

Correlation between polymorphism of vitamin D receptor TaqI and susceptibility to tuberculosis

An update meta-analysis

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Abstract

Background: To investigate the association between TaqI polymorphism of the vitamin D receptor gene and tuberculosis (TB).

Methods: A systematic search was performed in PubMed, Embase, Web of Science, Elsevier Science Direct, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, and Chongqing VIP databases for case-control study on TaqI gene polymorphism and TB susceptibility. Quality assessment of studies was performed using the Newcastle–Ottawa Scale for the methodological assessment of case-control studies, and R 4.0.5 software was used for the meta-analysis.

Results: Among the 243 selected articles, 27 in the meta-analysis. The meta-analysis showed that the TaqI gene polymorphism allene gene model (t vs T, odds ratio [OR]: 1.12, 95% confidence interval [CI]: 0.99–1.27); dominant model (tt + tT vs TT, OR: 1.12, 95% CI: 0.98–1.29); recessive model (tt vs tT + TT, OR: 1.25, 95% CI: 1.03–1.51); codominant A (tt vs TT, OR: 1.37, 95% CI: 1.00–1.87); codominant B (tT vs TT, OR: 1.09, 95% CI: 0.99–1.19). And subgroup dominant model (tt + tT vs TT, OR: 1.27, 95% CI: 1.03–1.55) in Indianas, recessive model (tt vs tT + TT, OR: 1.49, 95% CI: 1.05–2.11) in Iranians, co-dominant B (tT vs TT, OR: 1.28, 95% CI: 1.03–1.59; OR: 1.42, 95% CI: 1.05–1.93) in Indianas and Iranians.

Conclusion: This meta-analysis suggests a significant association between TB and the risk of TaqI in Iranians and Indians, but the vitamin D receptor polymorphism TaqI was not associated with Chinese. Thus, validation studies will be required to confirm these findings.

Abbreviations: CI = confidence interval, MTB = *Mycobacterium tuberculosis*, OR = odds ratio, TB = tuberculosis, VDR = vitamin D receptor.

Keywords: meta-analysis, TaqI, tuberculosis, vitamin D receptor

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Data availability statement is not needed.

All data generated or analyzed during this study are included in this published article [and its Supplementary information files].

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1. Introduction

Tuberculosis (TB) is a common and chronic infectious disease, with nearly 10 million people are infected and 1.4 million died, in 2019. Worldwide, TB is still major killers of communicable diseases and as a cause of death in top 10. According to the World Health Organization survey, it is found that most of the TB patients are in Southeast Asia, Africa, and the Western Pacific region.^[1] And about a quarter of the world's people lives with *Mycobacterium tuberculosis* (MTB), but only 5% to 10% develop active pulmonary TB.^[2] The role of pathogen, host and environmental factors interactions affecting the MTB susceptibility,^[3] and host genetic background response directed in a small number of infected individual active TB.^[4,5]

Modulation of the immune response by active vitamin D (1,25-dihydroxyvitamin D₃) and its nuclear receptor. It stimulated activation of macrophages restrict MTB growth. So the polymorphisms vitamin D receptor (VDR) is associated with the pathogenesis of TB. Human VDR gene is located on chromosome 12 (12q13.11) and polymorphisms contribute to the expression and function.^[6] BsmI, TaqI, ApaI, and FokI polymorphisms in the VDR gene and the risk of TB. But to date, the literature contains many studies and several meta-analysis focused on polymorphisms in VDR TaqI gene and susceptibility to TB, the studies results are not consistent.^[7–10] Thus, we performed update meta-analysis to contain a more conclusive result.

2. Materials and methods

2.1. Literature search strategy

This meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses guideline.^[11] The electronic databases PubMed, MEDLINE, Embase, Cochrane Library, Web of Science, Elsevier ScienceDirect, SinoMed database, Chinese National Knowledge Infrastructure, Wanfang, and VIP database were systematically retrieved by us and using the following search strategy: (“vitamin D receptor” OR “VDR” OR “rs10735810” OR “TaqI”) AND (“single nucleotide polymorphism” OR “SNP” OR “mutation” OR “polymorphism”) AND (“tuberculosis” OR “TB” OR “Pulmonary tuberculosis” OR “MTB”). All the databases retrieved is from the time when the database establishment to November 2020, additional we also identified from the references of the enrolled articles related literatures.

