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REVIEW ARTICLE

FTO gene polymorphisms SNP rs9939609 and rs1421085 as Risk Factors for High Visceral Fat: A Systematic Review Study

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ABSTRACT

Fat build-up can lead to inflammation, which in turn exacerbates health conditions and intensifies complications associated with obesity. This is also related to obesity related gene factors, the FTO gene, which is thought to increase visceral fat. This review investigates the relationship between FTO gene polymorphisms rs9939609 and rs1421085 and visceral fat accumulation. A systematic review was carried out through searches in PubMed, Science Direct, and Cochrane databases, from the index date from 2010 to October 2024. Studies with case control, cohort, and cross-sectional designs that discussed the relationship between FTO gene polymorphisms rs9939609 and rs1421085 and increased risk of visceral fat in obese patients were included in this study. This study included 19.732 samples from 11 cohort, case-control, and cross-sectional studies. Five studies revealed that the A allele of rs9939609 and the T allele of rs1421085 were significantly associated with increased visceral fat levels. Findings on the involvement of FTO gene polymorphisms rs9939609 and rs1421085 in visceral fat risk remain inconclusive and warrant further investigation. Therefore, we as researchers support further research that includes the role of this gene in visceral fat using analysis so that it can confirm more precise results in statistics.

***Keywords*:** Obesity, Fat mass, Obesity related gene, FTO polymorphism, rs9939609, rs1421085, Visceral fat.

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Introduction

The rising prevalence of obesity presents a major worldwide health concern that contributes to the increasing incidence of various non-communicable diseases and accelerates the risk of premature death, especially among adults (1). Globally, more than 1.9 billion people are classified as overweight, with approximately 650 million considered obese, according to data from the World Health Organization (WHO), which shows that obesity has increase the prevalence nearly tripled since 1975. This trend indicates that obesity is not just an individual problem of health but also affects the health system as a whole (2). Adipose tissue has a complex role in the body, such as mechanical cushioning, energy storage, and regulating homeostasis. Based on its distribution, this tissue can be categorized into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT).

The distribution of VAT can be found in intraperitoneal and retroperitoneal tissues, while SAT can cover up to 80% of healthy adult total body fat. SAT can be found in superficial and deep subcutaneous adipose tissue. Metabolically, VAT and SAT have different functions. VAT has more active metabolic activity and higher lipolysis compared to SAT. Excess energy accumulation will be stored in adipose cells in SAT and act as a metabolic buffer. Accumulation in VAT will only occur if the SAT capacity has exceeded or impaired (3).

Accumulation of VAT, which often occurs in obese individuals, can result in homeostasis disorders and organ dysfunction. Obesity can lower quality of life and increase the risk of developing major chronic diseases like type 2 diabetes, hypertension and heart disease if it is not adequately controlled. Accumulation of VAT, especially in the omentum and mesentery, has the potential to increase intra-abdominal pressure, which can contribute to various health problems, such as oesophageal reflux and hypertension. In addition, fat accumulation in soft tissues can increase the risk of airway obstruction and osteoarthritis due to excessive body weight (4). The factors contributing to obesity are complex, involving genetic and environmental interactions. Low energy expenditure and excessive calorie intake are major contributors to body fat formation. There was studies that shown that the FTO gene is thought to have the most decisive influence on eating behaviour and energy balance regulation, which is closely related to body fat accumulation ((5, 6). A allele in rs9939609 can increase food intake and activate the lipolysis process in individuals with the gene. The genotype rs1421085, one of variants of the FTO gene polymorphism, is have a crucial role in the adiposity and thermogenesis regulation pathway (7). The rising prevalence of obesity and its long-term consequences on health have underscored the importance of investigating how FTO gene polymorphisms relate to visceral fat accumulation. While earlier systematic reviews and meta-analyses have mostly examined the link between FTO variants and obesity, they primarily relied on waist circumference or Body Mass Index (BMI) as outcome measures (7, 8).

