Review

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Pengfei Liu , Mengdi Zhang , Ang Li , Tongzhe Lv , Jiale Lu , Wenbo Chen *, Kaili Yin *, Guo Zhang *

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Review

Heterogeneity of Obesity and Its Predictive Factors

Pengfei Liu [1,2,†], Mengdi Zhang [1,2,†], Ang Li [1,2], Tongzhe Lv [1,2], Jiale Lu [1,2], Wenbo Chen [1,2,*], Kaili Yin [3,*] and Guo Zhang [1,2,*]

[1] Institute of Metabolism and Health, School of Basic Medical Sciences, Henan University, Kaifeng, Henan 475004, China

[2] Zhongzhou Laboratory for Integrative Biology, Zhengzhou, Henan 450046, China

[3] Key Laboratory of Environmental Health, Ministry of Education, Department of Toxicology, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

[†] These authors contributed equally.

[*] Correspondence: chenwenbo@henu.edu.cn (W.C.); kaili_y2021@hust.edu.cn (K.Y.); gzhang@henu.edu.cn (G.Z.)

Abstract: With the increasing prominence of "obesogenic environments", obesity has emerged as a major challenge to human health. Notably, humans and animals have different responses to the obesogenic environment created by affluent societies, and the susceptibility of both humans and animals to diet-induced obesity appears to be a stable phenotype. Biomarkers and specific genes, which influence body composition through long-term exposure to obesogenic environments, have been identified as higher risk indicators of individuals future weight gain. By utilizing a broad range of pre-exposure characteristics as predictive factors, we can better quantify the heterogeneity of obesity, offering novel perspectives for personalized clinical prevention and treatment.

Keywords: obesity; obesity heterogeneity; predictive factors

1. Introduction

The escalating global prevalence of obesity, coupled with a rise in metabolic disorders, represents one of the most significant threats to human health in the 21st century [1]. By 2022, one in eight people worldwide was classified as obese [2]. Alarmingly, projections for the United States indicate that one in two adults will be obese by 2030 [3]. Besides, obesity is associated with numerous detrimental health outcomes, such as cancer, type 2 diabetes, and cardiovascular diseases, positioning it as a major contributor to decreased life expectancy [4]. The Global Burden of Disease 2019 study projects a 42.7% increase in global obesity-related mortality between 2020 and 2030 [5]. To reduce the health, economic, and societal burdens of obesity, it is crucial to further investigate the environmental and biological factors that regulate weight and how their disruption contributes to obesity. At its core, obesity is caused by an imbalance between energy intake (EI) and energy expenditure. Mechanistic models of obesity, informed by experimental data, can help refine our understanding of these contributing factors and aid in developing more effective prevention and treatment strategies [6]. However, an important question remains: why do individual differences in susceptibility to obesity persist, even in today's obesogenic environment?

Obesity is undoubtedly influenced by both genetic and environmental factors [7]. It is estimated that body mass index (BMI) is highly heritable, with genetics accounting for 40-70% of variations in BMI [8,9]. Yet, the rapid increase in obesity prevalence over the past four decades cannot be attributed to genetic underpinnings [10]. With shifts in the food environment, increased consumption of energy-dense foods and lifestyle changes are primary drivers behind the rising prevalence of obesity in recent decades [11,12]. Prolonged exposure to high-fat diets leads to obesity in most species. While obesogenic environments might suggest that all individuals would eventually become obese, notable

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variability exists even among obese populations. In animal studies, genetically similar inbred mice fed the same high-fat diet under identical conditions still display varying degrees of obesity. This suggests that significant BMI variability remains within the same species, likely driven by genetic and metabolic factors [13]. In the 1980s, in a controlled overfeeding study, six young men gained an average of 6 kg over six weeks, with notable individual differences in weight and fat gain. The study found that metabolic rate increases during overfeeding were primarily linked to body size and tissue gain, rather than adaptive thermogenesis. This suggests that individual susceptibility to weight gain may stem from inherent differences in energy metabolism and fat storage efficiency [14]. However, research exploring the underlying obesity heterogeneity remains limited. Identifying high-risk populations and developing early interventions are critical for addressing the obesity epidemic. Given that both humans and animal models exhibit obesity heterogeneity, often predicted by early-life characteristics [15], this review examines the heterogeneity of obesity in both human and animal studies.

2. Regulation of Body Weight

Two principal systems in the brain regulate body weight: the energy homeostasis system and the cognitive-emotional control system [16]. The homeostatic regulation relies on neural signals originating from adipose tissue, the endocrine system, the nervous system, and the gastrointestinal system, which are integrated by the central nervous system [17]. Subsequently, the central nervous system relays signals to peripheral organs to control EI and expenditure, thereby maintaining energy homeostasis (Figure 1). The gastrointestinal tract, liver, pancreas, and adipose tissue secrete a variety of hormones that regulate food intake. These hormones act on the brain, particularly the hypothalamus and the hindbrain, to modulate appetite and satiety [18,19]. Notably, gut hormones such as cholecystokinin, peptide YY, glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, oxyntomodulin, ghrelin and insulin-like factor 5 et al. serve as short-term regulators [20,21]. In contrast, hormones associated with adipose storage, such as leptin, insulin, and amylin, function as long-term regulators [7,22]. Communication between the periphery and the brain occurs through the circulation, which reaches the brain via the hypothalamus or brainstem [23], or through afferent fibers of the vagus nerve that project to structures such as the nucleus tractus solitarius in the hindbrain [17]. The hypothalamic melanocortinergic system serves as a central hub in the regulation of homeostasis. Within this system, two key populations of neurons located in the hypothalamus—the neuropeptide Y/Agouti-related peptide (NPY/AgRP) neurons and the Pro-opiomelanocortin/Cocaine amphetamine-regulated transcript (POMC/CART) neurons—have opposing roles in controlling food intake and energy expenditure [24]. Activation of NPY/AgRP neurons inhibits satiety and drives food consumption, whereas activation of POMC/CART neurons induces satiety, reduces intake, and enhances energy expenditure [25,26]. In addition, cognitive-emotional control is regulated by higher brain centers and is influenced by environmental stimuli (e.g. visual, olfactory, and gustatory cues), past experiences, and emotional triggers [27,28]. This system works in concert with the energy homeostasis system to regulate body weight [16].

