Genetic Variants in the FTO Gene and Their Association with Type 2 Diabetes Risk - A Meta-Analysis

Soumya Abraham [1], Swati Paliwal [2], Mohammad Chand Jamali [3*]

Abstract

Background: The global prevalence of type 2 diabetes mellitus (T2DM) is projected to rise significantly, with an estimated increase from 536.6 million cases in 2021 to 783.2 million by 2045. Genetic predisposition plays a crucial role in T2DM susceptibility, with the FTO gene, particularly the single nucleotide polymorphism (SNP) rs11076023, being linked to the disease. Methods: A comprehensive literature search was conducted using PubMed, Scopus, and Google Scholar to identify relevant studies that examined the association between the FTO gene rs11076023 polymorphism and T2DM. Case-control studies published until December 31, 2023, were included, adhering to PRISMA guidelines. Data extraction was performed systematically, and statistical analysis was conducted using MetaGenyo to assess the association across various genetic models. Results: The meta-analysis encompassed three studies involving 3,887 participants (1,985 cases and 1,902 controls). The findings demonstrated a significant association between the T allele of rs11076023 and increased T2DM risk, particularly within the recessive genetic model (TT vs. TA + AA), indicating a higher susceptibility among individuals with the TT genotype. In contrast, the over-dominant model suggested a protective effect associated with the TA heterozygous genotype. Notable heterogeneity was observed across the studies, and sensitivity analyses confirmed the robustness of the associations. Conclusion: This meta-analysis highlights the FTO gene rs11076023 polymorphism as a significant genetic factor influencing T2DM susceptibility, particularly within certain population subsets. The findings underscore the complexity of T2DM risk, emphasizing the interplay between genetic factors and lifestyle choices. Further research with larger, diverse populations is necessary to validate these associations and explore the underlying biological mechanisms, which may inform targeted interventions for T2DM prevention and management.

Keywords: Type 2 Diabetes, FTO gene, SNP rs11076023, genetic association, population-specific risk

Significance | This study elucidates the genetic contributions to T2DM, highlighting the FTO gene's variants and their implications for precision medicine approaches.

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Editor Md Shamsuddin sultan khan And accepted by the Editorial Board October 12, 2024 (received for review August 11, 2024)

1. Introduction

The global burden of type 2 diabetes mellitus (T2DM) is on the rise, with projections by the International Diabetes Federation (IDF) estimating an increase from 536.6 million cases in 2021 to 783.2 million by 2045—a 46% surge (IDF Atlas, 10th edition, 2021). T2DM development is driven by a complex interaction of genetic, behavioral, and environmental factors. Twin and family studies suggest that genetics account for 25% to 72% of the risk for T2DM, revealing the substantial influence of heredity on the disease (Florez, Udler, & Hanson, 2018). Over 100 gene regions have been

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Please Cite This:
Soumya Abraham, Swati Paliwal, Mohammad Chand Jamali (2024). "Genetic Variants in the FTO Gene and Their Association with Type 2 Diabetes Risk - A Meta-Analysis", Journal of Angiotherapy, 8(10),1-10,10000.

linked to T2DM, with variations contributing to different risk profiles. A particularly well-studied gene in relation to T2DM and obesity is the FTO gene, which initially emerged as a susceptibility gene for obesity and was later linked to T2DM, specifically in populations with high body mass index (BMI) (Loos & Yeo, 2021). The FTO gene encodes for the enzyme Beta-Ketoglutarate Dependent Dioxygenase, a protein involved in nucleic acid demethylation. This gene is mainly expressed in the hypothalamus and has been shown to influence energy balance and lipolysis regulation, affecting metabolic processes relevant to T2DM risk (NCBI, 2023). Certain variations in the FTO gene, such as the single nucleotide polymorphism (SNP) rs11076023, have shown associations with metabolic traits including obesity, insulin resistance, and altered lipid profiles, factors that are closely linked with T2DM risk (Frayling et al., 2007).

The role of FTO gene variants extends beyond susceptibility, as some polymorphisms may offer protective effects against T2DM. For instance, in various populations, including Caucasians, Finns, and Sikhs, the PPARG gene variant Ala12 has been associated with reduced plasma glucose levels, offering insight into how genetic variations can mediate disease risk even in populations with predisposition due to factors such as high BMI (Scott et al., 2007). Research from the Broad Institute and Massachusetts General Hospital also highlights that specific gene variants can mitigate T2DM risk in individuals with obesity, suggesting potential for gene-based interventions.

The SNP rs11076023 in the FTO gene has been investigated for its role in T2DM susceptibility in different populations. In South Indian populations, this polymorphism was observed to have a protective association against T2DM, whereas in the Chinese population, no significant association with T2DM was found, although there was a link with BMI (Ramya et al., 2011; Chang et al., 2008). Similarly, studies in the Iraqi population identified the TT homozygous genotype as protective against T2DM (Younus et al., 2020). Such findings illustrate the genetic heterogeneity in T2DM susceptibility across different ethnic groups, emphasizing the role of population-specific genetic studies.