However, there is a noticeable gap in the literature regarding the relationship between FTO variants and visceral fat accumulation. This is particularly significant because visceral fat is a more metabolically active and pathogenic fat depot than subcutaneous fat. It is strongly associated with increased risks of cardiovascular disease, insulin resistance, type 2 diabetes and metabolic syndrome, independent of BMI measurements (9). Unlike BMI and waist circumference, which provide general or indirect assessments of body fat, visceral fat directly reflects ectopic fat accumulation around internal organs, making it a more precise marker for metabolic health risks (10, 11). Therefore, exploring the impact of FTO gene variations on visceral fat accumulation could provide deeper insights into the genetic mechanisms underlying obesity-related metabolic disorders and offer more targeted strategies for prevention and intervention. The aim of this study is to conclude the relationship between FTO gene rs9939609 polymorphisms and rs1421085 and visceral fat.

Methods

The Research strategy

This study followed the 2020 guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to ensure transparent and standardized reporting (12). This systematic review study has been registered to PROSPERO with registration ID CRD42024623196. The population, exposure, comparison, and outcome (PECO) formulation is used to answer this question, presented in Table 1. This study used three databases: PubMed,

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ScienceDirect, and Cochrane date from 2010 up to October 2024. The literature search utilized a combination of keywords including "FTO," "FTO gene," "fat mass and obesity-related gene," "FTO polymorphism," "rs9939609," "rs1421085," along with "visceral," "visceral fat," and "visceral adiposity." The search was restricted to English-language studies with case-control, cross-sectional, and cohort designs. Studies were drawn from diverse populations across multiple countries.

Table 1. The framework of population, exposure, comparison, and outcomes (PECO)

Component	Detail
Population	Obese individuals
Exposure	FTO gene polymorphism rs9939609 and rs1421085
Comparison	Individuals with normal body weight or without FTO gene polymorphisms rs9939609 and rs1421085
Outcomes	Risk factors for high visceral fat levels

Inclusion and exclusion criteria

The data collection process was performed electronically. An initial review was conducted, followed by a detailed screening to evaluate each article based on predefined inclusion and exclusion criteria. Studies were included if they involved human participants, investigated the association between FTO gene polymorphisms and the risk of elevated visceral fat, were available in full-text English, and employed cohort, cross-sectional, or case-control designs in adult populations from various regions globally. The exclusion criteria are if the study uses animal subjects, is a case report, does not include genetics and visceral fat, individuals with severe or chronic medical, pregnant women or breastfeeding, patient that taking medications or supplements that could affect body weight.

Study Selection and Screening Process

The selection process adhered to the PRISMA 2020 framework and is illustrated in Figure 1. Initially, 313 records were retrieved from three databases: PubMed (n = 153), ScienceDirect (n = 126), and the Cochrane Library (n = 34). After eliminating 12 duplicate entries, 301 articles remained for title and abstract review. Among these, 261 were excluded due to various reasons, including mismatch in population or sample characteristics (n = 178), unsuitable study designs (n = 34), and focus on unrelated alleles or gene variants (n = 49). The remaining 40 full-text articles were retrieved and assessed for eligibility. Fifteen were excluded due to comorbid populations (n = 8) or incomplete data (n = 5), while two lacked sufficient outcome reporting. After full evaluation, a total of 12 studies met the inclusion criteria and were included in the final systematic review. This multistage screening process was performed independently by two researchers using pre-defined eligibility criteria. Any disagreements encountered during the study selection were addressed through discussion and mutual agreement. Justifications for exclusion at each phase were recorded to maintain transparency and support the reproducibility of the review methodology.

Data Extraction

Researchers independently search for the required data which is then named according to the author's name, year of publication, study method, sample size, exposure, output, dietary assessment, physical activity assessment and study output. The data was then organized and tabulated in the Microsoft Excel application to facilitate analysis. The selected studies underwent a critical appraisal to evaluate their quality before being included in this systematic review.

