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Established and Emerging Biomarkers to Characterize Persons at Risk for Obesity—Paving the Way for Targeted Clinical Intervention Trials—A Comprehensive Position Paper

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ABSTRACT

Despite all efforts, obesity remains a major health concern worldwide, with continuously increasing rates, affecting approx. 14% of the total world population, being as high as 43% in some countries. As obesity is related to numerous comorbidities, including type 2 diabetes, cardiovascular diseases, and some types of cancer, the consequences for the individual and society at large are drastic. Therefore, it is crucial to understand and predict who is at risk of developing obesity in order to implement early prevention strategies. Many individual risk factors have been emphasized. However, as obesity is a rather multifactorial complication, single markers/biomarkers have thus far not allowed for an efficient prediction of obesity. In addition to less modifiable parameters, such as environment

Abbreviations: AA, amino acids; AAA, aromatic amino acids; ADCY5, adenylate cyclase 5; ADHD, attention-deficit/hyperactivity disorder distribution; ADME, absorption excretion metabolism; AHEI, alternative healthy eating index; AI, artificial intelligence; APV, adiposity patient registry; BCAAs, branched-chain amino acids; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CAT, catalase; CCL2, chemokine (C-C motif) ligand 2; CHF, congestive heart failure; CRP, C-reactive protein; CVD, cardiovascular disease; DAI, dietary antioxidant index; DHA, docosahexaenoic acid; DII, dietary inflammatory index; DQI-I, diet quality index international; ELISA, enzyme-linked immunoassay; EPA, eicosapentaenoic acid; ER, endoplasmatic reticulum; FABP4, fatty acid binding protein 4; FAs, fatty acids; FBG, fasting blood glucose; FDA, food and drug administration; FFA, free fatty acids; FFQ, food frequency questionnaire; GPx, glutathione peroxidase; GRS, genetic risk score; GWAS, genome wide analysis; HDL-c, high-density lipoprotein cholesterol; HEI, healthy eating index; HOMA-IR, homeostasis model assessment of insulin resistance; IGF, insulin-like growth factor; IGF, insulin-like growth factor; IL, interleukin; KSR2, kinase suppressor of ras 2; LC, liquid chromatography; LDL-c, low-density lipoprotein cholesterol; LEP, leptin; LEPR, leptin receptor; MC4R, melanocortin 4 receptor; MD, Mediterranean diet; MDA, malondialdehyde; MDS, Mediterranean diet score; MetS, metabolic syndrome; ML, machine learning; MRAP2, melanocortin 2 receptor accessory protein 2; MS, mass spectrometry; NCDs, noncommunicable diseases; NTRK2, neurotrophic receptor tyrosine kinase 2; OR, odds ratio; OS, oxidative stress; PA, physical activity; PCSK1, proprotein convertase 1; POMC, proopiomelanocortin; PPARs, peroxisome proliferator-activated receptors; PTM, posttranslational modification; PT-Q, chrononutrition profile–questionnaire; RAR, retinoic acid receptor; ROS, reactive oxygen species; RXR, retinod-X-receptor; SFAs, saturated fats; SIM1, single-minded homolog 1; SMD, standard mean difference; SNPs, single-nucleotide polymorphisms; SOD, superoxide dismutase; T2D, type 2 diabetes; TG, triglycerides; TNF-α, tumor necrosis factor alpha; VDR, vitamin D receptor; WAT, white adipose tissue; WHO, World Health Organization.

and socio-demographics, studies have revealed that obesity is related to several interacting aspects, including host factors such as genetics/epigenetics or gut microbiota, and more readily modifiable factors, including nutrition and physical activity, as well as sleep patterns and psychological well-being. It is likely that combining markers from across different domains, that is, multimodal markers, allows for better predictability for the risk of developing obesity. However, it must be considered that not all markers are fully predictive; many are rather reactive or even both. In this review and position paper, we emphasize the state-of-the-art regarding (bio) markers that have successfully been employed for predicting obesity risk. An emphasis will rest on novel, emerging biomarkers, and the need for a more integrative, multimodal assessment of obesity risk for a combined assessment aimed at improving risk prediction.

1 | Introduction

Obesity, classically and often defined as having a body mass index (BMI) of $\geq 30\,kg/m^2$, has become a major health pandemic, affecting on average 14% of the world population and being as high as 43% in some countries, such as the USA [1]. Together with overweight, affecting on average 42% of the population worldwide [2], obesity has become a more prevalent form of malnutrition than being underweight [3]. Obesity is related to many comorbidities, including type 2 diabetes (T2D) [4], cardiovascular diseases (CVDs) [5], certain types of cancer [6], and a higher risk of severe infections, as emphasized during the COVID-19 crisis [7].

The reasons for these unabated trends in obesity have been the topic of much controversial discussion but may include a multitude of factors, including mainly modifiable lifestyle ones such as poor dietary habits [8, 9] and insufficient physical activity (PA) [10], though also disturbed sleeping patterns [11], psychological aspects including stress [12], the gut microbiome [13] and rather non- or less readily modifiable factors such as genetic predisposition [14], foodscape [15] and built environment at large [16], as well as socio-demographic aspects [17] that have been regarded as playing a role.

Although treatment for persons with obesity is available, including medication (such as semaglutide injection) and/or bariatric surgery for more severe obesity, which are by now considered the treatments of choice for more advanced stages of obesity [18], such treatment is costly and still requires adjustments in lifestyle habits for optimal success. Therefore, early preventive measures appear to be much more promising in terms of efficacy and cost-benefits, reaching a larger part of the population [19–21]. Such preventive measures would ideally target especially persons at risk for developing obesity, such as those with overweight or socially disadvantaged, in order to address them specifically. However, to date, the ability to predict the risk of developing obesity is limited [22]. Such risk-predictors, or (bio-)markers, can be used for diagnosis, risk prediction, and stratification, as well as therapeutic targets when causality is proven.

There is not even an explicit agreement on the definition of obesity. While BMI, for practical reasons, is the most widely used one, it is obviously prone to disrespecting individual physiognomic aspects. The waist-to-hip ratio may be a better marker for diagnosis, with a value above 0.9 and 0.85 for men and women, respectively, reflecting obesity [23]. This is related to the percentage of body fat, for which a value of over 25% and 35% in men and women [24] is likewise regarded as an indication of obesity. In addition to the waist-to-hip ratio, the waist-to-height ratio has been suggested as an alternative measure, with some evidence indicating that it may be a simpler and more accurate predictor of cardiometabolic risk [25]. The best marker to diagnose obesity may be visceral body fat, expressed as visceral cross-sectional area, and a value above $100\,cm^2$ may indicate obesity [26]. While these measures provide useful population-level estimates of adiposity, they do not capture the complex biological mechanisms underlying obesity. These limitations highlight the need for more specific and mechanistically informative biomarkers that can better predict associated metabolic risk and disease progression beyond simple body size indicators.

Research has highlighted several risk factors for developing obesity that could serve as early warning signs, including the levels of specific biomarkers in blood/body fluids/tissues (Table 1) and/or more general ones (Figure 1 and Table 2). It is also important to note that there exists a continuum of markers, ranging from being fully predictive, such as genetic markers, to rather reactive ones (Table 3), such as cytokines secreted by visceral adipose tissue, with many showing both features, such as insulin. This aspect, along with the possible strengths of associations, should also be considered when combining individual risk factors into multimodal ones. In this regard, indeed, most biomarker studies have compared cross-sectionally individuals with obesity (or preobesity) to those with normal weight, which may identify markers of existing obesity rather than early predictors of risk, limiting their utility for preventive strategies. In this regard, longitudinal studies offer a more convincing insight into the causality of a marker. In addition, because of the often severe comorbidities, most of the biomarkers suggested in the literature are markers of diseases associated with obesity rather than markers of obesity risk. Therefore, it is important to distinguish biomarkers that may predict future obesity ("preobesity markers") from those that primarily reflect existing obesity-related comorbidities.

Among individual markers of relevance, clearly poor eating habits, such as consuming a Westernized Diet rich in saturated fat (SFA), salt, and simple sugars, while low in whole grains, fruits, and vegetables, constitute a risk for developing obesity [131]. More traditional methods/approaches have included measuring hormones such as leptin [100] or insulin [98], as high leptin may be regarded as a sign of leptin resistance, which tends to correlate with higher body weight [132], and also insulin resistance (such as measured by HOMO-IR) has been associated with a higher BMI [133], and both may owe some predictive power. Such traditional biomarkers have greatly advanced our understanding of the metabolic and hormonal regulation of obesity. However, these single markers often reflect only isolated aspects of the condition and show considerable variability across individuals, limiting their individual predictive value for obesity-related complications.

TABLE 1 | Selected biomarkers of obesity/obesity risk in body fluids.

Type of marker	Molecule(s)	Change level	Population and further details	Matrix	Ref.
Hormones	Insulin	Fasting levels have a positive correlation with BMI	Children, adolescents, and adults	Plasma Saliva	[27–30]
	Cortisol*	Lower cortisol responsiveness (lower changes amplitude through the day) is associated with being overweight	Children (cortisol measured at different times of day during 3 different days)	Saliva	[31]
	Resistin	Blood resistin levels positively correlated with increases in BMI and body composition	Adults. Blood levels of resistin are suggested to be related to human insulin resistance. The way through which this hormone may help in predicting obesity risk is through the prediction of insulin resistance	Blood	[32]
	Leptin	Higher blood levels predict leptin resistance and obesity Higher levels associated with obesity	Adults. Results obtained from blood proteomics show that leptin is highly associated with obesity. Children and adolescents	Blood Gingival crevicular fluid	[33, 34]
Inflammatory markers	Interleukin-8	Associated with higher BMI	Children and adolescents	Gingival crevicular fluid	[35]
	Interleukin 1-beta	Increased in obesity	Children and adolescents	Gingival crevicular fluid	[34]
	CRP	Increased in obesity	Children	Saliva	[30, 35]
	TNF-α	Upregulated in obesity	Adults (women) Children Different age ranges	Saliva Saliva	[34–37]
	Adiponectin	Increased in obesity	Children and adolescents	Saliva Gingival crevicular fluid	[34, 38]
	Omentin	Reduced in obesity	Adults	Blood	[39]

(Continues)

TABLE 1 | (Continued)

Type of marker	Molecule(s)	Change level	Population and further details	Matrix	Ref.
Oxidative stress markers	F-2 isoprostanes	Associated with BMI, total body fat, and abdominal subcutaneous fat Associated with abdominal obesity, with weight gain during the 5-year follow-up period, BMI, and WC	Older adults Adults	Plasma Urine	[40, 41]
	DNA/RNA breakdown products	Significant difference between participants with obesity and healthy controls Increased urinary levels associated with central obesity	Adults Adults	Plasma Urine	[42, 43]
	Elevated MDA	Serum concentrations of MDA associated with obesity Urinary MDA was significantly higher in the obesity and central obesity group than the lower or normal BMI and WC group	Adults Adults	Plasma Urine	[44, 45]
Other markers	FABP-4	Higher levels predict worse cardiometabolic profile and metabolic syndrome development	Adults	Plasma	[46]
	Complement factors B (CFAB), H (CFAH), and I (CFAI), proline-rich acidic protein 1 (PRAP1), proteins S100-A8 and S100-A9	Higher levels of chronic inflammation markers in obese persons	Adults	Plasma	[47]
	Cathepsin A	Higher levels are related to an increased risk of obesity	Adults	Plasma	[33]
	Dermapontin	Higher levels are related to an increased risk of obesity	Adults	Plasma	[33]
	C-peptide	Positive correlation with BMI	Adults	Plasma	[33]
	Advanced glycation end-products receptor (AGER)	Sign of insulin resistance related to elevated BMU	Adults	Plasma	[33]
	Insulin-like growth factor binding protein 1	Lower levels resulting in elevated BMI	Adults	Plasma	[33]
	Dickkopf-related protein 3	Higher levels resulting in elevated BMI	Adults	Plasma	[33]
	Uric acid	Higher levels indicative of a higher body fat percentage	Adolescents	Saliva Plasma	[48]
	Cystatins A, B, and SA	Increase in obesity	Children	Saliva	[49]
	Matrix-metalloproteinase 2	Positive association with BMI	Adults (women)	Saliva	[36]

Abbreviations: CRP, C-reactive protein; FABP-4, fatty acid binding protein; TNF-α, tumor necrosis factor alpha.
*In the case of cortisol, despite the referred works, care needs to be taken in considering this biomarker alone, because a meta-analysis reported lack of significant association in several studies [50].

