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CARDIOVASCULAR GENOMICS (P NATARAJAN, SECTION EDITOR)

Obesity Genomics and Metabolomics: a Nexus of Cardiometabolic Risk

Jessica A. Regan[1,2] · Svati H. Shah[1,2]

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Abstract

Purpose of Review Obesity is a significant international public health epidemic with major downstream consequences on morbidity and mortality. While lifestyle factors contribute, there is an evolving understanding of genomic and metabolomic pathways involved with obesity and its relationship with cardiometabolic risk. This review will provide an overview of some of these important findings from both a biologic and clinical perspective.

Recent Findings Recent studies have identified polygenic risk scores and metabolomic biomarkers of obesity and related outcomes, which have also highlighted biological pathways, such as the branched-chain amino acid (BCAA) pathway that is dysregulated in this disease. These biomarkers may help in personalizing obesity interventions and for mitigation of future cardiometabolic risk.

Summary A multifaceted approach is necessary to impact the growing epidemic of obesity and related diseases. This will likely include incorporating precision medicine approaches with genomic and metabolomic biomarkers to personalize interventions and improve risk prediction.

Keywords Obesity · Genomics · Metabolomics · Cardiometabolic · Polygenic risk score · Branched-chain amino acids

Introduction

The epidemic of overweight and obesity is an important contributor to short- and long-term cardiometabolic morbidity and mortality across the world. The negative health consequences of obesity reach across the life span contributing to adverse outcomes for adults, and unfortunately now even in children. While lifestyle factors such as diet and sedentary behavior contribute, novel insights including from genomic and metabolomic studies have highlighted the underlying biology, and, in parallel, have identified clinically relevant biomarkers for personalized medicine approaches to potentially decrease the prevalence of obesity and improve cardiometabolic outcomes.

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✉ Svati H. Shah
svati.shah@duke.edu

Jessica A. Regan
jessica.a.regan@duke.edu

[1] Department of Medicine, Duke University, Durham, NC, USA

[2] Duke Molecular Physiology Institute, Duke University, 300 N. Duke Street, DUMC, Box 104775, Durham, NC 27701, USA

Obesity: the Scope of the Problem

Epidemiology The prevalence of overweight (body mass index [BMI] ≥ 25) and obesity (BMI ≥ 30) has reached epidemic proportions in developed countries such as the United States (U.S.), and is starting to increase in prevalence even in the developing world. In the U.S., greater than 40% of adults are obese and Hispanic and Black adults have higher rates of obesity [1]. Internationally, the prevalence of obesity nearly doubled between 1980 and 2014. Sadly, rates of childhood obesity are also rising, creating additional concern for the true extent of long-term health consequences [2]. For example, in the U.S., the 2015–2016 NHANES study reports that 20.6% of children and adolescents 12–19 years old are obese [3]. These rising rates of obesity contribute to significant morbidity and mortality worldwide [4–8]. In 2010, overweight/obesity were estimated to account for 3.4 million deaths per year globally [9].

Cardiometabolic Consequences of Obesity Obesity is a major risk factor for metabolic diseases including dyslipidemia, insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, and non-alcoholic fatty liver disease (NAFLD) (Fig. 1).

A systematic review and meta-analysis of 37 studies noted childhood overweight/obesity to be associated with a higher risk of T2DM in adulthood (odds ratio [OR] 1.70, 95% confidence interval [CI] 1.30–2.22) [10]; a 10-kg increase in body weight is associated with 3.0 mmHg and 2.3 mmHg in systolic and diastolic blood pressure, respectively [11]; and high BMI (75th vs. 25th percentile) is associated with increased risk of NAFLD (OR 1.96, CI 1.51–2.56 for Blacks; OR 2.33, CI 1.70–3.19 for Whites) [12]. Obesity also increases risk of downstream cardiovascular disease (CVD)–related morbidity and mortality and other consequences, partially mediated through these metabolic risk factors. Markers of obesity such as BMI and waist-hip circumference are independent predictors of atherosclerotic CVD and CVD events [13]. These rising rates of obesity contribute to significant morbidity and mortality worldwide [4–8], with each five-unit increase in BMI above 25 kg/m^2 associated with a 30% increase in overall mortality, 40% increase in ischemic heart disease and stroke mortality, 120% increase for diabetes-related mortality, 80% increase in hepatic mortality, and a 10% increase for cancer-related mortality [14]. In 2017, overweight/obesity were estimated to account for 4.72 million deaths per year [15]. Even in adolescent obesity, a study found increased risk of death attributable to coronary artery disease in adulthood after adjustment for sex, age, and sociodemographic characteristics (hazard ratio [HR] 4.9, CI 3.9–6.1) [16] and obesity is associated with presence and progression of subclinical atherosclerosis [17–19]. Further, obesity is related to the increasing incidence of heart failure with 9% of cases in males and 14% of cases in females being attributable to obesity [17, 20–22]. Obesity is also an established risk factor for stroke (4% increased risk of ischemic and 6% increased risk of hemorrhagic stroke per 1 unit increase in BMI) [11], atrial fibrillation (RR 1.28, CI 1.20–1.38 per 5 unit increase in BMI) [23], and venous thromboembolism (RR 2.39, CI 1.79–3.17) [24, 25].

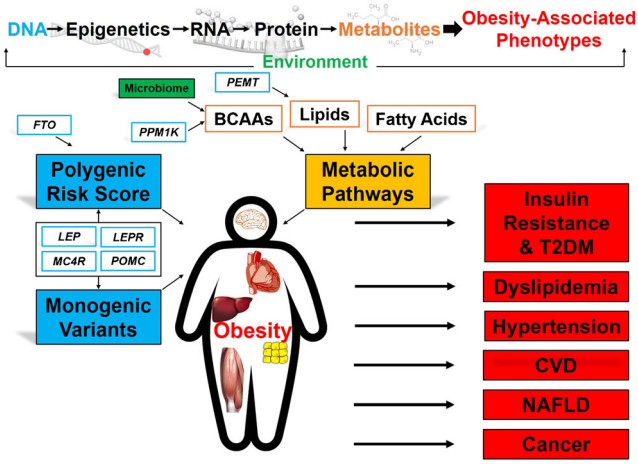

Fig. 1 Genomics and metabolic pathways of obesity and associated cardiometabolic risk. Obesity is a systemic disease with impact on the liver, heart, adipose tissue, skeletal muscle, and brain, particularly the hypothalamic-pituitary axis. High-throughput multi-omic profiling (genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiome) has advanced the understanding of dysregulated molecular pathways in obesity to improve prediction of cardiometabolic risk. Abbreviations: *POMC*, pro-opiomelanocortin; *LEPR*, leptin receptor; *LEP*, leptin; *MC4R*, melanocortin 4 receptor; *FTO*, fat mass and obesity-associated gene; *PPM1K*, protein phosphatase 1K; *PEMT*, phosphatidylethanolamine *N*-methyltransferase; BCAAs, branched-chain amino acids; T2DM, type 2 diabetes mellitus; CVD cardiovascular disease; NAFLD, non-alcoholic fatty liver disease

While these studies provide strong evidence for the association between obesity and cardiometabolic endpoints, such observational studies can be prone to unmeasured confounding. Mendelian randomization leverages genetic variants as instrumental variables for causal inference to help determine potential causality between an intermediate factor and an endpoint. Recent Mendelian randomization studies of obesity have shown that genetic susceptibility to obesity is associated with cardiometabolic diseases, suggesting that obesity has a causal association (i.e., not just due to confounders) with these diseases, including hypertension, hypertriglyceridemia, T2DM, coronary artery disease, atrial fibrillation, venous thromboembolism, aortic stenosis, and heart failure [26–28]. Mendelian randomization analyses of polygenic risk scores for obesity traits including BMI, waist-to-hip ratio (WHR), and BMI-adjusted WHR have identified additional causal associations with stroke, chronic obstructive pulmonary disease, lung cancer, non-alcoholic fatty liver disease, and renal failure, further informing the global impact of obesity on human disease [29].