Quality assessment

To maintain the integrity of the evaluation, this review applied the Risk of Bias in Nonrandomized Studies of Exposures (ROBINS-E) tool to assess all included studies. Each researcher independently performed the ROBINS-E assessment to identify potential sources of bias. In cases of differing judgments, resolution was achieved through discussion. The level of bias for each study was categorized as low, moderate, high, or very high, based on ROBINS-E criteria. This assessment helped ensure the overall accuracy and reliability of the study's findings.

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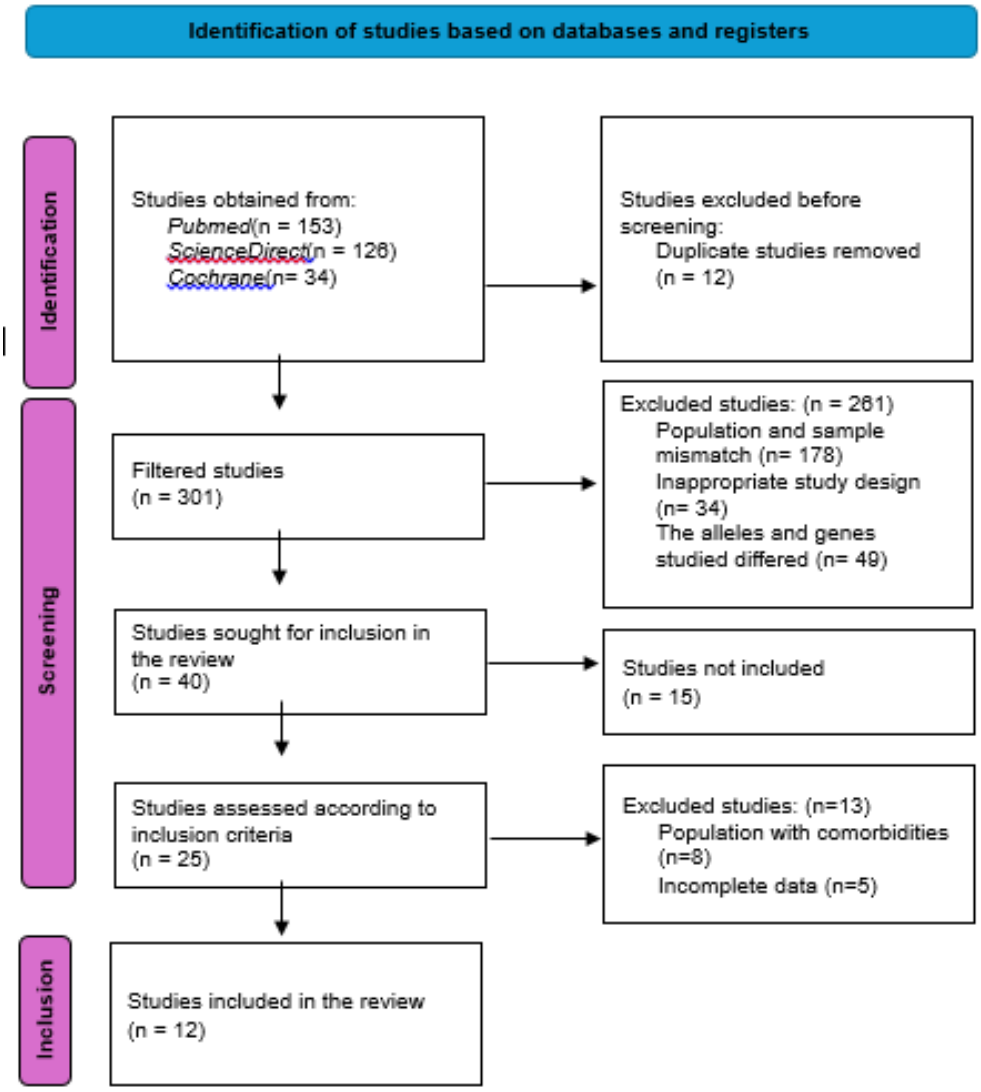


Figure 1. Study selection process by using PRISMA Flowchart for systematic review.