2.2. Literature inclusion and exclusion criteria

The literature inclusion criteria: case-control study on relationship with VDR gene polymorphism and TB, provide distribution of allele frequencies, odds ratio (OR) and 95% confidence interval (95% CI) were calculated, full text in Chinese and English available, controls were healthy subjects with no history of contact with TB, and both case group and control group are not HIV infection and aged ≥ 16 years.

The literature exclusion criteria: noncase-control study, no association between VDR and TB, animals and cells were used in the study, and repeated research.

2.3. Data extraction and quality assessment

Two authors independently complete the data extraction of the documents that eligible the inclusion criteria. If there are different between the 2 authors, we will discuss and resolve the disagreement. We extracted data from the included literature including the following: first author name, year of publication, country, case and control group sample, and Hardy–Weinberg equilibrium test. In this study 2 authors using Newcastle–Ottawa Scale^[12] evaluated the included literature.

2.4. Statistical analysis

In this study t allele is increasing or risk gene, therefore, we use the 4 models: allele model (t vs T); dominant model (tt + tT vs TT); recessives model (tt vs tT + TT); co-dominant (tt vs TT, tT vs TT) as need, the OR and 95% CI were calculated.

Chi-square base Q test and I^2 was used to check heterogeneity between studies. If the heterogeneity test result was $P > .05$ or $I^2 \leq 50\%$, the heterogeneity was not significant between the studies, we used the fixed effect model, otherwise, used the random effect model. To evaluate the impact of the same polymorphism on the risk in different ethnic, we performed the subgroup analysis in different ethnic groups as an exploratory analysis. Subsequently, the sensitivity analysis was performed by successively removing 1 study at a time to recalculate OR and 95% CI to investigate the stability of the results of the meta-analysis. Publication bias was examined by Begg and Egger test.^[13,14] All the test was used R software (version 4.0.5) (<https://www.r-project.org/>) to analyze the data.