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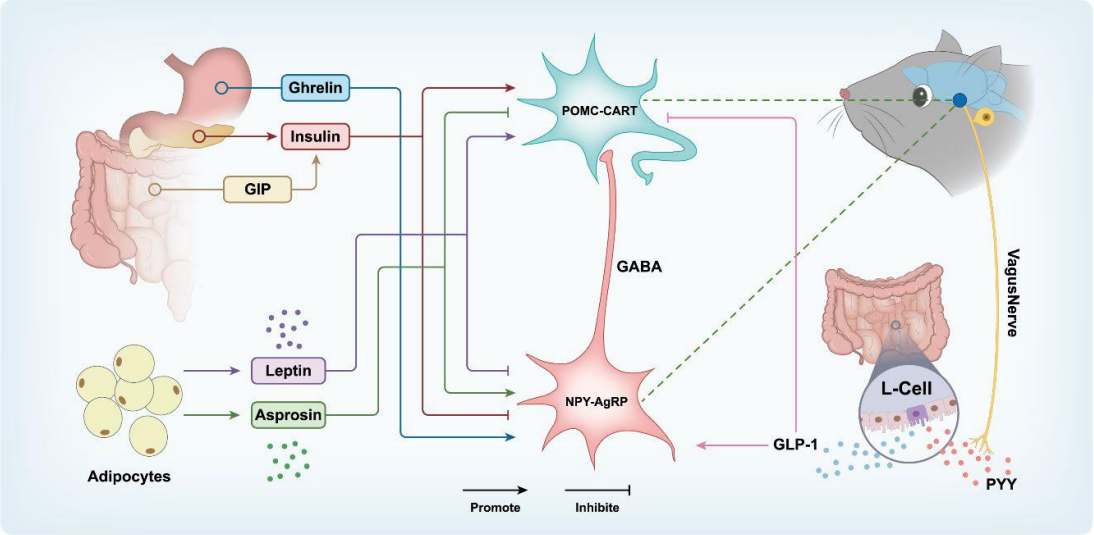

Figure 1. Hypothalamic-Neuron and Peripheral-Hormone Interactions in Energy Homeostasis. Energy balance and weight regulation involve complex central-peripheral interactions. In the hypothalamus, AgRP neurons promote appetite, while POMC neurons suppress it. They interact with each other to regulate the peripheral hormones like leptin, adiponectin, insulin, Ghrelin, PYY, GIP， and GLP-1 on energy balance.

3. Risk Factors for Obesity

Obesity results from a complex interplay between genetic predispositions and environmental factors. While monogenic obesity, caused by mutations in individual genes, is rare—accounting for less than 1% of cases—most instances of obesity stem from the interaction of multiple genetic and environmental influences [29,30]. These factors, which vary across individuals and change over time, primarily contribute to obesity by disrupting the balance between EI and expenditure. Furthermore, gene-environment interactions help explain the variability in how individuals respond to obesogenic environments (Figure 2).

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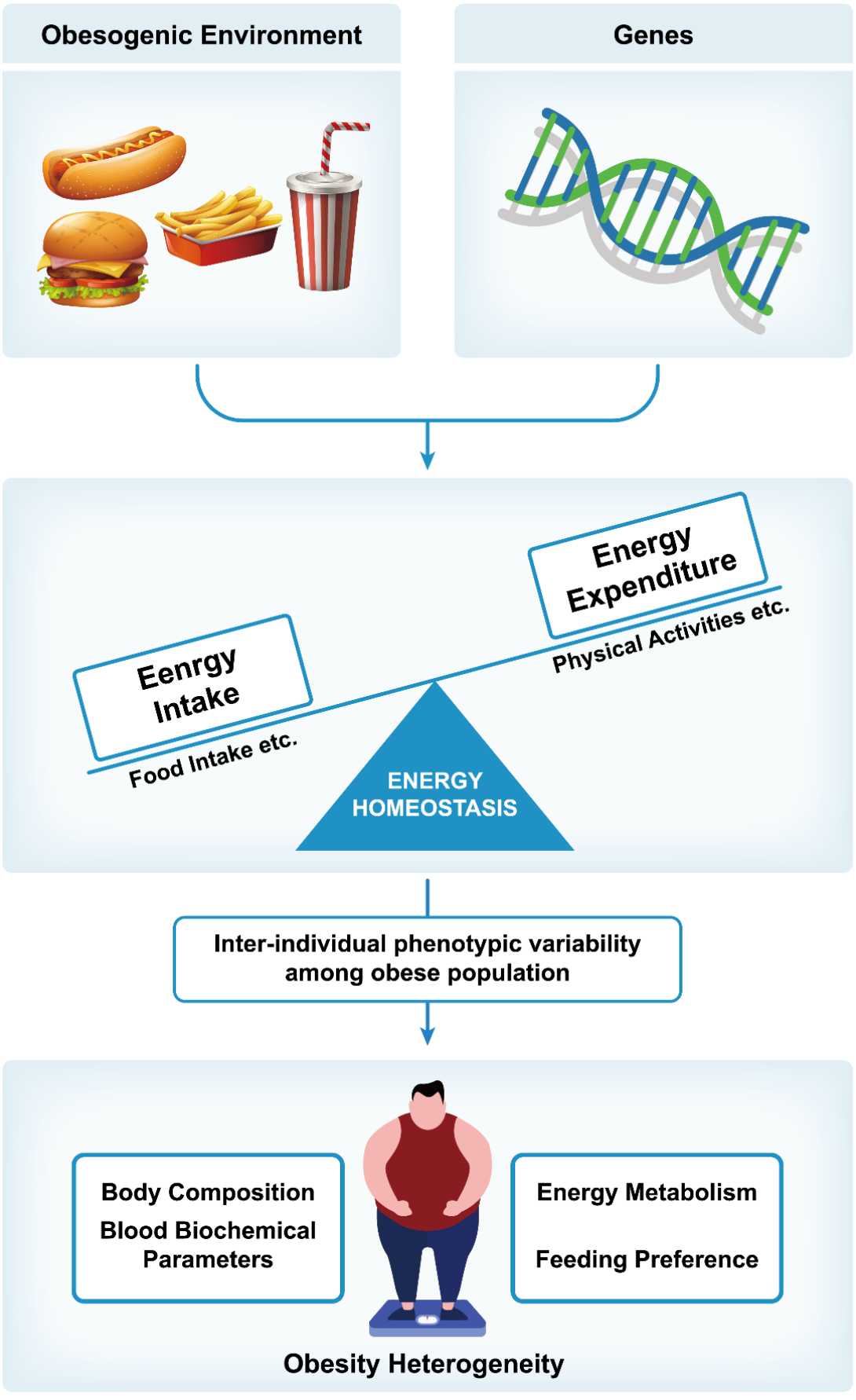

Figure 2. Key Factors Influencing Energy Homeostasis and Obesity Heterogeneity. Obesity reflects a chronic energy imbalance in which calorie consumption is greater than energy expenditure and is influenced by a

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number of factors. Genetic background is a key factor influencing susceptibility to obesity, and the main reason for the increasing global prevalence of obesity may have developed in the current environment of overnutrition. Increased energy intake, decreased physical activity and lower energy expenditure due to changes in people's lifestyles can all lead to weight gain. Few people have paid attention to the individual phenotypic variation of these obese people, such as Body Composition; Blood Biochemical Parameters; Energy Metabolism; Feeding Preference.

