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Research Article

A Systematic Review On The Role Of The FTO Rs9939609 Variant In Regulating Appetite In Adults

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ABSTRACT

Background: Several studies have reported that the fat mass and obesity-associated (FTO) rs9939609 polymorphism influences hunger and satiety sensations, affecting appetite. The A allele of rs9939609 is specifically associated with altered postprandial satiety levels. Carriers of the A genotype often experience lower postprandial fullness and higher postprandial appetite levels compared to TT homozygotes.

Objective: The present study aimed to evaluate the role of the rs9939609 single-nucleotide polymorphism of the FTO gene on appetite in adults through a systematic review across different populations.

Methodology: In this study, systematic review evaluated the influence of the rs9939609 single-nucleotide polymorphism of the FTO gene on appetite. Articles from Scopus, PubMed, and Google Scholar, published between 2008 and 2024, were searched. Data identification, screening, and extraction were performed as per the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Result: The systematic review analyzed seven studies investigating the role of the FTO rs9939609 variant in regulating adult appetite. Important conclusions from this study are the following:

Post-Exercise Hunger: Individuals with the TT genotype may experience greater hunger and appetite after exercise than those with the AT allele.

Postprandial Responses: Weak associations were reported between the FTO rs9939609 genotype and fasting or postprandial appetite-related outcomes in healthy individuals. In another study, polymorphism significantly influences postprandial Ghrelin and leptin levels, potentially impacting hunger and satiety in morbidly obese women and overweight men.

Ghrelin and Leptin: AA genotype of FTO rs9939609 would have higher postprandial acylated ghrelin (AG) levels and energy intake.

Protein Intake Interaction: The A allele may be associated with a high decrease in food cravings and appetite scores with a high-protein diet.

Conclusion: The overall findings from these studies underscore the complex role of the FTO rs9939609 variant in regulating appetite and related hormonal responses. The genotype appears to modulate hunger, appetite, and food cravings through various mechanisms, including hormonal changes, exercise responses, and dietary interactions.

KEYWORDS: Appetite, FTO gene, Single Nucleotide Polymorphism, Systematic review, acylated ghrelin

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Introduction

Appetite is the craving to eat food, naturally initiated by hunger, leading to malnutrition and related conditions, such as Overweight, obesity, and its associated health issues like Type 2 Diabetes. Appetite is crucial in regulating energy intake to meet metabolic needs (1). A complex interaction between the digestive tract, adipose tissue, and the brain controls it. Dysregulation of appetite is associated with conditions such as anorexia nervosa, bulimia nervosa, cachexia, overeating, and binge eating disorder. Table 1 shows the neural and humoral signals in the brain and gut hormones that control appetite, with managing food intake and energy expenditure (2,3,4,5,6). Signals from the gut and adipose tissue play crucial roles in regulating sensations of appetite and satiety, respectively. Ghrelin is produced by the gut, whereas leptin is derived from adipose tissue. The hypothalamus integrates these signals to regulate the body's energy homeostasis (6).

Table – 1: Major Gut and Brain hormones in Appetite regulation

Hormone Name	Location of Secretion	Function
PYY (3-36)	L cells of the distal gut	Reduces food intake
Pancreatic Polypeptide (PP)	PP cells in pancreatic islets	Reduces food intake
Glucagon-Like Peptide-1 (GLP-1)	L cells in the intestine	Reduces food intake, suppresses glucagon secretion, delays gastric emptying
Glucagon-Like Peptide-2 (GLP-2)	Enteroendocrine cells	Intestinal trophic effect
Oxyntomodulin (OXM)	L cells of the intestine	Reduces food intake, increases energy expenditure
Ghrelin	Stomach	Increases food intake
Cholecystokinin (CCK)	I cells of the small intestine	Reduces food intake
Insulin	β cells of pancreas	Suppresses food intake
Leptin	Adipocytes	Suppresses food intake
NPY	Hypothalamus	Stimulates food intake
AgRP	Hypothalamus	Stimulates food intake
CART	Hypothalamus	Suppresses food intake
α-MSH	Hypothalamus	Suppresses food intake