Heterogeneity in Development of Adverse Cardiometabolic Consequences of Obesity Although it is clear that obesity is a strong risk factor for these cardiometabolic consequences, there is marked heterogeneity in their development, complicating risk prediction models [30]. For example, a 2008 NHANES study examined the prevalence of poor metabolic health in obesity and found that a surprising one-third of obese individuals were metabolically healthy despite being obese when evaluating the prevalence of cardiometabolic abnormalities (hypertension, elevated levels of triglycerides, fasting plasma glucose, C-reactive protein, insulin resistance, and low high-density lipoprotein [HDL]) [31]. Younger age, non-Hispanic Black ethnicity, and higher physical activity were independent correlates of metabolic health in overweight and obese individuals. Similar heterogeneity is seen in development of CVD outcomes in individuals with obesity: a systematic review of all-cause mortality for obesity demonstrated that while obesity was a consistent risk factor, hazard ratios varied from 0.95 to 1.29 across BMI categories with the majority of patients with obesity not suffering from the endpoint [32]. Given this heterogeneity, additional measures of obesity and body fat distribution, such as WHR, may be better markers than BMI for certain cardiometabolic comorbidities. For example, a polygenic risk score for waist-to-hip ratio was

associated with T2DM and coronary heart disease even after adjustment for BMI [26, 33].

This disconnect between obesity measures and cardiometabolic consequences leads to incomplete risk prediction models and difficulty in identifying obese individuals with the greatest need for therapeutic interventions to prevent future events. While lifestyle factors such as diet and sedentary behavior are important risk factors for overweight and obesity, and public health measures aimed at the prevention of obesity nationally and internationally through targeting these lifestyle factors are key, it is also imperative to understand the biology and related biomarkers that could help prevent and treat overweight and obesity to prevent downstream consequences.

The Genetics of Obesity: a Prototypical Common Complex Genetic Disease

Monogenic Forms of Obesity Monogenic forms of obesity identified through linkage analyses of families with obesity account for an extremely small proportion of obesity. These include syndromic and nonsyndromic forms of obesity and usually result in severe obesity that manifests in childhood. Syndromic monogenic obesity disorders are rare (1 in 565 to < 1 in 1,000,000) [34] and include Bardet-Biedl syndrome, an autosomal recessive disorder accompanied by retinal defects and caused by one of 21 genes that encode structure and function of cilia [35–37], and Prader-Willi syndrome, caused by loss of imprinted genes that are paternally expressed from the chromosome 15q11-q13 region and accompanied by hypogonadism, short stature, and mild learning and behavioral problems [38]. Nonsyndromic monogenic forms of obesity are caused by loss-of-function variants in the leptin (*LEP*), the leptin receptor (*LEPR*), proopiomelanocortin (*POMC*), or melanocortin 4 receptor (*MC4R*) genes which impact obesity susceptibility usually through dysregulated food intake [39–42].

Polygenic Common Complex Obesity: Common Variants, Common Disease Although obesity is influenced by lifestyle and environmental factors, heritable genetic determinants that contribute to obesity risk and the underlying heritability of obesity have been identified. Heritability estimates for obesity calculated from studies of families range from 59 to 77% [43, 44]. Overweight and obesity in the majority of the population operates as a prototypical common complex disease. Early genome-wide studies that attempted discovery beyond candidate gene studies utilized linkage analysis in families with non-monogenic obesity, operating under the assumption that genetic discovery techniques for monogenic diseases would also be useful in common complex diseases. These first genome-wide linkage analyses of obesity identified a locus on chromosome 10p [45] that was replicated in two additional cohorts [46, 47]. Fine-mapping of this locus identified association of BMI with common variants in glutamate decarboxylase 2 (*GAD2*) [48]; however, these results were not widely replicated [49, 50]. The first genome-wide association studies (GWAS) of BMI and childhood and adult obesity identified common intronic single nucleotide polymorphisms (SNPs) in the *FTO* (fat mass and obesity associated) gene as the most strongly associated gene, with each risk allele increasing obesity risk 1.2 times compared with no risk alleles [51–53]. Common SNPs in *FTO* have remained the most consistent and strongest GWAS locus. As GWAS expanded in sample sizes through collaborative consortia studies and meta-analyses, additional loci were identified albeit less significant than *FTO*, and included common variants near *MC4R* (a monogenic cause of obesity) [54], coding missense variants in *NPC1* (endosomal/lysosomal Niemann-Pick C1 gene), and noncoding SNPs near *MAF* (encoding the transcription factor c-MAF), *PTER* (phosphotriesterase-related gene), and *PRL* (prolactin) [55]. In fact, greater than 200 loci associated with BMI and obesity have been identified by GWAS to date and have estimated > 20% of BMI heritability can be attributed to inheritance of common variants [56, 57••].

Rare Variants, Common Disease? Unfortunately, these common variants identified from GWAS individually have small effect sizes and in aggregate, loci from these initial GWAS studies only explain 2–3% of the variance in BMI; even *FTO* with high population frequency and the largest effect size only explains 0.34% of inter-individual BMI variation [56, 58–60]. As such, as high-throughput next-generation sequencing technologies evolved, the genomics community looked to analysis of rare variation as a solution to the conundrum of the "missing heritability" in common complex diseases, in line with the "rare variant, common disease" hypothesis where variants albeit rare exert larger effect sizes and in aggregate can thus account for a common disease. Interestingly, the first whole-exome sequencing (WES) studies of obesity identified rare coding variants in the known monogenic obesity gene *LEPR* [61, 62], suggesting that this gene contributes to both monogenic and more common later-onset forms of obesity. These WES also identified new genes such as density lipoprotein receptor–related protein 2 (*LRP2*), uncoupling protein 2 (*UCP2*), dynein axonemal assembly factor 1 (*DNAAF1*) [63], and laminin subunit beta 3 (*LAMB3*) [64]. A more recent study of 2737 severely obese cases used exome and targeted sequencing to identify this missing heritability and found rare variants in Pleckstrin homology domain–interacting protein (*PHIP*), diacylglycerol kinase iota (*DGKI*), and zinc-finger-MYM-type-containing 4 (*ZMYM4*) [65•]. A large study using a hybrid approach of whole-genome sequencing (WGS) and GWAS confirmed considerable overlap between monogenic and polygenic contributors to BMI and other anthropometric traits, compromised of mostly common variants with small effect sizes [66]. Overall, these studies suggest that a combination of common and rare variants contributes to the burden

of common obesity, as the scientific community is finding to be the case for many common complex diseases. A summary of genes identified through genomic studies of obesity is provided in Table 1.