Eligibility criteria

In this analysis, the population included were adults with obesity and FTO polymorphism rs9939609 and rs1421085 genotype variation. This study looked at the FTO variant rs9939609 and rs1421085 against visceral fat in various countries. Exclusion criteria included incomplete articles, inappropriate or irrelevant data, and studies involving pregnancy.

Results

This systematic review includes 11 studies and total sample size of 19.732 patients published between 2010 and 2024. The included investigations were conducted in Iran, Thailand, Pakistan, Germany, Indonesia, Japan, and Canada and used cross-sectional, cohort, and case-control research designs. The relationship between the FTO gene polymorphisms rs9939609 and rs1421085 and an elevated risk of visceral fat was evaluated in every study in this systematic review. Researchers sorted the data that had been searched and then included in this study by following the inclusion and exclusion criteria. The entire selection process is illustrated in Figure 1, while the PRISMA checklist is provided in Supplementary Material S1.

The result of the risk bias of entire studies is mostly low, which we assessed from 6 domains based on ROBINS-E. (Figure 2)**.** Description of studies focusing the relationship rs9939609 and visceral fat that included in the systematic review. [Insert Table 2 and 3].

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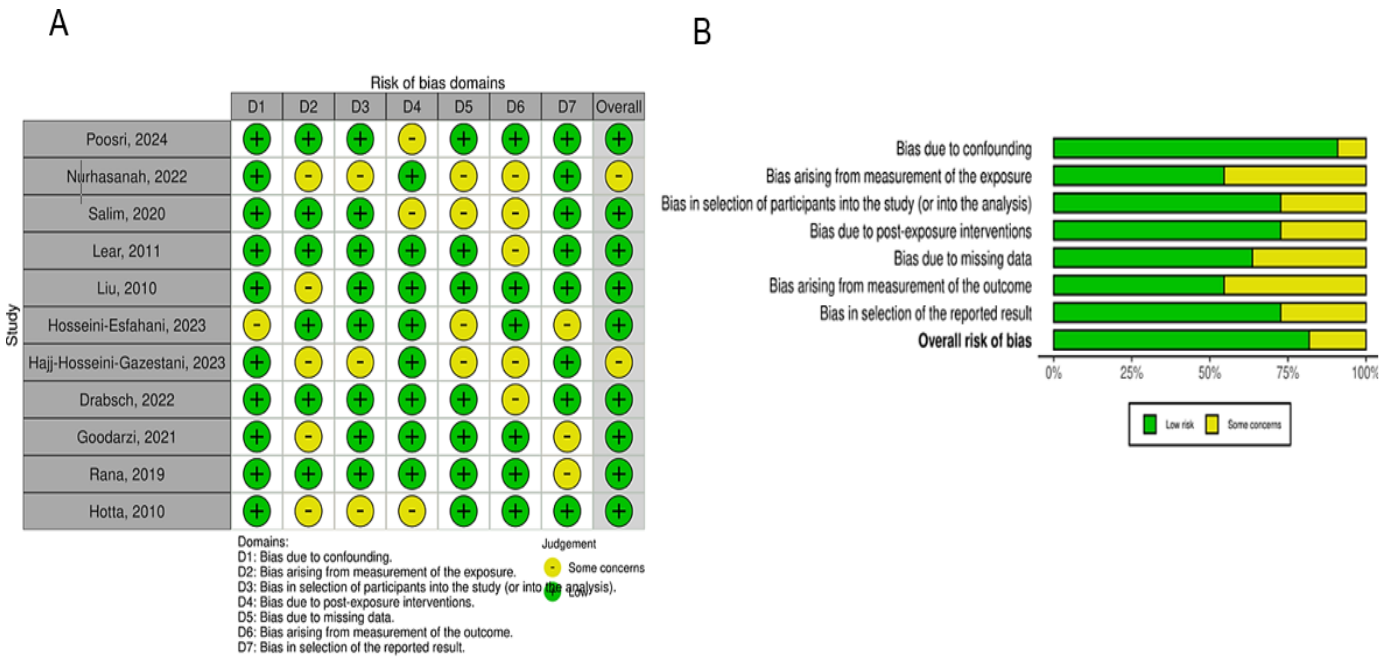


Figure 2. Risk of Bias of all studies included, (A) ROBINS-E Traffic Light Plot, (B) ROBINS-E Summary Plot.

