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Genetic Variation's Impact on Weight: Systematic Review and Meta-Analysis

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ABSTRACT

This study investigates the genetic factors influencing precision weight management, contributing insights to the enduring debate on hereditary versus environmental influences on obesity. The primary objective is to identify genetic variations as predictive markers for weight management and evaluate their impact on weight control. Following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline, this research systematically reviews articles that meet specific criteria, with no specific timeline due to limited research on genetic variation in this context. Inclusion criteria mandate the provision of weight and BMI data at the beginning and end of interventions, demonstrating weight reduction. Exclusions cover animal studies, non-English papers, and articles lacking baseline or pre/post-intervention data. The review incorporates comprehensive searches on Scopus, Medline, PubMed, and Web of Science, employing Review Manager for meta-analysis. The study concentrates on Single Nucleotide Polymorphisms (SNPs) rs9939609, rs10830963, and rs1052700 across 10 investigations. Despite lacking statistical significance, the findings suggest that these genetic polymorphisms enhance weight loss potential for recessive genotypes. A discernible preference for non-risk genotypes in weight loss efforts emerges. For instance, individuals with the non-risk A allele of rs9939609 experience weight loss with a Polyunsaturated Fatty Acid (PUFA) diet, while those with the non-risk G allele of rs10830963 effectively manage weight with a low-fat diet. Similarly, rs1052700 indicates that individuals with the T allele shed more weight by consuming meals earlier during the day. Although statistically insignificant, the non-risk genotype for all three SNPs demonstrates potential for weight loss. This suggests that participants possessing the non-risk allele can effectively manage their weight through interventions provided by weight loss programs.

Keywords: genetic, nutrigenomics, obesity, weight management program

INTRODUCTION

Obesity is a major global health concern that impacts developed and developing nations (Nutter *et al.* 2024). Its prevalence has reached unprecedented levels, overshadowing malnutrition and infections as a leading health issue (Nutter *et al.* 2024). Notably, the rise in obesity has been most pronounced in the highest weight categories, underscoring the urgency of the issue (Shi *et al.* 2024). Amidst this, genetic diversity within the population plays a backdrop role (Jin *et al.* 2024), contributing to varying responses to obesity treatment (Heitkamp *et al.* 2021).

In the past two decades, obesity gene research has swiftly evolved, uncovering the genetic underpinnings of energy balance (Lee 2009). Traditional approaches, including genome-wide scans, linkage, and association studies, have identified obesity-related genes (Lee 2009). Genetic predisposition continues to influence susceptibility to obesity significantly (Snyder *et al.* 2004). There has been a debate regarding the cause of obesity, genetics or the environment. Studies have shown that identical twins tend to be more similar in body weight compared to non-identical twins (Elks *et al.* 2012). The study suggests that there is a genetic element which is the cause of obesity.

Weight management programs, incorporating tailored exercise and behaviour therapy, aim to empower individuals for

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sustainable weight loss (Liu *et al.* 2024). Weight loss programmes are among the most crucial preventative health measures to lower the occurrence of obesity (Sharifi *et al.* 2013). Many seek ongoing support post-program (Hall & Kahan 2018), as even modest weight loss can yield positive health outcomes (Mertens *et al.* 2012). While weight-loss initiatives in developing nations emphasise nutrition and exercise, the study demonstrates that most perceived obstacles are linked to lifestyle and behaviour (Vranešić Bender & Krznarić 2012).

A research gap persists in systematic reviews and meta-analyses exploring the influence of specific genetic variants on weight management through programs. This is evident in a review article conducted by Jeanne McCaffery in 2018, where it is affirmed that there is currently inadequate evidence to utilise genetics or genomics for enhancing obesity treatment. A 2013 review by El-Sayed Moustafa and Froguel also explores the relationship between genetic variation and environmental elements, including diet, highlighting the need for more research on this topic. The review aims to pinpoint predictive genetic markers and determine the impact of genetic variants on weight management, addressing a crucial gap in current knowledge.

