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Lifestyle Interventions for Weight Control Modified by Genetic Variation: A Review of the Evidence

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Weight loss · Gene variation · Lifestyle intervention · Obesity

Abstract
Background/Aims: Excess weight gain is a result of the interaction between diet, environment, and genes. Evidence suggests that responses to lifestyle interventions to manage weight are partially modified by genetic factors. This review is aimed at summarizing the current evidence from studies done on gene variants – single nucleotide polymorphisms (SNPs) – and intervention outcomes on weight loss and obesity-related traits. ***Methods:*** Intervention studies published in English between 2000 and August 2018 were retrieved from PubMed, Google Scholar, and Web of Science using various keywords. ***Results:*** This article is a review of 36 studies conducted in 13 different countries which included a total of 15,931 participants between 19 and 70 years of age. The effect of 26 genes and 64 SNPs on the reduction of body weight and metabolic risk factors in response to diet, exercise, and lifestyle interventions was reviewed. ***Conclusion:*** Gene-lifestyle interaction studies on the same candidate gene in different populations have reported information which is challenging to interpret. Thus, it is difficult to arrive at a particular model for a strategy on weight management at this point in time. Most of the intervention studies focus on the effect of variants of a single candidate gene on weight loss. Further evidence from large-scale studies is necessary to assess the effect of multiple candidate genes to compute a gene score that could be used in a model intervention programme. Our review suggests that a healthy lifestyle with a balanced diet and regular physical activity will benefit individuals who carry the risk alleles of the obesity-related candidate genes. This message should be the mainstay of the recommendations and guidelines published by nutrition societies across the world.

Introduction

The current weight management programmes that combat obesity primarily focus on reducing energy consumption and increasing energy expenditure [1]. These strategies may result in reduction in weight and improvement in metabolic risk factors in obese individuals, but individuals from different populations may differ in their responses to the same intervention, making it difficult to arrive at a model for an ideal weight management strategy. Further, evidence suggests that these differences may be due to genetic factors [2]. Investigating genetic variation, i.e., single nucleotide polymorphisms (SNPs) of candidate genes (identified to be associated with excess

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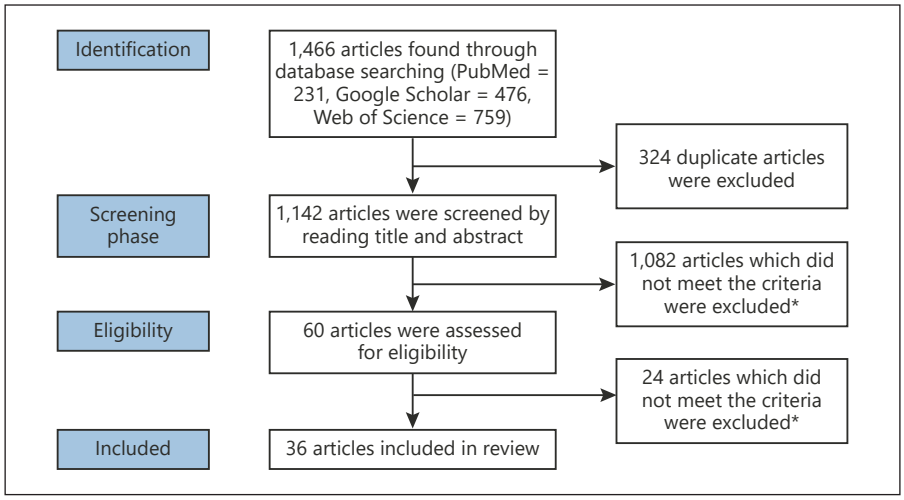

Fig. 1. Flow chart of data extraction. * Intervention studies using approaches on dietary, exercise, or lifestyle modification were included in this review. Studies using pharmacological and surgical approaches and intervention studies which involved subjects with diagnosed diseases were excluded. Articles without full-text access were excluded as well.

weight gain) and their interactions with lifestyle interventions may explain interindividual variability on weight loss outcomes [3].

Intervention trials (reviewed in this article) for weight management employed intervention strategies with hypocaloric diets, low-fat/high-fat diets, low-protein/high-protein diets, and exercise and interaction with single genes in individuals carrying different variants of the given gene. The duration of the above intervention programmes differed from 3 months to 2 years. Most studies assessed body weight, body mass index (BMI), and fat mass as the anthropometric outcomes, and lipid profile, insulin, and glucose levels as the biochemical outcome measures. Advanced techniques such as DNA microarrays or variant detector arrays were employed in these studies to detect the SNPs [4].

Genes involved in energy homeostasis, adaptive thermogenesis, lipoprotein metabolism, appetite control, and insulin signalling pathway are the main candidate genes that were reviewed. The studies on how these SNPs or gene variants may or may not affect the effectiveness of weight loss interventions have not been reported in great detail earlier [5]. This study aimed at summarizing the current literature on already reported candidate genes and gene variants (SNPs) which modulate the outcome of various weight loss interventions on obesity-related traits.

Methods

Search Strategy

Articles published in English between 2000 and August 2018 were searched in PubMed, Google Scholar, and Web of Science. The keywords used were divided into two themes. (1) The first theme included "weight loss," "dietary intervention," "exercise intervention," "physical activity," "caloric restriction," "lifestyle intervention," "low calorie diet," "macronutrient composition ratio," "high or low fat diet," "high or low carbohydrate diet," and "high or low protein diet." These search terms were combined with the second theme: (2) "gene variants" and "single nucleotide polymorphisms (SNPs)." Intervention studies using approaches on dietary, exercise, or lifestyle modification were included in this review. Studies using pharmacological and surgical approaches and intervention studies which involved subjects with diagnosed diseases were excluded. Articles without full-text access were excluded as well. For the presentation of the results, the intervention studies were divided into different categories according to the component of the affected physiological/metabolic processes.

Data Extraction

Data were reviewed and extracted by one author and checked for accuracy by two other authors. Data were extracted on the following variables: (1) study details (lead authors, year, duration, and study design), (2) population characteristics (sample size, nationality/ethnicity, sex, and age range), (3) gene variants (candidate gene, SNPs, and major and minor alleles), (4) method (weight reduction strategies used [dietary, exercise, or both] and short description of the intervention), (5) outcome measures (obesity-related anthropometric and blood biochemical parameters, e.g., BMI, body fat mass, percent body fat, waist circumference, fasting blood glucose, lipid levels, etc.), and (6) main findings. Discrepancy in the extracted data was solved by discussion among the reviewers.

Results and Discussion

A total of 36 articles were included in this review (Fig. 1), with total of 15,913 overweight/obese participants. The age ranged from 19 to 70 years. Participants were from 13 different countries, i.e., Spain, Korea, United States, Japan, Germany, Poland, Sweden, Denmark,

UK, The Netherlands, Czech Republic, Israel, and France. The duration of the intervention ranged from 1 month to 2 years. These studies had investigated the gene-lifestyle interaction in weight loss intervention in 26 different genes including *ADCY3*, *ADIPOQ*, *ADRB2*, *ADRB3*, *AMY1-AMY2*, *APOA1*, *APOA5*, *CB2R*, *CETP*, *CLOCK*, *FABP2*, *FTO*, *GHRL*, *GIPR*, *IRS1*, *LEPR*, *LIPC*, *MC4R*, *MTNR1B*, *PCSK7*, *PPARγ*, *TCF7L2*, *TFAP2B*, *TNF*, *UCP2*, and *UCP3*, with a total of 64 SNPs. Table 1 summarizes the outcome of weight loss interventions in the presence of different SNPs.

