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Precision medicine of obesity as an integral part of type 2 diabetes management – past, present, and future

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Obesity is a complex and heterogeneous condition that leads to various metabolic complications, including type 2 diabetes. Unfortunately, for some, treatment options to date for obesity are insufficient, with many people not reaching sustained weight loss or having improvements in metabolic health. In this Review, we discuss advances in the genetics of obesity from the past decade—with emphasis on developments from the past 5 years—with a focus on metabolic consequences, and their potential implications for precision management of the disease. We also provide an overview of the potential role of genetics in guiding weight loss strategies. Finally, we propose a vision for the future of precision obesity management that includes developing an obesity-centred multidisease management algorithm that targets both obesity and its comorbidities. However, further collaborative efforts and research are necessary to fully realise its potential and improve metabolic health outcomes.

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Introduction

The global prevalence of obesity has increased greatly over the past four decades[1] and can have life-threatening consequences due to its many associated comorbidities. The potentially fatal nature of this condition accentuates the need for comprehensive and effective treatment strategies and poses a considerable public health challenge. In 2016, more than 1·9 billion adults were classified as having overweight, of whom more than 650 million were diagnosed with obesity, constituting about 13% of the world's adult population.[1,2] This rising trend is not restricted to adults; data also suggest a substantial escalation in children and adolescents aged 5–19 years living with overweight or obesity, with rates increasing from 4% in 1975 to more than 18% in 2016.[2] Overweight and obesity, previously considered mainly an issue in high-income countries, are now increasing in frequency in low-income and middle-income countries, particularly in urban settings. Excess weight is one of the leading causes of death worldwide, as it is the main shared risk factor for several diseases, including type 2 diabetes, cardiovascular disease, chronic kidney disease, and musculoskeletal disorders.[3–5] Furthermore, in some cases, excess weight can result in obesity-related multimorbidity. Crucially, the risks associated with excess weight are not confined to adults, but are also a rising concern among children and adolescents.[6]

Obesity is a heterogeneous, multifactorial condition that is managed to date by use of a one size fits all approach, wherein treatment strategies are selected predominantly on the basis of the side-effects, costs, availability, or existing comorbidities, rather than addressing the specific underlying pathophysiological processes. With the increasing prevalence of obesity globally and substantial variability in response to existing therapeutic modalities, this approach is inadequate, and calls for the introduction of precision medicine in managing excess body weight to test whether we can provide the most appropriate therapy for the right person at the right time. The first step towards the goal of precision medicine for obesity is precision diagnosis, which depends on accurate and meaningful patient stratification to implement therapy optimisation and prognosis. Despite extensive progress in the epidemiological, genetic, and physiological characterisation of obesity and its metabolic consequences, there remains no widely validated stratification algorithm for individuals with obesity at risk of metabolic disease that successfully reflects the broad range of clinical manifestations of excess weight. As a result, there is an urgent need to develop a novel classification system to reveal the pathophysiology underlying patient heterogeneity, improve the prediction of clinical outcomes, and facilitate precision medicine in weight management. Several attempts have been made to reclassify individuals with obesity in the context of metabolic risk, but no single strategy has emerged as a universal classifier.

Most individuals with type 2 diabetes have excess body weight, making precise obesity management a crucial component of diabetes care,[7] as weight reduction is essential in the prevention and management of type 2 diabetes.[8] Numerous studies have shown that sustained weight loss of at least 15% of an individual's body weight substantially affects the progression of type 2 diabetes, inducing remission in a large proportion of patients and greatly improving the metabolic health of many others.[7,9,10] Previously, bariatric surgery was the only intervention capable of achieving and maintaining such substantial weight loss. However, the introduction of novel weight loss medications based on incretins has changed the field, allowing pharmacotherapy to have comparable results to bariatric surgery.[11] These new obesity medications not only facilitate weight loss, but also exhibit glucose-lowering effects independently of weight, an achievement in diabetes pharmacotherapy.

As a result, the convergence of type 2 diabetes and obesity management is becoming increasingly apparent, with a gradual transition towards a more comprehensive approach to diabetes treatment moving beyond a solely glucose-centric focus to include weight management as a coprimary goal and target of diabetes therapy.[7]

Weight loss can be achieved with different therapeutic strategies, including lifestyle intervention (diet and exercise), pharmacotherapy, or bariatric surgery. In clinical practice, however, variation in weight loss between patients receiving the same treatment method is commonly observed.[12] As of 2023, the management of excess weight loss in obesity generally follows a universal approach with standard treatment guidelines that are applied to a broad population. However, these standard guidelines are often only applicable for generalised patient groups and lack the specificity required for individualised management plans.[13–18] With the increasing availability of big data, including omics (genomics, epigenomics, transcriptomics, proteomics, metabolomics, or the microbiome), combined with detailed phenotypic data and electronic health-care records, precision medicine in weight loss management, an integral part of diabetes treatment, is slowly becoming a reality. With existing and ongoing studies exploring the genetics of weight loss therapies, including the pharmacogenetics of novel incretin-based medications, we are entering a new phase of precision medicine in which integrated genetic, phenotypic, and lifestyle factors might predict response to weight loss therapies in both body composition changes and metabolic improvements.

In this Series paper, we discuss the heterogeneity of the metabolic consequences of obesity and describe existing efforts to diagnose it into more meaningful subtypes, combining genetics, lifestyle, and environmental exposures, which can precisely classify and identify people at risk of metabolic consequences of excess weight, including diabetes. We also review the genetics of response to existing weight loss strategies, including pharmacotherapy, lifestyle, and surgical interventions. Finally, we discuss the implementation of genetic data and novel subtypes of diabetes and prediabetes in excess weight management and present the application of precision medicine in weight loss in the context of diabetes care.

Heterogeneity of obesity and its metabolic consequences

Obesity is defined by calculating BMI, an individual's weight divided by their height squared (kg/m²), and categorised according to WHO.[2,19] This classification system is intended to help health-care professionals and researchers standardise terms and assess clinical severity on the basis of the correlation between BMI and health outcomes, such as cardiometabolic conditions. However, the development of obesity and its metabolic implications are not solely due to increased body weight, but also due to the excessive buildup of adipose tissue, its malfunction—such as impaired lipid storage, chronic inflammation, and insulin resistance—and ectopic fat accumulation.[20] Relying on BMI alone does not provide an accurate representation of body composition and merely serves as an indirect measure of body fat content. Furthermore, the use of BMI for obesity diagnosis has revealed substantial metabolic phenotype diversity among people with a BMI greater than or equal to 30 kg/m².[21]

Obesity and type 2 diabetes are closely related, yet distinct and highly heterogeneous conditions, the prevalence of which has risen tremendously in the past 3 decades.[3,4,22] They frequently coexist, and obesity is considered a primary feature of type 2 diabetes, but their relationship is intricate and not fully understood.[23,24] Many people with obesity present with a metabolically healthy phenotype (or are metabolically healthy);[25] conversely, approximately a third of people of healthy weight (defined as a weight corresponding to a BMI of 18·5–24·9 kg/m²) exhibit metabolic abnormalities.[26] These findings have prompted the notion of metabolically healthy obesity (MHO)[21,25] and metabolically unhealthy obesity (MUO) for those with obesity and comorbidities, such as type 2 diabetes, hypertension, or dyslipidemia.[26,27] Integrating BMI and metabolic phenotype resulted in distinguishing the metabolically unhealthy normal weight (MUNW) individuals group that can account for approximately 20% of the adult population with BMI less than 25 kg/m².[26] The MUNW population have a risk of cardiovascular events and all-cause mortality three times higher than their metabolically healthy counterparts. Despite the widespread concepts of MHO and MUO, there is no unified definition of metabolic health,[28] which makes it difficult to estimate the prevalence of these phenotypes. Studies show that the MHO prevalence varies from 3% to 70% among people with obesity, depending on the defining criteria.[28–31] Initially, MHO was diagnosed in people with a BMI greater than or equal to 30 kg/m² who had fewer than two metabolic pathologies (including dysglycaemia, dyslipidaemia and hypertension), although this term was later updated to exclude people presenting with any of these metabolic syndrome-related components.[32] This refined definition is more suitable, but the term healthy should be used with caution and can be misleading, suggesting a benign nature of obesity in these people. Numerous studies, including several meta-analyses, underline that such individuals are not exempt from cardiometabolic complications and the mechanical complications of excess weight (eg, obstructive sleep apnoea, gastroesophageal reflux disease, and osteoarthritis) remain; thus comorbidity risks might be lower than in the MUO group, but not absent.[33–35] MHO should not be considered a safe form of obesity exempt from treatment, but can help guide personalised, risk-based obesity treatment.