Genetic and environmental factors play roles in regulating appetite. Various environmental factors, such as package size, plate shape, lighting, socializing, and food variety, can significantly influence how much food people consume, often more than they realize. Atmospherics, like temperature, lighting, odor, and noise, affect the eating environment. Distractions, such as reading or watching TV, can increase food intake by initiating, obscuring, and extending consumption (7). The European Food Information Council (EUFIC) identifies several social determinants, including culture, family, peers, and meal patterns, as well as psychological determinants like mood, stress, and guilt that influence appetite.

Studying genetic variants in digestive neuroendocrine hormones like CCK, leptin, and Ghrelin offers new insights into how these hormones regulate appetite and eating behavior. Variations in genes like FTO, leptin, the leptin receptor, and Ghrelin, which control food intake, may influence satiety and hunger, contributing to obesity risk and increased caloric intake (8). The fat mass and obesity (FTO) gene, which is associated with obesity, has been strongly linked to an increased risk of obesity-related diseases. The FTO gene is located on chromosome 16 at position 16q12.2, with the rs9939609 single nucleotide Polymorphism (SNP) being a critical variant within the gene's first intron. FTO is expressed in adipocytes, the pancreas, and the hypothalamus, especially in areas that regulate appetite (9). The FTO rs9939609 polymorphism has been extensively studied for its association with obesity and appetite regulation. The FTO rs9939609 gene influences appetite and hunger and presents three polymorphisms: AA, AT, and TT (10). The FTO rs9939609 polymorphism significantly predisposes individuals to severe obesity. Several studies have reported that FTO rs9939609 influences hunger and satiety sensations, affecting appetite and food choices (11).

MATERIALS AND METHODS

Study Design

A comprehensive systematic review aimed to evaluate the relationship between the FTO gene variant rs9939609 and appetite in adults from various populations. The research followed the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses (12) guidelines and conducted searches across three databases—PubMed, Scopus, and Google Scholar—for relevant studies published between January 2008 and January 2024.

Publication Search strategy

The outcome variable was appetite, while the exposure variable was the FTO gene polymorphism rs9939609. The search specifically targeted studies examining the connection between this polymorphism and appetite-related factors, such as satiety, fullness, and hunger sensations. The keywords used to find relevant articles were "(FTO rs9939609 AND Appetite)".

Eligibility criteria—inclusion and exclusion criteria

The selection and screening criteria for the systematic analysis were based on PRISMA protocols. Inclusion criteria were studies involving adults (aged 18 and above), irrespective of gender, published in English between 2008 and 2024 and focused on human research. Sources included Google Scholar, Scopus, and PubMed. The Excluded were studies published in languages other than English, duplicate data, research conducted in silico or on computers, animal studies, reviews or meta-analyses, studies focusing on appetite with specific disease conditions, reports, and studies with incomplete data.

Data extraction

Articles were downloaded from PubMed, Scopus, and Google Scholar. Duplicate studies were eliminated, followed by excluding publications that did not meet our inclusion criteria based on title and abstract scanning. The final screening involved a full-text review, after which articles were selected for the systematic review. The following information was extracted from each study: the name of the first author, year of publication, country of origin, sample size (n), aim of the study, and effect on the FTO rs9939609 variant.

Data analysis

The data was analyzed using a systematic review approach, which collects and critically analyzes multiple research studies on FTO rs9939609 variant and appetite. This methodology follows a structured, standardized approach to minimize bias and provide reliable results. Specifically, the systematic review provides a qualitative synthesis, summarizing the findings of the included studies narratively when a meta-analysis is not possible. The review adheres to the PRISMA guidelines, ensuring that all necessary components are included and reported comprehensively.

Results

Data Screening and Extraction

A total of 1,225 published articles were downloaded for the study from PubMed, Scopus, and Google Scholar. After initial data gathering, 217 duplicate articles were removed. Subsequent screening based on title and abstract excluded 947 articles that did not meet the inclusion criteria. Further screening during full-text analysis led to the exclusion of 54 records. The remaining seven articles were selected for further research analysis. Figure 2 illustrates the study selection and literature search process using the PRISMA flow chart, visually representing the systematic approach in selecting and screening studies for inclusion in the analysis.

