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Genetic Influences on Obesity: The Role of FTO and the Promise of Precision Nutrition in Personalized Weight Management

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Abstract

Obesity is a multifactorial condition arising from complex interactions between genetic susceptibility, environmental exposures, and behavioural factors. Among the genetic contributors identified through genome-wide association studies, variants within the fat mass and obesity-associated (FTO) gene represent some of the most consistently replicated loci associated with body mass index, adiposity, and appetite regulation across populations. Experimental and observational evidence suggests that FTO variants may influence energy intake, food preference, and metabolic pathways through effects on hypothalamic signalling, adipocyte biology, and epigenetic regulation. These findings have stimulated interest in precision nutrition approaches that aim to tailor dietary strategies according to individual genetic profiles. This narrative review critically examines the role of FTO gene variants in polygenic obesity and evaluates the current evidence supporting gene-diet interactions relevant to personalized weight management. We synthesized data from mechanistic studies, observational cohorts, randomized controlled trials, and meta-analyses to assess whether dietary interventions, including macronutrient composition, mediterranean-style dietary patterns, and discretionary food intake, can meaningfully modify obesity risk in individuals carrying FTO risk alleles. While mechanistic plausibility and observational associations are well established, evidence from intervention studies indicates that genotype-specific responses are generally modest and context-dependent. Overall, current findings support the potential of precision nutrition as a complementary framework rather than a deterministic approach to obesity management. Further large-scale, long-term, and ethnically diverse intervention studies are required to clarify clinical utility and inform evidence-based implementation.

Keywords: Nutrigenetics, Obesity, precision nutrition, FTO gene

Introduction

Obesity is classified by the World Health Organization (WHO) as a chronic, relapsing disease arising from complex interactions between genetics, neurobiology, eating behaviours, access to healthy diet, market forces, and the broader environment(1). According to the WHO, worldwide adult obesity has more than doubled since 1990, and adolescent obesity has quadrupled. (1). While obesity was once considered a problem primarily affecting high-income nations, its prevalence has surged in middle and low income countries, reflecting broader shifts in dietary patterns, physical activity levels, and urbanization(1). This alarming rise underscores the urgent need to address obesity as a critical public health challenge.

Obesity is a multifactorial condition influenced by a complex interplay of environmental, behavioural, and genetic factors. Environmental changes, such as the widespread availability of energy dense, nutrient poor foods and increasingly sedentary lifestyles, have been significant drivers of the obesity epidemic(2). However, these factors alone do not fully explain the variability in obesity risk among individuals. A growing body of evidence highlights the strong genetic underpinnings of obesity, which can amplify an individual's susceptibility to weight gain in obesogenic environments(3). Understanding the genetic contributions to obesity is therefore essential for developing targeted interventions and personalized management strategies.

The genetic basis of obesity has been a subject of scientific inquiry for nearly a century. Early studies, such as Davenport’s 1923 investigation were among the first to suggest a hereditary influence on body weight and body mass index (BMI)(4,5). Obesity can broadly be classified into monogenic and polygenic forms. Monogenic obesity is rare and typically results from highly penetrant mutations in single genes involved in appetite regulation and energy balance, often leading to severe, early-onset obesity. In contrast, polygenic obesity which accounts for the vast majority of obesity cases, arises from the cumulative effects of multiple common genetic variants, each conferring a small increase in risk, acting in concert with environmental and lifestyle factors(2). Advances in genetic research, particularly genome-wide association studies (GWAS) have revolutionized our understanding of the genetic architecture of obesity(5,6). A strong correlation exists between an individual's BMI and the obesity of their biological parents(7,8)**.** GWAS have identified numerous genetic variants associated with obesity risk, including the fat mass and obesity-associated (FTO) gene, which has been consistently linked to susceptibility to polygenic obesity(9). Understanding the genetic basis of obesity is essential for developing more effective, personalized interventions(10). Traditional weight management strategies, such as general dietary and exercise recommendations do not work equally well for everyone, highlighting the need for personalized approaches. The field of precision nutrition aims to address this gap by tailoring dietary interventions based on genetic profiles, including variations in the FTO gene.

Therefore, this narrative review explores the role of the FTO gene in the development of polygenic obesity and examines the potential of precision nutrition as a tool for personalized weight management. By synthesizing findings from genetic studies, nutrigenetic research, and public health interventions, this review aims to provide insights into how genetic information can inform dietary recommendations to improve health outcomes. Furthermore, it highlights the need for further research to address gaps in our understanding of the genetic and environmental determinants of obesity and to assess how dietary interventions tailored to individual genetic profiles can be used to improve overall health and well-being.

Methodology

A comprehensive search strategy was implemented to identify relevant studies published between January 2008 and January 2025. Literature searches were conducted using PubMed, Google Scholar, and ScienceDirect, and the retrieved information was synthesized into a structured narrative review. The following keywords and their combinations were used: Nutrigenetics, Nutrigenetic Testing, Precision Nutrition, Obesity, Body Composition, FTO Gene, FTO Variant, Polygenic Obesity, Personalized Weight Management, Dietary Interventions, High-Calorie Foods, High-Protein Diet, and Weight Loss. Boolean operators (AND/OR) were applied to refine searches and ensure comprehensive retrieval of relevant literature. To ensure a focused exploration of the impact of the FTO gene on polygenic obesity and the role of precision nutrition in personalized weight management, studies were included if they, examined the genetic influences of obesity, particularly the role of the FTO gene and/or investigated gene-diet interactions and personalized dietary interventions for obesity management, and/or explored the FTO gene's influence on appetite regulation and energy expenditure, and/or assessed the potential of precision nutrition for personalized obesity management and were primary research studies, including clinical studies, genome-wide association studies (GWAS), randomized controlled trials (RCTs), and intervention studies. Only studies published in English were included to ensure consistency in interpretation and analysis. The selection process followed a structured approach to identify and evaluate relevant studies. First, titles and abstracts were screened to determine alignment with the review's aim. Studies meeting the initial criteria underwent a full-text review to assess methodological rigor, relevance, and contribution to the understanding of FTO gene-driven obesity and precision nutrition interventions. The synthesized evidence was organized thematically to provide a comprehensive narrative on how nutrigenetics informs personalized weight management strategies, highlighting key findings, emerging trends, and research gaps.

Details of the image-gathering procedures

All images were created by the author with the aid of artificial intelligence (https://www.bing.com/images/create)

Fat mass and obesity-associated gene (FTO) - A key player in polygenic obesity

The FTO gene, located on chromosome 16q12.2, encodes the fat mass and obesity-associated protein, which is involved in energy homeostasis, appetite regulation, and body mass regulation(11). Notably, the obesity associated single nucleotide polymorphisms (SNPs) within FTO are not randomly distributed but are highly clustered within the first and second introns of the gene. These intronic variants are in strong linkage disequilibrium, meaning that many commonly studied SNPs (e.g., FTO rs9939609, FTO rs1421085, FTO rs1558902) are highly correlated and often tag the same underlying genetic signal. This genomic architecture explains why multiple FTO SNPs have been repeatedly associated with obesity-related traits across studies(12).

FTO gene can experience both homozygous and heterozygous types of mutations which leads to polygenic obesity. As a member of the AlkB-related non-heme iron and 2-oxoglutarate-dependent oxygenase superfamily, the FTO protein is involved in the demethylation of nucleic acids, particularly mRNA, which influences gene expression related to adipogenesis, fat storage, and energy intake(13). The gene's involvement in demethylation processes suggests that it may modulate the expression of other genes involved in metabolic pathways, but the precise biological pathways remain under investigation. This gap in knowledge highlights the need for further research to elucidate the molecular mechanisms by which FTO influences obesity.

