM-related health outcomes (179, 180).

Beyond metabolic health, it is equally important to consider the mental health and biomechanical impacts in individuals with obesity. Limitations in physical functioning due to joint disease, poor sleep quality due to OSA, and exposure to societal bias and stigma are all important impacts on health outcomes (181, 182). These health outcomes are costly and debilitating, with implications for metabolic and overall health. Ultimately, the evidence suggests that the impact of untreated obesity over time is largely negative, as it drives abnormalities in health and has broad effects on individuals from metabolic health to physical function to mental health.

### *Treated obesity: risks of treatment*

The risks of treating obesity with GLP-1 RA or GIP/GLP-1 RA medicines have emerged from evidence from large clinical trials and real-world evidence. The primary risk is experiencing an adverse event, predominantly GI side effects (Fig. 2), which frequently occur early in the course of treatment (39, 40, 183).

The most frequently reported GI side effects include nausea, diarrhea, constipation, and vomiting; they tend to appear early in the treatment course during initiation of medications and are often associated with dose up-titration, especially when (inappropriately) rapid. GI side effects are generally mild to moderate in severity and diminish over time with ongoing use. While many patients may experience a GI-related side effect, only a small percentage of people discontinue therapy due to side effects in the clinical trials. For example, in the SURMOUNT-5 trial comparing tirzepatide with semaglutide, only 2.7% and 5.6% of patients, respectively, discontinued treatment due to GI side effects (184). Gallbladder disease is associated with weight loss with various forms of treatment including bariatric surgery and very low-calorie diet (185), noted in up to 1% of people treated with GLP-1 RA or GIP RA/GLP-1 RA medicines (185), whereas pancreatitis, listed as an adverse event in prescribing recommendations, has not been consistently detected in randomized controlled trials where all suspected pancreatitis events are adjudicated (Fig 2) (183).

Loss of fat-free mass accompanies weight loss achieved by any means: lifestyle modification, bariatric surgery, and GLP-1 RA or GIP RA/GLP-1 RA medicines (49, 105, 180). The central question is whether the lean-mass loss seen with these potent agents is a drug-specific effect or the expected physiologic consequence of large-magnitude weight loss, and the most recent evidence points firmly to the latter. In a 2026 systematic review and meta-analysis of 20 randomized trials (15 782 participants) restricted to DXA- or MRI-based body composition, lean mass accounted for approximately 26% of total weight loss overall, with no significant difference between GLP-1 RA based medications and intensive lifestyle intervention (approximately 30% vs 26%; $P = .42$) (186). The proportion did vary by agent, higher with semaglutide (35.2%) than with tirzepatide (25.4%) or liraglutide (26.8%), and a meta-regression showed that greater total weight loss predicts a proportionally greater lean-mass fraction. The distinction between absolute and relative change is critical: because these medicines produce larger total weight loss, absolute lean-mass loss is correspondingly greater, yet relative lean mass, its share of body weight, is typically preserved or improved as fat is lost preferentially. What matters clinically is function rather than the kilograms lost: current evidence indicates that muscle quality and physical function are largely preserved, supporting improvements in patient-reported physical function and quality of life after substantial weight loss (171). Strength, mobility, and fall or fracture outcomes, particularly in older adults and those with preexisting low muscle mass, remain inadequately studied.

The psychiatric safety of GLP-1 RA and GLP-1/GIP RA medicines, particularly any association with suicidality, has been intensively scrutinized, and the highest-quality evidence does not support an increase in risk. A 2025 systematic review and meta-analysis of randomized placebo-controlled trials (>107 000 participants) found no difference between GLP-1 RAs and placebo in serious (log risk ratio [RR], −0.02; 95% CI, −0.20 to 0.17) or nonserious psychiatric adverse events, no change in depressive symptoms, and improvements in mental health–related quality of life, emotional eating, and dietary restraint. A separate meta-analysis of 144 randomized trials focused specifically on suicide and self-harm found very low and statistically indistinguishable event rates in GLP-1 RA and placebo arms (0.047 vs 0.042 per 100 person-years; RR, 0.76; 95% CI, 0.48-1.21) (187). Drug-specific post hoc analyses are concordant: in the STEP 1, 2, 3, and 5 trials, semaglutide 2.4 mg showed no difference from placebo in Patient Health Questionnaire-9 depression or Columbia-Suicide Severity Rating Scale suicidal ideation/behavior scores, and in the SURMOUNT trials tirzepatide was associated with a small improvement in the Patient Health Questionnaire-9 score (treatment difference −0.6)

and equivalent rates of suicidal ideation (approximately 0.6% in both arms) (188).

## What are the potential impacts on obesity-related disease (heart, kidney, OSA, etc)?

### *Treated obesity-health impacts*

Health improvements, including blood pressure and glycemia, have been documented with weight reduction, beginning with losses of 3% to 5% of body weight (189). However, greater weight loss often leads to larger magnitudes of health improvements, and several complications of obesity can be resolved or remitted with sufficient weight reduction. Additionally, greater weight loss may be necessary to achieve health improvements associated with the mechanical effects of excess adiposity, such as OSA and osteoarthritis (189). GLP-1 RA or GIP RA/GLP-1 RA medicines frequently generate weight loss exceeding the 5% threshold associated with clinical effectiveness, and as a result of >10% weight reduction achieved in most trials, there has been a greater number of health improvements observed with treatment.

### *Type 2 diabetes and glycemia outcomes*

Clinical trial data from phase 3 obesity programs demonstrate that once-weekly semaglutide 2.4 mg and tirzepatide 10 to 15 mg produce clinically meaningful and durable improvements in glycemic control for adults with obesity and T2D. In the STEP 2 trial, once-weekly semaglutide 2.4 mg lowered mean HbA1c from 8.1% to about 6.5% over 68 weeks, and more than two-thirds of participants achieved an HbA1c of <7% (190). In patients treated with tirzepatide in the SURMOUNT-2 trial, HbA1c fell from 8.0% to approximately 6% at 72 weeks, and more than three-fourths of participants reached ≤6.5%; nearly half attained HbA1c <5.7%, a level consistent with diabetes remission (191). Similarly, mean HbA1c reduction was 2.23% in tirzepatide-treated youth with T2D (192). Both semaglutide and tirzepatide also produce large reductions in fasting plasma glucose, lowering the need for background glucose-lowering medications, while maintaining glycemic improvements through >1 year of follow-up. These results demonstrate that modern GLP-1 RA or GIP RA/GLP-1 RA medicines used for obesity management enable a high proportion of patients with T2D to meet or even surpass current glycemic targets while concurrently achieving significant weight loss.