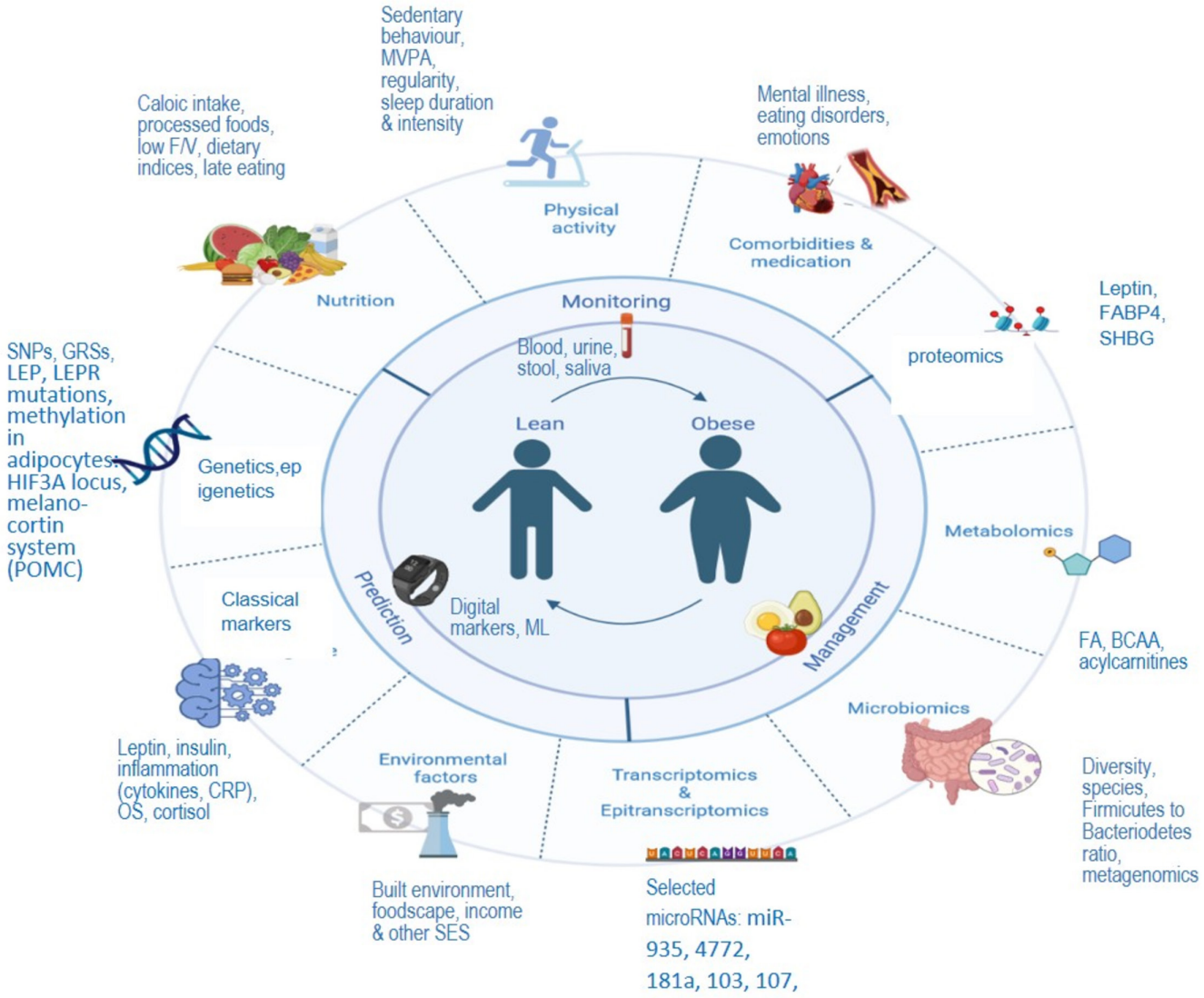

FIGURE 1 | Biomarkers of obesity. Obesity is a multifactorial condition influenced by various factors such as genetics, environment, diet, physical activity, existing health conditions, and medication usage. Recently, advancements in different scientific approaches have provided a more comprehensive understanding of the molecular mechanisms underlying this disease. Disciplines like genomics, epigenomics, metabolomics, microbiomics, transcriptomics, and epitranscriptomics have emerged, allowing researchers to identify molecular signatures associated with obesity risk. These molecular signatures, measurable and present in biological samples, have the potential to serve as biomarkers for obesity. Furthermore, in the era of new technologies, integrating digital biomarkers, artificial intelligence, and machine learning will provide additional insights. Collectively, these approaches will aid in the prediction, early detection, monitoring, and management of obesity. BCAAs = branched chain amino acids, FAAs = fatty acids; F4BP4 = ADD, F/V = fruits/vegetables, GRSs = genetic risk scores, LEP = Leptin gene, LEPR = leptin receptor gene, HIF3A = hypoxia inducible factor 3 subunit alpha, ML = machine learning, MVPA = moderate-vigorous physical activity, OS = oxidative stress, POMC = proopiomelanocortin gene, SES = socio-economic status, SHBG = sex hormone binding globulin.

A sedentary lifestyle with limited PA has also been associated with an increased risk of weight gain [134], as have insufficient sleep duration [135] and decreased psychological well-being; for instance, obesity may lead to depression, although depressive feelings could also result in emotional eating and low PA, resulting in obesity [136].

More novel approaches have been included, such as measuring alternative markers in the bloodstream, such as by multiomics approaches, combining, for example, genomics, epigenomics, proteomics, metabolomics, and transcriptomics, that have also been proposed in obesity research [137]. Within transcriptomics, microRNAs have also been targeted, as these may have some biological activity, and their expression has been related to the risk of obesity [138], highlighting about 2 dozen potentially obesity-related microRNAs. More recent studies have also focused on the gut microbiota, as its composition and diversity have been linked to obesity [139], for example, by means of traditional 16SsRNA or more advanced metagenomics or metatranscriptomics, allowing for the study not only bacterial species but also their functionality [140], going beyond the classical Firmicutes/Bacteroidetes ratio as a risk factor [13]. However, cause and consequence in relation to obesity are often only poorly understood [141, 142]. The use of saliva has also gained interest, because of the noninvasive

TABLE 2 | Overview of promising potential risk factors related to obesity and suitable as markers of risk prediction including selected examples.

Domain	Class	Requirements	Examples	Advantages/disadvantages, challenges	Ref.
General/classical circulating markers, plasma or urine based, and emerging ones	Markers of inflammation/ oxidative stress	Sampling of plasma, urine, saliva	High circulating levels of TNF-α, CRP, IL-6 Low levels of circulating adiponectin	Requires expensive analysis, low storage half-time of samples, inflammation/ox. stress also a consequence of obesity	[51]
	Hormones	Sampling of plasma, urine, saliva	Hormones such as leptin Inflammatory markers such as cytokines Oxidative stress, such as F-2 isoprostanes	All fairly established and accepted marker Can be elevated by many other reasons (diseases) This could be the consequence of obesity rather than the cause	[30, 33, 52]
Omics-and multiomics	Individual gene mutations	Whole blood collection	LEP, LEPR	High correlation with obesity, but not very common	[53]
	Genetics: risk scores based on variants	Whole blood collection, plasma, buccal cells	Genetic risk score	Often low correlation to obesity, even when combining several genes -The combination of many genes required, still relatively expensive	
	Proteomics	Sampling of plasma, saliva	Leptin, fatty acid-binding protein 4 (FABP4), and sex hormone-binding globulin (SHBG)	Might help in the early detection of obesity Gender difference (women leptin levels are higher in women than in men)	[52, 54]
	Metabolomics	Sampling of plasma, urine, saliva	Amino acids (BCAAs, tyrosine, glutamic acid...)	Direct correlation with the increase in fat mass, metabolic syndrome, waist circumference, ability to be used as biomarkers for obesity Remains a wide range of variability, can be difficult to interpret	[55]
	Transcriptomics, including coding and noncoding RNA (microRNA ...)	Sampling of plasma, saliva	Panels of RNAs associated with obesity risk merged with demographic and clinical data	Can be assessed in noninvasive blood samples. Molecular diagnostic assays are applicable to clinical routines and are cost-effective. Ongoing research topic.	[56, 57]
	Epigenetics: histone modification, methylation	Sampling of plasma, saliva	Methylation in adipocytes of the HIF3A locus 147, as well as POMC and the melanocortin system, and the PGC1 encoding PPARGC1A	Can be assessed in either routine clinical (blood) or noninvasive (saliva) samples. Cause or consequence not known. Ongoing research topic.	

(Continues)

TABLE 2 | (Continued)

Domain	Class	Requirements	Examples	Advantages/disadvantages, challenges	Ref.
	Gut microbiota: 16S rRNA gene based, meta-genomics and transcriptomics, Metabolomics	Stool collection	Increased gut microbial short-chain fatty acid production; high fat diet increases secondary bile acids, microbial *N*-acyl amides capable of interacting with G-protein-coupled receptors (GPCRs), reduced tryptophan-based metabolites in individuals with obesity, increased metabolic endotoxemia in obesity.	Cause and consequence of specific microbes are often not understood.	[58, 59]
Nutritional status	Nutrient intake	Questionnaires such as FFQ, multiple 24-h recalls, blood/urine samples	Energy intake Low fiber intake High sugar intake Micronutrient aspects, e.g., low vitamin C intake	Alone, i.e., without PA, low correlation with obesity. Alone insufficient correlation with obesity. Often, poor correlation to obesity-related outcomes	[60–63]
	Indices, overall patterns	Questionnaires such as FFQ, multiple 24 h recalls, food records	Overall dietary pattern (nutrients and food groups)/indices -Low MD-score -Low DASH-score -High intake of processed foods -Late and high-caloric meals	Overall patterns rather more important than individual aspects, strong interplay with PA, long questionnaires required (FFQ, multiple 24-h recalls).	[64, 65]
24-h movement behavior	Physical behavior	Accelerometer	Time spent in MVPA Sedentary time accumulation Light PA Regularity in PA volume Intensity gradient	All not easy to determine accurately (research-grade accelerometer required) Some of these metrics can be obtained from smartwatches and activity trackers.	[66–70]
	Sleep patterns	Accelerometer	Low amount of sleeping time Irregular sleeping patterns Sleep efficiency	The causal relationship still needs to be investigated using the appropriate study design. The underlying mechanisms most probably involve perturbations in eating habits.	[71–73]

(Continues)

TABLE 2 | (Continued)

Domain	Class	Requirements	Examples	Advantages/disadvantages, challenges	Ref.
(Built) environmental aspects and socio-demographics	Build environment	Questionnaires, in-depth interviews, direct observations, place of residence data	Foodscape, green areas -High density of fast-food restaurants Few green areas	Complex data and effects may differ between urban and rural places of living. Unclear if the density of absolute counts is more important. Risk factors on a population level but for individual poor prediction, hesitation of a person to reveal such personal data, country-dependent.	[74, 75]
	Socio-demographics	Surveys, interviews, direct observations	Low income Low education	Direct and positive relationship between low income and low education in relations with the access of unhealthy food products.	[76–84]
Mental health	Emotions	Questionnaires	Emotional eater questionnaire: 3 different dimensions (disinhibition, type of-food, and guilt), explaining 60% of total emotional variance	Very often closely linked to obesity, where emotion and stress influence eating behavior and eating behavior emotion and stress.	[85, 86]
	Perceived stress	Questionnaires (perceived stress questionnaire PSQ)	Normal version: 30 items (7 subscales: harassment, overload, irritability, lack of joy, fatigue, worries, tension) and in the short version: 20 items (4 subscales: worries, tension, joy, and demands)	Very often interlinked with emotion, eating behavior, and stigma.	[87, 88]
	Depression	Questionnaires (Brief Symptom Inventory (BSI), Mini Symptom Checklist)	E.g., BSI: 53 items covering nine symptom dimensions: somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism; and three global indices of distress: Global Severity Index, Positive Symptom Distress Index, and Positive Symptom Total.	Can be used in research and treatment. Quick and easy to administer. Covers multiple entities of mental disorders that can be related to obesity (anxiety, depression, somatization disorders). Norm values from general populations available.	[89, 90]

(Continues)

TABLE 2 | (Continued)

Domain	Class	Requirements	Examples	Advantages/disadvantages, challenges	Ref.
Combined multimodal and multicomponent markers	Nutrition and general/ classical markers	Blood, saliva, questionnaires	High-glucose and high-fat meals and inflammation.	Potential for higher correlation when combined; more data and statistics needed.	[91]
	Nutrition and PA	Questionnaires	Odds of losing weight much higher for patients changing both PA and diet (17.5) vs. only PA (5.2) or only diet (7.2).	Advantage of not needing blood samples/tissues for risk assessment.	[92]
	Nutrition, built environment and genetics	Whole blood, geolocation of home addresses (ArcGIS 10, ESRI)	Combining dietary exposure to fast-food outlets and genetic risk factors: increased RR of 2.7 vs. 1.73 and 1.58 vs. genetic and dietary exposure alone	Demonstrating the usefulness on including data on food outlets, challenging to collect geolocation-data and neglecting people's work-location.	[93]
	Nutrition, PA, emotions	Questionnaires	Combining dietary aspects, negative attitudes/emotions, and social influences and PA. Regression analysis combining all factors explained about 56% of BMI variance	Emphasizing important interactions between diet, PA, and emotions. Difference to more simple models with fewer components not studied. Relative simple assessment of components (only questionnaires).	[94]
	Nutrition, PA, genetics, epigenetics	Whole blood, urine, questionnaires	Risk score including genetics, epigenetics and lifestyle factors, developed with 1600 participants, based on ML, incorporating 21SNPs, 230 DMSs in genes such as CPT1A, ABCG1, SLC7A11, RNF145, and SREBF1, plus 26 dietary factors: 70% overall accuracy in risk prediction	High predictability shown, though challenging to compile all data.	[95]
	Nutrition, PA, genetics, SES	Questionnaires, whole blood	Ranking predictor variables of obesity across different domains in children, covering ca. 200 variables from several domains, including the following: age, genetics, lifestyle aspects such as PA and diet, and SES. Top-ranked 30 predictors: familiarity with nutrition status perception, the relation of total energy intake minus total energy expenditure, BMI of parents, meals of mother, IPAC (individual PA coefficient), and GRS (genetic risk score).	A combination of factors for risk prediction was not attempted. Much data collection was needed.	[96]

TABLE 3 | Overview of obesity-related markers by class, predictive value, and supporting literature.

Class of marker	Specific markers and prominent examples	Predictive/reactive (causal vs. consequence)	Ref.
Individual traditional metabolic markers	-Lipid profile, e.g., TGs, LDL-c, -Hormones such as insulin and leptin	-Mostly reactive -Both predictive and reactive	[97–101]
Inflammatory markers (IL-6, TNF-α)	-CRP, acute phase proteins -Cytokine profiles -Markers of oxidative stress	-Both predictive and reactive. -Both predictive and reactive. -Both predictive and reactive.	[102–105]
Genetic markers	-SNPs, polygenic risk scores	Predictive (causal).	[106, 107]
Epigenetic markers	-DNA methylation -Histone modification -microRNA presence	-Both predictive and reactive.	[108–110]
Microbiota composition	-GM diversity -Firmicutes/bacteroidetes ratio -Presence of specific strains, e.g., *Akkermansia muciniphila*	-Both predictive and reactive. -Both predictive and reactive. -Both predictive and reactive.	[111–116]
Dietary patterns and indices	-Indices such as DII -Processed food intake -Regularity of food intake (chrononutrition aspects)	Mostly predictive (causal).	[117–120]
Physical behaviors	-METs -TV time	Predictive (causal).	[121–123]
Environmental aspects	-Greenness of living area -Fast food restaurant density	-Mostly predictive (causal). -Mostly predictive (causal).	[124–128]
Mental health	-Depression, stress	-Both predictive and reactive.	[129, 130]

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DII, Dietary Inflammatory Index; IL-6, interleukin-6; LDL-c, low-density lipoprotein cholesterol; METs, metabolic equivalents; TGs, triglycerides; TNF-α, tumor necrosis factor-alpha.

nature of the collection, with some studies reporting variations in saliva composition that can relate to obesity [49, 143, 144].