3.1. Genetic Factors

Genetics plays a critical role in obesity, with heritability estimates suggesting that around 40%–70% of inter-individual variability in BMI can be attributed to genetic factors [31]. Obesity can be divided into two types based on genetic mutations: monogenic and polygenic obesity. Monogenic obesity results from mutations in specific genes, such as the *MC4R* gene, which is the most common gene linked to single-gene obesity [32]. It is estimated that 11.3% of obese participants (BMI ≥ 30) carried at least one coding variant in MC4R coding region [33]. Recent population-based studies have identified rare mutations in the *BSN* and *APBA1* genes that are strongly associated with obesity risk, and they have a much greater impact than the *MC4R* gene [34]. Several other genes, including *LEPR*, *LEP*, *POMC*, and *SIM1*, have also been implicated in obesity through various mechanisms [35]. Polygenic obesity, the most common form of obesity, results from the combined influence of many gene variants, with each variant contributing a small effect. To date, over 1,000 genetic loci have been identified as associated with BMI and common polygenic obesity [36]. Genome-wide association studies have been instrumental in identifying susceptibility genes for polygenic obesity. Among the most significant findings is the single-nucleotide polymorphism in the first intron of the *FTO* gene, which has the strongest statistical correlation with obesity [37]. Despite identifying many loci, these genetic signals account for only 6% of the variation in BMI, indicating that genetic predisposition alone cannot explain obesity [38].

3.2. Environmental Factors

Environmental factors have played an increasingly prominent role in the rising prevalence of obesity. Over the past six decades, advances in food production, transportation, and technology have made calorie-dense foods more accessible, while also reducing opportunities for physical activity (PA) [39–43]. These changes provided a modern "obesogenic" environment which contributed to an imbalance between EI and energy expenditure, ultimately resulting in a widespread weight gain and obesity [44,45]. Furthermore, environmental factors can influence obesity through epigenetic mechanisms (BOX 1). Studies have shown that diet and exercise can induce epigenetic changes, affecting gene expression and altering an individual's metabolic and physiological state [46,47]. Additionally, exposure to endocrine-disrupting chemicals, such as certain industrial solvents, plastics, and pesticides, has been linked to the development of obesity by interfering with hormone receptors and disrupting hormonal signaling pathways [48].

Obesity arises from a combination of genetic and environmental factors. Apart from genetic predispositions play a significant role, environmental influences (especially those related to diet, lifestyle, and exposure to certain chemicals) can also significantly impact an individual's risk of becoming obese. Environmental factors may influence gene expression through epigenetic modifications (e.g., DNA methylation, histone acetylation, and microRNA changes), without modifications in the DNA nucleotide sequence, contributing to inter-individual variability [49]. As genetic and environmental factors interact, they contribute to the variability in obesity seen across populations.

BOX1

Environmental factors induce epigenetic modifications linked to DNA methylation, histone modifications, non-coding RNA regulation, and chromatin remodeling. A study explored the effects of high-fat diet (HFD) feeding on epigenetic alterations in the hypothalamus. The results from mice showed that dysregulation in DNA methylation and histone modification was most prominent in

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those fed an HFD for one month, compared to those fed for three or six months. However, the impact of HFD on chromatin remodeling within hypothalamic cells varied [50]. In a separate study, researchers analyzed genome-wide DNA methylation in blood samples collected from participants before and after a randomized controlled trial involving a low-carbohydrate, low-fat diet (LFD), with or without exercise. The results indicated that weight changes after 18 months of lifestyle intervention were associated with specific gene methylation profiles [51].

4. Pathophysiology of Obesity

Throughout human evolution, environmental survival pressures have predisposed the body to store fat. However, with the rise of industrialization and easy access to high-calorie foods, this adaptive mechanism has become a liability [52]. Obesity is a complex, chronic, and progressive disease characterized by excessive adiposity and dysregulation of enteroendocrine and neurohormonal signaling pathways, which result in heightened appetite and increased energy storage [53]. It is also recognized as a state of chronic low-grade systemic inflammation, marked by elevated levels of circulating proinflammatory cytokines, which adversely impact the central nervous system and organs involved in energy and metabolic homeostasis [54]. In the context of a long term positive energy leveling balance under which excessive adiposity develops slowly over time [55]. Compared with individuals who are not overweight or obesity, obese individuals have larger fat and lean mass, as well as higher resting energy expenditure, cardiac output, blood pressure and greater pancreatic β-cell mass et al [56]. As weight is gained over time, fat accumulates in the subcutaneous and around the viscera, leading to a wide range of metabolic disorders and associated complications [57,58]. At the same time, adipocyte apoptosis induces adipose tissue remodeling, leading to an increase in macrophages and other immune cells within the tissue [59]. These immune cells interact with adipocytes to secrete proinflammatory cytokines, thereby promoting a low-grade systemic inflammatory state in some individuals with obesity [60,61]. Adipocytes also synthesize adipokines and hormones, which are influenced by the distribution and amount of adipose tissue [62]. The hydrolysis of triglycerides within adipocytes releases free fatty acids, which are then transported through the plasma and deposited in various cells, particularly hepatocytes, where they induce cytotoxicity and contribute to a range of metabolic disorders in the liver [63,64]. Obese individuals differ in etiology, pathogenesis, symptom presentation and response to treatment and this phenomenon is referred to as obesity heterogeneity [65,66].

5. Heterogeneity of Obesity

The variability in human responses to obesogenic environments, often observed in affluent societies, is a crucial aspect of the obesity epidemic. Traditional approaches often compare the physiological functions of obese individuals to those of lean controls. However, these studies face challenges in distinguishing whether the observed differences are causes or consequences of obesity. Clearly, obesity heterogeneity also exists among obese people (Figure 2), and experimental studies—particularly those focusing on individuals—can reveal novel causal risk factors or potential pathways of disease.

5.1. Obesity Heterogeneity in Human Population

In recent years, food supply per capita has increased significantly, leading to an unprecedented abundance of energy availability. This, combined with the increasing consumption of energy-dense foods, has resulted in overnutrition in the general population [67]. Despite these obesogenic conditions, the extent of obesity varies greatly from person to person, a phenomenon referred to as obesity heterogeneity [68]. Body mass index (BMI), calculated as weight in kilograms divided by height in meters squared (kg m^{-2}), is a commonly used metric for assessing obesity. The World Health Organization defines obesity as BMI ≥ 30 [69], while China Obesity Task Force defines obesity as BMI ≥ 28 [70]. Although obesity is widespread, its severity varies among individuals with obesity. For

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example, a study in China revealed a nearly Gaussian distribution of BMI in adults, with a range between 28 and 40 on the BMI scale (Figure 3A,B) [71]. Similarly, in Denmark, the BMI distribution of obese adults extends from 30 to 45, showing a wider range compared to China [72]. A study of 3 million adults in the United States also highlighted substantial variation in BMI among obese individuals [73]. These differences in BMI are not region-specific but reflect the global variability in obesity across different populations [74,75].