Further meta-analyses of case-control studies using the PRISMA methodology have focused on understanding the association of the FTO gene variation rs11076023 with T2DM risk. Through tools like MetaGenyo, researchers analyze data for statistical associations, evaluating odds ratios and confidence intervals across genetic models. These studies reinforce that the genetic landscape of T2DM is complex, with multiple gene-environment interactions shaping risk. Understanding the genetic basis of T2DM, particularly through SNPs like rs11076023, can guide precision medicine approaches in diabetes care, potentially leading to targeted interventions based on individual genetic profiles (MetaGenyo, 2023).

2. Methodology

2.1 Publication Search Strategy

A comprehensive literature search was conducted using PubMed, Scopus, and Google Scholar to identify studies examining the association between the FTO gene rs11076023 polymorphism and Type 2 Diabetes (T2D). The search terms "rs11076023 AND Type 2 Diabetes" were employed, retrieving relevant studies up to December 31, 2023. Only publications that directly investigated the relationship between T2D and FTO gene variation rs11076023 were selected for meta-analysis.

2.2 Eligibility Criteria

The inclusion and exclusion criteria for the meta-analysis were established in line with PRISMA guidelines. Studies included had to meet the following conditions:

Population: Adult participants aged 18 years or older, of any gender, and human subjects only.

Study Design: Only case-control studies adhering to Hardy-Weinberg Equilibrium (HWE) and reporting genotype frequencies, odds ratios (OR), or 95% confidence intervals (CI) were considered.

Language and Date: Publications were restricted to those available in English up to the set cutoff date. Studies were excluded if they were conducted in non-human models, non-English languages, or consisted of reviews, meta-analyses, or in silico studies. Studies with specific health conditions, nutritional interventions, case reports, animal models, and incomplete data were also excluded. Duplicate publications and studies not meeting eligibility criteria were excluded based on title and abstract screening.

2.3 Data Extraction

Data extraction followed a systematic protocol. After filtering out duplicates and irrelevant studies, the titles and abstracts were initially reviewed to confirm alignment with inclusion criteria. In the final screening phase, full-text articles were thoroughly assessed, and qualifying studies were selected for meta-analysis. The following data were extracted from each study: the first author's name, publication year, country of origin, participant numbers, body mass index (BMI), age (of cases and controls), the polymorphism investigated, and the distribution of cases and controls.

2.4 Statistical Analysis

MetaGenyo, an online tool optimized for Genetic Association Studies (GAS), was utilized for statistical analysis (https://metagenyo.genyo.es/). Study data, including author names, publication year, country, age, and BMI subgroup information, were uploaded in Excel format. MetaGenyo facilitated various analytical models, assessing allele contrast, recessive, dominant, and over-dominant genetic models, as well as genotype comparisons. The DerSimonian-Laird random-effects model and the fixed-effect estimation approach (Inverse variance) were used to calculate

pooled odds ratios (ORs) and 95% confidence intervals (CIs), which were visualized through forest plots.

Heterogeneity across studies was assessed using the I^2 statistic, with p-values less than 0.10 indicating significant heterogeneity. An I^2 value above 50%, particularly above 75%, suggested substantial heterogeneity—a common finding in genetic association studies. Sensitivity analyses were conducted to confirm result consistency, employing funnel plots and Egger's test to detect any publication bias.

To account for multiple testing, the False Discovery Rate (FDR) adjustment was applied to HWE p-values, rendering adjusted p-values in the range of a significant threshold of 0.05 or 0.001. This statistical adjustment helped control for false positives and ensured the reliability of the findings.

3. Results

The present meta-analysis provides compelling evidence supporting the association between the FTO rs11076023 SNP and T2D risk across Asian populations. The findings underscore the significance of the TT genotype, which appears to confer a higher susceptibility to T2D compared to other genotypes, particularly in recessive and allelic models.

3.1 Data Screening and Extraction

The current meta-analysis focused on the single nucleotide polymorphism (SNP) rs11076023 located in the non-translated region of the FTO gene, given its limited exploration in existing literature concerning Type 2 Diabetes (T2D). An extensive search across PubMed, Scopus, and Google Scholar yielded 45 potentially relevant publications. After the initial data gathering, four duplicate articles were removed. A preliminary screening based on title and abstract further excluded 31 articles due to ineligibility. Following a detailed examination of full-text articles, seven additional studies were deemed unsuitable, resulting in a final selection of three studies eligible for meta-analysis.

The PRISMA flow chart (Figure 2) illustrates the systematic approach taken to select and screen studies, outlining the various stages of the literature search process. Among the 45 articles, 42 were excluded for reasons such as duplication, focus on epigenetic studies, reviews, animal studies, non-English languages, nutritional research, and other unrelated health conditions involving children or adolescents. The selected papers consisted solely of case-control studies, culminating in a combined sample size of 3,887 participants, with 1,985 cases and 1,902 controls.

