Systematic Review/Meta-analysis

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Lack of association of the alpha-ketoglutarate-dependent dioxygenase (FTO) gene polymorphisms with pulmonary tuberculosis risk: a systematic review and meta-analysis

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Objective: Our meta-analysis aims to explore the association of two single nucleotide variants; rs9939609 and rs8050136, within the FTO gene with risk of pulmonary tuberculosis (PTB).

Methods: The association of two single nucleotide variants with PTB in three genetic models was evaluated using pooled odds ratios (ORs) with 95% CIs.

Results: No significant association was observed between the rs9939609 polymorphism and PTB when assuming an allelic model (OR: 1.10; 95% CI: 0.85–1.41; $P=0.47$; $I^2 = 64.98\%$), a recessive model (OR: 2.04; 95% CI: 0.87–4.77; $P=0.10$; $I^2 = 67.18\%$), or a dominant model (OR: 0.96; 95% CI: 0.83–1.11; $P=0.56$; $I^2 = 27.45\%$). Likewise, no association was observed between rs8050136 polymorphism and PTB when assuming allelic model (OR: 1.17; 95% CI: 0.87–1.58; $P=0.31$; $I^2 = 64.20\%$) or recessive model (OR: 1.04; 95% CI: 0.32–3.38; $P=0.95$; $I^2 = 68.82\%$) or dominant model (OR: 1.22; 95% CI: 0.87–1.71; $P=0.26$; $I^2 = 58.69\%$).

Conclusion: There might be no association between the rs9939609 and rs8050136 variants in the FTO gene, and the risk of PTB.

Keywords: FTO gene, polymorphism, rs8050136, rs9939609, single nucleotide variant, tuberculosis

Introduction

Tuberculosis (TB) affected about 9.9 million people and caused about 1.3 million deaths globally in 2020. South-East Asia and Africa contribute to a large number of TB cases every year. TB is an infectious disease caused by *Mycobacterium* species that can potentially affect virtually every human body system. Even though a quarter of the global population is estimated to have been infected with TB bacteria, most people will not develop the disease. The infection may be cleared up or stay latent in most affected individuals. The clinical appearance of active TB disease has been associated with multiple risk factors. The presence of an immunocompromised state in an individual due to any underlying condition is one of the risk factors for development of active disease. HIV infection, undernutrition, diabetes, smoking and alcohol consumption are the most common risk factors for TB[1]. Studies have shown that the underweight individuals were 4.96 times more likely to suffer from TB than individuals with normal BMI[2]. On the contrary, studies have also reported that overweight and obesity have been linked with a decrease in the risk of developing TB in many studies[2,3]. Although obesity is frequently associated with many non-communicable diseases, the literature has also described the relationship with many infectious diseases, such as community-acquired tuberculosis, influenza, coxsackievirus and Helicobacter pylori[4].

HIGHLIGHTS

- No significant association was observed between the rs9939609 polymorphism and pulmonary tuberculosis (PTB) when assuming an allelic model or recessive model or a dominant model.
- No significant association was observed between the rs8050136 polymorphism and PTB when assuming an allelic model or recessive model or a dominant model.
- Haplotypes of FTO gene might play a role in risk of development of PTB.

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Obesity is influenced by the gene *FTO* (alpha-ketoglutarate-dependent dioxygenase, Gene 79068, previously named fat mass and obesity associated) in various populations[5,6]. The *FTO* gene, located on chromosome 16q12.2 in the human genome, encodes a 2-oxoglutarate (2-OG) Fe (II)-dependent AlkB family dioxygenase, with a total length of 410.50 kb, including nine exons and eight introns (https://www.uniprot.org/uniprotkb/Q9C0B1/entry). FTO proteins are widely involved in adipogenesis and tumorigenesis through m6A-dependent demethylase activity, which influences several mRNA processing events[7,8]. In the *FTO* gene, the two single nucleotide variants (SNVs), rs9939609 and rs8050136, were significantly associated with obesity in different populations[5,9–13]. Since obesity and the risk of infectious diseases have been well established, and it has been speculated that the *FTO* gene polymorphisms might also play important roles in the risk of pulmonary TB (PTB). The two SNVs (rs9939609 and rs8050136) of the *FTO* gene have been studied in association with the risk of development of TB by some recent studies. Our meta-analysis aims to assess the association of two common *FTO* polymorphisms with PTB.