5.2. Obesity Heterogeneity in Animals

To model the obesogenic environments seen today, high-fat diet (HFD) models using inbred mouse strains like C57BL/6J are commonly employed in obesity studies [76]. Significant differences in the weight of mice exposed to HFD have been demonstrated even within genetically identical populations [77]. When subjected to HFD feedings, C57BL/6J mice display marked variability in weight gain (Figure 3C). This variability becomes more pronounced with prolonged exposure to the diet [78]. In one study, 219 male C57BL/6J mice fed a 58% fat diet for four weeks showed a bell-shaped weight distribution ranging from 24 to 37 grams [79]. In addition, 60 male C57BL/6J mice of similar age were fed an HFD with 45% kcal fat for 4, 8, 12 and 16 weeks, with a body weight distributions of 24.40-32.80, 27.83-48.13, 28.78-56.24 and 29.17-55.44 grams, respectively [80]. Similarly, 324 male mice on a 60% fat diet for 20 weeks exhibited weights between 27.2 and 52.7 grams [81]. For female, 255 C57BL/6J mice fed an HFD with 45% kcal fat from 8 to 43 weeks of age showed weight gains from 0 to 32 grams, also reflecting considerable variability [82]. These studies highlight significant individual differences in weight gain under HFD [82], and the heterogeneity persisted across different nutrient ratios [83].

Extensive experimental data indicate that obesity heterogeneity is a common phenomenon in experimental animal models and even wild rodent. Considerable individual variation exists in the weight gain of voles, an animal widely used to study obesity, after exposure to high-fat conditions [84]. Rats, another commonly used model in obesity research, also show substantial variability in weight gain when subjected to HFD feeding [85]. Mickelsen et al. first identified differences in obesity susceptibility across various rat strains [86,87]. Sprague-Dawley and Wistar rats, in particular, exhibit wide variability in weight gain under hypercaloric conditions (Table 1) [88–91]. These differences are attributed to factors such as genetic diversity, differences in energy expenditure, and variability in feeding behavior. Thus, obesity heterogeneity is a common phenomenon in experimental models of metabolic disorders.

6. Predictive Factors for Obesity Heterogeneity

Few studies have examined how pre-existing individual differences in animals or humans, prior to exposure to obesogenic environment, affect their susceptibility to obesity. Identifying biomarkers or gene responses before exposure could help predict later changes in body composition, enabling early detection of individuals at higher risk for obesity. These new analyses also offer the potential to develop novel hypotheses about the causes of variability in obesity across populations.

6.1. Human Studies

Understanding how pre-existing individual differences influence weight gain in obesogenic environments is crucial. Recent studies have begun to uncover early-life predictors of obesity, suggesting that specific biomarkers may be significantly associated with an individual's susceptibility to future weight gain before they are exposed to obesogenic conditions [92].

Bouchard et al. investigated the predictors of body composition and energy changes in response to chronic overfeeding in a study involving 24 young, sedentary male twins. Participants were subjected to a standardized overfeeding protocol of 1,000 kcal per day above maintenance levels for 100 days, resulting in significant weight, fat mass (FM), and fat-free mass (FFM) gains. The study not only highlighted the notable individual variability in response to overfeeding with the average gains

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in FM and FFM for 5.4 kg and 2.7 kg respectively, but also indicated that pre-overfeeding levels of fat-free mass, muscle oxidative capacity, maximal oxygen uptake (VO_2max), androgen levels, and plasma leptin concentrations were identified as potential predictors of future body composition changes. Specifically, fat-free mass and muscle oxidative capacity were inversely correlated with energy and weight gain, while plasma leptin levels were positively correlated with these outcomes. Additionally, the thermic effect of a meal and specific hormonal levels (e.g., testosterone and androstenediol-sulfate) were linked to reduced fat gain, highlighting metabolic efficiency as a protective factor against excessive fat accumulation [93].

The study concluded that a combination of metabolic, hormonal, and fitness-related baseline traits can predict individual differences in body composition changes due to overfeeding. These findings provide insights into why some individuals may be more prone to increased fat storage than others under the same overfeeding conditions and emphasize the importance of personalized approaches to weight management. Furthermore, baseline characteristics within the population—such as FFM, muscle oxidative capacity, VO_2max, androgen levels, plasma leptin levels—can serve as predictors of future variations in weight gain and offer an important framework for predicting obesity risk and tailoring prevention strategies based on early biomarkers (Figure 4, Table 2).