Insight into the Biology of Obesity Afforded by Genomic Studies While genomic studies have highlighted potential genetic risk markers of obesity, they have also highlighted the underlying biology of obesity risk. For example, genetic variants in the leptin-melanocortin pathways (*LEP*, *LEPR*, *LRP2*, *POMC*, and *MC4R*) contribute to obesity, at least in part, through hypothalamic control of energy balance and susceptibility to increased food intake. Leptin, secreted from adipose tissue, acts in the arcuate nucleus of hypothalamic satiety center where melanocortin neurons produce POMC that ultimately stimulate MC4R to reduce feeding [68]. PHIP enhances transcription of POMC, lending further evidence to the biologic pathways affected by genetic variants associated with obesity. When GWAS studies first identified the association between *FTO* and obesity, the biologic role of *FTO* was unknown, but mouse models have subsequently shown the importance of *FTO* in regulation of fat mass and adipogenesis [69]. *FTO* is highly expressed in the hypothalamus and pituitary and adrenal glands [83]; it has a role in development, as postnatal mortality and growth retardation have been observed in *FTO* deficiency [67]. Data has suggested that the influence of *FTO* SNPs on obesity may be due to their impact on expression of neighboring genes [70, 71, 84]; however, work in human fibroblasts and blood cells have confirmed the link between SNP risk genotype and FTO expression [72–74]. From studies of *NPC1* mutations in the lipid storage disease Niemann-Pick type C, the NPC1 protein is known to be involved in endosomal cholesterol transport in the central nervous system, liver, and macrophages [77, 85, 86], but further studies of the specific *NPC1* variants associated with obesity are warranted. The c-MAF transcription factor is involved in cellular differentiation in the pancreas and adipose tissue as well as tissue-specific gene expression, including insulin and glucagon [87, 88]. At a molecular level, UCP2 functions in oxidative phosphorylation and mitochondrial membrane transport to regulate energy balance and ultimately body weight [89]. In the same study that used WES to identify *LAMB3* to be associated with BMI, the investigators found LAMB3 mRNA levels to be correlated with BMI and adipose morphology and in vitro knockdown of LAMB3 inhibited adipogenesis [64]. Additional loci identified by GWAS in association with obesity have replicated genes implicated in neuronal processes, hypothalamic function, and energy homeostasis. Little is known about the biology of *DGK1* and *ZMYM4*.

Transethnic Genetic Studies of Obesity The majority of the initial GWAS and WES studies was done in primarily European cohorts. More recent studies have evaluated transethnic genetic analyses (African, Hispanic/Latino, Asian, and European descent) of BMI and obesity and found consistency with previously reported SNPs like in *FTO* (lead SNP effect 1.34%, standard error 0.10%, $p = 2.3E^{-42}$); nearly a quarter of 170 established BMI SNPs studied and 29 out of 36 fine-mapped BMI loci replicated in these analyses [90]. Further, the investigators found novel loci at *LYPLAL1, COBLL1*, *IRS1*, *SLC39A8*, *TFAP2B*, and *STK33/TRIM66*, expanding our understanding of the heterogeneity in genetic architecture of obesity across diverse populations.

Polygenic Risk Scores in Obesity More recently, aggregating these common variants in polygenic risk scores (PRS) has demonstrated a stronger combined effect of many variants [91–95]. The most recent robust PRS, created from 2.1 million genetic variants identified from a GWAS of BMI [56], found a strong correlation with BMI (0.292, $p < 0.001$) and a 13-kg gradient in average weight comparing the top and bottom deciles of PRS.. The effect of the PRS was comparable to that of rare monogenic obesity-associated variants; individuals with the top 1.6% of PRS had a mean BMI 4.1 kg/m^2 higher than the rest of population, equivalent to the BMI increase seen in individuals with rare *MC4R* mutations [57••]. A high PRS (i.e., the top decile of the 306,134 participants studied) was associated with a 25-fold gradient risk of severe obesity, including earlier in life with a mean higher weight of 3.5 kg by 8 years of age and 12.3 kg (both $p < 0.0001$) by 18 years of age as compared with those in the bottom decile. However, polygenic risk of obesity is not deterministic, as greater than 17% of these adults with a high PRS remained normal weight or underweight [57••]. In addition to being a risk factor for obesity, Khera et al. also found that a high BMI PRS is associated with increased risk of cardiometabolic disease and mortality, with a 23% increased risk of ischemic stroke, 27% increased risk of coronary artery disease, 33% increased risk of heart failure, 35% increased risk of hypertension, 40% increased risk of venous thromboembolism, and 70% increased risk of T2DM [57••]. Taken together, these findings suggest that genetic variants, and in particular the combination of many common variants such as through a BMI PRS, do not only increase susceptibility to obesity, but also may help identify patients most at risk for severe obesity and cardiometabolic complications to best target intervention strategies.

Genes, Obesity, and Lifestyle BMI-associated genetic variants have been shown to be associated with food preferences, thereby potentially modulating the impact of diet on obesity and cardiometabolic outcomes [96–98], although the data are inconsistent. Concordantly, in a pooled study of 30,904 individuals, an interaction of a PRS of 97 BMI-associated SNPs and diet quality found an attenuated effect of PRS on obesity risk in individuals who reported eating a healthier diet [99].