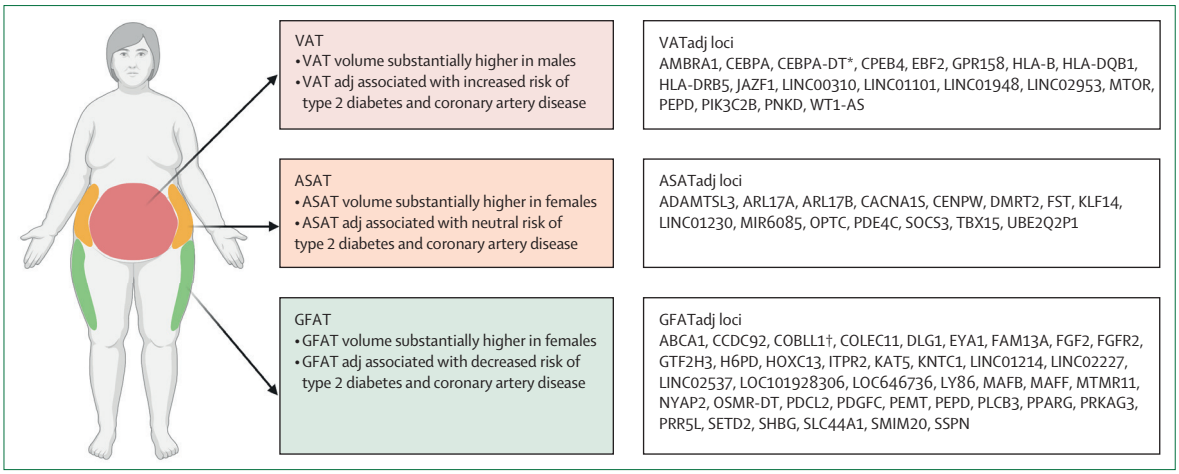


Figure 1: **Associations of specific adipose tissue depots with metabolic consequences and distinct genetic loci**
The locations of three specific adipose tissue depots and their associations with type 2 diabetes and coronary artery disease, and the text boxes highlight distinct genetic loci, denoted by the nearest gene, uniquely associated with one of the VAT, ASAT, and GFAT volumes, and adjusted for BMI and height. Figure created with Biorender.com. Adapted from Agrawal and colleagues.[44,45] VAT=visceral adipose tissue. Adj=adjusted for BMI and height. ASAT=abdominal subcutaneous adipose tissue. GFAT=gluteofemoral adipose tissue. *Two independent loci. †Three independent loci.

A comprehensive review[36] of the evolving concept of metabolic health and cardiometabolic risk clusters is helpful for this context.

Several factors have been proposed to explain the seemingly less harmful metabolic profile (characterised by typical insulin sensitivity, favourable lipid profiles, and typical blood pressure) in metabolically healthy individuals with BMI greater than or equal to 30 kg/m². The main driver could be the preferential distribution of fat in subcutaneous adipose tissue (SAT), especially in the gluteofemoral region, instead of the visceral adipose tissue (VAT). Multiple studies showed that VAT strongly correlates with obesity-related comorbidities, while SAT offers some protection.[27,37–43] In a study published in 2023, Agrawal and colleagues analysed raw MRI imaging data from 40 032 UK Biobank participants and showed that SAT volumes adjusted for BMI had substantial heterogeneity in associations with metabolic outcomes[44] (figure 1). VAT adjusted for BMI was associated with an increased risk of type 2 diabetes and coronary artery disease, abdominal subcutaneous adipose tissue (ASAT) adjusted for BMI was largely risk neutral, and gluteofemoral adipose tissue (GFAT) adjusted for BMI was associated with protection for type 2 diabetes and coronary artery disease. These results emphasise that different fat depots have unique metabolic profiles and confirm the need to replace or supplement BMI with other anthropometric parameters that more accurately reflect excess adiposity, including imaging-based measurements of different fat depots.[46] Another driver could be an ectopic accumulation of lipids in non-adipose tissues. Emerging evidence suggests that ectopic fat deposition, especially in hepatic and epicardial regions, might contribute to increased atherosclerosis and cardiometabolic risk.[46] These findings underscore the need to shift the goals of weight loss therapies from solely measuring the total weight loss or fat loss to also assessing the specific depots where fat loss occurs. However, devising weight loss treatments that target these depots is a considerable challenge. Moreover, although incorporating skeletal muscle mass in these assessments can help evaluate the metabolic consequences of obesity, individuals with visceral obesity—characterised by excess intra-abdominal adipose tissue accumulation—often show increased lipid infiltration in skeletal muscle, which can exacerbate their cardiometabolic risk. This occurrence emphasises the importance of considering sarcopenic obesity (characterised by the presence of excess body fat and reduced muscle mass and strength), which is associated with decreased insulin sensitivity, compared with obesity alone.[47,48]

Genetics and the metabolic heterogeneity of obesity

Obesity arises from an intricate interplay between genetic predisposition and environmental influences. A genetic component underlies the variation in body weight between individuals and can affect their response to the modern environment which is increasingly obesity-promoting.[49] The heritability of obesity estimated from family and twin studies ranges from 40% to 70% depending on the methods used.[50] Consequently, genetic research can be used to understand the physiological and molecular mechanisms regulating body weight, address the disease's observed diversity, and understand the relationship between obesity and type 2 diabetes. Traditionally, from the genetics perspective, obesity has been divided into two main categories: rare monogenic obesity (characterised by early-onset, severe obesity due to chromosomal deletions or single-gene defects) and polygenic obesity (the most common form, caused by numerous genetic polymorphisms with small individual effects).[49]

Monogenic obesity results from a single rare mutation that has a large effect on weight gain, generally affecting less than 5% of people with obesity.[51] These individuals often exhibit severe early-onset obesity and hyperphagia, potentially accompanied by endocrine disorders. Monogenic obesity can present by itself or in the context of a syndrome, such as obesity combined with other distinct features, for example, cognitive impairment, delayed motor development, learning difficulties, or autism spectrum disorders, coupled with various organ-specific genetic abnormalities. Despite many such syndromes being identified, most of their genetic foundations remain elusive.[52]

In monogenic non-syndromic obesity, most causative genes encode proteins that function within the hypothalamic leptin-melanocortin signalling pathway, which is crucial for controlling food intake, body weight, and energy balance. Typically, mutations in genes encoding leptin (*LEP*),[53] leptin receptor (*LEPR*),[54] proopiomelanocortin (*POMC*),[55] proprotein convertase subtilisin/kexin type 1 (*PCSK1*),[56] and melanocortin 4 receptor (*MC4R*)[57,58] are the most prevalent causes of monogenic obesity.[49,59] Nonetheless, technological progress and continuing research efforts are yielding novel genes linked to monogenic obesity, such as the discovery of the gene encoding the agouti signalling protein (*ASIP*) in 2022.[60]

Technological advancements, such as whole-exome sequencing, together with decreasing sequencing costs, have allowed for the discovery of obesity mutations in people who are not presenting with extreme or early-onset forms of obesity, which has started to blur the line between monogenic and polygenic obesity.

