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Review article

Genetics of Exercise and Diet-Induced Fat Loss Efficiency: A Systematic Review

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Abstract

Physical exercise and dieting are well-known and effective methods for fat loss and improving cardiovascular health. However, different individuals often react differently to the same exercise regimen or dietary plan. While specific individuals may undergo substantial fat loss, others may observe only limited effects. A wide range of inter-individual variability in weight gain and changes in body composition induced by physical exercises and diets led to an investigation into the genetic factors that may contribute to the individual variations in such responses. This systematic review aimed at identifying the genetic markers associated with fat loss resulting from diet or exercise. A search of the current literature was performed using the PubMed database. Forty-seven articles met the inclusion criteria when assessing genetic markers associated with weight loss efficiency in response to different types of exercises and diets. Overall, we identified 30 genetic markers of fat-loss efficiency in response to different kinds of diets and 24 in response to exercise. Most studies (n = 46) used the candidate gene approach. We should aspire to the customized selection of exercise and dietary plans for each individual to prevent and treat obesity.

Key words: SNP, physical activity, weight loss, dieting.

Introduction

Weight loss encompasses factors such as body mass index (BMI), body weight, waist circumference, and data on absolute fat mass and fat mass percentage. On the other hand, fat loss involves explicit data related to absolute fat mass and fat mass percentage, including measurements for different body areas like the whole body and visceral fat. Therefore, it can be understood that fat loss is a component of overall weight loss.

Weight and fat loss, a pervasive global concern, present a formidable challenge for most individuals, with a high risk of regaining lost weight. The intricacies of weight management involve multifaceted environmental factors, encompassing nutrition, physical activity levels, lifestyle choices (Serio et al., 2023), and psychological, social, and medical contributors. Calorie-dense foods, identified through various studies, contribute to excessive calorie intake, exacerbating weight-related challenges (Camachoa and Ruppela, 2017; Romieu et al., 2017; Hall et al., 2019). Moreover, the decline in physical activity levels, notably lower than that of our ancestors, emerges as a significant factor contributing to weight gain (Chaput and Tremblay, 2009). Fundamental principles of weight loss involve reducing calorie intake and strategies like intermittent fasting. However, these approaches may not significantly affect body fat ratio or lipid profile. Instead, they tend to induce short-term weight loss (Ooi and Pak, 2019). The intricate dynamics of weight regulation become evident in the short term, where a decrease in energy intake is often counteracted by mechanisms lowering metabolic rate and increasing calorie intake, contributing to weight regain (Benton and Young, 2017). However, the persistent pattern of achieving less weight loss than anticipated or desired, followed by subsequent weight regain, underscores the complexity of the body's response to changes in energy balance (Evert and Franz, 2017). Therefore, incorporating long-term regular physical exercise into a weight loss strategy is deemed crucial, creating a more significant caloric deficit and a positive influence on metabolic rate and overall body composition, promoting a more sustainable and practical approach to weight management (Cox, 2017).

Interestingly, modifications in diet and exercise do not always lead to weight loss success. The consequence of fat gain is obesity, which plays a pivotal role in the development of significant chronic conditions, including cardiometabolic diseases, specific cancers, type 2 diabetes, and metabolic syndrome (Scully et al., 2021). Nevertheless, not all individuals residing in obesogenic settings develop the condition, indicating that the reaction to environmental influences is also influenced by additional factors, such as genetic predispositions (Loos and Yeo, 2022). Similarly, among Olympic athletes, there are individuals with obesity. There is compelling evidence of a significant influence of genetic factors on weight control, as indicated by numerous studies (McPherson, 2007; Albuquerque et al., 2017; Sivasubramanian and Malhotra, 2023). In exploring the complexities of weight management, it becomes evident that genetic predispositions play a substantial role alongside individual efforts. Recent research has revealed a complex interaction between genes and the response to fat loss induced by exercise or food intake. Genetic factors influence the body's reactions to fat loss through aerobic exercise and dieting in recreational and professional athletes. In the context of this review, the term "genetic factors" refers specifically to single nucleotide polymorphisms (SNPs).

The rationale for this review stems from the alarming increase in obesity rates over the last four decades.

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Upon an in-depth examination of the extensive literature, it is evident that individual research papers contribute valuable components to the overarching puzzle. Therefore, synthesizing these findings is imperative to construct a coherent narrative, with particular consideration given to insights derived from studies conducted in 2023. The primary goal of this systematic review is to recognize the genetic markers linked to fat loss induced by diet and exercise.

Biological significance of SNPs

The simplest and most common genetic alterations in the human genome involve changing in a single base pair. This type of alteration can be a Single Nucleotide Polymorphism (SNP), or a point variant. It is known that when a variant occurs in less than 1% of the population, it is considered a mutation, while when its incidence exceeds 1%, it is regarded as a polymorphism (Karki et al., 2015). SNPs occurring in coding regions can influence the amino acid sequence of a protein. This might result in a change in the protein's structure or improper folding, ultimately leading to a complete lack or significant limitation of its biological activity. SNPs occurring in non-coding regions might be necessary for the organism's physiology, especially by influencing gene expression regulation (Robert and Pelletier, 2018). SNPs are considered the most valuable markers for diagnosing or predicting diseases due to their widespread occurrence, ease of analysis, low genotyping costs, and the possibility of conducting association studies based on statistical and bioinformatic tools (Srinivasan et al., 2016). Until two years ago, almost 60 Genome-Wide Association Studies (GWAS) had revealed over 1100 distinct loci linked to various obesity-related traits (Buniello et al., 2019). Recently, 55 SNPs associated with sarcopenic obesity have been identified. The risk alleles of most of these SNPs were also associated with low physical activity in the European-ancestry UK Biobank (Semenova et al., 2023). Identifying novel polymorphisms influencing the variability in fat loss efficiency is expected to yield valuable information, establishing it as a practical tool for clinicians and physical activity coaches.

Diet and weight loss

To lose one pound per week, one must restrict 500 kcal per day. Most weight-loss diet strategies limit caloric intake in some way. There are many different diets. Described below are the most popular. Very-low-calorie diets (modified fats) allow for approximately 800 kcal per day, while some go as low as 400 to 500 kcal per day. They are intended to produce faster weight loss than traditional low-calorie diets. The latter allows for 1,000 to 1,200 kcal per day. Low-calorie diets are seen to be safer than very low-calorie regimens, and some research and reports claim that they offer better long-term benefits (Heymsfield et al., 2003; Howard et al., 2006). Low-fat diets limit fat consumption to 20% to 30% of total daily calories. However, a low-fat diet without a reduction in total caloric intake will not promote weight loss (Baker, 2006). Controversially, cutting down on calories might not lead to weight loss. This is because when calorie intake is reduced, the body compensates by either lowering its metabolic rate or increasing food consumption (Benton and Young, 2017). Some low-fat and very low-fat diets (in which fat accounts for up to 15% of calories ingested) have a higher proportion of complex carbohydrates (Seid and Rosenbaum, 2019). Individuals who substitute fat calories with high-fiber, low-calorie fruits and vegetables will consume fewer calories and lose weight. A recent study compared the Ornish diet, a vegetarian diet with 10% fat calories, to three other popular diets: a low-carbohydrate diet (Atkins diet), a moderate-carbohydrate diet (Zone diet), and a calorie-restricted diet (Weight Watchers) (Dansinger et al., 2005). A moderate-fat, low-calorie diet (also known as a Mediterranean-style diet) permits the intake of up to 35% of calories from fats while restricting carbohydrates and proteins (Kim, 2021). A randomized controlled trial investigating whether the consumption of fats affects weight loss revealed an average weight loss of 4.1 kg in individuals adhering to the Mediterranean-style diet, demonstrating better long-term participation and adherence. The findings were based on an 18-month evaluation comparing a Mediterranean-style diet (with 35% of calories from fat) and a low-fat diet (with 20% of calories from fat) (McManus et al., 2009). Next, low-carbohydrate, high-protein diets typically allow only 20 to 90 g of carbohydrates per day, with no restrictions on protein or fat (Kushner and Doerfler, 2008). When carbohydrate consumption is reduced, glycogen stores and lipids are used as energy sources, affecting the body's metabolism and resulting in initial weight loss due to ketosis and diuresis (Ashtary-Larky et al., 2022). However, there is no single, universally effective diet for promoting weight loss. In the short term, high-protein, low-carbohydrate diets and intermittent fasting are recommended for achieving significant initial weight loss and can be considered a kick-start. Caution is advised due to potential adverse effects. In the long term, evidence suggests that various diets result in comparable weight loss, and the key to success lies in adhering to the chosen diet. Ultimately, it is crucial to adopt a diet that establishes a negative energy balance and prioritizes consuming high-quality foods to enhance overall health (Freire, 2020).