Our review revealed that *FTO* was the most investigated gene for gene-lifestyle interaction studies. Between 2009 and 2015, there were a total of 6 studies investigating the interactions between *FTO* rs9939609, rs1558902, and rs8050136 SNPs with various weight loss strategies. The second most investigated gene SNPs are *ADRB3* (rs4994) and *ADRB2* (rs1042713 and rs0142714), in 3 studies. *MTNR1B* (rs10830963), *PPARγ* (rs1801282), *MC4R* (rs17782313 and another 19 SNPs), *APOA5* (rs964184, rs662799, and rs3135506), *TCF7L2* (rs7903146 and rs12253372), and *IRS1* (rs2943641 and rs1522813) SNPs were examined in 2 studies each. *ADIPOQ*, *APOA1*, *AMY*, *UCP2*, *UCP3*, *GHRL*, *ADCY3*, *NPY*, *LIPC*, *TFAP2B*, *TNF*, *GIPR*, *FABP2*, *CB2R*, *PCSK7*, *LEPR*, and *CLOCK* were only reported once. In this review, a total of 36 gene-lifestyle interaction studies identified 64 SNPs from 26 genes from five different physiological/metabolic processes: (1) energy homeostasis, (2) adaptive thermogenesis, (3) lipoprotein metabolism, (4) appetite regulation, and (5) insulin signalling.

Gene Involved in Energy Homeostasis: Fat Mass and Obesity-Associated Protein Gene

The fat mass and obesity-associated protein (*FTO*) gene is highly expressed in the arcuate nucleus of the hypothalamus and is known to play an important role in energy homeostasis [42]. *FTO* polymorphisms are linked to appetite responses and therefore influence energy intake [43]. Besides, studies have suggested that *FTO* genes regulate body fat mass through lipid metabolism [44], and they have reported to alter body weight, BMI [45], as well as waist and hip circumference [46]. Among all the reported *FTO* SNPs (rs9939609 [T>A], rs1558902 [T>A], and rs8050136 [C>A]), rs9939609 (T>A) was the most investigated SNP in gene-diet interaction studies. This was assessed in 4 dietary intervention studies. The effect of *FTO* SNPs on weight loss outcomes will be discussed based on the following subheadings depending on the intervention strategies employed.

Low-Calorie Diet Interventions. In a population of obese Spanish women, Labayen et al. [11] found no significant association between rs9939609 alleles (T>A) and the changes in body weight and body composition after 14 weeks of calorie-restricted dietary intervention. Individuals with the risk allele (AA) of *FTO* rs9939609 had similar improvement in body weight, anthropometric parameters, and blood biomarkers compared to the non-carriers (TT). With respect to insulin sensitivity, a 10-week randomized controlled trial, NUGENOB, conducted by Grau et al. [8], reported that TT genotype carriers of the same gene and SNP had a greater reduction in homeostatic model assessment of insulin resistance (HOMA-IR) and homeostatic model assessment beta (HOMA-β) with a 10-week low-fat diet compared to a high-fat diet in the European population. The beneficial effect of a low-fat diet on insulin sensitivity was not found in the risk allele carriers (AA) [8]. Matsuo et al. [6] reported that no significant association was found between rs9939609 (T>A) and weight loss outcomes after a 14-week calorie-restricted dietary intervention in obese Japanese women. The 2-year POUNDS LOST trial compared the effects of an energy-restricted diet (an energy deficit of 750 kcal/day) with different compositions of fat, protein, and carbohydrate. Improvements in weight management and insulin sensitivity were observed in both gene variants (risk allele carriers [AA] and non-carriers [TT] of *FTO* rs9939609) in an American population; however the differences were not statistically significant [7]. It is to be noted that female carriers of the TT genotype of rs9939609 were more numerous in the NUGENOB study (75%) compared to the POUNDS LOST trial (62%). Moreover, NUGENOB participants were significantly younger (age range 20–50 years) compared to the POUNDS LOST participants (50.1 ± 9.9 years, age range 20–70 years). We suggest that these differences between the two studies (POUNDS LOST and NUGENOB) may be explained by the differences in age and sex. Further, a study conducted by Zhang et al. [9], comparing the effect of four hypocaloric diets with different macronutrient compositions, reported that the risk allele carriers (A) of rs1558902 showed a higher reduction in BMI and body adiposity on a high-protein diet compared to non-carriers (T) in overweight and obese American adults.

Exercise Interventions. Evidence from previous observational studies suggest that physical activity can attenuate the effect of genetic mutations of *FTO* rs9939609 on obesity and body fat accumulation [47, 48]. This finding was replicated in a recent observational study in a Nigerian population. The study reported that the carriers of

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Table 1. Lifestyle interventions for weight control modified by genetic variation: a review of the evidence

Physiological/ metabolic processes	SNPs (major > minor)	Intervention	Reference	Population characteristic (sample size, nationality/ethnicity, age range)	Duration and study design	Short description of the intervention	Outcome measures	Findings
Energy homeostasis	*FTO* rs9939609 (T>A)	calorie restriction	Matsuo et al. [6], 2012	204 obese Japanese women with BMI ≥25; 24–66 y	14 w of PPQES	a dietary modification programme instructing participants how to consume a nutritionally balanced diet of 1,200 kcal/day	BW, BMI, WC, FM, PBF, SBP, DBP, AEE, TC, TG, HDL-C, LDL-C, FBG	no significant associations between rs9939609 and weight loss or changes in metabolic risk factors, but the change in FM is smaller in the AA genotype carriers
	independent effect of *FTO* rs1558902 (T>A) and rs9939609 (T>A)	4 hypocaloric diets with different macronutrient compositions	Zheng et al. [7], 2015	743 overweight and obese Americans (White, African, Hispanic, Asian, others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, FBG, FI, HOMA-IR, HOMA-β	HFD (40% TE from fat) was more effective in improving insulin sensitivity in A allele carriers of rs1558902 compared to LFD; no significant association was found in rs9939609
	FTO rs9939609 (T>A)	LFD vs. HFD	Grau et al. [8], 2009	771 obese Europeans from Sweden, Denmark, UK, The Netherlands, Czech Republic, France, and Spain with BMI ≥30; 20–50 y	10 w of RCT	NUGENOB	BW, BMI, WC, FM, FFM, REE, FBG, FI, HOMA-IR, HOMA-β	TT genotype carriers showed greater reduction in HOMA-IR and HOMA-β in LFD compared to HFD
	FTO rs1558902 (T>A)	4 hypocaloric diets with different macronutrient compositions	Zhang et al. [9], 2012	742 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, FM, PBF, TAT, VAT, SAT, deep SAT	A allele carriers showed greatest reduction in BMI and body adiposity in HPD
	FTO rs8050136 (C>A)	exercise	Mitchell et al. [10], 2010	234 overweight and obese Caucasian postmenopausal women with BMI 25–43; 45–75 y	6 months of RCT	dose response to exercise comparing the effect of different amounts of exercise training on CRF (50, 100, and 150% of the consensus physical activity recommendation)	BW, BMI, FBG, FI, HOMA-IR, CRF	A allele carriers had significant reduction in BW and increase in CRF with moderate-intensity exercise compared to non-carriers
	independent and combined effect of *FTO* rs9939609 and *MC4R* rs17782313 polymorphisms	LFD vs. HFD	Labayen et al. [11], 2015	78 obese Spanish women with BMI 30–39.9; 19–49 y	3 months of PPQES	dietary intervention using a low-energy mixed diet (55% TE from CHO, 30% TE from fat, 15% TE from PRO) providing 600 kcal less than individually estimated energy requirements	BW, BMI, WC, FM, PBF, LM, REE, NPRQ, leptin, TSH	there was no independent or combined effect of *FTO* rs9939609 and *MC4R* rs17782313 on weight loss outcomes
Adaptive thermogenesis	independent and combined effect of *UCP2* –1957G>A, –866G>A, +4787C>T, and +7941_45del>ins; and *UCP3* –35C>T, +2564G>C, +2887C>T, +3106A>G, +3854C>T, and +4589T>C	calorie restriction	Yoon et al. [12], 2007	301 overweight and obese Korean women with BMI ≥25; mean age 29 ± 9 y	1 month of PPQES	a weight control programme composed of a very-low-calorie diet (700 kcal/day)	BW, BMI, WHR, FM, protein mass	AA genotype carriers had less reduction in BMI and fat compared to GG genotype carriers of UCP2866 G>A polymorphism