Among the 1,225 published articles, 1,218 were excluded due to various reasons, including duplication, focus on food preference studies, studies on hunger hormones, studies related to surgery, meta-analyses/systematic reviews, animal studies, studies in languages other than English, studies on other diseases, studies involving children or adolescents, studies with insufficient data, and studies unrelated to the research topic. Following a thorough screening process, seven studies with a total of 1,420 subjects were ultimately included in the systematic review.

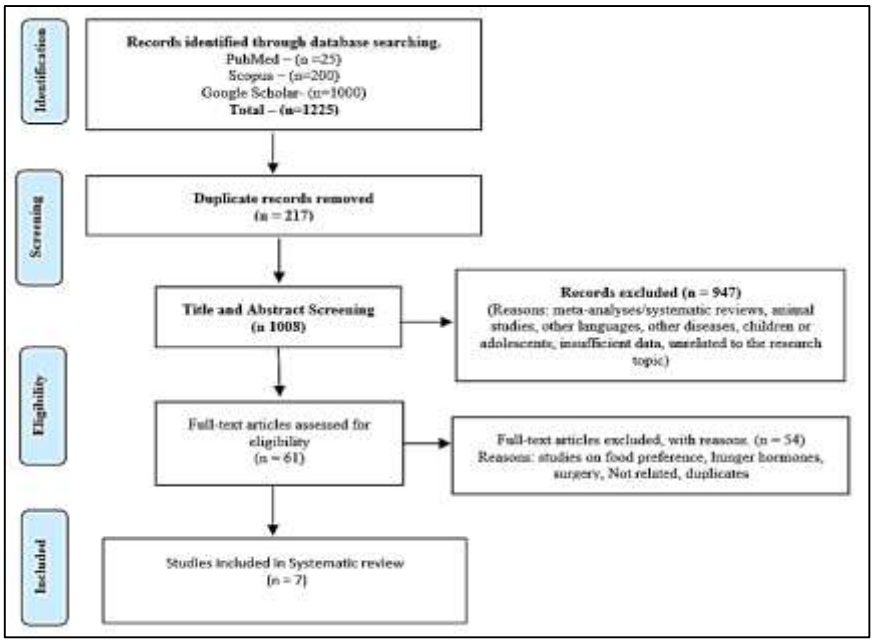

Figure 1 - 1. PRISMA flow diagram showing the screening process for the FTO rs9939609 polymorphism on appetite

Study characteristics

Out of the seven selected studies, three were conducted in the United Kingdom, two in Boston, United States, one in the Netherlands, and one in Brazil. The studies examining the effect of the FTO rs9939609 polymorphism on appetite are summarized in Table 3. While the primary aim of most studies was to investigate the influence of the FTO rs9939609 polymorphism on appetite, they varied in specific conditions and contexts. These included:

- The role of the FTO rs9939609 polymorphism on appetite after exercise
- Influence on fasting and post-meal appetite
- Feelings of fullness
- Appetite in response to a hypocaloric and higher-protein weight-loss diet
- Responses to hunger and satiety

These variations provide a comprehensive overview of how the FTO rs9939609 polymorphism affects appetite under different scenarios.