METHODS

Design, location, and time

This study followed the guidelines of the "Preferred Reporting Items for Systematic Review and Meta-Analyses" (PRISMA). The systematic review and meta-analysis, which will be conducted in the research, have already been submitted to the International Prospective Register of Systematic Reviews (PROSPERO). The review is registered under identification CRD42022371341. The research obtains ethical clearance with approval no REC/04/2023 (ST/EX/7) by the University Technology Mara (UiTM) Research Ethics Committee.

Materials and tools

Four databases' titles, abstracts, keywords, and full texts of documents were thoroughly searched in October 2022, including PubMed, Medline, Scopus, and Web of Science (WoS). Terms used in the search algorithm included genetic variation (e.g., genetics, gene expressions), weight management terms (e.g., nutrigenomics, weight management), and population-setting terms (e.g., overweight, obese participants). In addition, a manual snowballing search of the reference lists of the studies that were included was conducted to locate and incorporate pertinent publications that the database search had not previously turned up.

Inclusion and exclusion criteria. Studies included in the analysis had to fulfil several eligibility criteria. First, the article must conduct a genomic study to be included. Secondly, it must contain genetics or polymorphism, which studies the effect of weight reduction on obese participants. Next, the participant needed to undergo a weight management program. The article also needed to be open access with the document in English. There is no restriction on the document type. The participant also needed to be overweight and obese or with a Body Mass Index (BMI) above 24.9 kg/m^2 squared. There is no restriction on the age of the subjects, time, and study design. The weight/BMI must have data before and after the intervention so that we can measure the weight loss of the participant. Lastly, the genotype data must be associated with weight/BMI before and after the intervention to ensure a direct weight change in the genotype.

Study selection. After eliminating duplicate data, the titles and abstracts were checked against the inclusion criteria. When the abstracts of papers didn't include enough details to select determination, the full texts of those articles were read. Figure 1 showed the PRISMA diagram illustrating the selection process of the articles.

Procedures

The qualitative data were extracted in each study included in terms of the study's characteristic genetic variation (SNP ID), study location, population, study design, age group, risk allele, allele, and intervention. Mean and standard deviation of BMI/weight loss before and after intervention were collected for subgroup analyses. Subgroups were defined based on statistical, sensitivity, and stratified analyses.

Data analysis

Calculations were done as the initial stage in the analysis to standardise the data from various research. In this review, all included studies

reported the outcomes where the effect measure of interest through mean difference and standard deviation before and after the intervention. The difference is used to estimate the amount by which the participant loses weight. For each study, group-specific Standard Deviation (SD) was used to calculate the mean difference for each group. The Review Manager calculator was also used to calculate the correlation between the studies for stratified analysis.

RESULTS AND DISCUSSION

Study characteristics: Qualitative review

Ten investigations underpinning the systematic review and meta-analysis spanned 2008 to 2021 across various countries, as detailed in Table 1 (10 papers/investigations in PRISMA and, focused on 9 Genetic Variation, SNP ID). The total analysis included 4,094 study participants with sample sizes ranging from 30 to 1,287. Geographical distribution comprised six European countries, two from the United States and two from South America. Participant ages ranged from 10 to 70 years, with baseline BMI varying between 25 and 40 kg/m^2. Gender representation was mixed, with one study exclusively female. Most studies focused on adults, except one involving children and adolescents. Eight studies employed diet modifications, while two used distinct strategies like low-impact aerobics and High-Intensity Interval Training (HIIT) combined with dietary restrictions. Intervention durations ranged from 4 weeks to 2 years, with a median of 12 weeks.

Across the ten trials, 1,603 participants bore non-risk alleles, while 2,491 carried risk alleles. A correlation between nine SNP IDs and weight reduction emerged in weight management programs, with each SNP's risk allele influencing weight management. Most studies adjusted their results for BMI, gender, and sex. Refer to Table 1 of the study characteristics.