Variants of the FTO gene have been strongly associated with an increased risk of obesity, making it one of the most studied genes in the context of polygenic obesity. FTO gene has high and low obesity risk variants. Each person inherits two copies, one from each parent.

Inheriting two high-risk copies increases obesity risk by around 70%⁽¹⁴⁾. FTO gene variants (such as FTO rs9939609) are strongly associated with increased BMI and obesity. These variants are linked to increased food intake and preference for energy-dense, high-calorie foods. The mechanism involves the regulation of hypothalamic neurons, which control hunger and satiety^(15,16). In individuals with risk variants, FTO expression is altered, leading to dysregulated appetite signalling, increased caloric intake, and ultimately, weight gain.

Additionally, studies have shown that the FTO gene appears to influence the browning of adipose tissue, a process where white fat is converted into brown-like adipocytes, which affects energy expenditure and fat storage. Claussnitzer et al. demonstrated that a specific single-nucleotide polymorphism (SNP) in the FTO gene (FTO rs1421085) disrupts a conserved motif for ARID5B repressor, leading to increased expression of IRX3 and IRX5. This shift promotes the development of white adipocytes over brown adipocytes, thereby reducing thermogenesis and increasing fat storage. The interaction between dietary components and FTO gene variants also plays a role in adipose tissue browning. Omega-3 fatty acids have been found to promote the browning of WAT, potentially counteracting the effects of FTO risk alleles⁽¹⁷⁾. Since this variant shifts the balance from energy-burning brown adipocytes to energy-storing white adipocytes, reducing heat production and fat-burning capacity. As a result, individuals with this variant are more prone to storing fat and have a reduced ability to metabolize it efficiently, contributing to obesity. These studies highlight how specific FTO variants, like FTO rs1421085, can directly impact metabolic processes and energy balance, emphasizing the importance of understanding genetic influences on obesity and tailoring interventions accordingly. However, the exact mechanism of the FTO gene regulating body fat and body weight is under study⁽¹⁸⁾.

A case-control study done by Proença da Fonseca et al. examined the association of genetic polymorphisms with obesity class II or greater and related obesity traits in a Brazilian cohort of 501 participants. Results showed that the FTO rs17817449 TT genotype was significantly linked to severe obesity and distinct cytokine expression. Moreover, this study also revealed that individuals with severe obesity (cases group) were more likely to carry eight or more genetic risk alleles compared to those in the normal-weight control group⁽¹⁹⁾. Indicating that a higher number of these obesity-related genetic variations was more common among people with severe obesity, suggesting a stronger genetic influence on their condition.

De Soysa et al. examined the association between FTO rs9939609 genotypes and appetite-related hormones in 96 adults with severe obesity and found that women with the AA genotype, having more body fat was linked to higher ghrelin levels compared to those with the TT or AT genotypes(20). This suggests that body fat may influence hunger signals differently in people with certain FTO gene variations, which needs further study. Similarly, a recent study in the Journal of Lifestyle Genomics examined FTO gene SNP rs9939609's association with appetite traits in people who are normal-weight. It compared subjective appetite sensations, ghrelin and insulin levels, and dietary intake based on the FTO rs9939609 genotype. The study concluded that carriers of the A allele of FTO rs9939609 may have a stronger preference for foods, particularly added sugars(21). Supporting these findings, studies on adiposity-matched, people who are normal-weight demonstrated that AA carriers of FTO rs9939609 exhibit higher circulating acyl-ghrelin (AG) levels, attenuated postprandial appetite suppression, and altered neural responses to food cues in homeostatic and reward-related brain regions. Mechanistically, FTO was shown to regulate ghrelin expression via reduced m6A methylation of ghrelin mRNA, providing a direct link between FTO risk alleles and increased energy intake(22). In a randomized crossover study of twelve males with the AA genotype of FTO rs9939609 and twelve males with the TT genotype, participants completed a control (8 hours rest) and exercise (1 hours at 70% peak oxygen uptake, 7 hours rest) trial, with a fixed meal at 1.5 hours and an ad libitum buffet at 6.5 hours. AA genotype of FTO rs9939609 individuals showed lower baseline BChE activity, higher AG:DAG ratios, attenuated postprandial AG suppression, and greater ad libitum energy intake. Exercise increased BChE activity and suppressed AG and the AG:DAG ratio, effectively normalizing the higher ghrelin profile in AA carriers of FTO rs9939609, though energy intake remained unchanged(23). These findings suggest that the FTO rs9939609 A allele influences appetite and energy intake through both hormonal and neural mechanisms, and that lifestyle interventions such as exercise may mitigate these genotype-related effects.

It has been revealed that the FTO gene's influence on obesity is more complex than previously believed(24). These findings reveal the potential for precision nutrition to address the genetic and behavioural factors contributing to obesity. By tailoring dietary recommendations to an individual’s genetic profile, it may be possible to mitigate the effects of high-risk FTO variants. However, the implementation of such strategies requires robust evidence from large-scale, long-term studies to ensure their effectiveness and safety.

Role of precision nutrition in obesity management- A promising approach to personalized obesity management

Precision Nutrition and Nutrigenetics intersect by using genetic information to customize and personalize dietary guidance. As outlined in Figure 1, Precision nutrition incorporates genomic data, alongside lifestyle, behaviour, and physiological factors, to develop personalized and universal guidelines for maintaining health, managing non-communicable diseases, and implementing health strategies(25).

Unhealthy dietary patterns are associated with an increased risk of obesity. Associations between non-modifiable risk factors, such as genetic variations and obesity, may be modified by diet(26). High intake of sugar-sweetened beverages, fried food, and a sedentary lifestyle are particular risk factors for obesity among adults and children due to their complex interaction with genetic variants associated with obesity(27).

In recent years, precision nutrition has emerged as a transformative approach to obesity management. By leveraging insights from an individual's genetic makeup, healthcare providers can tailor dietary recommendations to optimize macronutrient composition, portion sizes, and specific dietary adjustments. This personalized strategy not only enhances the effectiveness of weight loss interventions but also improves long-term weight management outcomes(28).

As shown in **Table 1**, different FTO variants are associated with specific dietary patterns to help manage BMI and obesity risk. These findings highlight the growing importance **of precision nutrition,** which lies in its ability to move beyond a "one-size-fits-all" approach to offering targeted interventions that align with an individual's unique biological and genetic profile(29). As research continues to uncover the complex interactions between genetics, diet, and lifestyle, precision nutrition represents a promising frontier in the fight against obesity.

Reduced intake of discretionary foods for individuals with the FTO rs9939609 genotype

Recent research on gene-environment interactions has highlighted how dietary intake influences the relationship between genetic markers and metabolic health, body composition, and fat accumulation.