### *Prediabetes and prevention of T2D*

Both semaglutide and tirzepatide significantly attenuate the proportion of patients progressing from impaired glucose tolerance to T2D. In the STEP-10 trial program for obesity, once-weekly semaglutide 2.4 mg led to 81% of participants with prediabetes achieving normoglycemia at 1 year, vs only 14% on placebo (193). Adolescents in the STEP TEENS trial treated with once-weekly semaglutide 2.4 mg had a 0.3% placebo-subtracted reduction in HbA1c after 68 weeks (194). Similarly, analysis of extended follow-up in the SURMOUNT-1 trial confirms longer-term sustained effects of tirzepatide evident over approximately 3 years in patients with obesity and prediabetes, with tirzepatide reducing progression to T2D by approximately 94% (158). Notably, 17 weeks after discontinuation of study medication, T2D was diagnosed in 2.4% versus 13.7% of tirzepatide versus placebo-treated participants.

### *Metabolic dysfunction-associated steatotic liver disease*

Bariatric surgery consistently reduces liver fat and improves liver architecture, while reducing rates of progression to MASH (180, 195). In the phase 3 ESSENCE trial studying particpants with biopsy-proven MASH (fibrosis stages 2 and 3), once-weekly semaglutide 2.4 mg led to 62.9% of patients achieving MASH resolution (without fibrosis worsening) after 72 weeks, compared with 34.3% on placebo (10). Fibrosis progression was also attenuated: 36.8% of semaglutide-treated patients had fibrosis stage improvement (no worsening of steatohepatitis) vs 22.4% with placebo. Mean weight loss was about 10%. There is emerging evidence from phase 2 trials that GLP-1 RA based medicines that include glucagon receptor agonism may have even greater effectiveness for improving MASH (196, 197). The dose–response relationship for GLP-1 RA based medicines and improvement in MASH has not been defined and may vary across different populations.

### *Cardiovascular risk factors and events*

GLP-1 RA and GIP RA/GLP-1 RA medicines improve multiple cardiovascular risk factors simultaneously. Semaglutide lowers systolic blood pressure by approximately 2 to 6 mmHg, and tirzepatide somewhat more. In SURMOUNT-1, pooled doses reduced systolic pressure by approximately 6.8 mmHg and diastolic by approximately 4.2 mmHg versus placebo at 72 weeks (5). Stratified analysis indicates that weight reduction mediates roughly 70% of the blood-pressure effect, with the remainder attributable to weight-independent actions including natriuresis, improved endothelial function, direct vasodilation and reduced vascular inflammation (198, 199). Both classes also improve atherogenic lipids, lowering triglycerides (by roughly 20-27%) and low-density lipoprotein, very low-density lipoprotein, and non–nonhigh-density cholesterol, while modestly raising high-density lipoprotein cholesterol and reducing inflammatory markers such as hsCRP and IL-6, effects that likely contribute to cardiovascular protection beyond traditional risk-factor modification (4, 5).

These changes in risk factors translate into fewer cardiovascular events. In people with overweight or obesity and established CVD but without diabetes, the SELECT trial showed that once-weekly semaglutide 2.4 mg reduced MACE by 20% (hazard ratio [HR], 0.80; 95% CI, 0.72-0.90) and all-cause mortality by 19%, with concordant reductions in nonfatal myocardial infarction and the heart-failure composite (8). These benefits emerged despite mean weight loss (about 9-10%) lower than in shorter trials such as STEP 1 (weight loss of about 15%), were independent of baseline HbA1c, and were only modestly mediated by weight loss; prespecified analyses attributed roughly one-third of the risk reduction to the decrease in WC, pointing to direct, weight-independent vascular mechanisms (184). On this basis, semaglutide now carries an FDA indication to reduce cardiovascular risk in adults with established CVD and overweight or obesity. The class-level signal is robust in T2D, where a 2025 meta-analysis of 21 trials (99 599 patients) found that GLP-1 RAs reduced MACE by 13% (IRR, 0.87; 95% CI, 0.83-0.91), with consistent reductions in cardiovascular and myocardial infarction endpoints (200). For tirzepatide, a dedicated placebo-controlled cardiovascular outcome trial in obesity (SURMOUNT-MMO; NCT05556512) is ongoing; to date, tirzepatide has shown cardiovascular safety

and noninferiority to dulaglutide in patients with T2D and atherosclerotic disease (mean BMI 32.6 kg/m$^2$) in SURPASS-CVOT, and an imputed-placebo analysis estimated a roughly 28% MACE reduction (HR, 0.72; 95% CI, 0.55-0.94) (201). Nevertheless, substantial data support weight loss-independent benefits of GLP-1 RA based medicines to reduce atherosclerotic heart disease, and whether lower doses of these medicines might also produce robust cardioprotection has not been determined.

#### *Heart failure with preserved ejection fraction*

Obesity-related heart failure with preserved ejection fraction (HFpEF) has emerged as a treatable target for these medicines. In the STEP-HFpEF program (once-weekly semaglutide 2.4 mg in patients with HFpEF and BMI ≥30; pooled nondiabetic and diabetic trials, n = 1145), semaglutide improved the Kansas City Cardiomyopathy Questionnaire clinical summary score by 7.5 points more than placebo (95% CI, 5.3-9.8), reduced body weight by approximately 8%, and increased 6-minute walk distance by about 17 m, with concordant reductions in C-reactive protein and N-terminal pro–B-type natriuretic peptide and lower diuretic requirements (202, 203). The SUMMIT trial provided additional event-driven evidence: over a median of 104 weeks, tirzepatide (up to 15 mg weekly) reduced the composite of cardiovascular death or worsening heart failure by 38% (HR, 0.62; 95% CI, 0.41-0.95; 9.9% vs 15.3%), driven principally by fewer worsening heart failure events and accompanied by symptomatic and functional gains (204). A pooled analysis of semaglutide trials (SELECT, FLOW, and both STEP-HFpEF trials) was concordant, reducing cardiovascular death or worsening heart failure by 31% (HR, 0.69; 95% CI, 0.53-0.89) (202). The benefit appears specific to the phenotype: meta-analysis shows reduced HF-worsening events in HFpEF (HR, 0.67; 95% CI, 0.50-0.89) but none in HFrEF (HR, 1.23), where these agents should not be used for heart failure.