Meta-analysis results

rs9939609 analysis. Figure 2 portrays a meta-analysis involving four studies (666 subjects) focusing on rs9939609 genotypes (TT

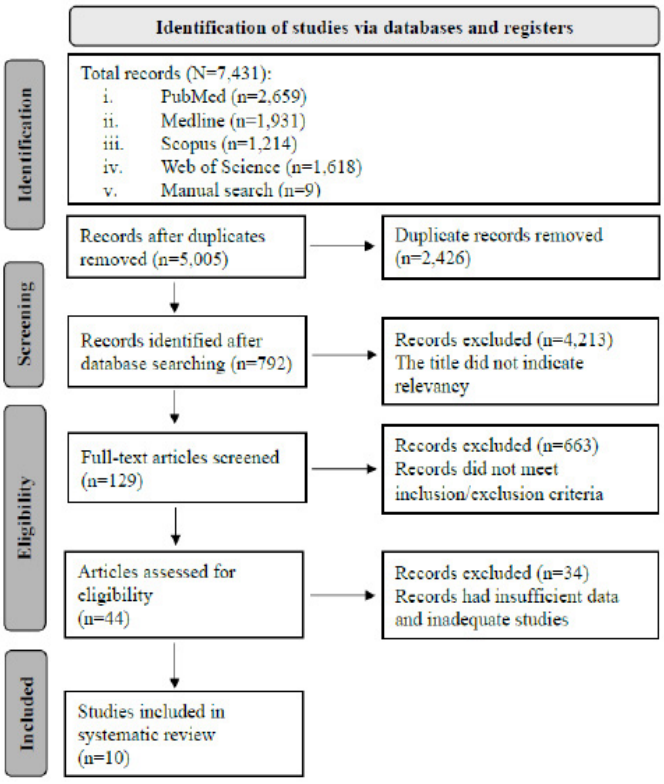

Figure 1. PRISMA diagram illustrating the selection process

Table 1. Baseline characteristics of studies included in the qualitative analysis

Genetic Variation, SNP ID	First Authors, publication year	Study location, Population	Study design	Age group	Number of risk/non-risk allele in participant	Risk allele	Alleles	Intervention	NOS score
rs9939609	Leońska-Duniec *et al.* 2018	Poland, Polish	Randomise controlled trials	Adults	146/55	A	A/T	12 weeks program of low and high impact aerobics	7
	de Luis *et al.* 2015	Spain, Spanish	Randomise controlled trials	Adults	119/114	A	A/T	3 months of diet in-tervention Diet M & Diet P	7
	de Luis *et al.* 2020a	Spain, Spanish	Non-randomise controlled trials	Adults	16/28	A	A/T	12 weeks partial meal replacement hypocaloric diet (pMRHD)	6
	Di Renzo *et al.* 2018	Italy, Italian	Randomise controlled trials	Adults	37/151	A	A/T	4 weeks nutritional intervention Mediterranean diet (MeD)	6
rs10830963	Goni *et al.* 2018	USA, Americans	Randomise controlled trials	Adults	146/55	G	C/G	2 years randomise clinica trial	7
	de Luis *et al.* 2020b	Finland, Finnish	Clinical Trial	Adults	119/114	G	C/G	3 months of diet in-tervention Diet M & Diet P	8
	Mirzaei *et al.* 2014	USA, Americans	Randomise controlled trials	Adults	721/722	G	C/G	2 years randomise weight loss diet intervention trial	8
rs1052700	Andrade-Mayorga *et al.* 2021	Chile, Chileans	Non-randomise controlled trials	Adults	13/17	T	T/A	12 weeks HIIT training & dietary energy restriction	6
	Deram *et al.* 2008	Brazil, Brazilian	Non-randomise controlled trials	Children & Adolescent	116/118	T	T/A	20 week lifestyle and weight loss program	6
	Garaulet *et al.* 2016	Spain, Spanish	Non-randomise controlled trials	Adults	1,058/229	T	T/A	28 weeks of treatment of ONTIME study	8
rs2289487	Garaulet *et al.* 2016	Spain, Spanish	Non-randomise controlled trials	Adults	1,058/229	T	T/A	28 weeks of treatment of ONTIME study	8
	Deram *et al.* 2008	Brazil, Brazilian	Non-randomise controlled trials	Children & Adolescent	116/118	T	T/A	20 weeks lifestyle and weight loss program	6