Materials and methods

Ethical compliance

All collected data in our meta-analysis were extracted from the published studies, and hence there is no ethical issue. The current study was conducted abiding by the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14]. The PRISMA checklist, Supplemental Digital Content 1, http://links.lww.com/MS9/A214 has been completed and provided. The meta-analysis was registered prospectively at PROSPERO. The article has been assessed using AMSTAR 2 checklist, Supplemental Digital Content 2, http://links.lww.com/MS9/A217 which showed the review being a moderate quality.

Search strategy

A comprehensive literature search strategy was used to review the literature in PubMed/MEDLINE, Embase, Google Scholar and Web of Science databases from inception to January 2023. The relevant publications were identified using the following keywords: "fat mass and obesity-associated gene", "*FTO*", "tuberculosis", "polymorphism", "mutation", "variant", "gene", "genotype", "SNP", "SNV", "rs9939609", "rs8050136" and "allele". The titles and abstracts were screened, and the full text of all the papers that could possibly meet the inclusion criteria were obtained. The reference list of the published original articles and previous reviews were also scanned for more relevant studies that could have been missed in the initial database search. Two authors screened and retrieved reports and also excluded irrelevant studies. The authors of selected studies were contacted via Researchgate and e-mail to obtain the full-text articles whenever necessary. A consensus among all the authors solved any uncertainty about the eligibility of these studies. The details of search startegy used in the literature review are provided in Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A216.

Eligibility criteria

We included studies that were conducted on human subjects and published in the English language. In this meta-analysis, all included studies met the following criteria: (a) case-control studies focused on the association between either of two common *FTO* gene polymorphisms (rs9939609 and rs8050136) and PTB susceptibility; (b) there were sufficient data of the genotypes in the case-control groups to evaluate the odds ratios (ORs) and 95% CIs. The exclusion criteria were: (a) publications with overlapping cases and controls from a similar study; (b) no genotypic data available; and (c) publications with the study of gene polymorphism other than rs9939609 and rs8050136.

Data abstraction and assessment of the methodological quality

The relevant data from each study were extracted in a structured form in MS Excel 2016 which included the first author, study design, site of study, racial origin of patient, year of publication, the sample size of cases and controls, control design, Hardy–Weinberg equilibrium, genotyping method and data of the genotypes in the case-control groups. The methodological quality of each study was assessed independently by two reviewers using Newcastle Ottawa Scale for case-control studies (https://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf). The scale assessed study quality under three major headings: selection, comparability and exposure. The studies with scores of five or more qualified for inclusion, and studies with score more than seven were also deemed high-quality. A consensus among all the authors solved any uncertainty about the eligibility of these studies.

Statistical analysis

The association between *FTO* gene polymorphism and PTB susceptibility was evaluated by calculating the pooled ORs and 95% CIs. The heterogeneity between the included studies was determined with the I^2 test (0–40%: not important; 30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; 75–100%: considerable heterogeneity), which indicates the percentage of total discrepancy due to study variation[15]. A random effects model using the DerSimonian Laird was utilized when significant heterogeneity was present. Otherwise, a fixed-effects model using the Mantel–Haenszel method was used. The allelic, dominant and recessive genetic models were examined for both SNVs. The meta-analysis examined the association of *FTO* rs9939609 polymorphism for three models: allele (A vs. T), dominant (AA + AT vs. TT) and recessive (AA vs. AT + TT) models. Likewise, the meta-analysis also examined the association of *FTO* rs8050136 polymorphism for three models: allele (C vs. A), dominant (CA + AA vs. CC) and recessive (AA vs. CC + CA) models. All analyses were performed with the STATA version 16.0 (StataCorp). A *P* value less than 0.05 was regarded as significant.

Results

Literature search

The systematic literature search process and selection results are summarized in Figure 1. We identified 128 articles through database search. After excluding duplicates, 72 articles remained,