The investigation of the genetic architecture of polygenic obesity initially relied on candidate genes and genome-wide linkage studies,[49] but encountered challenges due to restricted sample sizes, inadequate coverage of genetic variation, and difficulties in replication. The emergence of genome-wide association studies (GWAS) has substantially advanced gene discovery in common diseases, including obesity. Since 2007, numerous GWAS have identified more than 1100 independent loci associated with diverse obesity traits, leading to the characterisation of novel pathways and genes linked to obesity.[61] Among the earliest findings of obesity-related GWAS was the identification of common variants in the *FTO* gene, which has since become a prominent focus in obesity research.[62] Large-scale international collaborations, such as the Genetic Investigation for Anthropometric Traits (GIANT) consortium, have been established to merge datasets from individual GWAS, yielding even greater sample sizes. As the sample sizes in successive GWAS have expanded, so has the statistical power to detect additional loci, particularly those that occur less frequently or exhibit smaller effects. However, even with this considerable progress, GWAS-discovered loci account for only about 6% of the variation in BMI[63] compared with the estimated heritability, leading to the so-called missing heritability.[64]

For more on **GWAS** see https://www.ebi.ac.uk/gwas/home

For more on the **GIANT consortium** see https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium

Given the polygenic nature of common obesity and the fairly small influence of individual common variants on disease risk, efforts have focused on developing polygenic scores (PSs, also known as genetic risk scores) that combine multiple genotyped variants for an individual, offering more information on a person's risk profile. Khera and colleagues[65] developed a globally expanded polygenic score (gePS), incorporating data from more than 2·1 million common genetic variants and BMI effects from the largest obesity GWAS available to date.[65] The gePS accurately predicted statistically significant differences in weight, severe obesity, cardiometabolic disease, and overall mortality. For the top 1·6% of the population with the highest gePS, the increase in BMI was similar to large-effect pathogenic mutations in *MC4R*. The score showed minimal association with birthweight and was strongly linked to an increasing weight gradient that began in early childhood and presented as more substantial differences in weight and severe obesity in later decades. This score shows the value of small-effect genetic variants that do not meet the threshold of genome-wide significance. However, polygenic risk is probabilistic, not deterministic: among those in the top gePS decile, not all were diagnosed with obesity—17% had a BMI within the normal range and 0·2% had underweight (BMI <18·5 kg/m²). It is therefore essential to recognise the roles of non-genetic factors, such as lifestyle, environment, and socioeconomic status in shaping the manifestation of both polygenic and specific monogenic forms of obesity (eg, penetrance of *MC4R* deficiency that might show a generational effect, possibly tied to the development of an obesogenic environment[66]). To accurately predict obesity risk, effective prediction models must incorporate both genetic and non-genetic factors, including a wide array of demographic, environmental, clinical, and potentially molecular markers. Nonetheless, PSs could serve as an additional tool for screening and identifying high-risk individuals before clinical risk factors become apparent.

Although BMI has been widely used as the primary measure of obesity in GWAS due to its convenience and widespread availability, it is an imprecise measure of overall adiposity because it does not differentiate between distinct components of body weight, such as muscle mass or bone mass. Moreover, as discussed earlier in this Review, defining obesity based solely on BMI does not provide information about the metabolic consequences of excess body fat. To address this limitation, some GWAS have explored more refined obesity traits, such as waist-to-hip ratio, body fat percentage, and lean mass, and imaging-derived adipose tissue volume, which distinguishes between specific anatomical fat depots.[67–71] These more precise phenotypes offer a more comprehensive understanding of body weight composition and result in the identification of loci that more accurately reflect the

biological pathways underlying obesity. Building upon this evolution of obesity genetics, a 2018 study by Lotta and colleagues[72] identified specific genetic variants associated with elevated waist-to-hip ratio through differential fat distribution—either reduced gluteofemoral or increased abdominal accumulation. These variants, when combined into PSs, were found to be associated with increased cardiometabolic risk, further substantiating the link between genetically influenced fat distribution and metabolic diseases. A 2022 study by Agrawal and colleagues[45] provided additional insights into the genetics of depot-specific fat accumulation (figure 1). The researchers investigated the inherited architecture of three MRI-driven distinct fat depots (VAT, ASAT, and GFAT) and identified several loci associated with the depot-specific distribution of fat, indicating distinct genetic architecture. They found that individuals with a high GFAT BMI-adjusted PS had a profile corresponding to a so-called healthy obesity phenotype (individuals in the top 5% of the PS distribution presented with higher concentrations of high-density lipoprotein cholesterol, lower concentrations of serum triglycerides and alanine aminotransferase, and lower risk of type 2 diabetes and coronary artery disease compared with the remaining individuals). This study is the largest imaging-based study to date to analyse the genetic architecture of different fat depots and provides insights into the pathomechanisms of metabolically unhealthy obesity by supporting the hypothesis that the inability of the GFAT depot to adequately expand might be a primary insult in a metabolically unhealthy fat distribution.

Genetics can provide insights into the heterogeneity of metabolic consequences associated with obesity and elucidate mechanisms underlying the decoupling of adiposity from its cardiometabolic complications. Most genetic variants linked to obesity also increase the risk of poor metabolic health. However, some BMI and adiposity-raising alleles have been connected to a more positive metabolic profile.[69,73–77] The reason for this inconsistency remains unclear, but understanding it could reveal the causal factors of obesity-related conditions, providing new opportunities for drug development and risk evaluation. One of the earliest observations of genetic discordance between obesity and cardiometabolic disease is the association of a locus near *IRS1* where the body-fat-increasing allele was also linked to a favourable cardiometabolic risk profile, including reduced risk of type 2 diabetes.[73] Moreover, the same study showed that the risk allele preferentially promotes fat deposition in SAT, rather than VAT, which is a potential driver of observed discordance. Subsequent studies have identified additional loci associated with a similar pattern of discordance. In 2021, Huang and colleagues[78] used a genome-wide cross-phenotype meta-analysis of adiposity–cardiometabolic trait pairs to identify 62 loci associated with an apparent paradoxical association between adiposity (measured by BMI, waist-to-hip ratio, or body fat percentage) and a favourable effect on cardiometabolic risk factors or outcomes (such as high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting glucose, fasting insulin systolic blood pressure, coronary artery disease, or type 2 diabetes). 37 of the loci had not been reported before, and they were grouped into three clusters on the basis of their association with adiposity and cardiometabolic traits. The mediating effect of fat distribution was predominantly seen for loci in cluster 1, which are associated with a broad range of cardiometabolic traits.[78] For loci in clusters 2 and 3, a favourable fat distribution played a less crucial role in mediating protective cardiometabolic effects.

Coral and colleagues[79] investigated the metabolic heterogeneity of obesity by analysing genetic variants associated with both BMI and type 2 diabetes. They classified variants as either concordant, in which the same allele increases the risk for both obesity and type 2 diabetes, or discordant, in which the same allele increases the risk for obesity but decreases the risk for type 2 diabetes. These variants were used to define two distinct genetic profiles: one that conveys highly concordant diabetogenic effects and one that conveys highly discordant diabetogenic effects. Machine learning methods were then used to identify traits, other than type 2 diabetes, that characterise these profiles. The study identified key differences in a range of traits, such as fat distribution, cardiovascular mortality, liver metabolism, blood pressure, specific lipid fractions, and blood concentrations of proteins involved in extracellular matrix remodelling that contribute to the so-called healthy obesity phenotype and causal pathways between obesity and metabolic disease. The study provides insights into mechanisms of action, identifies potential drug targets, and could aid in further obesity stratification.