Physical exercise in fat loss

Aerobic training

The metabolism of fat is possible only at a slow rate of change and exclusively under aerobic conditions (van Loon et al., 2003). Triacylglycerol (TAG) is the stored fat in adipocytes and striated muscle. It comprises a glycerol molecule linked to three chains of fatty acids (FAs). The intracellular mechanism involved in freeing FAs from the glycerol backbone is referred to as lipolysis. Following this process, liberated FAs are released into the bloodstream and conveyed to actively contracting muscles for subsequent oxidation (Purdom et al., 2018). If exercise intensity is maintained below 65% of the maximal oxygen uptake (VO_2max), prolonged exercise can theoretically be sustained due to the oxidation of endogenous triacylglycerol (TAG) stores. Nevertheless, as exercise intensities exceed approximately 65% of VO_2max, the oxidation of FAs diminishes, resulting in an increased reliance on carbohydrates for energy (Brooks and Mercier, 1994; Venables et al., 2005). During moderate-intensity exercise,

approximately 50% of the total energy expenditure is derived from fat oxidation, where plasma-free fatty acids (FFA) serve as the principal source of fat (Martin et al., 1993; Romijn et al., 1993). The FA oxidation rate in trained male cyclists during exercise of moderate intensity constitutes 50% of the overall fat oxidation (van Loon et al., 2001). FAs derived from adipose tissue, muscle lipid droplets, and dietary sources constitute the primary energy substrate during exercise within the intensity range of 45% to 65% of the maximal oxygen uptake (VO_2max) (Purdom et al., 2018; Muscella et al., 2020). Aerobic training involves various exercises lasting from a few minutes to several hours. Common aerobic exercises include jogging, running, cycling, swimming, brisk walking, dancing, Nordic walking, and aerobics classes.

A solitary attempt to burn fat should be prolonged and avoid excessive intensity (van Loon et al., 2001). This is attributed to the fact that the initiation of lipolysis is a relatively gradual process (Duncan et al., 2007; Lass et al., 2011). In a randomized, controlled study, it was also demonstrated that among overweight and obese participants who engaged in supervised exercise five days a week over 10 months while maintaining their usual diet, aerobic exercises alone led to significant weight loss in both men and women. Moreover, the differences in weight loss from baseline to the 10th month between men and women within the groups were not statistically significant, suggesting that gender does not influence weight reduction (Donnelly et al., 2013). More specifically, the weight loss from baseline to the end of the program was 4.3% for the group exercising with an intensity of 400 kcal per session and 5.7% for the group exercising with an intensity of 600 kcal per session, compared to a weight gain of 0.5% in the control group (Donnelly et al., 2013). For example, Weiss et al. (2017) illustrated not only successful weight reduction (7% over 16.8 weeks) solely through exercise but also the conservation of lean body mass (LBM) and enhancement in VO_2max in contrast to weight loss achieved by an equivalent energy deficit through calorie restriction alone. The latter approach led to a decline in lean body mass and a reduction in VO_2max (Weiss et al., 2017).

Nevertheless, the literature is not unequivocal regarding aerobic exercise and fat burning. This is elegantly reviewed by Harris and Kuo (2021) (Harris and Kuo, 2021). The classic theory of fat burning is commonly used to explain the reduction of abdominal fat resulting from exercise training. This theory is based on the idea that exercise, an energy-consuming activity, will enhance the oxidation of fatty acids from abdominal fat stores compared to a sedentary state, thereby contributing to the fat loss observed in exercise training (Abbasi, 2019). This theory appears supported by enhanced lipolysis with raised circulating fatty acids and increased oxygen consumption during exercise (Mora-Rodriguez and Coyle, 2000). Yet, the absolute energy contribution from plasma fatty acids, assuming all are from adipose tissue, diminishes as exercise intensity rises (from 25 to 85% of VO_2max) and aligns with a reduction in tissue fatty acid uptake during exercise (Romijn et al., 1993). Moreover, the augmented energy expenditure, particularly during high-intensity exercise, primarily stems from the fuel stored in skeletal muscle, predominantly glycogen, rather than adipose tissue (fatty acids) (Romijn et al., 1993). Surprisingly, neither aerobic exercise nor resistance exercise leads to an increase in 24-hour fatty acid oxidation, as reported by Melanson et al. (2002) (Melanson et al., 2002). Increased lipolysis, combined with elevated circulating fatty acids and increased oxygen consumption during aerobic exercise, seems to contribute to fat tissue loss (Harris and Kuo, 2021). Many clinical studies reveal a paradox between the fat-burning process and the effect on fat tissue loss. For instance, Willis et al. (2012) conducted a study where they compared the effects of aerobic exercise (equivalent to a caloric expenditure of 12 miles per week), resistance exercise (performed three days per week), and a combination of both on changes in body mass. This investigation involved individuals with a sedentary history and without diabetes, falling within the BMI range of 25–35 kg/m^2. Following an 8-month trial, weight loss and reduction in fat mass were more pronounced with aerobic training compared to resistance training (1.76 kg vs. 0.83 kg for the aerobic and resistance groups, respectively) (Willis et al., 2012). However, a 15-week sprint training, mainly relying on anaerobic metabolism, effectively leads to a reduction in abdominal fat tissue, while moderate-intensity training relying on aerobic metabolism, with similar energy expenditure (60% VO_2max, about 200 kcal, three times a week), did not result in fat tissue reduction in young women (Trapp et al., 2008).

Therefore, exploring alternative theories explaining the effects of fat tissue loss during exercise is essential to establish a robust scientific foundation for designing effective training programs aimed at fat tissue reduction. In clarification, a repetitive and focused training regimen initiates the activation of specific genes, leading to transcription that produces mRNA complementary to DNA. Subsequently, during the second phase of gene expression, known as translation, a polypeptide chain is synthesized on the generated mRNA by sequentially attaching amino acids, forming a protein. Understanding the significance of including complete proteins in the diet is crucial. These proteins release exogenous amino acids through digestion, which are supplied through food since the body cannot synthesize them independently. These amino acids play a crucial role in translation (Humińska-Lisowska et al., 2021). In this light, it can be said that various genetic and environmental factors influence response to aerobic training. In terms of genetics, the idea of variability among individuals in their responsiveness to exercise training was introduced by Bouchard and his group (Bouchard and Rankinen, 2001; Rankinen and Bouchard, 2008; Bouchard et al., 2011b; Bouchard et al., 2011a; Bouchard, 2012). The HERITAGE Family Study, which involved 742 healthy but sedentary participants completing a highly standardized, meticulously monitored, laboratory-based endurance-training program for 20 weeks, provided the most comprehensive data on individual variations in response to the training (Bouchard et al., 1999; Bouchard and Rankinen, 2001).

Resistance training

Resistance training (RT) stimulates the enlargement of skeletal muscles. This occurs as a physiological response involving the structural reconstruction of muscle tissue, leading to the expansion of muscle fibers and, ultimately, an increase in the cross-sectional area of the entire muscle (Booth and Thomason, 1991). Contemporary weight loss and maintenance recommendations incorporate resistance training into the prescribed workout routine. Nevertheless, few studies have directly evaluated the effects of comparable aerobic and resistance training periods on overweight individuals' adult body mass and fat mass. According to Donnelly et al. (2009) guidelines on body weight reduction and maintenance, resistance training (RT) has been linked to a potential decrease in fat mass (Donnelly et al., 2009). The authors claim that RT does not contribute to weight loss improvement, but it might lead to an increase in fat-free mass and more significant fat mass loss (Donnelly et al., 2009). As Willis et al. (2012) discussed, guidelines might occasionally cause practitioners, fitness experts, and laypeople to misinterpret the quality of the data supporting RT's ability to cause weight loss and fat mass loss (Willis et al., 2012). Some publications suggest that RT has been proven to decrease fat mass. Nevertheless, a thorough examination of the available literature indicates that randomized controlled trials do not provide conclusive evidence (Castaneda et al., 2002; Schmitz et al., 2003; 2007; Sigal et al., 2007). One of the studies aiming to compare the advantages of resistance training in contrast to aerobic exercise and the combination of both, specifically focusing on their effects on body composition measures such as total body mass and fat mass, was The Study of a Targeted Risk Reduction Intervention through Defined Exercise randomized trial (STRRIDE AT/RT) (Willis et al., 2012). The trial sought to compare alterations in body composition resulting from equivalent durations of resistance training, aerobic training, or a combination of both in individuals who did not have diabetes, were previously inactive, and were overweight or obese. The key findings of the study can be summarised as follows: 1) Engaging in a significant amount of RT alone did not lead to a reduction in body mass or fat mass; 2) prescribed amounts of aerobic training (AT) were notably more effective than RT in decreasing measures of body fat and body mass; and 3) the combination of aerobic and resistance training did not result in an additional effect in reducing fat mass or body mass when compared to aerobic training alone. Consequently, the combined training modes did not demonstrate synergy or interference but instead appeared to have a linear impact when body composition measures were considered outcome variables. Considering the trade-off between time commitment and health benefits, AT seems to be the optimal exercise mode for reducing fat and body mass. On the other hand, incorporating resistance training RT becomes essential for middle-aged, overweight, or obese individuals seeking to increase lean mass (Willis et al., 2012). An issue in the literature exploring the impact of resistance training (RT) on weight and fat loss is the common practice of combining RT with other interventions. In a recent meta-analysis (Lopez et al., 2022), the authors reported that 56 out of 114 studies, accounting for 49.1%, incorporated RT, followed by a combination of RT and AT (51 out of 114 studies, representing 44.7%). Including RT and AT alongside caloric restriction was observed in 7.0% of the studies, and the combination of resistance training and caloric restriction was present in 5.3% (Lopez et al., 2022). Debate continues about the best strategies for the reduction in weight and fat. However, there is no straightforward answer to whether resistance training burns fat. For the mobilization of triglycerides from fat tissue to occur, the body must be in a caloric deficit. This was the primary conclusion drawn from the review. The authors concluded that resistance-based exercise programs prove effective and should be incorporated into a comprehensive therapy regimen when caloric restriction is employed for adults dealing with overweight or obesity. Given their comparable impact on fat and weight loss and distinctive influence on lean mass, prioritizing resistance training over aerobic exercise alone is advisable in formulating a multicomponent fat loss prescription for individuals struggling with overweight or obesity (Lopez et al., 2022).