A cross-sectional analysis of baseline data from the Food4Me study, a 6-month randomized controlled trial conducted across seven European countries, examined the association between the FTO rs9939609 genotype, dietary intake, and adiposity-related outcomes in approximately 1,280 adults focusing on discretionary foods, energy-dense, nutrient-poor items like sugary snacks and fast food. The study found that a dietary pattern high in discretionary foods was linked to higher BMI and larger waist circumference (WC). In parallel, the FTO rs9939609 risk genotype was associated with higher BMI and waist circumference; however, no evidence of a dietary interaction with genotype was observed(26). The large multicountry sample and standardized methodology strengthen the reliability of these observations, although the cross-sectional design and reliance on self-reported dietary data limit causal inference. This may be due to limited power to detect interaction effects, reliance on self-reported dietary intake, and the observational nature of the analysis. Future research using longitudinal or intervention designs with improved dietary exposure assessment and larger genotype-stratified samples could be used to clarify the interaction further. Overall, this evidence reinforces population-wide recommendations to limit discretionary foods high in saturated fat and low in fibre. For individuals carrying the FTO rs9939609 genotype, who already exhibit higher BMI and waist circumference, adherence to a low-discretionary-food, fibre-rich dietary pattern could be important for supporting healthy weight maintenance.

Further mechanistic evidence comes from pediatric research, where children and adolescents carrying one or two FTO rs9939609 A alleles (AA/AT) exhibited greater BMI, fat mass, and loss-of-control (LOC) eating episodes compared with TT subjects. In a buffet-style test meal, AA/AT youth consumed a higher proportion of energy from fat, suggesting that both LOC eating and preferential selection of energy-dense, palatable foods may mediate the effect of FTO on excess body weight(30). These findings highlight potential behavioral mechanisms underlying gene–diet interactions and suggest that early dietary interventions targeting discretionary and high-fat foods may be particularly important for at-risk youth. In contrast,, Sonestedt et al. explored how dietary fat intake interacts with the FTO rs9939609 genotype and found that individuals with the risk allele are more likely to gain weight when consuming high-energy diets, highlighting the importance of dietary control(31). This observational cohort study used a modified diet history method to assess habitual dietary intake, incorporated direct anthropometric measurements, and collected detailed information on leisure-time physical activity, strengthening exposure and outcome assessment compared with studies relying solely on self-report. Significant interactions were observed between FTO genotype and energy-adjusted fat intake ($P = 0.04$), as well as carbohydrate intake ($P = 0.001$), in relation to BMI. Notably, the increase in BMI across FTO genotypes was confined to individuals consuming high-fat diets. however, the observational design, reliance on self-reported dietary data, and predominantly European study population may introduce residual confounding and limit generalisability. Future studies could improve the detection of gene–diet interactions by using prospective or intervention designs, larger genotype-stratified samples, more objective dietary assessments, and greater ethnic diversity to better clarify how dietary patterns influence obesity risk according to genetic background.

Adding to this evidence, a recent cross-sectional study in an urban Argentinian population (n = 173) found that A-carriers of rs9939609 consumed more total fat, saturated fatty acids, monounsaturated fats, and fat-rich ultraprocessed foods, while consuming slightly less carbohydrate than TT homozygotes. A-carriers also adhered more to a Western dietary pattern and consumed more “milk and yogurt” and “animal fats” (32). These findings confirm that the FTO rs9939609 A allele contributes to nutrient and food intake variability across populations, particularly increasing the consumption of SFA-enriched foods. From a public health perspective, this highlights that A-carriers may be less adherent to dietary guidelines limiting saturated fat intake, reinforcing the relevance of tailored dietary advice in precision nutrition approaches.

High-level evidence from a systematic review and meta-analysis by Livingstone et al. indicates that, at individuals with the FTO risk allele (rs9939609) show increased energy intake, especially from high-calorie, low-nutrient foods, and how reducing discretionary foods could help manage obesity risk. despite higher energy intake observed among risk allele carriers, carriage of the FTO rs9939609 minor allele does not impair response to dietary, physical activity, or drug-based weight loss interventions(33). This suggests that lifestyle interventions remain effective for individuals with genetic susceptibility. Future research could explore whether personalized dietary strategies, such as targeted reduction of discretionary foods, further enhance intervention efficacy across different populations or ethnic groups.

FTO rs9939609 and reduced response to diet and lifestyle interventions

Recent advances in research on gene-environment interactions have deepened our understanding of how dietary intake influences the relationship between genetic markers and metabolic health, body composition, and fat mass accumulation. Individuals carrying the risk allele (A) of FTO rs9939609 tend to have a higher BMI and are at greater risk of obesity.

Research shows that despite engaging in dietary changes and physical activity, individuals with the FTO rs9939609 variant may experience less significant weight loss compared to non-carriers. This diminished response is believed to result from the FTO gene's influence on appetite regulation and energy intake. Individuals with the risk allele have been shown to have a stronger preference for high-calorie foods and may exhibit less satiety after meals, leading to increased energy consumption. Although lifestyle interventions, such as calorie restriction and increased physical activity, are effective in managing weight, carriers of the FTO rs9939609 variant may need more tailored and intensive strategies to achieve comparable weight loss results. Moreover, some studies suggest that while the short-term response to interventions might be limited, long-term adherence to a healthy diet and regular physical activity can still benefit individuals with the FTO risk allele.

A nutrigenetic intervention study in 18 overweight or adults with obesity examined multiple genetic variants, including FTO rs9939609, in the context of adherence to a Mediterranean diet (Med-diet) and physical activity. Individuals carrying the A allele of FTO rs9939609 exhibited smaller reductions in weight and BMI and differential changes in PREDIMED scores (a measure of Med-diet adherence) compared with TT homozygotes, suggesting a potential interaction between genotype and dietary adherence (34). While the intervention design allowed careful monitoring of diet, the small sample size and possible metabolic confounders (e.g., type 2 diabetes, impaired glucose regulation) limit statistical power and generalizability. Additionally, unassessed factors such as gut microbiota and epigenetic modifications may influence response. In a longitudinal study of 193 adults with obesity, participants completed a 12-week formula-based weight loss program followed by a 40-week weight maintenance phase. Homozygous A allele carriers (AA) of FTO rs9939609 had higher baseline BMI and body weight than TT homozygotes. Although initial weight loss was similar across genotypes, AA carriers of FTO rs9939609 showed less additional weight loss and greater weight regain during maintenance, highlighting a potential role of FTO in long-term weight stabilization(35).

Evidence from meta-analysis and controlled trials provides additional context. A meta-analysis of 10 studies (comprising 6951 participants) found that individuals carrying the FTO rs9939609 homozygous A allele may experience slightly greater weight loss than non-carriers in some settings, particularly in diet-only interventions and after adjusting for baseline BMI. However, effect sizes were generally small, and heterogeneity across studies limited the certainty of subgroup analyses(36). Similarly, the two-year CALERIE™ phase 2 trial demonstrated that in healthy, adults who are normal weight, FTO rs9939609 genotype did not significantly influence adherence to prolonged caloric restriction or most body composition and biomarker outcomes, though minor genotype-specific differences in resting metabolic rate were observed(37). Together, these studies highlight that the influence of FTO rs9939609 on intervention response is modest, context-dependent, and not uniformly observed across study designs, revealing the need for larger, controlled, and diverse cohorts.

Mechanistic studies provide biological plausibility for these findings. Controlled trials have shown that rs9939609 A allele carriers exhibit attenuated postprandial suppression of acylated ghrelin, an orexigenic hormone, alongside altered neural responses to food cues in brain regions related to homeostatic and reward signaling. These hormonal and neural differences may promote increased energy intake and reduced satiety, partially explaining why standard interventions may be less effective in carriers(22,23). Importantly, these studies are mostly conducted in adults who are normal weight under controlled conditions, and further work is needed to confirm whether these physiological differences translate to real-world dietary behaviors and weight outcomes across diverse populations.