Continue from Table 1

Genetic Variation, SNP ID	First Authors, publication year	Study location, Population	Study design	Age group	Number of risk/non-risk allele in participant	Risk allele	Alleles	Intervention	NOS score
rs2304795	Garaulet *et al.* 2016	Spain, Spanish	Non-randomise controlled trials	Adults	1,058/229	T	T/A	28 weeks of treatment of ONTIME study	8
	Deram *et al.* 2008	Brazil, Brazilian	Non-randomise controlled trials	Children & Adolescent	116/118	T	T/A	20 weeks life-style and weight loss program	6
	Andrade-Mayorga *et al.* 2021	Chile, Chileans	Non-randomise controlled trials	Adults	13/17	T	T/A	12 weeks HIIT training & dietary energy restriction	6
rs894160	Deram *et al.* 2008	Brazil, Brazilian	Non-randomise controlled trials	Children & Adolescent	116/118	T	T/A	20 weeks lifestyle and weight loss program	6
	Garaulet *et al.*2016	Spain, Spanish	Non-randomise controlled trials	Adults	1,058/229	T	T/A	28 weeks of treatment of ONTIME study	8
rs11605924	Mirzaei *et al.* 2014	USA, Americans	Randomise controlled trials	Adults	721/722	G	C/G	2 years randomise weight loss diet intervention trial	8
rs283	Andrade-Mayorga *et al.* 2021	Chile, Chileans	Non-randomise controlled trials	Adults	13/17	T	T/A	12 weeks HIIT training & dietary energy restriction	6
rs4994	Andrade-Mayorga *et al.* 2021	Chile , Chileans	Non-randomise controlled trials	Adults	13/17	T	T/A	12 weeks HIIT training & dietary energy restriction	6

FTO: Fat Mass and Obesity-associated; SNP: Single Nucleotide Polymorphism; HIIT: High-Intensity Interval Training,
Diet M: Monosaturated Fatty Acid; Diet P: Polyunsaturated Fatty Acid; BMI: Body Mass Index; NOS: Newcastle-Ottawa Scale

vs TA + AA). Although not significantly different, the (TA + AA) genotype groups demonstrated greater weight loss (MD=0.51, 95% CI:-0.38, 0.95, p=0.40), favouring the FTO gene. Standard deviations for certain studies were imputed from Corr values. de Luis *et al.* (2015) had two interventions combined for the analysis.

rs10830963 analysis. Figure 3 illustrates a meta-analysis encompassing three studies (1,905 subjects) examining rs10830963 genotypes (CC vs CG + GG). Despite no significant difference, the (CG + GG) genotype group exhibited favourable weight loss (MD=0.24, 95% CI: -0.57, 1.04, p=0.56). Substitutions for missing data were made where needed.

rs1052700 analysis. Figure 4 presents an analysis of rs1052700 across three studies (1,551 subjects). Genotypes (AA vs AT+TT) showed the AT +TT genotype group favouring weight loss (MD=0.56, 95% CI:-0.74, 1.86, P=0.40).