Table 1 Overview of key genes identified from studies of obesity

Gene	Biology	Other associated phenotypes
Identified from genome-wide association studies (GWAS)		
Fat mass and obesity-associated gene (*FTO*) [47–49, 63, 65•, 67–69]	• Expressed in hypothalamus, and pituitary and adrenal grands • Energy homeostasis, regulation of fat mass, and body weight • Adipogenesis • m^6A demethylase, reduced m^6A ghrelin methylation and increased ghrelin expression	• Postnatal mortality • Growth retardation • T2DM
Melanocortin 4 receptor (*MC4R*) [36, 38, 39, 50]	• Expressed in hypothalamus • Acts as a receptor for pro-opiomelanocortin (POMC)-derived peptides to regulate appetite, energy homeostasis, and satiety	• Monogenic obesity • Hyperinsulinemia • Hypertriglyceridemia • Polyphagia • Tall stature • T2DM • Hypertension
Endosomal/lysosomal Niemann-Pick C1 gene (*NPC1*) [51, 70–72]	• Ubiquitous expression, highest in immune cells and hypothalamus • Resides in endosomes and lysosomes and mediates intracellular cholesterol trafficking	• Niemann-Pick disease type C • Hypertriglyceridemia • Coronary artery disease
c-MAF proto-oncogene (*MAF*) [51, 73–75]	• Ubiquitous expression • Developmental and cellular differentiation processes in the immune system, pancreas and adipose tissue • Tissue-specific transcriptional regulation of gene expression including insulin and glucagon	• Congenital cerulean cataract 4 (CCA4) • Chronic obstructive pulmonary disease • Lysophosphatidylcholine levels
Phosphotriesterase-related gene (*PTER*) [51]	• Hydrolase activity • Biology related to obesity is unknown	• Adolescent idiopathic scoliosis • Fractures in osteoporosis • Height
Prolactin (*PRL*) [51]	• Anterior pituitary hormone • Growth regulator with roles in immune cells • Essential for lactation	• Chronic obstructive pulmonary disease • Osteitis deformans
Identified from whole-exome sequencing (WES)		
Leptin receptor (*LEPR*) [36, 39, 56, 57••]	• Receptor for leptin for regulation of body weight via hypothalamic control to reduce feeding and regulate energy balance • Stimulates POMC	• Monogenic obesity • Pituitary dysfunction • Hypothyroidism • High rate of childhood infections
Lipoprotein receptor-related protein 2 (*LRP2*) [58, 76]	• Regulation of leptin-melanocortin pathways • Appetite regulation and generation of satiety signals in hypothalamic neurons • Multi-ligand endocytic receptor, including for leptin	• Donnai-Barrow/facio-oculo-acoustico-renal (DB/FOAR) syndrome • Developmental delay • Urate levels • Renal function and proteinuria • Ocular phenotypes
Uncoupling protein 2 (*UCP2*) [58, 77–79]	• Separate oxidative phosphorylation from ATP • Facilitate transfer of anions across inner mitochondrial membranes • Regulate energy balance, body weight, and thermoregulation • Role in response to inflammatory stimuli	• Hyperinsulinemia hypoglycemia • Hepatomegaly • Predictive of lesser weight loss
Dynein axonemal assembly factor 1 (*DNAAF1*) [58, 80, 81]	• Stability of ciliary architecture	• Primary ciliary dyskinesia (PCD)
Laminin subunit beta 3 (*LAMB3*) [59, 82]	• Basement membrane protein • Elevated LAMB3 mRNA levels correlate with BMI • In vitro LAMB3 knockdown inhibits adipogenesis	• Growth delay • Skin abnormalities including epidermolysis bullosa
Pleckstrin homology domain interacting protein (*PHIP*) [60]	• Binds insulin receptor substrate 1 protein and regulates glucose transporter translocation in skeletal muscle • Enhances transcription of POMC	• Developmental delay • Sjögren's syndrome • Hypertension
Diacylglycerol kinase iota (*DGKI*) [60]	• Regulates intracellular diacylglycerol concentrations	• Schizophrenia • Age-related cognitive decline • Retinal degeneration
Zinc-finger-MYM-type-containing 4 (*ZMYM4*) [60]	• Regulation of cell morphology and cytoskeletal organization	• Schizophrenia

Conversely, in a randomized trial of 609 overweight or obese individuals comparing low-fat vs. low-carbohydrate diets for weight loss, patterns of alleles in three SNPs in genes relevant to fat and carbohydrate metabolism (*FABP2*, *PPARG*, *ADRB2*) showed no significant interaction with diet on amount of weight loss at 12 months [100]. Genetic susceptibility also interacts with other lifestyle factors in association with obesity and related metabolic consequences. For example, genetic susceptibility to obesity may be "unmasked" by increasingly obesogenic environmental factors, such as ease of access to inexpensive calorie-dense foods and reduced need for physical activity [101]. Although initial studies showed inconsistent results, a meta-analysis of *FTO* variants found a modest interaction between genotype and physical activity on obesity risk [102]. Multiple additional studies have described the interaction of unhealthy diet and sedentary behaviors in individuals with polygenic predisposition to obesity (32–69 variants) showing that the combination of lifestyle factors and genetic risk is interactive on obesity risk [103–106]. Although the detailed biology of potential pleiotropy warrants further study, the impact of genetic variants associated with obesity on cardiometabolic phenotypes appears to be driven through altered food intake and energy homeostasis.

Epigenetics and Obesity Epigenetic changes are modifications to DNA that are heritable and can affect gene activity and expression without changing the underlying DNA sequence, for example, DNA methylation and histone modifications. Epigenetic modifications can be induced by environmental factors and can contribute to disease risk across the life span, including in utero modifications that can transmit future disease risk. The study of epigenetic modifications, which have both genetic and environmental effects, provides additional insight into obesity and cardiometabolic disease risk. The most well-studied epigenetic modification, DNA methylation, has been investigated through genome-wide, genetic variant and candidate gene approaches in obesity and obesity-associated traits. Genome-wide methylation analyses of whole blood and adipose tissue show associations between methylation patterns of hypoxia-induced factor 3A (*HIF3A*) and other genes involved in adipogenesis, insulin, and glucose metabolism with higher BMI [107]. Candidate gene approaches to methylation identified pathways in eating behavior and lipid metabolism associated with obesity and related traits. *FTO* may provide key epigenetic regulation as it has been identified as a N^6-methyladenosine (m^6A) demethylase. An *FTO* SNP associated with obesity and increased FTO expression shows reduced m^6A ghrelin methylation and increased ghrelin expression in blood cells, providing a mechanism for increased food intake and preference for energy-dense food [73]. The m^6A activity of FTO provides a biologic link between obesity and cancer risk, as FTO provides transcriptional regulation impacting tumorigenesis [69].

Obesity Metabolomics: Novel Molecular Pathways and Metabolic Biomarkers

Germline genetic variants provide a static view of risk of obesity and related cardiometabolic disease. Environmental influences that change throughout the lifetime can dynamically alter biologic pathways that may contribute to obesity and cardiometabolic disease risk. Novel omic technologies have yielded the opportunity to examine how biomarkers change over time as chronic diseases develop and may provide more proximal insight into dysregulated disease biology. These technologic advances have allowed for the high-throughput measurement of hundreds to thousands of metabolites in small amounts of biospecimen samples enabling biomarker discovery work. Molecular profiling of circulating metabolomic measurements integrate environmental and genetic factors, and thus can provide insight into obesity and risk of cardiometabolic complications, allowing simultaneous identification of biology and biomarkers.