Methods

Literature research strategies

The selection criteria were previously described in detail in our previous work (Egorova and Ahmetov, 2023). We have adopted methodology from our systematic review to minimize bias in selecting current articles for the current review and to implement an effective bibliographic research strategy (Egorova and Ahmetov, 2023). Briefly, PubMed was searched for relevant publications following PRISMA guidelines. The analysis included English-language literature without date restrictions, using keywords like "polymorphism," "SNP," "genotype," "diet," "nutrition," "physical activity," "physical exercises," "training," "weight loss," and "fat loss." However, the PubMed database was searched for works indexed from 1997 to no later than 30 November 2023.

Studies selection

This review included intervention studies with specified diet or exercise details, duration, evidence of genetic polymorphism, and changes in anthropometric parameters or body composition. Exclusion criteria encompassed non-interventional longitudinal studies, non-human studies, and those involving subjects with severe illnesses such as cancer. Additionally, studies with children, athletes, pregnant and lactating women, and surgical patients were excluded (Egorova and Ahmetov, 2023).

Data extraction

Studies retrieved from the databases were extracted using Microsoft Excel 2016 and automatically screened for duplicates. The remaining works, post-duplicate removal, underwent a two-stage evaluation based on title, abstract, and full text. Full works were assessed for eligibility according to the specified inclusion and exclusion criteria.

Quality assessment and risk of bias

The bias risk assessment in randomized controlled trials was conducted using a modified and validated version of the Cochrane Collaboration tool (Higgins *et al.*, 2011). The study evaluation criteria were as follows: method of randomization of study participants into groups and concealment of the randomization sequence; blinding of study subjects, medical staff, and investigators evaluating the effect of the intervention; missing outcome data; incomplete reporting of results; and other sources of bias (for example, conflict of interest). Each criterion's risk of bias was evaluated and categorized as low, high, or unclear.

Bias risk for the publication of cohort studies was evaluated using the Newcastle–Ottawa quality rating scale (Wells *et al.*, 2000). The assessment criteria for the research encompassed cohort design, cohort comparability, and outcome assessment, with eight subitems contributing to a maximum score of 9. Publications were categorized based on their final scores: studies with a risk of bias graded as high (0 - 5 points), studies with an average risk of bias (6 - 7 points), and studies deemed to have a low risk of bias (8 - 9 points). Furthermore, the methodological quality of the publications was appraised following criteria deemed crucial for studies exploring genetic associations (Campbell and Rudan, 2002; Dietrich et al., 2019). The assessment of study quality was grounded in eight distinct criteria, encompassing the primary objective of interaction, statistical testing for interaction, adjustments for multiple testing, considerations for ethnicity or population stratification, Hardy-Weinberg equilibrium examination, baseline group similarity testing, sample size or power analysis, and a comprehensive specification of the study procedure (Supplementary Tables). Assigning positive (1 point), neutral (0 points), or negative (-1 point) ratings to each criterion, the cumulative score for each publication ranged from -8 to 8 points. Consequently, publications achieving scores between 6 and 8 points were categorized as exhibiting high methodological quality, those scoring between 2 and 5 were deemed moderate quality, and those scoring between -8 and 1 were classified as low quality.

Results

Selection and characterization of studies

The literature search revealed 4187 publications (Figure 1). In addition, 22 publications were included in the analysis found by searching for similar articles and not by searching for keywords. After removing 2969 duplicates, 1240 articles were screened based on the title. Next, 286 full-text articles were read for detailed evaluation, of which 238 articles were excluded. The reasons for study exclusion were: no fat mass loss outcomes (n = 155); no significant differences in changes in fat mass between genotypes (n = 34); non-interventional research (n = 17); no gene-diet or gene-training interaction in studies (n = 13); unspecified intervention parameters (n = 5); medical or surgical interventions (n = 4); studies that did not have uniform intervention parameters for all subjects (n = 3); testing of athletes (n = 3) and children and adolescents (n = 2); unspecified level of p-value (n = 1); and no full-text available (n = 1).

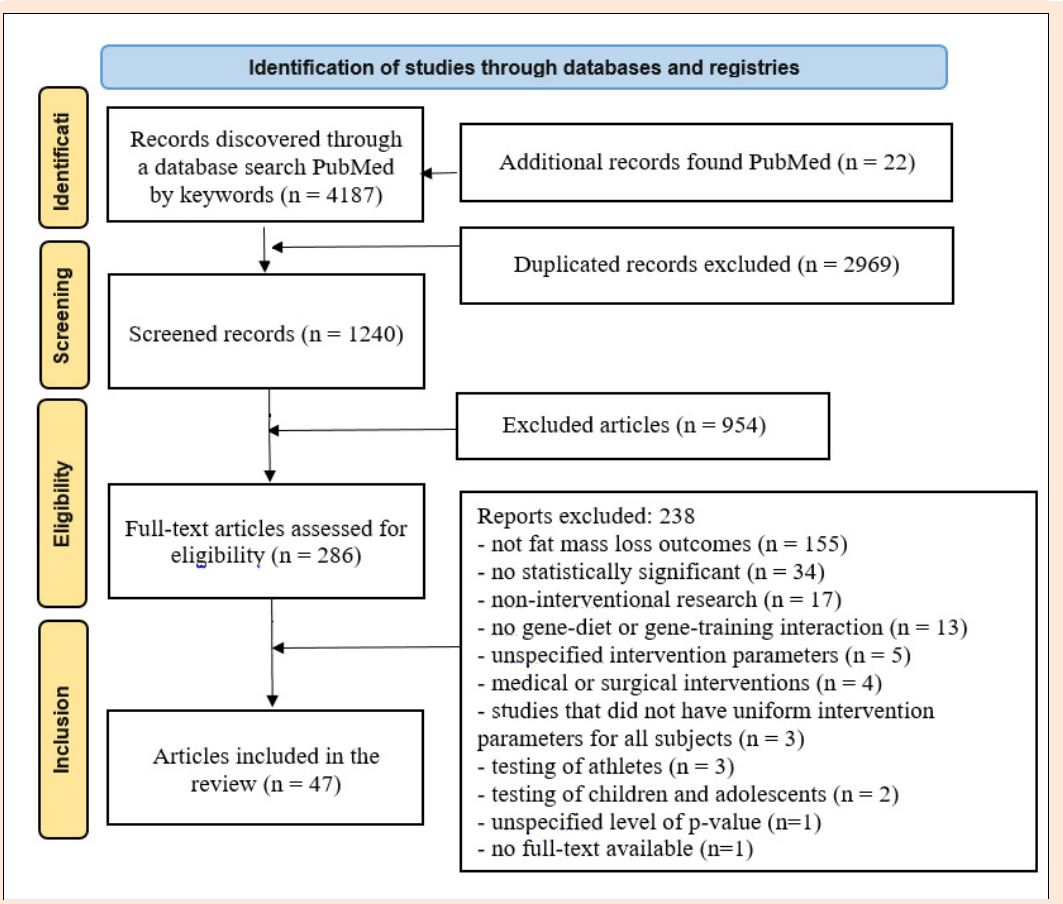

Figure 1. PRISMA flow chart for the study selection.

This resulted in 48 articles being included in the systematic review. The timeframe of the publications encompassed the years 1997 to 2023. The collective count of genetic polymorphisms identified in the selected articles amounted to 48. All interventions and genetic screenings involved 12434 participants, with sample sizes ranging from 24 to 1004. The duration of the interventions varied from four weeks to two years. There was variability among the studies regarding participant characteristics, dietary intervention types, physical activity (PA) types, and intervention durations (Table 1 and Table 2).

Study quality and risk of bias

Applying the Cochrane Collaboration tool (Higgins et al., 2011), 13 randomized controlled trials were appraised with a low risk of bias, while one randomized controlled trial was classified as having a moderate risk (Supplementary Tables). The rationale behind the lower rating for randomized controlled trials is attributed to the inherent challenges of blinding both patients and staff due to the nature of lifestyle interventions. The Newcastle–Ottawa quality rating scale (Wells et al., 2000) was employed to assess bias in nonrandomized controlled trials, revealing 30 studies with a low risk of bias and 4 studies with a moderate risk (Supplementary Tables). The lower quality ratings were attributed to insufficient information on additional criteria for cohort comparability, specifically, statistically significant differences in diet adherence and the level of physical activity among subjects. The evaluation of the analytical quality in genetics studies, employing a tailored scale for investigations into the correlation between genes and diet/exercise, classified 30 publications as high-quality. In contrast, the quality of 18 articles was deemed moderate (Supplementary Tables). The primary factors contributing to the lower quality of these publications were the absence of correction for multiple testing, inadequate correction for population stratification, and insufficient size of the study sample.

Genetic markers associated with weight loss efficiency in response to different types of diets

There is ongoing research into genetic markers associated with reduction efficiency in response to diverse diets. According to several studies, genetic variables might alter an individual's responsiveness to specific dietary interventions. For example, certain genes may influence how the body processes fats or carbohydrates, influencing weight loss outcomes. However, the field is complex, and the interplay between genetics and diet response is not fully understood. Individual differences in weight loss success are believed to be influenced by numerous genes.