Table 2. Description of studies focusing the relationship rs9939609 and visceral fat that included in the systematic review.

Author, year	Study Design	Country	Sample Size	Exposure/ Exposure Assessment	Output/Output Assessment	Dietary Assessment	Study Output
Poosri, 2024	Cross-sectional	Thailand	384	rs9939609/ PCR NCBI Primer-BLAST	Visceral fat rating	Semi-quantitative FFQ	FTO rs9939609 genotype, the obese group had an average visceral fat that was higher than that of the non-obese group, both for the TT genotype with p = 0.000 and TA + AA with p = 0.000.
Nurhasanah, 2022	Cross-sectional	Indonesia	80	rs9939609 / ARMS-PCR gene polymorphism	Visceral fat percentage/ BIA	NR	FTO rs9939609 gene polymorphism had no significant relationship with visceral fat with p>0.05.
Salim, 2020	Cross-sectional	Indonesia	38	rs9939609 / PCR-RFLP	Visceral fat area/InBody720	NR	FTO rs9939609 has a significant relationship with increased visceral fat in men. FTO rs9939609 AT has significantly higher visceral fat

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Author, year	Study Design	Country	Sample Size	Exposure/ Exposure Assessment	Output/Output Assessment	Dietary Assessment	Study Output
							than other allele groups with p=0.010.
Lear, 2011	Cohort	Canada	706	rs9939609 / RT-PCR with TaqMan assay	Visceral adipose tissue/CT scan	NR	FTO rs9939609 minor allele of was significantly associated with a relative increase in visceral fat with p=0.047 in Europeans population.
Liu, 2010	Cross-sectional	Netherland	1978	rs9939609 / RT-PCR with TaqMan assay	Visceral adipose tissue/MRI	NR	FTO rs9939609 A allele showed higher visceral fat than carriers of the TT allele, but the difference was not significant with p = 0.98 .

P<0.05 was considered significant. Abbreviation: RT, real time; PCR, polymerase chain reaction; NR, not reported.

Table 3. Description of studies focusing the relationship rs1421085 and visceral fat that included in the systematic review.

Author, year	Study Design	Country	Sample Size	Exposure/ Exposure Assessment	Output/ Output Assessment	Dietary Assessment	Study Output
Poosri et al., 2024	Cross-sectional	Thailand	384	rs1421085 (DNA genotyping from blood, sequencing/HRM)	Visceral fat	Self-reported food intake; comparison between risk vs non-risk allele carriers	FTO rs1421085 associated with higher visceral fat intake (OR for high fat intake = 1.86, p = 0.041)
Hosseini-Esfahani. et al, 2023	Prospective cohort (3 years)	Iran	4480	rs1421085 (genotyping using TLGS cohort DNA samples)	Visceral fat	FFQ; DASH and HEI scores	FTO rs1421085 linked to lower visceral fat gain with high HEI adherence (P trend = 0.01)

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Author, year	Study Design	Country	Sample Size	Exposure/ Exposure Assessment	Output/ Output Assessment	Dietary Assessment	Study Output
Haji-Hosseini-Gazestani et al., 2023	Prospective cohort	Iran	4480	rs1421085 (genotyping in TLGS cohort, SNP analysis)	Visceral fat	FFQ and DII calculation	FTO rs1421085 × DII interaction affected visceral fat (WC); TT genotype: OR = 1.43, 95% CI 1.04–1.97, p = 0.03
Drabsch et al., 2023	Cross-sectional	Germany	92	rs1421085 (genotyping via SNP analysis, blood sample)	Visceral fat	None	No significant association between rs1421085 and visceral fat (p > 0.05)
Rana et al., 2020	Case-control	Pakistan	612	rs1421085 (TaqMan allelic discrimination assay)	Visceral fat	Not reported	FTO CT genotype of rs1421085 associated with increased visceral fat (OR = 1.583, 95% CI 1.147–2.185, p = 0.005)
Hotta et al., 2010	Cross-sectional	Japan	1228	rs1421085 (genotyping in Japanese population DNA samples)	Visceral fat	Not reported	FTO rs1421085 significantly associated with increased visceral fat area (VFA) (p = 0.040)