Branched-Chain Amino Acid Catabolic Pathway in Obesity and T2DM Early studies applied high-throughput metabolomics to studies of obesity in an unbiased fashion to identify potential novel biological pathways and biomarkers related to this disease over a decade ago. In a study of 74 obese and 67 lean individuals from the STEDMAN study, Newgard et al. used targeted tandem flow injection mass spectrometry to measure 53 metabolites in plasma and identified a cluster of branched-chain amino acid (BCAA) and related mitochondrial catabolic byproducts that discriminated obese from lean individuals. Further, this cluster of BCAA and related metabolites was associated with homeostatic model assessment (HOMA, a marker of insulin resistance) in both obese and lean individuals [108]. To determine whether BCAAs are markers of the obesity and insulin resistance process or are potentially involved in the causative pathway, Zucker obese rats were fed standard chow vs. high fat chow vs. chow supplemented with BCAAs. After 13 weeks, despite lesser weight gain due to lesser food intake, the BCAA-supplemented rats were equally insulin resistant to those fed high fat chow, suggesting that BCAAs are not merely markers but appear to be involved in induction of insulin resistance in the setting of obesity. Supportive of this, in other studies in both mice and rodents, BCAA restriction has been shown to improve insulin sensitivity and metabolic health [109, 110]. Potential mechanisms of BCAA interference with insulin signaling were identified: insulin resistance was accompanied by phosphorylation of mTOR and was reversed by treatment with rapamycin, an mTOR inhibitor [108]. More recently, Vogelzangs et al. used nuclear magnetic-resonance spectroscopy to measure 17 serum metabolites in 634 overweight or obese adults without T2DM and found BCAA levels associated with both hepatic and muscle insulin resistance [111•].

Determinants of elevations in circulating BCAA levels in obesity are diverse. Decreased rates of BCAA oxidation in adipose tissue secondary to suppression of catabolic enzymes likely contribute to circulating levels [112]. Genetics appears to also influence circulating BCAA levels: a genome-wide meta-analysis of 16,596 individuals found the strongest association near the protein phosphatase 1K (*PPM1K*) gene with higher circulating levels of BCAAs and risk of T2DM; this gene encodes an activator of mitochondrial branched-chain alpha-ketoacid dehydrogenase [113]. The microbiome also appears to play a role in BCAA pathways in obesity and in BCAA levels. Ridura et al. performed an elegant study of fecal transplantation from human twins discordant for obesity into gnotobiotic mice [114]. Fecal communities clustered based on twin obesity phenotype and transplantation with the obese twin's feces was sufficient to induce obesity in the mice, with coordinated upregulation of BCAA pathways in the mice as they developed obesity. A 2016 study of 277 lean and obese individuals without T2DM found BCAAs to correlate with both insulin resistance and gut microbiota, enriched with species for biosynthetic potential of BCAAs and with fewer genes related to inward amino acid transport, further showing the interrelated metabolomic and microbiome pathways underlying obesity and cardiometabolic risk [115]. These and other studies display the multifactorial reasons and complex feedback loops that determine elevated circulating BCAA levels in obesity which are determined partially by genetics; dietary sources including meat, fish, dairy products, and eggs; and the microbiome [116, 117].

Recently, the liver has emerged as an important organ for BCAA catabolism in obesity. Insulin signaling inhibits branched-chain α-keto acid dehydrogenase (BCKDH, the first irreversible step in BCAA catabolism); fructose feeding in rats, as seen in obesity, inhibits hepatic BCKDH via phosphorylation of its inhibitor kinase BDK leading to hepatic lipogenesis, suppression of fatty acid oxidation, and increased fat storage in the lipid [118]. In Zucker obese rats, a BDK inhibitor molecule relieved the inhibition of BCKDH, lowering circulating branched-chain keto acid (BCKA) and BCAA levels, improving glucose tolerance and insulin resistance and decreasing hepatic fat storage. Overexpression of the phosphatase PPM1K increased BCKDH activity and had similar effects on BCAA levels and hepatic lipid metabolism. In the setting of insulin resistance, impaired hepatic BCAA metabolism is also linked to a compensatory upregulation of skeletal muscle BCAA oxidation, altering mitochondrial substrate utilization and decreasing acylglycine efflux [110]. Heart failure is an important cardiometabolic consequence of both obesity and T2DM and BCAA restriction in obese rats shifts myocardial fuel metabolism in favor of fatty acids over glucose metabolism and reduces myocardial triglyceride stores independent of BCKDH [119].

In addition to highlighting a novel biological pathway underlying obesity and insulin resistance, BCAAs have also been shown to serve as biomarkers in obesity and obesity-related diseases [120], including risk of incident T2DM, even independent of BMI [121, 122]. In a study of metabolomic profiling in 2422 individuals from the Framingham Offspring Study, Wang et al. found that BCAA and related metabolites were the metabolites most associated with measures of insulin resistance, and further, these metabolites predicted risk of incident DM up to 12 years in the future in individuals free of insulin resistance or T2DM at baseline [121]. Circulating BCAAs have also been identified as a biomarker for discrimination of metabolic wellness independent of BMI. In a study of 1872 individuals classified as metabolically well or unwell based on impaired fasting glucose, hypertension, high triglycerides, low HDL, or impaired insulin resistance, BCAA levels were higher in metabolically unwell overweight individuals compared with metabolically well obese individuals, suggesting these metabolites may be more granular markers of metabolic health than traditional clinical lab values [123]. Relatedly, BCAAs and related metabolites have been found to be similarly upregulated between overweight-obese individuals and normal weight-obese individuals (defined as BMI < 25 and body fat > 30% for women and > 25% for men) compared to lean individuals [124]. Finally, circulating BCAA levels have been shown to discriminate patients with coronary artery disease incremental to clinical risk factors [125, 126]. A summary of BCAA studies relevant to obesity, as well as the subsequent metabolic pathways discussed, is provided in Table 2.

Lipid-Related Metabolic Pathways in Obesity Identified Through Metabolomic Profiling Evolution of mass spectrometry and other methods for comprehensive metabolomic profiling has enabled discovery of a broader set of metabolic pathways underlying obesity and related phenotypes, including many lipid-related pathways. For example, lipid profiling of 1076 individuals revealed higher ceramide levels ($\beta = 2.01$) and lower lysophospholipids ($\beta = -1.44$ to -2.04) associated with BMI (all $p < 0.001$) [127]. A second large study of 1176 women found higher sphingomyelin and diacylphosphatidylcholine levels and lower lysophosphatidylcholines associated with waist circumference and BMI; a subset of the associated lipids also correlated with HOMA [144]. Two smaller studies replicated BCAA findings and similarly identified choline-containing phospholipids to be lower in individuals with metabolic unhealthy obesity as compared with normal weight metabolically healthy or metabolically health obesity [128, 145]. A factor composed of lysophosphatidylcholines was inversely associated with cardiometabolic biomarkers such as hemoglobin A1C ($\beta = -0.010$, $p = 0.028$, 95% CI [−0.018 to −0.001]) and CRP ($\beta = -0.22$, $p < 0.001$, 95% CI [−0.334 to −0.110]) in metabolically healthy obese, and with HOMA ($\beta = -0.118$, $p = 0.021$, 95% CI [−0.217 to −0.018]) in metabolically unhealthy obese; and a diacyl-phosphatidylcholine factor was directly correlated with