Mechanistically, the benefit is attributed to reductions in visceral and epicardial/paracardiac adipose tissue, anti-inflammatory effects that are partly independent of the magnitude of weight loss, and volume unloading, consistent with an adipokine-driven model of obesity-related HFpEF (178). Several caveats temper the enthusiasm: the pivotal HF trials required BMI ≥30, so the evidence applies specifically to the obesity-related HFpEF phenotype; cardiovascular death was not significantly reduced in any individual trial, and the numerical imbalance in cardiovascular death favored semaglutide but ran against tirzepatide, and event numbers remain relatively small. Neither agent yet holds an FDA heart failure indication.

#### *Obstructive sleep apnea*

Weight loss is one of the most effective therapies for OSA, as reducing pharyngeal fat and abdominal pressure improves airway patency (9). However, substantial weight loss is usually required (ie, on the order of 10-15%) to meaningfully reduce apnea–hypopnea index severity. The first dedicated pharmacotherapy trial for OSA studying the efficacy of once-weekly tirzepatide 10 to 15 mg demonstrated a roughly 60 % reduction in the apnea–hypopnea index and allowed many participants to achieve mild or no clinical OSA after 52 weeks, underpinning its 2024 FDA approval for adults with obesity and OSA (9).

#### *Renal outcomes*

GLP-1 RA based medicines slow diabetic kidney disease progression; semaglutide recently received an FDA label to reduce risk of kidney function decline, end-stage kidney disease, and renal death in at-risk individuals with T2D based on the results of the FLOW trial studying 1 mg semaglutide qw over a mean follow-up period of 3.4 years (205). Mechanistically, contributions from lowering of BP and anti-inflammatory effects together with direct effects of GLP-1 RA based medicines on the kidney contribute to conferring renoprotection in patients with obesity without diabetes, as revealed by a reduction of renal outcomes in people with overweight or obesity treated with semaglutide in the SELECT trial (206). The potential for tirzepatide to confer renoprotective benefits in people with obesity with or without T2D is being studied in the TREASURE-CKD trial (NCT05536804).

#### *Quality of life and patient-reported outcomes*

Across the STEP and SURMOUNT trials, >50% of treated participants attained clinically meaningful improvements in weight-specific quality of life versus approximately 25% on placebo (207, 208). Improved weight-related quality of life was also seen in treated STEP TEEN trial participants (194). In a dedicated knee/osteoarthritis study, semaglutide reduced the Western Ontario and McMaster Universities Osteoarthritis Index pain score by 42 points (58% from baseline) and improved physical function, delaying joint-replacement consideration (209). Notably, self-esteem and emotional well-being improved in participants achieving weight loss with semaglutide or tirzepatide: both drugs reduced feelings of public distress and weight-related stigma (207, 208). GLP-1 RA and GIP RA / GLP-1 RA medicines also impact eating behavior and associated emotional health. A meta-analysis of over 100 trials found significantly decreased maladaptive eating behaviors, with a moderate effect size for reducing emotional eating. Patients reported feeling more control over food and less compelled to eat when stressed or upset (210).

## What are the gaps in our knowledge?

As noted, for many health improvements, there appears to be a threshold effect such that achieving a particular percent weight loss is associated with an increase in the probability of detecting improvements in specific health conditions and related outcomes (189). However, some of the health improvements observed in clinical trials, including SELECT and ESSENCE, have been achieved without achieving the same extent of weight reduction effect seen in the primary registration trials. For example, the mean weight reduction achieved in the SELECT trial was <10% compared with the mean weight loss reported in STEP 1 of roughly 15% (4, 8), yet the SELECT trial showed clear benefit for secondary prevention of cardiovascular events. These observations, along with the early separation of the event curves prior to significant reductions in body weight, add to the clinical evidence linking GLP-1 RA and GIP RA / GLP-1 RA medicines to weight loss–independent benefits on multiple health outcomes (14). This raises several important points. One is regarding targets (discussed in previously) and whether the percent weight loss should be replaced with a more clinically meaningful target. The second is that these medicines likely

have disease-modifying effects that are separate from the weight reduction itself. And lastly, it raises the question of whether maintenance of the health benefits requires long-term exposure to the treatment and not just maintenance of a lower weight.

## What are the weight-dependent versus weight-independent effects of the novel medications?

It is difficult to isolate the health benefits ensuing from weight reduction from the weight loss–independent benefits of GLP-1 RA and GIP RA/GLP-1 RA medicines based on observations in clinical trials. The dose–response relationships for clinical benefit are different for multiple outcomes. For example, effective glucose control is achieved without weight reduction, as there are significant improvements in glycemia based on mechanism of action (ie, stimulation of insulin and inhibition of glucagon secretion and reduction of gastric emptying, actions that do not require weight loss (211). However, remission of T2D may depend on reduction in ectopic fat stores reflecting achievement of a weight reduction to enable simultaneous improvements in β-cell function and insulin sensitivity (191, 212).

The value of understanding the weight loss–independent contributions and mechanisms linking improved health outcomes with use of a GLP-1 RA or GIP RA/GLP-1 RA medicine is that it helps to define treatment targets. If weight reduction is the primary driver of the health benefits, clinicians should inform patients about treatment targets based on health goals. If the weight reduction target is not likely to be achieved with a given therapy, the treatment strategy should be revised. On the other hand, if the exposure to the drug is the primary driver of the health benefits, then the type of therapy and weight loss-independent goals may be critical to the treatment strategy. The dose–response relationships for weight loss–independent benefits of GLP-1 RA based medicines have not been carefully studied. Furthermore, for investigation of CNS disorders such as Parkinson disease, prevention of Alzheimer disease, and treatment of substance use or neuropsychiatric disorders, the optimal dose–response relationships and the importance of brain penetration of these medicines are not well understood.