FTO rs9939609 and response to the Mediterranean diet

Variants of the FTO gene, particularly FTO rs9939609, have been consistently associated with increased obesity risk, largely mediated through effects on appetite regulation and energy intake. Given the anti-inflammatory and nutrient-dense characteristics of the Mediterranean diet (Med-diet), several studies have investigated whether adherence to this dietary pattern can modify the association between FTO rs9939609 and adiposity-related outcomes.

Evidence from large observational cohorts suggests that adherence to the Med-diet may attenuate the relationship between FTO risk alleles and measures of adiposity. In the PREDIMED trial, involving over 7,000 older adults at high cardiovascular risk, lifestyle factors including Med-diet adherence and physical activity were shown to modify associations between FTO rs9939609 and body weight outcomes. Participants with higher adherence to the Med-diet exhibited a reduced expression of genetic susceptibility to obesity, regardless of genotype(38). Strengths of this study include its large sample size and validated dietary assessment tools; however, reliance on self-reported intake, the older age of participants, and the high baseline cardiometabolic risk limit generalizability to younger and more diverse populations.

Supporting evidence from related PREDIMED analyses and other Mediterranean cohorts indicates that greater adherence to the Med-diet is associated with lower BMI and waist circumference among FTO rs9939609 risk allele carriers(39). Nevertheless, these findings are predominantly observational and do not establish causality. Furthermore, genotype–diet interactions were generally modest, suggesting that the Med-diet does not eliminate genetic risk but may partially offset it through favourable effects on satiety, energy density, and metabolic health.

Intervention evidence specifically testing genotype-stratified responses to the Med-diet remains limited. Small nutrigenetic trials have reported differential adherence or weight outcomes by FTO genotype; however, these studies are constrained by short duration, limited statistical power, and potential confounding from unmeasured factors such as gut microbiota or baseline metabolic status. Meta-analyses of dietary interventions more broadly indicate that lifestyle modification is effective across genotypes, with no consistent evidence that FTO rs9939609 carriers derive uniquely greater or lesser benefit from Med-diets.

Collectively, current evidence suggests that adherence to the Med-diet is associated with favourable weight and metabolic outcomes irrespective of FTO rs9939609 genotype, with possible modest attenuation of genetic risk among carriers. Rather than supporting genotype-specific dietary prescriptions, these findings reinforce the Med-diet as a broadly beneficial dietary pattern that may be particularly relevant for individuals with elevated genetic susceptibility to obesity. Further well-powered randomized controlled trials in diverse populations are required to clarify whether genotype-informed dietary guidance provides clinically meaningful advantages over standard evidence-based recommendations.

FTO rs9939609 and artificially sweetened beverages

Artificially sweetened beverages (ASBs) have been the subject of debate regarding their role in weight management. Individuals carrying FTO rs9939609 linked to increased appetite, energy intake, and a higher risk of obesity. Studies suggest that individuals with these genetic variants may have different responses to ASBs compared to the general population. Similarly, individuals with the risk variant, known for its role in regulating hunger and energy balance, may experience compensatory overeating when consuming ASBs due to incomplete satiety signalling. Research has found that despite their low caloric content, ASBs may not effectively reduce overall energy intake or body weight in carriers of these risk alleles, potentially leading to weight gain or limited effectiveness in weight loss strategies. While the exact mechanisms remain unclear, the interaction between ASBs and the FTO rs9939609 variant suggests that ASBs may not be a beneficial tool for weight management in individuals carrying the rs9939609 obesity-risk allele

A Norwegian study by Grill et al. investigated the modifying effects of age, sex, and lifestyle factors on the association between the FTO rs9939609 variant and obesity in 25,686 participants. The genetic association with BMI was stronger in younger compared with older individuals and more pronounced among physically inactive participants. Sex-specific differences were observed in relation to artificially sweetened beverage intake. Although BMI increased with increasing intake of artificially sweetened beverages in both men and women, a significant gene–environment interaction between FTO rs9939609 and artificially sweetened beverage consumption was observed only in men. Among men with high intake, carriers of the FTO risk allele exhibited a higher BMI compared with non-carriers, whereas no genotype-related differences were evident among men with low intake. In women, no significant interaction was detected, with BMI increasing at a similar rate across FTO genotypes. The impact of FTO can differ between both age and gender(40). Many studies of FTO rs9939609 across diverse ethnic groups have included mixed-gender populations(26,30–33). This indicates the importance of analyzing gender separately, as observed differences could reflect true biological variation, gender-specific responses, age-related effects or differences in dietary and lifestyle habits. Understanding these variations could be important for developing personalized strategies for obesity prevention and management.

While ASBs are often promoted as a healthier alternative to sugar-sweetened beverages, their effectiveness may be limited in individuals with the FTO rs9939609 variant due to altered appetite regulation and compensatory eating behaviours. Therefore, generic dietary recommendations, such as replacing sugar-sweetened beverages with ASBs, may not be effective for everyone and could even be counterproductive for those with specific genetic variants. Future studies could be done to confirm this association.

FTO rs1558902 and high protein diet

The FTO rs1558902 variant, similar to other FTO gene polymorphisms, has been associated with increased BMI and a predisposition to obesity. Research indicates that dietary composition, particularly a high-protein diet, may mitigate some of the negative effects of this variant. High-protein diets are known to enhance satiety, preserve lean muscle mass, and promote fat loss, which can be especially beneficial for individuals with genetic susceptibility to weight gain, such as those carrying the FTO rs1558902 risk allele. Several studies suggest that individuals with the FTO rs1558902 variant may experience better weight loss outcomes and improvements in body composition when following a high-protein diet compared to other macronutrient compositions. This enhanced response is likely due to the protein's ability to suppress appetite and reduce overall energy intake, helping to offset the increased hunger and food preference for energy-dense foods commonly observed in individuals with FTO variants. While the FTO rs1558902 variant has been linked to higher risk of obesity, adopting a high-protein diet may provide an effective dietary intervention for better weight management and appetite control.

Studies examining gene-diet interactions have shown that certain dietary factors, such as low-fat intake, can modify the impact of the FTO gene on BMI or fat distribution. Stronger evidence comes from a randomized controlled trial, which investigated the potential influence of the FTO rs1558902 variant on weight loss in a 2-year dietary intervention study involving 742 adults with obesity of mixed gender, predominantly of European ancestry. Findings indicated that individuals carrying the risk allele of the FTO variant experienced greater reductions in weight when following a high-protein diet. Conversely, a contrasting genetic effect was observed regarding changes in fat distribution in response to a low-protein diet. This study suggests that a high-protein diet may be beneficial for weight loss for individuals with the risk allele of the FTO variant rs1558902. The long follow-up duration controlled dietary intervention, and adjustment for key confounders strengthen the internal validity of these findings. However, the limited ethnic diversity of the cohort restricts extrapolation to non-European populations, and changes in body composition beyond body weight were not comprehensively assessed(41).

In contrast, cross-sectional observational studies can show associations, but they cannot prove cause and effect. A study of 1,491 young adults (20–29 years) from mixed ethnic backgrounds reported that East Asian individuals homozygous for the rs1558902 risk allele exhibited significantly higher BMI and waist circumference under conditions of low protein intake ($\leq$18% of total energy). In contrast, no statistically significant genotype-related differences in BMI or waist circumference were observed among individuals consuming higher-protein diets (>18% of total energy), consistent with a significant FTO–protein interaction (BMI: $p = 0.01$; waist circumference: $p = 0.007$). Although the overall sample size and ethnic stratification strengthen the exploratory value of the analysis, the number of risk-allele homozygotes was small, particularly among East Asians, limiting statistical power.

