Journal of Bacteriology and Vaccine Research

Associations between Tumor Necrosis Factor-Alpha Polymorphisms and the Risk of Tuberculosis: A Meta-Analysis

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Abstract

Background: Tuberculosis (TB) is a global infectious disease that seriously threatens human health, but the association between tumor necrosis factor-alpha (TNF- α , TNF) gene and TB remains controversial.

Methods: Relevant studies published in English or Chinese up to April 12, 2019, were searched from PubMed, Embase, Metstr, Web of Science, Medline, and CNKI databases. The associations were estimated by Odds Ratios (ORs) and 95% Confidence Intervals (CIs). The heterogeneity was evaluated by a Chi² based Q test and an I² test Cochran Q test. Begg's and Egger's tests were used to assess the publication bias.

Results: Forty studies involving 5790 patients with TB and 6529 healthy controls were selected. Our results showed that the TNF Single Nucleotide Polymorphisms (SNPs) rs361525, rs1800629, and rs1799724 rather than rs1800630 were significantly associated with TB risk in the overall cohort. Furthermore, in the subgroup analyses by ethnicity, we found that:1) SNPrs361525 was associated with a decreased TB risk under the dominant genetic model (OR=0.41, 95% CI [0.28,0.59], P<0.00001), but an increased TB risk under recessive genetic model (OR=2.45, 95% CI [1.70, 3.51], P<0.00001) in Asian population. 2) SNPrs1800629 was significantly associated with a decreased TB risk under the homozygote genetic model (OR=0.15, 95% CI [0.07, 0.36], P<0.0001; OR=0.64, 95% CI [0.42, 0.99], P=0.04) in African or Asian population. 3) SNPrs1799724 was associated with an increased TB risk under the homozygote genetic model (OR=2.21, 95% CI [1.02, 4.79], P=0.04) and the dominant genetic model (OR=0.49, 95% CI [0.33, 3.16], P=0.001), and a decreased TB risk under the recessive genetic model (OR=0.49, 95% CI [0.32, 0.75], P=0.001) in Asian population.

Conclusions: This meta-analysis suggested that TNFSNPsrs361525, rs1800629, and rs1799724 rather than rs1800630 might be associated with susceptibility to TB, especially in the Asian population.

Keywords: Tumor necrosis factor-alpha; Tuberculosis; Single nucleotide polymorphisms; Metaanalysis; Susceptibility

Abbreviations

CI: Confidence Intervals; CNKI: China National Knowledge Infrastructure; EPTB: Extrapulmonary TB; HIV: Human Immunodeficiency Virus; MHC: Major Histocompatibility Complex; OATB: Osteoarticular TB; Ors: Odds Ratios; PTB: Pulmonary TB; SNPs: Single Nucleotide Polymorphisms; STB: Spinal TB; TB: Tuberculosis; TNF- α : Tumor Necrosis Factor-alpha; WHO: World Health Organization

Introduction

Tuberculosis (TB) is a significant human infectious disease that has been considered severe and lethal, responsible for 1.3 million deaths in 2017 globally [1]. As the World Health Organization (WHO) reports, 1/3 of the people in the world have been infected by *Mycobacterium tuberculosis*, whereas only 10% of these infected individuals ever progress to disease [2], which means that the risk of developing TB in humans is strongly dependent on host-pathogen interactions, the environment,

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E-mail: xueqiongwu @139.com Received Date: 14 Oct 2020 Accepted Date: 06 Nov 2020 Published Date: 10 Nov 2020

Citation: Gong W, Duan L, Wu X. Associations between Tumor Necrosis Factor-Alpha Polymorphisms and the Risk of Tuberculosis: A Meta-Analysis. J Bacteriol Vaccin Res. 2020; 2(1): 1008.

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Table 1: Quality criteria for the included studies.

Quality parameter	Scoreª									
	3	2	1	0						
No. of case patients	>200	>100 and ≤200	>50 and ≤100	≤50						
No. of hospitals or centers	≥4	3	2	1						
SNP detection method ^b	DNA sequencing	AS-PCR, ARMS-PCR, RT-PCR, M-PCR	PCR-RFLP, PCR-SSP	NA						
Matching of case and control subjects°	A+G+N	A+S, A+N, or S+N	A, S, or N	None						
HIV	Negative	-	-	NA						

a: The scores based on following studies, 1) Wei L, Zeng Y, Wang J, et al. Predicting sustained viral response to hepatitis C using a rapid and simple IL28B rs8099917 genotyping assay. Antiviral Res. 2012; 94: 54-56. 2)Liu S, Zhang H, Gu C, et al. Associations Between Hepatitis B Virus Mutations and the Risk of Hepatocellular Carcinoma: A Meta-Analysis. J Natl Cancer Inst. 2009; 101: 1066-1082.

b: AS-PCR: Allele-Specific Polymerase Chain Reaction; ARMS-PCR: Amplification Refractory Mutation System-Polymerase Chain Reaction; RT-PCR: Real-Time Polymerase Chain Reaction; PCR-RFLP: Polymerase Chain Reaction with Restriction Fragment Length Polymorphism; PCR-SSP: Polymerase Chain Reaction with Sequence-Specific Primers; M-PCR: Multiplex Polymerase Chain Reaction.

c: A=Age; G=Gender; N=Nationality.

and the genetic background [3]. Recently, some studies have proven that TB risk is associated with polymorphisms in candidate genes related to the immune system and inflammatory response [4-6].

Tumor Necrosis Factor-alpha (TNF- α) is an important cytokine in the pathogenesis of several inflammatory diseases [7], and the gene encoding it is located on chromosome 6 within the Major Histocompatibility Complex (MHC) class III region. The associations between TNF polymorphisms and the risk of contracting several inflammatory diseases have been widely reported [8-14]. A growing number of studies indicated that TNF- α plays an important role in forming microbiocidal granulomas and inhibiting M. tuberculosis proliferation [15-17]. Thousands of Single Nucleotide Polymorphisms (SNPs) in TB patients have been identified based on increasing numbers of individual gene sequences and whole genomes [18]. Accordingly, a phylogenetic tree was constructed using those SNPs, and an evolutionary hypothesis for lineages of M. tuberculosis was proposed [19]. Previous studies have showed that certain SNPs of TNF gene were associated with the risk of TB or pulmonary TB in different populations, such as rs361525 (-238G>A) [20-32], rs673 (-244G>A) [28], rs1800629 (-308G>A) [20,22-40], rs1800750 (-376G>A) [31], rs1799724 (-857C>T) [20,22,25,26,28,29,41], rs1800630 (-863C>A) [20,22,24,25,28,29,41], rs1799964 (-1031T>C) [22], TNF -224G>A [20], and TNF +488G>A [32]. However, the conclusions of these studies were inconsistent or even contrary. To avoid the errors caused by a single study, we performed a meta-analysis based on casecontrol designed studies to evaluate the associations between 4 SNPs (rs361525, rs1800629, rs1799724, and rs1800630) and susceptibility to TB.

Methods

Ethics committee and institutional review board

Ethical approval was not necessary since this was a meta-analysis of published articles.

Search strategy

PubMed, Embase, Metstr, Web of Science, Medline, and China National Knowledge Infrastructure (CNKI), http://www.cnki. net/) were used to search publications on the associations between TNF polymorphisms and TB susceptibility until April 12, 2019. All papers were identified with a literature search using the terms "tuberculosis" or "TB" and "TNF- α " or "tumor necrosis factor-alpha" and "polymorphisms" or "polymorphism." The searched publications were limited to English or Chinese language journals.

Inclusion and exclusion criteria

Publications were considered candidates if they meet the following criteria: 1) It was case-control designed study; 2) The study should evaluate the associations between TNF polymorphisms and TB susceptibility; 3) Data of genotype frequencies in TB patients and healthy controls were available; 4) The study should be openly published in peer-reviewed journals. Publications were excluded if: 1) The study belonged to a review or meta-analysis; 2) The study focused on TB treatment, other diseases, other gene mutations, or animals; 3) The full text was unavailable; 4) The study was performed in patients with potential confounding diseases; 5) The study was based on family members or sibling pairs rather than on the unrelated subjects.

Data extraction and assessment of study quality

Data from the included articles were independently extracted by two authors (WP Gong and LY Duan) and reviewed by the third author (XQ Wu) according to our data extraction form. Disagreements were resolved by discussion. The following data were extracted from each included study: publication year, first author, country or area, ethnicity, sample size (cases and controls), number of hospitals or centers, TB type, Human Immunodeficiency Virus (HIV) status, mutation site, genotype information, mutation detection method, age, gender, and nationality.

Two authors (WP Gong and LY Duan) independently conducted assessments of the study quality by using a 15-point scoring system (Table 1). Disagreements were resolved by consensus. The scoring system consisted of elements such as the number of case-patients, number of hospitals or centers, SNP detection method, matching of case and control subjects (age, gender, and nationality), and HIV status, which might be necessary for enhancing the quality of included studies. The overall score was divided into three categories according to the distribution of relative quality scores of all the included studies: 1) High-quality studies: overall score \geq 9; 2) Medium-quality studies: $6\leq$ overall score <9; 3) Low-quality studies: overall score <6.

Statistical analysis

Reviewer Manager 5 software (Cochrane Community, London, UK) was used to determine the associations between TNF polymorphisms and TB susceptibility by Z test, and the results were presented as Odds Ratios (ORs) with their corresponding 95% Confidence Intervals (95% CI). The heterogeneity of included publications was evaluated by a Chi² based Q test and an I² test; two different effect models were used according to the I² value of heterogeneity assessment. If there was no significant heterogeneity



among the included studies (Pheterogeneity>0.01 and I2<50%), the Fixed-effect model was used [42]; otherwise, the Random-effect model was used [43]. Five comparison genetic models (allele model, homozygote model, heterozygote model, dominant model, and recessive model) were used to evaluate the association between the chosen polymorphisms of the TNF gene and TB risk. Sensitivity analysis was conducted to evaluate the influence of the individual study on the pooled results by removing one study each time. The potential publication bias was evaluated by using the Begg test and Egger regression test in Stata 15 software (Stata Corp LLC, Texas, USA). *P*<0.05 indicates a significant difference.