Weight loss encompasses parameters such as BMI, body weight, waist circumference, absolute fat mass, and fat mass percentage data. Fat loss refers explicitly to the reduction in absolute fat mass and fat mass percentage data, including measurements for the entire body and specific areas like visceral fat. Therefore, it is essential to understand that fat loss is a component of overall weight loss. We intended to compose a review specifically focusing on fat loss. Therefore, we omitted publications that included information about BMI, weight, and waist circumference and retained those mentioning absolute or relative fat mass. Some research works incorporate various measurements, such as weight and fat data. In such cases, we kept those in Table 1 and Table 2, showing key findings. Table 1 summarizes SNPs associated with fat loss efficiency in response to different types of diets.

Genetic markers associated with exercise-induced weight loss efficiency

Not only have genetic changes associated with obesity and the response to physical activity been identified, but significant progress has also been made in research into the links between genes, physical activity, and their interactions to understand how these factors affect the body's composition. Breakthrough research has come from the Bouchard laboratory. Along with collaborators, they described 23 autosomal genes that significantly interacted with physical activity or exercise, influencing body composition (Rankinen et al., 2001; Bray et al., 2009). However, research is ongoing on genetic markers associated with exercise-induced weight loss and fat loss efficiency. In fact, over the past ten years, significant advancements have been made in pinpointing genetic loci linked to obesity through genome-wide association studies (GWAS) (Fox et al., 2012; Vogelezang et al., 2015; Yoneyama et al., 2017; Yengo et al., 2018; Wong et al., 2022). As highlighted in our recent review, by increasing the sample size to encompass several million individuals in the foreseeable future, it is expected that numerous additional common genetic variants (occurring more than 5% of the time) will be uncovered, accounting for up to 30% of the variance in BMI. Simultaneously, low-frequency (1 - 5%) and rare genetic variations (≤1%) are expected to account for the remaining portion of the BMI's heritability ((Egorova and Ahmetov, 2023) referring to (Locke et al., 2015; Ge et al., 2018; Wainschtein et al., 2022)). Table 2 summarises the genetic variants associated with exercise-induced fat loss efficiency.

Discussion

The current systematic review included 47 studies investigating the association between genetic variants and the efficacy of weight loss. Among them, 27 studies explored the impact of diet on fat loss, while 20 studies evaluated the influence of exercise. The selected studies spanned a substantial timeframe of 26 years. This systematic review discloses findings from 27 studies investigating the association between 30 genetic markers and fat loss in response to dietary interventions. Furthermore, examining 20 studies within the exercise contexts identified an association between 24 genetic markers and fat loss in response to exercise.

Table 1. Genetic markers associated with weight loss efficiency in response to different types of diets.

Gene	Polymorphism	Cohort (sex, sample size)	Population	Favorable allele/ genotype	Type of diet therapy	Outcome	References
ACE	rs4646994 I/D	n=32, women 100%	European	I	hypocaloric diet for 8 weeks	carriers of the I allele with significantly reduced relative body fat percentage compared to carriers of the DD genotype (-2.3±1.4% vs. -0.8±1.6%, P<0.05)	(Hamada et al., 2011)
ACSL5	rs2419621 C/T	n=44, women 100%	European	T	hypocaloric high-protein diet for 12 weeks	carriers of the T allele had significantly reduced body mass compared to carriers of the CC genotype (-9.3±1.8 kg vs. -7.4±2.1 kg, P=0.01), BMI (-3.4±0.5 units vs. -3.1±0.4 units, P=0.02), body fat mass (BFM) (-6.4±1.2 kg vs. -5.2±1.4 kg, P=0.01), and waist circumference (WC) (-8.6±0.8 cm vs. -6.1±1.1 cm, P=0.02)	(Jáuregui et al., 2020)
ACSL5	rs2419621 C/T	n=211, women 100%	European (Canada)	T	hypocaloric diet for 24 weeks	carriers of the T allele had significantly reduced body fat mass (BFM) compared to carriers of the CC genotype (-3.82±1.66 kg, P<0.001), relative body fat mass (-2.99±1.08 kg, P<0.001), and visceral fat mass (-5.74±2.87 kg, P=0.003)	(Rajkumar et al., 2016)
ADCY3	rs10182181 A/G	n=147, women 67,3%	European	G	hypocaloric low-fat diet for 16 weeks	carriers of the G allele had significantly reduced trunk fat mass (n/d, P=0.04), android fat mass (n/d, P=0.02), gynoid fat mass (n/d, P=0.03), and visceral fat mass (n/d, P=0.02) compared to carriers of the AA genotype.	(Goni et al., 2018)
ADRB2	rs1042714 G/C	n=95 women 100%	European	G	partial meal replacement hypocaloric diet 12 weeks	carriers of the G allele had larger reductions: (CC versus CG + GG) body weight (-7.1±0.3 vs. -13.5±0.5 kg: P = 0.03), BMI (-0.9±0.1 vs -1.2±0.2 kg/m^2; P = 0.03), fat mass (-4.9±0.5 vs. -10.2 ±1.2 kg; P = 0.01), and waist circumference (-5.1± 0.2 vs. -10.1±1.9 cm; P = 0.03)	(de Luis et al., 2023)
ADRB3	rs4994 A/G	n= 24, women 100%	Mixed (USA)	A	low-calorie diet for 13 months	carriers of the A allele had significantly reduced visceral fat mass by 43% compared to carriers of the GG genotype (-46±27 cm^2 vs. -81±51 cm^2, P=0.05)	(Tchernof et al., 2000)
BDNF	rs6265 C/T	n= 201, women n/d	European	T	hypocaloric high-protein diet for 16 weeks	carriers of the T allele had significantly reduced body fat mass (BFM) compared to carriers of the CC genotype (-5.3±3.2 kg vs. -3.9±2.5 kg, P=0.023)	(Ramos-Lopez et al., 2019)
BDNF	rs11030104 A/G	n= 201, women n/d	European	G	hypocaloric high-protein diet for 16 weeks	carriers of the G allele significantly had reduced body fat mass (BFM) compared to carriers of the AA genotype (-5.2±3.1 kg vs. -3.8 ±2.4 kg, P=0.013)	(Ramos-Lopez et al., 2019)
BDNF	rs10767664 T/A	n=80, women n/d	European	AA	hypocaloric diet for 3 months	individuals with the AA genotype significantly reduced body mass (MT) (-3.4±2.9 kg vs. -1.7±2.0 kg, P=0.01), BMI more (-1.5±0.2 units vs. -1.2±0.5 units, P=0.02), body fat mass (BFM) more (-2.3±1.1 kg vs. -1.7±0.9 kg, P=0.009), and waist circumference (WC) more (-3.8±2.4 cm vs. -2.1±3.1 cm, P=0.008) compared to carriers of the G allele.	(de Luis et al., 2018c)
CB2R	rs3123554 A/G	n=280, women 76,6%	European	GG	hypocaloric low-carbohydrate diet in conjunction with aerobic physical exercises for 12 weeks	carriers of the GG genotype had significantly reduced body mass (BM) (-3.3±1.1 kg vs. -1.9±1.0 kg, P=0.01), BMI (-1.3±0.1 units vs. -1.0±0.5 units, P=0.03), body fat mass (BFM) (-2.7±1.1 kg vs. -2.2±0.7 kg, P=0.02), and waist circumference (WC) (-3.4±1.0 cm vs. -2.5±1.1 cm, P=0.009) compared to carriers of the A allele	(de Luis et al., 2018a)
CB2R	rs3123554 A/G	n=280, women 76,6%	European	GG	hypocaloric diet with aerobic physical exercises for 12 weeks	carriers of the GG genotype had significantly reduced body mass (MT) (-4.0±1.2 kg vs. -2.1±1.1 kg, P=0.01), BMI (-1.3±0.2 units vs. -1.1±0.3 units, P=0.02), body fat mass (BFM) (-2.4±1.0 kg vs. -1.5±0.8 kg, P=0.02), and waist circumference (WC) (-3.7±1.1 cm vs. -2.9±1.0 cm, P=0.01), compared to carriers of the A allele	(de Luis et al., 2018a)

n/d- no data; MT- body mass; BMI- body mass index, FM- fat mass; WC- waist circumference