3.2 Characteristics of the Eligible Studies

The main characteristics of the selected studies are summarized in Table 1. All included studies were conducted in Asian countries: China, India, and Iraq. The mean age of participants was 55.6 years for cases and 53.37 years for controls. The mean body mass index (BMI) for cases ranged from 24.66 to 34.11 kg/m², while for controls, the BMI varied from 23.63 to 34.08 kg/m².

3.3 Meta-analysis of FTO rs11076023 Variant

The analysis targeted the impact of FTO gene SNP rs11076023 polymorphisms on T2D across diverse population datasets. The results from these studies were synthesized to assess the association between the genetic variant and the likelihood of developing T2D.

3.4 Hardy-Weinberg Equilibrium

The study by Laith A. Younus (2020) reported a mild deviation from Hardy-Weinberg Equilibrium (HWE) with a p-value of 0.0349, indicating that the distribution of genotypes was not in equilibrium, likely due to the small sample size. The authors noted that the sample size was derived from previous findings, with limited data available from resources like www.Hapmap.org. This study provided foundational data that could enhance genetic power in future investigations of rs11076023.

Conversely, Kandaswamy Ramya's 2011 study in India found no significant deviation from HWE, suggesting that genotype distributions were consistent with expected frequencies. However, a study by Yi-Cheng Chang (2008) in China indicated a significant deviation from HWE (HWE p-value = 0), necessitating further examination of potential underlying causes. The results of HWE testing were summarized in Table 2, along with the adjusted p-values for each study included in the meta-analysis.

3.5 Test of Association

The results indicated a significant association between the T allele and increased risk of developing T2D, particularly for the TT genotype. In the allelic contrast model (T vs. A), the fixed-effect model revealed a statistically significant association (p-value = 0.043) with an odds ratio (OR) of 1.1363 (95% CI [1.0370; 1.2450]), suggesting that individuals carrying the T allele have a slightly elevated risk of T2D compared to those with the A allele. However, in the random-effects model, the OR was 1.1849 (95% CI [0.7100; 1.9775]), and the p-value was not significant (p-value = 0.516), indicating potential heterogeneity among the studies.

For the recessive model (TT vs. TA + AA), both the fixed-effect model (OR: 1.3473, 95% CI [1.1193; 1.6218], p-value: 0.00163, adjusted p-value: 0.011381) and the random-effects model (OR: 1.9899, 95% CI [0.4302; 9.2039], p-value: 0.379) demonstrated a statistically significant association, suggesting that individuals with the TT genotype are at higher risk of T2D compared to those with TA or AA genotypes.

In the dominant model (TT + TA vs. AA), no significant association was found in either the fixed-effect model (OR: 0.9491, 95% CI [0.8235; 1.0939], p-value: 0.471) or the random-effects model (OR: 0.9931, 95% CI [0.7405; 1.3321], p-value: 0.963). This implies that the combined TT and TA genotypes do not significantly impact T2D risk compared to the AA genotype (Figure 3).

5' upstream 30bp	(allele seq)	3' downstream 30bp
ATACAAATGAAGCACTTCTAGCAGGCGGAG	(A)	TTCCCTTTGTTTCTGATCTGGTAAATGCGG
ATACAAATGAAGCACTTCTAGCAGGCGGAG	(T)	TTCCCTTTGTTTCTGATCTGGTAAATGCGG