As obesity is a multifactorial and biologically heterogeneous condition influenced by genetic, metabolic, inflammatory, and environmental factors, there is growing recognition that integrated approaches, combining data from genomics, transcriptomics, metabolomics, proteomics, and the gut microbiome, may offer a more comprehensive representation of obesity's complex pathophysiology. Here, one may distinguish multicomponent markers composed of several individual biomarkers reflecting interconnected biological pathways (e.g., metabolic, inflammatory, and hormonal) [145] and multimodal ones, derived from the integration of various data modalities, such as anthropometric, biochemical, genetic, imaging, or clinical data, that together capture multiple dimensions of obesity-related risk [146]. Such marker search has frequently been supported by machine learning (ML) and artificial intelligence (AI) [147, 148]. However, multimodal and multicomponent markers are clearly a new emerging trend in biomarker research [149].

Incorporating these approaches may provide a more comprehensive and biologically informed assessment of obesity and its complications than reliance on single markers alone. For example, it has been acknowledged that measuring different circulating biomarkers together, such as tumor necrosis factor-alpha (TNF-α) and insulin, improves the prediction of coronary artery disease due to a certain independency of both markers [150] and may thus constitute a multicomponent marker with better predictability than a single marker. Likewise, intervention studies have shown that combining, for example, PA and dietary measures can, in the long term, more efficiently reduce body weight than diet alone [151], and thus it can be assumed that combining information across several domains also allows for a better multimodal predictor than merely assessing one aspect alone. Another practical example is the definition of metabolic syndrome (MetS), which by itself is a multicomponent approach to define the risk of several associated comorbidities such as diabetes, as it includes anthropometric measures as an indication for obesity and blood lipids for disturbed lipid homeostasis [152]. Such multiple predictors have also been termed multidimensional in some investigations, such as when combining medical conditions and several biomarkers to predict the risk of various health conditions [153], and also multidomain [154] or multidisciplinary [155]; in other studies, thus, there is no clear and unanimously accepted definition for such multiple-biomarker approaches.

In this position paper, we strive to emphasize which markers and combinations thereof have been proposed to be related to obesity that could serve as promising risk markers for developing obesity, with a particular focus on novel approaches and multicomponent and multimodal combinations thereof.

2 | Individual Existing and Emerging Biomarkers

2.1 | Hormonal Markers

Obesity is currently recognized as a systemic chronic disease, where excessive accumulation of adiposity leads to adverse health effects. The underlying biological mechanisms of this disease are not totally understood, and different biological samples (e.g., blood, saliva, and urine) have been used in an attempt to better comprehension, as well as for searching biomarkers of risk and/or disease progression [30, 33, 156]. Of note, because visceral body fat and other anthropometric measures such as BMI have been rather used to define BMI, these measures will not be considered here.

2.1.1 | Insulin

While hormones such as leptin and insulin are elevated in obesity, evidence for their role as predictive markers has also been emphasized, as insulin resistance may precede and contribute to weight gain in individuals [157]. Similar findings have been reported for leptin resistance [158]. Nevertheless, using bioinformatics and predictive models, a causal relationship between some markers in the bloodstream and increased risk of developing elevated BMI has been proposed. In addition to insulin and leptin, several hormones, including insulin-like growth factor (IGF), ghrelin, and adiponectin, have been studied as potential predictors of obesity [33, 159].

Among the different body fluids, blood analysis has been long accepted as the best way to assess what is happening "clinically inside the body." Common blood analyses, such as fasting blood glucose (FBG), triglycerides (TGs), and cholesterol (HDL-c and LDL-c), provide general information on cardiometabolic health. In contrast, measuring more specific biomarkers, particularly hormones, can help assess systemic dysfunctions associated with obesity and, in some cases, may serve as potential preobesity markers [160–162].

In a review by Nimptsch et al. [52], it was concluded that the molecular pathways most clearly linked to obesity risk are the insulin/IGF axis and chronic low-grade inflammation. According to the authors, this is explained by obesity (or even overweight) being frequently linked with insulin resistance and hyperinsulinemia, resulting in higher levels of free IGF-1 due to a downregulation of IGF binding proteins and an upregulation of IGF-1 hepatic synthesis. A positive relationship was observed between the concentrations of molecules indicative of the function of this pathway and BMI, namely, fasting insulin and C-peptide, the latter resulting from the cleavage of proinsulin, indicating endogenous insulin secretion. Moreover, increased levels of fasting insulin and C-peptide have also been related to other conditions that have been frequently associated with obesity and comorbidities, such as CVDs, diabetes, and some types of cancer, highlighting their potential as markers of obesity severity [163]. Therefore, insulin resistance, characterized by reduced responsiveness of cells to circulating insulin, is a classical hallmark of obesity and related metabolic dysfunction [164], and longitudinal studies support the role of insulin also as a biomarker of developing obesity [98, 99, 165].

Consequently, further biomarkers indicative of insulin resistance, such as fasting insulin levels or the homeostasis model assessment of insulin resistance (HOMA-IR), comprising measurements of FBG and insulin, can provide valuable insights into the body's ability to regulate blood sugar levels [166]. High levels of fasting insulin or insulin resistance are often observed in individuals with poor dietary habits, including excessive consumption of sugar-sweetened beverages, refined carbohydrates, and processed foods [167]. Insulin resistance promotes weight gain by impairing glucose uptake in muscle and adipose tissue, leading to elevated blood sugar levels and increased fat storage [168, 169]. A study reported that, in participants who gained ≥ 50% of body weight during adulthood, HOMA-IR was significant, that is, 3.22 (95% CI = 2.76–3.77) times higher than in persons who maintained weight, and total body fat mediated this association by 8.1%, visceral fat by 32.0%, and liver fat by 22.5% [170], also emphasizing the important role of visceral body fat.

2.1.2 | Leptin

In addition to insulin, leptin, a hormone produced by adipose tissue to signal satiety, has been related to the risk of developing obesity [171]. Similar to insulin, the problem (except for very few people) is not an absolute lack of leptin but rather leptin resistance [171]. Leptin is produced in proportion to the TG content of adipocytes and is involved in the control of energy balance by signaling the energy stores to the central nervous system. Whereas leptin increases satiety, when these high levels are continuous, the body stops responding in terms of decreasing appetite and/or increasing energy expenditure [172]. Hypothalamic endoplasmic reticulum (ER) stress, as well as inflammation, which are both common in obesity, impair leptin action [173]. Leptin action may also be affected by mutations in the leptin receptor gene, as well as in genes related to molecules from downstream signaling [174]. Whether leptin resistance is a cause or consequence of obesity can be debatable [175], but higher levels of leptin are observed in persons with overweight and obesity [33]. In this regard, a study showed a significant positive correlation between leptin levels and body fat mass ($p < 0.001$, $r = 0.521$) [176]. In addition, this study showed that mean leptin concentrations in participants with obesity (BMI ≥ 30 kg/m^2) was significantly higher than in participants without obesity (BMI < 30 kg/m^2) (28.25 ± 4.35 vs. 23.14 ± 4.07 pg/mL) [176]. Additional evidence suggests that leptin resistance may contribute to the development of obesity by impairing satiety signaling and promoting energy imbalance in the long term [132, 177, 178]. Conversely, increased adiposity itself can exacerbate leptin resistance, for example, through chronic inflammation and ER stress, indicating a bidirectional relationship between leptin dysfunction and obesity.

2.2 | Markers of Inflammation and Oxidative Stress

2.2.1 | Inflammatory Biomarkers

Additional hallmarks related to obesity are inflammation and oxidative stress (OS) [179]. Chronic low-grade inflammation is a key feature of obesity and its associated metabolic complications [180, 181]. A high amount of adipose tissue has also been related

to hypoxia in these tissues, which could likewise trigger inflammation [182]. Biomarkers of inflammation, such as acute phase proteins, including C-reactive protein (CRP) and cytokines such as interleukin-6 (IL-6) and TNF-α, can indicate the presence of systemic inflammation driven by dietary factors [183]. Diets high in processed foods, trans-fats, and refined sugars promote inflammation, contributing to insulin resistance, endothelial dysfunction, and atherosclerosis related to overweight/obesity [184–187].

Elevated levels of inflammatory markers are associated with existing obesity [188, 189], but their role as predictors of future obesity remains to be more clearly established. For example, one study found that after adjusting for age and sex, there was a significant association between CRP and BMI ($R^2 = 11.8\%, \beta = 0.158$) and IL-6 and VAT ($R^2 = 12.4\%, \beta = 0.012$) [190]. The same study showed mild and strong correlations between anthropometric measurements or abdominal adiposity and cytokine concentrations (e.g., CRP vs. BMI: $\rho = 0.69$) [190]. However, longitudinal studies have also shown the value of cytokines as predictors of developing obesity [37, 191, 192]. Clearly, higher levels of adipose tissue can drive inflammation, and especially IL-6 and TNF-α have been regarded as markers related to the risk of obesity, as such markers were already elevated in persons with normal weight, though already higher proportions of body fat [193].

By contrast, high levels of adiponectin, secreted by adipose tissues [194], have rather an anti-inflammatory character and higher levels have been related to decreased risk of obesity [195]. However, also adiponectin may likely rather be an indicator of associated complications of obesity and not a reliable marker of developing obesity [196]. However, recent evidence has also revealed a decrease in pro-resolving mediators such as resolvins, lipoxins, and protectins in persons with obesity, which would contribute to chronic inflammation [197].

2.2.2 | Biomarkers of OS

OS may be related to inflammation, but could also originate independently, further triggering inflammation [198]. OS, resulting from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense, plays a significant role in the pathophysiology of obesity and related metabolic disorders [199]. Markers of OS, including lipid peroxidation products, protein carbonyls, and DNA oxidation products, serve as indicators of cellular damage and oxidative burden [200]. In a recent meta-analysis of 22 studies with almost 4000 participants, antioxidant capacity was reduced in persons having obesity (SMD = −0.86,95% CI = −1.38 to −0.34), while malondialdehyde (MDA) and OS index and status were significantly increased. Recent research has also shown that measuring a panel of enzymatic antioxidants, namely, catalase (CAT), glutathione reductase (GRd), glutathione peroxidase (GPx), superoxide dismutase (SOD), and mitochondrial SOD (MnSOD), are useful for monitoring the progression and/or reversal of obesity [51]. In the context of obesity, several factors contribute to increased OS, which likely enabling OS markers to also further aggravate obesity [201] and thus could act as a marker for increased risk:

i. Adipose tissue dysfunction in obesity is characterized by adipocyte hypertrophy, inflammation, and altered adipokine secretion [202]. Enlarged adipocytes undergo hypoxia and release pro-inflammatory cytokines, promoting OS and impairing insulin signaling [203];

ii. In obesity, mitochondrial dysfunction is commonly observed in adipose tissue, skeletal muscle, and liver, contributing to impaired oxidative metabolism and insulin resistance [204]. Dysfunctional mitochondria generate excessive ROS, exacerbating OS and cellular damage [204].

iii. Chronic low-grade inflammation, characteristic of obesity, amplifies OS through the activation of immune cells and the release of pro-inflammatory mediators [189]. Inflammatory cytokines stimulate ROS production and inhibit antioxidant defenses, creating a pro-oxidant environment conducive to cellular damage and insulin resistance [205].

iv. Dietary factors, including consuming high amounts of fats, simple sugars, and processed foods, can promote OS by increasing ROS production and reducing antioxidant capacity [206]. Monitoring biomarkers of OS, such as markers of lipid peroxidation (e.g., MDA), protein oxidation (e.g., protein carbonyls), and antioxidant enzyme activity (e.g., SOD and CAT), can provide insights into the oxidative status of individuals and their susceptibility to obesity and related complications [207–209].

In addition to plasma/serum, urinary markers related to obesity have also been proposed and may, in part, be easier to detect due to a less complex matrix, including some of the markers mentioned above of OS, namely, F-2-isoprostanes, MDA, and DNA/RNA breakdown products [41, 210]. For example, urinary 8-hydroxyguanosine was pointed out as a reliable indicator of OS, correlating with insulin sensitivity in children with obesity [211]. In general, urinary biomarkers of chronic inflammation and endothelial dysfunction have been emphasized for their value in obesity assessment [156, 212, 213]. Taken together, OS could be both a consequence of obesity [214] or preceding it. In normal-weight persons, it was emphasized that elevated OS can be a causal risk factor for developing obesity [199].

2.3 | Other Blood and Salivary Biomarkers

In addition to hormone, inflammatory, and OS markers, other markers in the bloodstream, such as free fatty acids (FFA), have also been proposed as markers related to obesity risk, in part due to their increased levels being related to insulin resistance [215]. As such, they could play a role as a predictive marker. However, the increased plasmatic levels of FFA in obesity are due to a higher release from the enlarged adipose tissue and thus also a consequence of obesity. These individuals show, together with lower clearance levels, inhibited insulin antilipolytic action [215]. Therefore, and for altered blood lipids in general, they could be both cause and consequence [216, 217]. In one study, after adjusting for various covariables, elevated circulating TGs were associated with a 54% increased OR for the risk of ectopic fat and considered as a risk for developing obesity [218]. Of note, TGs may also be elevated without having obesity, such as in the metabolic unhealthy nonobesity phenotype [219].

Different studies have proposed and enlarged the list of molecules that may help identify individuals at risk of obesity, or at least that can help in better understanding obesity and its consequences. Especially adipokines, including resistin [32] and omentin [220], among others, have been observed to be dysregulated in obesity. Resistin was initially referred to as secreted by adipocytes, although significant levels of resistin are also found in mononuclear leukocytes, spleen, and bone marrow cells. The increased levels of this protein are related to insulin resistance, atherosclerosis, nonalcoholic fatty liver, and CVDs and have been suggested as a good indicator of MetS [32].

Contrarily, omentin-1 levels in the blood circulation have been inversely related to obesity. This protein, which appears to be an anti-inflammatory adipokine in humans, enhances the insulin-induced glucose uptake in human visceral and subcutaneous adipocytes and reduces the activation of inflammation factors such as CRP, TNF-α, and NF-κB [221]. Another adipokine decreased in obesity is adiponectin. In rodents, it was observed that administration of this protein improves insulin sensitivity, whereas in animals deficient in this adipokine, insulin resistance develops when the diet is rich in fat [220]. However, more research is needed to differentiate whether these additional adipokines are better suited as early predictors of obesity or are rather consequences.