Table 1. (continued)

Physiological/ metabolic processes	SNPs (major > minor)	Intervention	Reference	Population characteristic (sample size, nationality/ethnicity, age range)	Duration and study design	Short description of the intervention	Outcome measures	Findings
	ADRB2 rs1042714 (C>G) and rs1042713 (G>A)	calorie restriction	Ruiz et al. [13], 2011	83 obese Spanish women with BMI 30–39.9; 19–49 y	3 months of PPQES	a dietary intervention using a low-energy mixed diet (55% TE from CHO, 30% TE from fat, 15% TE from PRO) providing 600 kcal less than individually estimated energy requirements	BW, BMI, WC, LM, FM, RMR	both genotypes of rs1042713 showed reduction in BW; women carrying G allele of rs1042714 had greater reduction in BW and LM than non-carriers (CC)
	ADRB2 rs1042714 (C>G), *ADRB2* rs1042713(A>G), *ADRB3* rs4994 (T>C), and *GHRL* rs696217 (G>T)	lifestyle modification (diet and exercise)	Saliba et al. [14], 2014	109 obese Brazilian women with BMI ≥30; 20 to >50 y	9 w (2 w of pre-intervention and 7 w of intervention) of PPQES	the intervention included 3 sessions of individualized dietary counselling, 2 sessions of nutritional lecture and workshop, and an orientation for physical activity	BW and BMI	polymorphisms in *ADRB2*, *ADRB3*, and *GHRL* did not lead to greater or lesser weight loss in response to dietary intervention
	ADRB3 rs4994 (T>C)	lifestyle modification (diet and exercise)	Tahara et al. [15], 2010	57 overweight and obese Japanese men with BMI ≥23; mean age 60 ± 7 y	3 months of PPQES	individual nutritional guidance was provided at least once during the 12-w period and a goal of 10,000 walking steps/day was requested	BW, BMI, WC	no association was found between *ADRB3* rs4994 and weight loss after an exercise-based intervention programme
	ADRB3 rs4994 (T>C)	lifestyle modification (diet and exercise)	Shiwaku et al. [16], 2003	76 overweight and obese Japanese premenopausal women with BMI ≥21; 35–69 y	3 months of PPQES	the behavioural weight loss programme included 10% reduction in dietary caloric intake and a goal of 7,000 steps/day	BW, BMI, WC, HC, WHR, PBF, SBP, DBP, REE, TC, LDL-C, HDL-C, TG, NEFA, FBG, FI, HOMA-IR, leptin, phospholipid	C allele carriers showed difficulty in losing weight through behavioural intervention compared to non-carriers
	PPARγ rs1801282 (C>G), *ADRB2* rs1042714 (C>G), and *FABP2* rs1799883 (A>G)	LFD vs. LCD	Gardner et al. [17], 2018	609 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 28–40; 18–50 y	2 y of RCT	DIETFITS (a dietary intervention comparing the effect of LCD and LFD on weight loss)	BW, BMI, WC, PBF, SBP, DBP, REE, TG, HDL-C, LDL-C, FBG, FI	no significant diet-genotype interaction was found in both LCD and LFD
Lipoprotein metabolism	*PPARγ* rs1801282 (C>G)	exercise	Zarebska et al. [18], 2014	201 Polish women with an average BMI of 21 ± 2.5; 19–24 y	3 months of PPQES	the low-high-impact aerobics programme was divided as follows: (1) 6 w (18 training units), 60 min each at about 50–60% of HR_{max}, (2) 3 w (9 training units), 60 min each with an intensity of 60–70% of HR_{max}, and (3) 3 w (9 training units), 60 min each with an intensity of 65–75% of HR_{max}	BW, BMI, FM, FFM, PBF	CC genotype carriers resulted in greater reduction in BW and FM after an exercise training programme compared to G allele carriers
	APOA5 rs964184 (C>G)	4 hypocaloric diets with different macronutrient compositions	Zhang et al. [19], 2012	734 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, LM, FM, PBF, SBP, DBP, FBG	G allele carriers had greater reduction in TC and LDL-C levels by LFD (20% TE from fat)
	independent and combined effect of *APOA5* rs662799 (T>C) and Ser19Trp/rs3135506 (C>G)	lifestyle modification (diet and exercise)	Suchanek et al. [20], 2008	98 overweight and obese non-diabetic Czech women with BMI ≥27.5; 25–55 y	9 w of PPQES	the lifestyle modification programme consisted of a reduction in energy intake and an exercise programme (aerobic exercise 4 times/w, 60 min each)	BW, BMI, WHR, SBP, DBP, TC, TG, HDL-C, LDL-C, glycaemia	TG levels was significant reduced in Ser19Ser carriers, but were increased in Trp allele carriers; similarly, LDL-C was not reduced in the carriers of at least one less common variant of *APOA5* compared to TT/ Ser19Ser carriers

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Table 1. (continued)

Physiological/ metabolic processes	SNPs (major > minor)	Intervention	Reference	Population characteristic (sample size, nationality/ethnicity, age range)	Duration and study design	Short description of the intervention	Outcome measures	Findings
	ADIPOQ rs1501299 (G>T)	calorie restriction	De Luis et al. [21], 2019	82 obese Caucasians with BMI ≥30; 20–65 y	3 months of PPQES	a hypocaloric diet with a Mediterranean pattern (52% TE from CHO, 25% TE from fat, and 23% TE from PRO, and 15 g of fibre) of 1,500 kcal/day	BW, BMI, WC, WHR, FM, SBP, DBP, FBG, FI, HOMA-IR, TC, TG, HDL-C, LDL-C	GG genotype carriers had better outcomes on FBG, insulin, HOMA-IR, and LDL-C compared to T allele carriers after a Mediterranean hypocaloric diet
	APOA1 rs670 (G>A)	calorie restriction	De Luis et al. [22], 2018	82 obese Caucasians with BMI ≥30; 20–65 y	3 months of PPQES	a hypocaloric diet with a Mediterranean pattern (52% TE from CHO, 25% TE from fat, and 23% TE from PRO, and 15 g of fibre) of 1,500 kcal/day	BW, BMI, WC, WHR, FM, SBP, DBP, FBG, FI, HOMA-IR, TC, TG, HDL-C, LDL-C, resistin, adiponectin, leptin	A allele carriers had better outcomes on anthropometric parameters, TC, LDL-C, insulin, and HOMA-IR compared to non-carriers after a Mediterranean hypocaloric diet
	LIPC rs2070895 (G>A)	4 hypocaloric diets with different macronutrient compositions	Xu et al. [23], 2015	743 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, SBP, DBP, FBG, FI, HOMA-IR, TC, TG, HDL-C, LDL-C	in the LFD, A allele carriers were associated with decrease in LDL-C and TG and a lower increase in HDL-C, whereas an opposite effect was found in HFD
	CETP rs3764261 (C>A)	POUNDS LOST, DIRECT	Qi et al. [24], 2015	POUNDS LOST: 723 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y; DIERCT: 171 overweight and obese Israelis with BMI ≥27; 30–70 y	2 y of RCT	POUNDS LOST, DIRECT	BW, BMI, TC, LDL-C, HDL-C, TG	In POUNDS LOST, CC genotype carriers of *CETP* rs3764261 had higher increase in HDL-C and decrease in TG on an HFD compared to an LFD, while no significant difference between these two diets was observed in the non-carriers; these findings were replicated in DIRECT
Appetite regulation	*MTNR1B* rs10830963 (C>G)	calorie restriction	De Luis et al. [25], 2018	80 obese Caucasians with BMI ≥30; 20–65 y	3 months of PPQES	a Mediterranean dietary intervention (52% TE from CHO, 25% TE from fat, and 23% TE from PRO) providing 500 kcal/day less than individually estimated TE expenditure	BW, BMI, WC, FM, SBP, DBP, FBG, FI, HOMA-IR, adiponectin, CRP, leptin, resistin	C allele carriers had greater reduction in FI and HOMA-IR compared to non-carriers after a Mediterranean hypocaloric diet
	MTNR1B rs10830963 (C>G)	4 hypocaloric diets with different macronutrient compositions	Goni et al. [26], 2018	722 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, PBF, TC, TG, HDL-C, LDL-C	G allele carriers had greater reduction in TC and LDL-C levels when undertaking an energy-restricted LFD compared to an HFD