Figure 1. Observed allele of the rs11076023 from GWAS Central

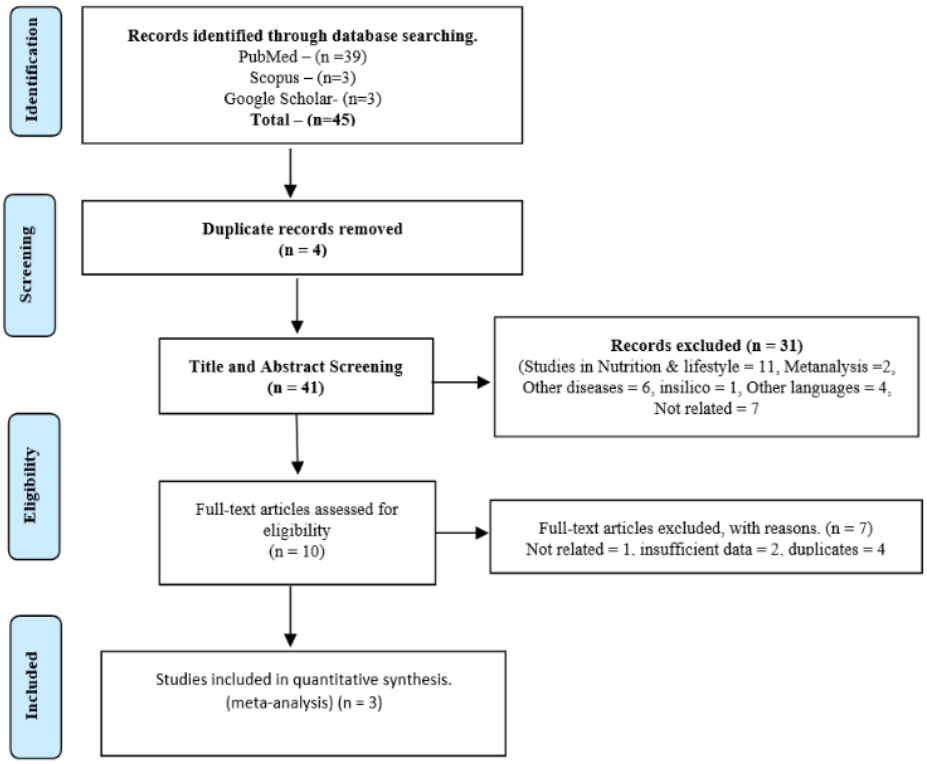

Figure 2. PRISMA flow diagram showing the selection process for the FTO gene SNP rs11076023 and T2D

Table 1. Characteristics of the studies included in the meta-analysis

			Sample Size (n)		Mean Age(n)		Mean BMI (n)		Genotype					
First Author	Year	Country	Cases	Control	Cases	Control	Cases	Control	AA cases	AT cases	TT cases	AA Control	AT Control	TT Control
Laith A. Younus	2020	Iraq	400	400	55.77	55.74	34.11	34.08	175	195	30	180	190	30
K. Ramya	2011	India	851	1001	51	41	25.3	23.4	256	424	171	250	521	230
Yi-Cheng Chang	2008	China	759	784	60.03	63.37	24.66	23.63	140	351	243	114	362	25

Table 2. HW-P. Value and HWE-adjusted. P.value of the studies

First Author	Year	Country	AA cases	AT cases	TT cases	AA Control	AT Control	TT Control	HW P value	HW adjusted P value
Laith A. Younus	2020	Iraq	175	195	30	180	190	30	0.0349	0.0524
K Ramya	2011	India	256	424	171	250	521	230	0.1905	0.1905
Yi-Cheng Chang	2008	China	140	351	243	114	362	25	0	0