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Table 1. Continue …

Gene	Polymorphism	Cohort (sex, sample size)	Population	Favorable allele/ genotype	Type of diet therapy	Outcome	References
FGF21	rs838147 A/G	n=715, women 61%	Mixed (USA)	G	hypocaloric low-fat diet for 2 years	carriers of the G allele had significantly reduced body fat mass (BFM) (n/d, P=0.01) and trunk fat mass (n/d, P=0.02) compared to carriers of the AA genotype	(Heianza et al., 2016)
FTO	rs9939609 T/A	n=233, women 75,9%	European	A	hypocaloric diet with high polyunsaturated fat content in conjunction with aerobic physical exercises for 12 weeks	carriers of the A allele had significantly reduced body mass (MT) (-5.1±3.9 kg vs. -3.0±2.8 kg, P<0.05), BMI (-2.0±1.4 units vs. -1.1±1.2 units, P<0.05), and body fat mass (BFM) (-4.2±2.9 kg vs. -3.0±2.8 kg, P<0.05) compared to carriers of the TT genotype	(de Luis 2015b)
FTO	rs9939609 T/A	n=195, women 70,2%	European	TT	hypocaloric high-protein diet for 9 months	carriers of the TT genotype had significantly reduced body mass (MT) (n/d, P<0.05), BMI (n/d, P<0.05), and body fat mass (BFM) (n/d, P<0.05) compared to carriers of the A allele	(de Luis 2015a)
FTO	rs9939609 T/A	n=195, women 70,2%	European	TT	hypocaloric diet for 9 months	carriers of the TT genotype with significantly reduced body mass (MT) (n/d, P<0.05), BMI (n/d, P<0.05), and body fat mass (BFM) (n/d, P<0.05) compared to carriers of the A allele	(de Luis 2015a)
FTO	rs1558902 T/A	n=742, women 61%	Mixed	A	high-protein diet for 2 years	carriers of allele A, compared to carriers of the TT genotype, significantly reduced total body fat (n/d, P=0.049), visceral fat (n/d, P=0.012), and subcutaneous fat (n/d, P=0.002)	(Zhang et al., 2012)
LCT	rs4988235 G/A	n=583, women 56,3%	European (USA)	G	high-protein diet for 2 years	carriers of the G allele, compared to carriers of the AA genotype, had significantly reduced relative body fat (n/d, P=0.04), subcutaneous fat (n/d, P=0.04), visceral fat (n/d, P=0.03), and total body fat (n/d, P=0.03)	(Heianza et al., 2018)
LEPR	rs1137100 A/G	n=170, women 47,1%	European	AA	hypocaloric diet for 8 weeks	carriers of the AA genotype, compared to carriers of the G allele, had significantly reduced body fat (-4.1±2.1% vs. -2.9±3.6%, P=0.013)	(Abete et al., 2009)
LYPLAL1	rs2605100 A/G	n= 201, women n/d	European	GG	hypocaloric high-protein diet for 16 weeks	carriers of the GG genotype, compared to carriers of the A allele, significantly reduced waist circumference (WC) (-9.8±3.9 cm vs. -8.0±4.9 cm, P=0.046) and body fat mass (BFM) (-4.9±2.7 kg vs. -3.8±2.8 kg, P=0.05)	(Ramos-Lopez et al., 2019)
MTHFR	rs1801133 C/T	n= 56, women 66,1%	European	CC	hypocaloric Mediterranean diet for 12 weeks	carriers of the CC genotype, compared to carriers of the T allele, had significantly reduced relative body mass (-9.3±4.0% vs. -8.6±3.5%, P<0.05) and relative body fat mass (BFM) (-18.0±8.6% vs. -13.1±7.8%, P<0.05)	(Renzo et al., 2013)
MTNR1B	rs10830963 C/G	n=80, women 75,0%	European	CC	hypocaloric Mediterranean diet for 12 weeks	male carriers of the CC genotype, compared to carriers of the G allele, had significantly reduced body mass (-3.8±3.1 kg vs. -3.1±3.2 kg, P<0.05), BMI (-0.9±1.0 units vs. -0.7±1.0 units, P<0.05), and body fat mass (BFM) (-2.4±1.5 kg vs. -1.1±1.1 kg, P<0.05) among women, carriers of the CC genotype, compared to carriers of the G allele, had significantly reduced body mass (-3.2±1.1 kg vs. -2.1±1.0 kg, P<0.05), BMI (-1.1±1.0 units vs. -0.6±1.3 units, P<0.05), and body fat mass (BFM) (-2.4±1.0 kg vs. -1.3±1.2 kg, P<0.05)	(de Luis et al., 2018b)

n/d- no data; MT- body mass; BMI- body mass index, FM- fat mass; WC- waist circumference

Table 1. Continue …

Gene	Polymorphism	Cohort (sex, sample size)	Population	Favorable allele/ genotype	Type of diet therapy	Outcome	References
MTNR1B	rs10830963 C/G	n=361, women n/d	European	CC	hypocaloric diet with a high content of monounsaturated fats or with a high content of polyunsaturated fats for 12 weeks	carriers of the CC genotype, compared to carriers of the G allele, significantly reduced body mass (-4.1±0.9 kg vs. -2.9±0.8 kg, P<0.05), BMI (-0.7±1.1 units vs. -0.5±1.2 units, P<0.05), body fat (-3.0±0.8 kg vs. -2.0±1.0 kg, P<0.05), and waist circumference (-3.4±1.0 cm vs. -2.9±0.9 cm, P<0.05) on a hypocaloric diet with a high content of monounsaturated fats carriers of the CC genotype, compared to carriers of the G allele, significantly reduced body mass (-3.7±1.0 kg vs. -2.5±0.9 kg, P<0.05), BMI (-0.7±1.0 units vs. -0.2±1.1 units, P<0.05), body fat more (-3.3±1.0 kg vs. -1.4±0.9 kg, P<0.05) and waist circumference (-3.8±1.0 cm vs. -2.6±0.8 cm, P<0.05) on a hypocaloric diet with a high content of polyunsaturated fats	(de Luis et al., 2020b)
MTNR1B	rs10830963 C/G	n=270, women %	European	CC	highly hypocaloric high-protein/low-carbohydrate diet for 9 months.	carriers of the CC genotype, compared to carriers of the G allele, had significantly reduced BMI (-3.3±0.2 units vs. -3.2±0.2 units, P=0.02), body mass (-8.6±1.1 kg vs. -6.2±0.9 kg, P=0.01), body fat mass (BFM) (-6.2±1.8 kg vs. -3.7±1.2 kg, P=0.01), and waist circumference (WC) (-11.7±2.1 cm vs. -6.7±1.9 cm, P=0.02)	(de Luis et al., 2020a)
MTNR1B	rs10830963 C/G	n=270, women %	European	CC	highly hypocaloric diet for 9 months	carriers of the CC genotype, compared to carriers of the G allele, significantly reduced BMI (-3.1±0.2 units vs. -2.7±0.3 units, P=0.04), body mass (-7.6±1.4 kg vs. -5.1±1.2 kg, P=0.03), body fat mass (BFM) (-6.3±1.2 kg vs. -4.2±1.1 kg, P=0.03), and waist circumference (WC) (-10.7±1.4 cm vs. -6.3±1.8 cm, P=0.01)	(de Luis et al., 2020a)
NFAT C2IP	rs11150675 G/A	n=692, women 61,1%	Mixed	A	low-carbohydrate diet for 2 years	carriers of the A allele, compared to carriers of the G allele, significantly reduced body fat mass (BFM) (-5.2±1.1 kg vs. -4.2±1.0 kg, P=0.02) and trunk fat (-16.1±3.2% vs. -12.8±2.8%, P=0.01)	(Sun et al., 2018)
NPY	rs16147 T/C	n=723, women 61%	Mixed	C	low-carbohydrate diet for 2 years	carriers of the C allele, compared to carriers of the T allele, had significantly reduced waist circumference (WC) (n/d, P<0.001) after 6 months, subcutaneous fat (n/d, P=0.04), body fat mass (BFM) (n/d, P=0.05), and abdominal fat (n/d, P=0.01) after 2 years	(Lin et al., 2015)
PPARD	rs1053049 C/T	n=156, women 60,1%	European	T	low-fat diet with aerobic exercise for 9 months	carriers of the TT genotype, compared to carriers of the C allele, had significantly reduced non-visceral fat mass (-1.6 kg vs. -0.8 kg, P=0.02) and visceral fat (-0.4 kg vs. -0.3 kg, P=0.01)	(Thamer et al., 2008)
PPARD	rs2267668 G/A	n=156, women 60,1%	European	AA	low-fat diet with aerobic exercise for 9 months	carriers of the AA genotype, compared to carriers of the G allele, had significantly reduced non-visceral fat (-1.4 kg vs. -0.6 kg, P=0.04)	(Thamer et al., 2008)
PPARG	rs1801282 C/G	n=144, women100%	European	G	hypocaloric Mediterranean diet for 16 weeks	carriers of the G allele, compared to carriers of the CC genotype, had significantly reduced abdominal fat (-4.23±0.41 kg vs. -3.31±0.26 kg, P<0.05)	(Chmurzyn-ska et al., 2019)
TCF7L2	rs7903146 C/T	n= 771, women n/d	European	T	highly hypocaloric low-fat diet over 10 weeks	individuals with the TT genotype on a low-fat diet lost significantly more body mass (-6.9±4.0 kg vs. -4.8±3.3 kg, P=0.023), fat mass (-5.4±3.4 kg vs. -4.4±3.2 kg, P=0.048), and waist circumference (WC) (-6.8±6.1 cm vs. -4.2±4.8 cm, P=0.023) compared to those on a low-carbohydrate diet; carriers of the C allele were equally effective in reducing body mass regardless of the diet type	(Grau et al., 2010)
TCF7L2	rs7903146 C/T	n= 201, women n/d	European	TT	hypocaloric high-pro-tein diet for 16 weeks	individuals with the TT genotype, compared to carriers of the C allele, had significantly reduced body fat mass (BFM) (-5.6±2.4 kg vs. -4.1±2.8 kg, P=0.049)	(Ramos-Lopez et al., 2019)

n/d- no data; MT- body mass; BMI- body mass index, FM- fat mass; WC- waist circumference

Table 1. Continue …

Gene	Polymorphism	Cohort (sex, sample size)	Population	Favorable allele/ genotype	Type of diet therapy	Outcome	References
UCP2	rs660339 G/A	n= 386, women 100%	East Asian	G	Caloric restriction diet for 4 weeks.	carriers of the G allele had significantly reduced body fat mass (BFM) (-5.0±0.2 kg vs. -3.9±0.3 kg, P=0.016) compared to carriers of the AA genotype	(Cha et al., 2007)
UCP2	rs659366 G/A	n= 458, women 100%	East Asian	G	markedly hypocaloric diet for 4 weeks.	individuals with the G allele showed a significant reduction in BMI (-2.8±0.8 units vs. -2.4±1.0 units, P=0.02) and body fat mass (BFM) (-5.3±3.6 kg vs. -4.2±2.1 kg, P=0.03) compared to those with the AA genotype	(Yoon et al., 2007)
UCP3	rs1800849 rs2075576 rs1800006 rs1685325 rs2734827 rs2075577	n= 214, women 100% the average age is 28.6±9.6 years	East Asian	Haplotype [CGTACC]	extremely hypocaloric diet for 4 weeks	carriers of the haplotype [CGTACC], compared to carriers of the haplotype [TCCGTT], had significantly reduced body mass (BMI: -7.7±2.2 kg vs. -6.5±2.5 kg, P=0.016), body mass index (BMI: -2.98±0.91 vs. -2.54±0.94, P=0.039), and fat mass (FM: -5.5±4.6 kg vs. -4.3±1.8 kg, P=0.028)	(Cha et al., 2006)

n/d- no data; MT- body mass; BMI- body mass index, FM- fat mass; WC- waist circumference

Table 2. Genetic markers associated with exercise-induced weight loss efficiency.