Results

Characteristics of included studies

We used unified search terms to search the literature in 6 databases (see Table S1, Supplemental Content, which illustrates the search terms in six databases). The results showed that 829 articles were retrieved from these databases (Figure 1). A total of 439 articles were selected in the primary elections after excluding duplicated literature. Then, 379 articles were excluded by reading the titles and abstracts, and 20 articles that did not meet the inclusion criteria were excluded by reading the full text. Finally, a total of 40 articles that met the inclusion criteria were included in this meta-analysis [20,22-41,44-62].

The characteristics of these included studies are listed in Table 2. There were 6529 cases of healthy controls, and 5790 cases of TB in our meta-analysis, including 4395 cases of Pulmonary TB (PTB), 481 cases of Spinal TB (STB), 208 cases of Extra Pulmonary TB (EPTB),

231 cases of Osteoarticular TB (OATB), and 475 cases where TB types were not available. Among these included studies, 3 studies were performed in an African population [36,38,56], 29 in Asian population [20,22-29,32,33,35,39,41,44-52,54,58-62], and 8 in a Caucasian population [30,31,34,37,40,53,55,57]. Furthermore, the HIV status was available in 15 studies (37.5%), and quality scores of 26 studies (60%) were higher than 5, which suggested that the methodological quality was high. In addition, a total of 9 TNF SNPs were involved in these studies, including rs673, rs361525, rs1799724, rs1799964, TNF +488G>A, rs1800629, rs1800630, rs1800750, and TNF -224G>A, and the distribution of these SNPs among 40 studies was listed in Table 3. Finally, 4 SNPs (rs361525, rs1800629, rs1799724, and rs1800630) were analyzed in our meta-analysis based on their high distribution frequencies (see Table S2, Supplemental Content, which illustrates the genotype distributions in cases and controls).

Meta-analysis of the association between 4 SNPs and TB susceptibility by overall cohort and ethnicity subgroup

This meta-analysis showed no association between SNP rs1800630 and TB sensitivity under any genetic models in the overall cohort and ethnicity subgroups (Table 4). However, our meta-analysis revealed associations between the remaining SNPs (rs361525, rs1800629, and rs1799724) and TB risk (Table 4).

SNP rs361525 polymorphism

Twenty-four case-control studies on the relationship between rs361525 polymorphism and TB risk were identified, including 3,431 cases, and 3,934 controls. In the overall cohort analysis, significant heterogeneity was observed in the allele genetic model, the homozygotegenetic model, and the heterozygote genetic model, but not in the dominant genetic model and recessive genetic model. Thus the Random-effect model and Fixed-effect model were used, respectively (Table 4). Our results showed that rs361525 polymorphism was significantly associated with decreased TB risk under the dominant genetic model but with increased TB risk under the recessive genetic model in the overall population (Table 4). To determine the source of heterogeneity, the stratified analysis by ethnicity was performed. It was found that the rs361525 polymorphism has a significant association with TB risk in the Asian population rather than the African or Caucasian population. Metaanalysis showed that rs361525 polymorphism was significantly associated with decreased TB risk under the dominant genetic model (Figure 2A), but with increased TB risk under the recessive genetic model (Figure 2B) in the Asian population.

SNP rs1800629 polymorphism

Thirty-eight case-control studies on the relationship between rs1800629 polymorphism and TB risk were identified, including 4,945 cases, and 5,683 controls. In the overall cohort analysis, significant heterogeneity was observed in the allele genetic model and the heterozygote genetic model, but not in the homozygotegenetic model, the dominant genetic model, and the recessive genetic model (Table 4). Therefore, the Random-effect model was used in the former, and the Fixed-effect model was used in the latter. Overall, rs1800629 polymorphism was significantly associated with decreased TB risk under the homozygote genetic model (Table 4). In the stratified analysis by ethnicity, the rs1800629 polymorphism has a significant association with TB risk in African and Asian populations rather than the Caucasian population. Our results showed that rs1800629 polymorphism was significantly associated with a decreased TB risk



Figure 2: Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of individual studies for associations between the rs361525 polymorphism and TB in the Asian population under the dominant genetic model (A), and the recessive genetic model (B). Blue squares represent study-specific estimates, the horizontal lines represent 95% CIs, and the black diamonds represent summary estimates with corresponding 95% CIs. The size of the squares and diamonds means the weight assigned to each study. Risk of bias legend, (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Incomplete outcome data (attrition bias); (F) Selective reporting (reporting bias); (G) Other bias.

under the homozygote genetic model and the dominant genetic model in the African or Asian population (Figure 3).

SNP rs1799724 polymorphism

Ten case-control studies on the relationship between rs1799724 polymorphism and TB risk were identified, including 2,446 cases, and 1,866 controls. In the overall cohort analysis, there was no significant heterogeneity in the homozygotegenetic model, dominant genetic model, and recessive genetic model, and the Fixed-effect model was used in three genetic models (Table 4). In contrast, significant heterogeneity was observed in the allele genetic model and heterozygote genetic model. Thus the Random-effect model was used. In total population, the data indicated that the rs1799724 polymorphism was significantly associated with increased TB risk under the homozygote genetic model, and the dominant genetic model, but with decreased TB risk under the recessive genetic model (Table 4). In the stratified analysis by ethnicity, the rs1799724 polymorphism has a significant association with TB risk in the Asian population rather than the African or Caucasian population. An ethnicity-specific meta-analysis revealed that rs1799724 polymorphism was significantly associated with increased TB risk under the homozygotegenetic model (Figure 4A) and the dominant genetic model (Figure 4B), but it was opposite under the recessive genetic model (Figure 4C) in the Asian population.

Meta-analysis of the association between 4 SNPs and TB susceptibility by confounders

To further assess the role of these 4 SNPs in susceptibility to TB, we performed subgroup analyses based on potential confounders such as the number of hospitals or centers, TB types, and HIV status. We found significant associations between 4 SNPs and TB susceptibility in the number of hospitals or centers, TB types, and HIV status subgroups (Table 5).

Number of hospitals or centers: For the rs361525 polymorphism, decreased TB risk was observed in the single-center source population under the allele model, the homozygote genetic model, the heterozygote model, and the dominant genetic model, and an increased TB risk under the recessive genetic model. Interestingly,