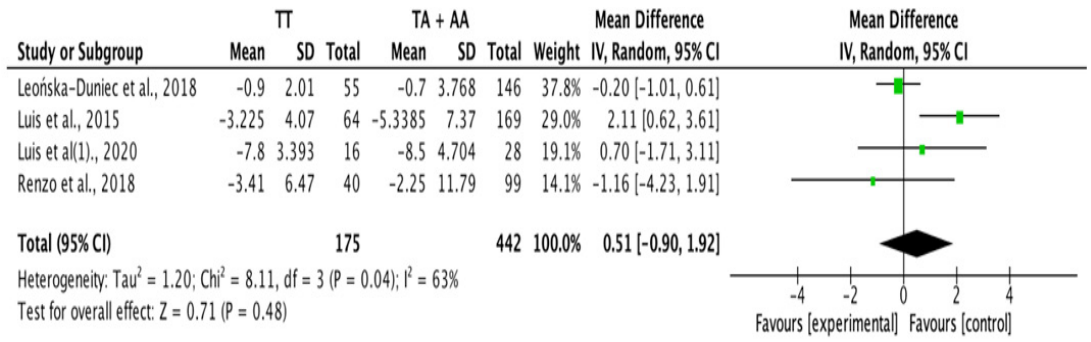

Figure 2. The result of forest plot of rs9939609, where the graph favours recessive genotype (TA + AA).

Substitutions were made to address data gaps and the correlation coefficient influenced calculations.

Sensitivity analysis

Sensitivity analysis of rs9939609. Sensitivity analysis for rs9939609 assessed the effect by excluding specific studies. Eliminating Leónka-Duniec *et al.* (2018) showed no significant difference (MD=0.93, 95% CI:-0.86, 2.73; p=0.31, I^2=48%). The removal of de Luis *et al.* (2015) and de Luis *et al.* (2020a) also had no substantial impact (MD=-0.17, 95% CI:-0.92, 0.57; p=0.65, I^2=0% and MD=0.44, 95% CI:-1.38, 2.26; p=0.64, I^2=75%, respectively). Similarly, excluding Di Renzo *et al.* (2018) yielded no significant weight loss (MD=0.80, 95% CI:-0.82, 2.41; p=0.33, I^2= 72%). Despite individual eliminations, rs9939609 still did not associate significantly with weight loss.

Sensitivity analysis of rs10830963. Sensitivity analysis for rs10830963 excluded Goni *et al.* (2018) and Mirzaei *et al.* (2014), revealing no significant weight loss for allele (CG + GG) (MD=-0.03, 95% CI:-2.27, 2.22; p=0.98, I^2=99%).

Sensitivity analysis of rs1052700. Sensitivity analysis for rs1052700 removed Andrade-Mayorga *et al.* (2021) and Deram *et al.* (2008), with no significant influence due to lower overall weight compared to Garaulet *et al.* (2016). Removing Garaulet *et al.* (2016) emphasised significant weight loss for allele (AT + TT) (MD=1.28, 95% CI:0.45, 2.11; p=0.003, I^2=0%).

Stratified analysis

Stratified analysis of rs9939609. Studies were stratified based on mean BMI and program duration. Studies with mean BMI<30 kg/m^2 showed no significant weight loss (MD=-0.26, 95% CI:1.05, 0.52; p=0.51), while those with mean BMI>30 kg/m^2 exhibited significant weight loss (MD=1.72, 95% CI:0.45, 2.99; p=0.008). Duration-based stratification showed no significant weight loss for both 4-week (MD=-1.16, 95% CI:-4.23, 1.91; p=0.46, I^2=0.00) and 12-week programs (MD=0.80, 95% CI:-0.82,

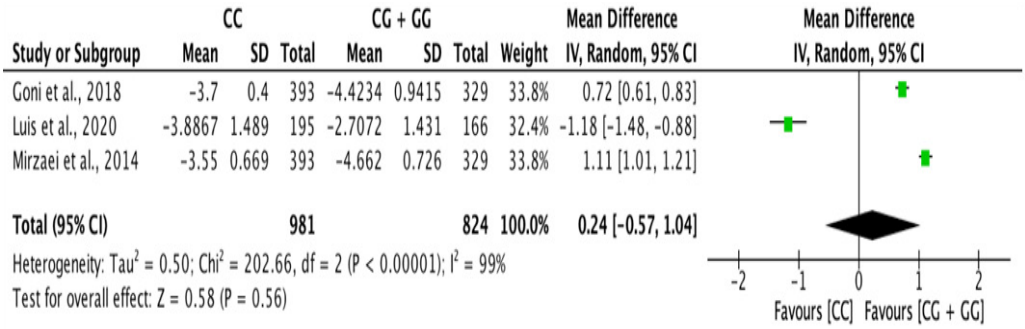

Figure 3. The result of forest plot of rs10830963, where the graph favours recessive genotype (CG + GG)