In addition to blood, saliva has gained interest as a noninvasive alternative source of biomarkers for different pathological and physiological conditions [222]. This fluid contains molecules that are synthesized by salivary glands (e.g., amylase, type S cystatins, etc.) and blood-borne molecules that pass to saliva through the glands or directly through the gingival crevicular fluid. However, the number of studies looking for salivary biomarkers related to obesity is much lower than in blood. Even so, variations in saliva composition have been associated with obesity [143, 223]. However, more research is needed to clarify the fundamental differences that saliva from individuals with overweight and/or obesity presents compared to normal-weight individuals. Salivary uric acid levels were suggested as important markers of body fat accumulation in adolescents [48]. Salivary levels of salivary oxidative biomarkers, such as ferric-reducing antioxidant power, sulfhydryl groups, and lipid peroxidation, were increased in young adults with obesity, which may indicate the regulation of various processes in the adipose tissue [224]. The salivary level of CRP was also referred to as a potential noninvasive biomarker for obesity and risk of developing metabolic dysregulation in children [225] and adolescents [226], as well as salivary levels of hormones such as leptin [227] and insulin [226]. The increased levels of salivary IL-6 [228] and other inflammatory markers [229] were related to obesity by different authors. Taken together, these observations suggest that saliva may be a promising fluid for gaining an understanding of this condition. Moreover, changes in saliva due to obesity reduction through bariatric surgery were observed [143, 144]. Together with diet and exercise, although the literature on humans is scarce, studies using animal models also reinforce the potential of this fluid to reflect metabolic changes [143, 223, 230].

The potential of saliva as a source of obesity biomarkers may be particularly important in more vulnerable groups, such as children and older adults, where drawing blood samples would impose additional stress. Most of the salivary molecules suggested as potential biomarkers in the context of obesity are molecules passing to saliva from the bloodstream, with a lower consensus about gland-produced salivary proteins, such as amylase. This last protein was suggested as a potential predictor of obesity susceptibility in animal models [231] and observed to be present in higher levels in women with morbid obesity [143], although the literature shows no consensus about the levels of this enzyme in saliva, with some studies observing lower levels in individuals with obesity [232]. However, such digestive enzymes may plausibly mechanistically be linked to causes of obesity [143, 232, 233].

Despite not being specific to obesity or obesity-related metabolic alterations, salivary cortisol has also been evaluated in this context. The interrelation between stress and obesity (particularly abdominal obesity) is accepted, although it is not observed in all individuals, and the cause and consequence may remain unclear. This complexity is suggested to be due to interindividual variation in glucocorticoid sensitivity, which leads to different vulnerabilities in different individuals to stressor agents [234]. The effect of stress in obesity development can be tentatively and partly explained by the increases in blood glucose that accompany a rise in cortisol release, which occurring repeatedly and may result in insulin resistance [235]. Despite this, some authors suggest that it is not just the cortisol levels at one point that are affected by obesity, but rather the secretion rhythm of cortisol. Children with obesity were observed to have lower salivary cortisol levels in the morning (8:00 a.m., when it peaks) and higher salivary cortisol levels at night (11:00 p.m., when it is lowest), compared to healthy weight controls [31]. In this study, a diurnal cortisol slope (i.e., the decline in cortisol over the day) was almost half in children with obesity than in controls [31]. In children who were vulnerable, decreased release of cortisol in the morning was pointed out as a predictor of the likelihood of being overweight, with this last group being observed with approximately 20% lower salivary cortisol levels in the morning than in children with normal weight [236]. In the opposite direction, some studies reported that increases in salivary cortisol awakening response are associated with abdominal obesity in male adults (though not in females) [237, 238]. In this study, increases of approximately 50% in the saliva concentration between awakening and 30 min after were observed for males with obesity, whereas males who were lean only registered increases of approximately 20%. This lack of consensus among different studies may be related to the effect of age and gender on this relationship or even due to the methodological differences among studies. Nevertheless, studies agree on the existence of a relationship between hypothalamus-pituitary–adrenal axis activity and obesity [50], with saliva being an excellent source for cortisol assessment and, thus, an interesting biomarker in obesity studies. Therefore, because of the relation of cortisol with diurnal rhythm and downstream metabolic changes, it is plausible that it has some predictive value and does not only constitute a marker of present obesity [239].

In summary, the most traditional individual markers in this domain, including insulin (resistance) and leptin, are considered to be the most specific markers related to obesity risk, as many other markers, such as inflammation and OS-related ones, are also elevated in many other NCDs and infections (Table 1)

[132, 208]. The role of cortisol, as also assessed, for example, in saliva, deserves further investigation. While many markers are also elevated and driven by present obesity, some do also have a certain prognostic value as markers preceding obesity.

3 | Multiomics, Epigenetics, and Gut Microbiome

Whereas initially, biomarker search resulted from the quantification of individual molecules, in the last decades, the "omics" revolution has accelerated biomarker identification, which has also been applied to obesity [240]. Through various omics approaches, including genomics to identify genetic variants, epigenetics to characterize reversible DNA modifications, transcriptomics and epitranscriptomics to analyze RNA expression and its modifications, proteomics to identify and quantify proteins, metabolomics to study metabolites, and microbiomics to investigate microorganisms (especially in the gut), a more comprehensive understanding of the molecular and cellular mechanisms underlying obesity and its complications can be obtained [241].

3.1 | Genetic Variants, Gene Mutations, and Specific Genetic Risk Scores

The genetic component of obesity is significant, with heritability estimates ranging between 40% and 70% [242, 243]. This genetic predisposition to obesity can be categorized into monogenic obesity, polygenic obesity, and syndromic obesity, each involving different genes and genetic mechanisms [242]. As the genes are stable during the lifetime, any association of genes and obesity would be truly predictive. For this reason, a number of genetic risk scores have been developed.

Monogenic obesity is rare and results from mutations in a single gene or chromosomal deletions. It typically occurs early in life, is severe, and is inherited in a Mendelian pattern. The most well-studied pathway involved in monogenic obesity is the leptin-melanocortin pathway, which plays a crucial role in regulating energy balance and appetite (see Section 2). Studies [242] have reported that single gene defects account for approx. half of the early onset obesity. While single gene defects within the leptin–melanocortin pathway are well-established causes of monogenic obesity, their prevalence among children with obesity is low. Most studies report a diagnostic yield of approximately 3%–7% [244], with higher rates (~13%) [245] observed in individuals presenting with a strong clinical phenotype, such as very early-onset obesity and pronounced hyperphagia. Therefore, monogenic obesity represents a rare but important subset of obesity cases rather than a common cause of early-onset obesity. Key genes implicated in monogenic obesity include the following:

i. LEP (Leptin): Mutations in this gene can lead to a lack of leptin, which signals the brain to reduce appetite and increase energy expenditure [246].

ii. LEPR (Leptin Receptor): Mutations in this gene can disrupt the ability of leptin to bind to its receptor, leading to unregulated appetite [247].

iii. POMC (Proopiomelanocortin): Mutations in this gene can affect the production of several peptides, including those that stimulate the melanocortin 4 receptor (MC4R), influencing appetite and energy homeostasis [248].

iv. MC4R (Melanocortin 4 Receptor): MC4R is responsible for binding melanocortin peptides and the AGRP gene to mediate appetite behavior and autonomic output. Mutations in MC4R are among the most common causes of monogenic obesity, affecting the receptor's ability to regulate energy balance [249].

Other important genes identified for monogenic obesity are proprotein convertase 1 (PCSK1), single-minded homolog 1 (SIM1), neurotrophic receptor tyrosine kinase 2 (NTRK2), brain-derived neurotrophic factor (BDNF), SH2B1, melanocortin 2 receptor accessory protein 2 (MRAP2), kinase suppressor of ras 2 (KSR2), and adenylate cyclase 3 (ADCY3) [242].

Although heritability estimates suggest that approximately 40%–70% of interindividual variation in obesity is attributable to genetic factors, this does not correspond to distinct "genetic forms" of obesity. Polygenic obesity reflects the cumulative effect of multiple genetic variants that confer susceptibility rather than directly causing obesity. Importantly, polygenic risk scores cannot be used to classify individuals as having a genetic form of obesity, as their phenotypic expression depends strongly on interactions with environmental and lifestyle factors [250]. Genome-wide association studies (GWAS) have identified numerous genetic variants (>1100 loci) associated with BMI and obesity. The fat mass and obesity-associated (FTO) gene was one of the first and is among the most significant genes associated with polygenic obesity [251]. Variants in the FTO gene and others, such as MC4R and TMEM18, contribute to obesity risk by influencing appetite, metabolism, and energy expenditure [242, 252].

Syndromic obesity is characterized by obesity along with other phenotypes, such as intellectual disability or dysmorphic features. It can result from mutations in a single gene or chromosomal abnormalities affecting multiple genes. Examples include Bardet–Biedl syndrome, which is caused by mutations in multiple genes, leading to symptoms including obesity, retinal degeneration, and kidney abnormalities [253], and Prader–Willi syndrome, often resulting from deletions on chromosome 15, which leads to uncontrolled appetite and obesity, among other features [253].

Genetic Risk Scores (GRS) for obesity have been established, which aim to summarize the cumulative effect of various genetic variants on an individual's risk of developing obesity. Recently, GRS developed from GWASs have predicted BMI and obesity risk beyond demographic and geographic information [254]. For example, one recent study included >2 million variants to quantify the susceptibility to obesity in >300,000 individuals, explaining 8.4% of the variation in BMI [255]. Another published GRS showed a prediction of only around 1.5% [254], and in another study, subjects with seven risk alleles showed an increase of 0.93 kg/m^2 [256]. Therefore, the predictive power of these scores is still limited and needs to be further evaluated before using them in clinical risk assessments [242], although surely the genetic component should not be overlooked when aiming to predict obesity risk.

3.2 | Epigenetics

Epigenetics has evolved since Conrad Waddington defined it as "the science that analyses the link between genes and the events that give birth to the phenotype" [257]. Now, it is considered a dynamic interplay between the environment and DNA modifications, which do not alter the underlying DNA sequence maintained through cell division. These modifications particularly include DNA methylation and structural factors such as histone modifications that contain additional information about the underlying DNA sequence. Due to adaptations with time, epigenetics may either precede obesity or may be a consequence. A recent study has shown that obesity leaves a kind of epigenetic imprint or memory even after weight loss [258], reflective of epigenetics being able to constitute markers following obesity. However, many environmental factors that have been associated with the development of obesity, such as sedentary lifestyles and high-fat diets, all leave a long-lasting epigenomics imprint [259]. A number of studies have examined epigenetic mechanisms in obesity, although comorbidities such as T2D complicate the attribution of these changes to one disease or the other. Indeed, many epigenetic changes involving, for example, FTO, adenylate cyclase 5 (ADCY5), or peroxisome proliferator-associated receptor gamma (PPARG), are common in obesity and T2D [260] and also are often related to an inflammatory phenotype [261].

The data available shows an interplay between monocyte- and macrophage-induced inflammation of adipose tissues that leads to adipocytes secreting inflammatory molecules such as chemo- and cytokines [262]. As such, a lot of effort has been put into understanding how epigenetic changes in both adipocytes and immune cells are associated with inflammation in adipose tissues. Among the epigenetic regulators, DNA methylation, histone modifications, and microRNAs have all been shown to regulate adipose tissue inflammation [263]. CpG dinucleotide methylation was associated with altered transcriptional patterns of both mRNA and smaller noncoding miRNAs as adipocytes develop and differentiate. At the gene level, differential methylation in adipocytes of the HIF3A locus [264], as well as POMC and the melanocortin system and the PGC1 encoding *PPARGC1A*, was observed and suggested that epigenetically dysregulated mitochondrial processes may play a role in the development of obesity [265]. These changes resulted in changes not only in insulin sensitivity but also in the overall adipose tissue lipid metabolism that was thought to induce dysfunction of pancreatic β-cells and chronic low-grade inflammation (reviewed in [263]).

Interestingly, in Goto-Kakizaki rats that had T2D but did not have obesity, the peripheral inflammation was absent, hinting that inflammation was associated with obesity rather than concomitant T2D [266]. At the histone level, there is a clear association between obesity and H3K4 trimethylation (a marker of active euchromatin) at the IL-6 and TNF-α-*promoters* [267], and this has also been associated with changes in insulin signaling [263]. Furthermore, in agreement with the inflammation-theory of obesity and T2D, the cytokine CCL2, which is linked to TNF-α, IL-6, and IL-1β, is influenced by more than 20 miRNAs [263] (see also the following section). Despite these promising and insightful findings, for many epigenetic markers of signatures, more research is needed with respect to their predictability of developing obesity.

3.3 | (Epi)transcriptomics

Transcriptomics sheds light on RNA molecules, including protein-coding (messenger RNAs [mRNAs]) and noncoding transcripts (noncoding RNAs [ncRNAs]). NcRNAs are classified into small (< 200 nucleotides) and long ncRNAs (lncRNAs; > 200 nucleotides). In both classes, RNAs are further classified according to their role, cellular localization, and structure [268]. Because ncRNAs can regulate gene expression and are dynamically regulated in disease states, the characterization of changes in RNA profiles by transcriptomics analysis can highlight regulatory mechanisms underlying the development and progression of obesity. This may provide important new insights into the mechanisms underlying obesity pathophysiology, including malfunctions in adipose tissue, metabolic abnormalities, and systemic inflammation [269].

Recent technological advances have accelerated the study of the transcriptome, enabling the identification of sometimes weakly expressed RNA molecules implicated in various diseases, including obesity. Cutting-edge techniques have helped to shed light on the roles of different RNA species and have facilitated the discovery of new targets for prediction and therapy. Among these methods are microarrays, sequencing, quantitative RT-PCR, and fluorescence in situ hybridization [270]. For example, Milagro et al. utilized high-throughput sequencing to investigate the entire microRNA (miRNA) transcriptome and identify miRNA biomarkers of weight loss [271]. Their study identified several prognostic biomarkers, including miR-935 and miR-4772, in 10 women with obesity undergoing weight loss trials with energy-restricted treatments (Pearson correlation coefficients were 0.72 and 0.77, respectively) [271]. Indeed, miRNAs, including miRNA-181a, miR-103, and miR-107, have been shown to regulate adipogenesis [272–274].

Another study examined transcriptomic alterations in adipose tissue among individuals with obesity undergoing a low-calorie diet intervention. Utilizing RNA sequencing, 1173 genes were differentially expressed compared to the baseline clinical model, some of which showed promise as predictors of weight and glycemic outcomes [56]. Microarray analysis has facilitated the discovery of differentially expressed lncRNAs implicated in lipid metabolism and adipocyte differentiation. For instance, in children having obesity, the lncRNA RP11-20G13.3 has been identified as a modulator of adipogenesis in preadipocytes (RP11-20G13.3 was found to be upregulated in children with obesity, with a fold change of 3.5) [275].