Despite substantial progress in obesity genetics research, most discoveries have been based on populations primarily of European ancestry, reducing their applicability to diverse populations. This issue is particularly problematic due to known ethnic and racial differences in adiposity and its metabolic consequences. Although some genetic loci are transferable across ancestries, ancestry-specific loci have yet to be uncovered. Efforts over the past decade have addressed this disparity by exploring the genetic architecture of obesity in more diverse cohorts and biobanks, aided by international consortia, such as GIANT.[80–84] Additionally, although GWAS are useful for flagging genomic regions of interest, identifying causal genes, variants, and mechanisms remains challenging. Enrichment analyses of genes in GWAS loci can provide preliminary insights into potential mechanisms, which consistently highlight the central nervous system as a crucial factor in regulating body weight.[49] However, the function of most obesity-associated loci have yet to be elucidated, and expanding our understanding of obesity-associated variants will involve integrating GWAS results

with functional cell type-specific genomics data. Future work with single-cell data, gene-editing technologies, and cellular phenotyping will be essential in this endeavour.[85]

Obesity stratification efforts

Accurate diagnosis is the initial stage in providing precision obesity care. Patient stratification is crucial for implementing precision medicine approaches, such as tailored treatment plans, predicting disease progression, and anticipating complications. Despite considerable progress in the epidemiological, genetic, and physiological profiling of individuals at risk for or affected by obesity, there is no widely validated stratification strategy that effectively captures the disease's clinical heterogeneity and integrates risk factors, triggering events, pathophysiology, prognosis, and effective treatment indications. Existing obesity classifications based on BMI, abnormal waist circumference (usually defined as <94 cm for men and <80 cm for women) or the presence of metabolically abnormal obesity focus on cardiometabolic risk, but fail to account for the disease's heterogeneity, including its pathogenesis, clinical features, and course of excess adiposity.[32] Therefore, to improve clinical outcome predictions and facilitate precision medicine in managing excess weight, a refined classification of obesity is needed. To date, there have been only a few attempts, using various methods to reclassify people with obesity beyond traditional anthropometric features and the MHO and MUO concepts, reflecting differences in disease development and progression.

In 2021, Acosta and colleagues[86] proposed a novel classification of obesity that emphasises the underlying mechanisms of weight gain rather than traditional anthropometric and metabolic features[86] (figure 2). They designed a series of tests to assess energy balance components, such as satiation (calories consumed to reach fullness and terminate the meal), satiety (duration or fullness or return to hunger), emotional hunger, and energy expenditure. Consequently, they identified four unique obesity phenotypes on the basis of a cutoff of the 25th or 75th percentile of each measurement: abnormal satiation (hungry brain; 16% prevalence), abnormal hedonic eating (excessive or compulsive consumption of food driven by pleasure, reward, or to modulate emotional states rather than by physiological hunger; emotional hunger; 12% prevalence), abnormal satiety (hungry gut; 18% prevalence), and low predicted energy expenditure (slow burn; 12% prevalence). In 27% of patients, two or more phenotypes were documented, and 15% of patients did not exhibit any of the phenotypes. Despite no statistically significant differences in age, BMI, waist or hip circumference, and comorbidities, each group displayed unique characteristics. The hungry brain group consumed 62% more calories before reaching fullness compared with non-hungry brain obesity phenotypes; the emotional hunger group reported 2·8 times higher anxiety levels compared with non-emotional hunger obesity phenotypes; the hungry gut group had a 31% faster gastric emptying rate compared with non-hungry gut non-emotional eating obesity phenotypes; and the slow burn group had a 12% lower predicted resting energy expenditure, compared with non-slow burn obesity phenotypes. Individuals with slow burn obesity also had reduced muscle mass and were less active than their counterparts. The authors also proposed a targeted lifestyle therapy and pharmacotherapy for each group (figure 2).[86,87] The proposed therapies are recommended on the basis of literature-derived assumptions and not on evidence from direct, randomised controlled trials, and therefore require validation through rigorous clinical studies. Furthermore, the generalisability of the proposed obesity phenotypes is contingent on confirmation in broader cohorts with diverse populations extending beyond the initial study group. Nonetheless, this phenotype-based classification could enhance our understanding of obesity pathogenesis and promote the development of targeted, phenotype-specific clinical trials. Additionally, the concept could be expanded to include other factors, such as genetics, epigenetics, the microbiome, and the exposome, potentially uncovering new causes of obesity and refining treatment strategies. However, clustering methods based on clinical parameters face limitations due to their instability over time, as factors (eg, disease progression, medications, and lifestyle changes) can alter a patient's cluster assignment. This dynamic nature is exemplified in diabetes research, such as in the diabetes clusters proposed by Ahlqvist and colleagues[88] in which 23% of individuals transitioned between clusters over 5 years of follow-up.[89] Similarly, a 2021 study by Wagner and colleagues[90] investigated individuals at high risk of developing diabetes and found that a substantial proportion of participants were reassigned to different clusters over 4 years of follow-up. These findings show that phenotype-based cluster assignments can be fluid, suggesting that such dynamics should be factored into precision diagnosis efforts.

Using genetic information in the form of PS might offer more consistent and stable classifications. The exploration of PS in obesity is scarce, but constructing partitioned or process-specific PS along pathomechanistic axes (specific biological processes that are mechanistically relevant to the disease, such as β cell function or insulin resistance) could be a promising strategy, especially in the context of type 2 diabetes.[91–93]

Watanabe and colleagues[94] questioned the application of conventional BMI and used machine learning models to develop omics-based BMI measurements. They analysed a cohort of 1277 individuals with various phenotype data, including human genomes, longitudinal measurements of metabolomics, proteomics, clinical laboratory tests, gut microbiomes, physical activity, and health and lifestyle

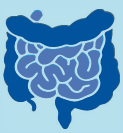
	Hungry brain	Emotional hunger	Hungry gut	Slow burn
				
Main obesity phenotype	Abnormal satiation*	Abnormal hedonic eating†	Abnormal satiety‡	Low predicted energy expenditure
Features (compared with a non-phenotype group)	• Consume 62% more calories before reaching fullness	• 2·3 times higher anxiety levels	• 31% faster gastric emptying rate	• 12% lower predicted resting energy expenditure • Reduced muscle mass • Less active
Proposed targeted LIFESTYLE therapy	• Time-restricted eating	• Low-calorie diet with intensive behavioural group therapy	• Low-calorie diet with pre-meal protein supplements	• Low-calorie diet with post-workout protein supplementation and high-intensity interval training
Proposed targeted PHARMACOTHERAPY	• Phentermine plus topiramate extended release	• Oral naltrexone plus bupropion sustained release	• Liraglutide	• Phentermine

Figure 2: **Novel obesity classification and targeted therapies based on underlying mechanisms of weight gain**
The obesity classification system proposed by Acosta and colleagues.[86,87] Presented are the mechanisms of weight gain, their main characteristics, and targeted lifestyle therapies and pharmacotherapies for each phenotype. Suggested therapies are based on assumptions derived from existing literature rather than the outcomes of randomised controlled trials. *Characterised by excessive calories consumed to reach a feeling of fullness and terminate a meal. †Characterised by excessive or compulsive consumption of food driven by pleasure, reward, or to modulate emotional states instead of by physiological hunger, involving cravings and emotional eating. ‡Characterised by reduced duration of fullness post-meal, quantified by a rapid gastric emptying rate. This is different from abnormal satiation in which the focus is on the number of calories needed to initially feel full.

questionnaires. The researchers used machine learning to create omics-based BMI models and compared them with classifications based on standard BMI thresholds. The misclassification rate against the omics-inferred BMI class was approximately 30% across all omics categories and BMI classes: individuals misclassified into the normal BMI class displayed less healthy molecular profiles, similar to those with overweight or obesity, whereas individuals misclassified as having obesity exhibited healthier blood signatures, similar to individuals with overweight or normal weight. Furthermore, metabolomics-inferred BMI decreased more than actual BMI in response to a healthy lifestyle intervention, and proteomics-inferred BMI showed greater resistance to change than actual BMI and metabolomics-inferred BMI. These results indicate that omics-inferred BMIs are associated with heterogeneous metabolic health states not captured by classic BMI standard thresholds. However, whether these big data approaches are reproducible, interpretable, and actionable, warrants further investigation, particularly in the context of treatment response prediction, disease prognosis, and incidence of complications.

Precision obesity treatment

The idea behind precision medicine involves categorising patients into groups with similar characteristics to make the most effective therapeutic choices and achieve the best treatment results with minimal side-effects.[95,96] Over the past decade, insights into obesity have necessitated an essential re-evaluation of therapeutic endpoints. With growing recognition of the depot-specific effects of fat accumulation on cardiometabolic risk, the traditional focus on overall weight or BMI as primary indicators of adiposity appears to be inadequate, and underlines the need for more nuanced therapeutic outcomes that capture the intricate nature of obesity.