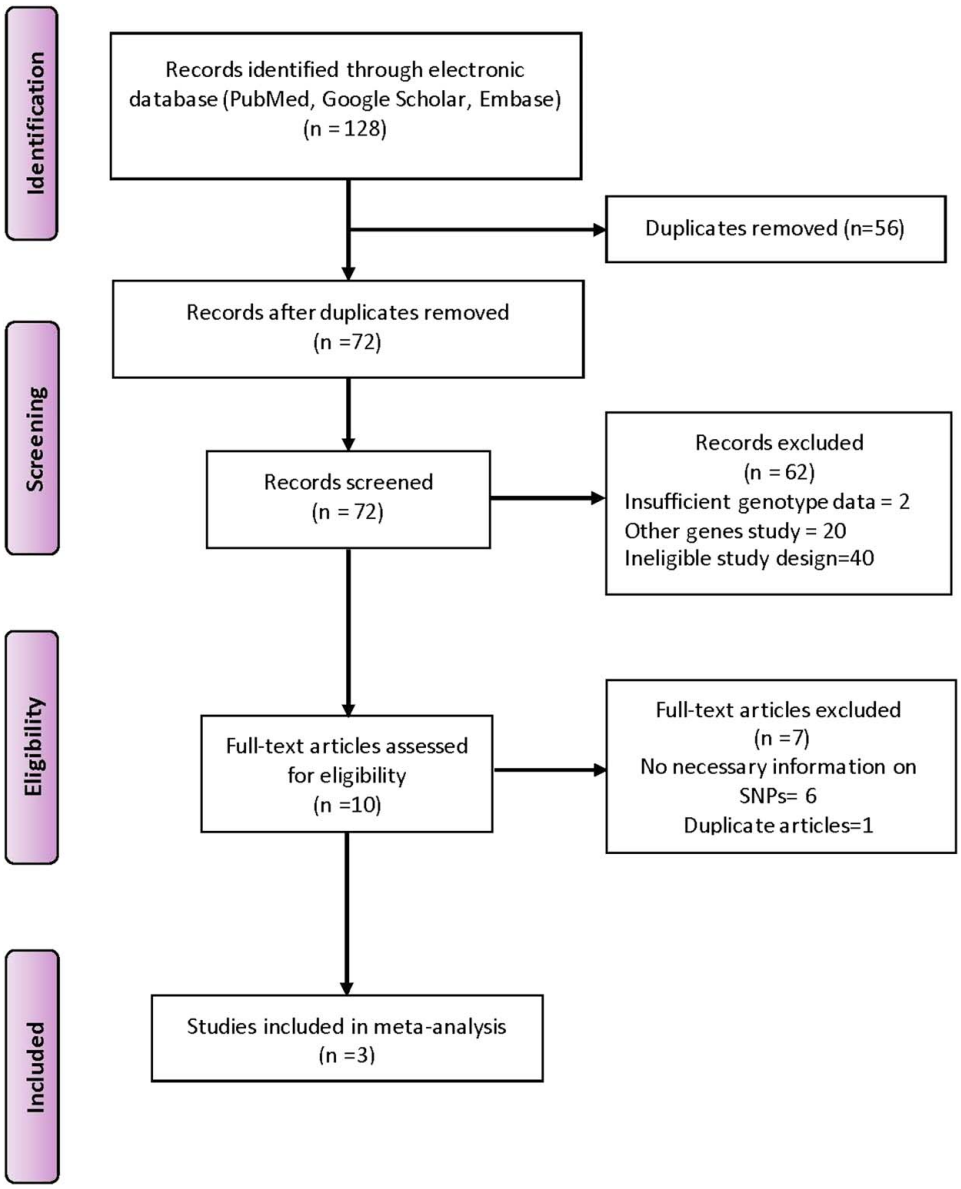

Figure 1. PRISMA Flow diagram of selection of studies.

and after screening titles and abstracts, 10 relevant full-text articles were left. After further screening, only three studies qualified for final analysis, and the applicable data were extracted.

Study and patient characteristics

This meta-analysis includes three case-control studies[16–18], two from China and one from Iran. The total number of participants was 4461, with 2259 cases and 2202 controls. The publication date ranges from 2014 to 2022. In all of the included studies, Hardy–Weinberg equilibrium was reached. All the controls of the study were population-based. The methodological quality score ranged from 6 to 7 according to quality assessment tools. None of the studies were of low quality. The details of quality assessment are available in Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A216. All the study and patient characteristics are tabulated in Table 1. Tables 2 and 3 present the two SNVs' genotyping data details.