Table 1. (continued)

Physiological/ metabolic processes	SNPs (major > minor)	Intervention	Reference	Population characteristic (sample size, nationality/ethnicity, age range)	Duration and study design	Short description of the intervention	Outcome measures	Findings
	MC4R rs17066866 (A>T), rs1943226 (T>G), rs11875096 (T>G), rs1943224 (A>G), rs7235242 (A>C), rs11872992 (G>A), rs8093815 (C>T), rs17066856 (T>C), rs17066836 (C>G), rs1943227 (A>G), rs1943218 (T>C), rs17066829 (T>A), rs9966412 (G>A), rs17066859 (G>A), rs9965495 (C>T), rs12970134 (G>A), rs17700633 (C>T), rs11873305 (T>G), rs8091237 (C>G), and rs7240064 (C>T)	lifestyle modification (diet and exercise)	Pan et al. [27], 2013	718 overweight and obese Americans (White, African, Hispanic, Asian and others) with BMI ≥24 (≥22 in Asian Americans); ≥25 y	2 y of RCT	participants from the Diabetes Prevention Program were randomized to placebo, metformin (850 mg twice daily), troglitazone (400 mg daily), or an intensive lifestyle modification programme (aimed at ~7% weight loss with healthy eating and at least 150 min of physical activity/w)	BW, BMI, WC, diabetes incidence	in the lifestyle intervention group, T allele carriers of rs17066866 were associated with less short-term and long-term weight loss compared to non-carriers
	LEPR rs1805094 (G>C)	lifestyle modification (diet and exercise)	De Luis Roman et al. [28], 2006	67 obese Spanish patients with BMI >30; mean age 46 ± 17 y	3 months of PPQES	the lifestyle modification programme consisted of a hypocaloric diet (1,520 kcal/day, 52% TE from CHO, 25% TE from fat, and 23% TE from PRO); the exercise programme consisted of aerobic exercise for at least 3 times/w (60 min each)	BW, BMI, WC, WHR, FM, FFM, SBP, DBP, FBG, FI, HOMA-IR, TC, TG, HDL-C, LDL-C, resistin, adiponectin, CRP, leptin, IL-6, TNF-α	GG genotype carriers had significant reduction in BW, BMI, WC, FM, SBP, and leptin levels, whereas C allele carriers had significant reduction in BW, BMI, WC, and LDL-C
	NPY rs16147 (T>C)	4 hypocaloric diets with different macronutrient compositions	Lin et al. [29], 2015	723 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, SAT, VAT, TAT	C allele carriers had significant reduction in WC at 6 month and SAT, VAT, and TAT at 24 months with an HFD compared to an LFD
Insulin signalling	*GIPR* rs2287019 (C>T)	4 hypocaloric diets with different macronutrient compositions	Qi et al. [30], 2012	737 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, SBP, DBP, FBG, FI, HOMA-IR, TC, TG, HDL-C, LDL-C	T allele carriers had greater reduction in weight and HOMA-IR when undertaking an LFHCD diet
	IRS1 rs2943641 (C>T)	4 hypocaloric diets with different macronutrient compositions	Qi et al. [31], 2011	738 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, SBP, DBP, TC, TG, HDL-C, LDL-C, FBG, FI	CC genotype carriers had greater weight loss and improvement in insulin sensitivity by HCD and LFD

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Table 1. (continued)

Physiological/ metabolic processes	SNPs (major > minor)	Intervention	Reference	Population characteristic (sample size, nationality/ethnicity, age range)	Duration and study design	Short description of the intervention	Outcome measures	Findings
	IRS1 rs1522813 (G>A) and rs2943641 (C>T)	4 hypocaloric diets with different macronutrient compositions	Qi et al. [32], 2013	738 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, SBP, DBP, HDL-C, TG, FBG, MetS	individuals carrying A allele of the rs1522813 but not rs2943641 showed greater improvement in MetS with HFD (40% TE from fat) than LFD (20% TE from fat)
	TCF7L2 rs7903146 (C>T)	LFD vs. HFD	Grau et al. [33], 2010	771 obese Europeans from Sweden, Denmark, UK, The Netherlands, Czech Republic, France, and Spain with BMI ≥30; 20–50 y	10 w of RCT	NUGENOB	BW, BMI, WC, FM, FFM, REE, FBG, FI, HOMA-IR, HOMA-β	T allele carriers had greater reduction in BW, WC, and HOMA-IR in LFD compared to HFD
	TCF7L2 rs12255372 (G>T) and rs7903146 (C>T)	4 hypocaloric diets with different macronutrient compositions	Mattei et al. [34], 2012	588 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, LM, FM, PBF, FBG, FI	T allele carriers of rs12255372 had significant reduction in BMI and total FM and improvement in plasma glucose, insulin levels, and glycaemic control after an LFD, but not in other macronutrients; greater loss of LM was found in CC genotype of rs7903146 when consuming an LFD
	PCSK7 rs236918 (C>G)	4 hypocaloric diets with different macronutrient compositions	Huang et al. [35], 2015	730 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, SBP, DBP, FBG, FI, HOMA-IR	GG genotype carriers had greater reduction in FI and HOMA-IR by consuming an HCD
Others	*AMY1-AMY2* rs11185098 (G>A)	4 hypocaloric diets with different macronutrient compositions	Heianza et al. [36], 2017	692 overweight and obese Americans (White, African, Hispanic, Asian, and others) with BMI 25–40; 30–70 y	2 y of RCT	POUNDS LOST	BW, BMI, WC, SBP, DBP, FBG, FI, HOMA-IR, HbA_{1c}	A allele carriers had greater reduction in BMI and WC compared to non-carriers in all 4 hypocaloric diets with different macronutrient compositions
	TNF rs1800629 (G>A)	lifestyle modification (diet and exercise)	De Luis et al. [37], 2009	203 obese Spanish with BMI >30; mean age 46 ± 16 y	2 months of RCT	participants were randomly allocated to either an LFD (1,500 kcal/day, 52% TE from CHO, 20% TE from PRO, and 27% TE from fat) or an LCD (1,507 kcal/day, 38% TE from CHO, 26% TE from PRO, and 36% TE from fat); aerobic exercise was allowed for at least 3 times/w (60 min each)	BW, BMI, WC, WHR, FM, FFM, SBP, DBP, RMR, $VO_{2\,max}$, FBG, FI, HOMA-IR, TC, TG, HDL-C, LDL-C, CRP, resistin, adiponectin, leptin	GG genotype carriers showed greater improvement in metabolic parameters in both hypocaloric LFD and LCD compared to non-carriers
	ADCY3 rs10182181 (A>G)	LFD vs. moderate HPD	Goni et al. [38], 2018	147 obese Caucasians with BMI 25–40; mean age 46 ± 11 y	4 months of RCT	participants were randomized to an LFD (60% TE from CHO, 18% TE from PRO, and 22% TE from fat) or a moderate HPD (40% TE from CHO, 30% TE from PRO, and 30% TE from fat) with a restriction of 30% of TE expenditure	BW, BMI, WC, PBF, LM, trunk fat, android fat, gynoid fat, visceral fat	G allele carriers had better outcomes on weight loss and improvement in body composition measurements when consuming a hypocaloric LFD as compared to a moderate HPD