Current guidelines for managing obesity do not consider most factors that could predict treatment success and help personalise treatment plans, such as sociodemographic factors, anthropometric parameters, and psychological and behavioural factors. Generally, various organisations suggest similar basic steps, with lifestyle changes being the initial approach to managing excess weight.[13–18] If this approach proves unsuccessful, second-line treatments, such as medication, devices, or surgery might be recommended. The starting criteria for drug therapy include a BMI greater than 30 kg/m², or a BMI greater than 27 kg/m² with at least one obesity-related health issue, such as type 2 diabetes, cardiovascular disease, or non-alcoholic fatty liver disease (NAFLD). Additionally, for individuals with a BMI of 35 kg/m² or higher, particularly when drug therapy has been ineffective, bariatric endoscopy or surgery can be considered.[97]

Genetic discoveries might enable the application of precision medicine to directly affect health. Understanding a patient's genetic profile could lead to more accurate diagnoses, as the causes of the patient's phenotype would be better defined, allowing for treatments tailored to the patient's underlying pathophysiology. In cases where

a disease arises from a single mutation, as seen in specific forms of severe early-onset obesity, genetic testing can be vital for accurately diagnosing patients and, when targeted treatments are available, directing the appropriate therapy for each individual. The progress in applying precision treatment varies between monogenic obesity, in which personalised drug therapy is already available, and common obesity, in which increased diversity poses considerable challenges in incorporating precision weight loss treatments into clinical practice. Although monogenic obesity has distinct and non-overlapping causes that can be pinpointed through a single genetic test, common polygenic obesity arises from various interrelated factors.[49] Despite substantial advancements in our understanding of obesity's complexity and new efforts to classify it, we have yet to identify specific causal subtypes that would allow for targeted treatment based on known pathophysiology Two primary approaches can be pursued to further the development of precision treatment of common obesity. The first investigates the connections between genetic variation and therapeutic interactions that affect treatment responses. This approach could lead to the identification of genetic markers that, either individually or in conjunction with clinical factors, could inform drug therapy selection for individuals. The second approach examines whether new attempts at obesity classification can aid in determining therapy choices through a more mechanism-driven process; a method of obesity classification that accounts for underlying biological pathways or factors involved in the disease eg, insulin sensitivity, lipid metabolism, or inflammatory pathways.

Monogenic obesity

Although monogenic obesity accounts for a small fraction of cases, it is an example of precision medicine applied to obesity treatment.[98] To date, two approved genotype-based obesity treatments exist.[98] The first involves administering metreleptin (recombinant human leptin) to patients with congenital leptin deficiency. Various *LEP* mutations causing congenital leptin deficiency or dysfunction have been identified,[53,99–102] although these rare variants have only been reported in about 60 patients globally.[102–104] Mutation carriers exhibit low or undetectable serum leptin concentrations and have typical birth weight, followed by rapid weight gain, hyperphagia, hyperinsulinemia, type 2 diabetes, sympathetic system dysfunction, hypothalamic-pituitary-gonadal axis dysfunction, and hepatic steatosis.[102] Subcutaneous administration of metreleptin leads to rapid changes in eating behaviour, reduced food intake, and subsequent loss of fat mass and body weight. Moreover, improvements in hyperinsulinemia, hyperlipidaemia, liver steatosis, and resolved central hypogonadism are also observed.[102,105–107] By contrast, the administration of recombinant leptin in patients with common, polygenic obesity showed insufficient effectiveness in randomised controlled trials and did not lead to clinically significant weight loss.[108–110] The second precision treatment for monogenic obesity is setmelanotide, a selective MC4R agonist effective in individuals with POMC, LEPR, or PCSK1 deficiencies for whom traditional treatments are less successful.[111–114] Mutations in the *LEPR*, *POMC*, and *PCSK1* genes, which encode proteins upstream of MC4R, cause hyperphagia and severe early-onset obesity.[54–56,59] Setmelanotide compensates for these deficiencies by acting on the leptin–melanocortin pathway's convergence point,[115,116] and clinical studies have shown substantial weight loss in patients with these deficiencies.[111–113] Specifically, 1 year of treatment in patients with a POMC-deficiency resulted in an average 25·6% loss of initial weight, and patients with a LEPR-deficiency had an approximate 12·5% loss of initial weight.[112] This superior effect of setmelanotide in patients with a POMC-deficiency could stem from LEPR's position upstream of POMC in the leptin–melanocortin pathway. Thus, setmelanotide might fully restore MC4R signalling in POMC deficiency, but only partially in LEPR deficiency. Although the number of patients with obesity carrying mutations suitable for effective setmelanotide treatment is small, this treatment directly targets the disease's pathophysiology, resulting in successful weight loss and hunger reduction. As of 2023, the drug is being evaluated in clinical trials for its application in other genetic defects in the leptin-melanocortin pathway, potentially leading to expanded indications for its use and a broader range of targeted treatment options in monogenic obesity.[98]

Polygenic obesity and pharmacogenomics

Pharmacogenomic research, which investigates how genetic variation influences an individual's response to medications, aims to identify subgroups of people who are more or less likely to benefit from specific drug therapies.[117] Over the past two decades, technological advancements and reduced costs of genetic testing have led to a rapid expansion of pharmacogenomic research. However, our understanding of the genetics behind weight loss medication responses remains in its early stages, partly due to the low number of pharmaceutical options that were available and widely adopted until 2014, when incretin analogues were introduced. Several medications are now approved for obesity treatment, including short-term treatments and chronic weight management drugs[11] (table 1). Novel potential molecules are also in the clinical trial phase of development,[11] and the use of anti-obesity medications is gradually becoming more widespread. Substantial variability in weight loss response to obesity pharmacotherapies is observed, with only 30% of patients losing more than 10% of their total body weight in 1 year.[12,120–131] Our understanding of the factors determining treatment response to specific medications in obesity treatment remains insufficient. The choice of medication is currently based on patient preferences, costs, medication availability, and to some extent, comorbidities and adverse event profiles. Studies

	Approval date	Mechanism of action	Common side-effects	Efficacy in weight loss (placebo-subtracted)	Study
Phentermine*	1959	Sympathomimetic amine and central appetite suppressant	Dry mouth, insomnia, constipation, dizziness, palpitations, hypertension, irritability, and anxiety	6% weight loss (20 weeks)	Weintraub et al (1984)[118]
Orlistat	1999	Inhibitor of gastric and pancreatic lipase	Bloating, steatorrhoea, flatulence, faecal urgency, and fat-soluble vitamin deficiency	4% weight loss (one year)	Torgerson et al (2004)[119]
Phentermine plus topiramate	2012	Sympathomimetic amine and central appetite suppressant (phentermine); GABA receptor agonist, glutamate antagonist, and carbonic anhydrase inhibitor (topiramate)	Dry mouth, insomnia, constipation, dizziness, palpitations, hypertension, irritability, paraesthesia, dysgeusia, depression, and anxiety	9% weight loss (56 weeks)	Allison et al (2012)[120]
Naltrexone plus bupropion	2014	Opioid receptor antagonist (naltrexone); dopamine and norepinephrine reuptake inhibitor (bupropion)	Nausea, dizziness, dry mouth, constipation, headache, insomnia, and hypertension	5% weight loss (56 weeks)	Greenway et al (2010)[121]
Liraglutide	2014	GLP-1 receptor agonist	Nausea, vomiting, diarrhoea, abdominal pain, and dyspepsia	6% weight loss (56 weeks)	Pi-Sunyer et al (2015)[122]
Semaglutide	2021	GLP-1 receptor agonist	Nausea, vomiting, diarrhoea, abdominal pain, and dyspepsia	12·5% weight loss (68 weeks)	Wilding et al (2021)[123]
Tirzepatide	2023†	GLP-1 receptor and GIP receptor agonist	Nausea, diarrhoea, constipation, vomiting, and dyspepsia	17·8% weight loss (72 weeks)	Jastreboff et al (2022)[124]

FDA=US Food and Drug Administration. GABA=gamma-aminobutyric acid. GLP-1=Glucagon-like peptide-1. GIP=glucose-dependent insulinotropic polypeptide. *Short-term treatment. †Expected (currently under fast track FDA review).