Association of rs9939609 polymorphism of FTO gene with risk of PTB

The association of rs9939609 polymorphism with the risk of PTB was inconsistent throughout the studies. Of the three studies, two found no association between the rs9939609 polymorphism of the *FTO* gene and with risk of PTB in all three genetic models. However, Feng and colleagues showed that allele A carriers had a significantly increased risk of clinical tuberculosis (OR: 1.26, 95% CI: 1.08–1.48, $P = 0.004$). Additionally, compared to genotype TT, individuals carrying the AA genotype had a significantly increased risk, with an OR of 3.77 (95% CI: 2.26–6.28, $P < 0.001$). Likewise, the same study showed an increased risk of

Table 1

Characteristics of the included studies

References	Study site	Sample size (cases/controls)	Race	SNVs studied	Genotyping method	Hardy–Weinberg equilibrium (*P*)
Feng *et al.*[16]	China	3127 (1583/1544)	Asian (Chinese)	rs9939609, rs8050136	TaqMan PCR	0.381* 0.368**
Naderi *et al.*[17]	Iran	354 (185/169)	Persian (Iranian)	rs9939609, rs8050136	PCR-RFLP	0.475* 0.347**
Zhang *et al.*[18]	China	912 (449/463)	Asian (Chinese)	rs9939609	Flexxi gene-DNA Kit	Not available

All studies are from community-based sources and under a case-control study design.
PCR, polymerase chain reaction SNVs, Single nucleotide variants.
**P* value for rs9939609.
***P* value for rs8050136.

PTB when the recessive genetic model was assumed (OR = 3.82, 95% CI:2.30–6.37, $P < 0.001$).

Meta-analysis of rs9939609 polymorphism of FTO gene

Meta-analysis results did not show a significant association between rs9939609 polymorphism of the *FTO* gene and PTB when assuming allelic model (OR: 1.10; 95% CI: 0.85–1.41; $P = 0.47$; $I^2 = 64.98\%$) or recessive model (OR: 2.04; 95% CI: 0.87–4.77; $P = 0.10$; $I^2 = 67.18\%$) or dominant model (OR: 0.96; 95% CI: 0.83–1.11; $P = 0.56$; $I^2 = 27.45\%$). The forest plot of the result for the allelic, recessive and dominant models is demonstrated in Figure 2, respectively.

Association of rs8050136 polymorphism of FTO gene with risk of PTB

The association of rs8050136 polymorphism with the risk of PTB was inconsistent between the two studies. Feng and colleagues found no association between the rs8050136 polymorphism with the risk of PTB in all three genetic models. However, Naderi and colleagues reported that the A allele significantly increases the risk of PTB (OR = 1.42, 95% CI = 1.02–1.97, $P = 0.045$) compared with the C allele. But that significative association could not be observed when dominant or recessive genetic models were applied in the same study.

Meta-analysis of rs8050136 polymorphism of FTO gene

Meta-analysis results did not show a significant association between rs8050136 polymorphism of the *FTO* gene and PTB when assuming the allelic model (OR: 1.17; 95% CI: 0.87–1.58; $P = 0.31$; $I^2 = 64.20\%$) or recessive model (OR: 1.04; 95% CI: 0.32–3.38; $P = 0.95$; $I^2 = 68.82\%$) or dominant model (OR: 1.22; 95% CI: 0.87–1.71; $P = 0.26$; $I^2 = 58.69\%$). The forest plot of the result for the allelic, recessive and dominant models is demonstrated in Figure 3, respectively.

Sensitivity analysis

In order to determine the effect of each study on the pooled ORs, we performed sensitivity analysis by using a leave-one-out method of all three genetic models. The sensitivity analysis was performed on pooled ORs for rs9939609 polymorphism and not for rs8050136 polymorphism owing to availability of only two studies for the latter. The sensitivity analysis of three studies showed no significant effect of any of the studies on the pooled OR in the dominant model. However, Zhang and colleagues had a significant effect on the pooled OR both in the allelic model and the recessive model. The details of the sensitivity analysis are provided in Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A216.

Discussion

This is the first meta-analysis to quantify the association of the two SNVs (rs9939609 and rs8050136) in the *FTO* gene with the risk of PTB. Our study revealed a lack of association of rs9939609 and rs8050136 polymorphisms of the *FTO* gene with PTB in Asian and Persian populations in all three different genetic models. Even though no association was observed between these SNVs and disease risk in our study, some findings suggest that the *FTO* gene might still play a role in the host's susceptibility to PTB. Haplotypes have a stronger power to predict disease-related genes when compared with single SNVs[19]. One of the studies in our review detected a significantly lower frequency of the *FTO* GAAA haplotype in PTB patients. The study also demonstrated an abnormally reduced levels of FTO in the patients[18]. This suggested that the *FTO* gene must have a definite role in the