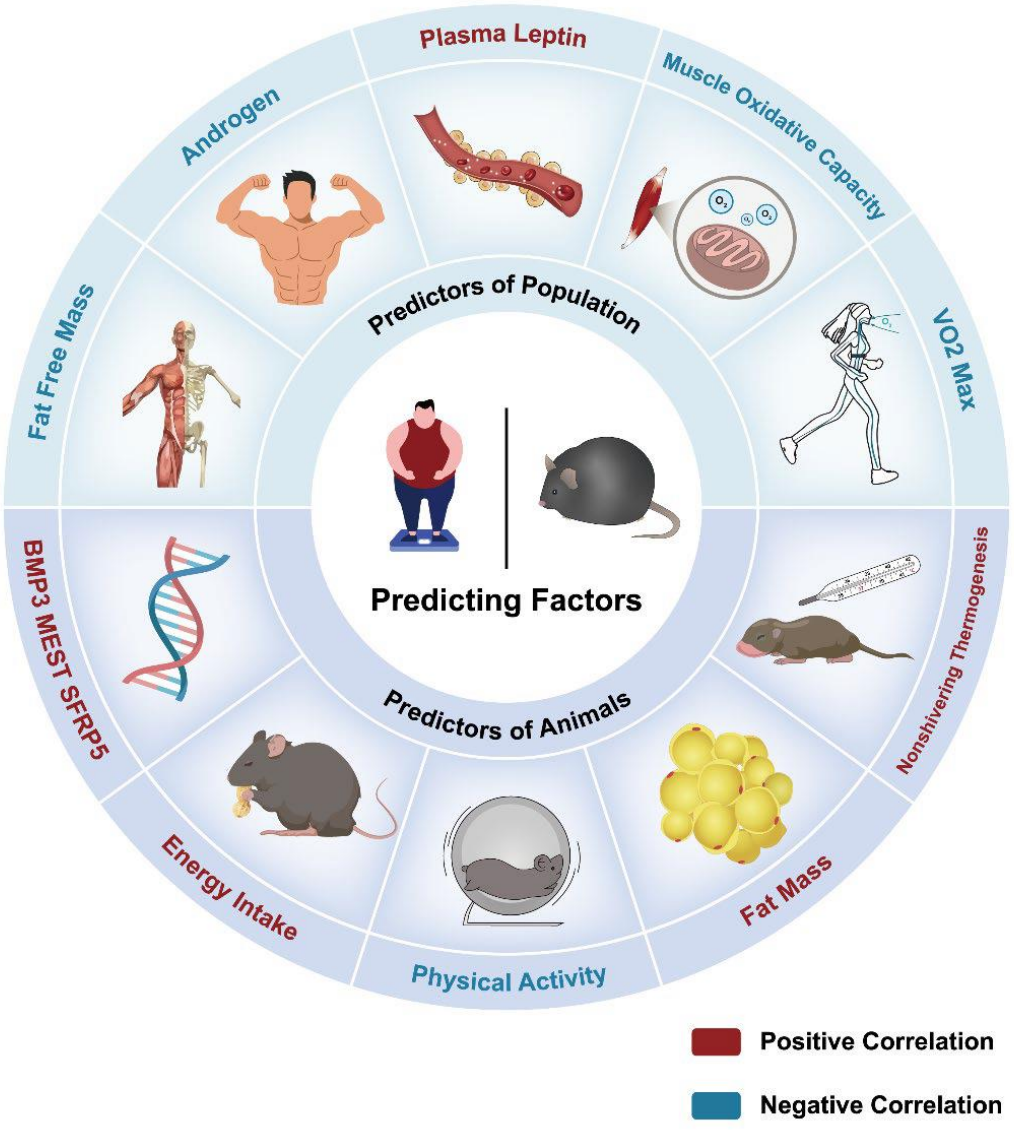

Figure 4. Predictors of obesity heterogeneity in population and animals. Baseline characteristics within the population—such as FFM, muscle oxidative capacity, VO_2max, androgen levels, and plasma leptin levels—can serve as predictors of future variations in weight gain. Baseline characteristics of C57BL/6J mice, including FM,

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FFM, PA, and EI along with the expression levels of SFRP5, MEST, and BMP3 genes in adipose tissue, can serve as non-genetic predictors of future differences in weight gain. Baseline NST was the strongest predictor of body weight gain during the high-calorie diet in voles.

Table 2. Predictors of nongenetic variability of obesity heterogeneity.

Predictors	Relationship with BW change	Research object	Methods	Ref.
SFRP5	Positive	Mice	Microarray analysis and qRT-PCR	[79]
MEST	Positive	Mice	Microarray analysis and qRT-PCR	[79]
BMP3	Positive	Mice	Microarray analysis and qRT-PCR	[79]
Fat Mass	Positive	Mice	Transmitter and dual-energy X-ray absorptiometry	[80,82]
Physical Activity	Negative	Mice	Transmitter and dual-energy X-ray absorptiometry	[80]
Energy intake	Positive	Mice	HFD:4.73kcal/g; LFD:3.85kcal/g	[82]
Non-shivering thermogenesis	Positive	Voles	Induced by a subcutaneous injection of NE around the interscapular BAT	[84]
Plasma Leptin	Positive	Population	Specific enzyme-linked immunosorbent assay	[93]
Muscle Oxidative capacity	Negative	Population	Enzyme Activity Measurement	[93]
Maximal oxygen uptake	Negative	Population	Open gas circuit system	[93]
Androgen	Negative	Population	Ethanol extraction, enzymatic hydrolysis, Sephadex chromatography.	[93]
Fat Free Mass	Positive in mice Negative in population	Mice and Population	Transmitter and dual-energy X-ray absorptiometry ; Standardized equations for body weight and percentage of fat mass	[80,82,93]

6.2. Animal Studies

In order to unravel the heterogeneity of obesity, both human and animal studies have unveiled a spectrum of predictive factors that can foreshadow the development of excess adiposity. While human studies have focused on a diverse array of predictors, animal models have provided a controlled environment to dissect the early signs of obesity with precision.

Expression levels of some genes can serve as predictors of obesity following exposure to HFD. Koza et al. have delineated a compelling narrative: the obesity phenotype in inbred C57BL/6J mice at 7 weeks of age exhibits a striking variability and differences in epididymal fat gene expression at 7 weeks of age (prior to a high-fat diet) correlated with obesity after 8 weeks on a high-fat diet in mice. *SFRP5*, *MEST*, and *BMP3* gene expression levels in epididymal fat biopsies from 7-week-old mice were significantly and positively correlated with obesity at week 16, with *SFRP5* correlating with obesity up to 45% and being a strong predictor. Interestingly, this difference also remained stable during subsequent caloric restriction [79]. In particular, elevated expression of these genes may be causally linked to fat mass expansion. Building upon these genetic insights, Speakman et al. also found significant differences in weight gain among mice fed an HFD, which could be predicted by early baseline measures of FM, FFM, and PA. The study selected 60 age-matched male C57BL/6J mice to measure baseline characteristics under a standard LFD, including FM, FFM, PA, food intake, and resting metabolic rate. Subsequently, these mice were switched to HFD and the mice body weights were recorded at weeks 4, 8, 12, and 16 of high-fat feeding. The results showed that baseline FM was strongly positively correlated with weight gain from weeks 4 to 16, baseline FFM was positively correlated with weight gain at weeks 12 and 16, and baseline PA was negatively correlated with weight gain at weeks 8, 12, and 16. However, baseline “food intake”, “resting metabolic rate”, and “body temperature” were not related to later obesity at any time point. Thus, baseline FM, FFM, and PA can serve as predictors of weight gain differences under hypercaloric conditions in this strain of mice, with FM being the strongest predictor [80]. The reasons for this need to be further explained (Box 2).

Moreover, Yang et al. discovered gender differences in multivariable weight prediction models for inbred mice. The study involved 6-week-old C57BL/6J mice (277 males and 278 females), which were fed standard chow until week 8, at which point baseline FM, FFM, and EI were measured and

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calculated. The mice were then switched to a high-fat diet until week 43. Body weight was measured weekly for the first month, and subsequently every 4 weeks. Multivariable variance analysis for weight prediction indicated that, for male mice on the HFD, baseline FM, FFM, and EI were significant positive predictors of future weight throughout the study. For female mice on the HFD, baseline FM and FFM were significant predictors at all time points, while baseline EI was only a significant predictor of weight at week 35 [82]. In conclusion, baseline characteristics of C57BL/6J mice, including FM, FFM, PA, and EI along with the expression levels of *SFRP5*, *MEST*, and *BMP3* genes in adipose tissue, can serve as non-genetic predictors of future differences in weight gain (Figure 4). Since these inbred mice have homogenous genes, they offer a model for predicting future obesity risk in humans due to non-genetic factors.

Thermogenic Capacity in wild Brandt's voles predicts differences in susceptibility to obesity. 30 age-matched adult male Brandt's voles were fed a standard LFD for 10 weeks, followed by a HFD for 12 weeks. Baseline levels of non-shivering thermogenesis (NST) were measured during the last 2 weeks of LFD feeding, and body mass was measured at weeks 4, 8, and 12 of the HFD. Multiple regression analyses revealed that baseline NST was the strongest predictor of body weight gain during the high-calorie diet, and that voles with a high maximal thermogenic capacity during low-fat feeding were at high induced obesity risk and had a higher susceptibility to obesity [84].