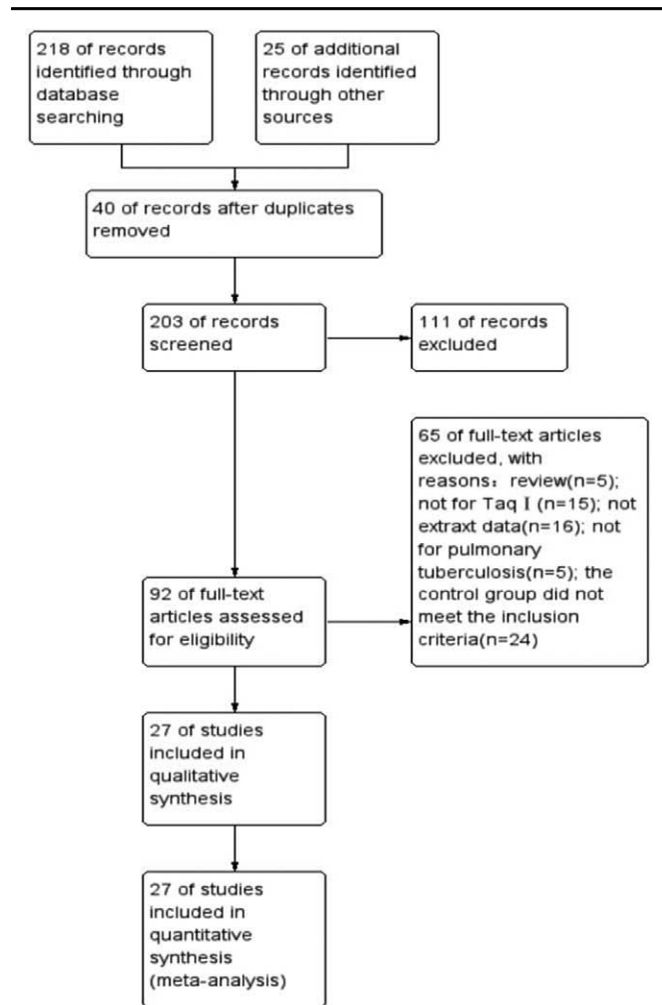


Figure 1. Flow chart literature retrieval and screening for meta-analysis. According to PRISMA requirements, PubMed, MEDLINE, Embase, Cochrane Library, Web of Science, Elsevier ScienceDirect, SinoMed database, Chinese National Knowledge Infrastructure, Wanfang, and VIP database and other databases were selected for retrieval, and 243 literatures were retrieved eventually. 27 literatures were included for meta-analysis through inclusion and exclusion criteria.

3. Results

3.1. Selection of the included studies and characteristics

Based on presenting previously databases, 243 articles were initially included. And a total of 27^[15–41] articles were contained in the present study according to the inclusion and exclusion criteria. The Figure 1 shows in the preferred reporting items for systematic reviews and meta-analyses flow diagram. And detailed characteristics of the enrolled studies were shown in Table 1.

3.2. Meta-analysis results

27 articles were included into comprehensive quantitative analysis for the association between gene polymorphism of VDR TaqI at risk of TB. And the random effect model was used for analysis in allelic model (t allele vs T allele) 1.12 (95% CI: 0.99–1.27); dominant model (tt + tT vs TT) 1.12 (95% CI: 0.98–1.29); co-dominant A (tt vs TT) 1.37 (95% CI: 1.00–1.87). The