Table 2

Genotyping data of rs9939609 polymorphism of *FTO* gene among study subjects

	Allele distribution (case/control)		Genotype distribution (case/control)		
References	T	A	TT	TA	AA
Feng *et al.*[16]	2777 (89.8%)/ 2767 (87.4%)	397 (12.5%)/ 313 (10.2%)	1258 (79.5%)/ 1250 (80.9%)	253 (15.9%)/ 275 (17.9%)	72 (4.5%)/ 19 (1.2%)
Naderi *et al.*[17]	243 (65.7%)/ 234 (69.2%)	127 (34.3%)/ 104 (30.8%)	74 (40.0%)/ 74 (43.8%)	95 (51.4%)/ 86 (50.9%)	16 (8.6%)/ 9 (5.3%)
Zhang *et al.*[18]	817 (91.0%)/ 827 (89.3%)	81 (9.0%)/ 99 (10.7%)	372 (82.9%)/ 369 (79.7%)	73 (16.3%)/ 89 (19.2%)	4 (0.9%)/ 5 (1.1%)

Table 3

Genotyping data of rs8050136 polymorphism of *FTO* gene among study subjects

	Allele distribution (case/control)		Genotype distribution (case/control)		
References	**C**	**A**	**CC**	**AC**	**AA**
Feng *et al.*[16]	2849 (89.8%)/ 2774 (90.1%)	325 (10.2%)/ 306 (9.9%)	1265 (80.0%)/ 1250 (80.9%)	311 (19.6%)/ 282 (18.3%)	7 (0.4%)/ 12 (0.8%)
Naderi *et al.*[17]	252 (68.1%)/ 254 (75.1%)	118 (31.9%)/ 84 (24.9)	81 (43.8%)/ 92 (54.5%)	90 (48.6%)/ 70 (41.4%)	14 (7.6%)/ 7 (4.1%)

occurrence of PTB. The genetic variations in the *FTO* gene need to be explored before a clear association can be established. The FTO levels could be used as a potential supplementary diagnostic parameter for TB diagnosis in the future. There is a need of further studies in this area to verify this utility of the FTO .

A large number of reproducible association studies among multiple populations of diverse origin had demonstrated a strong relationship between *FTO* gene variants and obesity. The *FTO* gene polymorphism has been linked to increased predisposition to adulthood and childhood obesity. Animal models with loss or gain of *FTO* function displayed altered body mass and adipose tissue, which confirms its physiological role in regulating food-energy homoeostasis. Additionally, FTO senses nutritional status and influences appetite and food intake of an individual directly by adipocytes or indirectly by hypothalamus-controlled neurologic circuitry, according to in-vivo and in-vitro studies[5,20].

Several SNVs in the *FTO* gene, such as rs1477196, rs9939609, rs17817449, rs11075995, rs8050136, rs6499640, rs16953002 and rs1121980, have been identified. All the SNVs identified so far are located in the first and largest intron of the gene, where the sequence is strongly conserved across species[21]. Of these SNVs, the rs9939609 polymorphism, caused by an A to T transition, and the rs8050136 polymorphism, caused by an A to C transition, are some of the most commonly studied polymorphisms[16,17]. The