Circular RNAs (circRNAs) have also emerged as critical players in adipogenesis. Zhang et al. demonstrated that circRNAs expression profiles vary during adipogenesis and may act as miRNA sponges to modulate gene expression, highlighting their potential role in obesity-related pathways [276]. These findings collectively underscore the intricate regulatory roles of RNA molecules in adipose tissue biology. Further characterization of their roles, specificity, stability, and their value as predictors of obesity may lead to a better understanding of the molecular mechanisms gearing obesity and to the development of targeted prognostic and therapeutic approaches.

Epitranscriptomics is complementary to transcriptomics in that it investigates the chemical modifications decorating RNA molecules as well as RNA editing (i.e., nucleotide substitution, the most well-known being A to I editing). It is a relatively novel field that holds great promise to enhance our knowledge of molecular mechanisms of disease. Chemical modifications include methylation, acetylation, and pseudouridylation, which modulate RNA stability, splicing, translation efficiency, and localization [277]. Still at an early stage in obesity research, delving into epitranscriptomics holds promise for unraveling complementary layers of regulation governing adipogenesis, metabolic homeostasis, and inflammatory responses.

While multiple proteins process RNA modifications, the fat mass and obesity-associated FTO protein are now well known as RNA N6-methyladenosine (m6A) demethylase, being the most abundant RNA posttranscriptional modification [251, 277]. Studies have emphasized the link between m6A methylation, FTO, and obesity, particularly in the context of adipogenesis in preclinical models [278]. Overexpression of FTO has been associated with increased food intake (standard and high-fat diets) and subsequent obesity, further confirming its role in metabolic regulation [279]. Another m6A regulator, the protein YTHDF1 (YTH domain-containing family protein 1), emerges as a significant player in obesity. Serving as an m6A-related reader, YTHDF1 acts as a vital regulator of white adipose tissue (WAT) metabolism. Studies have revealed that its expression decreases in the adipose tissue of male mice subjected to a high-fat diet [280], which may point to having some predictive power. Intriguingly, male mice with WAT-specific YTHDF1 overexpression exhibit resistance to obesity and promote beigeing, a process crucial for energy expenditure related to more active adipose cells. Conversely, its deficiency in adipocytes exacerbates obesity-induced metabolic defects and inhibits the beginning of iWAT (inguinal WAT) formation in male mice, potentially implicating m6A RNA modification in this intricate interplay [280]. In summary, (epi-)transcriptomics has already demonstrated some value to contribute to markers preceding obesity, and clearly, more research in this novel domain related to obesity is warranted.

3.4 | Proteomics

Comparing protein patterns and levels between healthy and diseased states provides valuable insights into potential biomarkers for various conditions. Variations in protein expression, functions, interactions, and structure can help predict obesity and identify effective therapeutic strategies. Protein analyses are facilitated by classical molecular tools such as enzyme-linked immunosorbent assay (ELISA), western blot, and targeted and nontargeted proteomics. Advances in analytical technologies have significantly enhanced the sensitivity and precision of proteomics. Mass spectrometry (MS) stands out as a leading analytical tool in this regard, offering high sensitivity, precision, and accuracy. Typically coupled with liquid chromatography (LC), this technique enables the separation of proteins from complex mixtures, followed by their identification through MS analysis [281]. In a study investigating the human plasma proteome of individuals with obesity undergoing weight loss, LC–MS/MS allowed the detection of 93 differentially expressed proteins within subjects (compared to the onset of intervention) [282]. Among these proteins, the pigment epithelium-derived factor SERPINF1, secreted by adipocytes and reported to be involved in neuronal survival, inhibition of angiogenesis, and lipid metabolism [283], demonstrated a notable decrease in expression levels in response to weight loss [282]. The inflammatory proteome of these persons was also examined, revealing that 39 out of 42 individuals who responded to weight loss exhibited decreased inflammation compared to nonresponders. Such responses to weight loss may be regarded as further evidence of the causal relation of such markers and ensuing obesity. In line with these findings, a recent systematic review of 16 studies found 41 proteins that were reported to be altered more than once to be associated with obesity [284].

Given that proteins circulate throughout the organism, with approximately 25% of the human proteome present in the blood, they offer accessibility for measurements and are highly amenable to being targeted therapeutically. In a cohort of 2737 participants, the impact of adiposity on a specific set of proteins was assessed. Leptin, fatty acid-binding protein 4 (FABP4), and sex hormone–binding globulin (SHBG) emerged as the proteins most significantly influenced by BMI, supporting the role of these proteins in obesity [285], although it remained unclear whether such markers are rather cause or consequence of obesity.

An additional layer in the exploration of the proteome is post-translational modifications (PTMs). PTMs involve biochemical modifications occurring in proteins after their synthesis, influencing various aspects such as activity, subcellular localization, interactions, and other functions. With >20 PTMs identified so far, including phosphorylation, acetylation, methylation, ubiquitination, and glycosylation [286], these modifications are implicated in various diseases, including diabetes, fatty liver diseases, hyperlipidemia, and obesity. Many PTMs have been characterized explicitly in the context of obesity [287], where they regulate the activity of associated enzymes or cytokines, leading to the generation of FAs that accumulate in adipose tissue and contribute to the development of obesity [288].

Taken together, various proteomic signatures and PTMs have been identified, collectively revealing the dysregulation of proteins associated with obesity. These signatures present a plethora of opportunities to gain deeper insights into obesity. Some challenges need to be addressed, such as the heterogeneity of obesity, the biological variability among individuals, the lack of absolute cutoff levels, relative expression, and their predictability for obesity. However, a recent study has developed, akin to genetics, protein prediction scores for obesity [289]. Integrating proteomics with other omics approaches will strengthen our comprehension of obesity, elucidate the molecular pathways, and facilitate the identification of biomarkers that can predict and enable therapeutic interventions.

3.5 | Gut Microbiome

One of the factors in the interplay of environment and host that contributes to the pathogenesis of obesity is the gut microbiome, a collection of all microorganisms and their genetic material in the gut [290]. The effect of the gut microbiome on obesity involves

the metabolism and absorption of food. However, it is not necessarily clear whether gut microbiota are the cause, the consequence, or involved in both aspects of obesity. Various dietary components—such as fibers, fat, proteins, polyphenols, vitamins, etc.—influence the metabolism of the gut microbiome and the metabolites that the microbiome produces [291], thereby affecting the host energy metabolism [59]. The first studies that related gut microbiota to obesity involved studying germ-free rats and chicks and showed that gut microbiota influenced the absorption of fat [292, 293]. Later pioneering studies showed that germ-free mice gained less adipose mass as compared to conventional mice that contained the gut microbiota [294, 295]. Other studies convincingly showed that when the gut microbiota is altered with subtherapeutic doses of antibiotics in mice either during early life [296] or from birth [297], the body weight and adipose tissue mass of the animals were increased. Some of the mechanisms through which the gut microbiota is thought to contribute to weight gain are through the production of metabolites such as short-chain fatty acids, secondary bile acids, endocannabinoid compounds, tryptophan metabolites, AhR ligands, and lipopolysaccharides [59]. Cross-sectional studies on individuals with obesity and healthy controls have shown an association of various microbial taxa to obesity [298, 299], and the ratio of Firmicutes to Bacteroidetes has been several times proposed to be related to the risk of obesity as reviewed previously [113], yet prediction of the disease based on generalizable specific bacterial taxa or a network of taxa has until now not been realized. Nevertheless, approaches such as fecal transplant, shown in earlier trials with mice [300] and now even with humans [301, 302], suggest some predictability of gut microbiota for developing obesity.

Interestingly, host genetics is known to impact the make-up of the human gastrointestinal microbiome so as to influence the host metabolism [303]. However, knowing whether specific gut microbes are favorable or harmful for the management of obesity is still a challenge. On the other hand, personalized prediction of the disease based on the gut microbiota could be a possibility in the future, which can also help modulate the microbiota in a more targeted fashion in the management of obesity. In this quest, the functional microbial readouts, such as the metabolites produced by the gut microbiome, combined with their validation in ex-germ-free mice reconstituted with the microbial taxa of interest, could offer some possibilities of identifying, validating, and leveraging the gut microbial biomarkers in the management of obesity.

In this quest, the functional microbial readouts, such as the metabolites produced by the gut microbiome combined with their validation in ex-germ-free mice reconstituted with the microbial taxa of interest, could offer some of the possibilities of identifying, validating, and leveraging gut microbial biomarkers in the management of obesity. Building on this, recent studies have begun to identify specific gut microbial signatures that may influence obesity risk, using high-throughput sequencing and metagenomic approaches [304]. For example, specific bacterial genera, such as *Akkermansia* and *Bifidobacterium* [305], have been associated with leanness, while others, including some Firmicutes species, have been linked to increased adiposity [306]. However, translating these findings into predictive or therapeutic applications remains challenging. Human microbiome studies are often limited by cross-sectional designs, small sample sizes, and high interindividual variability. Additionally, diet, medications, age, and host genetics can all profoundly influence microbial composition, making it difficult to establish causal relationships [307, 308].

Despite these limitations, integrating multiomics approaches, including metagenomics, metabolomics, and germ-free animal experiments, holds promise for identifying robust microbial biomarkers and potential targets for personalized interventions in obesity management.

3.6 | Metabolomics

Metabolomics, as the most downstream omics technique, has become a powerful tool for understanding the biochemical changes associated with obesity. However, as the most downstream of the –omics techniques, it may be more prone to reveal associations than markers preceding obesity, although it may be employed for both purposes. Recently, a number of metabolites and biomarkers have been identified in different animal models of obesity as well as in human subjects, using metabolomics methods and metabolomics profile evaluation [55]. The metabolome perturbation in obesity is complex and involves various metabolic pathways, including lipid and FAs metabolism, amino acid (AA) metabolism, and carbohydrate metabolism [309]. The main challenges of metabolomics are due to the heterogeneity of metabolic profiles among individuals, absolute levels of metabolites, complex methodology for data acquisition, and technological aspects.

One of the major groups dysregulated in obesity is AAs, particularly branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs). BCAAs, including leucine, isoleucine, and valine, have been consistently associated with obesity and insulin resistance [310, 311]. Elevated levels of BCAAs have been found in individuals with obesity and are thought to play a role in the development of obesity and related metabolic disorders [312]. AAAs, such as phenylalanine, have been observed in many studies to be increased in individuals with obesity, whereas tyrosine has been associated with an increase in hepatic fat content [313]. Another group of compounds, acylcarnitines, are organic compounds containing an FA, with the carboxylic acid attached to carnitine through an ester bond. Their elevated levels have been associated with obesity and may reflect incomplete FA oxidation or mitochondrial dysfunction [314, 315]. Indeed, comprehensive metabolomics profiling has revealed that many lipid-related pathways are altered in obesity. This includes changes in FAs, such as polyunsaturated FAs and saturated FAs, as well as more complex lipids, such as sentinel lysophospholipids and sphingomyelins, which are crucial for energy storage and cellular function [316]. In addition, increased levels of newly esterified FAs (neFAs) have been identified in the obesity state. These FAs are released from adipose tissue and have been linked to the development of insulin resistance and obesity [314, 317].

Regarding carbohydrates, mannose is one of the most common glucose metabolites, and it has been reported in both adults and children diagnosed with obesity. Metabolites related to glucose metabolism, such as 6-phosphogluconate and pentose-phosphate, have also been found to be significantly altered in individuals with obesity, particularly those with T2D [318].

Due to a relatively shorter duration of obesity, linear growth, and changes in hormones due to puberty, a separate systematic review was reported for metabolomics studies in childhood obesity. However, similar to adults, metabolic perturbations were observed in AAs (particularly branched-chain and aromatic), short-chain acylcarnitines, glycerophospholipids, sphingolipids, polyamines, polyamines peptides, purines, and steroid hormones [319]. However, the value of many such markers to predict obesity is still disputed, although some articles have emphasized their predictive value, with cord-blood metabolomics being a good example to predict ensuing obesity risk [320].

3.7 | Deep Phenotyping and Digital Tools

In an era where digital tools govern every single part of human life, there is a considerable threat that the overuse of digital devices, such as smartphones, may contribute to the continuously increased prevalence of obesity through lower levels of PA. On the other hand, smartphone apps, wearables, and other connected technologies monitoring PA or sleep quality, for instance, hold great potential to aid in the primary and secondary prevention of obesity [321].

One challenge resides in the analysis of large high-throughput datasets that require high computing power and sophisticated mathematical models, including decision trees. AI and ML are revolutionizing multiomics data mining and allow the selection of the most relevant features that may be used as biomarkers in various conditions, including obesity [322]. Analysis of multiomics datasets with AI/ML was emphasized to potentially uncover novel biomarkers for the management of CVD, for which obesity is a major risk factor [323].

Digitalization and novel digital technologies are also very useful in the field of deep phenotyping. This comprehensive approach, made of a combination of digital, clinical, and biological omics data, allows us to characterize individuals and phenotypic abnormalities deeply. Such advancements in understanding obesity heterogeneity can lead to improved care strategies. This can be facilitated with the collection of large datasets from wearable devices and smartphone apps that could span questionnaires, monitor dietary intake, and regular measures such as heart rate, pulse, oxygen uptake, 24-h movement behavior, among others [324, 325], and perhaps even voice biomarkers [326]. Indeed, digital biomarkers provide opportunities to develop proactive strategies for obesity prevention, early intervention, drug prescription, and personalized management, and they have the capacity to incite subjects to take an active role in managing their health and achieving their wellness goals, for example, providing healthy lifestyle recommendations [327–329].

In summary, in the context of complex and multifactorial conditions such as obesity, integrating several omics layers ("multiomics") may best enable the identification of molecular signatures associated with or even causally linked to obesity risk. Overall, multiomic biomarkers constitute a reservoir of novel clinically applicable tools for the early detection, prediction, and monitoring of obesity development and its associated disorders (Figure 1).