Table 1**Main characteristics of included studies summarized for the meta-analysis.**

First author	Year	County	patients	controls	Genotyping method	HWE	NOS
Liu Wei	2003	China	110	180	PCR-RFLP	N	8
P Selvaraj	2004	India	46	64	PCR	Y	9
Liu Wei	2005	China	152	259	PCR	Y	8
Liu Yidian	2008	China	30	30	PCR	Y	7
P Selvaraj	2009	India	65	60	PCR	N	9
M Vidyarani	2009	India	40	49	PCR	N	8
Feng Fumin	2009	China	122	248	PCR-RFLP	N	7
Mohammad Mehdi Banoei	2010	Iran	60	62	PCR	N	8
Wang Xi	2011	China	213	211	PCR-RFLP	Y	7
Wang Xi	2011	China	224	225	PCR-RFLP	Y	8
J Rathored	2012	India	692	205	PCR-RFLP	N	8
Xiang Ying	2013	China	198	195	PCR	Y	7
Dai Yaoyao	2013	China	1584	1566	PCR	Y	9
Chen Dandan	2013	China	993	880	PCR	Y	7
Jalil Rashedi	2014	Iran	84	90	PCR-RFLP	N	8
Wu Linlin	2015	China	151	453	PCR-RFLP	Y	9
Saeedeh Salimi	2015	Iran	120	131	PCR-RFLP	Y	8
Zhang Juan	2015	China	300	300	HRM-PCR	Y	7
M Harishankar	2016	India	90	81	PCR	Y	9
Mohammad Jafari	2016	Iran	96	122	ARMS-PCR	N	8
Shih-Wei Lee	2016	ChinaTaiwan	198	170	PCR	Y	7
Shi Jie	2017	China	260	258	PCR	Y	9
Kangjam Rekha Devi	2018	India	169	227	PCR-RFLP	Y	8
Zhang Ye	2018	China	180	59	PCR	N	7
Beatriz Silva-Ramírez	2019	Mexico	257	457	RT-PCR	Y	8
Liu Xing	2020	China	300	300	PCR	Y	7
MaXiaoguang	2020	China	80	80	PCR	Y	7

HWE=Hardy-Weinberg equilibrium, N=no calculate HWE, NOS=Newcastle-Ottawa Scale, Y=calculate HWE.