Table 1. (continued)

Physiological/ metabolic processes	SNPs (major > minor)	Intervention	Reference	Population characteristic (sample size, nationality/ethnicity, age range)	Duration and study design	Short description of the intervention	Outcome measures	Findings
	TFAP2B rs987237 (A>G)	LFD vs. HFD	Stocks et al. [39], 2012	771 obese Europeans from Sweden, Denmark, UK, The Netherlands, Czech Republic, France, and Spain with BMI ≥30; 20–50 y	10 w of RCT	NUGENOB	BW, BMI, WC	AA genotype carriers showed greater weight loss in LFD, while GG genotype carriers showed greater weight loss in HFD
	CB2R rs3123554 (G>A)	calorie restriction	De Luis et al. [40], 2018	280 obese Caucasians with BMI >30; 20–65 y	3 months of RCT	the lifestyle modification programme consisted of a Mediterranean hypocaloric diet (1,508 kcal/day, 52% TE from CHO, 25% TE from fat, and 23% TE from PRO)	BW, BMI, WC, WHR, FM, SBP, DBP, FBG, FI, HOMA-IR, CRP, TC, TG, HDL-C, LDL-C, leptin, adiponectin, resistin, IL-6, TNF-α	non-A allele carriers had greater reduction in BW, FM, WC, FI, HOMA-IR, IL-6, and CRP levels compared to A allele carriers after consuming a Mediterranean hypocaloric diet
	CLOCK rs1464490 (T>C), rs3749474 (C>T), rs4580704 (C>G), rs4864548 (A>G), and rs1801260 (A>G)	lifestyle modification (diet and exercise)	Garaulet et al. [41], 2010	500 overweight and obese Spanish subjects with BMI 25–40; 20–65 y	9 months of PPQES (4-month intervention followed by 5-month maintenance period)	the diet and lifestyle intervention consisted of a weekly 60-min therapy session in a support group, and the dietary energy content ranged from 1,200 to 1,800 kcal/day for women and from 1,500 to 2,000 kcal/day for men to induce a weight loss of 0.5–1 kg/w	BW, BMI, WC, HP, WHR, PBF, Hb, FBG, TC, uric acid	G allele carriers of rs1801260 had significantly less reduction in BW compared to the non-carriers in response to diet and lifestyle intervention, but no effect was found in other polymorphisms

ADCY3, adenylate cyclase; *ADIPOQ*, adiponectin; *ADRB2*, beta-2 adrenergic receptor; *ADRB3*, beta-3 adrenergic receptor; AEE, activity energy expenditure; *AMY*, alpha-amylase; *APOA*, apolipoprotein A; BMI, body mass index; BW, body weight; *CB2R*, cannabinoid receptor type 2; CHO, carbohydrates; *CLOCK*, circadian locomotor output cycles kaput; CRF, cardiorespiratory fitness; CRP, C-reactive protein; DBP, diastolic blood pressure; DIETFITS, Diet Intervention Examining The Factors Interacting with Treatment Success; DIRECT, Dietary Intervention Randomized Controlled Trial; *FABP2*, fatty acid-binding protein 2; FBG, fasting blood glucose; FFM, fat-free mass; FI, fasting insulin; FM, fat mass; *FTO*, fat mass and obesity-associated protein; *GHRL*, ghrelin and obestatin prepropeptide; *GIPR*, gastric inhibitory polypeptide receptor; Hb, haemoglobin; HbA_{1c}, glycated haemoglobin; HC, hip circumference; HCD, high-carbohydrate diet; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; HFLCD, high-fat low-carbohydrate diet; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment beta; HPD, high-protein diet; HR_{max}, maximum heart rate; IL-6, interleukin-6; *IRS1*, insulin receptor substrate-1; LCD, low-carbohydrate diet; LDL-C, low-density lipoprotein cholesterol; *LEPR*, leptin receptor; LFD, low-fat diet; LFHCD, low-fat high-carbohydrate diet; *LIPC*, hepatic triglyceride lipase; LM, lean mass; *MC4R*, melanocortin 4 receptor; MetS, metabolic syndrome; *MTNR1B*, melatonin receptor 1B; NEFA, non-esterified fatty acid; NPRQ, non-protein respiratory quotient; *NPY*, neuropeptide Y; NUGENOB, Nutrient-Gene Interactions in Human Obesity (a dietary intervention comparing the effect a hypocaloric HFLCD (20–25% TE from fat) or a hypocaloric LFHCD (40–45% TE from fat) with an energy deficit of 600 kcal/day); PBF, percent body fat; *PCSK7*, proprotein convertase subtilisin/kexin type 7; POUNDS LOST, Preventing Overweight Using Novel Dietary Strategies (a dietary intervention comparing the effects of four energy-restricted diets [energy deficit of 750 kcal/day] with different compositions of fat, protein, and carbohydrate); *PPARγ*, peroxisome proliferator activated receptor gamma; PPQES, quasi-experimental study; PRO, proteins; RCT, randomized controlled trial; REE, resting energy expenditure; RMR, resting metabolic rate; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; SNPs, single nucleotide polymorphisms; TAT, total abdominal adipose tissue; TC, total cholesterol; *TCF7L2*, transcription factor 7 like 2; TE, total energy; *TFAP2B*, transcription factor AP-2 beta; TG, triglyceride; TNF-α, tumour necrosis factor alpha; TSH, thyroid-stimulating hormone; *UCP*, uncoupling protein; VAT, visceral adipose tissue; $VO_{2\,max}$, maximal oxygen uptake; w, week(s); WC, waist circumference; WHR, waist-hip ratio; y, years.

the risk allele (A) of *FTO* rs9939609 had higher odds of being overweight/obese compared to non-carriers (T), but this association was attenuated by high physical activity of the participants [49]. Further, lifestyle intervention (through lower energy intake and increased physical activity) showed better improvement in C-reactive protein and fasting plasma glucose in Brazilians at high cardiometabolic risk who carried the risk allele (A) of *FTO* rs9939609 [50]. Similar positive results were reported in gene variant rs8050136. Individuals carrying the risk allele (A) demonstrated a greater reduction in weight compared to the non-carriers (C) after a moderate-intensity exercise intervention in Caucasian postmenopausal women [10]. The mechanism of action of FTO in mediating satiety and hunger signals is yet to be elucidated. It is known that FTO is a DNA/RNA demethylase which influences the splicing, stability, and export of mRNA. Animal studies provided evidence that FTO is expressed in the arcuate nucleus of the hypothalamus and is associated with appetite and energy intake. A study conducted by Karra et al. [51] showed that *FTO* gene variants were associated with obesity and obesity-prone behaviour due to a higher level of the circulating "hunger hormone" ghrelin that eventually increased food intake and a preference for energy-dense foods. It is known that exercise can suppress appetite by reducing the circulating ghrelin levels in an intensity-dependent way. Thus, exercise followed by reduced energy intake can eventually improve body composition [52], and individuals with *FTO* gene variants who are genetically predisposed to obesity may benefit from increased physical activity. It must be emphasized that although physical activity modifies the effects of FTO, the latter has no influence on energy expenditure. This has been adequately proved by a study by Kring et al. [46] where the authors reported no effect of FTO on resting energy expenditure, glucose-induced thermogenesis, cardiorespiratory fitness, and leisure time physical activity. Recently, a new mechanism was proposed that *FTO* SNPs may remotely alter the expression of other downstream genes such as genes involved in body mass regulation by changes in epigenetic mechanisms including methylation of other genes [53, 54]. The presence of *FTO* variants increased adipocyte-specific expression of IRX3 and IRX5 during early adipocyte differentiation, causing a reduction in mitochondrial thermogenesis and increased lipid storage [55]. With respect to lifestyle interventions, it can be said that individuals carrying minor alleles of *FTO* may benefit from calorie restriction and low-fat diets. A study suggested that high-protein diet can be beneficial as well. Further exercise intervention can positively impact weight management in all individuals, including those with minor alleles. This review reports that, overall, dietary intervention does not affect individuals with *FTO* minor and major alleles differentially.