Additional data are required to better understand the ideal time to initiate treatment with a GLP-1 RA or GIP RA/GLP-1 RA medicine to achieve the best health outcomes. Initiating treatment early in the development of complications related to obesity would be prudent but costly in the short term. If modest weight reduction is the primary treatment goal, lower-cost, more accessible medications may be key to scaling cost-effective treatment of obesity, reserving newer and more costly agents for specific treatment targets or goals not feasibly achieved with older agents.

Personalization of treatment recommendations could be a function of the associated symptoms of obesity, contributing factors supporting excess weight gain, and health goals related to established complications of obesity. To achieve the intended target effects, specific molecules with targeted metabolic actions may be necessary. For example, achieving optimal resolution of steatohepatitis without worsening fibrosis may especially benefit from a GLP-1 RA based medicine with glucagon receptor agonism as a part of the treatment strategy.

### *What research is needed to address these gaps and improve clinical outcomes?*

The arrival of highly effective GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator medicines has transformed therapeutic possibilities but also exposed critical evidence gaps. Clinicians do not always know whether the various health improvements reported are due principally to weight reduction or to weight-independent drug actions. It remains uncertain when in the obesity trajectory pharmacotherapy should begin, how long treatment must be continued to sustain health improvements, and how benefits and risks vary across diverse patient groups. Addressing these questions requires a coordinated research agenda that combines mechanistic experimentation, comparative-effectiveness trials, and pragmatic real-world investigations.

### *Weight-dependent and drug-specific treatment effects*

A fundamental research question is how much of the benefits produced by GLP-1/GIP RA/GLP-1 RA and other NuSH receptor modulator medicines are a function of weight loss vs direct pharmacologic activity that may be slightly different with various agents. To answer this question, future trials could assign individuals with obesity and associated health complications to various treatment strategies (eg, a combination of intensive behavioral intervention ± early generation OM ± metabolic and bariatric surgery versus OM) with the goal of achieving a specific weight loss threshold (15-20%) that is matched across the treatment strategies. In this context where weight loss is matched, we can test whether remission of T2D, regression of MASH, resolution of OSA, or prevention of MACE differs by treatment modality. Embedded mechanistic substudies that assess changes in fat depots, metabolomics, proteomics, and changes in obesity-related signaling pathways may identify weight-independent mechanisms, while propensity-matched analyses within electronic health record networks can corroborate trial findings at scale.

## When should we be treating in the trajectory of obesity?

### *Timing and personalization for disease prevention*

By the time an individual has accumulated sufficient excess fat stores to reach a BMI of 30 kg/m$^2$, that individual has been exposed to the adverse effects of positive energy balance for an extended period; this means that accumulation of excess body weight is a lagging indicator of metabolic dysregulation in response to the environment. Preventing early metabolic dysfunction raises the question of when in the course of disease pathophysiology should GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator medicines be introduced as viable treatment options. Research is also needed to elucidate the impact of treating obesity at varying stages of childhood and adolescence, including in relation to puberty. It is not currently known whether newer OMs confer different effects on end organ outcomes in children and adolescents compared with adults or whether these effects vary by developmental stage.

Future clinical trials are needed that include individuals with early weight gain and limited or mild cardiometabolic disease

risk that may be outside of the current indications for OM. These individuals would be randomized to early treatment versus standard initiation (ie, watching and waiting). Endpoints such as incident diabetes, hypertension, and chronic kidney disease will quantify the yield of early therapy. Adaptive platform designs can simultaneously test personalized algorithms that assign drug class according to phenotype, such as visceral adiposity, liver fat content, appetite dysregulation, or atherosclerotic CVD risk score, thereby establishing whether precision prescribing outperforms a one-size-fits-all approach.

#### *Duration of treatment to sustain health outcomes*

Phase 3 trials show substantial weight gain and metabolic relapse when a GLP-1 RA, GIP RA/GLP-1 RA, or other NuSH receptor modulator medicine is withdrawn, suggesting long-term therapy is necessary for most patients. Randomized withdrawal and step-down designs should therefore compare continued full-dose treatment with alternative maintenance regimens that taper to intermittent dosing, combine a lower-dose injectable with supportive lifestyle interventions, use flexible dosing based on symptoms or metabolic parameters, or substitute inexpensive, earlier-generation agents once the target weight reduction is achieved. Key outcomes must include long-term weight trajectory, muscle and bone preservation, control of obesity-related conditions, cardiometabolic markers, health-related quality of life, and cost per quality-adjusted life year. Cost-utility and budget-impact analyses will inform payers about the affordability of continuous vs staged therapy. It is currently not known whether a defined treatment period with obesity medicines will confer any subsequent health benefits even years after the medicines are stopped, and future longitudinal research and longer follow-up is need to address this question.

#### *Broadening the health outcomes evidence base*

Important populations remain underrepresented. Older adults require trials that monitor sarcopenia, bone density and fracture outcomes, and impacts on physical function; we have much to learn about what is needed to safeguard functional status with these agents. Reproductive-aged women need robust pregnancy exposure registries capable of detecting rare teratogenic signals and clarifying safe wash-out intervals before conception. We should also include follow-up of the infants conceived posttreatment to understand the implications for the metabolic health and trajectory for these offspring. Pediatric trials will continue to be needed to evaluate effects of GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator medicines on physical health, mental health, development, and long-term health impacts. Purposeful enrollment of racially and socioeconomically minoritized groups is critical for understanding the potential of these medications to address health outcome disparities that may be driven in part by social determinants of health. If optimal health outcomes are only achievable in supportive environments, this reinforces the need for policy that addresses the drivers of disparities. If therapy with GLP-1 RA, GIP RA/ GLP-1 RA, or other NuSH receptor modulator medicines is effective regardless of the surrounding context, this reinforces the need for building strategies that improve equitable access to treatment.