fixed effect model was used for analysis in recessives model (tt vs tT+TT) 1.25 (95% CI: 1.03–1.51); co-dominant B (tT vs TT) 1.09 (95% CI: 0.99–1.19). It was shown that TaqI gene polymorphism was associated with susceptibility to pulmonary TB in the co-dominant A (tt vs TT) and recessives model (tt vs tT+TT). The significant association has not been in other 3 genetic models between TaqI gene polymorphism and susceptibility to pulmonary TB. Pooled analysis in 5 models by subgroup based on country (China, India, Iran, and Mexico). We found that t allele polymorphisms are associated with an increased risk of pulmonary TB in India and Iran (tt+tT vs TT: OR: 1.27, 95% CI: 1.03–1.55; tt vs tT+TT: OR: 1.89, 95% CI: 1.23–2.92; tT vs TT: OR: 1.28, 95% CI: 1.03–1.59; OR: 1.42, 95% CI: 1.05–1.93). The results were listed in Table 2, Figures 2 and 3.

3.3. Sensitivity analysis

In the sensitivity analysis, each study was deleted every study at a time to evaluate the influence of each individual data set on the combined OR. Results showed no significant differences in the corresponding combined ORs, suggesting the stability of this meta-analysis.

3.4. Publication bias

We performed Begg funnel plots were used to visually assess the publication bias and Egger linear regression were used to quantitative publication bias. As showed in Figure 3 the funnel plots demonstrated that no publication bias existed among the

included studies for 5 models. Then, the Egger linear regression test was offered to statistical evidence for funnel plots symmetry. The consequences of Egger test found no significant evidence of publication bias. Therefore, the results were not any significant publication bias in this present study. The results were listed in Table 3 and Figure 4.

4. Discussion

The World Health Organization estimated that TB was the 13th leading cause of death and remains a disease caused by a single pathogen.^[42] Approximately a quarter of the world's population is infected with MTB, the bacterium that causes TB, however, only a fraction of the infected person develop TB. This illustrates that factors other than Mycobacteria play a major role in the development of TB. Other than this effect, there are many other factors such as poverty or under-nutrition and gene polymorphisms that affect the onset of TB.^[1,39,42] Vitamin D usually exerts its effect through binding with its receptor (VDR).^[19,43] VDR play an important role in the monocytes and macrophages production of the intracellular antimicrobial peptide cathelicin. Therefore, VDR genetic variation may confer a risk of their activity and influence the susceptibility to TB. Genetic studies have shown that VDR gene expression is significantly associated with changes in the circulating cytokine environment in the inflammatory response of MTB.^[44] In addition, other studies have shown that MTB infection down-regulates the expression of the VDR gene in macrophages.^[45] However, the results of those studies have been inconsistent.^[16,30,31] Epidemiological studies have shown that VDR polymorphisms are significantly

Table 2
meta-analysis of Taq I polymorphism and TB.

polymorphism	Population	No. of studies	Test of association	
			OR	95% CI
Allele (t allele vs T allele)	overall	27	1.12	0.99–1.27
	China	16	1.01	0.87–1.19
	India	6	1.18	0.98–1.43
	Iran	4	1.59	0.98–1.43
	Mexico	1	0.95	0.74–1.21
	Overall	27	1.12	0.98–1.29
Dominant (tt+tT vs TT)	China	16	1.01	0.87–1.18
	India	6	1.27	1.03–1.55
	Iran	4	1.77	0.91–3.43
	Mexico	1	0.94	0.69–1.28
	Overall	27	1.25	1.03–1.51
	China	16	1.27	0.90–1.79
Recessive (tt vs tT+TT)	India	6	1.10	0.82–1.48
	Iran	4	1.89	1.23–2.92
	Mexico	1	0.88	0.46–1.67
	Overall	27	1.37	1.00–1.87
	China	16	1.17	0.75–1.82
	India	6	1.29	0.78–2.12
Co-dominant A (tt vs TT)	Mexico	1	2.66	0.93–7.63
	Overall	27	0.86	0.45–1.66
	China	16	1.09	0.99–1.19
	India	6	1.01	0.90–1.14
	Iran	4	1.28	1.03–1.59
	Mexico	1	0.92	1.05–1.93
Co-dominant B (tT vs TT)	Iran	1	0.95	0.70–1.31

CI=confidence interval, OR=odds ratio, TB = tuberculosis.