4 | Diet and Nutrition

The association between nutritional status and the risk of developing overweight or obesity is multifaceted and is related to overall dietary patterns, nutrient intakes, and other eating behaviors such as the composition of consumed foods, portion sizes, or time of eating [8, 181, 330]. Although it is also considerable that persons with obesity will change their diet as a consequence of the disease, it is more likely that diet will causally impact weight changes [331, 332]. Mechanistically, it is plausible that several dietary factors could contribute to the risk of developing obesity. These include, among other factors, the following:

- High caloric intake, creating the potential for an imbalance of energy intake and expenditure, thus resulting in the storage of energy in adipose tissues [333, 334];
- High intake of simple sugars and sugar-sweetened beverages, as these may contribute to an increased risk of insulin insensitivity, which is an independent risk factor for obesity [167];
- High intake of food items of low satiety value, such as ultra-processed foods [335] or those low in dietary fiber [61], due to low residence time in the gastrointestinal tract and low volume;
- Intake patterns, including late heavy evening meals, which the body may have more difficulties in processing due to circadian changes in hormones and digestive enzymes, that is, aspects of chrononutrition [336, 337];
- Low intake of fruits and especially vegetables, partly due to their satiety value and being low in calories, but also due to their positive impact on gut microbiota related to their dietary fiber content [13, 338] and also being rich in anti-inflammatory, antioxidant vitamins, and secondary plant compounds [339], which could slow down the development of obesity.

Numerous studies, including various meta-analyses, have explored how different dietary patterns and dietary components (nutrients and nonnutrients such as dietary fiber) influence obesity risk, shedding light on the intricate interplay between nutrition and body weight regulation [340–343].

Specific nutrients play critical roles in obesity development. High consumption of energy-dense foods rich in sugars and fats contributes to excess calorie intake and weight gain [344, 345] and is associated with pro-inflammatory pathway activation, such as the formation of prostaglandins from lipids [346]. In addition, alcohol use emerged as a risk factor for obesity, particularly among women, with an OR of 3.84 in one study [347]. In contrast, diets high in fiber, protein, and multiunsaturated fats promote satiety and may help prevent overeating and weight gain [348–351], again in part also due to their anti-inflammatory properties, such as omega-3 FAs. Therefore, indices summarizing nutrient intakes, such as the index of nutritional quality (INQ) [352], could pose a better marker related to obesity risk rather than individual nutrients only. In a recent investigation, especially indices focusing on food group intakes, such as the AHEI, were related better to various biomarkers of metabolic complications [64].

Specific dietary patterns, such as the Western diet, are characterized by a high intake of ultra-processed foods, rich in sugar, salt, and SFAs, and low in fruits and vegetables, which are associated with an increased risk of obesity [184, 353, 354]. Conversely, adherence to healthy dietary patterns, such as the Mediterranean diet (MD), rich in fruits, vegetables, whole grains, and proteins and moderate in fat, has been linked to a lower risk of obesity [355, 356]. For some of these diets, there also exist indices, such as the Mediterranean diet score (MDS), determined by food frequency questionnaires (FFQs) and could constitute a marker related to obesity risk [357].

In addition, the time of eating, that is, chrononutrition aspects, related to circadian rhythm, may also be relevant, as (a) the time of day of eating [358], (b) the frequencies of the meals [359], and (c) the time of fasting in between meals have all shown to be related to the risk of obesity [360], for reasons such as relative lack of enzymes needed for digestion in the late evening [361] or the activation of sirtuin 1 (SIRT1) and other mechanisms by prolonged fasting, enhancing the bodies' resilience against stress, also improving insulin sensitivity [362].

4.1 | Individual Nutritional (Bio)markers Related to the Risk of Obesity

Markers of dietary intake of nutrients (macronutrients, micronutrients) and nonnutrients (e.g., dietary fiber and secondary plant metabolites) serve as valuable indicators of an individual's dietary habits and their potential impact on obesity risk [363]. These quantitative intakes of nutrients/nonnutrients may be derived from food FFQs or multiple 24-h recalls, but are a more indirect measure of dietary status, as many absorption, distribution, metabolism, and elimination (ADME) factors do influence the status of nutrients/nonnutrients [364, 365]. More directly, biomarkers may be derived from blood or other bodily fluids such as urine and should ideally [366] (i) reflect the body's response to dietary components, that is, mid-long term intake, and perhaps status, that is, how well the body is provided with relevant nutrients (biomarker of intake), and (ii) relate this marker of intake/status to the risk of developing obesity (biomarker of effect).

In this regard, elevated levels of circulating TGs and other lipid profile biomarkers, such as individual FAs, for example, stearic acid [367], have been frequently associated with poor dietary quality and excessive intake of fats [368]. While measured individual lipids such as FFA [369] and also TGs [370] have been shown to be well related to the risk of obesity, these factors are also influenced by a number of other dietary compounds, namely, sugar and calorie intake [371, 372] and are not very specific for lipid intake. Contrarily, blood levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which may reflect dietary intake of fatty fish and seafood, are associated with reduced inflammation/improved metabolic health, including overweight/obesity [373, 374], as these lipids are precursors for resolvins and other anti-inflammatory compounds [375]. In addition, diets rich in refined carbohydrates, especially fructose [376], can contribute to increased TG levels, promoting weight gain and insulin resistance [377], in addition to fostering inflammation via, for example, uric acid production following fructose intake [378]. Sugar intake has to be assessed by questionnaires, as there is no accepted biomarker reflecting sugar intake, as it is rapidly metabolized [366].

In addition to macronutrients, specific circulating micronutrient concentrations may indicate nutritional deficiencies or imbalances that may contribute to obesity risk [379, 380]. For example, inadequate intake of minerals essential for metabolism and energy production, such as magnesium and zinc, may impair metabolic function and contribute to weight gain [381] by disrupting metabolic function, appetite regulation, hormonal balance, inflammation, and muscle function [382]. In addition, low levels of vitamin D, required for bone health and immune function, have been linked to obesity [383], but vitamin D supplementation is not associated with weight loss, and the link between vitamin D status and obesity needs further investigation [384]. Vitamin D is implicated in many physiological processes through its interaction with the vitamin D receptor (VDR), a nuclear receptor that primarily regulates calcium–phosphate homeostasis and modulates gene expression involved in metabolic, immune, and cellular regulatory pathways [385].

Secondary plant metabolites such as polyphenols and carotenoids are related to a plant-based diet and have been proposed to independently interact with health status via their anti-inflammatory and antioxidant properties, thus impinging on markers related to inflammation and OS. These are likely in part directly related to free radical quenching [386, 387], but more likely due to their interaction with transcription factors such as NF-kB and Nrf2. Carotenoids and their metabolites are of further interest as some of them, namely, the pro-vitamin A ones and their resulting retinoids, can interact with the nuclear receptors RXR/PPARs, which have been suggested to be implicated in adipocyte differentiation [388]. A recent meta-analysis of intervention trials with carotenoid supplements involving almost 30.000 participants has shown that their intake (1.2–60 mg/d for 20 d to 16 weeks) was strongly associated with a significantly reduced risk of obesity, that is, with a reduced SMD for BMI of −0.95 kg/m^2 [389].

However, none of these biomarkers alone are overly specific for obesity, that is, they can occur in many dietary patterns and conditions and appear to have low predictability for obesity. Nevertheless, such dietary aspects are likely to reflect a cause, not a consequence, of obesity. However, for this reason, they may only be used together with other (dietary) markers to assess obesity risk.

4.2 | Dietary Pattern-Related (Bio)markers Risk of Obesity

The totality of food intake may be best taken into account by considering overall dietary patterns. Irregular eating patterns [390], frequent snacking [391], and large portion sizes have been associated with higher calorie intake and greater risk of obesity [392, 393]. These associations indicated that the timing of the largest meal and reporting dinner as the largest meal of the day were associated with higher BMI, that is, 0.07 and 0.85 kg/m^2, respectively, and significantly increased odds of obesity (OR = 1.04 and 1.67, respectively) [393]. In addition, higher fast-food exposure was associated in one study with a 58% increased risk of obesity [393]. Such patterns are determined by questionnaires,

including the chrononutrition profile–questionnaire (CP-Q) [394], and could thus serve as a marker related to obesity risk. By contrast, mindful eating, that is, paying attention to hunger and satiety cues and adopting regular meal patterns, may help prevent excessive calorie consumption and promote weight management [395, 396]. Such studies have, for example, been related to a 5% reduction in weight [397].

Dietary indices that summarize rather global dietary patterns and do not focus only on individual components are likely more integrative and have been related to the risk of developing obesity. For example, a high alternative healthy eating index (AHEI) score has been linked to a reduced risk of developing obesity; for example, a 10-unit increase in AHEI in a fully adjusted model was significantly associated with a 39% reduced risk of obesity [398]. In addition, another study employing the MDS showed that after adjusting for various confounding factors, there was a significant inverse association with BMI and WC; betas were −0.259 and −0.607, respectively [64]. In other words, a unit (minimum 0–maximum 9) increase in the MDS was associated with a 25.9% decrease in BMI and a 60.7% decrease in WC [64]. Regarding chrononutrition and overall dietary patterns, a recent meta-analysis in children summarizing results from 16 cross-sectional and cohort studies [399] showed that nondaily breakfast consumers had a significantly 45% higher OR of overweight/obesity and that eating ≥4 times a day showed significant preventive tendencies against overweight/obesity development versus ≤3 times/d, that is, a 17% lower risk.

In summary, many examples of the association of nutrient surplus intake on the one hand, especially sugar and saturated lipids, and low intake on the other hand, including dietary fiber and some secondary plant metabolites, have been related to an increased risk of developing obesity. However, such associations are far from constituting robust and accepted biomarkers. Rather, it is the totality of dietary constituents and their overall balance that is best related to the risk of diet-related complications, including obesity. As such, dietary indices such as AHEI, MDS, diet quality index-international (DQI-I), and dietary approaches to stop hypertension (DASH) scores are likely to be more successfully employed in judging the risk of developing obesity and associated metabolic risk factors [64]. In a recent study, AHEI and DASH-S were better associated with BMI, WC, and waist-to-hip ratio (WHR), rather than MDS, DQI-I, DII, and DAI [64], perhaps as the former were rather food group-oriented and less biased. A novel perspective in the area of nutrition is precision nutrition, which refers to nutrition research that aims to comprehend individual differences in metabolism and provides individualized dietary regimens that take into account genomics, epigenetics, microbiome, and environmental factors [400]. Integration of precision nutrition into standard care showed a significant improvement in the risk prediction of T2D, anxiety, depression, and irritable bowel syndrome [401]. On the other hand, the Food4Me study, including adults in seven countries, investigating which level of personalization of diet for improving BMI, suggested that there was little benefit of overly sophisticated and costly phenotypic and genotypic information compared to a simple internet-based approach to adapt a somewhat personalized diet [402], raising caution against merely adding more and more information, especially when it comes with a high price tag attached to it.

5 | 24-H Movement Behavior and Relation to Obesity Risk

Data on PA monitoring, collected via wearable technologies, such as fitness trackers and smartwatches, can offer real-time details on people's daily activity, exercise habits, sedentary behavior, sleep, and calories burned. PA is defined as any bodily movement produced by skeletal muscles that results in energy expenditure [403]. PA in daily life refers to all movement, including leisure time, transport, occupational and household activities. The World Health Organization (WHO) has provided guidelines for different age groups and specific population groups on how much PA is needed to maintain a healthy body weight and for good health in general [404]. Given that every movement contributes to the total daily energy expenditure of an individual, PA appears to be a strong predictor of healthy body weight, as well as an important behavioral target for public health interventions with a focus on preventing weight gain, supporting weight loss, and maintaining weight [405]. However, it should not be overlooked that many persons with severe obesity or even obesity are not capable of exercise or even extensive low-intensity movement due to barriers such as pain or physical discomfort [406], cautioning their relevance for interventions targeting such populations.

From a movement perspective, a day is distributed among sleep, sedentary behavior, and PA of all intensities on a continuum from no movement to high-intensity movement [407]. An integrated movement behavior paradigm has recently emerged, acknowledging that daily time is fixed to 24 h and is subject to competing demands [408]. Accordingly, a change of time in one movement-related behavior will result in an equal and opposite time displacement in at least one other behavior [409]. While it may seem counter-intuitive to include sedentary behavior and sleep in a list of "movement behaviors," the aim is to encompass the full movement continuum and capture the relevant components of the whole day [410].

5.1 | Physical Behaviors

The way in which an individual combines these time-use components throughout the day can have a significant impact on health. For instance, substantial evidence shows the importance of substituting sedentary time with PA, in particular PA at vigorous intensities, to counterbalance unhealthy fat-mass gain in children [411]. Similarly, reallocating time from sedentary behavior to standing time or moderate-to-vigorous PA has been associated with significant reductions in multiple obesity indicators in adults [412]. The replacement of 30 min of sedentary time with light PA was also beneficially associated with lower total body fat proportion and lower fasting insulin concentrations, yet the effect sizes were smaller than those observed when replacing sedentary time with moderate-to-vigorous PA. Interestingly, the former was the only time substitution associated with lower TGs and a lower ratio of ApoB/A1 in an adult European population, suggesting that light PA may have specific beneficial effects on lipids metabolism [66]. Indeed, from an energy balance perspective, the time spent in moderate-to-vigorous PA (e.g., sports practice) appears to be more efficient for counterbalancing excessive energy intake than lower PA intensities.

Nevertheless, some evidence suggests that light PA is the main contributor to PA energy expenditure for the majority of the general population (59% in women and 51% in men) [413]. Actually, it is hard to accumulate high levels of PA energy expenditure over the day without a reasonable amount of light PA. Furthermore, as the majority of time is spent asleep or sedentary in adults from Western societies [413, 414], people accumulate most of their PA energy expenditure during a relatively small fraction of the day. Promoting light PA breaks would help reduce prolonged sedentariness and simultaneously increase PA volume. Replacing sedentary time with light PA may confer some additional and unique cardiometabolic benefits [66]. It is feasible to introduce light PA into daily routines and across domains, including the workplace. It is also easier for many individuals to initiate light PA rather than more strenuous, higher-intensity activity. For instance, time spent in light PA is unrelated to self-rated health status [414], which demonstrates that light PA is widely accessible [414]. It is also easier to encourage participation in lighter than higher intensity PA. This can be used to help prepare individuals who do not currently meet recommended moderate-to-vigorous PA levels before introducing higher-intensity PA.