Table 2 Overview of metabolomic studies of obesity

Study population and sample size	Platform	Key significant metabolites	Other outcomes
Obesity/BMI			
STEDMAN [104] - 74 obese - 67 lean	Targeted MS/MS	• BCAAs and aromatic AAs • C3 and C5 acylcarnitines • Glycine (−)	Insulin resistance
European Diogenes Study [107] - 634 overweight/obese	NMR	• BCAAs • Triglycerides • Lactate • Glycine (−)	Hepatic insulin resistance and skeletal muscle insulin sensitivity
MURDOCK [119] - 610 overweight - 852 obese - 410 lean	MS/MS	• BCAAs	Metabolic health
- 43 normal weight obesity [120] (BMI < 25 and body fat > 30% for women and > 25% for men) - 110 overweight/obesity - 26 lean	LC ESI-MS	• BCAAs and aromatic AAs • Linoleic acid	Body composition subtypes
SAFHS [123] - 1431 adults	LC ESI-MS/MS	• Cholesterol esters • Triacylgylcerols • Ceramide • Lysophospholipids (−)	Anthropometric and biochemical measurements
Western Australian Pregnancy Cohort [124] - 1176 women	MS	• Sphingomyelins • Diacylphosphatidylcholines • Lysophosphatidylcholines (−)	Waist circumference Insulin resistance
- 34 metabolically healthy obese [125] - 38 metabolically unhealthy obese	LC/MS & GC/MS	• Glycerophosphocholine (−) • Glycerol 1-phosphate (−)	Metabolic health
- 107 metabolically healthy obese [126] - 100 metabolically unhealthy obese - 78 normal weight metabolically healthy	LC-MS/MS	• BCAAs • Diacylphosphatidylcholines • LCAC (−) • Acyl-lysophosphatidylcholines (−) • Alkyl-lysophosphatidylcholine (−) • Acyl-alkyl-phosphatidylcholine (−)	Metabolic health Cardiometabolic biomarkers
- 10 obese without T2DM [127] - 9 obese T2DM - 11 lean	LC/MS	• Lysophosphatidylcholines (−)	
Boston Puerto Rican Health Study [128] - 781 adults	LC/MS	• 148 metabolites correlated metabolites with BMI • 86 metabolites correlated with SSB intake • Phosphatidylcholine and lysophospholipid pathways linked to SSB intake and obesity	Sugar-sweetened beverage (SSB) consumption and obesity risk
- 14 obese without T2DM [129] - 10 T2DM - 12 lean	MS/MS	• LCACs • Free Carnitines	Glycemic control Acylcarnitines levels following insulin infusion
- 6 obese [130] - 6 lean Before and after 5-day high-fat diet	MS/MS	• Plasma SCACs • Skeletal muscle AAs (−) • Skeletal muscle MCACs	Plasma and skeletal muscle metabolomics
Six independent cohorts [131] - 739 adults	Targeted MS	• BCAAs and aromatic AAs • MCACs and LCACs • Glycine (−)	Age
- 35 men [132] - 47 women	NMR	• Serine (−) • Glycine (−)	Metabolic health Activity Energy Expenditure Sedentary Time and Activity Reporting Questionnaire
TwinsUK Registry [133]	UPLC-MS/MS	• Nucleotides, including urate	Cardiovascular events

Table 2 (continued)

Study population and sample size	Platform	Key significant metabolites	Other outcomes
- 1969 twins - 85 obese [134] - 42 non-obese	LC ESI-MS/MS	• Peptides • Kynurenine/tryptophan ratio • Serotonin (5-HT) and indoles (−)	Interleukin-6 C-reactive protein
Gestational obesity			
HAPO Study [135••] - 1600 pregnant women	Targeted MS/MS	• BCAAs and aromatic AAs • Glycine (−) • Triglycerides • NEFA • MCACs • LCACs	Insulin resistance
HAPO Study [136] - 1412 pregnant women	Targeted MS/MS and Non-targeted GC-MS	• Variants in glucokinase regulatory protein gene associated with palmitoleic acid	GWAS Insulin resistance
Pediatric obesity			
- 80 obese children [137] - 40 normal weight children	LC-MS/MS	• Glutamine (−) • Methionine (−) • Proline (−) • Phosphatidylcholines (−) • LCACs	Pubertal stage
- 2191 healthy participants (age 3 months to 18 years) [138]	LC-MS/MS	• BCAAs and aromatic AAs • C3 carnitine • Citrulline (−) • Glycine (−)	Pubertal stage
- 524 adolescents (age ~ 13 years) [139]	Non-targeted LC-MS	• BCAAs • Diacylgylcerols • Steroid hormones • LCACs	Metabolic health
Systematic review [140] - 10 studies - 2673 participants	Varied	• BCAAs and aromatic AAs • Lipid metabolism	Insulin resistance
Behavioral weight loss intervention			
Weight Loss Maintenance Study [141] - 500 participants with ≥ 4-kg weight loss - 22 participant independent validation cohort	Targeted MS/MS	• BCAAs and associated catabolites	Change in insulin resistance independent of amount of weight lost
Surgical weight loss intervention			
- 16 gastric bypass [142] - 17 dietary intervention Matched 10 kg weight loss	MS/MS	• BCAAs, total AAs and C3 and C5 acylcarnitines derived from BCAA oxidation decreased after gastric bypass but not dietary intervention and correlate with insulin resistance.	Insulin resistance
- 10 gastric bypass [143] - 10 laparoscopic adjustable gastric banding ~ 20% weight loss	MS/MS	• BCAAs, C3 and C5 acylcarnitines decreased similarly between surgical groups and correlate with insulin resistance	Insulin resistance

Except where specified by (−), higher metabolites levels are associated with increased BMI or other outcomes noted in the table. In studies where examined, metabolic health is defined as a combination of one or more abnormal measures of waist circumference, blood glucose, hypertension, dyslipidemia, and insulin resistance

Abbreviations: *MS*, mass spectrometry; *MS/MS*, tandem mass spectrometry; *LC*, liquid chromatography; *GC*, gas chromatography; *LC ESI-MS*, liquid chromatography-electrospray ionization-mass spectrometry; *UPLC-MS/MS*, ultra-high-performance liquid chromatography-tandem mass spectrometry; *NMR*, nuclear-magnetic-resonance; *BCAA*, branched-chain amino acid; *AA*, amino acids; *NEFA*, non-esterified fatty acids; *SCACs*, short-chain acylcarnitines; *MCACs*, medium-chain acylcarnitines; *LCACs*, long-chain acylcarnitines

cardiometabolic markers in metabolically unhealthy obese individuals [145]. In mice, 12 weeks of high-fat feeding resulted in reduction of lysophosphatidylcholines with the greatest changes occurring in the first week [146]. Mechanistically, treatment of isolated adipocytes and mice with lysophosphatidylcholines improves glucose uptake in a dose-dependent manner [147]. A recent study investigating the metabolic mechanisms linking sugar-sweetened beverage intake and obesity used plasma metabolomic profiling of 781 individuals and found phosphatidylcholine and lysophospholipid pathways to be enriched with amount of beverage intake and BMI [148]. Lending further support, 8 of 10 genes in these pathways interacted with sugar-sweetened beverage intake on BMI. Based on data from isolated perfused rat livers [149] and obese beagles [150], decreased activity of lecithin:cholesterol acyltransferase (LCAT) may contribute to altered lysophosphatidylcholine levels. Further, genetic deficiencies or polymorphisms in phosphatidylethanolamine *N*-methyltransferase (*PEMT*) may contribute to altered lysophosphatidylcholine levels as data from both mice and humans show risk of NAFLD in *PEMT* KO or polymorphisms [129, 151, 152].