Genes Involved in Adaptive Thermogenesis

The components of total energy expenditure are (1) obligatory energy expenditure required to perform cellular and organ functions, (2) adaptive thermogenesis induced by diet or cold exposure, and (3) physical activity. At the cellular level, biochemical processes involved in energy expenditure that happen in the mitochondria hold a key to the modulation of adaptive thermogenesis in order to expend excess energy and prevent obesity. Therefore, identification of target tissue and intracellular mechanisms mediating adaptive thermogenesis is an area of intense interest. Many pieces of evidence support the view that brown adipose tissue is responsible for beta-adrenergic receptor-mediated thermogenesis and that uncoupling protein 1 (UCP1)-driven uncoupled respiration is the intracellular mechanism. Other than brown fat, skeletal muscle, liver, and white adipose tissue can be the sites of interest because they could be involved in weight control in humans.

A study reported that energy expenditure standardized for lean body mass predicted future weight gain [56]. Excess food intake is sensed by the brain, which, to prevent excess weight gain, triggers an increase in energy expenditure through adaptive thermogenesis. An example of uncoupling as a means of increasing energy expenditure is mediated by UCP1. Sympathetic nerve activity is thought to be the efferent pathway to the brain by which the brain regulates adaptive thermogenesis. It has been proved in rodent models that the activity of UCP1 in brown fat is controlled by sympathetic nerve activity. The evidence for this is as follows: (1) cold exposure and diet increase sympathetic nerve activity, (2) exogenous administration of neurotransmitters (norepinephrine and epinephrine) stimulates energy expenditure, and (3) the thermogenic target tissue, brown adipose tissue, is heavily innervated by sympathetic nerves. *ADRB2* and *ADRB3* genes coding for β2- and β3-adrenergic receptors, respectively, have received significant attention in this respect. These receptors are part of the adrenergic system and stimulate lipid mobilization in adipose tissue through the action of catecholamines [57]. The effect of *ADRB2*, *ADRB3*, *UCP2*, and *UCP3* gene polymorphisms on weight loss outcomes is discussed below based on the intervention strategies employed:

Low-Calorie Diet Interventions. A 2-year DIETFITS intervention study reported no significant gene-diet inter-

action between the two alleles of *ADRB2* rs1042714 (C>G) in weight loss in response to two hypocaloric diets (low-carbohydrate diet versus low-fat diet) in overweight and obese Americans [17]. A study conducted by Yoon et al. [12], which investigated the individual and combined effect of 10 SNPs from *UCP2* and *UCP3* polymorphisms, reported that the major allele carriers (GG) of UCP2866 G>A polymorphism showed a greater reduction in BMI and fat compared to the risk allele (AA) after 1 month of low-calorie diet (700 kcal/day) in overweight and obese Korean women. No significant difference was found in the other nine SNPs. Another study with calorie restriction as dietary intervention conducted by Ruiz et al. [13] reported that both genotypes of *ADRB2* rs1042713 (G>A) showed a similar reduction in body weight; however, obese Spanish women carrying the risk allele (G) of *ADRB2* rs1042714 had a greater reduction in body weight compared to the non-carriers (CC) after 3 months of energy-restricted diet. This finding suggests that there may be a sex-specific genetic association between rs1042714 and intervention employed on the changes in body weight.

Diet and Exercise Interventions. In an obese Brazilian population, polymorphisms in *ADRB2* rs1042714 (C>G), *ADRB2* rs1042713 (G>A), and *ADRB3* rs4994 (C>G) did not affect the two allele carriers differently in a 7-week lifestyle modification with a combination of dietary and exercise intervention [14]. Mutation in the aforementioned genes did not lead to greater or lesser weight loss in response to calorie restriction. Besides, a study conducted by Tahara et al. [15] also showed that weight reduction was not affected by *ADRB3* rs4994 polymorphism in obese Japanese men after a 3-month lifestyle modification intervention. Failure to observe significant gene-lifestyle intervention may be due to the small reduction in BMI and short duration of intervention (<1 kg reduction in 3 months). Conflicting results were observed in other studies. Shiwaku et al. [16] reported that obese premenopausal Japanese women carrying the risk allele (C) of *ADRB3* rs4994 had difficulty in losing weight through lifestyle modification intervention compared to non-carriers (T).

In summary, individuals with minor alleles of *UCP2* and *ADRB2* SNPs reported difficulty in losing weight with calorie restriction compared to the major allele carriers. However, with both diet and exercise intervention, with the exception of one study, individuals carrying minor alleles of *ADRB2* and *ADRB3* SNPs benefitted with respect to body composition and metabolic health. However, our findings suggest that there may be a sex-specific genetic association between *ADRB2* and *ADRB3* SNPs and weight loss. Women carrying the minor alleles of the latter showed difficulty in losing weight when using calorie restriction and lifestyle intervention, but this effect was not observed in male participants.

Genes Involved in Lipoprotein Metabolism

Gene variants that cause any defect in the pathway of lipoprotein metabolism can lead to the development of atherogenic dyslipidaemia, including increased small low-density lipoprotein (LDL) particles, increased triglyceride (TG), and reduced high-density lipoprotein cholesterol (HDL-C) levels. Previous reviews have reported that there was a consistent association between apolipoprotein E (*APOE*) gene with total cholesterol (TC) and LDL cholesterol (LDL-C); cholesteryl ester transfer protein (*CETP*), apolipoprotein A1 (*APOA1*), and hepatic lipase (*LIPC*) genes with HDL-C; and apolipoprotein A5 (*APOA5*) gene with TG concentrations [58, 59]. APOA1 is a major component of HDL particles and plays an important role in lipoprotein metabolism. *LIPC* gene, which encodes for hepatic lipase, also plays an important role in HDL metabolism.

The *CETP* gene exerts a profound impact on HDL metabolism and lipid transport [60]. Its action affects the net transfer of cholesteryl ester from HDL to apolipoprotein B-containing lipoproteins including LDL in exchange for TGs, thus modulating the levels of these lipoproteins and hence influencing the risk of atherosclerosis. Low levels of CETP may increase the circulating HDL-C particle size and reduce the transfer of cholesteryl ester from HDL to other lipoproteins. A study reported that losing weight by consuming a low-carbohydrate high-fat diet benefited individuals carrying the risk allele (CC) of *CETP* rs3764261 (G>A). The latter had greater reduction in TG levels and elevation of HDL-C levels compared to a high-carbohydrate low-fat diet [24]. In case of *CETP* rs5882 (G>A), overfeeding by 1,000 kcal/day in the individuals carrying the minor allele (A) resulted in unfavourable changes in adiposity and reduction in HDL-C levels [61], although this study did not specify the macronutrient compositions of the experimental diet. How the *CETP* gene modulates fat depots is unclear, but it has been proposed that the observed gene-diet interaction on serum lipid profile may be due to the fuel storage portioning between adipose tissue and other tissues. TG-enriched HDL is preferentially hydrolysed by hepatic lipase, and the released non-esterified fatty acids are more likely to be taken up by liver cells, reducing the fat store in adipocytes [62].

Genetic association and animal studies have indicated a plasma TG-modulating effect of *APOA5* [63]. This pro-

tein reduces plasma TG by (1) reducing the rate of hepatic very-low-density lipoprotein (VLDL)-TG production [64] and (2) enhancing the rate of lipoprotein lipase-mediated intravascular TG lipolysis [65]. Hydrolysis of VLDL-TG by lipoprotein lipase releases fatty acids into skeletal muscle and adipose tissue, leading to clearance of plasma TG. Therefore, overexpression of *APOA5* lowers plasma TG but increases body weight and the inguinal fat pad in mice [66]. It has been suggested that gene variants of *APOA5* may modulate the effect of dietary fat intake on weight reduction [67]. Further, a wide interindividual variability in lipid and lipoprotein concentrations in these gene variations has been reported in response to dietary fat intake [60]. The effect of *APOA5*, *LIPC*, *ADIPOQ*, *APOA1*, and *PPARγ* gene polymorphisms on weight loss outcomes is discussed below based on the intervention strategies employed.