Prepubertal rat weight gain model accurately predicts risk of obesity in adult rats. Leibowitz et al. fed a high-calorie diet to 24 newly born Sprague-Dawley male rat pups until adulthood. The body fat was measured on day 80 or 100 before death. Experimental data showed that the average daily weight gain for rats at 30-35 days of age was 5-10 g, which was strongly and earliest positively correlated with body fat in adulthood and can be considered a predictor of future obesity [94].

Rodent experimental models are commonly used in studies of obesity heterogeneity. Early measurements of FM, FFM, PA, EI and some gene expression levels in inbred mice can predict future body weight. Since these mice have homogenous genes, they offer a model for predicting future obesity risk in humans due to non-genetic factors. In studies using wild voles, baseline NST on a high-fat diet was a predictor of future susceptibility to obesity. While in outbred rats, weight gain during puberty under a high-fat diet can also predict future obesity levels. Particularly, the genetic heterogeneity in wild voles and outbred rats makes them suitable for simulating human population states and weight gain in early NST or pubertal children might also serve as a predictor of future obesity under today's hypercaloric conditions. Early measurements of body composition, gene expression, and PA in animal models can provide valuable information for predicting weight gain in response to obesogenic environments (Table 2). These predictive factors could guide the development of more targeted interventions for individuals at risk of obesity (Box 2). Importantly, the phenotypic differences observed before HFD exposure remain stable, persisting even when a restrictive LFD is introduced, demonstrating the robustness of these early traits.

BOX2

Several studies have examined the factors contributing to obesity heterogeneity among inbred mice on high-fat diets, including the roles of gender and age in obesity susceptibility [95–97]. Other factors such as intrauterine conditions (e.g., uterine position, blood supply, fetal size, and neighboring fetal sex), early postnatal influences (e.g., fetal size, sex ratio, maternal behavior, social interactions, and stress), and adult factors (e.g., social dominance, stress, and health issues) also play a role in obesity susceptibility [15,98]. Research has also explored how different dietary components influence obesity risk in these mice [99–101]. Due to their genetic uniformity, individual differences in inbred mouse strains can often be attributed to random events or specific environmental conditions [102]. Environmental factors may influence gene expression through epigenetic modifications (e.g., DNA methylation, histone acetylation, and microRNA changes), contributing to inter-individual variability [49]. Importantly, environmental factors are believed to affect the likelihood of consuming high-fat diets through such epigenetic changes. Studies suggest that non-genetic variation in mice's responses to high-fat diets is shaped by early-life conditions, such as litter size and nutritional status in early development [103,104]. Inadequate fetal nutrition is associated with an increased risk of

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obesity in adulthood when exposed to obesogenic environments [105]. Consistent with other findings, litter size during lactation inversely correlates with body weight at weaning, likely due to the limited availability of maternal milk when divided among more offspring. Epigenetic mechanisms, which alter chromatin structure and gene expression without changing the underlying genetic code, are thought to underlie this relationship [106]. These modifications provide a mechanism for obesity that is independent of new genetic mutations. Furthermore, maternal nutritional status significantly affects offspring outcomes. In studies using inbred C57BL/6 mice, maternal consumption of a high-fat diet during pregnancy and lactation led to reduced DNA methylation in the promoters of genes related to the dopamine and opioid systems. This epigenetic alteration influenced long-term gene expression in mesolimbic pathways, increasing dietary fat preference in adulthood and contributing to variations in weight gain later in life [107].

Khera et al. provide an in-depth analysis of genetic contributions to obesity by employing a genome-wide polygenic score (GPS). This GPS was constructed using data from over 300,000 individuals and analyzed 2.1 million genetic variants, offering a comprehensive approach to identify individuals at high risk for severe obesity. The study found that BMI differences due to genetic predisposition emerge early in childhood and persist into adulthood. Notably, individuals in the highest decile of the GPS had a significantly higher risk of obesity compared to those in the lowest decile. This underscores the role of genetic susceptibility in obesity heterogeneity, moving beyond traditional polygenic risk scores that utilized fewer genetic variants with lower predictive power [108]. The study observed a pronounced gradient in body weight and obesity risk, with individuals in higher deciles of the polygenic score being 13 kg heavier on average and 25 times more likely to develop severe obesity. Longitudinal data from a birth cohort study showed minimal differences in birth weight across polygenic score deciles, but by 18 years of age, individuals with higher polygenic scores exhibited a 12 kg weight difference [108]. This study examines the potential of GPS in predicting obesity, thereby providing new insights for clinical decision-making and public health interventions. We expect better prevention and management of obesity and its problems in the future with continuous research and application of these indices. We highlight that integrating genetic risk factors with early biochemical markers could refine predictions of obesity risk. While the GPS alone proved to be a powerful predictor, combining it with metabolic and biochemical indicators could improve precision in identifying individuals at greater risk. This suggests a future direction where genetic data and early life biomarkers work together to enhance individualized approaches for prevention and intervention in obesity (Figure 5).

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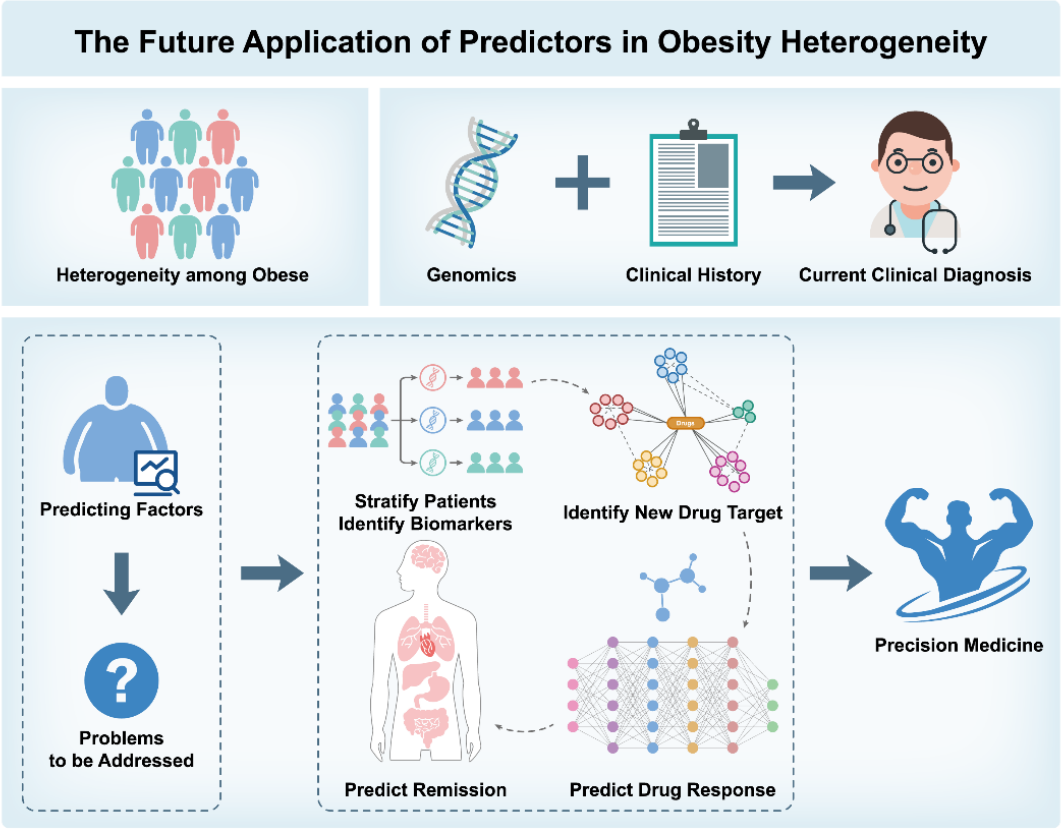

Figure 5. The future application of predictors in obesity heterogeneity.