Table 1: **FDA-approved medications for obesity treatment, mechanism of action, side effects, and efficacy in weight loss**

have shown that the best predictor of sustained long-term weight loss response is the initial weight loss within the first few months of treatment (in most studies, defined as a minimum of 5% weight loss in 3 months).[132–138] Genetic factors might contribute to the observed heterogeneity in response.

To date, only a few studies have assessed the genetic predictors of weight loss pharmacotherapy response.[139–151] Most existing pharmacogenomic studies on obesity drugs have been done with small sample sizes, without replication, and focused on selected candidate genes only, making their clinical relevance weak. Therefore, it is probable that many reported pharmacogenomic findings are false positives. Given the highly polygenic nature of obesity, with multiple small-effect variants contributing to the phenotype, it is expected that most pharmacogenetic effects will also be small.[49] The high prevalence of obesity in health-care systems that generally have low resources makes it unlikely that clinicians will select the best drug for an individual if it requires a genetic test. However, as genetic testing costs decrease and the possibility of incorporating genome-wide information into medical records arises, pharmacogenomic findings could be integrated into obesity management decision algorithms, probably in conjunction with other phenotypic characteristics that have yet to be described.

The rapid growth in medications targeting weight loss, many of which are also used for type 2 diabetes therapy, is gradually leading to a parallel progression in pharmacogenomic research; more pharmacogenomic studies are being done, including studies on these new medications. However, a substantial challenge remains: these new studies of obesity drugs should shift their focus from candidate-gene approaches to GWAS, which require larger sample sizes in the hundreds or even thousands to achieve the statistical power necessary for relevant discoveries. One such GWAS identified loci associated with HbA_{1c} reduction in response to GLP-1 receptor agonist treatment; however, no associations with weight loss were found.[152] New studies focusing on the genetics of weight loss response to medications are already underway. Our research group is evaluating the genetic determinants of response to commonly used diabetes medications, including weight changes, as part of the Glycemia Reduction Approaches in Diabetes: a comparative effectiveness study (GRADE).[153] Additionally, we initiated the Genetics of the Acute Response to Oral Semaglutide (GAROS) study,[154] which investigates the genetic determinants of response to a 12-week semaglutide treatment in individuals with obesity or overweight (if accompanied by prediabetes diagnosis). In this study, we assess the effects of genetic factors on changes in body weight and composition, as well as several other metabolic parameters.

To overcome the obstacle of sample size, collaborations between pharmaceutical companies and academia are essential for analysing genetic data from trial participants. Academic and investigator-initiated studies alone might struggle to achieve the necessary scale without such

cooperation. Therefore, greater engagement from pharmaceutical companies is needed to advance our understanding of the genetic basis of response to obesity treatment. In our opinion, regulatory bodies overseeing drug registration could also mandate data access for academia from industry partners as part of the registration process for novel drugs. However, this approach would require the establishment of regulations for sharing genetic data and the anonymised clinical data of patients participating in trials. Another approach is the use of biobanks and electronic health records;[155,156] longitudinal data, including medication and disease outcomes, combined with genetic information, can be used to evaluate the genetics of response to obesity treatment. By leveraging these resources, pharmacogenomic research can continue to expand and refine our understanding of individual responses to weight loss medications, ultimately leading to more personalised and effective treatment strategies for obesity. In the future, this collaborative approach, involving academia, industry partners, and regulatory bodies, will be key to unlocking the full potential of pharmacogenomics in obesity management.

Non-pharmacological treatment

Precision treatment goes beyond pharmacotherapy and can be applied to other obesity management approaches, such as bariatric surgery and lifestyle modification. Bariatric surgery is recommended for patients with a BMI of 35 kg/m² or higher, particularly when conventional medical treatments fail to achieve therapeutic goals.[97] Furthermore, there is increasing evidence supporting the benefits of bariatric surgery for patients with a BMI between 30 kg/m² and 35 kg/m² and poorly controlled type 2 diabetes, as substantial weight loss can impede disease progression. Laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB) are the most frequent procedures, backed by strong evidence of long-term outcomes and safety.[157] Bariatric surgery seems to achieve greater weight loss than available pharmacological therapies. In the short term (1 year), weight loss of approximately 30% of total body weight is similar between LSG and RYGB. However, long-term studies of 5–10 years reveal greater weight loss with RYGB.[158–160] Nevertheless, individual responses to different bariatric surgeries can vary considerably, especially during extended follow-up periods.[161] Numerous studies have investigated patient characteristics associated with weight loss response following bariatric surgery, and as with pharmacotherapy, early weight loss is a strong predictor of sustained response.[138] Furthermore, factors, such as higher initial BMI, older age, elevated fasting blood glucose concentrations above normal, and the presence of type 2 diabetes have been linked to poorer surgery outcomes.[162,163] Some research has also explored genetic predictors of weight loss response following bariatric surgery.[164] Current studies focus on candidate genes involved in obesity development, such as *MC4R*, *FTO*, and *PCSK1*.[165] Several genetic variants connected to post-surgery weight loss have been identified, and efforts to combine different genetic variants into PS have shown considerable predictive value for surgery outcomes.[164] However, the clinical relevance of most studies is restricted due to their fairly small sample sizes and highly heterogeneous study populations. Further research with larger sample sizes is required to examine the relationship between genetics and bariatric surgery outcomes, enabling well-powered GWAS discoveries with proper replications.

Current obesity management guidelines typically recommend lifestyle interventions focusing on dietary changes and physical activity as the initial treatment step.[13–18] There is considerable variability in the amount of weight lost with these interventions; although some individuals have substantial weight loss, others receive little or no benefit from such intensive therapy.[166,167] For example, in the Look AHEAD (Action for Health in Diabetes) study,[168] which evaluated the long-term effects of an intensive weight loss programme in individuals with overweight or obesity diagnosed with type 2 diabetes, those in the top 90th percentile of weight loss reduced their weight by 18% after 1 year, compared with less than 1% for the bottom 10th percentile. Existing studies indicate that adherence to the programme and early weight loss are essential factors in predicting long-term weight loss success.[138,169,170] Efforts have also been made to assess whether genotype affects the outcomes of diet or exercise on weight loss.[171] Most studies—including analyses on the Look AHEAD studies—focusing on GWAS-derived obesity-related loci did not find meaningful associations with weight loss in response to lifestyle interventions.[172–175] These studies evaluated not only single variants, but also the PS constituting these variants, without any relevant success. However, most of these studies focused on weight or BMI only, not more detailed phenotypic features of obesity. In 2022, McCaffery and colleagues[176] evaluated waist circumference and its association with variants linked to abdominal obesity. They found that a PS related to abdominal obesity predicted a smaller waist circumference reduction, but the effect was minimal compared with the overall intervention benefits. These studies suggest that genetic variants linked to obesity phenotypes should not considerably hinder the success of lifestyle-based weight loss interventions. However, further studies with larger sample sizes, a genome-wide approach, and additional focus more detailed phenotypic characteristics of obesity, including adipose tissue volume and location, are needed to elucidate the genetics of exercise-induced and diet-induced weight loss to guide tailored interventions.