In summary, addressing research gaps related to GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator medicines and health outcomes requires a collective research agenda that is agnostic of the specific medicine but addresses some broader therapeutic class effects. Addressing these fundamental questions will allow for greater personalization of treatment as the toolbox of available therapies continues to expand. Integrating real-world evidence with a broad array of comparative effectiveness trials that assess objective health outcomes, patient-reported outcomes, and remotely monitored outcomes (eg, physical activity, function, adherence), will allow us to advance the application of current and emerging GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator medicines to achieve optimal health outcomes for all while minimizing undue adverse effects. Understanding region-specific barriers such as cost, insurance coverage, variability in medication access, and strategies to improve long-term adherence may enable improvement of outcomes across health care systems.

# Safety

1. What are the safety concerns as millions of people take these medications?
2. What are the negative impacts of losing a substantial amount of weight (bone, muscle, nutrient deficiency?) Is there a role for new medicines such as myostatin/activin pathway inhibitors?
3. What are the hypothetical risks or safety concerns (ie, cancer)?
4. What is the optimal approach to collecting and using RWD with medications?

## What are the safety concerns in broader populations taking the OMs? What are the hypothetical risks or safety concerns (ie, cancer)?

GLP-1 RA medicines have been extensively studied in people with T2D and individuals with overweight and obesity with or without T2D in multiple phase 3 trials. Nevertheless, the duration of many of these trials may be as short as 6 months for people with T2D and range from 52 to 104 weeks in people with obesity. Although the safety and efficacy of GLP-1 RA and GIP/GLP-1 RA medicines used for the treatment of obesity such as liraglutide, semaglutide, and tirzepatide have been scrutinized in tens of thousands of individuals with overweight and/or obesity in phase 3 trials, these trials are neither long enough nor large enough to detect rare safety events, including many types of cancer or rare infections that might arise only in 1:10 000 people with more prolonged drug exposure. Remarkably, despite initial concerns about increased risks of pancreatic or thyroid cancer with GLP-1 medicines, there is emerging enthusiasm for the possibility that GLP-1 RA based medicines may reduce rates of cancer development or recurrence, and trials are planned or underway to test these hypotheses (183, 213, 214).

Historically, most trials of OMs specify precise eligibility criteria, generally excluding individuals with fluctuations in body weight, type 1 diabetes, New York Heart Association class IV heart failure, varying degrees of renal impairment, a recent (ie, within 5

years) history of cancer, active thyroid disorders, a history of major psychiatric disorders, and a recent history of depression, including a history of suicidal ideation. Hence, there is limited understanding of whether these broad categories of individuals might be uniquely susceptible to a subset of adverse events.

Moreover, individuals with a history of acute or chronic pancreatitis, active or chronic hepatitis, substance abuse, pregnancy, or breastfeeding are also excluded from most of these diabetes and obesity trials (183, 215). Some of the semaglutide or tirzepatide trials also exclude individuals with obesity secondary to endocrine causes or a genetic disorder (4, 5). Hence, clinicians looking for evidence and guidance supporting the safety and efficacy of these medications in people with the aforementioned conditions will not find relevant, useful information in most clinical trial publications. Additional scrutiny of safety in the real world would benefit from regular analyses of large registries, pharmacovigilance studies, and periodic scrutiny of health care claims linking use of OMs with rare reports of adverse events in multiple populations.

The popularization of GLP-1 RA and GIP RA/GLP-1 RA medicines for weight reduciton has led to their use among many individuals seeking weight loss who were not studied in or excluded from phase 3 clinical trials, including people with a BMI <27, individuals with type 1 diabetes, and individuals using the medicines for short periods of time, sometimes at doses above or below those recommended for clinical use in extensively studied populations. Collectively, the expanding use of these medicines in people not previously studied in clinical trials creates an evidence gap and uncertainty regarding their efficacy and safety (Fig. 2) beyond that defined for other populations in phase 3 trials. Larger outcome studies have been carried out in people with T2D and/or obesity, usually with risk factors for or known preexisting CVD, yet the long-term safety of these medicines in other populations is not yet supported by rigorous evidence (183).

Although the GLP-1 RA class of medicines was introduced clinically for the treatment of T2D in 2005, the first GLP-1 RA medication was approved for obesity treatment in 2014 (liraglutide), and the FDA-approval of semaglutide at a maximum dose of 2.4 mg weekly and tirzepatide at doses up to 15 mg weekly for obesity treatment occured in 2021 and 2023, respectively. Although many individuals with T2D are also living with overweight or obesity, information on the long-term safety of GLP-1 RA based medicines in people with obesity but without T2D is more limited with thus far one outcome trial, the SELECT trial, has reported on the safety of a GLP-1 RA medicine, semaglutide, in people with overweight or obesity with a previous history of atherogenic CVD (8). Although the results of the SELECT trial included a 19% reduction in all-cause mortality and no new safety concerns, our understanding of the long-term safety of GLP-1 RA medicines in people with obesity without T2D, including individuals without CVD, is still limited.

Detection of rare safety issues arising from more prolonged exposure to GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator medicines in susceptible individuals is currently challenging due to insufficient durations of exposure in clinical trials, compounded by evidence suggesting that many individuals discontinue these medicines in the real world after 12 to 24 months and may cycle on and off therapy. Rates of persistence vary widely in the real world, with some studies reporting up to 55% to 68% persistence (216), with others reporting much lower rates after 1 year of follow-up (217, 218). Although ongoing use of the medications remains high, often exceeding 90% in phase 3 weight loss trials with semaglutide and tirzepatide, rates of discontinuation and reinitiation of liraglutide, semaglutide, and tirzepatide are higher and lower, respectively, for people with obesity versus individuals with T2D in real-world observational studies, hampering studies of long-term safety (218).