The heterogeneity within obesity populations highlights the limitations of using gene testing and clinical measures, especially BMI, in diagnosing and defining obesity. Moving forward, integrating genetic data, early biochemical biomarkers, and intelligent learning systems holds great potential for optimizing personalized strategies for obesity prevention and treatment. This multi-dimensional integration approach is expected to not only enhance the precision of obesity risk prediction but also improve the efficiency and accuracy of disease management. This approach will contribute to:

1. **Patient Stratification and Biomarker Identification**: Combining genetic and biochemical markers to identify high-risk individuals for personalized prevention;
2. **Identification of Novel Drug Targets and Drug Response Prediction**: Identifying therapeutic targets and predicting individual responses to treatments;
3. **Application of Artificial Intelligence**: Using machine learning to enhance obesity risk prediction accuracy;
4. **Predicting Remission and Long-Term Management**: Analyzing genetic and biochemical data to support personalized interventions and manage obesity progression.

7. Concluding Remarks and Future Perspectives

Obesity is a complex metabolic disorder influenced by both genetic and environmental factors. Recent studies in genetically identical organisms, such as inbred mice and monozygotic twins, have revealed significant individual variability in response to obesogenic environments. Despite identical genetic backgrounds, different individuals or animals exhibit varying degrees of obesity when exposed to the same high-fat diet or overfeeding protocols. This phenomenon challenges current paradigms of obesity research and suggests the existence of non-genetic factors that contribute to

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obesity susceptibility. This review explores the role of early biochemical markers and gene expression patterns in predicting long-term obesity outcomes. Additionally, it discusses how environmental factors, combined with genetic predispositions, influence obesity development. Through understanding the molecular and physiological mechanisms behind these variations, this review proposes potential biomarkers for predicting obesity susceptibility, particularly focusing on characteristics such as FM, FFM, PA, EI, NST, muscle oxidative capacity, VO2max, and gene expressions like *SFRP5*, *MEST*, *BMP3* and androgen level, which could inform personalized prevention and treatment strategies.

The heterogeneous nature of obesity remains one of the most intriguing challenges in metabolic research.

While genetic predisposition undoubtedly plays a role, it is clear that environmental factors and early-life biomarkers contribute significantly to individual variability in obesity outcomes. The findings from studies on inbred mice and twin cohorts suggest that obesity susceptibility can be predicted by early genetic and biochemical markers, even before the onset of excessive caloric intake. Integrating genetic data, early biochemical biomarkers, and intelligent learning systems holds great potential for optimizing personalized strategies for obesity prevention and treatment. This multi-dimensional integration approach is expected to not only enhance the precision of obesity risk prediction but also improve the efficiency and accuracy of disease management.

Moving forward, more research is needed to identify specific molecular signatures that can be used to predict obesity risk, particularly in humans. Future studies should focus on integrating genetic, epigenetic, and environmental data to develop comprehensive predictive models. Additionally, intervention strategies aimed at modulating early biochemical markers or gene expression patterns could hold promise in preventing obesity before its onset.

Figures

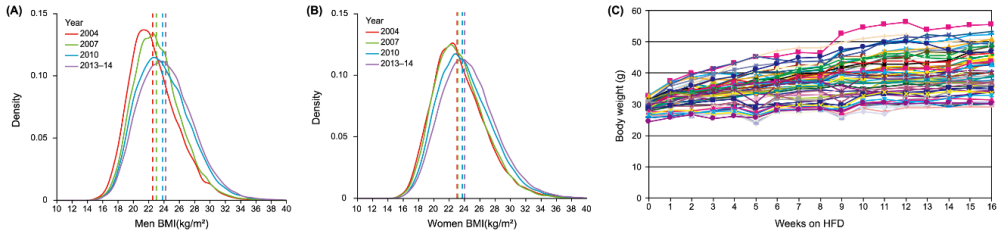

Figure 3. Heterogeneity of obesity among populations and inbred mice. (**A, B**) BMI distribution curves of Chinese men (**A**) and women (**B**) aged 18-69 from 2004 to 2013-14(Using the lambda-mu-sigma method. The area under each curve is 1) Normal distribution fitting of the entire population in both men and women. When we focus only on obese people, the BMI ranges from 28 to 40. (Adapted with permission from ref. [71], Lancet. Rightslink® by Copyright Clearance Center) (**C**). Speakman and colleagues revealed the heterogeneity of obesity in inbred mice under experimental conditions, with mice of the same genetic background showing variable weight gain. After 16 weeks of HFD, the smallest individual weighed 29.17 g, while the largest individual weighed 55.44 g. (Adapted with permission from ref. [80], Wiley. https://onlinelibrary.wiley.com/journal/1930739x).

Tables

Table 1. Summary of studies on obesity heterogeneity in mice, rats, and humans.

Author year	Model	Design	Findings	Ref.
Xiong-Fei Pan 2021	China's Chronic Disease and Risk Factors Surveys: 2004, 2007, 2010, 2013-14.	Cross-sectional Analysis	Obesity rates rose steadily among all groups. Overweight and obesity raise the risk of chronic diseases and early death	[71]