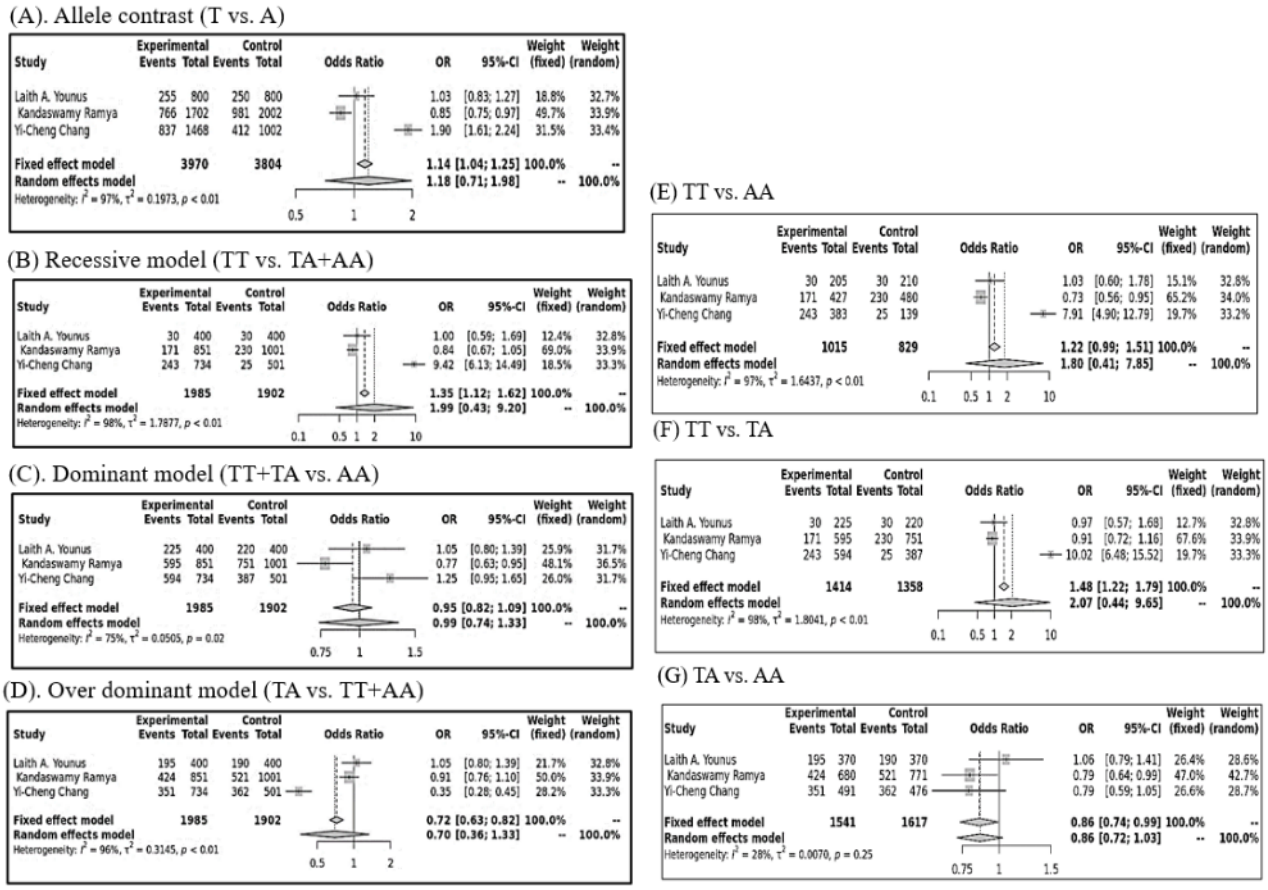

Figure 3. Forest plot for the association of FTO Gene Variant rs11076023 on Type 2 Diabetes in (A) allelic model (B) Recessive Mode, (C) dominant model, (D Over dominant model, and comparisons (E) TT vs. AA, (F) TT vs. TA, (G) TA vs AA

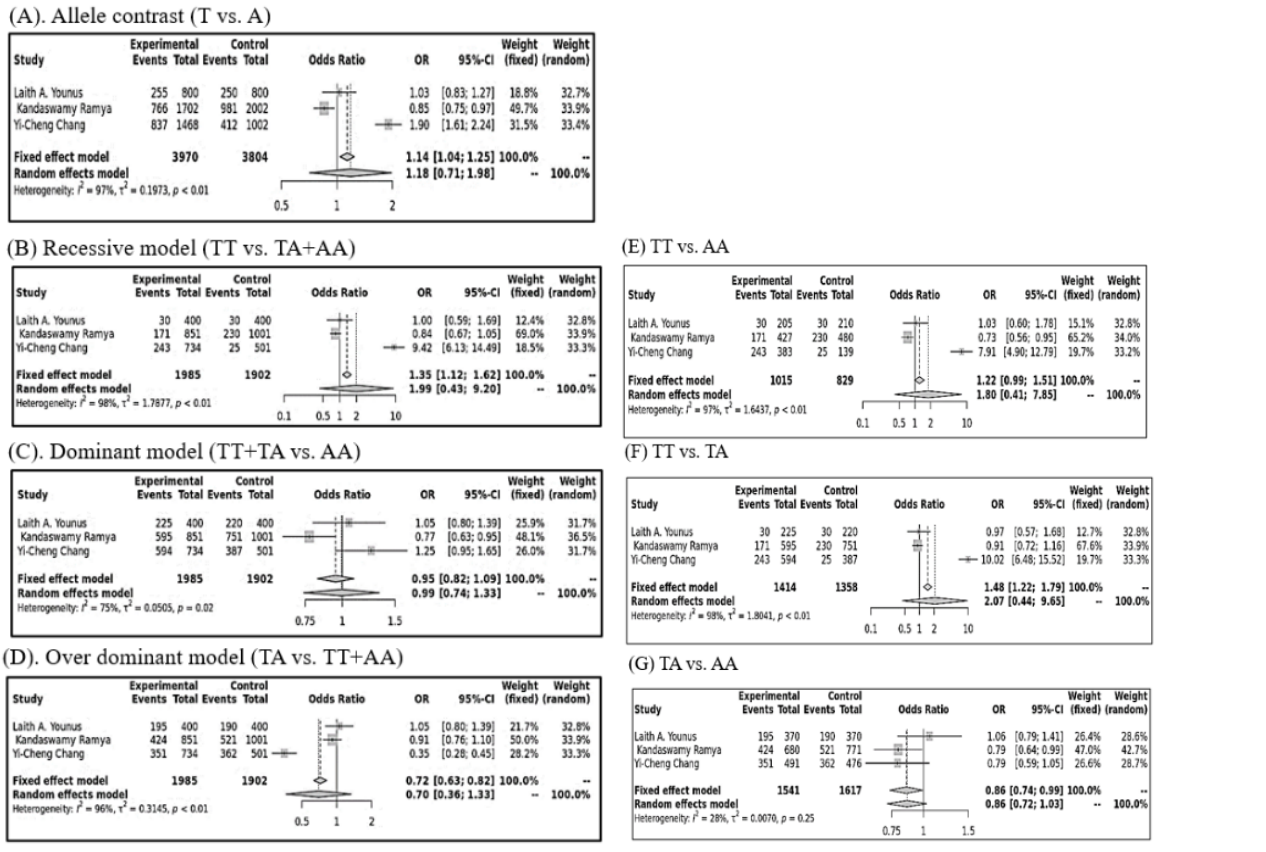

Figure 5. Sensitivity Forest plot of the association FTO Gene Variant rs11076023 on Type 2 Diabetes in (A) allelic model (B) Recessive Mode, (C) dominant model, (D Over dominant model and comparisons (E) TT vs. AA, (F) TT vs. TA, (G) TA vs AA