## Compounded semaglutide and tirzepatide

The use of GLP-1 RA and GIP RA/GLP-1 RA medicines to achieve weight reduction and improved health is ideally achieved together with an experienced health care practitioner and often a team approach that involves counseling in lifestyle management, optimization of mental health, and recommendations for activity, appropriate exercise, nutrition, and diet. Obesity medicines are medicines like any other medicine with potential risks and benefits and thus should be used under the guidance of a trained health care provider. Due to drug shortages and FDA regulation governing supply shortages, considerable quantities of semaglutide and tirzepatide were dispensed that were not made by the manufacturers Novo Nordisk and Eli Lilly. Rather, they were synthesized by a large number of suppliers providing synthetic peptides, often of uncertain quantity and purity. In late 2024, one estimate suggested that at least 80 million prescriptions for compounded semaglutide had been filled in the previous 12 months (219). Multiple reports of harm and several dozen deaths have been reported to date associated with the use of compounded medicines, and the potential for long-term safety issues to arise secondary to the use of compounded semaglutide or semaglutide is not yet known and requires evaluation (219). Moreover, the quality of information and guidance surrounding the dispensing and use of compounded GLP-1 RA medicines that is provided by the suppliers appears to be highly variable (219). Whether the extensive use of dozens of different versions of semaglutide and tirzepatide is associated with safety and efficacy profiles resembling those described for FDA-approved semaglutide and tirzepatide produced by Novo Nordisk and Eli Lilly is not known and requires ongoing scrutiny. It is not currently known whether the effectiveness of the compaunded substances and attainable weight loss is similar to that achieved in clinical trials with authentic semaglutide or tirzepatide. However, evidence suggests that the ultimate dose level and weight loss achieved may be less in the real world relative to that reported in randomized controlled studies (216). Although supply constraints are easing, compounded GLP-1 RA medicines are still sold in many jurisdictions; hence, lingering safety concerns surrounding the supply chain endure. The FDA as well as various societies, including the Obesity Action Coalition, The Obesity Society, and Obesity Medicine Association, also issued statements advising against the use of compounded alternatives (https://www.fda.gov/drugs/drug-alerts-and-statements/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss).

## Pregnancy

Obesity may be associated with impaired fertility and delayed time to successful pregnancy in both men and women (220); however, there are insufficient data to determine whether treatment with GLP-1 RA or GIP RA/GLP-1 RA medicines improves fertility in people living with obesity. Furthermore, whether the

putative improvement in fertility is related to specific weight loss thresholds or reflects contributions from weight loss–independent mechanisms is uncertain. Current guidance does not recommend the use of GLP-1 RA or GIP RA/GLP-1 RA medicines during pregnancy, largely due to preclinical studies demonstrating small for gestational age babies and some congenital abnormalities, where nonobese pregnant animals were exposed to high doses of GLP-1 RA medicines, resulting in fetal energy restriction and suboptimal weight gain or weight loss during pregnancy (221).

Current standards of practice include counseling women to consider birth control to avoid pregnancy and/or cessation of GLP-1 RA medicines several months prior to attempts at conception. Nevertheless, after 20 years of GLP-1 RA medicines in the clinic, it seems likely that thousands of pregnancies have been carried to term in women with T2D and/or obesity who were exposed at some point during pregnancy to GLP-1 RA medicines, and little information has been reported on the outcomes for mother and baby. The available evidence from registry and real-world databases does not reveal an increased risk of major malformations for women with T2D or obesity exposed to GLP-1 RA medicines in the first trimester (222, 223). Hanif et al identified 1826 pregnant women with T2D exposed to GLP-1 RA medicines in the first trimester of pregnancy in the TriNetX database. Compared with data from propensity-matched nonexposed control pregnancies, there was no difference in a wide range of maternal outcomes, nor any imbalance in rates of fetal cardiac or kidney abnormalities in the GLP-1 RA medicine-exposed cohort (224). However, longer follow-up and careful scrutiny of maternal and infant outcomes in the context of women with obesity previously treated with GLP-1 RA medicines is needed.

Given the increased risk of hypertension and preeclampsia in pregnant women with obesity, as well as anovulation frequently associated with polycystic ovary syndrome, there is considerable interest in understanding whether prior or continued use of GLP-1 RA, GIP RA/GLP-1 RA, or other NuSH receptor modulator medicines in women planning pregnancy might be advantageous to improve chances of conception and outcomes. A retrospective study of female patients in the TriNetX database, age >18, who had used GLP-1 RA medicines at some point in the 2 years prior to conception (4267 individuals in exposed vs control cohorts), demonstrated reduced rates of gestational diabetes, hypertensive disorders, preterm delivery, and cesarian deliveries in the GLP-1 RA–exposed cohort (225).

Nevertheless, there is currently little evidence to guide timing and optimal use of GLP-1 RA based medicines prior to conception in at-risk women and some real-world studies report an increase in adverse outcomes, such as greater gestational weight gain, birth weight, gestational diabetes, hypertensive disorders, and preterm deliveries, in women who stopped GLP-1 RA based medicines prior to or at the start of pregnancy (226). As evidence accumulates supporting the safety of GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator medicines during pregnancy, it would seem reasonable to initiate randomized controlled trials to examine the safety and possible benefits of continuing use of GLP-1 RA based medicines during pregnancy for women with obesity at high risk for pregnancy-associated complications.

The timing of reinitiation of GLP-1 RA, GIP RA/GLP-1 RA, or other NuSH receptor modulator medicines following delivery in breastfeeding women has not been established. Semaglutide was not detected in the breast milk of 8 women, assessed at 12 and 24 hours after semaglutide administration, suggesting a low likelihood of harm to breastfed infants, especially since semaglutide is unlikely to be absorbed across the infant gut at meaningful levels in the absence of coformulated absorption enhancers (227). Nevertheless, a more extensive dataset, associated with clinical outcomes, and data informing guidance for reinitiation of GLP-1 RA, GIP RA/GLP-1 RA, or other NuSH receptor modulator medicines postpartum, would be useful. Moreover, the forthcoming introduction of small molecule GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator, each with different potential for excretion into breast milk, and varying potential for transplacental passage will require careful scrutiny of the unique safety of these medicines for use, before, during, and after pregnancy.