Table 2: The review of the effect of FTO rs9939609 polymorphism on appetite

First Author	Year	Country/ Ethnicity	Sample size(n)	Aim of the study	Effect on FTO rs9939609 Variant	Reference
Jesús G. Ponce-Gonzalez	2023	Spain	73	influence on appetite, hunger, and fat oxidation during exercise	TT genotype showed higher values of hunger and appetite after exercise	13
Fernanda R Goltz	2019	United Kingdom	121	influence of FTO rs9939609 genotype on fasting and postprandial appetite-related hormones and perceived appetite	FTO rs9939609 genotype minimally influences fasting and post-meal appetite and appetite-related blood markers in healthy men and women.	14
James L. Dorling	2019	United Kingdom	202	A-allele would have higher postprandial AG and energy intake than T-allele carriers, but exercise would increase BChE activity and reduce these differences.	AAs had lower fasting butyrylcholinesterase (BChE) activity, higher post-meal AG and AG:DAG ratios, and greater energy intake compared to TTs. exercise can mitigate some appetite-related effects associated with the FTO rs9939609 obesity-linked SNP.	15
Fernanda Cristina Carvalho Mattos Magno	2018	Brazil	70	influence of the FTO rs9939609 polymorphism on appetite, ghrelin, leptin, inflammatory cytokines, and food intake in morbidly obese women	the FTO rs9939609 polymorphism significantly influences postprandial appetite and related hormone levels.	16
Anestis Dougkas	2013	United Kingdom	40	examine the relationship between specific SNP and appetite responses and energy intake in overweight men.	FTO polymorphism are related to the variation in the feeling of fullness and may play a role in the regulation of food intake	17

Tao Huang	2014	Boston	811	examined the interaction between FTO genotype and protein intake on the long-term changes in appetite in a randomized controlled trial.	FTO rs9939609 A allele might obtain more benefits in a reduction of food cravings and appetite by choosing a hypocaloric and higher-protein weight-loss diet.	18
Marcel den Hoed	2009	Netherlands	103	investigated whether postprandial responses in hunger and satiety are associated with the FTO rs9939609 polymorphism.	shows an association between postprandial responses in hunger and satiety with the rs9939609 SNP in FTO, with the TA/AA genotype predisposing individuals to reduced postprandial responses in hunger and satiety.	19

Systematic review

The studies give valuable insights into the complex relationship between the FTO rs9939609 variant and adult appetite regulation.

Post-Exercise Hunger and Appetite:

In a 2023 study, Jesús G. Ponce-Gonzalez investigated the influence of the FTO rs9939609 gene on appetite, hunger, and fat oxidation during exercise among the population of Spain. The results indicated that participants with the TT allele experienced significantly higher levels of hunger ($p = 0.049$) and appetite ($p = 0.043$) after exercise compared to those with the AT allele. This finding highlights the impact of the FTO rs9939609 gene, showing that individuals with the TT allele have greater post-exercise hunger and appetite than those with the AT allele.

Postprandial Appetite-Related Outcomes:

In 2019, Fernanda R. Goltz explored the influence of the FTO rs9939609 genotype on fasting and postprandial appetite-related hormones and perceived appetite in a diverse sample of men and women. His study found that the associations between the FTO rs9939609 genotype and the fasting or postprandial appetite linked effects were weak in healthy individuals in the United Kingdom.

Fernanda Cristina Carvalho Mattos Magno, in 2018, conducted a study among the population of Brazil to evaluate the influence of the FTO rs9939609 polymorphism on appetite, ghrelin, leptin, inflammatory cytokines, and food intake in morbidly obese women. The study found that the postprandial ghrelin levels decreased in AA genotype women, corresponding to lower hunger sensations, while TT and TA genotypes had higher postprandial ghrelin levels. Postprandial leptin levels increased in AA but decreased in TT, with AA individuals experiencing greater satiety. These findings suggest that the FTO rs9939609 polymorphism significantly influences postprandial appetite and related hormone levels.

In 2013, Anestis Dougkas conducted a study in United Kingdom to examine the relationship between FTO rs9939609 SNPs and appetite responses in overweight men. The study found that postprandial fullness ratings were 17.2% lower in A carriers compared to TT homozygotes for the FTO rs9939609 polymorphism ($P= 0.026$). This suggests that the FTO rs9939609 polymorphism is associated with variations in the feeling of fullness, potentially influencing the regulation of food intake.