Dietary intake was assessed using a food frequency questionnaire, which is subject to recall bias and measurement error(42). Taken together, evidence from randomized controlled trials and observational studies suggests that higher dietary protein intake may partially offset the obesogenic effects of the FTO rs1558902 variant, although the strength and generalizability of this interaction vary by study design and population.

Dietary macronutrient distribution and fiber intake in carriers of FTO rs3751812 and FTO rs8050136

Evidence from observational studies suggest that macronutrient composition and dietary fiber intake may modify the association between certain FTO variants and adiposity-related outcomes. A study conducted by Czajkowski et al., in a Polish Caucasian population, demonstrates that carriers of the GG genotype of FTO rs3751812 and the CC genotype of FTO rs8050136 exhibit lower body weight, BMI, and total body fat when their habitual energy intake included, more than 48% of carbohydrates and less than 30% fat(43). While these findings are consistent with dietary reference ranges for carbohydrates and fat intake(44), the cross-sectional design limits causal inference, and dietary intake was assessed using self-reported methods, which are prone to recall bias and measurement error. Additionally, Esfahani et al. reported that fiber intake influenced the association between multiple FTO variants, including FTO rs3751812, FTO rs8050136, FTO rs1421085, FTO rs1121980, FTO rs17817449, and FTO rs9939973 and obesity risk, with stronger effects observed among individuals consuming higher levels of dietary fiber and carrying multiple risk alleles(45). Consistent with this, another study found that daily fiber intake above 18 g was associated with lower hip circumference in GG carriers of FTO rs3751812 and CC carriers of FTO rs8050136(46). Although these findings support a potential protective role of dietary fiber, the reliance on anthropometric proxies and observational designs precludes conclusions regarding causality or long-term effects.

However, the evidence base is largely observational, geographically limited, and heterogeneous with respect to dietary assessment methods and outcome measures. Multiple testing across SNPs also raises the possibility of chance findings. Despite these limitations, available data suggest that macronutrient composition and dietary fiber intake may modify obesity risk in carriers of FTO variants, supporting the conceptual promise of precision nutrition. Nonetheless, causality cannot yet be established. Confirmation in well-designed randomized controlled trials and in ethnically diverse populations is required.

Macronutrient intake patterns (carbohydrate and protein distribution) in relation to FTO rs8044769

Panoutsopoulou et al., have examined the role of the FTO rs8044769 in knee and hip osteoarthritis (OA) risk, considering BMI. Data from UK and Australian cohorts (5,409 knee OA cases, 4,355 hip OA cases, and up to 5,362 controls) showed that the FTO rs8044769 variant was significantly associated with overweight (BMI ≥25) and knee OA(47). Evidence for FTO rs8044769 remains inconsistent across populations, and some have reported no association. Dai et al., examined the association between the FTO rs8044769 and its potential link to BMI and osteoarthritis (OA) in a Chinese Han population. A case-control approach was used with 890 OA cases and 844 controls, but no significant association was found between rs8044769 and BMI or OA susceptibility(48). However, in African-Americans T allele carriers of FTO rs8044769, when present in heterozygous form, may protect against higher BMI levels, but only in early adulthood (20s and 30s)(49). These variants and their effect on BMI may vary by ethnicity and other factors, as different ethnic groups have distinct dietary practices. Given the limited studies on FTO rs8044769 and the mixed findings across populations, future research should focus more on diverse ethnic groups to better understand how these variants influence BMI and to develop personalized dietary recommendations for more effective obesity management.

Czajkowski et al, found that in Caucasian subjects of Polish origin, Body weight and BMI were significantly higher in TT and CT carriers of FTO rs8044769 if daily energy intake derived from carbohydrates was less than 48%. Moreover, TT carriers of FTO rs8044769, observed higher blood glucose concentration while fasting if more than 18% of total energy intake was derived from proteins(43). However, given the limited number of studies, mixed results across ethnic groups, and the observational nature of the evidence, these findings should be interpreted cautiously. Further studies in diverse populations are needed before translating these gene–macronutrient interactions into precise personalized dietary recommendations.

Table 02 outlines details of studies on the FTO gene and its association with obesity

Limitations and challenges of nutrigenetics and precision nutrition in obesity

While nutrigenetics and precision nutrition show great potential in preventing and managing obesity, some challenges and limitations hinder their implementation in biomedical research and clinical practice. One major limitation is the control of participants' dietary intake, however, the use of specific biomarkers for food intake could potentially overcome this obstacle(50).

High-energy and ultra-processed foods high in sodium, added sugars, and saturated fats are readily available in stores and restaurants, making them common in households. These environments, especially in lower socioeconomic neighbourhoods, create obstacles such as limited access to fresh and healthy products and an abundance of fast-food options. Additionally, high-energy and ultra-processed foods are often cheaper than healthier alternatives, leading to economic constraints that favour the consumption of less nutritious options. Social, cultural, economic, and political factors, including advertising and large portion sizes, further complicate efforts to promote healthy eating(51).

Public acceptance and ethical concerns also pose significant barriers. A population-based study from Quebec, Canada reported generally positive attitudes toward nutrigenetic testing and its potential benefits. However, participants expressed concerns regarding data privacy, ownership of genetic information, and confidentiality. Cost was identified as a major barrier, with willingness to pay strongly associated with higher socioeconomic status, suggesting that precision nutrition approaches may exacerbate existing health inequalities if access remains limited(52).

Regulatory oversight remains another challenge. Although the US Food and Drug Administration approved direct-to-consumer genetic testing by 23andMe in 2017, these tests have limited clinical sensitivity. Moreover, many unregulated companies now offer nutrigenetic-based dietary advice with variable scientific validity. A survey of online DNA testing services revealed that most provided health- and nutrition-related recommendations, raising concerns about accuracy, standardization, and the potential for misleading health claims(53).

Duygu et al., investigated the relationship between the FTO gene (rs9939609) polymorphism and body fat markers in 200 Turkish adults (18–65 years old). Results showed that individuals with the AA genotype had significantly higher total body fat percentages compared to those with AT and TT genotypes, especially in females. However, no significant differences were found in abdominal fat levels, BMI, body adiposity index (BAI), and lipid accumulation products (LAP) across genotypes(54). According to the study, the FTO rs9939609 variant influences overall body fat accumulation but not abdominal fat in Turkish adults. A similar cross-sectional study was done by Mohammed et al., which examined the association between the FTO rs9939609 and the risk of obesity and type 2 diabetes (T2D) in 201 healthy young university students in Kuwait, found no significant association between FTO variants and BMI or the risk of T2D. The study concludes that FTO is not a significant predictor of obesity or T2D in young Kuwaiti adults(55). Even though meta-analyses and genome-wide association studies (GWAS) have identified FTO as a significant contributor to obesity, findings from those cross-sectional studies highlight inconsistencies in specific populations. These discrepancies may be due to small sample sizes, which limit statistical power and the ability to detect significant associations, and their impact may vary across different ethnicities, lifestyles, and environmental factors. To improve the predictive strength of such studies, future research in this field should be conducted on a broader scale with larger, more diverse populations to better understand the FTO polymorphisms in obesity.