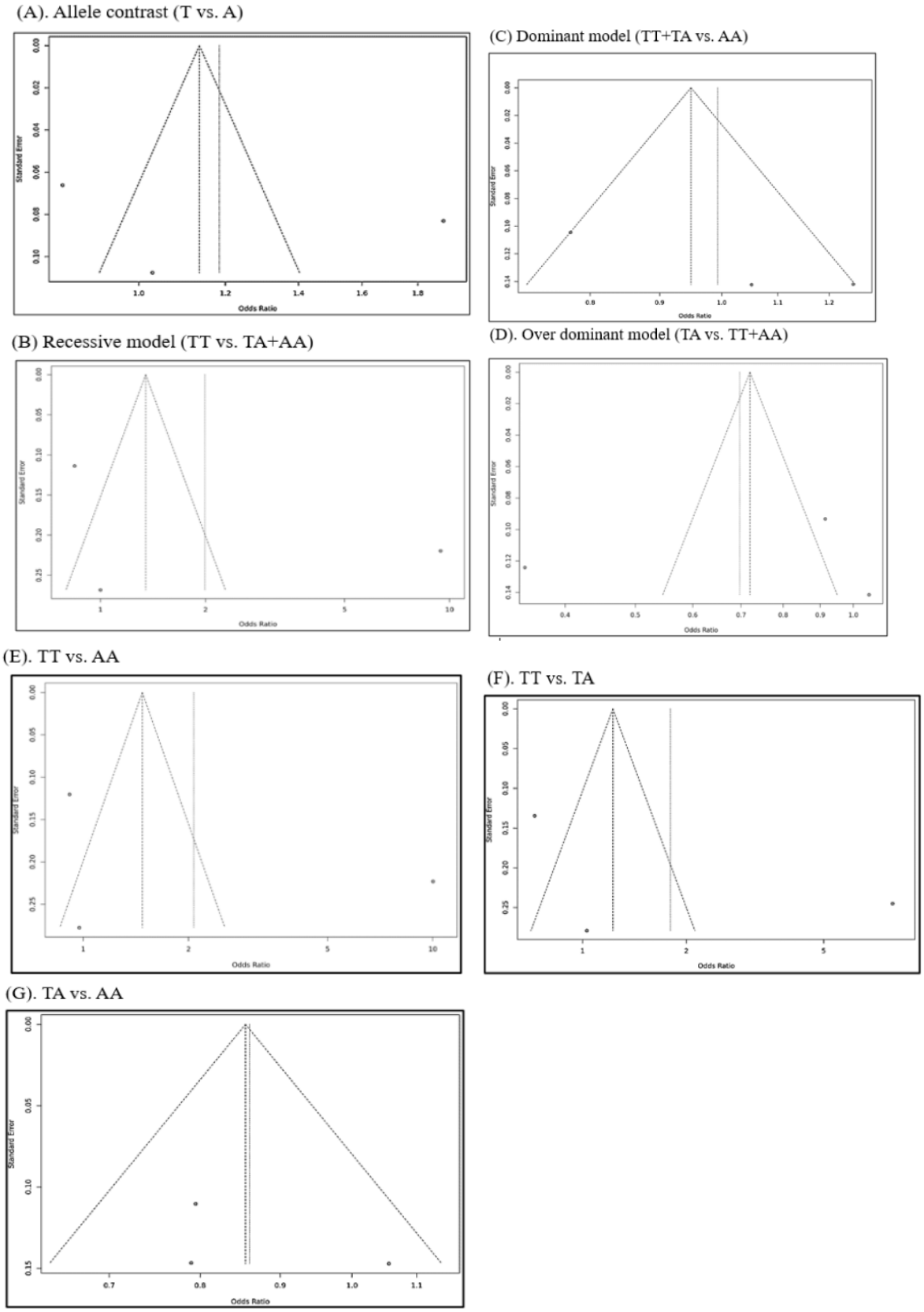

Figure 4: Funnel plots showing the Publication bias: the association FTO Gene Variant rs11076023 on Type 2 Diabetes in (A) allelic model (B) Recessive Mode, (C) dominant model, (D Over dominant model and comparisons (E) TT vs. AA, (F) TT vs. TA, (G) TA vs AA.