Gene	Polymorphism	Cohort (sex, sample size)	Population	Favorable allele/ genotype	Type of exercise	Outcome	References
ACSL1	rs116143768 C/T	n=126, women 100%	European	T	aerobic training for 12 weeks	carriers of the T allele, compared to those with the CC genotype, had significantly reduced relative fat mass (by 31.4% vs. -3.8%, P=1.18×10^{-9})	(Bojarczuk et al., 2022)
ADRA2B *ADRB3* *ADRB2*	rs28365031 I/D rs4994 A/G rs1042714 G/C	n=70, women 78,6%	Mixed (USA)	Haplotype [*ADRA2B II, ADRB3 G]*, Haplotype [*ADRA2B II, ADRB2* G]	aerobic exercises of moderate intensity for 24 weeks	carriers of the haplotype [*ADRA2B* II, *ADRB3* G], compared to non-carriers of this haplotype, had significantly reduced total body fat (-3.8±1.0 vs. -0.8±0.3 kg, P=0.007), relative total body fat (-4.0±0.9%, P=0.009), and relative trunk fat (-4.8±1.1%, P<0.01) carriers of the haplotype [*ADRB3 G*, *ADRB2 G*], compared to non-carriers of this haplotype, significantly reduced total body fat (-3.2 ± 0.8 kg vs. -1.4±0.6 kg, P=0.031) and relative total body fat (-4.2±0.8%, P<0.005)	(Phares et al., 2004)
ADRB2 *ADRB2* *ADRB3* *ADRA2A*	rs1042713 G/A rs1042714 G/C rs4994 A/G rs553668 G/A	n=163, women 100%	European	Alleles rs1042713 A, rs1042714 C, rs553668 A in combination	aerobic training for 12 weeks	carriers of a small number (0–3) of obesity risk alleles [rs1042713 G, rs1042714 G, rs553668 G] had significantly reduced relative total body fat compared to carriers of a high number (5-6) of risk alleles (7.7±9.8% vs. 4.0±9.4%, P = 0.0362)	(Leońska-Duniec et al., 2018)
ADRB2	rs1042714 G/C	n=70, women 78,6%	Mixed (USA)	G	aerobic exercises of moderate intensity for 24 weeks	carriers of the G allele, compared to carriers of the C allele, had significantly reduced relative total body fat (-2.7±0.4% vs. -1.3±0.4%, P=0.015) and relative trunk fat (-3.2±0.5% vs. -1.5±0.5%, P=0.02	(Phares et al., 2004)
ADRB3	rs4994 A/G	n=70, women 78,6%	Mixed (USA)	G	aerobic exercises of moderate intensity for 6 months	carriers of the G allele, compared to individuals with the AA genotype, had significantly reduced relative total body fat (-2.7±0.5% vs. -1.3±0.3%, P=0.027) and relative trunk fat (3.1±0.6% vs. -1.6±0.3%, P=0.03)	(Phares et al., 2004)
ADRB3	rs4994 A/G	n=65, women 72,3%	European	AA	aerobic exercise on the background of a hypocaloric diet for 12 weeks	individuals with the AA genotype, compared to individuals with the AG genotype, had significantly reduced BMI (n/d, P<0.05), body mass (n/d, P<0.05), fat mass (n/d, P<0.05), and waist circumference (WC) (n/d, P<0.05).	(de Luis et al., 2007)

n/d- no data; MT- body mass; BMI- body mass index, FM- fat mass; WC- waist circumference

Table 2. Continue ….

Gene	Polymorphism	Cohort (sex, sample size)	Population	Favorable allele/ genotype	Type of exercise	Outcome	References
AHSG	rs4917 T/C	n=105, women 100%	European	TT	high-intensity aerobic exercise on the background of a hypocaloric diet for 10 weeks	carriers of the TT genotype, compared to carriers of the C allele, had significantly reduced trunk fat (-3.7±11.4 kg vs. 1.5±15.1 kg, P<0.005)	(Suchanek et al., 2011)
COMT	rs4680 G/A	n=173, women 100%	Mixed (USA)	GG	aerobic exercise of moderate intensity for 1 year	carriers of the GG genotype, compared to carriers of the AA genotype, had significantly reduced relative total body fat (-1.9% vs. -0.7%, P=0.05)	(Tworoger et al., 2004)
CYP19	(TTTA)n	n=173, women 100%	Mixed (USA)	(TTTA)2-11	aerobic exercise of moderate intensity for 1 year	carriers of the (TTTA)2-11 allele, compared to non-carriers, had significantly reduced total body fat (-3.1 kg vs. -0.5 kg, P = 0.01) and relative total body fat (-2.4% vs. -0.6%, P=0.001)	(Tworoger et al., 2004)
DRD2	rs1800497 C/T	n=127, women 100%	European	C	resistance training with weights on the background of a hypocaloric diet for 6 months	carriers of the C allele, compared to carriers of the T allele, had significantly reduced BMI (-2.3 units vs. -1.4 units, P=0.001), body mass (-7 kg vs. -4.4 kg, P=0.001), and body fat mass (-6.2 kg vs. -4.4 kg, P=0.001)	(Cameron et al., 2013)
FABP2	rs1799883 T/C	n= 69, women 79,7%,	European	C	aerobic exercise in conjunction with a hypocaloric diet for 12 weeks	carriers of the C allele, compared to individuals with the TT genotype, had significantly reduced total body fat (-1.6 kg vs.-1.3 kg, P<0.05)	(de Luis et al., 2006)
FTO	rs8050136 C/A	n= 481, women 51,8%	European	CC	aerobic exercise of low/moderate intensity for 20 weeks	carriers of the CC genotype, compared to individuals with the AA genotype, had significantly reduced total body fat (-0.8±0.1 kg vs. -0.2±0.2 kg, P=0.0065) and relative total body fat (-1.0±0.1% vs. -0.3±0.2%, P=0.0087)	(Rankinen et al., 2010)
IL15	rs1057972 A/T	n= 163, women 100%	European	A	aerobic exercise of moderate intensity for 12 weeks	carriers of the A allele, compared to individuals with the TT genotype, had significantly reduced relative total body fat (n/d, P=0.00002)	(Ficek et al., 2019)
IL15	rs1589241 T/C rs1057972 A/T	n= 163, women 100%	European	Haplotype [TA]	aerobic exercise of moderate intensity for 12 weeks	carriers of the [TA] haplotype, compared to carriers of the [AT] haplotype, had significantly reduced relative visceral fat (n/d, P=0.027)	(Ficek et al., 2019)
INSIG2	rs7566605 C/G	n=752, women 60%	European	GG	resistance training with added weight for 12 weeks	among men, carriers of the GG genotype, compared to carriers of the C allele, had significantly reduced relative subcutaneous fat (-1.0±1.7% vs.6.4±1.8%, P=0.035)	(Orkunoglu-Suer et al., 2008)
NYD-SP18	rs6971091 G/A	n=139, women 100%	European	GG	high-intensity aerobic exercise in conjunction with a hypocaloric diet for 10 weeks	carriers of the GG genotype, compared to carriers of the A allele, significantly reduced fat mass (-5.0±3.3 kg vs. -3.7±3.5 kg, P=0.037)	(Suchánek et al., 2015)
PLIN1	rs1052700 A/T	n=30, women 100%	American	TT	high-Intensity Interval Training (HIIT) alongside a hypocaloric diet for 12 weeks	carriers of the TT genotype, compared to carriers of the AA and AT genotypes, had significantly reduced body fat mass (BFM)(-5.1±1.8 kg vs. -1.8±1.4 kg and vs. -2.1±2.3 kg, respectively, P=0.04)	(Andrade-Mayorga et al., 2021)

n/d- no data; MT- body mass; BMI- body mass index, FM- fat mass; WC- waist circumference