P<0.05 was considered significant. Abbreviation: RT, real time; PCR, polymerase chain reaction; NR, not reported.

Discussion

The primary cause of many chronic non-communicable diseases is obesity. In the adult age range, this illness can also result in early mortality and disability (1). According to the World Health Organization, the global prevalence of obesity has nearly tripled since 1975, with more than 1.9 billion individuals classified as overweight and approximately 650 million as obese. Obesity has become a major global health concern, impacting individuals as well as society at large. Recent research has indicated a global rise in the number of overweight and obese individuals, with approximately 2 billion people representing about 30% of the world's population classified as overweight (13). Accumulation of VAT can disrupt homeostasis and organ dysfunction. The pathological mechanisms due to VAT accumulation can be overcome if obesity has been diagnosed and treated correctly. If this condition is not treated, it can lead to chronic diseases and lead to decreased life expectancy. Accumulation of VAT, especially in the omentum and mesentery, can cause metabolic changes. Quantitative accumulation of VAT can be seen from changes in anthropometric and

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biochemical parameters. Overall, the distribution of body fat particularly visceral and abdominal fat plays a more critical role in the development of obesity-related disorders than the total amount of fat, as it significantly influences metabolic and functional alterations (4).

Several risk factors, including heredity and environmental variables like poor diet and physical inactivity, can combine to cause obesity. Excessive energy intake and low energy expenditure promote fat accumulation, which then triggers the development of obesity. The degree of obesity is related with some various inflammatory markers such sa IL-6, TNF-a, and-reactive protein (CRP). Inflammation in obesity can be triggered by adipose tissue through a two-way relationship that forms a mutually reinforcing cycle in which excess energy intake contributes to the inflammatory reaction. TNF-a, IL-6, and IL-1 as pro-inflamatory cytokines can increase appetite by promoting energy intake and fat storage (14).

Evidence from research has shown that the FTO (fat mass and obesity-associated) gene is a key contributor to the development of obesity. This gene significantly impacts appetite, eating habits, and energy balance. Recent research has indicated a strong correlation between fat storage and FTO, particularly the homozygous A allele of rs9939609 (5, 6, 15). Furthermore, people with the FTO risk allele have reduced levels of fat cell lipolysis in comparison to those without the allele, indicating that the FTO gene is crucial for fat metabolism (16). Twelve journals that looked at the connection between visceral fat risk and FTO gene polymorphisms were included in this systematic review. Out of all the research, five journals concluded that the risk of visceral fat accumulation was significantly influenced by the A risk allele of rs9939609 and the T risk allele of rs1421085.

A study by Salim et al. found that the FTO rs9939609 gene significantly relates to increased visceral fat levels in men. The population with AT allele carriers had a considerably higher VFA of 78.48 ± 15.18 cm2 than other allele groups (TT: 48.65 ± 10.61 cm2) with a p-value = 0.010 (17). These results are in line with studies conducted by Matsuo et al. in 2014 and Liu et al. in 2010, which found that A allele carriers were superior in increasing visceral fat levels compared to T allele carriers, although the results were not significant (18, 19). Human studies have shown that high-risk allele variation in the FTO rs9939609 gene, particularly in the A allele, is linked to obesity through increased hunger. One proposed explanation for the higher BMI observed in individuals with the A allele compared to those with the TT genotype is a lower resting energy expenditure (REE) associated with the A allele (17). According to a study by Lear et al. in Canada, the minor allele of rs9939609 was strongly linked to a 9.7±5.7% (p=0.047) relative increase in VAT in Europeans (20). According to studies conducted on mice, overexpression of FTO has been linked to gene expression alterations in anabolic pathways. It is speculated that obese women with the A gene have altered energy pathways that are triggered by diet, potentially making them more resistant to midsection fat loss. In addition, obese women carrying the A allele tend to eat more food than women without the A allele. This may be attributed to the A allele of the FTO rs9939609 variant, which has been associated with increased food intake in individuals carrying the allele (6, 21).