Marcel den Hoed, in 2009 investigated whether postprandial responses in hunger and satiety are associated with the FTO rs9939609 polymorphism. The study found a significant association between this SNP and postprandial hunger and satiety responses ($P = 0.036$ and $P = 0.050$, respectively) with the population of Netherlands. TA/AA carriers of rs9939609 were more likely to have lower postprandial responses in hunger and satiety compared to TT carriers (dominant and additive models: $P = 0.013$ and $P = 0.020$, respectively). These findings highlight the influence of the FTO rs9939609 polymorphism on appetite regulation.

Impact on Ghrelin and Leptin:

In 2019, James L. Dorling hypothesized that individuals with the obesity-risk A-allele (AAs) would have higher postprandial acylated ghrelin levels and energy intake than those with the low obesity-risk T-allele (TTs). Acylated Ghrelin, often referred to as the "hunger hormone," plays a crucial role in regulating appetite and energy balance.

The study found that AAs had lower fasting BChE activity, higher post-meal AG and AG:DAG ratios, and greater energy intake compared to TTs. However, exercise increased BChE activity and corrected the reduced meal-induced suppression of AG in AAs, without increasing energy intake in either genotype group. BChE is associated with metabolic processes and energy regulation. Lower fasting BChE activity in AAs suggests a metabolic profile that may predispose these individuals to higher energy intake. The study among the

population of United Kingdom found that exercise can increase BChE activity, which helps to normalize AG levels and reduce post-meal hunger.

These results suggest that exercise can mitigate some appetite-related effects associated with the FTO rs9939609 obesity-linked SNP. Exercise was shown to correct the reduced meal-induced suppression of AG in AAs, effectively normalizing hunger signals and potentially curbing excessive energy intake. This finding underscores the importance of physical activity in managing appetite and metabolic health, particularly in individuals with the obesity-risk A-allele.

Protein Intake Interaction:

Tao Huang (2014) explored the interaction between the FTO rs9939609 genotype and protein intake on long-term changes in appetite within a randomized controlled trial. The study found that the A allele of FTO rs9939609 was associated with a greater decrease in food cravings and appetite scores among participants in Boston, US, with high-protein-diet intake, but not among those in the low-protein-diet group. Interestingly, protein intake did not modify the effects of the FTO genotype on other appetite measures. The conclusion suggests that individuals with the FTO rs9939609 A allele may benefit more from a reduction in food cravings and appetite by opting for a hypocaloric and higher-protein weight-loss diet. The A allele was associated with a greater decrease in food cravings and appetite scores among participants with high-protein diet intake.

This suggests that the FTO rs9939609 polymorphism is associated with variations in the feeling of fullness, potentially influencing the regulation of food intake.

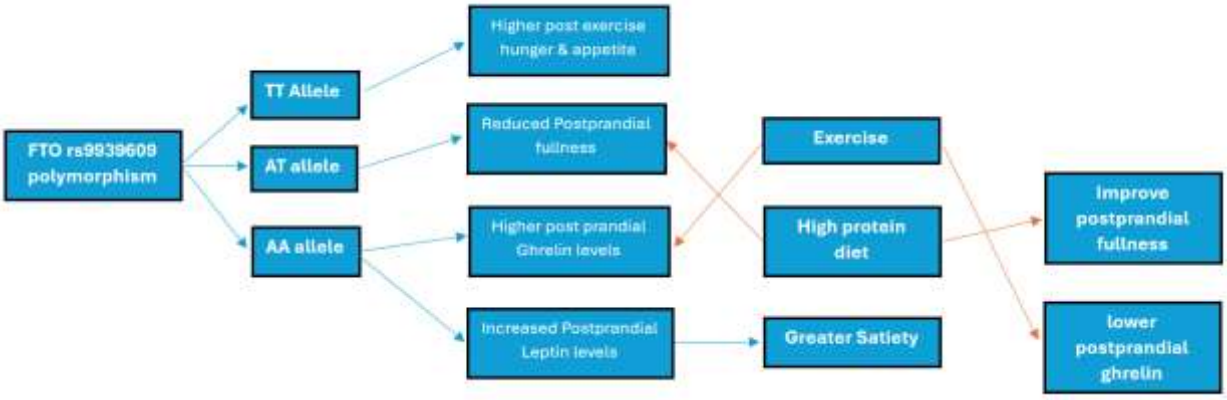

Figure 2 - illustrates the link between the FTO rs9939609 polymorphism and appetite regulation.