Table 2. **Continue ….**

Gene	Polymorphism	Cohort (sex, sample size)	Population	Favorable allele/ genotype	Type of exercise	Outcome	References
PPARG	rs1801282 C/G	n=201, women 100%	European	CC	aerobic training for 12 weeks	carriers of the CC genotype had significantly reduced fat mass (not specified, P=0.0002) and relative fat mass (not specified, P=0.00003) compared to carriers of the G allele	(Zarebska et al., 2014)
PPARG	rs1801282 C/G	n=79, women 45,6%	European	G	aerobic exercises for 10 weeks	carriers of the G allele, compared to individuals with the CC genotype, had significantly reduced body mass (-1.8±1.8 kg vs. -0.3±1.4 kg, P<0.05	(Østergård et al., 2005)
PPARG	rs1801282 C/G	n = 1004, women n/d	Mixed	G	moderate-intensity physical activity for one year (e.g., walking)	carriers of the G allele, compared to individuals with the CC genotype, significantly reduced body mass (n/d, P = 0.04) and subcutaneous fat mass (n/d, P=0.03)	(Franks et al., 2007)
PPARGC 1A	rs17650401 C/T	n=39, women 100%	European	T	high-intensity aerobic exercise alongside a hypocaloric diet for 12 weeks	carriers of the T allele, compared to individuals with the CC genotype, had significantly reduced relative body fat mass (BFM) by 2.5 times (P = 0.00013)	(Mazur et al., 2020)
TCF7L2	rs7903146 C/T	n=309, women 62,8%	European	CC	moderate-intensity physical activity over the course of 2 years	carriers of the CC genotype, compared to carriers of the T allele, significantly reduced BMI (-1.2±1.6 units vs. -0.7±1.5 units, P=0.0034), non-visceral fat mass (-2.7±3.6 kg vs. -1.3±2.9 kg, P=0.0022), and visceral fat mass (-0.5±0.6 kg vs. -0.3±0.6 kg, P=0.0165)	(Haupt et al., 2010)
UCP2	I/D	n=42, women 100%	East Asian	D	moderate-intensity aerobic exercise for 6 months	carriers of the DD and ID genotypes, compared to carriers of the II genotype, had significantly reduced body mass (-1.57 kg, P=0.001 for DD; -2.03 kg, P=0.003 for ID), body mass index (BMI) (-0.64 units, P=0.001 for DD; -0.83 units, P=0.003 for ID), relative fat mass (-1.24%, P=0.014 for DD), and waist circumference (WC) (-5.56 cm, P<0.001 for DD; -5.63 cm, P<0.001 for ID)	(Lim and Shin, 2014)
UCP3	rs1800849 C/T	n=107, women 74,7%	European	CC	low-intensity aerobic exercise alongside a hypocaloric diet for 12 weeks	carriers of the CC genotype, compared to carriers of the T allele, had significantly reduced fat mass (-2.9 kg, P<0.05) and waist circumference (WC) (-3.5 cm, P<0.05)	(de Luis et al., 2008)

n/d- no data; MT- body mass; BMI- body mass index, FM- fat mass; WC- waist circumference.

Most publications (n = 22) examine the efficacy of a traditional low-calorie diet. The goal of a hypocaloric diet is to create a calorie deficit, meaning that the energy intake is lower than the energy expenditure. This deficit is believed to prompt the body to use stored energy, typically fat, leading to weight loss. This approach represents the most straightforward and efficient method for weight loss (Koliaki and Katsilambros, 2022), and, for that reason, it is probably most often used in research. Nevertheless, the nutritional composition of a diet can impact diverse physiological aspects. This includes hormonal levels (Ryan and Seeley, 2013; Kim et al., 2021), metabolic pathways (Moszak et al., 2020), gene expression (Mierziak et al., 2021), and the composition of the gut microbiome (Singh et al., 2017). Therefore, this emphasizes the importance of conducting studies that explore the effectiveness of diets with varying macronutrient compositions for weight loss, taking into account the genetic status of individuals.

Individuals exhibit genetic variability, and specific alleles or genotypes might be more advantageous regarding fat loss efficiency in response to specific dietary interventions. Favorable alleles are those genetic variants linked to a more favorable outcome, such as efficient fat loss, in response to particular diets. These alleles might be associated with enhanced metabolism, improved nutrient utilization, or better responses to specific dietary components. Table 1 presents these alleles. Certain alleles or genotypes might also be linked to more efficient utilization of fat as an energy source during physical activity. As in the case of diet-induced fat loss, understanding an individual's genetic profile, including the presence of favorable alleles, can facilitate personalized exercise recommendations. Tailoring exercise routines based on genetic information seems a very attractive way to optimize individuals' fat loss outcomes and overall fitness. The favorable alleles related to exercise-induced fat loss are demonstrated in Table 2. The analyzed publications exhibited different SNPs for the same genes in most cases. However, among the studied genes in the context of diet-induced fat loss, for the *FTO* gene, 2 polymorphisms were identified, with one of them, rs9939609, appearing in 2 publications (de Luis et al., 2015a; 2015b), and the other, rs1558902, in one publication (Zhang et al., 2012).

Interestingly, there is no difference in weight loss outcomes between a high-protein/low-carbohydrate diet and a standard hypocaloric diet. The findings indicate an association between the *FTO* variant rs9939609 and weight loss reduction following hypocaloric diet interventions (de Luis et al., 2015a). In the case of *MTNR1B* and rs1083096, two studies indicated that carriers of the CC genotype, compared to carriers of the G allele, were more effective in fat loss (de Luis et al., 2020a, 2020b). However, inconsistent findings were also observed. For instance, a study by Phares et al. (2004) with 70 individuals carrying the G allele of *ADRB3* rs4994 showed an effective reduction in body fat mass (Phares et al., 2004). In contrast, de Luis et al. (2007) demonstrated the highest efficiency for carriers with the AA genotype (de Luis et al., 2007).

Notably, most of the genetic variants identified in intervention studies were revealed through the candidate-gene approach, constrained by the current understanding researchers possess regarding the biology of obesity. Specifically, in the 27 publications studied in Table 1 and the 20 publications studied in Table 2, genome-wide association studies (GWAS) were used only once in Table 2 and in Bojarczuk et al., (2022). This underscores the existing limitations in our knowledge of genetic markers influencing body weight and the physiological response to physical activity and macronutrient intake. Association studies are the most commonly used in genetic analysis in sports. However, they have two weaknesses - they rely on the analysis of candidate genes (somewhat closing themselves off to other potentially unrelated markers with the examined trait). GWAS, instead, can assess hundreds of thousands of SNPs, and it is not hypothesis-driven (Tam et al., 2019; Loos and Yeo, 2022) To overcome these limitations and gain a more comprehensive understanding, extensive GWAS, replication studies, and meta-analyses are crucial (Egorova and Ahmetov, 2023). To avoid false positive results in association studies, studies of this type should undergo repetition in so-called replication studies (Kraft et al., 2009), either in subgroups of the same population (internal replication) or in additional groups of athletes and non-athletes of diverse ethnic backgrounds (external replication) (Liu et al., 2008).

Furthermore, genetic markers explain the observed differences in how individuals respond to weight-loss interventions. Understanding these markers allows researchers and clinicians to tailor interventions for better outcomes. The ultimate goal is, therefore, to use genetic information to develop personalized strategies for weight loss. This involves recommending specific diets and exercise plans based on an individual's genetic profile.

Our methods involved a meticulous approach to ensure the inclusion of studies directly relevant to investigating genetic factors influencing fat loss outcomes. However, we do not exclude the possibility that our systematic review might have limitations, such as potential biases in individual studies (patient selection, performance evaluation, measurement) or publication biases (Yuan and Hunt, 2009; Vrabel, 2015). When assessing the literature, crucial factors include variables such as diet duration. For example, in the study of Hamada et al. (2011), the intervention period was relatively brief, and the dietary method was homogeneous. Thus, it is intriguing to explore whether the genetic effects identified in such a study manifest over the long term and/or with different dietary interventions (Hamada et al., 2011). Another primary source of uncertainty is the nature of the exercise, duration, and intensity. For instance, in (Phares et al., 2004), the participants were subjected to aerobic exercises of moderate intensity for 24 weeks. Similar to the publication (Hamada et al., 2011), the effects of long-term exercise training have not been determined (Phares et al., 2004). The subjects' recruited characteristics are also important considerations. This is because the body composition is determined by, e.g., age, sex, ethnicity, height, and weight. Despite adjustments for variables like age, sex, ethnicity, height, diabetes status, smoking, dietary intake, and physical activity, the heritability of percentage fat mass, whole-body fat mass, and whole-body lean mass (fat-free mass) persist at a notably high level (Bojarczuk et al., 2022). A key aspect of the response to training or diet is the nutritional status (normal, overweight, or obese). Not everyone within a specific weight category will respond the same way to dietary changes. Next, the training status also matters. Changes in traits are always more pronounced in untrained individuals than in their trained counterparts (Bojarczuk et al., 2022). As described, several methodological considerations regarding the response training or diet can significantly affect experimental outcomes. Moreover, systematic reviews have no rules regarding the sample size requirements (Ferrari, 2015). However, we used articles with representative sample sizes.

Conclusion

In conclusion, this comprehensive analysis highlights the intricate interplay between genetic factors and the effectiveness of weight loss strategies, shedding light on potential markers linked to fat loss in dietary and exercise interventions. The approach presented here identified 30 genetic markers associated with the efficiency of fat loss in reaction to dietary interventions and 24 markers in response to physical activity. If advancements are made in this field, a methodology could be developed to tailor the selection of diet and exercise based on genetics to prevent and treat obesity.

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Key points

- Inter-individual differences play a crucial role in determining body weight and shaping the body's response to changes in diet and engagement in physical activity.
- The review identified 30 genetic markers associated with fat-loss efficiency in response to various diets and 24 markers in response to exercise.
- In the future, the focus should be on tailoring the choice of diet and exercise types to individual genetic characteristics to prevent and treat obesity.

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Supplementary Table 1. Assessing the risk of bias for randomized controlled trials using an adapted, validated version of the Cochrane Collaboration's tool (0 – low risk, 1 – unclear risk, 2 – high risk) and final the risk of bias (A, B, C) according to the Cochrane Collaboration's tool.