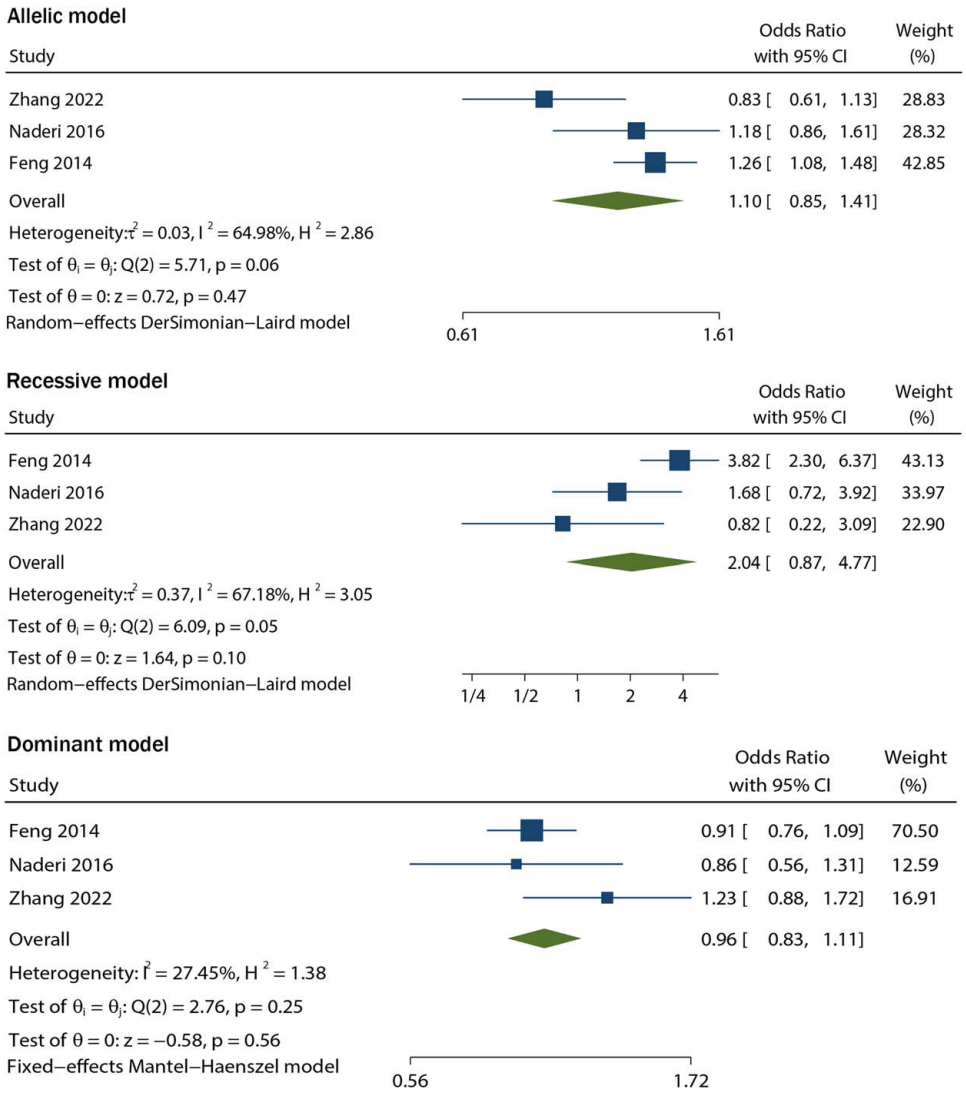

Figure 2. Forestplot of meta-analysis of association of rs9939609 polymorphism of with PTB risk in three genetic models.