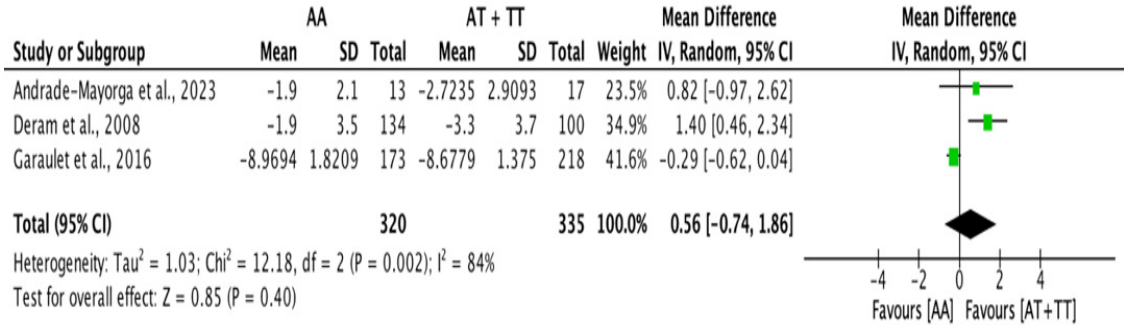

Figure 4. The result of forest plot of rs1052700, where the graph favours recessive genotype (AT + TT)

2.41; p=0.33, I^2=0.72). Diet-focused studies also didn't yield significant weight loss (MD=-0.20, 95% CI:-1.01, 0.61; p=0.63, I^2=0.00). Additionally, studies exploring low and high-impact aerobics (MD=0.93, 95% CI:-0.86, 2.73; p=0.31, I^2=0.48) indicated no significant weight loss regardless of intervention type.

Stratified analysis of rs10830963. Two studies had a mean BMI<35 kg/m^2 (Goni *et al.* 2018 & Mirzaei *et al.* 2014) with significant weight loss (MD=0.92, 95% CI:0.54, 1.30), p<0.00001, I^2=0. Another study had a mean BMI>35 kg/m^2 (de Luis *et al.* 2020b) with substantial weight loss (MD=-1.18, 95% CI:-1.48, -0.88), p<0.00001, I^2=0.96. The p-value between groups was <0.00001, signifying significant weight loss in both BMI categories. For program duration, one study had a 3-month program (de Luis *et al.* 2020b) showing substantial weight loss (MD=-1.18, 95% CI:-1.48, -0.88), p<0.0001, I^2=0.00. Conversely, the other three studies with 2-year programs (Goni *et al.* 2018 & Mirzaei *et al.* 2014) indicated noteworthy weight loss (MD=0.92, 95% CI:0.54, 1.30), p<0.00001, I^2=0.96. The p-value between groups underlined significant weight loss across participants. All three articles investigating diet effects showcased significant weight loss (MD=-0.26, 95% CI:-0.94, 0.42), p=0.0, I^2=0.00, highlighting intervention-based distinctions.

Stratified analysis of rs1052700. There is insufficient data in the listed papers for rs1052700 for a stratified analysis.

Summary of evidence

Weight loss is linked to the rs9939609 polymorphism (SNP ID), especially in those with the TA + AA genotype. In the study, four papers were reviewed. Leónska-Deuniec (2018) and Di Renzo *et al.* (2018) observed in two investigations that FTO did not result in weight reduction and carriers of the A allele had larger body mass. However, two more investigations by de Luis *et al.* (2015) and de Luis *et al.* (2020a) demonstrated that individuals with the A allele lost weight when eating a diet high in polyunsaturated fats (PUFA). According to Leónska-Deuniec *et al.* participants with the TA and AA genotypes consistently had higher BMIs and average body mass increases from 1.2 kg to 3.0 kg.