	Z.Z. I Allicall	Events	Total	Events	Total	Weight	M-H. Fixed. 95% C	M-H. Fixed. 95% Cl	ABCDEFG
	Ben-Selma 2011	83	89	70	72	4.9%	0.40 [0.08, 2.02]		
	Fitness 2004	132	134	344	345	2.7%	0.19 [0.02, 2.13]		
	Mabunda 2015	51	65	271	276	20.9%	0.07 [0.02, 0.19]		
	Subtotal (95% CI)	000	288	005	693	28.5%	0.14 [0.06, 0.32]	-	
	I otal events	266 3.40 df = 1	2 (P = 0	685 18)· I ² =	11%				
	Test for overall effect:	Z = 4.56 (F	2 (P = 0. 2 < 0.00	18); 1- = 001)	41%				
	2.2.3 Asian								-
	Amirzargar 2006	32	32	89	90	0.7%	1.09 [0.04, 27.42]		
	Anoosnen 2011 Chong 2015	84	84	87	87	2 10/	Not estimable		
	Ener 2010	55	57	49	49	2.1%	0.22 [0.01, 4.76]		· ·
	Ghamari 2016	122	123	71	71	1.0%	0.45 [0.12, 1.59]		
	Ghorghanlu 2016	78	80	148	151	2.4%	0.79 [0.13, 4.83]		
	Hasan 2014	57	58	70	70	1.5%	0.27 [0.01, 6.80]		
	Hu 2013	15	18	16	18	2.5%	0.63 [0.09, 4.28]	0	•
	Jafari 2016	64	69	100	101	5.5%	0.13 [0.01, 1.12]		
	Kumar 2008	113	113	178	179	0.6%	1.91 [0.08, 47.23]		
	Li 2017	160	176	166	174	14.2%	0.48 [0.20, 1.16]		
	Lin 2011	43	43	40	40		Not estimable		•
	LV 2016	95	95	91	92	0.5%	3.13 [0.13, 77.85]		-
	Metanat 2013	90	93	159	150	2.5%	1 49 [0.06 36 90]		
	Oh 2007	105	108	81	82	2 4%	0.43 [0.00, 30.89]		
	Qu 2007	52	52	101	102	0.6%	1.55 [0.06. 38.76]		•
	Selvaraj 2001	185	186	103	103	1.0%	0.60 [0.02, 14.80]	· · · · · · · · · · · · · · · · · · ·	ě
	Shahsavar 2016	94	94	62	62		Not estimable	_	•
	Sharma 2010	152	155	130	132	2.5%	0.78 [0.13, 4.74]		
	Tang 2008	34	34	96	96		Not estimable		•
	Varahram 2014	122	123	71	71	1.0%	0.57 [0.02, 14.21]		
	Vejbaesya 2007	128	129	132	132	1.4%	0.32 [0.01, 8.01]	<u> </u>	
	Yang 2010	174	1/5	1/5	1//	0.9%	1.99 [0.18, 22.13]		
	Zhang 2017 Zhang 2018	217	217	127	127		Not estimable		
	Zheng 2010 Zhou 2017	343	343	333	335	0.5%	5 15 [0 25 107 67]		
	Subtotal (95% CI)	0.0	2856	000	2887	51.4%	0.59 [0.38, 0.90]	•	
	Total events	2806		2857				к к <u>к</u>	il.
	Heterogeneity: Chi ² = 8	8.98, df = 2	20 (P = (0.98); l ² =	= 0%			0.001 0.1 1 10 1000	
в	Study or Subgroup	TB Events	Total	Contro Events	ol Total	Weight	Odds Ratio M-H. Fixed. 95% C	Odds Ratio M-H. Fixed. 95% Cl	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011	TB Events	Total	Contro Events	ol Total	Weight	Odds Ratio M-H. Fixed, 95% C	Odds Ratio	Risk of Bias A B C D E F G
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004	TB Events 125 159	<u>Total</u> 131 161	Contre Events 93 415	ol <u>Total</u> 95 416	Weight 4.7% 2.8%	Odds Ratio M-H. Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13]	Odds Ratio	Risk of Bias <u>ABCDEFG</u> ●
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015	TB Events 125 159 84	Total 131 161 98	Contr Events 93 415 362	ol <u>Total</u> 95 416 367	Weight 4.7% 2.8% 20.9%	Odds Ratio M-H. Fixed. 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24]	Odds Ratio M-H. Fixed, 95% Cl	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI)	TB Events 125 159 84	Total 131 161 98 390	Contro Events 93 415 362	ol <u>Total</u> 95 416 367 878	Weight 4.7% 2.8% 20.9% 28.4%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36]	Odds Ratio M-H. Fixed. 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3	TB Events 125 159 84 368 3.04, df = 2	Total 131 161 98 390 2 (P = 0.	Contro Events 93 415 362 870 22); I ² =	ol <u>Total</u> 95 416 367 878 34%	Weight 4.7% 2.8% 20.9% 28.4%	Odds Ratio M-H. Fixed. 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36]	Odds Ratio M-H. Fixed. 95% Cl	Risk of Bias <u>A B C D E F G</u>
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect:	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (F	Total 131 161 98 390 2 (P = 0. 2 < 0.00	Contro <u>93</u> 415 362 870 22); I ² = 01)	ol <u>Total</u> 95 416 367 878 34%	Weight 4.7% 2.8% 20.9% 28.4%	Odds Ratio M-H, Fixed, <u>95%</u> C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36]	Odds Ratio M-H. Fixed. 95% Cl	Risk of Bias <u>A B C D E F G</u>
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 3 2.4.3 Asian	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f	Total 131 161 98 390 2 (P = 0. > < 0.00	Contr <u>93</u> 415 362 870 22); I ² = 01)	ol <u>Total</u> 95 416 367 878 34%	Weight 4.7% 2.8% 20.9% 28.4%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36]	Odds Ratio M-H. Fixed, 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.4.3 Asian Amirzargar 2006	TB Events 125 159 84 3.04, df = 2 Z = 4.33 (F 40	Total 131 161 98 390 2 (P = 0. 2 < 0.00 40	Contro 93 415 362 870 22); I ² = 01) 122	ol <u>Total</u> 95 416 367 878 34%	Weight 4.7% 2.8% 20.9% 28.4%	Odds Ratio M-H. Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36]	Odds Ratio	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = (Test for overall effect : 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Obsesverts	TB Events 125 159 84 3.04, df = 2 Z = 4.33 (f 40 93 93	Total 131 161 98 390 2 (P = 0. < 0.00 40 93 67	Contro 93 415 362 870 22); I ² = 01) 122 103 22	ol <u>Total</u> 95 416 367 878 34% 123 103	Weight 4.7% 2.8% 20.9% 28.4%	Odds Ratio M-H, Fixed, 95% Ci 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable	Odds Ratio M-H, Fixed, 95% Cl	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 3 2.4.3 Asian Amizrargar 2006 Anoosheh 2011 Cheng 2015 Ever 2010	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 93 63 63	Total 131 161 98 390 2 (P = 0. < 0.00 40 93 65 110	Contr Events 93 415 362 870 22); I ² = 01) 122 103 50	ol <u>Total</u> 95 416 367 878 34% 123 103 500	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36]	Odds Ratio M-H. Fixed, 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = : Test for overall effect: : 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamad 2016	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106	$\begin{array}{c} \text{Total} \\ 131 \\ 161 \\ 98 \\ 390 \\ 2 \ (P = 0. \\ 0.00 \\ < 0.00 \\ 40 \\ 93 \\ 65 \\ 113 \\ 151 \end{array}$	Contr Events 93 415 362 870 22); I ² = 01) 122 103 50 109 29	ol <u>95</u> 416 367 878 34% 123 103 50 113 82	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.66 [0.16, 1.95] 0.60 [0.24, 24.42]	Odds Ratio	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect : 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorqhanlu 2016	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122	$\begin{array}{c} \text{Total} \\ 131 \\ 161 \\ 98 \\ 390 \\ 2 \ (P = 0. \\ > < 0.00 \\ 2 \\ 0 \\ 36 \\ 151 \\ 124 \\ \end{array}$	Contri- Events 93 415 362 870 22); I ² = 01) 122 103 50 109 83 197	ol Total 95 416 367 878 34% 123 103 50 113 83 200	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.49 [0.02, 2.13] 0.68 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.66 [0.16, 1.95] 0.60 [0.16, 1.95] 0.60 [0.16, 5.541]	Odds Ratio M-H, Fixed. 95% Cl	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% cl) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2.4.3 Asian Amirzargar 2006 Anocsheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93	Total 131 161 98 390 2 (P = 0. < 0.00 40 93 65 113 151 124 94	Contri- 93 415 362 870 22); I ² = 01) 122 103 50 109 83 197 80	ol Total 95 416 367 878 34% 123 103 50 113 83 200 80	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.660 [0.02, 14.91] 0.39 [0.2, 9.64]	Odds Ratio M-H. Fixed. 95% CI	Risk of Bias <u>A B C D E F G</u>
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 3 2.4.3 Asian Amizrargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Hasan 2014 Hua 2013	TB Events 125 159 84 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 22	Total 131 161 98 390 2 (P = 0. < 0.00 40 93 65 113 151 124 94 25	Contro Events 93 415 362 870 22); I ² = 01) 122 103 50 109 83 197 80 23	ol Total 95 416 367 878 34% 123 103 50 113 83 200 80 25	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 1.3% 2.6%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2,13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.60 [0.02, 14.91] 0.33 [0.15, 5.64] 0.59 [0.29, 9.64] 0.54 [0.10, 4.19]	Odds Ratio M-H. Fixed, 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 1 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 222 91	Total 131 161 98 390 2 (P = 0. 2 (P = 0. 2 < 0.00 40 93 65 113 151 124 94 25 96	Contr. <u>93</u> 415 362 870 22); I ² = 01) 122 103 50 109 83 197 80 23 121	ol Total 95 416 367 878 34% 123 103 50 113 83 200 80 25 122	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 1.3% 2.6% 5.3%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.60 [0.02, 14.91] 0.39 [0.15, 5.64] 0.39 [0.15, 5.64] 0.39 [0.15, 5.64] 0.64 [0.10, 4.19] 0.65 [0.02, 1.31]	Odds Ratio M-H, Fixed. 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% cl) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2.4.3 Asian Amirzargar 2006 Anocsheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008	TB Events 125 159 84 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 22 91 145	Total 131 161 98 390 2 (P = 0. 2 < 0.000 40 93 65 113 151 124 94 25 96 145 145 145 145 154 154 154 154	Contro Events 93 415 362 870 22); I ² = 01) 122 103 50 109 83 3197 80 23 121 210	ol <u>Total</u> 95 416 367 878 34% 123 103 50 113 83 200 80 25 122 211	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 1.3% 2.6% 5.3% 0.6%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.66 [0.16, 1.95] 0.66 [0.16, 1.95] 0.66 [0.16, 1.95] 0.66 [0.02, 14.91] 0.33 [0.15, 5.64] 0.39 [0.02, 9.64] 0.45 [0.02, 1.31] 2.07 [0.08, 51.26]	Odds Ratio M-H. Fixed. 95% CI	Risk of Bias <u>A B C D E F G</u>