PA frequency, intensity, time, and type (cf. the FITT framework [415]) should not be considered as the only vital dimensions of physical behavior. For instance, evidence exists that regularity in PA volume, more specifically, daily step count, may contribute to weight loss independently of total volume [67]. With raw acceleration signals from wearable devices, many features of the complex and multidimensional movement behavior can be investigated [416]. Besides regularity in PA, the way an individual accumulates activity or sedentary time also provides important information that complements the more conventional variables (e.g., time in moderate-to-vigorous PA) and relates to health, including weight and obesity-related outcomes. Indeed, a better cardiometabolic health profile (e.g., waist circumference, BMI, and TGs) was previously found in adults whose sedentary time was frequently interrupted compared to those who largely accumulated their sedentary time in prolonged, uninterrupted periods [68]. A recent scoping review identified several PA indicators developed to describe the activity intensity distribution, the accumulation pattern, and the temporal correlation and regularity of activity [417]. Some of these indicators have already been associated with body fat mass, BMI [69, 418], as well as other cardiometabolic outcomes [419]. Actually, the focus on moderate-to-vigorous PA is a consequence of the predominance of questionnaire-based studies, which have been mostly concerned with leisure-time PA in the scientific literature until recently [414]. More accurate evidence from large device-based cohorts will be valuable in terms of exploring other movement behavior intensities and dimensions, investigating their association with weight changes, and ultimately identifying individuals at higher risk of developing obesity.

5.2 | Sleep Patterns

More recently, sleep patterns have also been investigated using wearable digital devices. It is now commonly accepted that there is a strong correlation between obesity and both the duration and quality of sleep [325], although it is often unclear if disturbed sleep quality precedes obesity of whether it is a consequence, indeed both appears probable [420]. ML algorithms may be utilized to analyze sleep data and find patterns and trends that can indicate an increased risk of obesity [421]. Sleep represents one of the extremes on the full movement continuum. It is a rapidly reversible recurring state of inactivity associated with diminished responsiveness to the external environment [422]. Short *sleep duration* (< 6 h/day) was associated with a 38% absolute increase in the incidence of obesity in a meta-analysis of prospective cohort studies among adults [71], possibly via an increase in energy intake and a positive energy balance [72]. Still, further longitudinal and interventional studies are needed to establish whether this association is causal [423]. Besides insufficient sleep, circadian misalignment, such as present in shift workers, has also been correlated with obesity. Circadian misalignment encompasses a variety of patterns, such as inadequate sleep-wakefulness and fasting-energy intake cycles with regard to internal circadian and/or environmental time [72]. High *sleep (duration) variability* has been associated with higher daily energy intake [424], possibly because of a lack of synchronization in eating patterns due to variations in sleep. Late *sleep timing* (i.e., sleep midpoint) may also influence obesity by shifting the timing of eating patterns, which often leads to skipping breakfast and snacking after dinner [425].

Moreover, low *sleep efficiency* (proportion of sleep interval spent asleep) has been associated with obesity [73], potentially because of selective deprivation of deep (stage N3) sleep [422]. A higher *social jetlag score* (greater change in sleep timing between weekdays and weekends) is also positively associated with obesity in the general population [426]. Thus, some scientific evidence suggests that poor sleep habits are associated with obesity and appear to predict obesity risk and rate of weight gain longitudinally. Nevertheless, it is unclear whether or to which degree poor sleep actually causes obesity. Further studies are required to investigate how sleep health characteristics described above, individually as well as combined, may affect the risk of obesity.

To conclude, better use of device-measured movement behavior data will allow improvements regarding the identification of populations at risk of obesity and will give further insights on key modifiable movement behaviors in order to inform future intervention efforts. More research is crucial to investigate which features of movement behavior are relevant with regard to weight management and which PA indicators (e.g., those related to intensity distribution, the accumulation pattern, and the temporal correlation) are capable of predicting changes in weight and, ultimately, obesity. More high-quality research is also needed to better understand the interplay of PA with context, especially for occupational PA, as the latter increases total energy expenditure, yet it may come with negative consequences for the individual's health [427]. From a purely physiological perspective, weight management is primarily related to energy balance, and consistently, high-intensity aerobic exercise (at high frequency) appears to be the most efficient intervention in inducing weight loss during short to intermediate times, that is, within 6 months [405]. However, both adherence and maintenance to such programs are limited. Multimodal exercise and PA interventions combining aerobic exercise and strength training programs with recommendations on daily steps, sedentary behaviors, and sleep may potentially maximize the health benefits, while opportunities for tailoring lifestyle changes should help improve maintenance.

6 | (Built)environment and Socio-Demographics

Several factors in the social environment can contribute to obesity. Although persons with obesity may have lower SES and thus live in less healthy environments [75], it is mostly assumed that the environment is fairly predictive with respect to obesity prevention [76]. One of the key determinants is the food environment defined as "the collective physical, economic, policy and socio-cultural surroundings, opportunities and conditions that influence people's food and beverage choices and nutritional status" [74]. In particular, the concept of foodscape, which includes the proliferation of retail food establishments offering fast foods and poor nutritional quality preparations, quantity and variety of food products, and price, can be considered an important risk factor for obesity and comorbidities [77]. However, living near hypermarkets and supermarkets is associated with better food habits and improved eating behavior [78, 79]. This is not only due to the supply of fruits and vegetables being more abundant in these outlets and at a lower cost but also due to the variety, quality, and price of food available.

Another aspect closely linked to obesity is the role of the built environment in general, whose factors can contribute to the development and prevalence of obesity. For example, urban design and infrastructure can either facilitate or inhibit PA. Communities with sidewalks, bike lanes, parks, and recreational facilities encourage exercise, while areas lacking these amenities may discourage it [80, 81]. Furthermore, built food environments are not uniformly distributed across sociodemographic groups. Several sociodemographic factors, including income, education, age, and ethnicity, influence individuals' access to healthy food options and their ability to make informed dietary choices [428]. Hence, understanding the intricate relationship between constructed food environments and these sociodemographic characteristics is crucial for addressing public health concerns, particularly those related to nutrition and dietary habits.

6.1 | Income Disparities and Education

Research has consistently shown that income plays a relevant role in the food environment as it significantly influences dietary patterns [78, 82]. Literature suggests that neighborhood residents who have better access to supermarkets and limited access to convenience stores tend to have healthier diets and lower levels of obesity [429], while "neighborhoods with limited access to healthy food options are associated with higher obesity rates, particularly among socioeconomically disadvantaged populations" [430]. According to Morland, the density of supermarket/healthy food outlets reduced the prevalence of overweight by 9%, the prevalence of obesity by 24%, and the prevalence of hypertension by 12%, compared to those people who lived in an area without any supermarkets. Conversely, greater access to convenience stores was associated with a 20% increase in obesity rates [83]. Thus, either the count or the density of healthy food outlets could serve as an approximate risk factor for obesity [83].

Along the same line, low-income individuals often prioritize affordability over nutritional quality, leading to the consumption of calorie-dense, nutrient-poor foods [83]. Nutrient-dense foods such as fruits, vegetables, and lean proteins are often more expensive per calorie compared to processed, energy-dense foods. This pricing disparity poses economic barriers to healthy eating, as individuals with limited incomes may struggle to afford nutritious foods [431]. This is confirmed by the presence of food deserts where people are living in remote areas. They may have low access to food stores and high poverty levels, and their fresh produce and nutritious food intakes are scarce [77].

Related to low income is often poor education. Studies consistently demonstrate that individuals with lower education levels live in areas that often lack access to full-service grocery stores and are characterized by a higher density of fast-food restaurants and convenience stores. Thus, individuals may exhibit poorer dietary habits, including higher consumption of fast food, sugar-sweetened beverages, and processed snacks, which are associated with an increased risk of obesity, diabetes, and CVDs [431, 432]. Therefore, it is not too surprising that income has been directly related in some studies to the risk of obesity. For example, Vogel et al. [84], found that individuals with higher levels of education had better dietary quality, reflected in a higher Healthy Eating Index (HEI) score. In particular, those people with a college education had an average HEI score of 65 (out of 100), compared to an HEI score of 55 for those with only a high school education. Contrarily, areas with higher levels of education tend to have better access to nutritious foods, healthier food environments, and healthier dietary patterns, characterized by greater consumption of fruits, vegetables, and whole grains and a lower intake of processed and high-calorie foods [431, 432].

6.2 | Ethnicity and Age

Similar to education, the relationship between geographical origin/ethnicity and food environments has garnered significant attention in public health research due to its profound implications for dietary behaviors, nutritional outcomes, and health disparities [433]. Areas characterized by high poverty rates, unemployment, and social disorganization tend to have fewer supermarkets and full-service grocery stores, leading to reliance on convenience stores and fast-food outlets for food purchases. In the USA, neighborhoods with predominantly African American populations showed limited access to healthy food options, with fewer supermarkets and grocery stores compared to wealthier and predominantly white neighborhoods [434]. In addition, immigrants often encounter significant changes in their food environments upon migration, including differences in food availability, accessibility, affordability, and cultural appropriateness [435]. Therefore, also, the country of origin can be predictive and constitute a risk factor for developing obesity.

Food environments can vary and significantly impinge across different age groups. For example, the extant literature has shown that young children are highly susceptible to environmental influences, such as the availability of nutritious foods at home, in school settings, and within their communities. Birch and Davison [82] emphasized the critical role of family and home environmental factors in shaping children's food preferences and dietary habits during early childhood. Access to

healthy foods and opportunities for positive food experiences in the home environment play a crucial role in establishing lifelong dietary patterns. During adolescence, individuals experience significant changes in dietary behaviors influenced by factors such as peer pressure, media exposure, and autonomy in food choices. The impact of social and environmental factors on adolescents' food environments, including access to fast food outlets near schools and neighborhoods, has been clearly highlighted [436]. Adolescents' food choices are also influenced by marketing strategies targeting this age group, promoting the consumption of energy-dense, nutrient-poor foods. In adulthood, individuals navigate complex food environments characterized by work-related stress, time constraints, and competing demands on their resources. Studies have shown that adults' food environments are influenced by factors such as income, education, and employment status, which impact their access to healthy foods and their ability to make nutritious choices. Caspi et al. [437] underscored the importance of neighborhood infrastructure in shaping adults' dietary behaviors, with gaining access to supermarkets and grocery stores playing a critical role in promoting healthy eating habits. As individuals age, they may face unique challenges in accessing and preparing nutritious foods, particularly if they experience mobility limitations, chronic health conditions, or social isolation. Homebound older adults often face barriers such as limited mobility, lack of transportation, and financial constraints that restrict their ability to access healthy food options. In addition, as Locher [438] reported, age-related changes in sensory perception, appetite regulation, and dietary preferences in older adults' food environments may also occur [438]. On the other hand, those with better caregiver support and access to community resources were more likely to consume a higher quantity of fruits and vegetables compared to those without such support.

While thus age is related to specific dietary patterns and related risks of dietary behavior, it is difficult to turn this information into obesity risk prediction; however, this may indicate that potential risk indices of obesity may need to require adaptation for the age groups targeted.

To conclude, extensive research has consistently found that built food environment features contribute to the epidemic of obesity in various ways. Generally, the availability and accessibility of food outlets, or the density and proximity of supermarkets, significantly influence dietary behaviors and, consequently, the risk of being overweight or obesity. On the other hand, sociodemographic disparities in these environments significantly impact obesity and dietary habits. Factors such as income, education, and age influence access to healthy food options. Lower-income and less-educated individuals often face limited access to supermarkets, higher exposure to convenience stores, and fewer healthy food outlets. This situation leads to poorer dietary choices and increased obesity risk. In addition, older adults face unique challenges due to mobility and sensory changes. All these aspects are rather considered predictive than consequential of obesity.

Hence, addressing these disparities through targeted interventions that promote equitable access to healthy food options is crucial for improving public health outcomes and reducing the risk for developing obesity and comorbidities.

7 | Obesity and Mental Health

7.1 | Body Weight and Mood Disorders

The psychosocial effects of obesity and its comorbidities impose a significant burden, adversely affecting various domains of psychosocial functioning [439–441]. Empirical evidence suggests a heightened susceptibility to weight gain among individuals with chronic mental illnesses, pointing to a causal relationship between mental aspects and the risk of developing obesity. However, epidemiological and clinical studies also showed a high prevalence of persons with obesity between 20% and 60% for bipolar disorders [442, 443], 30% and 70% for psychotic disorders [444], and 20% and 50% for depression [440, 445]. Thus, this relationship exists bidirectionally, as also demonstrated by Afzal's synthesis of 120 studies from 43 countries. The pooled prevalence of obesity among individuals with severe mental illnesses, encompassing schizophrenia, psychotic disorders, bipolar disorder, and major depressive disorder with psychotic features, was found to be 25.9% (global 16%), with a combined prevalence of overweight and obesity reaching 60.1% (world average 46%). Regional disparities were evident, with Sub-Saharan Africa and South Asia reporting lower prevalence rates for obesity than North Africa and the Middle East. Individuals with severe mental illness were found to be 3.04 times more likely to have obesity compared to the general population [446]. This prevalence exceeded those observed in the general population [439, 446].

Data derived from the adiposity patient registry (APV) in Germany and Austria underscored the association between overweight or obesity and mental disorders among children, adolescents, and young adults aged 6–30 years. Among 114,248 individuals, 42.5% were diagnosed with attention-deficit/hyperactivity disorder (ADHD), 31.3% with anxiety disorders, 24.3% with depression, and 12.9% with eating disorders (EDs). Factors such as male gender, older age, and extreme obesity were identified as strong correlates of mental health comorbidity [447].

Thus, obesity has also been theorized to serve as a potential risk factor for anxiety disorders [439, 448]. Country-specific investigations underscore these findings. For instance, in a study conducted in Tehran, Iran, encompassing 732 patients with overweight/obesity from April 2016 to January 2017, the prevalence of anxiety was reported at 26.5% [441]. Similarly, a Swedish study focusing on children aged 6–17, utilizing data from the Swedish Childhood Obesity Treatment Register (BORIS, 2005–2015), revealed obesity to remain a significant risk factor for anxiety and depression, even after adjusting for factors such as Nordic background, neuropsychiatric disorders, family history of anxiety/depression, and socioeconomic status. Specifically, girls within the obesity cohort exhibited a 43% higher risk of anxiety and depression compared to girls in the general population. Boys with obesity displayed a comparable risk [449].

Research has also consistently indicated a correlation between excess body weight and depression [450]. Individuals with severe obesity (class 3) were reported to be nearly five times more likely to have experienced a major depressive episode in the past year compared to those of average weight [451]. This association between obesity and depression appears to be more pronounced

among women [439, 450]. Specifically, obesity has been linked to a significant increase in the lifetime diagnosis of major depression [452].