The FTO rs1421085 gene is one of the genes associated with macronutrient consumption, such as carbohydrates, proteins, and saturated and polyunsaturated fatty acids. Although rs9939609 is more often associated with obesity, rs1421085 also shows a relationship between the occurrence of obesity and changes in diet. Both in vivo and in vitro studies have shown that the rs1421085 variant can influence the transcription of genes involved in regulating food intake and adipocyte thermogenesis (22).

This result is consistent with the research by Claussnitzer et al., which showed that the rs1421085 variation is essential for the regulatory mechanisms governing thermogenesis and obesity. Therefore, manipulating these pathways can be a strategy to regulate obesity levels (7). Poosri et al. conducted a cross-sectional study in Thailand involving 384 participants, which found that individuals in the obese group had a significantly higher average visceral fat rating compared to those in the non-obese group. The TT genotype of rs1421085 (10.61 ± 3.73 vs. 5.30 ± 2.54; p = 0.000) and the combined TC + CC genotypes (10.65 ± 4.03 vs. 5.00 ± 2.12; p = 0.000) were both significantly associated with increased visceral fat accumulation (22). However, Hosseini-Esfahani et al. who conducted a cohort study in Iran involving 6,882 samples showed that changes in visceral adiposity index (VAI) based on quartiles of HEI (healthy eating index) and DASH (dietary approaches to stop hypertension) scores were not significant in either TT

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or TC + CC genotypes, with p-trend values of 0.55 and 0.38 for HEI and 0.35 and 0.35 for DASH (14).

Another study by Haji-Hosseini-Gazestani et al. on 4,480 samples in Iran found that in the TT allele of rs1421085, there was a significant increase in the odds ratio (OR) of VAI change from 1 in the first quartile (Q1) to 1.63 (95% CI: 1.12–2.37) in the fourth quartile (Q4) (p-trend = 0.01). However, the results were inversely proportional to the TC + CC genotype, where the OR of VAI change did not show a significant trend (p-trend = 0.71) (14). These findings are comparable to those of a study by Goodarzi et al. that was carried out in Iran using a cohort design with 4,480 samples. The study found no significant correlation between changes in the visceral adiposity index (VAI) based on the healthy diversity index (HDI) and the FTO rs1421085 gene polymorphism. In this study, the change in VAI in the TT genotype from the first quartile (Q1) was -0.00 ± 0.02 to 0.03 ± 0.02 in the fourth quartile (Q4) with a p-trend value = 0.21. A similar finding was found in the TC + CC genotype; the change in VAI from Q1 was -0.02 ± 0.01 to -0.01 ± 0.02 in Q4, showing no significant difference, with a p-trend value = 0.65 (23).

Another non-significant study was conducted by Drabsch et al. in Germany with a cross-sectional design involving 92 samples, there is no relationship between the C risk allele of rs1421085 and VAT (p = 0.711) (24). Rana et al. conducted a study in Pakistan with a case-control design on 612 samples, which also showed that VAI at rs1421085 was almost similar between the CT (3.09 ± 1.93 mmol/L) and TT + CC (3.00 ± 2.15 mmol/L) groups, with regression analysis showing no significant association in both adjusted and unadjusted models (p> 0.05). A study by Hotta et al. in Japan with a cross-sectional design involving 1,228 samples found a significant relationship between the rs1421085 genotype in the FTO gene and visceral fat area (VFA) based on multiple regression analysis (p = 0.040) (25). Overall, the findings suggest that the association between FTO gene polymorphisms and visceral fat is affected by factors such as population characteristics, study design, and the approaches used to assess dietary intake and physical activity.