Summary and vision of the future

This Review underscores the importance of managing obesity as an integral part of diabetes care. At present,

	Description	Proposed solution
Limited understanding of obesity pathophysiology	Current knowledge of the complex mechanisms underlying obesity and its comorbidities is insufficient for the development of precision medicine approaches, including diagnosis, treatment, and prevention	Encourage interdisciplinary collaborations and support large-scale projects to improve the understanding of obesity pathophysiology; these projects will require sustained funding and resources for research focusing on the integration of multiomic, environmental, behavioural, and lifestyle factors, and the development of advanced analytical methods to interpret complex data; the definitive identification of effector transcripts at obesity GWAS loci and their large-scale functional characterisation are needed
Insufficient effective and treatment-informing patient stratification	There is no standardised, widely accepted method for classifying patients based on underlying pathomechanisms, which is necessary for implementing precision medicine in obesity	Establish expert working groups with representatives from various disciplines to develop consensus guidelines for obesity patient stratification; invest in research to identify accessible biomarkers for stratification, ensuring that guidelines are based on rigorous scientific evidence and are easily applicable in clinical settings
Scarce targets of currently available medications	Existing obesity medications target a limited number of causes, which may not effectively address the diverse pathophysiology of disease; developing targeted therapies based on identified mechanisms will allow precise treatment; novel medications should not only target weight loss, but also demonstrate efficacy in treating obesity comorbidities	Describe the critical pathways involved in obesity pathogenesis emerging from genomic studies; invest in research and development of novel pharmacological agents targeting specific causes and comorbidities of obesity; this approach will require collaboration between academia, industry, and regulatory agencies to identify new drug targets, streamline the drug development process, and ensure the safety and efficacy of new treatments
Inequalities and insufficient diversity in currently available studies	Obesity research often lacks diversity, with insufficient information about the ethnic and racial differences in adiposity and its metabolic consequences, which may limit the global applicability of findings; implementing precision medicine approaches can be cost-prohibitive for some patients and health-care systems	Implement policies and funding initiatives that prioritise the inclusion of diverse populations in obesity research; promote international collaborations and data sharing among researchers to ensure the global applicability of findings; develop cost-effective precision medicine strategies and work with health-care systems, policymakers, and insurance providers to ensure equal access to innovative treatments and diagnostic tools

Table 2: **Existing gaps in implementing precision medicine for obesity and potential solutions**

precision medicine initiatives in obesity largely focus on the disease in its broadest sense, not yet addressing the complex needs of patients who, besides obesity, also present with specific comorbidities (eg, type 2 diabetes). In this context, our Review outlines existing efforts in precision weight management and emphasises the need to integrate weight loss strategies into diabetes care and the potential benefits this approach presents for improving outcomes beyond glycaemic control.

Although precision medicine in obesity is still in its early stages, some progress has been made in the past few years, particularly regarding the genetic discoveries of adiposity and our understanding of the heterogeneity of its metabolic consequences. However, we recognise the paucity of data from paediatric and adolescent populations in these investigations, an issue that needs urgent attention given the early onset and rapid progression of obesity in these groups. Although adult-derived genetic discoveries hold potential for generalisation across ages, comprehensive age-specific studies remain imperative for a nuanced understanding of weight and health trajectories in response to obesity. Precision obesity medicine is already becoming a reality in monogenic obesity, as precise diagnosis followed by tailored treatment can be successfully implemented in clinical practice. Nevertheless, in common polygenic obesity, the development of precision medicine remains in its early stages. Several gaps need to be addressed to enable progress and facilitate translation into clinical practice (table 2), and the broader context of precision population health needs to be considered to incorporate elements, such as behavioural patterns, environmental influences, and socioeconomic factors. This approach would entail a multifaceted strategy that recognises the interplay between obesity phenotypes and lifestyle choices, including physical activity and dietary habits.

Obesity and type 2 diabetes interact and overlap in clinical and causal terms, and developments in precision medicine for obesity closely resemble, and might be following the progress of, those observed in type 2 diabetes.[177] Both diseases are diagnosed on the basis of a single metric (glycaemia in diabetes and BMI in obesity), which serves as an end result or common final pathway of interactions among multiple patho-physiological processes, without distinguishing between different causes of disease. Thus, both diseases exhibit high heterogeneity, and management strategies to date necessitate greater granularity in the diagnostic process to enable effective precision management. Another similarity is the management of their monogenic forms; in diabetes, the management of maturity-onset diabetes of the young (MODY) or neonatal diabetes exemplifies precision medicine in action, as genetic testing can categorise patients on the basis of precise causal mechanisms, allowing precision treatment to correct the pathology. In obesity, the monogenic forms also invoke specific treatment approaches. Another similarity might involve the MHO subgroups, which could follow the

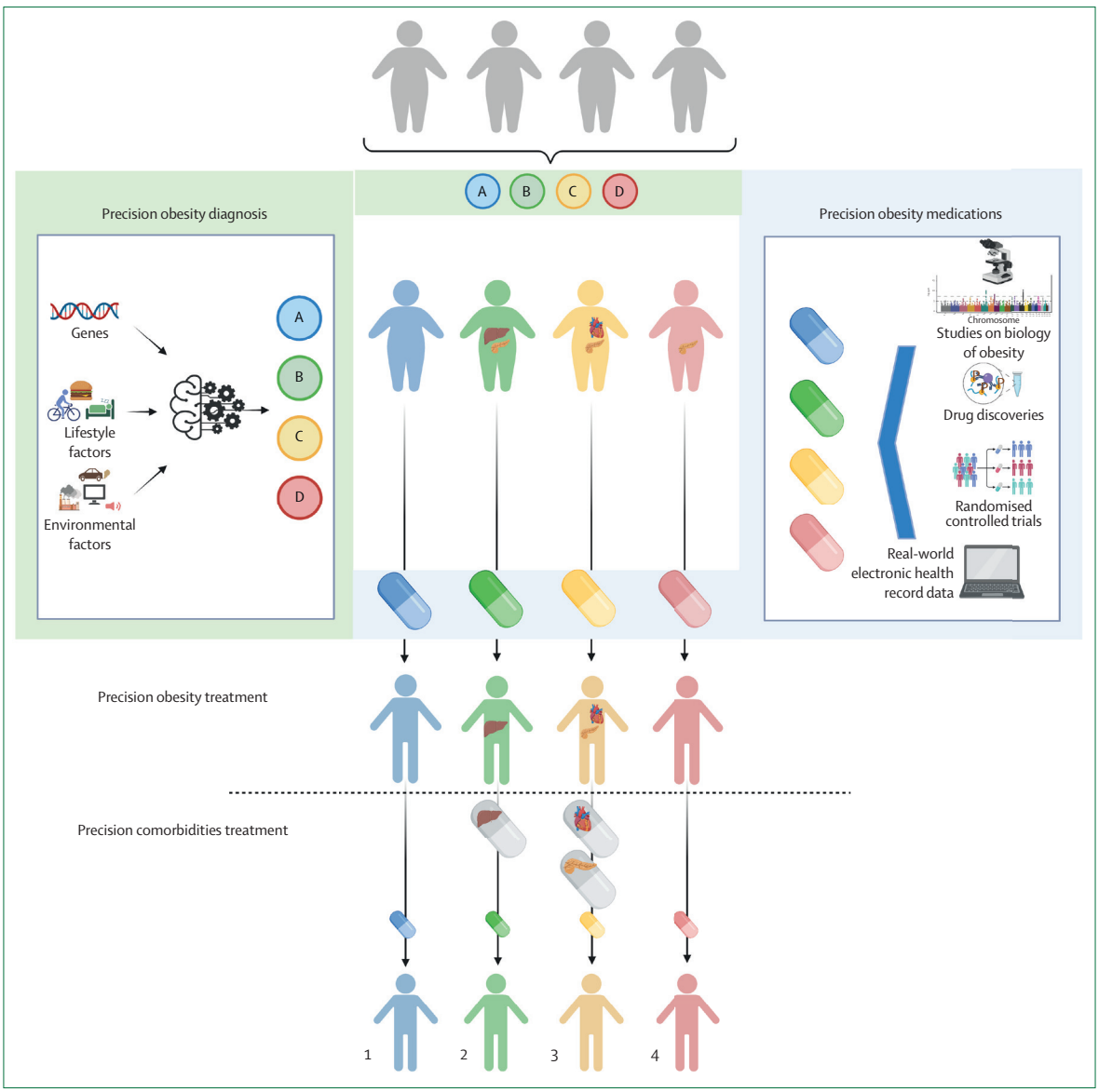


Figure 3: **Proposed integrated obesity-centred multidisease management algorithm in precision medicine of obesity**
This process consists of precision diagnosis, leading to targeted treatment for patients with excess weight, and addressing obesity-related comorbidities such as type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease. The algorithm highlights the steps from precision diagnosis to targeted treatments for obesity and its comorbidities and emphasises the importance of categorising patients on the basis of causal and contributing factors, with subsequent treatment phases tailored to individual needs. Numbers 1–4 correspond to example clinical scenarios (panel).