Importantly, evidence that genotype-based advice improves behaviour is limited. A randomized study in young adults found that FTO-based personalized dietary and physical activity advice did not significantly improve healthy eating motivation compared with non-genotype-based advice or controls(56). This suggests that the genetic component alone may not be enough to influence behaviour or motivate young adults to change their dietary habits. However, the study did not track actual changes in eating or physical activity behaviours, only self-reported motivation, so it’s unclear whether genotype-based advice influenced real-life dietary or activity changes. The study only followed participants for a short period (one week after receiving advice), which might not be enough time for significant behaviour changes. Long-term follow-up would be necessary to assess the sustained impact of personalized advice. There's often a gap in understanding complex genetic data, so simplifying explanations and using relatable language is key. Public health messages could focus on how genetics interacts with lifestyle and environment rather than providing overly technical information. Developing apps or websites where individuals can input basic health data (age, weight, activity levels, and genetic info) to receive personalized nutrition tips might be a fun and accessible way to engage people.

High costs of genetic testing and limited access to nutrigenetic services can restrict widespread implementation, especially in lower-income populations. Regulatory oversight is currently limited, raising concerns about the accuracy, standardization, and clinical validity of commercially available tests. Privacy, data security, and the potential for genetic discrimination are key ethical issues that must be addressed. Furthermore, there is a risk of overemphasizing genetic determinism, which may lead individuals to overlook the important role of lifestyle and environmental factors. Clear communication and education are essential to ensure that personalized nutrition recommendations are evidence-based, practical, and ethically responsible.

Future directions in nutrigenetics and precision nutrition for obesity

The application of genetic and molecular pathway information for understanding nutrient utilization and metabolism is crucial for personalized nutrition. This knowledge is made possible by the advancements in 'omics' technologies. Future research should aim to integrate data from genomics, epigenomics, transcriptomics, proteomics, and metabolomics to gain a comprehensive understanding of how individuals respond to different diets. By adopting this approach, more precise and actionable insights can be uncovered(57). By leveraging advanced technologies, genetic and environmental factors can be integrated more effectively and accurately. This includes utilizing methods like Genome-Wide Association Studies (GWAS), Genetic Risk Score (GRS) calculations, and machine learning models such as support vector machines and random forest algorithms. These technologies enable the analysis of large datasets and the identification of complex patterns, leading to more precise predictions. The application of these technologies and strategies in precision nutrition holds great promise for weight loss. They have the potential to accurately predict individual responses to different weight loss regimens and facilitate personalized dietary interventions(58). Precision nutrition encompasses big data management and ethical analysis. It involves incorporating genetic information, as well as phenotypic, cultural, behavioral, and lifestyle preferences, to maintain health and manage diseases. This approach guides both general and personalized counselling. Health information and communication technology, coupled with artificial intelligence (AI), can play a role in controlling and promoting nutritional health among diverse population groups(59). The promising use of AI necessitates the fast and dependable analysis of numerous variables gathered during monitoring. Artificial Neural Networks (ANNs) are crucial tools for achieving precision in AI, especially in precision applications. Nutrigenetic counselling provides personalized dietary advice based on an individual's genetic information. The accurate prediction of resting energy expenditure (REE) through ANNs enhances the information available for such counselling sessions, enabling more targeted and effective dietary recommendations(59,60).

Uncertainties of current predictions associated with nutrigenetics and how it affects the outcome.

Nutrigenetics and personalized nutrition represent a promising complementary approach. Nevertheless, uncertainties exist. Human genetics is highly complex, and the interactions between multiple genes and nutrients are not fully understood.

The complexity involved makes it challenging to foresee the effects of particular genetic variations on nutrient metabolism and health outcomes(41). Small effect sizes of individual genetic variants, such as those in the FTO gene, mean that very large sample sizes are required to reliably detect gene–diet or gene–lifestyle interactions. Many nutrigenetic studies have limited participant numbers, which reduces statistical power, increases the likelihood of false-positive findings, and limits reproducibility. Furthermore, predictions made by nutrigenetics often do not fully account for environmental and lifestyle factors, such as physical activity, stress, or overall diet, which can significantly influence health outcomes. As a result, dietary recommendations based on these studies may be incomplete or inaccurate. Until larger, well-powered, and diverse cohorts are studied, the clinical utility of many nutrigenetic findings remains uncertain(61). Many nutrigenetic claims are still based on emerging evidence. The findings of numerous studies may not always be reproducible due to their small sample sizes. The lack of robust evidence can result in uncertainty surrounding the recommendations given(62).

The issue of privacy, data security, and the possibility of genetic discrimination raises ethical concerns. Moreover, there is a potential for generating unrealistic expectations among consumers regarding the advantages of personalized nutrition(50). The issue of privacy, data security, and the possibility of genetic discrimination raises ethical concerns. Moreover, there is a potential for generating unrealistic expectations among consumers regarding the advantages of personalized nutrition(63).

These uncertainties can affect the outcomes of nutrigenetic predictions by leading to inconsistent or inaccurate dietary recommendations, which may not effectively improve health or could even cause harm if not properly validated.

Conclusion

Obesity reflects the cumulative effects of genetic susceptibility interacting with environmental, behavioural, and societal factors. Variants within the FTO gene remain among the most robustly associated genetic contributors to polygenic obesity, with evidence supporting roles in appetite regulation, energy intake, and adipocyte function. However, the effect sizes associated with individual FTO variants are small, and their influence on obesity risk is strongly modified by lifestyle and environmental context.

The emerging field of precision nutrition seeks to leverage genetic information to refine dietary guidance, yet current evidence does not support deterministic or genotype-exclusive dietary prescriptions based on FTO variants alone. While observational and mechanistic studies suggest that dietary patterns such as the Mediterranean diet, higher protein intake, or reduced consumption of energy-dense discretionary foods may attenuate genetic susceptibility, findings from randomized controlled trials and meta-analyses indicate that genotype-specific responses to dietary interventions are modest and inconsistent. Importantly, lifestyle interventions remain effective across genotypes, underscoring the primacy of behavioural strategies in obesity management.

Future advances in precision nutrition will require integration of polygenic risk scores, multi-omics data, and longitudinal phenotyping within diverse populations, alongside rigorous evaluation of behavioural, ethical, and socioeconomic considerations. Rather than replacing existing public health approaches, genetic information may be most valuable for enhancing risk stratification, understanding biological heterogeneity, and supporting individualized engagement with evidence-based dietary and lifestyle interventions. Cautious interpretation and responsible translation of nutrigenetic findings will be essential to ensure equitable, effective, and scientifically grounded applications in obesity prevention and management.