Di Renzo *et al.* (2018) also supported the idea that allele A carriers had higher BMI than the TT genotype. The other two articles also confirmed that carriers of the A allele had higher initial body weight. Still, they emphasised that these subjects experienced lower body weight gain when following a Mediterranean-style diet. de Luis *et al.* (2020b) found that TT and AT + AA genotype participants benefited from a low-calorie diet. However, A allele carriers had the most significant weight loss and improved metabolic outcomes when consuming a high PUFA, low-calorie diet. The interplay between dietary fat content and the FTO SNP variation may explain these benefits for A allele carriers. Two research studies supported weight reduction among A allele carriers, and two studies refuted this conclusion, according to the overall impact estimate from the forest plot.

The rs10830963 was analysed in three studies. Goni *et al.* (2018) found that the G genotype, associated with a 2 to 4-fold increase in MTNR1B mRNA expression, improved lipid profiles on a low-fat diet. However, weight loss may not significantly impact total cholesterol and LDL cholesterol concentration

despite its positive effects on the lipid profile in general. This study was the first to analyse the interaction between the MTNR1B genetic variant and dietary fat intake, showing that the G allele may benefit more from a low-fat diet to improve the lipid profile. On the other hand, de Luis *et al.* (2020b) contradicted these findings by stating that the G allele is associated with less weight loss. The forest plot suggested that the CC genotype may experience more weight loss than the recessive genotype. Mirzaei *et al.* (2014) investigated energy expenditure with Respiratory Quotient (RQ). They found that the G allele was significantly associated with a higher increase in RQ on a low-fat diet during the 2-year intervention. The relationship between RQ and weight loss suggests that the G allele may increase RQ, which could lead to more weight loss in individuals with obesity when following a low-fat diet (Weinsier *et al.* 1995). The overall effect estimate from the forest plot was not significant, mainly due to conflicting results between studies. However, after removing de Luis *et al.* (2020b) from the analysis, sensitivity analysis showed a significant result favouring the CG + GG genotype for weight loss.

In three investigations, the rs1052700 was examined. Both Andrade-Mayorga *et al.* (2021) and Aller *et al.* (2017) discovered that after treatments in overweight/obese participants, bearers of the TT genotype reported higher reductions in absolute fat mass and body mass, respectively. A PLIN1 x food timing interaction was seen in a different study by Garaulet *et al.* (2016), which revealed that those with the AA genotype had more difficulties losing weight, particularly when eating later in the day. The forest plot showed that the rs1052700 polymorphism had no significant overall effect. However, the AT + TT genotype favoured higher weight reduction, indicating that the T allele would be more advantageous for weight loss.

The study has strengths, including a comprehensive literature review identifying nine relevant SNPs related to weight control in obese individuals. Careful data retrieval of BMI/weight, mean difference, and standard deviation from selected papers enhanced methodological rigour. The strict inclusion criteria focused on three SNPs for meta-analysis, increasing its validity. The stratified analysis provided detailed insights into genetic variations' influence on weight control in various subgroups. Sensitivity analysis assessed the reliability of findings and the impact of different investigations on conclusions.

Investigating how these genetic variants interact with different weight-management therapies, such as dietary and lifestyle modifications, can lead to personalised approaches for more effective results.

CONCLUSION

In conclusion, our study establishes a correlation between genetic variation and weight management in obese subjects undergoing weight loss programs. We identified SNP IDs rs9939609, rs10830963, and rs1052700 as predictive markers for weight loss. Participants with recessive alleles (A for rs9939609, G for rs10830963, and T for rs1052700) are likelier to lose weight. The effect of genetic variants on weight management was observed with specific dietary interventions. For rs9939609, the A allele showed lower weight gain with a Mediterranean diet. rs10830963 non-risk allele G led to significant weight loss with a low-fat diet. rs1052700 T allele was associated with successful weight reduction when eating earlier meals. Participants with these genetic makeup and recessive alleles are more likely to benefit from diet and lifestyle change programs to reduce obesity.

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DECLARATION OF CONFLICT OF INTERESTS

The authors have no conflict of interest.

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