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 3 2.4.3 Asian Amizrargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Gharghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 322 91 145 229 91	Total 131 161 98 390 2 (P = 0. 5 < 0.00 40 93 65 113 151 124 94 25 96 145 306	Contr. Events 93 415 362 870 22); I ² = 01) 122 103 50 109 83 197 80 23 121 210 272	ol Total 95 416 367 878 34% 123 103 50 113 83 200 80 25 2211 280	Weight 4.7% 2.8% 20.9% 28.4% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 2.6% 5.3% 0.6% 5.3% 0.6% 5.3%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.55 [0.07, 0.36] 0.56 [0.02, 14.91] 0.56 [0.02, 14.91] 0.39 [0.02, 9.64] 0.54 [0.10, 4.19] 0.56 [0.02, 1.31] 0.56 [0.02, 1.4.19] 0.55 [0.22, 1.27]	Odds Ratio M-H. Fixed, 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = : Test for overall effect: : 2.4.3 Asian Amizrargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Gharghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lin 2011	TB Events 125 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 22 91 145 290 46 46	$\begin{array}{c} \text{Total} \\ 131 \\ 161 \\ 98 \\ 390 \\ 2 \ (P = 0. \\ 0 < 0.00 \\ 40 \\ 93 \\ 65 \\ 113 \\ 151 \\ 124 \\ 94 \\ 145 \\ 96 \\ 145 \\ 306 \\ 46 \\ 40 \\ 1$	Contr. Events 93 415 362 870 22); I ² = 01) 122 103 50 109 83 197 83 197 80 23 121 210 272 40 0	ol Total 95 416 367 878 34% 123 103 50 113 83 200 80 25 122 221 280 400	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 1.3% 2.3% 1.3% 2.6% 14.2%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.60 [0.02, 14.91] 0.39 [0.15, 5.64] 0.39 [0.15, 5.64] 0.39 [0.15, 5.64] 0.53 [0.02, 1.31] 0.7 [0.08, 51.26] 0.53 [0.22, 1.27] Not estimable	Odds Ratio M-H, Fixed. 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% c1) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merra 2009	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 106 150 122 93 145 2290 46 6 120	Total 131 161 98 390 22 (P = 0. - < 0.00 40 93 65 113 151 124 94 151 124 96 135 165 165 165 165 165 165 165 16	Contr. Events 93 415 362 870 22); I ² = 01) 122 103 50 109 83 197 80 23 121 210 272 40 99 90	ol Total 95 416 367 878 334% 103 50 113 83 200 80 80 25 122 211 280 00 80 40 100 00 90 90 90 90 90 90 90 90 90 90 90 9	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 4.1% 6.5% 1.0% 2.3% 2.6% 5.3% 0.6% 14.2% 0.6% 14.2%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.66 [0.16, 1.95] 0.60 [0.02, 14.91] 0.33 [0.02, 9.64] 0.45 [0.10, 4.19] 0.15 [0.02, 1.31] 2.07 [0.08, 51.26] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.71 [0.01, 5.90.17] 0.71 [0.01, 5.90.17] 0.72 [0.01, 5.90.17] 0.75 [0.01, 5.90.17]	Odds Ratio M-H. Fixed. 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 3 2.4.3 Asian Amizrargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamat 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merza 2009 Metanat 2013	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 3 22 91 145 290 46 120 0114 923	Total 131 161 93 2 (P = 0. 0.00 40 93 55 113 151 124 94 94 95 96 145 306 145 306 145 306 120 117 120 120 120 120 120 120 120 120	Contr. Events 93 415 362 870 22); I ² = 01) 122 103 50 109 83 197 80 023 197 80 023 121 210 272 40 99 60 91 93	ol Total 95 416 367 878 334% 123 103 50 113 34% 122 200 80 25 22 211 280 40 100 60 00	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 1.3% 2.6% 5.3% 0.6% 1.3% 0.6% 1.4.2% 0.4% 2.3% 0.4% 0.9% 0.6%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.56 [0.16, 1.95] 0.56 [0.02, 14.91] 0.39 [0.29, 9.64] 0.39 [0.29, 9.64] 0.54 [0.10, 4.19] 0.15 [0.02, 1.31] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.08, 51.26] 0.53 [0.15, 90.17] 0.27 [0.01, 53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.01, 53 [0.22, 1.27] 0.25 [0.15, 90.17] 0.27 [0.01, 53 [0.22, 1.27] 0.55 [0.15, 90.17] 0.27 [0.01, 53 [0.22, 1.27] 0.55 [0.15, 90.17] 0.27 [0.01, 53 [0.25] 0.55 [0.15, 90.17] 0.27 [0.01, 53 [0.25] 0.55 [0.15] 0.55 [0.15] 0.	Odds Ratio M-H. Fixed, 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: : 2.4.3 Asian Amizrargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Gharghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merza 2009 Metanat 2013 Oh 2007	TB Events 125 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 93 222 91 145 290 46 120 46 120 114 93	Total 131 161 98 390 2 (P = 0.00 40 93 65 113 151 124 94 94 93 65 113 151 124 96 145 306 46 120 117 93 145	Control Events 93 415 3415 22); I ² = 01) 102 103 50 109 83 197 80 83 197 80 83 197 212 212 212 40 960 193 316	ol Total 95 416 367 878 34% 123 103 50 34% 113 83 200 80 25 112 280 40 100 60 194	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 0.6% 1.3% 0.6% 14.2% 0.4% 2.3% 0.6% 2.5%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.56 [0.16, 1.95] 0.60 [0.02, 14.91] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.53 [0.02, 1.31] 2.07 [0.08, 51.26] 0.53 [0.02, 1.31] 2.07 [0.08, 51.26] 0.53 [0.02, 1.31] 2.07 [0.04, 51.26] 3.63 [0.15, 30.17] 0.27 [0.01, 5.32] 1.45 [0.06, 35.92] 0.41 [0.04, 3.98]	Odds Ratio M-H, Fixed. 95% CI	Risk of Bias <u>A B C D E F G</u>
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Filness 2004 Mabunda 2015 Subtotal (95% cl) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merza 2009 Metanat 2013 Oh 2007	TB Events 125 139 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 106 150 122 93 1145 290 46 120 1142 61	Total 131 161 98 390 2 (P = 0.00 40 93 65 113 151 154 154 96 145 306 46 120 117 93 145 61	Contr Events 93 362 870 222); l ² = 103 509 83 197 80 231 122 40 99 90 0193 116 121	ol Total 95 416 367 878 34% 123 103 50 113 3200 80 02 211 122 211 280 40 100 00 194 117 122	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 0.6% 14.2% 0.6% 14.2% 0.6% 2.3% 0.6% 2.5% 0.6%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.60 [0.02, 14.91] 0.39 [0.02, 9.64] 0.44 [0.10, 4.19] 0.15 [0.02, 1.31] 2.07 [0.08, 51.26] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.01, 5.32] 1.45 [0.06, 37.83] 1.52 [0.06, 37.83]	Odds Ratio M-H. Fixed. 95% CI	Risk of Bias <u>A B C D E F G</u>
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 3 2.4.3 Asian Amizrargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Metanat 2013 Oh 2007 Qu 2007 Selvaraj 2001	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 93 63 106 150 122 93 22 29 11 145 290 46 46 120 114 93 142 61 209	Total 131 161 98 330 2 (P = 0. 00 40 93 65 113 151 154 25 96 306 40 93 45 306 145 61 93 145 61 210	Contr Events 93 362 870 222); l ² = 103 50 00 109 83 3197 80 23 121 210 272 249 90 60 9193 116 121 121	ol Total 95 416 367 878 34% 123 103 50 113 83 200 80 25 211 280 60 40 100 60 60 112 122 117 122	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.3% 2.6% 5.3% 0.6% 14.2% 0.4% 2.3% 0.6% 14.2% 0.4% 2.5% 0.6% 1.0% 0.6%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.60 [0.02, 14.91] 0.39 [0.2, 9.64] 0.46 [0.10, 4.19] 0.15 [0.02, 1.31] 2.07 [0.08, 51.26] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.01, 53.92] 0.41 [0.04, 3.98] 1.52 [0.06, 37.83] 0.58 [0.02, 14.34]	Odds Ratio M-H. Fixed, 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 3 2.4.3 Asian Amizrargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merza 2009 Metanat 2013 Oh 2007 Qu 2007 Selvaraj 2001 Shahsavar 2016	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 322 91 145 229 91 145 122 290 46 120 114 93 3142 290 46 120 0114 93 93 1014	Total 131 161 98 390 2 (P = 0.00) 40 93 40 93 41 55 113 151 124 94 25 306 306 46 120 117 93 145 61 210 100	Contr Events 93 415 362 870 22); l ² = 01) 122 103 50 109 83 121 210 272 40 99 90 60 193 3121 212 121 120 101 101	ol Total 95 367 878 34% 123 103 50 113 83 200 80 80 80 80 80 80 80 80 80 80 80 80 8	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 0.6% 1.3% 2.6% 0.6% 1.4.2% 0.6% 2.3% 0.6% 1.0%	Odds Ratio M-H, Fixed, 35% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.09 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.56 [0.16, 1.95] 0.56 [0.16, 1.95] 0.59 [0.22, 1.27] Not estimable 0.53 [0.22, 1.27] Not estimable 0.53 [0.22, 1.27] Not estimable 0.53 [0.02, 1.33] 0.58 [0.06, 37.83] 0.58 [0.02, 1.434] Not estimable	Odds Ratio M-H, Fixed. 