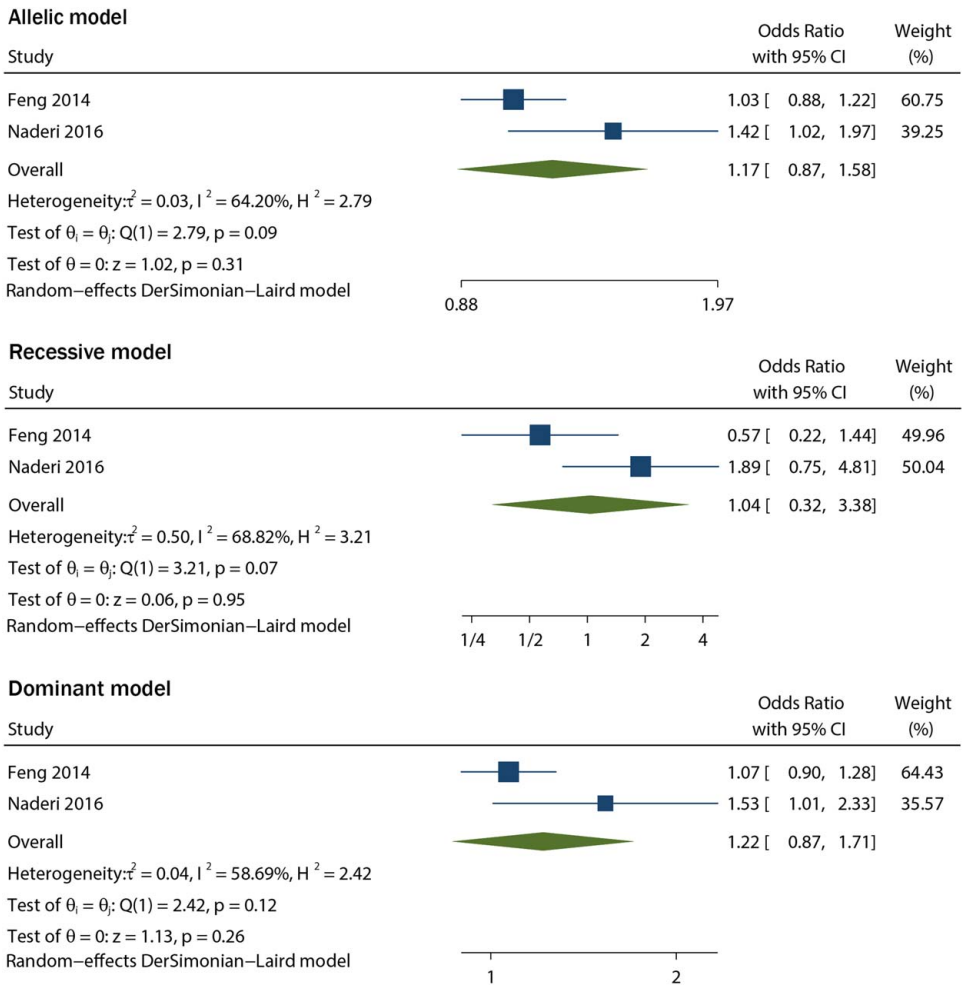

Figure 3. Forestplot of meta-analysis of association of rs8050136 polymorphism of with PTB risk in three genetic models.

rs9939609 SNV, apart from obesity, was found associated with type 2 diabetes mellitus and metabolic syndrome[22,23]. These SNVs have even been linked to cancers and psychiatric conditions such as major depressive disorders[24–26].

Higher BMI was associated with a higher risk of tuberculosis through a harmful pathway mediated through diabetes according to Lin *et al.*[3]. Studies have shown that the immunocompetence of an individual can be negatively affected by obesity, predisposing the patients to infectious diseases[4,27,28]. Diabetes has been identified as one of the significant risk factors for TB in a wealth of studies. Meanwhile, it might also affect the disease presentation, response to antitubercular treatment and overall prognosis of the patient[29,30]. Despite this, a decreased risk of tuberculosis among those with a high BMI has also been reported in the literature. Nevertheless, the complete understanding of the underlying biological mechanism of this conendrum remains obscure. Neyrolles *et al.*[31] suggested that the adipose tissue could act as a "safe haven" for *Mycobacterium tuberculosis*, by which the bacteria avoid detection by the immune system. Leptin, an adipose tissue-derived energy-regulating hormone, is positively associated with total body fat mass[32]. Leptin might also affect the T-helper 1 and T-helper 2 balance of the host immune system, subsequently altering the risk of TB infection[33,34]. Therefore, the interrelationship between obesity and the risk of TB can be assumed to be complex and non-linear.

Some limitations should be considered while interpreting the results of our study. Firstly, the number of studies included in the meta-analysis were limited and were performed in the Asian and Persian populations. No relevant studies on Caucasians, Africans or other populations were found. Therefore, to obtain a more precise estimate of the contribution of *FTO* gene polymorphisms on PTB risk, additional studies with larger sample sizes and involving different ethnicities, especially Caucasians and Africans, are essential. Second, publication bias may have occurred since we included articles published in English in the meta-analysis. Third, a detailed subgroup analysis based on race, sex and other characteristics could not be explored due to insufficient study data.

Conclusions

Our meta-analysis showed no association of *FTO* gene rs9939609 and rs8050136 polymorphism with PTB. Despite this,

genetic variations in the FTO gene need to be explored in different populations before a clear association can be established.

Ethical approval

No ethical approval was obtained due to the nature of the study being a systematic review.

Consent

Informed consent was not required for this systematic review.

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Author contribution

Conceptualization: P.L., M.R.Q., N.I. and A.A.; methodology: P.L., N.I. and S.S.; software: P.L.; validation: P.L. and R.F.-V.; formal analysis:, P.L. and R.F.-V.; investigation: P.L., S.S., V.G., S.D.R. and A.A.; resources: P.L.; data curation: P.L., V.G., S.D.R., A.A.; writing—original draft preparation: P.L., M.R.Q., N.I., S.S., V.G., S.D.R. and A.A.; writing—review and editing: P.L. and R.F.-V.; visualization: P.L.; supervision: R.F.-V.; project administration: P.L. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

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Data availability statement

Not applicable.

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