The diagram (figure 2) shows the different alleles of the FTO rs9939609 gene (TT, AT, and AA) and their respective impacts on post-exercise hunger, postprandial fullness, ghrelin and leptin levels, and satiety. It also highlights the effects of exercise and high-protein diets on appetite-related outcomes for individuals with specific alleles.

Discussion

The FTO rs9939609 variant has been strongly associated with an increased risk of overweight and obesity in both children and adults. This study suggests that the FTO rs9939609 polymorphism is associated with variations in the feeling of fullness, potentially influencing food intake regulation in adults. Similar studies in children confirm that the FTO rs9939609 polymorphism plays a crucial role in weight gain and obesity through appetitive mechanisms. (20). Jane Wardle, 2008, examined the association between obesity-risk alleles of the FTO gene and habitual appetitive behavior in UK children. The study found that the A allele was linked to increased adiposity and reduced Satiety Responsiveness scores. The conclusion suggests that the common obesity risk allele influences weight gain by affecting appetite (21).

Jennifer A. Emond (2017) investigated whether appetitive traits partially mediated the link between FTO genotype and elevated BMI in a group of US preadolescents. The findings suggest that FTO variants may influence obesity risk through appetite regulation. Considering numerous other genetic loci associated with increased obesity risk, further research is warranted to explore how additional genetic variants influence appetitive traits (22).

The relationship between postprandial acylated ghrelin levels and appetite is crucial in understanding the FTO rs9939609 variant's impact on hunger regulation. Higher post-meal AG levels in individuals with the A-allele lead to stronger hunger signals, increased energy intake, and potentially greater challenges in managing weight. Exercise is beneficial by modulating these hormonal responses, highlighting the importance of incorporating physical activity into lifestyle interventions for individuals with this genetic variant.

Overall, these findings underscore the significant impact of the FTO rs9939609 polymorphism on various aspects of appetite regulation, particularly highlighting the importance of tailored dietary and exercise interventions in managing hunger and satiety among individuals with different genotypes. Understanding these genotype-specific effects can inform personalized dietary and lifestyle interventions to manage appetite and prevent obesity, particularly in individuals with susceptibility alleles like the A allele.

Conclusion

The FTO rs9939609 polymorphism significantly influences appetite regulation in adults. Variations in

post-exercise hunger, postprandial satiety, ghrelin, and leptin levels were observed across different genotypes. Notably, the A allele was associated with altered appetite responses, which could be mitigated by exercise and a high-protein diet. The FTO rs9939609 variant seems to be associated with variations in appetite regulation, but the influence may depend on factors like exercise and dietary protein intake. Further research is needed to explore these associations in diverse populations and under different environmental conditions to fully elucidate the impact of the FTO variant on appetite regulation.

TABLES

1. Major Gut and Brain hormones in Appetite regulation
2. The review of the effect of FTO rs9939609 polymorphism on appetite

FIGURES

1. PRISMA flow diagram showing the screening process for the FTO rs9939609 polymorphism on appetite
2. Illustrates the link between the FTO rs9939609 polymorphism and appetite regulation.

ABBREVIATIONS

FTO – Fat Mass and Obesity-Associated Gene
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
AG - Acylated Ghrelin
SNP – Single Nucleotide Polymorphism
PYY (3-36) - Peptide YY (3-36)
PP - Pancreatic Polypeptide
GLP-1- Glucagon-Like Peptide-1
GLP-2 - Glucagon-Like Peptide-2
OXM - Oxyntomodulin
CCK - Cholecystokinin
NPY: Neuropeptide Y
AgRP: Agouti-related peptide
CART: Cocaine- and amphetamine-regulated transcript
α-MSH: Alpha-melanocyte-stimulating hormone
EUFIC - The European Food Information Council
BChE - Butyrylcholinesterase

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