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Filness 2004 Mabunda 2015 Subtotal (95% cl) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merza 2009 Metanat 2013 Oh 2007 Selvaraj 2001 Shahsavar 2016 Sharma 2010	TB Events 125 139 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 22 91 145 290 46 120 46 120 114 209 104 61 209 122	Total 131 161 98 390 2 (P = 0.00 40 93 151 124 94 95 145 306 145 306 145 306 124 93 145 306 120 1210 93 145 561 210 100 185	Contr Events 93 362 870 222): l ² = 103 50 109 83 3197 80 231 122 40 99 90 60 193 116 121 120 193 116 121 120 101 121 120 121 120 121 121 121	ol Total 95 416 367 878 34% 123 103 50 34% 113 83 200 80 25 211 280 00 194 100 194 117 222 120 1020 155	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 0.6% 14.2% 0.6% 2.3% 0.6% 2.3% 0.6% 2.5% 0.6% 2.5% 0.6% 2.5% 0.6% 2.6%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.66 [0.16, 1.95] 0.60 [0.02, 14.91] 0.39 [0.15, 5.64] 0.39 [0.02, 9.64] 0.45 [0.06, 21.31] 2.07 [0.08, 51.26] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.01, 5.32] 1.45 [0.06, 35.92] 0.41 [0.04, 3.98] 1.52 [0.06, 37.83] 0.58 [0.02, 14.34] Not estimable 0.79 [0.13, 4.81]	Odds Ratio M-H. Fixed. 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi² = 3 Test for overall effect: 2.4.3 Asian Amizrargar 2006 Anocsheh 2011 Cheng 2015 Fan 2010 Gharmari 2016 Gharghaniu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Metzaa 2009 Metanat 2013 Oh 2007 Selvaraj 2001 Shahsavar 2016 Sharma 2010 Test 2010	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 3 222 91 145 290 415 290 114 93 145 290 114 93 145 290 145 209 100 114 93 145 209 100 114 93 145 209 100 114 145 209 100 114 145 209 100 114 145 209 100 114 145 209 114 145 209 114 145 209 114 145 209 114 145 209 114 145 209 114 145 209 114 145 209 114 145 209 114 145 209 114 145 209 114 145 209 114 114 114 114 114 114 114 11	Total 131 161 98 330 2 (P = 0, 0.00 40 93 65 113 151 124 94 256 96 145 306 120 117 93 145 306 61 210 100 101 105 44	Contr Events 93 362 870 22); l ² = 103 50 01) 122 103 50 00 83 107 80 23 109 83 107 80 23 21 210 272 24 99 99 99 90 00 103 112 120 213 121 50 20 213 50 20 50 50 50 50 50 50 50 50 50 50 50 50 50	ol Total 95 367 878 34% 123 103 50 113 83 200 80 25 2211 280 40 100 60 60 194 117 2212 100 100 55 105 50 80 25 20 20 20 20 20 20 20 20 20 20 20 20 20	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 2.6% 5.3% 0.6% 14.2% 0.4% 2.5% 0.6% 2.5% 0.6% 2.5% 0.6% 2.5% 0.6% 2.5% 0.6% 2.5% 0.6% 2.5% 0.6% 0.4% 0.6% 0	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.60 [0.02, 14.91] 0.33 [0.02, 9.64] 0.44 [0.10, 4.19] 0.15 [0.02, 1.31] 2.07 [0.08, 51.26] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.01, 3.38] 1.52 [0.06, 37.83] 0.58 [0.02, 14.34] Not estimable 1.52 [0.02, 13, 4.81] Not estimable 0.79 [0.13, 4.81] Not estimable	Odds Ratio M-H. Fixed, 95% CI	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 3 2.4.3 Asian Amizrargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Metanat 2013 Oh 2007 Qu 2007 Selvaraj 2001 Shahsavar 2016 Sharma 2010 Tang 2008 Varahram 2014	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 322 91 145 2290 46 120 93 142 290 46 120 114 93 142 61 209 100 182 44 4 150	Total 131 161 98 390 2 (P = 0.000 40 93 40 93 40 93 113 151 124 94 25 306 46 120 117 93 145 61 210 100 185 44 151 100 185 44 151	Contr Events 93 415 362 870 22); l ² = 01) 122 103 0 0 109 83 121 210 272 40 99 90 60 193 3121 120 121 210 272 40 99 90 80 312 121 210 131 51 51 51 51 51 51 51 51 51 51 51 51 51	ol Total 95 416 367 878 34% 123 103 50 113 83 34% 123 200 80 25 122 211 280 40 100 194 40 100 194 122 120 100 195 122 120 100 195 100 100 100 100 100 100 100 100 100 10	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.3% 2.6% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.6% 1.0%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.50 [0.02, 14, 91] 0.56 [0.16, 1.95] 0.56 [0.16, 1.95] 0.56 [0.16, 1.95] 0.56 [0.16, 1.95] 0.59 [0.22, 1.27] Not estimable 0.53 [0.22, 1.27] Not estimable 0.79 [0.13, 3.8] 1.52 [0.06, 37.83] 0.58 [0.02, 14, 34] Not estimable 0.79 [0.13, 4.81] Not estimable 0.60 [0.02, 14, 94] 0.54 [0.04, 2.97] 0.54 [0.04, 2.97] 0.55 [0.02, 14, 34] Not estimable 0.60 [0.02, 14, 94] 0.64 [0.04, 2.97] 0.54 [0.04, 2.97] 0.54 [0.04, 2.97] 0.54 [0.04, 2.97] 0.54 [0.04, 2.97] 0.55 [0.22, 14, 34] Not estimable 0.60 [0.02, 14, 94] 0.64 [0.04, 2.97] 0.54 [0.44, 2.97] 0.54 [0.44, 2.97] 0.54 [0.44, 2.97] 0.55 [0.22, 14, 34] 0.55	Odds Ratio M-H, Fixed. 95% CI	Risk of Bias A B C D E F G
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Filness 2004 Mabunda 2015 Subtotal (95% cl) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merza 2009 Metanat 2013 On 2007 Selvaraj 2001 Shahsavar 2016 Sharma 2010	TB Events 125 159 84 368 3.04, df = ; Z = 4.33 (f 40 93 63 106 150 122 93 22 91 145 290 46 120 46 120 46 120 46 120 145 290 46 120 145 293 293 145 150 150 150 150 150 150 150 15	Total 131 161 98 3300 2 (P = 0.00 40 93 113 151 124 94 256 306 46 124 94 256 306 46 120 145 100 185 44 151 149 200	Contr Events 93 362 870 22); l ² = 01) 122 103 50 109 83 197 80 23 197 80 23 197 80 23 197 212 210 212 210 212 210 212 210 212 212	ol Total 95 416 367 878 34% 123 103 50 34% 123 200 80 80 25 211 280 00 194 117 200 100 194 1122 120 100 105 105 105 83 3147	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 0.6% 1.3% 2.6% 1.3% 2.6% 0.6% 1.0% 2.6% 1.0% 1.0% 1.0%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.66 [0.16, 1.95] 0.60 [0.2, 14.91] 0.33 [0.15, 5.64] 0.39 [0.02, 9.64] 0.44 [0.10, 4.19] 0.45 [0.05, 51.26] 0.53 [0.22, 1.31] 2.07 [0.08, 51.26] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.01, 5.32] 1.45 [0.06, 35.92] 0.41 [0.04, 3.98] 1.52 [0.06, 37.83] 0.58 [0.02, 14.31] Not estimable 0.79 [0.13, 4.81] Not estimable 0.79 [0.14, 92 [0.14] 0.71 [0.14, 92 [0.14] 0.71 [0.	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2.4.3 Asian Amirzargar 2006 Anocsheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merza 2009 Metanat 2013 Oh 2007 Selvaraj 2001 Shahsavar 2016 Sharma 2010 Tang 2008 Varahram 2014 Vejbaesya 2007 Yang 2010	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 222 93 1145 290 466 120 114 93 145 290 1145 209 100 1182 61 148 199 100 188 199 100 188 199 100 188 199 199 100 188 199 199 199 100 114 199 199 199 199 199 199 199	Total 131 161 98 380 2 (P = 0, 0.00 40 93 65 113 151 124 40 94 256 96 306 113 124 125 96 120 117 93 145 306 61 200 151 149 200 58	Contr Events 93 362 870 22); l ² = 103 50 01) 122 103 50 90 83 3197 80 23 121 210 272 240 99 90 00 272 121 210 272 210 121 210 272 210 121 210 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 212 121 50 50 121 212 121 50 212 121 50 212 121 50 121 212 121 210 121 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 210 212 121 121	ol Total 95 367 878 34% 123 103 500 113 83 200 80 200 201 22 211 280 00 100 60 60 194 117 122 120 100 100 83 3147 127 75 0	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 2.6% 0.4% 2.3% 0.4% 2.3% 0.4% 2.5% 0.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 0.	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.60 [0.02, 14.91] 0.33 [0.02, 9.64] 0.54 [0.10, 4.19] 0.15 [0.02, 1.31] 2.07 [0.08, 51.26] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.72 [0.01, 5.32] 1.45 [0.06, 37.83] 0.58 [0.02, 14.34] Not estimable 0.79 [0.13, 4.81] Not estimable 0.60 [0.02, 14.91] 0.34 [0.01, 8.30] 2.04 [0.18, 22.69] Not estimable	Odds Ratio M-H. Fixed. 95% CI	Risk of Bias A B C D E F G
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi² = 3 Test for overall effect: 3 2.4.3 Asian Amizzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamat 2016 Gharmar 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Metzra 2009 Metanat 2013 Oh 2007 Qu 2007 Selvaraj 2001 Shahsavar 2016 Sharma 2010 Tang 2008 Varahram 2014 Vejbaesya 2007 Yang 2010 Zhang 2017 Zhang 2018	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 222 91 145 290 46 120 142 61 209 100 182 441 153 142 61 209 100 182 44 159 100 182 44 159 100 182 44 199 100 182 44 199 100 182 44 199 100 182 44 199 100 182 44 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 100 182 199 199 199 199 199 100 182 199 100 182 199 100 182 199 100 182 199 199 198 198 199 100 182 199 100 182 199 199 199 199 199 199 199 19	Total 131 161 98 390 2 (P = 0.00) 40 93 40 93 40 93 113 151 124 94 296 3066 46 120 117 93 306 46 120 117 93 145 61 210 185 44 151 149 200 58 240	Contr Events 93 415 362 870 22); l ² = 01) 122 103 0 109 83 197 80 0 23 197 80 0 23 197 80 0 197 80 0 197 80 0 197 80 197 80 197 80 197 197 80 197 197 80 197 197 80 197 197 80 197 197 197 197 197 197 197 197 197 197	ol Total 95 416 367 878 34% 123 103 50 113 83 50 113 83 200 80 25 122 211 280 40 100 194 40 100 194 40 100 195 50 8 8 31 47 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.3% 2.6% 1.3% 2.6% 1.0% 1.0% 1.0% 1.4% 0.9%	Odds Ratio M-H. Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.50 [0.01, 5.36] 0.56 [0.16, 1.96] 0.56 [0.16, 1.96] 0.56 [0.10, 2.14.91] 0.33 [0.22, 9.64] 0.39 [0.02, 14.91] 0.53 [0.22, 1.27] Not estimable 0.53 [0.22, 1.27] Not estimable 0.53 [0.22, 1.27] Not estimable 0.53 [0.22, 1.27] Not estimable 0.53 [0.22, 1.23] 1.45 [0.06, 37.83] 1.52 [0.06, 37.83] 0.58 [0.02, 14.34] Not estimable 0.59 [0.13, 4.81] 0.54 [0.01, 8.20] 2.04 [0.01, 8.30] 2.04 [0.01, 8.30] 2.04 [0.01, 8.30] 2.04 [0.18, 22.68] Not estimable Not estimable	Odds Ratio	Risk of Bias A B C D E F G