## What are the negative impacts of losing a substantial amount of weight (bone, muscle, nutrient deficiencies), and what is the role for new medicines such as myostatin/activin pathway inhibitors?

### Fractures and loss of lean mass

GLP-1 RA and GIP RA/GLP-1 RA medicines do not exert direct effects on bone formation or resorption in humans. Although people with T2D may exhibit defects in bone structure and quality, there is little evidence linking use of GLP-1 RA medicines to nontraumatic fractures (228). Rapid and extensive weight loss will increase the loss of adipose tissue, bone, and lean mass, predisposing susceptible individuals to clinical sarcopenia, falls, and fractures (229, 230) (Fig. 2). A supervised exercise regimen together with daily liraglutide therapy improved the maintenance of weight loss even 1 year after discontinuation of the exercise/liraglutide regimen (231). There are limited data examining whether the extent of loss of lean mass in people with obesity treated with GLP-1 RA and GIP RA/GLP-1 RA medicines can be mitigated with a high-protein diet, resistance exercise, strategies to reduce the rates of weight loss, or with one of several pharmacological agents now being tested either with semaglutide or tirzepatide in the clinic (96). Furthermore, special populations including the frail elderly, individuals with chronic kidney disease, and metabolic liver disease may be at higher risk for fractures, and there are insufficient data examining the impact of GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator medicines on musculoskeletal health across a wide range of individuals living with overweight or obesity. As clinical trials assessing investigational anabolic agents that spare or augment lean mass in combination with semaglutide or tirzepatide are underway, how should we assess changes in muscle quantity, quality, and function, and judge the success of these agents, and what are the key outcomes? How do we select patient populations most likely to benefit from preservation of functional muscle mass, and what should the duration of therapy be? There are currently no guidelines addressing the type and frequency of monitoring of bone and functional muscle health to be considered in individuals using GLP-1 RA based medicines. More trials are needed to assess whether different types

and frequency of exercise, with or without high-protein diets, can effectively mitigate loss of functional lean mass and improve clinically meaningful outcomes in people with obesity treated with GLP-1 RA, GIP RA/GLP-1 RA, and other NuSH receptor modulator medicines.

### Eye disease

The safety of semaglutide in people with T2D is being studied in the FOCUS trial. The use of semaglutide in people with T2D has been linked to an increased risk of nonarteritic anterior ischemic optic neuropathy (NAION) in case series and real-world observational data in some but not all analyses (Fig. 2) (232–235). Less information is available about the relative risk of NAION with use of GLP-1 RA medicines for weight loss in people with obesity, and most of the data reflect use of semaglutide, not tirzepatide (235–237). Given the low rates of NAION, additional scrutiny of this entity in registries and real-world databases will be required to understand the validity of the possible association and relative risk.

### Persistence

Regarding persistence and adherence in the real world, what is known about why people stop? Rates of persistence vary widely in the real world, with some studies reporting 55% to 68% persistence (216). Whether rates of discontinuation predominantly reflect challenges with tolerability, supply chain constraints, affordability and reimbursement, attainment of weight loss goals, or individual decisions to interrupt or stop medications is not well understood and requires clarification for development of effective strategies to optimize persistence (238). Moreover, rates of discontinuation of GLP-1 RA and GIP RA/GLP-1 RA medicines in the real world are higher for individuals with obesity using these agents for weight loss, relative to lower rates of discontinuation in people with T2D (217, 239). The reasons why people discontinue GLP-1 RA and GIP RA/GLP-1 RA medicines, ranging from cost and challenges with access, to adverse events, lack of efficacy, and achievement of short-term goals, are poorly understood. Whether education, comprehensive care, or additional approaches will increase the long-term persistence and clinical benefits associated with these medicines requires additional scrutiny.

### Periprocedural managment

Regarding periprocedural management, concerns surrounding the potential for GLP-1 RA based medicines to slow gastric emptying and increase the risk of retained gastric contents and aspiration have sparked multiple recommendations surrounding the optimal management of individuals requiring anesthesia and diagnostic or surgical procedures (183). Initial recommendations to hold medications in all subjects for several weeks prior to an elective procedure have been modified to include a more individualized approach that addresses the presence of gastrointestinal symptoms and the potential use of periprocedural ultrasound in some scenarios. There is scant trial data to address optimal practice across a highly heterogeneous patient population, and individualized recommendations and guidance have been proposed in consensus statements (240).

## Safety research priorities

Are there any unique long-term safety issues for using new OMs in (*a*) children and adolescents, (*b*) pregnancy, or (*c*) the elderly?

What are the most effective adjunctive measures to offset deleterious loss of bone or muscle in at-risk individuals?

Will nationwide registries be useful for understanding whether new OMs increase the risk of rare eye conditions in specific at-risk populations?

Should all new OMs be studied in large, randomized trials in people with or at risk for cardiorenal complications of obesity?

Are new OMs similar or unique regarding their potential safety in people with cancer?

How can the adjustment of medicines in patients undergoing elective surgery and anesthesia best be managed?

### Real-world data collection

Because the registration trials for GLP-1 RA and GIP RA/GLP-1 RA, and other emerging NuSH receptor modulator medicines are too short, too small, and too narrowly enrolled to characterize rare adverse events, long-term safety, durability, and effectiveness as these drugs are actually used, RWD are not a supplement to the evidence base but an essential complement to it. The optimal approach begins by matching the data source to the question. Administrative claims capture dispensing, persistence, switching, and events such as hospitalizations across large defined populations but generally lack weight, BMI, and laboratory values; electronic health records add anthropometrics, vitals, and laboratory trajectories but are fragmented across systems and miss care delivered elsewhere; disease registries and spontaneous pharmacovigilance are better suited to detecting rare events such as NAION and to monitoring exposures of particular concern, including pregnancy and the use of compounded products; and linkage to patient-reported and remotely monitored data (activity, function, adherence) captures domains that neither claims nor electronic health records record. Distributed data networks built on common data models, such as the FDA's Sentinel System, PCORnet, and the Observational Health Data Sciences and Informatics/Observational Medical Outcomes Partnership community, allow these questions to be addressed reproducibly and at scale while keeping patient-level data local.