FTO rs1421085 involving T to C transition has been associated as a causative variant for obesity phenotype. Functional variations in the FTO gene, including rs1421085 genotype variants, can affect energy balance and contribute to the development of overweight or obesity phenotype. This suggests that alterations in rs1421085 may have a significant impact on regulating energy metabolism, directly related to obesity risk (26). When comparing non-obese and obese groups, it was discovered that the C risk allele of rs1421085 had a distinct effect on consuming high-energy items, such as those high in fat and sugar. . The study further demonstrated that within the obese group, carriers of the C risk allele of rs1421085 had a greater consumption of sugar and saturated fat compared to individuals with the wild-type genotype. These findings suggest that the rs1421085 variant plays a role in influencing dietary patterns associated with increased consumption of high-calorie foods, which may contribute to obesity development (22).

The findings of this review highlight a potential genetic contribution to visceral fat accumulation through FTO gene polymorphisms, particularly rs9939609 and rs1421085. These variants may influence adiposity by modulating energy intake, fat metabolism, and thermogenic activity. The A allele of rs9939609 has been associated with increased appetite and reduced satiety, potentially mediated through altered hypothalamic signaling, leading to greater caloric intake and fat storage. Similarly, the C risk allele of rs1421085 is known to disrupt the expression of IRX3 and IRX5, two genes involved in adipocyte thermogenesis, favoring the formation of energy-storing white adipocytes over thermogenically active beige adipocytes.

From a clinical perspective, these findings imply that individuals with FTO gene risk alleles may have a heightened susceptibility to visceral fat accumulation, placing them at increased risk for metabolic syndrome, type 2 diabetes, and cardiovascular disease regardless of their BMI. This supports the potential for personalized prevention and intervention strategies based on genetic risk profiling. Nevertheless, lifestyle factors such as dietary quality and physical activity continue to play a pivotal role and may influence or mitigate the genetic effects observed.

This systematic review has several limitations that should be acknowledged to provide a balanced interpretation of the findings. Firstly, the limited number of eligible studies investigating the association between FTO gene polymorphisms (rs9939609 and rs1421085) and visceral fat may limit the generalizability of the findings. Secondly, substantial heterogeneity was observed among the included

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studies, as they differed in study design, sample size, ethnic backgrounds, genotyping approaches, and methods of visceral fat assessment. Third, several studies did not adjust for confounding factors such as dietary intake, physical activity, or comorbidities, which may influence visceral fat accumulation independently of genetic factors. Fourth, the predominance of cross-sectional study designs among the included research limits the ability to establish causal relationships between FTO gene polymorphisms and visceral fat accumulation. Lastly, although ROBINS-E was used for risk of bias assessment, subjective interpretation and lack of blinding may introduce potential bias during study appraisal. Future research should aim for more standardized methodologies, larger sample sizes, and longitudinal designs to clarify the genetic mechanisms linking FTO polymorphisms with visceral fat. Integrating genetic data with dietary and behavioral interventions may help in developing more targeted and effective strategies for obesity management, particularly those addressing visceral fat as a critical cardiometabolic risk factor.

The overall result of this systematic review is that there is strong evidence for the involvement of FTO rs1421085 and rs9939609. Genetic variations in the FTO gene play a critical role in regulating body fat distribution and obesity risk. The C risk allele of rs1421085 has been strongly associated with increased susceptibility to obesity and visceral fat accumulation, while the A allele of rs9939609 appears to influence fat metabolism and appetite regulation, potentially contributing to greater visceral fat deposition and increased food intake. However, further research to deepen the relationship between FTO rs1421085 and rs9939609 with visceral fat should be done with the aim of explaining the genetic basis of the increased risk of increased visceral fat.

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