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect : 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merza 2009 Metanat 2013 Oh 2007 Qu 2007 Selvaraj 2001 Shahsavar 2016 Sharma 2014 Varahram 2017	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 22 91 145 290 46 120 46 120 46 120 142 61 209 100 46 120 142 61 209 100 120 142 61 209 100 120 120 120 120 120 120 120	Total 131 161 98 390 2 (P = 0.00 40 93 5113 151 124 96 145 306 46 120 145 61 210 185 44 210 185 44 200 58 240 373	Contr Events 93 362 870 22); ² = 01) 122 103 201 109 83 107 80 272 23 121 210 272 40 99 99 103 112 120 121 120 153 108 83 147 50 50 50 50 50 50 50 50 50 50 50 50 50	ol Total 95 416 367 878 34% 123 103 50 113 83 200 201 13 83 200 201 13 83 200 201 13 80 202 211 122 211 280 00 194 13 80 202 122 211 128 100 55 51 52 51 52 51 52 52 52 52 52 52 52 52 52 52 52 52 52	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 0.6% 1.3% 2.6% 1.0% 2.6% 1.0% 1.4% 0.9% 0.5%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.66 [0.16, 1.95] 0.60 [0.02, 14.91] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.01, 5.32] 1.45 [0.06, 35.92] 1.45 [0.06, 37.83] 0.58 [0.02, 14.34] Not estimable 0.79 [0.13, 4.81] Not estimable 0.60 [0.02, 14.91] 0.34 [0.01, 8.206] Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable	Odds Ratio M-H, Fixed. 95% CI	Risk of Bias A B C D E F G
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% cl) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2.4.3 Asian Amirzargar 2006 Anocsheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2011 Lv 2016 Merza 2009 Metanat 2013 Oh 2007 Selvaraj 2001 Shahsavar 2016 Sharma 2010 Tang 2008 Varahram 2014 Vejbaesya 2007 Yang 2010 Zhang 2017 Zheng 2018 Zhou 2017 Subtotal (95% Cl)	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 106 150 122 93 229 91 145 290 46 120 114 93 145 290 100 182 41 145 290 100 182 41 193 106 193 106 193 106 193 106 193 106 193 106 100 115 200 100 115 209 100 115 100 115 100 100 100 115 100 115 100 115 100 100	Total 131 161 98 3300 2 (P = 0, 0, 00) 40 93 151 124 94 95 113 151 124 94 94 95 661 120 1145 306 61 210 1185 44 151 149 200 58 240 58 240 373 3544	Contr 93 362 870 22); l² = 103 500 122 103 501 122 103 501 122 103 201 121 210 272 40 99 60 121 120 121 120 100 121 120 121 120 121 120 100 121 120 101 121 121 121 121 121 120 133 147 150 360	ol Total 95 416 367 878 34% 123 103 50 200 80 200 80 200 80 200 80 200 113 83 200 80 200 113 83 200 00 113 83 200 00 113 83 200 113 80 201 122 211 280 100 113 80 201 112 80 113 80 201 112 80 113 80 201 112 80 112 80 112 80 112 80 112 80 112 80 112 80 112 80 112 80 112 80 112 80 112 80 112 80 112 80 112 80 100 100 100 100 100 100 100 100 100	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.6% 1.3% 2.6% 1.4.2% 0.4% 2.5% 0.6% 1.0% 1.0% 2.6% 1.0% 1.0% 2.6% 1.0% 2.6% 5.3% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 0.6% 1.0% 0.6% 1.0% 0.6% 1.0% 0.6% 0.0% 0.5% 0.6% 0.0% 0.5% 0.0% 0.5% 0.0% 0.5% 0.0% 0.5% 0.0% 0.5%	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.60 [0.02, 14.91] 0.33 [0.15, 5.64] 0.39 [0.02, 9.64] 0.45 [0.06, 35.22] 0.15 [0.02, 1.31] 2.07 [0.08, 51.26] 0.53 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.01, 5.32] 1.45 [0.06, 37.83] 0.58 [0.02, 14.91] Not estimable 0.79 [0.13, 4.81] Not estimable 0.60 [0.02, 14.91] 0.34 [0.01, 8.30] 2.04 [0.18, 22.69] Not estimable 5.18 [0.25, 108.27] 0.64 [0.42, 0.99]	Odds Ratio M-H. Fixed. 95% CI	Risk of Bias A B C D E F G
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi² = 3 Test for overall effect: 2.4.3 Asian Amizzargar 2006 Anocsheh 2011 Cheng 2015 Fan 2010 Ghamari 2016 Gharari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Metzra 2009 Metanat 2013 Oh 2007 Selvaraj 2001 Shahsavar 2016 Sharma 2010 Tang 2008 Varahram 2014 Vejbaesya 2007 Yang 2010 Zhang 2017 Zheng 2018 Zhou 2017 Subtotal (95% CI) Total events	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 222 91 145 290 46 120 145 290 41 120 145 290 145 290 145 290 145 290 145 290 145 120 120 120 120 120 120 120 120	Total 131 161 98 330 2 (P = 0.00 40 93 65 113 151 124 25 96 306 113 151 124 255 96 145 306 145 210 100 185 44 151 149 200 584 200 3544	Contr Events 93 415 362 870 22); l ² = 01) 122 103 50 109 83 50 109 83 121 210 272 40 960 193 3127 272 40 960 193 3127 121 121 210 305 55 50 360 3365 55 50 360 3365 55 50 360 3365 55 50 360 3365 55 50 360 3365 55 50 360 3365 55 50 360 3365 55 50 360 360 360 360 360 360 360 360 360 36	ol Total 95 416 367 878 34% 123 103 50 113 80 200 80 25 122 211 280 40 00 60 194 40 100 105 122 201 1280 40 00 105 108 83 3495	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.3% 2.3% 1.3% 2.6% 1.0% 1.	Odds Ratio M-H. Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.50 [0.02, 14, 91] 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.60 [0.02, 14, 91] 0.33 [0.22, 9.64] 0.33 [0.22, 9.64] 0.33 [0.22, 1.27] Not estimable 0.53 [0.02, 14, 34] 0.54 [0.01, 5, 126] 0.53 [0.22, 1.27] Not estimable 0.53 [0.02, 14, 34] 0.27 [0.01, 5, 32] 1.45 [0.06, 37, 83] 0.58 [0.02, 14, 34] Not estimable 0.79 [0.13, 4.81] Not estimable 0.58 [0.02, 14, 34] Not estimable 0.58 [0.02, 14, 34] Not estimable 0.58 [0.02, 14, 34] Not estimable 0.58 [0.02, 14, 34] Not estimable 0.60 [0.02, 14, 34] Not estimable 0.60 [0.02, 14, 34] Not estimable 0.60 [0.02, 14, 34] Not estimable 0.61 [0.18, 30] 2.04 [0.18, 22, 69] Not estimable 5.18 [0.25, 108, 27] 0.64 [0.42, 0.99]	Odds Ratio	Risk of Bias
В	Study or Subgroup 2.4.1 African Ben-Selma 2011 Fitness 2004 Mabunda 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect : 2.4.3 Asian Amirzargar 2006 Anoosheh 2011 Cheng 2015 Fan 2010 Ghamani 2016 Ghorghanlu 2016 Hasan 2014 Hu 2013 Jafari 2016 Kumar 2008 Li 2017 Lin 2011 Lv 2016 Merza 2009 Metanat 2013 Oh 2007 Selvaraj 2001 Shahsavar 2016 Shahsavar 2016 Shahsavar 2016 Shahsavar 2016 Shahsavar 2016 Shahsavar 2016 Shahsavar 2010 Tang 2008 Varahram 2014 Vejabasya 2007 Yang 2010 Zhang 2017 Zheng 2018 Zhou 2017 Subtotal (95% CI) Total events	TB Events 125 159 84 368 3.04, df = 2 Z = 4.33 (f 40 93 63 106 150 122 93 22 91 145 290 46 120 145 290 46 120 145 290 161 209 100 162 61 209 100 162 61 209 100 165 293 322 91 145 290 165 293 322 91 145 290 165 165 165 165 165 165 165 165	Total 131 161 98 390 2 (P = 0.00 40 93 65 113 151 124 94 25 306 46 120 145 61 210 185 44 151 149 200 58 240 373 3544 20 (P = 1)	Contr Events 93 362 870 222); l ² = 01) 122 103 05 109 83 3197 80 022); l ² = 01) 121 120 133 137 80 022; l ² = 103 109 83 3121 121 210 122 103 109 83 3121 121 210 122 103 109 83 315 122 121 121 122 103 109 83 315 121 121 121 121 121 121 121 121 121 1	ol Total 95 416 367 878 34% 123 103 500 113 83 200 80 200 113 83 200 80 200 113 83 200 80 201 122 211 280 60 194 122 120 100 100 195 5 122 211 128 103 80 200 80 80 201 80 80 80 80 80 80 80 80 80 80 80 80 80	Weight 4.7% 2.8% 20.9% 28.4% 0.7% 2.1% 6.5% 1.0% 2.3% 0.6% 1.3% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.6% 1.0% 2.5% 1.0% 2.5% 1.0% 2.5% 1.0% 2.5% 1.0% 2.5% 1.0% 2.3% 0.6% 1.0% 2.5% 1.0% 2.5% 1.0% 2.3% 0.6% 1.0% 2.5% 1.0% 2.5% 1.0% 2.5% 1.0% 2.5% 1.0% 2.3% 0.6% 1.0% 2.5% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 2.5% 0.6% 1.0% 1.	Odds Ratio M-H, Fixed, 95% C 0.45 [0.09, 2.27] 0.19 [0.02, 2.13] 0.08 [0.03, 0.24] 0.15 [0.07, 0.36] 0.99 [0.04, 24.83] Not estimable 0.25 [0.01, 5.36] 0.56 [0.16, 1.95] 0.60 [0.02, 14.91] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.15, 5.64] 0.33 [0.22, 1.27] Not estimable 3.63 [0.15, 90.17] 0.27 [0.01, 5.32] 1.45 [0.06, 37.83] 0.58 [0.02, 14.34] 1.52 [0.06, 37.83] 0.58 [0.02, 14.34] Not estimable 0.79 [0.13, 4.81] Not estimable 0.60 [0.02, 14.91] 0.34 [0.01, 8.206] Not estimable 0.79 [0.13, 4.81] Not estimable 0.60 [0.02, 14.91] 0.34 [0.01, 8.269] Not estimable 5.18 [0.25, 108.27] 0.64 [0.42, 0.99]	Odds Ratio M-H. Fixed. 95% CI	Risk of Bias A B C D E F G