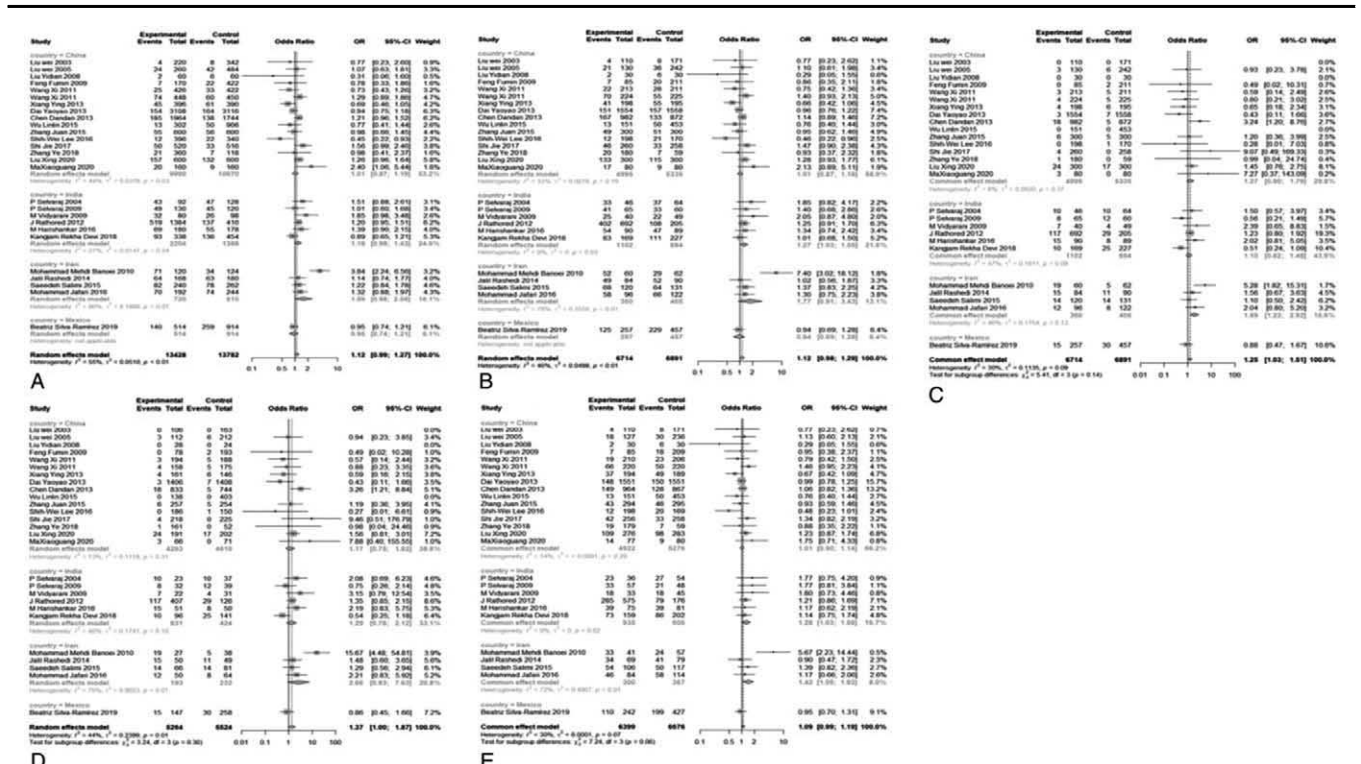


Figure 2. Forest plot for the association between Taq I polymorphisms and TB risk of meta-analysis. In this result, the square showed the OR for each study, the horizontal lines represent the 95% CI for each study, the diamonds represent the combined OR value and 95% CI. (A): allele model (t vs T) used random effect model (OR: 1.12, 95% CI: 0.99–1.27); (B) dominant model (tt+tT vs TT) used random effect model (OR: 1.12, 95% CI: 0.98–1.29); (C): recessive (tt vs tT+TT) used fixed effect model (OR: 1.25, 95% CI: 1.03–1.51); (D) co-dominant A (tt vs TT) used random effect model (OR: 1.37, 95% CI: 1.00–1.87); (E) co-dominant B (tT vs TT) used fixed effect model (OR: 1.09, 95% CI: 0.99–1.19). CI=confidence interval, OR=odds ratio, TB = tuberculosis.