Article	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Final the risk of bias assessment based on 6 questions	Other bias	Final the risk of bias assessment based on 7 questions
Goni et al., 2018	0	1	2	0	0	0	C	0	A
de Luis et al, 2018b	0	0	1	0	0	0	B	0	A
Zhang et al., 2012	0	0	0	0	0	0	A	0	A
Heianza et al., 2018	0	0	0	0	1	0	B	0	A
de Luis et al., 2020	1	1	1	0	0	0	B	0	A
de Luis et al, 2020	1	1	1	0	0	0	B	0	A
Sun et al., 2018	0	0	0	0	1	0	B	0	A
Lin et al., 2015	0	0	0	0	0	0	A	0	A
Chmurzynska et al, 2019	0	0	0	0	0	0	A	0	A
Grau K et al., 2010	0	1	2	0	0	0	C	0	A
Cameron et al., 2013	1	1	1	1	0	0	B	1	B
Franks et al., 2007	1	1	0	0	0	0	B	0	A
Ramos-Lopez et al., 2019	0	1	2	1	2	0	C	0	A
Heianza et al., 2016	0	0	0	0	0	0	A	0	A

Supplementary Table 2. **Quality assessment of cohort studies by using the Newcastle Ottawa Scale.**

Article	1. Representative of exposed cohort	2. Selection of non-exposed cohort	3. Valid ascertainment of exposure	4. Outcome of interest not present at start of study	5. Control for important factors (age, sex, BMI)	6. Control for additional factors (diet, physical activity)	7. Assessment of outcome	8. Adequate duration of follow-up (≥8 weeks)	9. Adequacy of follow-up (no more than 20%)	Score
Hamada et al., 2010	1	1	1	1	1	1	1	1	1	9
Izaola Jáuregui et al., 2020	1	1	1	1	1	1	1	1	1	9
Rajkumar et al., 2016	1	1	1	1	1	1	1	1	1	9
Tchernof et al., 2000	1	1	1	1	1	1	1	1	1	9
de Luis et al, 2018c	1	1	1	1	1	1	1	1	1	9
de Luis et al., 2015b	1	1	1	1	1	0	1	1	1	8
de Luis et al, 2015a	1	1	1	1	1	0	1	1	1	8
Abete et al, 2009	1	1	0	1	1	0	1	1	1	7
Di Renzo et al, 2013	1	1	1	1	1	0	1	1	1	8
de Luis et al, 2018a	1	1	1	1	1	0	1	1	1	8
Thamer et al., 2008	1	1	1	1	1	0	1	1	1	8
Cha et al., 2007	1	1	0	1	1	0	1	1	0	6
Yoon et al., 2007	1	1	1	1	1	0	1	0	0	6
De Luis et al., 2013	1	1	0	1	1	1	1	1	1	8
Cha et al., 2006	1	1	0	1	1	0	1	0	1	6
Bojarczuk et al., 2022	1	1	1	1	1	0	1	1	1	8
Phares et al., 2004	1	1	1	1	1	0	1	1	1	8
Leońska-Duniec et al., 2018	1	1	1	1	1	1	1	1	1	9
de Luis et al., 2007	1	1	0	1	1	1	1	1	1	8
Suchanek et al., 2011	1	1	1	1	1	0	1	1	1	8
Tworoger et al., 2004	1	1	1	1	1	0	1	1	1	8
de Luis et al., 2006	1	1	0	1	1	1	1	1	1	8
Rankinen et al., 2010	1	1	1	1	1	0	1	1	1	8
Ficek et al., 2019	1	1	1	1	1	0	1	1	1	8
Orkunoglu-Suer et al., 2008	1	1	1	1	1	0	1	1	1	8
Suchánek et al., 2015	1	1	1	1	1	0	1	1	1	8
Andrade-Mayorga et al., 2021	1	1	1	1	1	1	1	1	0	8
Zarebska et al., 2014	1	1	1	1	1	0	1	1	1	8
Østergård et al., 2005	1	1	1	1	1	1	1	1	1	9
Mazur et al., 2020	1	1	1	1	1	0	1	1	1	8
Haupt et al., 2010	1	1	1	1	1	0	1	1	1	8
Lim et al., 2014	1	1	1	1	1	0	1	1	1	8
de Luis et al., 2008	1	1	0	1	1	1	1	1	1	8
de Luis et al., 2023	1	1	1	1	1	1	1	1	1	9

Supplementary Table 3. **Scale for Quality Assessment of genetic association studies.**

Criteria	Low quality	Intermediate quality	High quality
Gene-diet or gene-physical exercise interaction as primary study goal	No = -1	Not known = 0	Yes = 1
Formal test for interaction	No = -1	Not known or stratified analysis = 0	Yes = 1
Correction for multiple testing	No = -1	Not known = 0	Yes or not necessary = 1
Correction for population stratification/ethnicity	No = -1	Not known = 0	Yes or not applicable = 1
Hardy-Weinberg equilibrium	No or not stated = -1	Not known = 0	Yes = 1
Group similarity at baseline tested		Not known = 0	Yes = 1
Power analysis and sample size	≤65= -1	65-322=0	>322 or power analysis is provided (>80%) = 1
Sufficient details of study procedure stated	No = -1	-	Yes = 1

*the cut offs used to define low, intermediate and high sufficiency of sample size were based on the 15th (n=65) and 75th percentile (n=322) of the sample size of the studies included.

Supplementary Table 4. **Risk of bias assessment outcomes for all studies reviewed according to Scale for Quality Assessment of genetic association studies.**

Article	Gene-diet or gene-physical exercise interaction as primary study goal	Formal test for interaction	Correction for multiple testing	Correction for population stratification/ ethnicity	Hardy-Weinberg equilibrium	Group similarity at baseline tested	Power analysis and sample size	Sufficient details of study procedure stated	Score
Goni et al., 2018	1	1	0	1	1	1	1	1	7
de Luis et al, 2018b	1	1	1	1	1	1	1	1	8
Zhang et al., 2012	1	1	-1	1	1	1	1	1	6
Heianza et al., 2018	1	1	0	1	1	1	1	1	7
de Luis et al., 2020	1	1	0	0	1	1	1	1	6
de Luis et al, 2020	1	1	1	0	1	1	1	1	7
Sun et al., 2018	1	1	1	0	0	1	1	1	6
Lin et al., 2015	1	1	1	1	1	1	1	1	8
Chmurzynska et al, 2019	1	1	-1	1	0	1	0	1	4
Grau K et al., 2010	1	1	1	1	1	1	1	1	8
Cameron et al., 2013	1	1	-1	0	1	1	0	1	4
Franks et al., 2007	1	1	1	1	1	1	1	1	8
Ramos-Lopez et al., 2019	1	1	1	1	1	1	1	1	8
Heianza et al., 2016	1	1	0	1	1	1	1	1	7
Hamada et al., 2010	1	1	0	0	1	1	0	1	5
Izaola Jáuregui et al., 2020	1	1	0	0	1	1	1	1	6
Rajkumar et al., 2016	1	1	0	1	1	1	0	1	6
Tchernof et al., 2000	1	1	1	0	0	1	0	1	5
de Luis et al, 2018c	1	1	0	1	1	1	1	1	7
de Luis et al., 2015b	1	1	0	1	1	1	1	1	7
de Luis et al, 2015a	1	1	0	0	1	1	1	1	6
Abete et al, 2009	1	1	1	0	1	1	1	1	7
Di Renzo et al, 2013	1	1	1	0	0	1	0	1	4
de Luis et al, 2018a	1	1	1	0	1	1	1	1	7
Thamer et al., 2008	1	1	1	1	0	0	0	1	5

Supplementary Table 4. Continue …

Article	Gene-diet or gene-physical exercise interaction as primary study goal	Formal test for interaction	Correction for multiple testing	Correction for population stratification/ ethnicity	Hardy-Weinberg equilibrium	Group similarity at baseline tested	Power analysis and sample size	Sufficient details of study procedure stated	Score
Cha et al., 2007	1	1	1	1	1	0	1	1	7
Yoon et al., 2007	1	1	1	1	1	0	1	1	7
De Luis et al., 2013	1	1	1	0	0	0	1	1	5
Cha et al., 2006	1	1	0	1	1	0	0	1	5
Bojarczuk et al., 2022	1	1	1	1	1	0	0	1	6
Phares et al., 2004	1	1	0	1	1	1	0	1	6
Leońska-Duniec et al., 2018	1	1	0	0	1	0	1	1	5
de Luis et al., 2007	1	1	1	0	0	1	1	1	6
Suchanek et al., 2011	1	1	1	0	0	1	0	1	5
Tworoger et al., 2004	1	1	1	1	1	1	0	1	7
de Luis et al., 2006	1	1	1	0	0	1	0	1	5
Rankinen et al., 2010	1	1	1	1	1	0	1	1	7
Ficek et al., 2019	1	1	1	0	1	0	0	1	5
Orkunoglu-Suer et al., 2008	1	1	-1	1	1	1	1	1	6
Suchánek et al., 2015	1	1	1	0	1	0	0	1	5
Andrade-Mayorga et al., 2021	1	1	0	0	1	1	-1	1	4
Zarebska et al., 2014	1	1	1	0	1	0	0	1	5
Østergård et al., 2005	1	1	0	0	1	1	0	1	5
Mazur et al., 2020	1	1	1	0	0	0	-1	1	3
Haupt et al., 2010	1	1	0	1	1	0	1	1	6
Lim et al., 2014	1	1	1	0	1	0	-1	1	4
de Luis et al., 2008	1	1	1	0	0	1	1	1	6
de Luis et al., 2023	1	1	1	1	1	1	1	1	8