homozygote genetic model (A) and the dominant genetic model (B) in African or Asian population.

for the rs1800629 polymorphism, similar results were observed in the multi-center source population under five genetic models. Unlike rs361525 and rs1800629, rs1799724 polymorphism had a significantly increased TB susceptibility under the homozygote genetic model, and the dominant genetic model in both single-center source population and multi-center source population, respectively. On the contrary, rs1799724 polymorphism had a significantly decreased TB susceptibility under the recessive genetic model in the population of both sources.

TB types

For the rs361525 polymorphism, decreased TB risk was observed in PTB rather than other TB types (including EPTB, STB, OATB, and NA listed in Table 2 under the homozygote genetic model, and the



allele genetic model (A), the homozygote genetic model (B), the dominant genetic model(C), and the recessive genetic model (D) in Asian population.



Figure 5: Begg's funnel plot analysis for the evaluation of potential publication bias in 40 included articles under the allele genetic model. (A) rs361525, (B) rs1800629, (C) rs1799724 and (D) rs1800630.

dominant genetic model, but an increased TB risk under the recessive genetic model. For the rs1800629 polymorphism, the similar results were observed in PTB rather than other TB types under the

homozygote genetic model, the dominant genetic model, and the recessive genetic model. Differently, rs1799724 polymorphism had a significantly increased TB susceptibility under the homozygote

Wu X, et al.,

Journal of Bacteriology and Vaccine Research

Table 2: Characteristics of studies included in the meta-analysis.

		Studies			Samula						Mutation	Cases			Matching fac	ors e	
No	Year	First author	Country or area	Ethnicity	size Cases/ controls	HWE*	Source of population ^b	Type of TB ^c	HIV status	Mutation site	detection method ^d	Mean age (year)	Gender (Male/ Female)	Age	Gender	nationality	Quality score ^r
1	2018	Zheng, M.F.	China	ES Asian	240/150	>0.05	1	STB	Negative	-224, rs361525, rs1800629, rs1799724, and rs1800620	DNA sequencing	NA	NA	+	+	+	12
2	2017	Li, Q.F.	China	ES Asian	306/280	0.67	2	PTB	NA	rs361525, rs1800629, rs1799724, rs1800630, and rs1799964	PCR-RFLP	47.69±13.37	173/133	+	+	+	8
3	2017	Ceylan, E.	Turkey	Caucasian	69/70	NA	1	NA	NA	rs1800629	PCR-RFLP	37.8 ± 12.7	47/22	+	+	+	5
4	2017	Zhou. Y.	China	ES Asian	373/362	>0.05	4	NA	NA	rs361525, rs1800629	M-PCR	45.11±14.53	199/174		-	+	9
5	2017	Zhang, Y. K.	China	ES Asian	58/50	NA	1	STB	Negative	rs361525, rs1800629	PCR-SSP	37.21±13.15	40/18	+	+	+	9
6	2016	Shahsavar, F.	Iran	SW Asian	100/100	NA	1	PTB	NA	rs361525, and rs1800629	PCR-RFLP	39.65 ± 3.87	40/60	+	+	+	5
7	2016	Lv, Y.J.	China	ES Asian	120/100	>0.05	1	OATB	Negative	rs361525, and rs1800630	PCR-RFLP	40.1 ± 8.5	72/48	+	+	+	9
8	2016	Jafari, M.	Iran	SW Asian	96/122	>0.05	3	PTB	NA	rs1800629	ARMS- PCR	51 ± 31	56/40		-	+	6
9	2016	Ghorghanlu, S.	Iran	SW Asian	124/200	0.91	3	NA	Negative	rs1800629	AS-PCR	NA	71/53			+	10
10	2016	Ghamari, E.	Iran	SW Asian	151/83	NA	1	РТВ	NA	rs1800629, rs1799724, andrs1800630	PCR-RFLP	49.2±21.2	78/73	+	+	+	6
11	2015	Mabunda, N.	Mozambique	African	102/456	0.52	3	РТВ	Negative	rs1800629	RT-PCR	33.8 ± 13	57/45	-	-	+	10
12	2015	Cheng, Z.G.	China	ES Asian	65/50	>0.05	1	OATB	Negative	rs361525, rs1800629	AS-PCR	39.24±13.56	38/27	+	+	+	10
13	2015	Caliskan, T.	Turkey	Caucasian	92/42	0.44	3	PTB	NA	rs1800629	DNA sequencing	29.75 ± 13.87	70/22	+	+	+	9
14	2014	Hasan, K. K.	Iraq	SW Asian	94/80	0.39	1	PTB	NA	rs361525, rs1800629 rs361525.	PCR-SSP	43.5±1.7	70/24	+	+	+	5
15	2014	Varahram, M.	Iran	SW Asian	151/83	0.48	1	РТВ	NA	rs1800629, and rs1799724	PCR- RFLP	48.7±22.1	78/73	+	+	+	6
16	2013	Hu, Y.L.	China	ES Asian	25/25	NA	1	NA	NA	rs1800629	PCR- RFLP	NA	NA	-	-	+	2
17	2013	Metanat, M.	Iran	SW Asian	100/194	0.52	1	EPTB/	NA	rs1800629	PCR-SSP	NA	49/51	+	+	+	5
18	2011	W.	Tunisia	African	131/95	0.95	1	EPTB	Negative	rs1800629	PCR-RFLP	44 and 39 g	68/63	+	+	+	9
19	2011	Lin, C. Y.	China	ES Asian	46/40	1	1	OATB	NA	rs1800629	AS-PCR	39.2±13.6	29/17	+	+	+	5
20	2011	Dong, J.	China	ES Asian	302/302	NA	1	PTB	Negative	rs1799724 rs361525, -244, rs1800629	PCR	34.7±16.2	219/83	+	+	+	11
21	2011	S.	Iran	SW Asian	93/103	0.39	2	PTB	NA	rs1799724 and rs1800630 rs361525,	PCR-RFLP	50.04	NA		+	+	5
22	2010	Sharma, S.	India	ES Asian	185/155	1	2	PTB	Negative	rs1800629, rs1799724, rs1800630, and rs1799964	NA	32.16 ± 13.8	78/107	-	-	+	7
23	2010	Fan, H. M.	China	ES Asian	113/113	0.77	1	РТВ	NA	rs361525, rs1800629	PCR-RFLP	71.1	113/0	+	+	+	6
24	2010	Ma, M.J.	China	ES Asian	543/544	0.04	2	PTB	NA	rs1799724, and rs1800630	ARMS- PCR	34.75 ± 16.67	151/392	+	+	+	9
25	2010	Yang, H.	China	ES Asian	200/197	>0.05	2	PTB	NA	rs361525, rs1800629	PCR-SSP	33.1 ± 10.7	112/88	-	-	+	5
26	2009	Merza, M.	Iran	SW Asian	117/60	0.79	1	PTB	NA	rs361525, -244, rs1800629, rs1799724,	PCR-RFLP	NA	NA	+	+	+	6
27	2009	Trajkov, D.	Macedonia	Caucasian	75/301	0.1089	2	РТВ	NA	rs1800630 rs361525, and	PCR-SSP	20-59	NA			+	4
28	2008	Tang, M. Q.	China	ES Asian	44/108	0.54	1	РТВ	NA	rs1800629	PCR-RFLP	NA	NA			+	2
29	2008	Kumar, V.	India	ES Asian	145/211	0.12	3	NA	NA	rs1800629	ARMS-	33.9	91/54	+	+	+	9
30	2008	Ates, O.	Turkey	Caucasian	128/80	1	1	NA	NA	rs361525, rs1800629, and	ARMS- PCR	47.84 ± 12.6	80/48	+	+	+	7
31	2007	Qu, Y.	China	ES Asian	61/122	0.11	1	PTB	Negative	rs1800750 rs1800629	PCR-RFLP	69.3±5.9	61/0	+	+	+	8
32	2007	Vejbaesya,	Thailand	ES Asian	149/147	0.51	1	РТВ	Negative	+488, rs361525, and	PCR-SSP	17-70	87/62	+	+	+	9
33	2007	Oh, J. H.	Korea	ES Asian	145/117	0.18	2	РТВ	Negative	rs1800629 rs1800629	ARMS-	49.8 and 47 g	100/45	+	+	+	12
34	2006	Oral, H. B.	Turkey	Caucasian	81/50	>0.05	1	NA	NA	rs1800629	PCR-SSP	NA	NA	+	+	+	5
35	2006	Amirzargar, A. A.	Iran	SW Asian	41/123	0.27	1	РТВ	NA	rs361525, rs1800629	PCR-SSP	NA	NA			+	2
36	2005	Correa, P. A.	Colombia	Caucasian	135/430	0.82	1	РТВ	Negative	rs361525, rs1800629	PCR-RFLP	40±16	17/118	-	+	+	8
37	2004	Fitness, J.	Malawi	African	181/533	0.1536	1	NA	Negative	rs361525, rs1800629,	ARMS- PCR	>15	NA	+	+	+	10
38	2003	Scola, L.	Sicilia	Caucasian	45/114	0.81	1	РТВ	NA	rs1800630 rs1800629	ARMS-	NA	NA	+	+	+	5
39	2002	Delgado, J. C.	Cambodia	Caucasian	358/106	NA	1	РТВ	Negative	rs1800629, rs1799724, rs1800630,	PCR-RFLP	42.2±14.1	134/224	-	-	+	8
40	2001	Selvaraj, P.	India	ES Asian	210/120	0.4	2	РТВ	NA	rs361525, rs1800629	NA	37.7±1.1	164/46			+	5