Low-Calorie Diet Interventions. A 2-year dietary intervention using different macronutrient compositions reported that 20% energy from fat had a positive impact on BMI and lipid profiles (TC and LDL-C levels) in the risk allele carriers (G) of *APOA5* rs964184 (C>G) in overweight and obese Americans [19]. Similar results were reported by Xu et al. [23]. Their study found that the risk allele carriers (AA) of *LIPC* rs2070895 (G>A) showed greater improvement in blood lipids (reduction in TC, LDL-C, and TG levels and increase in HDL-C levels) with a 2-year low-fat diet compared to GG and GA genotypes in an overweight and obese American population. This is supported by another study, which reported that individuals carrying the risk allele (T) of *LIPC* rs1800588 (C>T) had a significant increase in HDL-C with <30% of energy from fat in an American population [68]. Adiponectin is a protein hormone which is involved in regulating serum glucose levels as well as fatty acid breakdown. In humans it is encoded by the *ADIPOQ* gene and it is produced in adipose tissue. Circulating adiponectin concentrations increase during calorie restriction in animals and humans. Mutation in this gene is associated with decreased adiponectin production. Decrease in adiponectin leads to reduced efficiency in energy expenditure, reduced glucose utilization, and hence increased risk of obesity and type 2 diabetes [69–71]. Earlier studies have reported that weight reduction resulted in a significant increase in plasma adiponectin [71]. The binding of adiponectin to its receptors enhances the AMPK, PPARα, and Akt pathway in the liver and skeletal muscle, which decreases gluconeogenesis and free fatty acid influx into the liver and hence increases fatty acid oxidation. Circulating adiponectin enhances glucose uptake via glucose transporter 4 (GLUT4) [72, 73] and increases fatty acid uptake and oxidation in skeletal muscle in animal models [74]. This ultimately leads to a reduction in circulating free fatty acids and prevents insulin resistance. De Luis et al. [21] reported that the non-risk allele carriers (GG) of *ADIPOQ* rs1501299 (G>T) had better outcomes in LDL-C, fasting glucose, insulin levels, and HOMA-IR after 3 months of a Mediterranean hypocaloric diet compared to the risk allele carriers (T) in an obese Caucasian population. Another study reported that GG homozygotes of *ADIPOQ* rs1501299 (G>T) had a beneficial effect on insulin sensitivity after modest weight loss by 3 months of a calorie-restricted diet in an obese Korean population [75]. In case of *APOA1* rs670 (G>A), De Luis et al. [22] reported that the risk allele carriers (A) had better outcomes on anthropometric parameters, TC, LDL-C, insulin, and HOMA-IR compared to the non-carriers (G allele) after a Mediterranean hypocaloric diet.

Diet and Exercise Interventions. Suchanek et al. [20] reported that Czech women carrying at least one risk allele of *APOA5* rs662799 (T>C) and rs3135506 (C>G) did not benefit from a combination of reduction in total energy and exercise intervention (no reduction in plasma TG or LDL-C levels). However, with 3 months of a fat-restricted diet, risk allele carriers (CC) of rs6622799 (T>C) showed greater reduction in BMI compared to non-carriers (TT). It is worth noting that both risk and non-risk alleles of rs6622799 (T>C) showed reduction in TC, LDL-C, HDL-C, and TGs. Therefore, it was suggested by the authors that a fat-restricted diet may be considered as an intervention strategy to improve body composition in the risk allele carriers of *APOA5* rs6622799 [76]. Transcription factor peroxisome proliferator-activated receptor-γ (*PPARγ*) PPARG regulates fatty acid storage and glucose metabolism. The genes activated by PPARG stimulate lipid uptake and adipogenesis by fat cells [77]. Gardner et al. [17] reported no significant interaction between the *PPARγ* rs1801282 (C>G) allele carriers and weight loss diets in an American population. However, Zarebska et al. [18] found that CC genotype carriers of *PPARγ* rs1801282 had greater reduction in body weight and fat mass compared to the risk allele carriers (G) after an exercise training programme in obese Polish women.

In summary, individuals carrying the minor alleles of *LIPC*, *PPARγ*, and *APOA5* showed a positive impact on anthropometric parameters and blood lipid levels (reduced TC, LDL-C, and TG levels and increased HDL-C levels) with a hypocaloric low-fat diet compared to a hypocaloric high-fat diet. De Luis et al. [22] reported that the

minor allele carriers of *APOA1* SNP had a greater positive impact in anthropometric parameters, blood lipid levels, and insulin resistance compared to the major allele carriers after a Mediterranean hypocaloric diet. However, the minor allele carriers of *PPARγ*, *ADIPOQ*, and *APOA5* SNPs showed a less favourable effect on body composition and cardiometabolic parameters compared to the major allele carriers with calorie restriction and exercise intervention.

Genes Involved in Appetite Regulation

Genetic variants of hormones and proteins involved in appetite regulation have been reported to be potentially affected by calorie-restricted diet. In this respect, the genes that have been widely studied include leptin (*LEP*), leptin receptor (*LEPR*), pro-opiomelanocortin (*POMC*), melanocortin 3 receptor (*MC3R*), and melanocortin 4 receptor (*MC4R*) [78]. Leptin acts on the central nervous system by modulating the expression of some neuropeptides such as proopiomelanocortin (*POMC*) and neuropeptide Y (*NPY*). Mutation in these genes causes failure to signal satiety and leads to excess energy intake [79, 80]. Recent studies have identified the gene-diet interaction of melatonin receptor type 1B (*MTNR1B*) rs10830963 (C>G) gene polymorphisms on weight loss outcomes. Here we review the literature on the effect of the above gene variants on weight loss outcomes based on the intervention strategies employed.

Low-Calorie Diet Interventions. Mammès et al. [81] reported that French women carrying the T allele of Ser(T)343Ser(C) *LEPR* were predisposed to obesity and that women carrying the C allele lost more weight in response to a low-calorie diet compared to non-carriers. Interestingly, this effect was only observed in women, suggesting a gene-sex interaction. A study by Santoro et al. [82] in an Italian population found that subjects carrying the *POMC* R236G variant did not experience any difficulty in losing weight. They exhibited an adequate improvement in anthropometric as well as metabolic features after about 1 year of hypocaloric diet. Although the R236G variant of the *POMC* gene played a role in the development of early-onset obesity and its complications, it did not compromise the individual's ability to lose weight. Non-risk allele carriers (C) of *MTNR1B* rs10830963 had a greater reduction in fasting insulin and HOMA-IR compared to the risk allele carriers (G) after a Mediterranean hypocaloric diet in an obese Caucasian population [25], where G allele carriers had a greater reduction in TC and LDL-C levels with an energy-restricted low-fat diet compared to a high-fat diet in an overweight and obese American population [26]. These findings indicate that the circadian rhythm plays a role on metabolic responses to different dietary approaches. Lin et al. [29] also reported that the minor allele carriers of *NPY* benefited from a hypocaloric low-fat diet with reduction in body adiposity when compared to a high-fat diet. A large European NUGENOB study involving seven countries with a total of 760 obese participants investigated the effect of SNPs of melanocortin 3 receptor (*MC3R*) gene on a 10-week dietary intervention with either a low-fat or a high-fat hypocaloric diet [83]. The findings revealed that genetic variants in *MC3R* (rs1543873, rs6099058, rs3827103, rs3746619, rs6024728, rs6014646, rs6024730, rs6024731, rs11697509, and rs6127698) did not have difficulty in losing weight in response to a calorie-restricted diet regardless of the difference in macronutrient compositions. The POUNDS LOST trial reported that the risk allele carriers (C) of *NPY* rs16147 (T>C) had a significant reduction in waist circumference at month 6 and in subcutaneous adipose tissue, visceral adipose tissue, and abdominal adipose tissue at month 24 with a high-fat diet compared to a low-fat diet in an overweight and obese American population.