Fatty Acid–Related Pathways in Obesity Identified Through Metabolomic Profiling Plasma long-chain acylcarnitines, byproducts of mitochondrial fatty acid oxidation, are elevated in individuals with obesity and T2DM compared to lean individuals without metabolic syndrome and are associated with insulin resistance [130]. A study of 12 lean, 14 obese without T2DM, and 10 participants with T2DM found elevated levels of long-chain acylcarnitines (C14:1, C16, C18, C18:1) in subjects with obesity and T2DM compared to lean controls [153]. Insulin infusion reduced plasma levels of long-chain acylcarnitines in all groups but patients with T2DM had a blunted response. In rodents, high-fat feeding and obese, insulin-resistant Zucker rats have accumulation of long-chain acylcarnitines in skeletal muscle, representing incompletely oxidized lipid species and reporting on impaired mitochondrial fatty acid β-oxidation [154]. This substrate accumulation leads to mitochondrial stress and ultimately impaired responsiveness to insulin [131]. A study of plasma and skeletal muscle metabolomics from 6 obese and 6 lean individuals before and after high-fat diet found increased medium-chain acylcarnitines (C6, C8, C10:2, C10:1, C20 and C12:1) in skeletal muscle of obese subjects after high-fat diet, but decreased in lean subjects, potentially providing further evidence to the mechanisms of altered skeletal muscle metabolism in obesity [132]. Obesity and cardiometabolic disease represent pro-inflammatory states and though the detailed causal mechanisms and tissue-specific sources remain to be further elucidated, it has been shown that medium- and long-chain acylcarnitines activate pro-inflammatory signaling pathways [133, 155].

Other Major Metabolic Pathways in Obesity Beyond BCAAs, lipids, and fatty acid pathways, other biologic markers of metabolism have been identified in obesity. Metabolomic profiling of 739 subjects found in addition to the association of clusters of lipids and amino acid metabolites with BMI, glycine had an inverse association with BMI and has been found to be directly related to insulin sensitivity [156]. Similarly, a small study identified lower serine and glycine concentrations in patients with metabolic syndrome risk factors and greater adiposity that increased with activity energy expenditure [157]. A large study of 1969 unrelated individuals identified 49 significant metabolites associated with BMI across multiple time points that validated in an independent cohort [135••]. In addition to amino acids and lipids, the investigators found nucleotides related to purine metabolism (percent variation in BMI explained by metabolites 7.3–16.4%) and peptides (4.6 to 6.9%) associated with obesity, with urate being the most significant metabolite overall ($p = 1.2E^{-40}$). Assessment of CVD outcomes found lower event rates in participants with healthier metabolomic profiles compared to normal/overweight BMI with obese metabolic profile and obese individuals (2.6 events per hundred individuals, 3.4 events and 4.4 events, respectively, $p = 0.003$).

Metabolic Pathways and Biomarkers of Obesity in Pregnancy and in Childhood and Adolescence

In addition to genetic predictors of metabolic signatures and obesity, pregnancy represents an important time point in the lifespan, as obesity is associated with adverse pregnancy outcomes (pre-eclampsia [OR 3.15, CI 2.96–3.35], gestational hypertension [OR 2.91, CI 2.76–3.07], and gestational diabetes [OR 3.56, CI 3.05–4.21]) and may predict future risk of obesity and cardiometabolic disease for both the mother and newborn [158–160]. For example, a large targeted metabolomics study of 1600 pregnant women from four different ancestry groups identified BCAA, their carnitine esters, aromatic amino acids, triglycerides, non-esterified fatty acids, and medium- and long-chain acylcarnitines to be associated with maternal BMI, glucose levels, and insulin sensitivity [136]. This study also replicated the negative correlation of glycine with both maternal BMI and insulin resistance. Maternal BMI is also associated with fetal metabolites and after correction for maternal BMI and blood glucose, maternal levels of branched-chain and other amino acids, acylcarnitines, lipids, and fatty acids have been identified to correlate with fetal growth, adiposity, and hyperinsulinemia [137–139]. A recent study performed integrated GWAS and metabolomic analyses of insulin resistance in 1412 pregnant women and identified variants in the glucokinase regulatory protein gene that associated with palmitoleic acid levels [140].

With rising rates of childhood obesity, it is important to understand metabolic pathways and predictors of obesity early in life, to better understand earlier biological underpinnings and potential lifespan "setpoints," and to target earlier therapeutic interventions. Interestingly, metabolomic profiling in children and adolescents suggests some similar but also some potentially different dysregulated metabolic pathways. A study of 80 obese children and 40 normal weight children between the ages of 6 and 15 found increased levels of two long-chain acylcarnitines (C12:1 and C16:1) and decreased levels of the amino acids glutamine, methionine, and proline and of 9 phosphatidylcholines in obese children compared to controls, suggesting changes in oxidative stress, β-oxidation, and sphingomyelin metabolism in pediatric obesity [161]. No correlations in metabolite concentrations were seen with pubertal stage. Concordant with studies in adults, acylcarnitine levels were higher in obese children and phosphatidylcholine and lysophosphatidylcholines were lower, but in contrast to adult metabolomic findings in obesity, this study found no significant differences in BCAA levels. Conversely, a study of 2191 children between the ages of 3 months and 18 years did find associations between elevated levels of BCAAs, aromatic AAs and C3 carnitines (an intermediate of BCAA metabolism), and BMI, and found distinct metabolite patterns when comparing pubertal stages, with sex-dependent differences with males having higher metabolite levels in later pubertal stages [162]. The investigators also found negative associations between citrulline and glycine and BMI, but only in females. Similarly, a study of 524 overweight or obese adolescents found higher levels of BCCAs and related metabolites, as well as long-chain acylcarnitines, diacylglycerols, and steroid hormones in overweight/obese adolescents with high metabolic risk compared to non-overweight/obese with low metabolic risk [163]. A systematic review of metabolomic markers of insulin resistance in childhood obesity identified BCAAs, aromatic amino acids, and acylcarnitines to be most frequently associated with insulin resistance [164]. BCAAs and tyrosine were associated with future metabolic risk in cohorts with long-term follow-up; however, overall small scale and heterogeneity of study design limits these results. Larger metabolomic studies of children and adolescents that consider pubertal stage and include racially diverse cohorts are needed to better understand the metabolomics of obesity and cardiometabolic risk across the life span.