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Janne S Tolstrup 2023	91,684 Danes	Cross-sectional Surveys	BMI distribution shifted right from 1987 to 2021, with higher values across all percentiles and socioeconomic groups	[72]
Aditi Krishna 2015	3,050,992 non-Hispanic white, non-Hispanic black, and Hispanic men and women	Longitudinal Analysis	Growing inequalities in BMI at the population level are not driven by these socioeconomic and demographic factors	[73]
In Sil Park 2021	2,708,938 Korean women	Retrospective Cohort	The impact of obesity on the risk of female-specific cancers varies with cancer type and menopausal status	[74]
Min Gao 2021	6,910,695 British people	Prospective Cohort	The risk of severe COVID-19 hospitalization and death rises linearly from a BMI of 23 kg/m² upwards	[75]
Rémy Burcelin 2002	Male C57BL/6J mice (IFFACREDO, L'Arbresle, Franc) at 4-to 5-weeks age	Feeding a high fat diet (HFD) for 9 months	Approximately 50% of the mice became obese and diabetic, 10% lean and diabetic, 10% lean and non-diabetic, and 30% showed intermediate phenotypes	[77]
Sarah L.Johnston 2012	Female C57BL/6J mice (n=147; Harlan United Kingdom, Oxon, United Kingdom) at 6 weeks of age	Laboratory chow (Rat and Mouse Breeder Grower diet CRM; Special Diet Services, Essex, United Kingdom); A low-fat (10% kcal fat; n=47), medium fat (45% kcal fat; n=50) and high-fat diet (60% kcal fat, n=50; Research Diets, New Brunswick, NJ)	Female mice on a high-fat diet experienced weight gains ranging from 1.4% to 65%	[78]
Robert A Koza 2006	Fale C57BL/6J mice（ n=219;the Jackson Laboratory (Bar Harbor, Maine, United States).	Low-fat chow diet 5053 ad libitum (From weaning until 8 wk of age); High saturated fat diet D12331(At 8 wk of age)	Body weights of 219 mice fed a high-fat diet for 4 wk were distributed in a bell-shaped curve ranging from 24–37 g	[79]
Li-Na Zhang 2012	Male C57BL/6J mice (n=60; Charles River UK, Kent) and female C57BL/6J mice (n=40; Charles River UK)	Male：low-fat control diet (D12450B, 10% kcal/fat and HFD (D12451, 45% kcal/fat; Female: laboratory chow (Rat and Mouse Breeder Grower diet CRM)	Male mice from the same strain, after consuming a high-fat diet with 45% of calories from fat for 16 weeks, exhibited body weights ranging from 29.17g to 55.44g	[80]
Anne Kammel 2016	Male C57BL/6J mice (n=324；Charles River, Germany)	Pre-weaning: a standard chow (sniff) Post-weaning: HFD (60 kcal% fat, 21.9 kJ/g, D12492, Research Diets, Inc., USA)	324 male C57BL/6J mice on a 60 kcal% high-fat diet for 20 weeks exhibited body weights ranging from 27.2g to 52.7g	[81]
Yongbin Yang,2014	C57BL/6J mice (n=277 males and n=278 females) from the Jackson Laboratory (Bar Harbor, ME) at 6 weeks of age	A low-fat diet (LFD, 10% calories from fat; n=15 male, n=15 female) or high-fat diet (HFD, 45% calories from fat; n=277 male, n=278 female)	Males and females exhibit substantial fat mass variation, which grows over time, contrasting with the stable fat-free mass	[82]
Wu,2022	C57BL/6N, DBA/2, BALB/c, FVB, And C3H mouse strains	Series 1: D14071601–D14071606 and series 2: D14071607–D14071612 fixed the level of fat 60 or 20% by energy and Varied the protein content from 5 to 30% (5, 10, 15, 20, 25 and 30%, respectively) by energy; Series 3: D14071613–D14071618 and series 4: D14071619–D14071624 fixed the level of protein at 10% (series 3) (10,30, 40, 50, 70, and 80%, respectively) or 25% (series 4) (8.3, 25,33.3, 41.7, 58.3, and 66.6%, respectively) by energy	The variations in food intake and body weight changes increased with the elevation of dietary fat levels	[83]

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		and varied the fat content from 8.3 to 80% by energy		
Xue-Ying Zhang, Wei Shen,2018	Male and female Brandt's voles (3-4 mouth of age)	HFD (22.9 kJ/g, which consisted of 27% fat [soybean oil], 18% protein, 12% crude fiber, and 23% carbohydrate; Beijing HFK Bioscience Co.); A standard rabbit pellet chow (low-fat control diet [LFD]; 17.5 kJ/g, which consisted of 2.7% fat, 18% protein, 12% crude fiber, and 47% carbohydrate)	Diversity of Thermogenic Capacity Predicts Divergent Obesity Susceptibility in a Wild Rodent	[84]
Levin,1985	Male Sprague-Dawley rats (n=40; Charles River) at 3-mo of age	Purina rat chow caloric content by bomb calorimetry 4.0 kcal/g); A semisynthetic diet ("condensed milk;" CM diet) composed of chow, corn oil, sweetened condensed milk containing 16.3% fat, 14.7% protein, and 56.3% carbohydrate	After 15 wk on a moderately high-calorie high-fat (CM) diet, 43% of 40 3mo-old male Sprague-Dawley rats developed diet-induced obesity (DIO) (29% more weight gain), whereas 57% of diet-resistant (DR) rats gained no more weight than 20 chow-fed controls	[88]
Chang,1990	Female Wistar rats (n=70; Harlan Madison, WI)	A low-fat diet (20% of calories from fat, 20% from protein, and 60% from carbohydrate), the HFD diet (60% of calories from fat)	OP (obesity prone) rats gained approximately twice as much weight as OR (obesity resistant) rats, OR rats had a significantly lower 24h respiratory quotient, and Insulin sensitivity was significantly higher in OR than OP rats	[89]
Claude Bouchord 2013	24 young lean men (12 pairs of identical twins)	A standardized 353 MJ (84 000 kcal) overfeeding protocol:15 percent from protein, 35 percent from lipid, and 50 percent from carbohydrate	The 100-day overfeeding protocol resulted in an average weight gain of 8.1 kg, ranging from 4.3 to 13.3 kg	[93]
Amit V. Khera 2019	A polygenic predictor comprised of 2.1 million common variants	Using a Bayesian approach to calculate a posterior mean effect for all variants based on a prior and subsequent shrinkage based on linkage disequilibrium, with the optimal predictor chosen based on maximal correlation with BMI in the UK Biobank validation dataset (N = 119,951 Europeans)	Among middle-aged adults, there was a 13-kg gradient in weight and a 25-fold gradient in risk of severe obesity across polygenic score deciles. In a longitudinal birth cohort, minimal differences in birthweight were noted across score deciles, but a significant gradient emerged in early childhood, reaching 12 kg by 18 years	[108]
K L Leibowitz 2007	Ten-day pregnant Sprague–Dawley rats (200–225 g; Charles iver Breeding Labs, Kingston, NY, USA)	a high-fat diet (5.15 kcal/g) consisting of 50% fat (80% lard, 20% vegetable oil), 25% carbohydrates (30% dextrin, 30% cornstarch, 40% sucrose), 25% protein (casein with 0.03% L-cysteine hydrochloride), plus 4% minerals and 3% vitamins	Among rats, there is a variability in the rate of weight gain, with those exhibiting a rapid rate reaching up to 8-10 g per day. Rats with a slower rate of weight gain achieve increments of 5-7 g per day	[94]

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Abbreviations

EI	Energy Intake
BMI	Body Mass Index
NPY/AgRP	The Neuropeptide Y/Agouti-related peptide neurons
POMC/CART	The Pro-opiomelanocortin/Cocaine amphetamine-regulated transcript
PA	Physical Activity
HFD	High-Fat Diet
LFD	Low-Fat Diet
FM	Fat Mass
FFM	Fat-Free Mass
VO2max	Maximal Oxygen Uptake
NST	Non-Shivering Thermogenesis
GPS	Genome-Wide Polygenic score

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