Diet and Exercise Interventions. De Luis Roman et al. [28] reported that both genotypes of *LEPR* rs1805094 (G>C) showed a significant reduction in body weight and BMI after a 3-month lifestyle modification in an obese Spanish population. This finding was replicated in a 2-year lifestyle intervention study, which reported that no significant association was found between 19 *MC4R* SNPs and weight loss after a lifestyle modification intervention, and only the risk allele carriers (T) of rs17066866 (A>T) were associated with lesser short-term and long-term weight loss compared to the non-carriers (A) in overweight and obese Americans [27]. Therefore, calorie-restricted diets that reduce the total energy intake may be more effective in weight loss in case of individuals carrying these gene variants.

In summary, individuals carrying the minor allele of *MTNR1B* had a less favourable effect on insulin resistance compared to the major allele carriers in an intervention with a Mediterranean hypocaloric diet. However, another study reported that, with a hypocaloric low-fat diet, the minor allele carriers of the same gene had a positive impact on TC and LDL-C levels. Lin et al. [29] also reported that the minor allele carriers of *NPY* benefited from a hypocaloric low-fat diet with reduction in body adiposity when compared to a high-fat diet. Among 20 SNPs of *MC4R* reviewed, with the exception of one SNP, minor and major alleles of 19 other *MC4R* SNPs showed no significant difference in weight loss outcomes with dietary and exercise

intervention. The minor and major allele carriers of *LEPR* SNP had similar body weight changes with dietary and exercise intervention, but the beneficial effect on LDL-C levels was only observed in the minor allele carriers.

Genes Involved in the Insulin Signalling Pathway

Some genes that are involved in the insulin signalling pathway are insulin receptor substrate 1 (*IRS1*), proprotein convertase subtilisin/kexin type 7 (*PCSK7*), transcription factor 7 like 2 (*TCF7L2*), and gastric inhibitory polypeptide receptor (*GIPR*) [30, 31, 35]. There is a large body of evidence showing that dietary carbohydrate and fat can modulate the effect of these genetic variants on insulin sensitivity. For example, studies have reported that variation in the *IRS1*, gene which is a mediator between insulin receptor and phosphatidylinositol 3-kinase (PI3K) in the insulin signalling pathway, is associated with insulin resistance and type 2 diabetes [84]. To date, there are several gene polymorphisms related to the insulin signalling pathway, such as *GIPR* rs2287019 (C>T), *IRS1* rs2943641 (C>T), *IRS1* rs1522813 (G>A), *TCF7L2* rs7903146 (C>T), *TCF7L2* rs12255372 (G>T), and *PCSK7* rs236918 (C>G). These genes have been reviewed under calorie-restricted dietary interventions with different macronutrient compositions.

Low-Calorie Diet Interventions. In a 2-year Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial, the risk allele carriers (CC) of *IRS1* rs2943641 (C>T) had a greater reduction in weight and improvement in insulin sensitivity with a high-carbohydrate, low-fat diet compared to the non-risk allele carriers (T) in an overweight and obese American population [31]. The underlying mechanism is unknown, but the authors claimed that it may be due to lipid-induced insulin resistance. High-fat diet may increase plasma free fatty acids and impair the insulin signalling pathway by altering tyrosine/serine phosphorylation of IRS, leading to decreased activation of IRS-associated PI3K activity [85]. Thus, *IRS1*-associated PI3K activity may be enhanced by high-carbohydrate, low-fat diet in CC genotype. However, the findings were not replicated in other study. Qi et al. [32] reported that a high-fat diet was more effective in improving metabolic syndrome compared to a low-fat diet in subjects carrying A allele of rs1522813 *IRS1*, but no significant effect was found in *IRS1* rs2943641 in an overweight and obese American population with the same intervention. The interaction of gene variant at rs1522813 and dietary effect on reversion of metabolic syndrome was independent of weight loss and insulin resistance. It is very interesting to note that the authors report that gene-diet interaction in rs1522813, with a positive effect on the minor allele (high-fat diet), was independent of body weight, waist circumference, and insulin resistance, indicating modulation of a positive effect on serum lipid levels, independent of adiposity. The same authors did not find any gene-diet effect on rs2943641 on the same candidate gene. They speculate that SNP rs2943641 and rs1522813 near IRS1 fall into two independent linkage disequilibrium blocks with low correlation between them. The risk allele carriers (T) of gastric inhibitory polypeptide receptor (*GIPR*) rs2287019 (C>T) showed greater reduction in weight, fasting glucose, fasting insulin, and improvement in insulin sensitivity after 6 months of a low-fat, high-carbohydrate, high-fibre diet compared to a high-fat diet in an overweight and obese American population [30]. Similar finding was observed in *PCSK7* gene polymorphism: risk allele carriers (GG) of *PCSK7* rs236918 (C>G) had greater reduction in fasting insulin and HOMA-IR by consuming a hypocaloric low-fat, high-carbohydrate diet compared to the non-carriers (C) in an overweight and obese American population [35]. The risk allele carriers (T) of *TCF7L2* rs7903146 (C>T) and rs12255372 (G>T) had a greater reduction in plasma glucose, insulin levels, HOMA-IR, and glycaemic control after a low-fat diet compared to a high-fat diet in overweight and obese European and American populations [33, 34].

In summary, our findings show that a hypocaloric, low-fat, high-carbohydrate diet was effective in improving body composition, glycaemic control, and insulin sensitivity in the individuals carrying the risk allele of *GIPR*, *IRS1*, *TCF7L2*, and *PCSK7* SNPs. Contrary to this, Qi et al. [31] reported that the benefits of a hypocaloric low-fat diet on body composition and insulin sensitivity was only found in the major allele carriers of *IRS1* rs2943641. The same authors reported that the major allele carriers of *IRS1* rs1522813 had better improvement in metabolic syndrome after a hypocaloric high-fat diet. Therefore, we suggest that the composition of the diet with respect to the calories from fat and carbohydrate plays an important role in modulating the effect of genes involved in insulin signalling.

Conclusion

This review paper summarizes the current evidence on selected candidate genes and their effect on body composition and cardiometabolic parameters in response to dietary and/or exercise interventions to manage overweight and obesity. However, there are several limitations to the

studies reported so far, including small sample size, short duration for the intervention, and measurement of different outcomes. Most of the intervention studies focus on the effect of variants of single candidate genes on weight loss. Further evidence from large-scale studies is necessary to assess the effect of multiple candidate genes to compute a gene score that could be used in a model intervention programme. The studies reviewed included genotyping and lifestyle interventions through controlled energy and macronutrient intake. However, gene-lifestyle interaction studies on the same candidate gene in different populations have reported information which is challenging to interpret. Thus, it is difficult to arrive at a particular model for a strategy on weight management at this point in time.

At present, technology targeting personalization of healthcare may be a better way to fight the epidemic of obesity. However, for the latter to materialize, we need better understanding of genes and corresponding biochemical phenotypes. With the current data available, it is still premature to introduce or apply the use of genetic testing prior to weight loss intervention trials in the community. Due to the high cost involved in such diagnostics, only a handful of individuals will be able to afford such tests. At present, our review suggests that a healthy lifestyle with a balanced diet and regular physical activity will benefit individuals who carry the risk alleles of the obesity-related candidate genes. This message should be the mainstay of the recommendations and guidelines published by the nutrition societies across the world.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Author Contributions

F. Amini advised on the paper. P.Y. Tan and S.R. Mitra wrote the paper. All authors read and approved the final manuscript.

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