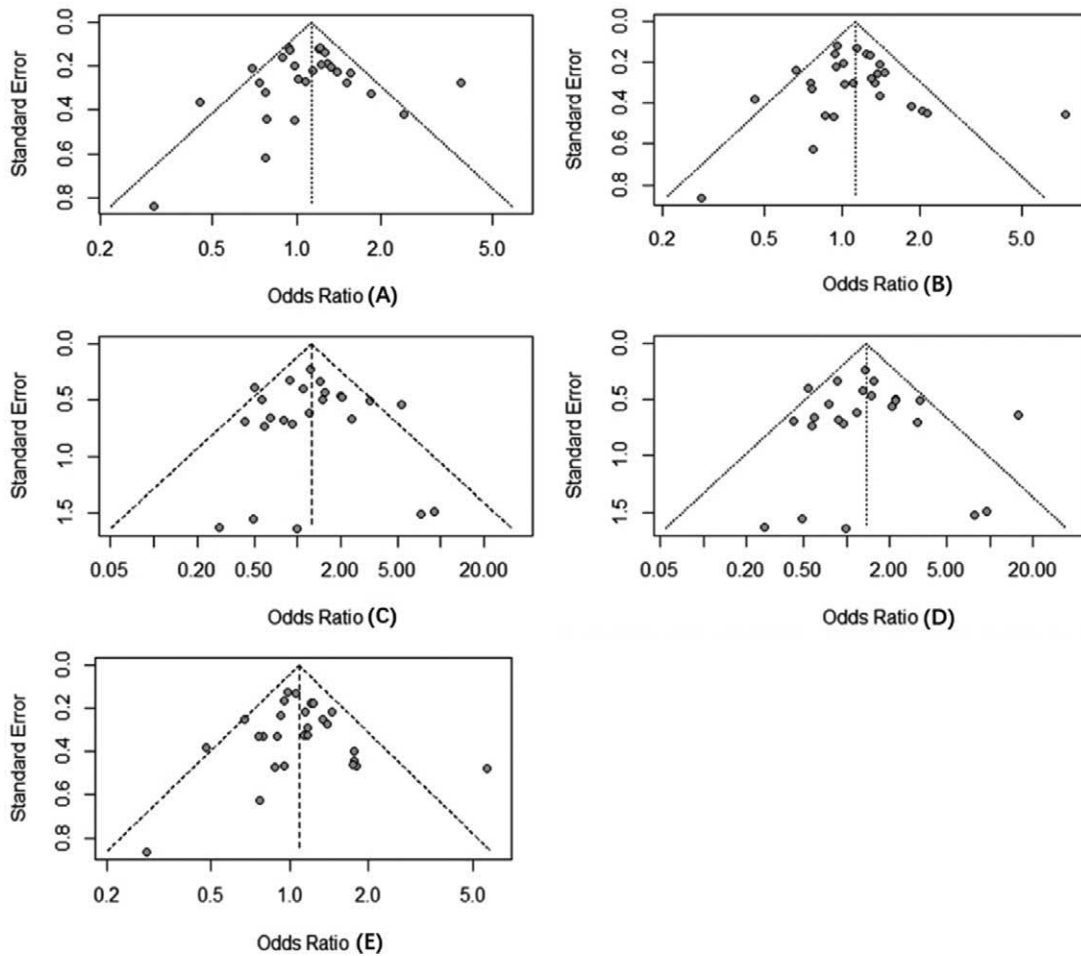


Figure 3. Forest plot of subgroup (by country: China, India, Mexico) meta-analysis. In this result, the square showed the OR for each study, the horizontal lines represent the 95% CI for each study, the diamonds represent the combined OR value and 95% CI. (A): allele model (t vs T) used random effect model. (B) dominant model (tt + tT vs TT) used random effect model. (C): recessive (tt vs tT + TT) used fixed effect model. (D) co-dominant A (tt vs TT) used random effect model. (E) co-dominant B (tT vs TT) used fixed effect model. CI=confidence interval, OR=odds ratio.

associated with an increased risk of TB in Iranian^[31] and Turkish^[46] populations. However, a case-control study^[47] in the United Kingdom found no association between VDR polymorphisms and an increased risk of TB. There is considerable evidence to suggest that the pathogenesis of TB is influenced by not only genetic factors, but also environmental factor (indoor conditions, work environment, etc) and ethnic factors (nation, BMI, etc).^[48]

As of November 2020, we obtained 27 publication literature that met all of the inclusion and exclusion criteria for meta-

analysis. In this study, we detected a significant correlation between VDR polymorphism of TaqI gene and susceptibility to TB in recessive model (tt vs tT + TT) and co-dominant A (tt vs TT), while the other 3 models showed no such association. Moreover, subgroup analysis according to country we found this same correlation between VDR polymorphism of TaqI gene and the susceptibility to TB in recessive model (tt vs tT + TT) and co-dominant B (tT vs TT) for Iranians. This result was consistent with Mohammadi et al^[49] research findings. Similarly, it was found that TaqI gene polymorphism was associated with the risk

Table 3
Statistics to test the publication bias.

Model	Polymorphism	Begg correlation test		Egger linear regression test	
		z	P value	t	P value
Allele	t vs T allele	0.06	.950	-0.02	.984
Dominant	tt + tT vs TT	0.31	.755	0.54	.594
Recessive	tt vs tT + TT	0.00	1.000	0.20	.842
Co-dominant A	tt vs TT	0.05	.960	0.37	.714
Co-dominant B	tT vs TT	0.23	.819	0.49	.626