Collecting the data is necessary but not sufficient; the harder problem is using it to draw valid causal inferences. Naïve comparisons of users and nonusers are vulnerable to confounding by indication, immortal-time bias, prevalent-user bias, and differential outcome ascertainment, biases that are especially pernicious for these medicines, because treatment is selectively initiated, frequently discontinued and reinitiated, and tied to behaviors and access that themselves predict outcomes. Observational analyses of OMs should therefore be designed within the target trial emulation framework, specifying eligibility, treatment strategies, an explicit time 0, and an active-comparator, new-user design before analysis; they should also incorporate negative-control outcomes and exposures, quantitative bias analysis, and preregistered protocols with transparent reporting of data provenance and reliability, consistent with current FDA guidance on RWD/real-world effectiveness and on noninterventional studies. Priorities specific to this class include capturing the dose and rate of titration, distinguishing branded from compounded products, modeling the dynamic on-and-off treatment patterns documented in practice,

and linking anthropometric and metabolic measures to separate weight-dependent and weight-independent effects rather than conflating them. Held to this standard, RWD can answer questions trials cannot: long-term safety in populations excluded from or poorly represented in trials; real-world effectiveness at the lower doses and lower persistence seen in practice; and head-to-head comparative effectiveness.

# Conclusion

Our overarching goal is to prioritize research to improve health outcomes for individuals with obesity. A focus on the 6 key areas described brings us closer to achieving this goal. A better understanding of obesity physiology and defended fat mass regulation enables the development of therapies targeted to obesity pathophysiology. Beginning to unravel the heterogeneity of obesity may enable pairing of pharmacotherapeutic treatments more specifically to disease (sub)type, allowing for less trial and error and thus earlier and better disease control. As with any chronic disease, targets supported by evidence of improvement in health outcomes shape standard-of-care guidance directly impacting clinical practice. Clarifying the physiology of treatment response and fat dynamics may provide critical insights into disease physiology. Improving and optimizing health outcomes are the goal of obesity treatment beyond weight reduction alone and, when paired with safety outcomes, enable ascertainment of the risk-to-benefit ratio of these therapeutics. There remains an important need to define how best to utilize these medicines across a wide range of health care systems and populations. Despite recognition by the World Health Organization that GLP-1 RA based medicines should be viewed as essential for improving health in susceptible populations (241), many individuals currently face multiple barriers to accessing these medicines. A better understanding of these areas as well as others will begin to fill gaps in knowledge about treatment with novel obesity medications and provide meaningful impact for improving the health of millions around the world.

# Disclosures

A. Jastreboff conducts multicenter trials with Amgen, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Rhythm Pharmaceuticals, and Roche; serves on scientific advisory boards for Amgen, AstraZeneca, Boehringer Ingelheim, Biohaven, Eli Lilly, i2o, Intellihealth/Flyte, Metsera, Novo Nordisk, Pfizer, Regeneron, Roche/Genentech, Scholar Rock, Structure Therapeutics, Syntis Bio, Viking, Wave, and Zealand Pharmaceuticals; and is the academic cofounder of State 4 Therapeutics. J.D. Ard reported research support from Eli Lilly, Boehringer Ingelheim, KVKTech, WW, Novo Nordisk, Regeneron, Amgen, Viking Therapeutics, and Roche; and Consulting/Advisory Board roles with Eli Lilly, Boehringer Ingelheim, KVKTech, WW, Novo Nordisk, Regeneron, Amgen, Viking Therapeutics, and Roche. K.D. Hall was an employee of the NIH when this article was written and subsequently became an employee of AstraZeneca Inc. L.M. Kaplan has served as a scientific and medical consultant to Altimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Dexligo, Dil Figaro, Eli Lilly, Helicore, Johnson & Johnson, Kallyope, The Last Food Fight, MetaVia, Neurogastrx, Novo Nordisk, Optum Health, Oxford Medical Products, Perspectum, Pfizer, Roche/Genentech, Skye Bioscience, State 4 Therapeutics, Structure Therapeutics and Wave Life Sciences. H. Krumholz has received stock options from Element Science, OpenEvidence, Arboretum, and Identifeye, and payments from Arboretum and F-Prime for advisory roles over the past three years. He was a cofounder of and held equity in Hugo Health. He is a cofounder of and holds equity in Refactor Health, Carabel, and Ensight-AI; is a cofounder of medRxiv; and serves on the board of openRxiv (nonpaid, volunteer). He is associated with research contracts through Yale University from Janssen, Kenvue, Novartis, and Pfizer. M. Van Name reports having received consulting/advisory fees from Mannkind, Novo Nordisk, and Soleno Therapeutics, and her institution has received research funding on her behalf from Lilly, Mannkind, Novo Nordisk, Provention Bio, and Sanofi. D.H. Ryan reports having received compensation for advisory or consulting services from Abbvie, Altimmune, Amgen, Biohaven, Boehringer Ingelheim, Calibrate, Carmot/Roche/Regeneron, CinRx, Currax, Eli Lilly, eMed, Epitomee, Fractyl, Genentech, ICON, i2o, Kailera, Nestel, Novo Nordisk, Pfizer, PPD Protagoinst, Regor, Rhythm, Souffle, Source Bio, Structure Therapeutics, Tenvie, Viking, Weight Watchers, Wondr Health, and Zealand; and for speaking from Eli Lilly and Novo Nordisk. She received stock options from Calibrate, Roman, Epitomee, and Scientific Intake. D.J. Drucker has received consulting fees from Amgen, Alnylam, AstraZeneca Inc, Crinetics, Eli Lilly, General Medicines Inc, Kallyope, Metsera, Pfizer Inc, Protagonist Therapeutics Inc, Roche, and Sanofi and speaking fees from Novo Nordisk Inc within the past 24 months. Mt. Sinai Hospital has received investigator-initiated grant support from Amgen, Eli Lilly Inc, and Zealand Pharmaceuticals Inc to support preclinical studies in the Drucker lab. GLP-2 intellectual property is the subject of a licensing agreement between the University Health Network, the University of Toronto, and D.J. Drucker.

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