Table 3. Pooled analysis values for test of association, test of heterogeneity, publication bias and sensitivity analysis for different genetic models

Genetic Model	Study	Number of studies	Model	Test of association				Test of heterogeneity					Publication bias	Sensitivity	
				OR	95% CI	P-value	Adjusted *P* -value	tau^2	H	I^2	Q	*P* -value	*P* -value (Egger's test)	OR	95% CI
Allele contrast	Overall	3	Fixed effect	1.1363	[1.0370; 1.2450]	6.14E-03	0.042992	0.2	5.39	0.97	58.1	0.00	0.7671	1.14	[1.04;1.29]
(T vs. A)			Random effect	1.1849	[0.7100; 1.9775]	0.51605	1								
Recessive model	Overall	3	Fixed effect	1.3473	[1.1193; 1.6218]	1.63E-03	0.011381	1.79	6.95	0.98	96.6	0.00	0.6008	1.35	[1.12;1.62]
(TT vs. TA+AA)			Random effect	1.9899	[0.4302; 9.2039]	3.79E-01	1								
Dominant model	Overall	3	Fixed effect	0.9491	[0.8235; 1.0939]	4.71E-01	1	0.05	2.01	0.75	8.1	0.02	0.1981	0.95	[0.82;1.09]
(TT+TA vs. AA)			Random effect	0.9931	[0.7405; 1.3321]	9.63E-01	1								
Overdominant model	Overall	3	Fixed effect	0.7199	[0.6326; 0.8193]	6.36E-07	0.000004	0.31	4.85	0.96	46.99	0.00	0.8397	0.72	[0.63;0.82]
(TA vs. TT+AA)			Random effect	0.6969	[0.3641; 1.3339]	0.275629	1								
TT vs. AA	Overall	3	Fixed effect	1.2242	[0.9894; 1.5147]	6.26E-02	0.438363	1.64	6.06	0.97	73.5	0.00	0.5484	1.22	[0.99;1.51]
			Random effect	1.7978	[0.4120; 7.8457]	0.435229	1								
TT vs. TA	Overall	3	Fixed effect	1.4759	[1.2157; 1.7916]	8.34E-05	0.000584	1.8	6.78	0.98	91.94	0.00	0.6411	1.48	[1.22;1.79]
			Random effect	2.0708	[0.4442; 9.6541]	0.354058	1								
TA vs. AA	Overall	3	Fixed effect	0.8552	[0.7373; 0.9919]	3.86E-02	0.270498	0.01	1.18	0.28	2.78	0.25	0.6262	0.86	[0.74;0.99]
			Random effect	0.8603	[0.7204; 1.0274]	0.096642	0.676496								

The over-dominant model (TA vs. TT + AA) indicated a significant association in both the fixed-effect model (OR: 0.7199, 95% CI [0.6326; 0.8193], p-value: 6.36E-07, adjusted p-value: 0.000004) and the random-effects model (OR: 0.6969, 95% CI [0.3641; 1.3339], p-value: 0.276). The lower OR suggests that the TA heterozygous genotype may confer protection against T2D when compared to the TT and AA genotypes.

When examining the TT and AA genotypes individually, neither the fixed-effect nor random-effect models revealed a statistically significant association (OR: 1.2242, 95% CI: [0.9894; 1.5147], p-value: 0.0626, and OR: 1.7978, 95% CI: [0.4120; 7.8457], p-value: 0.4352, respectively). Individuals with the TT genotype were more likely to develop T2D than those with the TA genotype, as indicated by both fixed-effect and random-effect models. However, no significant association was shown in the random-effects model when comparing the TT to the AA genotype.

A summary of the genetic models indicating associations between the FTO gene variation rs11076023 and T2D is depicted in Figure 3's forest plot. Sections A, B, C, and D illustrate the results for different inheritance models: allelic, recessive, dominant, and over-dominant. Additionally, comparisons between TT and AA genotypes, TT and TA genotypes, and TA vs. AA are included in the visual presentation.

3.6 Heterogeneity Assessment

Heterogeneity was assessed for each genetic model. In the allelic contrast model, significant heterogeneity was observed, with a p-value of 0.00 and an I^2 value of 58.1%. The recessive model exhibited high heterogeneity as well, with a p-value of 0.00 and an I^2 value of 96.6%. Conversely, the dominant model showed low to moderate heterogeneity, with a p-value of 0.02 and an I^2 value of 8.1%. The over-dominant model also demonstrated considerable heterogeneity, with a p-value of 0.00 and an I^2 value of 46.99%. Specific genotype comparisons (TT vs. AA, TT vs. TA, TA vs. AA) revealed substantial heterogeneity, particularly in the recessive model and genotype comparisons involving TT vs. AA and TT vs. TA.

3.7 Publication Bias

To assess potential publication bias, Egger's test was conducted, revealing high p-values across all genetic models: Allelic Contrast (p-value: 0.7671), Recessive Model (p-value: 0.6008), Dominant Model (p-value: 0.1981), Overdominant Model (p-value: 0.8397), and comparisons (TT vs. AA, p-value: 0.5484; TT vs. TA, p-value: 0.6411; TA vs. AA, p-value: 0.6262). These findings suggest no significant evidence of publication bias within the studies included in the meta-analysis. Figure 4 presents funnel plots illustrating symmetry, further corroborating the absence of publication bias.