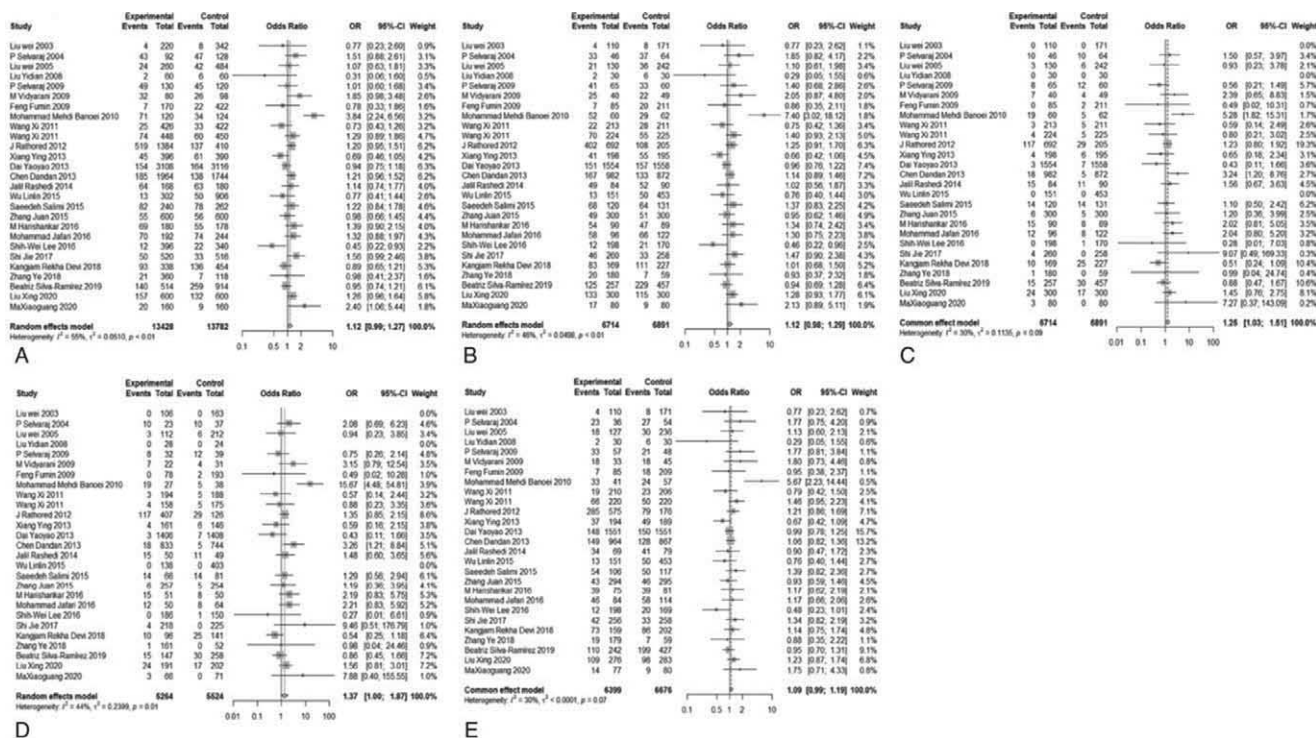


Figure 4. Begg funnel plots for publication bias test. This result showed funnel plots for publication bias test. (A) allele model (t vs T); (B) dominant model (tt + tT vs TT); (C) recessive (tt vs tT + TT); (D) co-dominant A (tT vs TT); (E) co-dominant B (tT vs TT).

of TB in dominant (tt+tT vs TT) and co-dominantB (tT vs TT) model for Indians. Results of the present study suggest that besides genetic polymorphisms should be considered as they may be involved in disease pathogenesis also examine the diverse genetic backgrounds, environmental factors and the synergistic effect of genetic and environmental factors.

4.1. Advantage and limitation

Advantage and limitation our study had some advantages was comparable to other studies. Firstly, the article is an updated meta-analysis. Our meta-analysis differs from previous meta-analysis in the inclusion and exclusion criteria utilized. In this study, only patients with simple TB without HIV infection were included to explore the relationship between TaqI gene polymorphism and the risk of disease. Cao et al^[9] study included patients with pulmonary TB and extrapulmonary TB accompanied by HIV infection. So this is different from Cao et al research. Second, we evaluate the quality of each included literature through the study quality was appraised using a tool for Newcastle–Ottawa Scale. Third, sensitivity analyses were attempted through excluding studies one by one and found results were stable. However, the present study still had limitations in our analyses. Although we did not observe apparent publication bias through statistical tests, it was difficult to completely rule out this problem. Secondly, the pooled result could be affected different aspects of degree of illness and gender. Third, polymorphism of the VDR gene may be associated with the clinical characteristics of patients with PTB. In view of this, more data and information need to be used for subgroup analysis of degree of illness, gender, different serum VD levels, etc, however, each literature did not provide

the corresponding data. Therefore, we were unable to further evaluate their role in TAQ and TB susceptibility through more subgroup analyses.

5. Conclusions

In summary, the results of this meta-analysis suggest a significant association between TB and the risk of TaqI in Iranians and Indians, but the VDR polymorphism TaqI was not associated with Chinese. Thus, validation studies will be needed in order to confirm these findings.

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Author contributions

W.ZF project administration, L.B. and W.F. contributed to the study screening and data extraction, L.B. contributed to data analysis and writing original draft preparation. All authors have both read and agreed to the published version of the manuscript.

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Software: Bin Li.

Writing – original draft: Bin Li.

Writing – review & editing: Bin Li.

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