path of MODY type 2, caused by mutations in *GCK*, where studies have shown that treatment is not needed.[177]

We propose a vision for the future of precision management of obesity as an integral part of diabetes and other obesity-related comorbidities care. Although an ideal scenario, considerable advancements in analytical methods, artificial intelligence, access to genetic data, and, international collaborations on big data projects make it a plausible reality for the future. We refer to this integrated vision of precision medicine for obesity as an obesity-centred multidisease management algorithm (figure 3). The first step in this approach is a precision diagnosis, in which patients with excess weight can be categorised into subtypes reflecting the causal and contributing factors to disease development. On the basis of this stratification, targeted treatments can be given. However, obesity is associated with various comorbidities; some patients develop none, others develop only some, and still others are at risk of developing most, or even all, of these complications. Thus, developing cause-informed subgroups can help treat or prevent obesity comorbidities, and identifying groups of patients at risk, or those who have already developed these comorbidities, will be the initial diagnostic stage of the algorithm. In the first phase

Panel: **Example scenarios of applying the obesity-centred multidisease management algorithm in clinical practice**

Scenario 1

A patient with obesity and no presence or risk of developing comorbidities is classified as group A. The patient receives treatment targeted for their mechanism of obesity development. In the first phase of the treatment, drug A is administered. After achieving substantial weight loss, the second phase focuses on maintaining the achieved weight loss, with a reduced dosing of drug A.

Scenario 2

A patient with obesity and existing comorbidities (type 2 diabetes and non-alcoholic fatty liver disease) is assigned to group B, corresponding to the mechanism of their obesity development. In their case, obesity resulted in the development of type 2 diabetes and partially resulted in the development of non-alcoholic fatty liver disease. In phase one, drug B is introduced, targeting the obesity cause of group B and showing efficacy in reducing glycaemia and hepatic steatosis. After achieving substantial weight loss, optimal control of type 2 diabetes and the remission of non-alcoholic fatty liver disease with reduced steatosis were achieved. However, the patient still requires additional treatment for non-alcoholic fatty liver disease. In phase two, the focus is on maintaining achieved weight loss and controlled type 2 diabetes (by reducing the dose of drug B, with dose adjustment controlling for glycaemia) and the precision management of non-alcoholic fatty liver disease. An additional algorithm is applied, introducing targeted treatment for non-alcoholic fatty liver disease and targeting the non-obesity related component of the cause of disease in this patient.

Scenario 3

A patient with obesity, cardiovascular disease, and type 2 diabetes is diagnosed as group C, corresponding to the mechanism of their obesity development that also contributes to the causes of their comorbidities. In phase one, drug C is introduced, targeting the obesity cause of group C and showing efficacy in reducing glycaemia and cardiovascular disease outcomes. After achieving substantial weight loss, there is improvement in type 2 diabetes and cardiovascular disease outcomes, but not enough to avoid introducing additional treatment. In phase two, the focus is on maintaining achieved weight loss, with a reduced dose of drug C, and the precision management of type 2 diabetes and cardiovascular disease algorithms are applied, introducing targeted treatments for both diseases, targeting the non-obesity related components of the cause of disease in this patient.

Scenario 4

A patient with obesity and existing comorbidities (type 2 diabetes) is assigned to group D, corresponding to the mechanism of their obesity development. In their case, the cause of type 2 diabetes is strongly related to obesity. In phase one, drug D is introduced, targeting the obesity cause of group D and showing efficacy in reducing glycaemia. After achieving substantial weight loss and optimal control of type 2 diabetes, the second phase focuses on maintaining achieved weight loss and controlled type 2 diabetes (by reducing the dose of drug D, with dose adjustment controlling for glycaemia), thus confirming the predominantly obesity-related cause of type 2 diabetes in this patient.

of treatment, weight loss is the initial goal, with treatment outcomes also including comorbidity-related monitoring parameters, such as glycaemia in type 2 diabetes, lipid concentrations and blood pressure in cardiovascular disease, or hepatic steatosis or fibrosis in NAFLD. Although some people might argue that the initial goal should be a change in behaviour and reduction of cardiometabolic risk rather than weight loss, in our view, these objectives are interconnected and need not be mutually exclusive. The proposed treatment approach will require the availability of targeted weight loss therapies that also have beneficial effects on comorbidities, as exemplified by incretin therapies in type 2 diabetes. Once substantial weight loss is achieved, the second phase of precision obesity treatment focuses on maintaining weight loss from phase one (dose adjustment will require close monitoring of comorbidity outcomes) and, if needed, precision treatment for comorbidities targeting the part of their cause not linked to obesity. For a clearer understanding of how the algorithm could be applied in clinical practice, we have provided four example scenarios in the panel.

To achieve this vision, we need a better understanding of the mechanisms leading to obesity, to establish patient stratification for obesity that reflects disease causes and facilitates the discovery of new therapeutic agents targeting these diverse pathways. A challenge will be discovering novel therapeutics that target pathways causing both obesity and its comorbidities, such as incretin therapies, which are effective for obesity and type 2 diabetes, and are being extensively studied for NAFLD as well. Biomarkers, including genetic markers, that reflect the engagement of specific pathomechanisms and predict the development of obesity complications will need to be identified for precise diagnosis. Insights into obesity have necessitated a re-evaluation of therapeutic endpoints; with growing recognition of the depot-specific effects of fat accumulation on cardiometabolic risk, the traditional focus on overall weight or BMI as primary indicators of adiposity appears to be inadequate. These insights show the need for more nuanced therapeutic outcomes, and predictive markers of treatment response, in terms of efficacy and side-effects, will be necessary to prescribe personally tailored treatments. To be successfully implemented in clinical practice, new approaches based on the precision medicine concept will need to be widely evaluated in terms of their efficacy and cost-effectiveness. This evaluation must be done across

Search strategy and selection criteria

Full-text articles for this Series paper were identified by searching PubMed for English language articles published from database inception to Apr 1, 2023, using the following terms alone or in combination: "precision medicine", "obesity", "type 2 diabetes", "obesity classification", "body composition", "body mass index", "body fat", "fat mass", "lean body mass", "visceral adipose tissue", "subcutaneous adipose tissue", "genetics", "GWAS", "polygenic score", "drug therapy", "pharmacotherapy", "weight loss", "bariatric surgery", "metabolic surgery", "lifestyle intervention", "weight loss", "physical activity", and "diet". Additional full-text Articles were identified by reviewing the reference lists of the selected publications. Full-text Articles were chosen based on criteria, such as the strength of evidence, clinical relevance, impact on the field, originality, and publication date. Preference was given to full-text Articles published in journals with transparent conflict of interest policies and rigorous peer-review processes. Emphasis was placed on original full-text Articles, meta-analyses, and reviews from the past 5 years.

the full diversity of the human population, spanning racial and socioeconomic contexts, to avoid further widening disparities in diabetes care.

The foundations for the development of precision medicine in obesity have already been laid; however, further intensive efforts are needed for its future development and translation into standard clinical care. This effort will require a partnership among all stakeholders, including the scientific community, patients, health-care providers, payors, the pharmaceutical industry, and regulatory bodies. We anticipate that obesity care in the next few decades will be dramatically improved, becoming more data-driven and biologically informed than what we see today.

Contributors

LS searched the literature and data, prepared the figures, and wrote the original draft of the Series paper. Both authors reviewed and edited the Series paper before submission.

Declaration of interests

JCF reports personal fees from AstraZeneca, Merck, and Novo Nordisk. LS declares no competing interests. The views expressed in this Series paper do not necessarily reflect those of the institutions to which the authors are affiliated.

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