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Table 1: Dietary pattern based on FTO variants

FTO variant	Dietary pattern	Study type	Population (Ethnicity, n)	Main outcomes	Strength of evidence	Reference
rs9939609	Dietary pattern characterised by high discretionary foods and saturated fat, and low fibre intake	Cross-sectional observational study	European adults, multi-country, predominantly White (n = 1280), mixed gender	A dietary pattern high in discretionary foods and saturated fat and low in fibre was associated with higher BMI and waist circumference. FTO risk genotype was independently associated with adiposity, with no evidence of gene-diet interaction	Moderate	[26]
rs9939609	Preference for high-fat, energy-dense foods; loss-of-control (LOC) eating behaviour	Cross-sectional study with laboratory test meal	Children and adolescents (6–19 y) from USA, mixed ethnicity, n = 289 (laboratory meal test conducted in a subsample, n = 190), mixed	Children and adolescents carrying one or two FTO rs9939609 risk alleles(AA/AT) reported more frequent loss-of-control (LOC) eating and showed a	Moderate	[30]

			gender	preference for high-fat, energy-dense foods, suggesting behavioral mechanisms linking FTO variants to excess body weight		
rs9939609	High-fat diet; low carbohydrate/fibre	Cross-sectional	Middle-aged adults, Sweden; n = 4,839; mixed sex	FTO risk allele (AA) associated with higher BMI only among high-fat diet consumers; low physical activity accentuated risk	Moderate	31
rs9939609	Western dietary pattern; higher total fat, SFA, MUFA; lower carbohydrate; higher intake of milk/yogurt, animal fats, fat-rich ultraprocessed foods	Cross-sectional	Adults, La Plata, Argentina; mixed gender; n = 173	‘A’ allele associated with higher fat intake, lower carbohydrate intake, and adherence to Western dietary pattern	Moderate	32
rs9939609	Varied dietary pattern (no standardized	Systematic review and meta-	Overweight/ adults with obesity, n =	Carriage of FTO minor allele did not influence	Strong	64

	diet)	analysis of RCTs	9,563; majority white, North America & European; mixed gender	weight loss; individuals with the allele responded equally well to interventions		
rs9939609	Formula-based low-calorie diet (800 kcal/day) during weight loss, followed by structured weight maintenance diet	Longitudinal intervention study	adults with obesity, 18–72 y, Caucasian, n = 193 (Germany)	AA genotype associated with higher baseline BMI; no genotype effect on weight loss during formula diet, but AA carriers showed poorer weight maintenance and higher risk of weight regain	Moderate	[35].
rs9939609	Adherence to Mediterranean dietary pattern	Cross-sectional analysis (baseline of RCT cohort)	Older adults at high cardiovascular risk, Spanish population, n = 7,052	FTO risk allele associated with higher BMI, WC, and obesity; higher physical activity abolished genetic associations; higher adherence to Mediterranean diet biologically counterbalanced genetic risk	Moderate	[38]
rs9939609	Mediterranean	Multicent	Spanish adults	Mediterranean		[39]

	diet (high unsaturated fat from olive oil or nuts	er randomized controlled trial	at high CVD risk (European ancestry, n = 7,447)	diet attenuated the adverse metabolic and adiposity-related effects associated with FTO risk alleles; significant gene–diet interactions observed	Strong	
rs9939609	intake of artificially sweetened beverages	Large population-based observational study with cross-sectional and longitudinal analyses	Norwegian adults, homogeneous population (Nord-Trøndelag, n = 25,686)	FTO obesity-promoting effects were stronger in younger adults (20–40 years), men, and physically inactive individuals; regular intake of artificially sweetened beverages amplified FTO effects on BMI and WHR in men	Strong	40
rs1558902	Randomized diets differing in macronutrient composition;	Randomized controlled trial (POUND	adults with obesity, predominantly European ancestry, n =	Significant FTO and dietary protein interaction: risk-allele carriers	Strong	41

	high-protein vs low-protein diets	S LOST Trial), 2-year intervention	742 ; mixed gender	showed greater reductions in weight, fat mass, visceral and subcutaneous adipose tissue on high-protein diets; opposite pattern on low-protein diets. Effects stronger at 2 years than 6 months.		
rs1558902	Dietary protein intake high-protein vs low-protein diets	Cross-sectional observational study	Young adults aged 20–29 years; mixed ethnicity: East Asian, Caucasian, South Asian (n = 1491)	Among East Asians, carriers of the AA risk genotype had significantly higher BMI and waist circumference when protein intake was low. These associations were not observed with higher protein intake. No significant associations were seen in Caucasian or	Moderate	42

				South Asian groups.		
rs3751812 rs8050136 rs8044769	High-carbohydrate diet (>48% energy), moderate-fat diet (≤30% energy), protein intake ≤18% energy	Observational cohort study	Caucasian adults of Polish origin, n = 1,549	GG genotype of rs3751812 and CC genotype of rs8050136 associated with lower BMI, body fat, waist and hip circumference when carbohydrate intake >48% and fat ≤30%. TT and CT genotypes of rs8044769 associated with higher BMI when carbohydrate intake <48%. TT genotype associated with impaired glucose homeostasis when protein intake >18%	Moderate	43
rs3751812 rs8050136	High dietary fiber intake (≥14 g/day) vs. low fiber intake	Nested case–control study within a	Iranian adults from Tehran Lipid and Glucose Study	Significant interaction between dietary fiber intake and FTO genetic risk	Moderate	45

		prospective cohort	(TLGS); n = 1,254 (627 obesity cases, 627 matched controls)	score on general obesity. Individuals with high genetic risk (GRS ≥6) benefited more from high fiber intake, showing the lowest obesity risk. Fiber intake also modified the association of rs3751812 with abdominal obesity (WC, WHR).		
rs3751812 rs8050136	High dietary fiber intake (>18 g/day) vs. lower intake	Cross-sectional gene–diet interaction study (within cohort)	Polish Caucasian adults from the 1000PLUS Cohort; n = 819 (52.5% female)	High fiber intake was associated with lower hip circumference and favorable anthropometric parameters in GG (rs3751812), CC (rs8050136), genotype carriers.	Moderate	46

Table 2: Details of studies on the FTO genes associated with obesity used in the literature search

FTO genetic varient	Study details	Results	References
rs17817449	Investigated the association of the FTO rs17817449 Variant Obesity in a Brazilian Cohort of 501 participants from Rio de Janeiro, Brazil.	observed an important association between FTO rs17817449 polymorphism with obesity and obesity-related traits.	[19]
rs1421085	Study aimed to examine the association between metabolites and obesity-related anthropometric traits based on the variant FTO rs1421085 involving a total of 542 participants In Pakistan[68]	Resulted The CT genotype of FTO rs1421085 may greatly increase the risk of overweight/obesity by changing the lipid metabolism-related metabolites.	[65]
rs1421085	The study analyzed the association between the FTO rs1421085 and obesity, dietary intake, cardiorespiratory fitness, physical activity, and socioeconomic status (SES) from age 9 to 25 years in Estonia.	The study found that the FTO rs1421085 gene variant is associated with higher obesity measures in males and different dietary and physical activity patterns in females, with SES further influencing obesity outcomes in females.	[66]

rs9939609	406 children with obesity in southern were assessed by BMI Polymorphism genotyping was performed by real time PCR	Among schoolchildren with the AA genotype of the rs9939609 (FTO) polymorphism, 57.4% had obesity, the percentage was lower for the AT and TT genotypes. Obesity was associated with a family history of obesity, especially among children with the AA genotype. The prevalence was higher among those with mother, maternal or paternal grandmother and paternal grandfather with obesity.	67
rs9939609 rs1421085	This study aimed to explore the association of the FTO gene variants (rs9939609 and rs1421085) with obesity, metabolic syndrome (MetS), and insulin-related parameters in a sample of 1967 Turkish adults (mean age 50.1 years)	Study found that in Turkish adults, FTO gene variants were associated with a higher risk of obesity in women (with female C-allele carriers having a 61% increased risk) and metabolic syndrome in men (with male C-allele carriers having a 44% increased risk)	68
rs1421085 rs9939609	The study aimed FTO gene (rs1421085 and rs9939609) on obesity in a sample of 190 patients with obesity and 97 healthy controls from Turkey.	The study found no significant differences in genotype frequencies of rs1421085 and rs9939609 between subjects with obesity and controls, nor significant correlations between these genotypes and obesity-related parameters. However, a significant difference in weight was observed among participants with obesity, with TT genotype carriers weighing more compared	69