Integrated Genomics and Metabolomics for Greater Understanding of Obesity Biology

The combination of genomic and metabolomic research can enhance our understanding of the biology of obesity. For example, metabolomic profiling of six individuals with homozygous loss-of-function mutations in *LEP* before and after leptin replacement showed decreases in BCAAs and phospholipids. These changes were not seen after caloric restriction, suggesting that leptin administration leads to changes in substrate utilization but that the effect of leptin on these metabolites is independent of caloric intake [165]. These patients also had increases in fatty acids and acylcarnitines, and overall a metabolomic score of 37 metabolites was similar to that of individuals with obesity in the absence of monogenic syndromes, suggesting the utility of metabolomic scores regardless of genetic risk of obesity. Beyond GWAS of BCAA discussed above, GWAS of metabolomic traits and even metabolome-wide genome-wide association studies have emerged as methods to understand the biologic impact on disease phenotypes. These studies allow for integrated analysis of genetic, metabolite, and environmental influences on disease phenotypes and genetic variants can in part explain metabolomic variance [166, 167]. For example, a study of 1809 individuals with targeted metabolomics identified that the genetic variant is located in or near genes encoding the enzymes associated with metabolic traits, including those related to lipid and fatty acid metabolism [141]. Interestingly, a metabolic score of 49 BMI-associated metabolites was not associated with a PRS for obesity, suggesting distinct pathways for these molecular predictors of obesity risk [135••]. Taking a broader approach to systems biology, integrating genetics and metabolomics, or genetics and gene expression, investigators have identified biologic pathways of adipogenesis and fatty acid metabolism associated with weight [168] and new genes associated with obesity [169, 170].

Personalized Approaches to Obesity Using Genomics and Metabolomics: One Size Does Not Fit All

There are many potential interventions for obesity, including behavioral, dietary, exercise, pharmacologic, and surgical therapies; however, there is marked heterogeneity among individuals in weight loss response to interventions and improvement in cardiometabolic risk factors like insulin resistance [171, 172]. Despite attempts to characterize predictors of response to weight loss intervention, only early weight loss response in the first few weeks of intervention and adherence to the weight loss program have been consistently identified predictors [173]. Many studies have documented this heterogeneity of response of metabolic risk factors in the context of weight loss [174]. This suggests that improvement in cardiometabolic health is not directly related to amount of weight lost and that additional genomic and metabolomic measures may be important in predicting heterogeneity.

As proof of this concept, a study evaluating a PRS comprised of 25 BMI-associated SNPs showed greater weight loss after dietary counseling in individuals with low PRS than in

individuals with higher PRS, with the PRS explaining 2.4% of weight change variance at 1 year [175]. Conversely, a study of a 15 SNP PRS was not associated with differential response to lifestyle interventions in children and adolescents with obesity [176]. Metabolites have also been shown to predict response to weight loss interventions. For example, baseline levels of BCAAs and related metabolites are responsive and predictive of improvements in insulin resistance in behavioral weight loss [171]. However, acylcarnitines levels, although elevated in obesity, have not been found to respond to weight loss and do not correlate with improvement in insulin resistance [177]. This suggests that certain metabolite levels could be used to identify individuals whose metabolic health would benefit most from specific types of weight loss intervention.

Surgical weight loss interventions also result in heterogeneous improvements in cardiometabolic risk factors. Three years after bariatric surgery in obese individuals, gastric bypass resulted in resolution of dyslipidemia in 62% of participants compared to only 27% of patients treated with laparoscopic gastric banding [178]. Similar heterogeneity was seen in this population and others for improvement in T2DM and hypertension after surgery [78, 79, 179–183]. As surgical interventions are costly and pose both short-term surgical complications and longer-term complications, the obesity guidelines indicate the need to characterize patients "most likely to benefit from and least likely to suffer adverse consequences of bariatric surgical procedures" [184]. Studies of genetic predictors of weight loss after gastric banding or bypass have identified polymorphisms in *UCP2* to be predictive of lesser weight and fat-free mass loss [142, 185]. A GWAS of 693 individuals found a variant at 15q26.1 to be associated with greater weight loss after gastric bypass; higher expression of *ST8SIA2*, a gene near this locus, in omental fat was associated with greater weight loss after gastric bypass surgery [143]. Patients undergoing gastric bypass have been observed to have greater improvement in metabolic health measures compared to dietary interventions, even after accounting for the amount of weight lost [75, 76]. Concomitantly, BCAAs and related metabolites have been shown to decrease to a greater extent after gastric banding or bypass than after dietary weight loss in weight loss–matched individuals and correlate with levels of insulin resistance [80, 81]. As such, there is already a robust literature supporting the use of genetic and metabolic biomarkers for identifying those individuals who may benefit the most from a given weight loss intervention with regard to its weight loss and metabolic health benefits. However, while these discovery studies are interesting and in parallel highlight important biology, biomarker-guided implementation studies to determine efficacy of such a personalized approach to weight loss interventions are necessary. As well, studies that incorporate genomic and metabolomic measures may aid in prediction of response to weight loss pharmacotherapy to limit exposure to risks and costs of therapies for those who do not respond with weight loss.

Future Directions: Multifaceted Approaches to Tackle the Obesity Epidemic

While metabolomics lends itself well scientifically to understanding the biology and biomarkers of obesity given its metabolic basis, the future landscape of obesity omics research will include a more comprehensive perspective incorporating epigenomics, proteomics, and the exposome and other environmental factors for a deep understanding of biology and a more precise prediction of obesity-related outcomes. The integration of these layers in parallel with advances in bioinformatics and computational biology is creating opportunities for clinical translation to improve patient outcomes, and to create a more personalized approach to obesity management and prevention of cardiometabolic disease. Stratifying individuals based on more personalized needs will hopefully allow for allocation of health care resources to individuals with the greatest need and to tailor interventions to a given patient. However, while discovery studies are vital, implementation research to show efficacy and utility of these personalized approaches is also necessary. Clinical implementation of these strategies will necessitate development of decision support tools, digital health device integration, and scaling for population-level strategies, with dynamic return of data to patients and communities stand to improve current outcomes for obesity and cardiometabolic disease.

Importantly, tackling the obesity epidemic will have to include partnerships between health systems, public health researchers, and local and federal governments to create policies and interventions that support the health of communities throughout their lifespan. This will require addressing socioeconomic and health disparities that impact access to healthy foods and the creation of opportunities for community education and engagement. These endeavors require a multidisciplinary team approach incorporating primary care physicians, endocrinologists, cardiologists, surgeons and dietitians, patients, and communities.

Conclusion

The past two decades have ushered in an era that has enabled application of high-throughput genomic and metabolomic technologies to identify the biology and biomarkers of obesity. These multi-omic measures have created a framework of important discoveries that can be used for precision medicine approaches to tackle obesity throughout the lifespan. Implementation studies are necessary to determine effectiveness and clinical utility of these approaches. Regardless, a multifaceted, interdisciplinary approach is essential to tackle the obesity epidemic and thereby mitigate the downstream adverse health consequences.

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Compliance with Ethical Standards

Conflict of Interest J. Regan declares no conflict of interest. S. Shah holds an unlicensed patent (10317414) on a related research finding, and receives research support through sponsored research agreements through Verily Life Sciences Inc. and Lilly Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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