However, obesity and mood disorders frequently occur together and can have a bidirectional relationship, being both cause and consequence of obesity. Obesity is a risk factor for mood disorders, and mood disorders are a risk factor for obesity [347, 453, 454]. Therefore, mood disorders could serve as a risk marker for developing obesity. Nevertheless, the evidence regarding the strength, direction, and potential moderators of the relationship between obesity and psychiatric disorders remains inconsistent [347]. A comprehensive review identified 21 eligible articles from a total of 2424 search results, encompassing studies on obesity and depression ($n = 15$), obesity and anxiety ($n = 4$), and one each on obesity and personality disorders, EDs, ADHD, and alcohol use [347]. Evidence was found for the bidirectional association between depression and obesity, with longitudinal studies demonstrating a reciprocal link between the two conditions. ORs were comparable for the development of depression in obesity (OR: 1.21–5.8) and vice versa (OR: 1.18–3.76), with a stronger association observed among women. Evidence regarding anxiety disorders was predominantly cross-sectional, with associations of modest magnitude (OR: 1.27–1.40). Additionally, obesity and EDs were found to have a close association (OR: 4.5).

7.2 | Obesity and Stress

The relationship between emotional eating, stress, and obesity is complex and multifaceted. Stress, whether mental or physical, has been implicated in various adverse health outcomes, including obesity and its associated complications [455, 456]. Mental stress, in particular, has been linked to changes in sleep patterns, cognition, and pain perception, as well as adverse effects on physiological systems such as the endocrine and immune systems [455]. Chronic mental stress can exacerbate an obesogenic environment by increasing attention to food cues, integrating emotions with eating, and stimulating the reward center, leading to overeating and weight gain [455, 457]. Moreover, emotional eating, characterized by the propensity to eat in response to emotions, has been identified as a critical risk factor for recurrent weight gain [347]. It is associated with overeating, unhealthy eating behaviors, and an increase in depressive symptoms and psychological distress [347, 458].

The co-occurrence of obesity and EDs further complicates the picture [85, 459]. Binge-ED, in particular, is strongly associated with obesity and is characterized by recurrent episodes of consuming large amounts of food within a short period, often accompanied by a loss of control [458, 460]. Adolescents with obesity are particularly vulnerable to the development of EDs due to factors such as body dissatisfaction, poor self-esteem, and engagement in dieting behaviors [459]. However, the impact of obesity and EDs can be bidirectional. Thus, these disorders should not be considered in isolation. Among the various EDs, binge eating has the highest prevalence of comorbid obesity, followed by bulimia nervosa. Additionally, following Agüera et al., ~30% of female patients with EDs had lifetime obesity [460].

An important issue is stigma, which is associated with both obesity and mental illnesses. Obesity stigma is characterized by prejudiced, stereotyped, and discriminatory views and actions toward people with obesity, often fueled by inaccurate ideas about the causes of obesity [461, 462]. Despite decades of research supporting the dominant influence of genetic and environmental factors in the development of obesity, obesity continues to be viewed by the public as a result of individual-level decision-making and lack of discipline. This misperception leads to harmful assumptions about the lifestyles and characters of people with obesity. Such resulting obesity stigma permeates our current sociocultural and political landscape and has severe consequences for people living with obesity, including worsened mental health [461–463].

Recent well-powered studies shed light on the significant relationship between weight stigmas and disordered eating outcomes. Lee et al. [464] discovered a strong correlation ($r = 0.54$) between a combined measure of anticipated and experienced weight stigma and global disordered eating. Wetzel and Himmelstein [465, 466] demonstrated that internalized stigma moderately correlated ($r = 0.36$) with increased binge eating. Moreover, Gerend et al. [467] conducted a large study that oversampled racial and sexual minorities, revealing that experienced weight stigma was associated ($\beta = 0.26$) with increased unhealthy weight control behaviors, even after controlling for various demographic factors. These findings align with pertinent meta-analyses, which have consistently reported medium effect sizes for the link between weight stigma and disordered eating outcomes [463, 468, 469]. Thus, although stigma is likely to a large degree a consequence of obesity, it may further aggravate its development.

In summary, psychological factors play a crucial role in both the development and exacerbation of obesity. Individuals with chronic mental illnesses, such as bipolar disorder, psychotic disorders, and depression, exhibit heightened susceptibility to weight gain, with prevalence rates of comorbid obesity ranging from 20% to 70%. This bidirectional relationship between obesity and mental health underscores the complex interplay between psychological well-being and weight management. Additionally, stress, emotional eating, and the co-occurrence of obesity, EDs, and mental health further complicate the picture, emphasizing the multifaceted nature of psychological risk factors associated with obesity.

8 | Combined Multimodal Biomarkers and Early Risk Stratification

8.1 | Multicomponent/Multimodal Markers and Challenges of Using Such Markers

Multiple (bio-)marker research refers to employing a combination of individual markers for improved risk prediction. It has been applied to a number of areas, including cancer research [470], dietary intake [471], and CVD [472]. For instance, joint associations combining various risk factors (CRP, TGs, and glycohemoglobin) for various CVDs (stroke, coronary heart disease [CHD], myocardial infarction, angina, and congestive heart failure [CHF]) in a multivariate model generally, though not

always, improved the OR for the prediction of MetS compared to individual markers, showing that such an approach can have some advantage. There is ample inconsistency in the literature about the terms referring to multiple biomarker analysis, including multimodal, composite, multivariate, multicomponent, multidimensional, and multiclass biomarkers, among others. In communication sciences, multimodal refers to the implication of several senses, such as visual and hearing [473, 474], while multicomponent could be various visual cues. In analogy, one may argue that multicomponent refers to measuring several markers of the same class, such as various plasma proteins, while multimodal refers to measuring markers across different domains or including different modalities of measurements, such as combining anthropometrics with proteins in plasma [475]. However, because of the lack of a consistent definition, the term multicomponent, as proposed by the US Food and Drug Administration (FDA) [149] will be used here together with multimodal, generally sticking to the terminology used by the authors of the cited literature.

According to the US FDA, a further distinction can be made between an integrative biomarker, consisting of individual markers combined into a single value (i.e., a score or index) by a defined algorithm, and a multiplex marker, that is, a set of individual markers used together. A good example of an integrative biomarker may be the MetS severity score [476] or, in the area of obesity, the risk score for childhood obesity, including the BMI of the mother before pregnancy, the child's sex, smoking habits during pregnancy, education of the mother and obesity state of the child at the age of 1 year, reporting predictive values around 22% for a specified cutoff point [477]. There is also a dispute on how to combine various markers statistically, such as by linear combinations [478], although this would be beyond the scope of this review. Regarding a multiplex marker, the classical definition of MetS as defined by the NCPE ATP-III [479] could serve as an example.

The advantage of combining individual markers rests in the multifactorial nature of obesity, related to host factors such as genetics as well as environmental factors such as lifestyle habits [475]. Combinations of genes [254], markers of inflammation [480], and proteins [481] have been applied for obesity risk prediction. While multicomponent markers such as combined genetics may yield some predictability, such as 17% in some studies [254] applying a genetic risk score, higher predictability is expected when combining markers from different domains, that is, being multimodal. Therefore, multicomponent/multimodal (bio-)markers may encompass a range of biological/host-related measurements, including but not limited to genetic markers, epigenetic modifications, metabolites, hormones, and inflammatory markers [482]. One such example of a multicomponent approach is multiomics, which has also been advocated for its use in obesity risk prediction [137] and has also been applied to detect the underlying molecular mechanisms for obesity [111, 483]. In one study [483], data from RNA analysis, whole genome sequencing, epigenetics, and metabolomics were combined for Mendelian randomization and network analysis, identifying 17 biomarkers that were implicated in the pathophysiology of obesity. In the study by Watanabe et al. [111], multiomics, host polygenetic risk scores, and gut microbiome composition were combined, and ML model predictions were applied. The usefulness of multicomponent approaches is confirmed by a risk score including both genetics and epigenetics as well as lifestyle factors, based on a training set of close to 1600 participants, based on ML and incorporating 21 SNPs, 230 DMSs in genes such as CPT1A, ABCG1, SLC7A11, RNF145, and SREBF1, and 26 dietary factors, resulting in a 70% overall accuracy in risk prediction [95].

However, multicomponent/multimodal biomarkers suffer from some challenges [149], including the following:

- High level of complexity and the need to collect (sampling, measuring) all components, which may be impractically and analytically more challenging;
- The independent nature of some components can lead to multidirectional changes of its components depending on slightly varying disease conditions, hampering a strong association with the outcome;
- The different and arbitrary nature of the components, which can impede a consistent combination of components;
- The difficulty of finding an algorithm to combine the components, especially when combining continuous, dichotomous, and ordinal data.

In addition, combining various markers with variable degree of predictability (such as genetics which are causally related to developing obesity versus blood lipids, which may be rather a consequence) may be challenging. However, even combinations of mostly reactive markers can be assumed to have some predictability when employed in normal-weight persons [484, 485].

8.2 | Examples of Multicomponent/Multimodal Risk Prediction From Different Domains

Even though less often than combining a number of markers from the same domain (e.g., various omics techniques), combinations of a number of different domains have been attempted to be considered for obesity risk prediction (Table 1). At present, it is difficult to say which combinations including at least two of those domains are the most promising, although a scoping review in this area is underway [475].

Though not strictly identical to risk prediction, such combinations of different domains can also be employed in multicomponent interventions in order to reduce the risk of developing obesity or even to treat it. Thus, some lessons may be learned from such successful interventions, as they may also suggest relevant domains of risk markers. For instance, a systematic review and meta-analysis on multicomponent workplace interventions ($n = 12$) to reduce weight [486] concluded that multicomponent intervention was more successful in reducing BMI compared to PA alone (0.14 vs. 0.09 kg/m^2, respectively). The nature of these so termed multicomponent interventions included PA (i.e., prevention of sedentary behavior but also exercise activities), financial incentives, healthy diets, and eating behavior, as well as education on healthy living. However, a low degree of certainty was found, and the overall BMI reduction was slight, and the time of intervention was not specified. Combining dietary exposure to fast-food outlets and genetic risk factors resulted in

an increased RR of 2.7 versus 1.73 and 1.58 compared to genetic and dietary exposure alone [93], also supporting the usefulness of combining risk factors from different domains.

Most multicomponent studies have mainly focused on the combination of PA and diet [487]. A multicomponent intervention in children and adolescents [488] showed that a combination of PA, nutritional, and psychological guidance for 6 months was successful in improving body compositional markers such as %age body fat (from 32% to 27%) or 16% relative improvement versus a control group, which may point toward a meaningful inclusion of emotions for a potential predictor for obesity risk. However, the individual components could not be evaluated in terms of their relative success against each other in such a design. Chambers and Swanson studied multiple risk factors for obesity in the UK within a cross-sectional pilot study in 80 adults based on questionnaires combining dietary aspects, negative attitudes/emotions, and social influences on PA (higher sedentary time and less exercise) [94]. A regression analysis combining all factors explained about 56% of BMI variance, highlighting the important interaction between diet, PA, and emotions. ML approaches have also been followed. For instance, in a study of > 5000 Chinese participants with overweight, the best predictors for obesity included waist and hip circumference, female gender, and systolic blood pressure, and a high mean value for area-under the curve of ROC of 0.87 was achieved [489]. Although BMI, WHR, etc. are rather the outcomes, that is, upon which the definition of obesity is based, a high starting value may also constitute a marker of increased risk. An ML approach has also been followed to rank predictor variables of obesity across different domains in children [96], covering almost 200 variables from several domains, including age, genetics, lifestyle aspects such as PA and diet, and socio-economic factors. Among the top-ranked 30 predictors for obesity were familiarity with nutrition status perception, the relation of total energy intake minus total energy expenditure, the BMI of parents, meals of the mother, IPAC (individual PA coefficient), and GRS (genetic risk score). A combination of factors for risk prediction was not attempted.

In summary, the area of multiple biomarkers and their combinations, that is, multicomponent or multimodal markers to more accurately predict the risk of developing obesity, is still comparatively new, and little is known about the best combinations for risk prediction. Although work suggests that the strongest predictors include energy intake and energy expenditure (i.e., PA), as well as parental factors such as meals eaten at home and BMI of parents, also host factors such as genetics play a certain role. Combinations, including psychological aspects or the environment of persons, still appear rather rare, but should surely be incorporated. More work in this promising area is warranted.

9 | Conclusions

Due to the typically, though not always, multifactorial risks of developing obesity, a prudent approach to better predict risk may strive to comprise a variety of individual risk factors, that is, both host and environmental factors. While it is clear that obesity has a hereditary component, this alone cannot explain the sharp increase in overweight and obesity numbers observed in the past decades, strongly pointing out the important role of the environment. Therefore, in addition to certain genetic polymorphisms such as SNPs, for which risk scores have been developed, epigenetic and gut microbiota aspects regarding host factors, as well as psychological aspects, and more volatile environmental factors such as diet, 24-h movement patterns such as PA and sleep, and also built environment such as foodscape should be considered. The main challenge may rest on one hand in collecting all the relative data and on the other hand in integrating these various domains into a single integrated score or multiplex marker that can be truly predictive for developing obesity, and may not just be associated with existing obesity.

With the help of wearables and AI/ML, combined assessment and analysis of multiomics and digital markers have the potential to reduce the still-increasing prevalence of obesity (Figure 1). However, attention should be brought to the overuse of these technologies, which may also reveal deleterious aspects such as hampering PA by excessive screen time. Information campaigns directed to high-risk population subgroups such as adolescents in low-income (parts of) countries will help circumvent this potential issue and make positive use of digital tools in collecting and integrating data from various domains. It can be hoped that the near future will allow for a more precise risk prediction in order to stimulate early interventions to stop the ongoing pandemic of obesity.

Author Contributions

T.B. and F.V. were involved in the concept, writing, and critical reviewing of the article. Y.D., L.M., S.F., J.T., M.S.D., T.d.M., and E.L. were involved in drafting individual chapters. G.R.H. and R.A. critically reviewed the chapters, adding comments and proposing further changes. M.P.J. and F.C.S. participated in the process of reviewing information about salivary biomarkers.

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Conflicts of Interest

Y.D. has filed patents related to the use of RNAs for diagnostic and therapeutic purposes and is a member of the Scientific Advisory Board of the molecular diagnostic company Firalis SA. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in Pubmed at https://pubmed.ncbi.nlm.nih.gov/. These data were derived from the following resources available in the public domain: - Peer Reviewed Publications, https://pubmed.ncbi.nlm.nih.gov/.

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