		to those with TC, CC (for rs1421085) and TA, AA (for rs9939609) genotypes.	
rs9939609	study aimed to investigate FTO rs9939609 in obesity and type 2 diabetes in the Chinese population, involving 638 ~~obese~~ cases and 1,610 controls for obesity	rs9939609 A allele was strongly associated with obesity in the Chinese population, with the odds ratio for obesity being 2.60 (95% CI 1.24–5.46) for the AA genotype and 1.32 (95% CI 1.05–1.66) for the AT genotype compared to the TT genotype. Each additional copy of the rs9939609 A allele was associated with an increase in BMI of approximately 0.37 kg/m². However, this allele was less common in the Chinese population (12.6%) compared to Europeans (45%).	[70]
rs1421085 rs17817449	The study aimed to replicate the association of FTO gene polymorphisms (rs1421085 and rs17817449) with BMI in Koreans, involving 1,733 participants from Korea	The rs1421085 C allele (P = 0.0015) and rs17817449 G allele (P = 0.0019) were significantly associated with increased obesity in the Korean population, marking the first positive association with BMI in an Asian group	[71]

rs8050136	This study aimed to investigate the impact of FTO rs8050136 on whole body fat distribution, insulin sensitivity, and weight change during a lifestyle intervention. Involved 1,466 German subjects	The A allele of the FTO polymorphism rs8050136 was significantly associated with higher BMI, body fat, and lean body mass (all $P < 0.001$). It also significantly affected subcutaneous fat ($P \leq 0.05$) and showed trends for liver fat, nonvisceral adipose tissue, and visceral fat (all $P \leq 0.1$).	[72]
rs9939973 rs9940128 rs1421085 rs1121980 rs7193144 rs17817449 rs8050136 rs9926289 rs9939609	Examined associations between 9 previously reported FTO SNPs with obesity, type 2 diabetes, and related traits in 4,298 participants (2,919 Chinese, 785 Malays, and 594 Asian Indians)	FTO variants common among European populations are associated with obesity in ethnic Chinese and Malays in Singapore. Study confirms that the SNP rs9939609, are significantly associated with increased BMI in Chinese and Malay populations	[73]
rs9939609	Investigated the association of the FTO rs9939609 T>A with selected anthropometric and metabolic parameters, blood pressure, in a large population of Polish children. The study included a total of 968 children aged 4 to 18 years	FTO rs9939609 T>A polymorphism is significantly associated with higher body mass, BMI, waist circumference, and other anthropometric measures in Polish children aged 4 to 18 years. Children with the AA genotype had a notably higher median BMI SDS and an increased risk of obesity compared to those with TT or AT genotypes, with the association being strongest under a recessive model of inheritance.	[74]

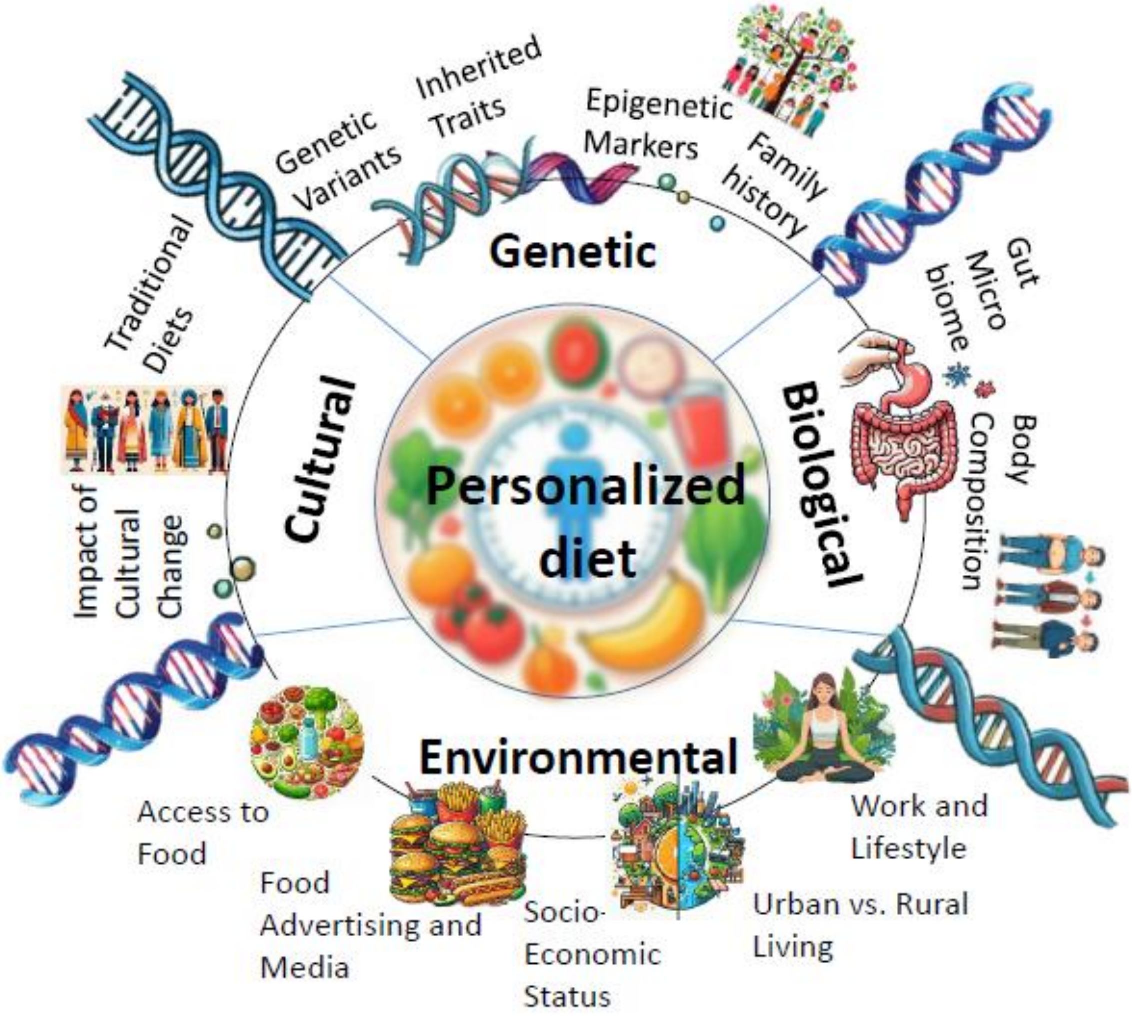

Fig. 1. The interplay between genetic background, biological, cultural and environmental variations on personalized nutrition.

Graphical abstract: Illustrates how FTO genetic variants influence body weight through interconnected biological and behavioural pathways. These variants act on the hypothalamus, disrupting appetite regulation by increasing hunger-inducing hormones (e.g., ghrelin) and reducing sensitivity to satiety signals. This dysregulation leads to behavioural outcomes such as loss-of-control eating and a heightened preference for energy-dense, discretionary foods (e.g., sugary snacks and fast foods). If unmanaged, these behaviours contribute to adverse clinical outcomes, including increased BMI, metabolic dysfunction, and central adiposity. The application of precision nutrition may help mitigate these effects, enabling more effective weight management and improved metabolic health.