3.8 Sensitivity Analysis

The results of the sensitivity analysis indicated that the relationships observed remained stable and robust across various genetic models. Specifically, the sensitivity analysis for the allelic contrast model yielded an OR of 1.14 (95% CI [1.04; 1.29]) and for the recessive model, an OR of 1.35 (95% CI [1.12; 1.62]), confirming the significant association. However, neither the original nor sensitivity analyses found a statistically significant correlation in the dominant model (TT + TA vs. AA), with both the main analysis OR of 0.9491 and the sensitivity analysis OR of 0.95 (95% CI [0.8235; 1.0939]) indicating a lack of meaningful connection.

For the over-dominant model (TA vs. TT + AA), both the sensitivity analysis (OR: 0.72, 95% CI [0.63; 0.82]) and the main analysis (OR: 0.7199, 95% CI [0.6326; 0.8193]) supported a significant protective association, even when individual studies were omitted, suggesting potential sensitivity to certain studies. The results for genotype comparisons (TT vs. AA, TT vs. TA, TA vs. AA) indicated that the sensitivity analysis maintained the primary findings, emphasizing the robustness of the associations found.

4. Discussion

The findings of this meta-analysis underscore the potential significance of the FTO gene rs11076023 polymorphism in the context of type 2 diabetes (T2D), particularly highlighting the associations revealed by the Allele Contrast and Recessive models. These models suggest a substantial link between the T allele and the TT genotype with increased T2D risk. In contrast, the Dominant Model and specific Genotype Comparisons (TT vs. AA, TT vs. TA) did not yield statistically significant associations, indicating that the relationship may be more nuanced than initially presumed. Notably, the Overdominant Model revealed a protective effect associated with the TA heterozygous genotype, suggesting that individuals carrying this genotype may have a reduced risk of developing T2D compared to those with either the TT or AA homozygous genotypes.

The interaction between genetic predisposition and environmental factors is critical in understanding T2D risk. As highlighted by Vimaleswaran (2016), dietary habits, particularly the intake of dietary fiber, can influence obesity-related characteristics and T2D risk among the Indian population. This study points to the potential mediating role of dietary factors on the genetic association between the FTO gene variant and T2D, suggesting a complex interplay where both genetics and lifestyle contribute to disease susceptibility. These findings align with the broader literature, which emphasizes that T2D is multifactorial, resulting from a combination of genetic variations, environmental exposures, and lifestyle choices.

However, it is essential to acknowledge the limitations inherent in this meta-analysis. The relatively small sample size across the three studies analyzed restricts the generalizability of the results. Larger and more diverse populations are necessary to validate these findings and to explore the extent to which the FTO rs11076023 polymorphism influences T2D risk in different demographic

contexts. Additionally, the specific biological mechanisms by which FTO gene variations contribute to T2D susceptibility remain poorly defined in the existing literature. Future studies should aim to elucidate these mechanisms, focusing on how the FTO gene influences metabolic pathways and interacts with lifestyle factors, such as diet and physical activity.

Furthermore, while our results suggest a potential protective role for the TA heterozygous genotype, it is crucial to approach these findings with caution. The implications of this genetic variant may not be applicable across different populations or ethnic groups, emphasizing the need for further research that accounts for population-specific genetic backgrounds and environmental influences. Longitudinal studies are particularly warranted to assess the long-term effects of the FTO rs11076023 variant on T2D risk and to determine whether the observed associations persist over time.

In summary, the current analysis contributes valuable insights into the relationship between the FTO gene rs11076023 polymorphism and T2D, highlighting significant associations within certain genetic models while also pointing to the complexity of this relationship in light of dietary and environmental factors. Continued research in this area is essential for developing targeted prevention and intervention strategies for T2D, ultimately aiming to mitigate the impact of this increasingly prevalent condition.

5. Conclusion

In conclusion, this meta-analysis reveals a significant association between the FTO gene polymorphism rs11076023 and the risk of developing type 2 diabetes mellitus (T2DM), particularly through the recessive and allelic models. The findings highlight the elevated risk linked to the TT genotype while suggesting a protective effect associated with the TA heterozygous genotype. These results underscore the intricate interplay of genetic predisposition and environmental factors in T2DM susceptibility, emphasizing that dietary habits and lifestyle choices also play critical roles. However, the small sample size and the limited diversity of the studies analyzed warrant caution in generalizing these findings. Future research should focus on larger, more heterogeneous populations to confirm these associations and explore the underlying biological mechanisms connecting FTO variations to T2DM. Ultimately, understanding these dynamics will be vital for developing personalized interventions aimed at reducing the global burden of T2DM.

Author contributions

S.A. and S.P. contributed to the conceptualization and design of the study. M.C.J. was responsible for data analysis, manuscript drafting, and provided critical revisions. All authors reviewed and approved the final version of the manuscript.

Acknowledgment

The authors were grateful to their department.

Competing financial interests

The authors have no conflict of interest.

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