7

a: HWE=Hardy-Weinberg Equilibrium, the data listed here indicate the HWE value of controls.

b: Source of population was obtained from each full article, the number in each form represent the number of hospitals or centers registered by TB patients. NA means this information was not given in the article.

c: EPTB=Extrapulmonary TB; OATB=Osteoarticular tuberculosis; PTB=Pulmonary TB; STB=Spinal TB; TB=tuberculosis.

d: ARMS-PCR=Amplification Refractory Mutation System-Polymerase Chain Reaction; AS-PCR=Allele-Specific PCR; DNA=Deoxyribonucleic Acid; M-PCR=Multiplex Polymerase Chain Reaction; PCR-RFLP=Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; PCR-SSP=Polymerase Chain Reaction-Sequence Specific Primers; RT-PCR=Real Time-Polymerase Chain Reaction.

e: There are three matching factors in this meta-analysis, age, gender, and nationality. If age, gender and nationality were matched in case group and control group, it was labeled +, otherwise it was labeled as -.

f: Studies that received an overall score of 9 or higher were classified as high-quality studies, those with an overall score of 6-8 were classified as medium-quality studies, and those with an overall score of 5 or lower were considered low-quality studies for the purpose of this analysis. These cut points were chosen according to the distribution of relative quality scores of all included studies.

g: The TB patients were divided into different groups, such as PTB and EPTB. Each number indicates the mean age of each group of TB patients, respectively.

Table 3: Distribution of gene polymorphism of studies included in the meta-analysis.

First author	Year	SNP [*]										
First author	rear	TNF-224	rs361525	rs673	rs1800629	rs1800750	TNF+488	rs1799724	rs1800630	rs1799964		
Amirzargar, A. A.	2006	0	•	0	•	0	0	0	0	0		
Anoosheh, S.	2011	0	•	•	•	0	0	•	•	0		
Ates, O.	2008	0	•	0	•	•	0	0	0	0		
Ben-Selma, W.	2011	0	0	0	•	0	0	0	0	0		
Caliskan, T.	2015	0	0	0	•	0	0	0	0	0		
Ceylan, E.	2017	0	0	0	•	0	0	0	0	0		
Cheng, Z.G.	2015	0	•	0	•	0	0	0	0	0		
Correa, P. A.	2005	0	•	0	•	0	0	0	0	0		
Delgado, J. C.	2002	0	0	0	•	0	0	•	•	•		
Dong, J.	2011	0	0	0	0	0	0	•	0	0		
Fan, H. M.	2010	0	•	0	•	0	0	0	0	0		
Fitness, J.	2004	0	•	0	•	0	0	0	•	0		
Ghamari, E.	2016	0	•	0	•	0	0	•	•	0		
Ghorghanlu, S.	2016	0	0	0	•	0	0	0	0	0		
Hasan, K. K.	2014	0	•	0	•	0	0	0	0	0		
Hu, Y.L.	2013	0	0	0	•	0	0	0	0	0		
Jafari, M.	2016	0	0	0	•	0	0	0	0	0		
Kumar, V.	2008	0	0	0	•	0	0	0	0	0		
Li, Q.F.	2017	0	•	0	•	0	0	•	•	•		
Lin, C. Y.	2011	0	•	0	•	0	0	0	0	0		
Lv, Y.J.	2016	0	•	0	•	0	0	0	•	0		
Ma, M.J.	2010	0	0	0	0	0	0	•	•	0		
Mabunda, N.	2015	0	0	0	•	0	0	0	0	0		
Merza, M.	2009	0	•	•	•	0	0	•	•	0		
Metanat, M.	2013	0	•	0	•	0	0	0	0	0		
Oh, J. H.	2007	0	0	0	•	0	0	0	0	0		
Oral, H. B.	2006	0	0	0	•	0	0	0	0	0		
Qu, Y.	2007	0	0	0	•	0	0	0	0	0		
Scola, L.	2003	0	0	0	•	0	0	0	0	0		
Selvaraj, P.	2001	0	•	0	•	0	0	0	0	0		
Shahsavar, F.	2016	0	•	0	•	0	0	0	0	0		
Sharma, S.	2010	0	•	0	•	0	0	•	•	0		
Tang, M. Q.	2008	0	0	0	•	0	0	0	0	0		
Trajkov, D.	2009	0	•	0	•	0	0	0	0	0		
Varahram, M.	2014	0	•	0	•	0	0	•	0	0		
Vejbaesya, S.	2007	0	•	0	•	0	•	0	0	0		
Yang, H.	2010	0	•	0	•	0	0	0	0	0		
Zhang, Y.K.	2017	0	•	0	•	0	0	0	0	0		
Zhou. Y.	2017	0	•	0	•	0	0	0	0	0		
Zheng, M.F.	2018		•	0	•	0	0	•	•	0		

	Comparison	Studies	Participants	Test of associ	Tes	Medalad			
SNP	Comparison	Studies	Participants	OR (95%CI)	<i>P</i> value	Chi ²	²	P _{heterogeneity} ^c	wodels
			<u>`</u>	rs361525 (TNF-238)					
African	G <i>v</i> s A	1	1428	1.25 [0.74, 2.11]	0.4	NA	NA	NA	R
	GG <i>v</i> s AA	1	626	Not estimable	NA	NA	NA	NA	R
	GG <i>vs</i> GA	1	714	1.27 [0.74, 2.17]	0.39	NA	NA	NA	R
	GG+GA vs AA	1	714	Not estimable	NA	NA	NA	NA	R
	AA vs GA+GG	1	714	Not estimable	NA	NA	NA	NA	R
Caucasian	G <i>v</i> s A	3	2298	0.67 [0.32, 1.41]	0.29	4.59	56%	0.1	R
	GG <i>vs</i> AA	3	955	0.97 [0.11, 8.75]	0.98	0.08	0%	0.78	F
	GG <i>vs</i> GA	3	1146	0.58 [0.26, 1.30]	0.19	4.94	60%	0.24	R
	GG+GA vs AA	3	1149	1.11 [0.12, 10.01]	0.93	0.02	0%	0.9	F
	AA vs GA+GG	3	1149	0.90 [0.10, 8.17]	0.93	0.02	0%	0.9	F
Asian	G vs A	20	10974	0.71 [0.47, 1.06]	0.09	92.91	80%	<0.00001	R
	GG vs AA	20	5012	0.49 [0.19, 1.23]	0.13	28.15	64%	0.002	R
	GG vs GA	20	5104	0.68 [0.45, 1.02]	0.06	60.81	69%	<0.00001	R
	GG+GA vs AA	20	5487	0.41 [0.28, 0.59]	<0.00001	14.04	29%	0.17	F
	AA vs GA+GG	20	5487	2.45 [1.70, 3.51]	<0.00001	14.04	29%	0.17	F
Total	G vs A	24	14700	0.73 [0.52, 1.02]	0.06	105.67	78%	<0.00001	R
	GG vs AA	24	6593	0.51 [0.22, 1.20]	0.12	29.57	59%	0.003	R
	GG <i>vs</i> GA	24	6964	0.70 [0.49, 0.99]	0.05	77.72	70%	<0.00001	R
	GG+GA vs AA	24	7350	0.42 [0.29, 0.60]	<0.00001	14.88	19%	0.25	F
	AA vs GA+GG	24	7350	2.38 [1.67, 3.39]	<0.00001	14.88	19%	0.25	F
				rs1800629 (TNF-308)					1
African	G vs A	3	2536	0.58 [0.32, 1.04]	0.07000	10.78	81%	0.005	R
	GG vs AA	3	981	0.14 [0.06, 0.32]	<0.00001	3.4	41%	0.18	F
	GG vs GA	3	1238	0.70 [0.47, 1.06]	0.09	3.61	45%	0.16	R
	GG+GA vs AA	3	1268	0.15 [0.07, 0.36]	<0.0001	3.04	34%	0.22	F
	AA vs GA+GG	3	1268	0.05 [0.02, 0.08]	0.26	25.91	92%	<0.00001	R
Caucasian	G vs A	8	4352	1.19 [0.95, 1.49]	0.33000	11.43	39%	0.12	R
	GG vs AA	8	1841	1.17 [0.66, 2.08]	0.58000	5.58	0%	0.47	F
	GG vs GA	8	2114	1.24 [0.94, 1.63]	0.12	13.99	50%	0.05	F
	GG+GA vs AA	8	2176	1.15 [0.65, 2.04]	0.62	5.59	0%	0.47	F
	AA vs GA+GG	8	2176	0.00 [-0.02, 0.01]	0.69	7.32	4%	0.4	F
Asian	G vs A	27	14078	0.81 [0.65, 1.00]	0.05	74.54	65%	<0.00001	R
	GG vs AA	27	5743	0.59 [0.38, 0.90]	0.02	8.98	0%	0.98	F
	GG vs GA	27	6959	0 80 [0 63 1 02]	0.07	76.56	66%	<0.00001	R
	GG+GA vs AA	27	7039	0.64 [0.42, 0.99]	0.04	8 19	0%	0.99	F
	AA vs GA+GG	27	7039	0.01 [0.00, 0.01]	0.05	21.69	0%	0.71	F
Total	G vs A	38	20966	0.84[0.70, 1.01]	0.06	116.87	68%	<0.00001	R
	GG VS AA	38	8565	0.58[0.42, 0.79]	0.0005	35.28	15%	0.23	F
	GG vs GA	38	10311	0.85[0.70, 1.04]	0.0000	102 45	64%	<0.00001	R
	GG+GA VS AA	38	10483	0.61 [0.45, 0.83]	0.002	32.02	6%	0.037	F
		38	10483		0.002	53.69	31%	0.037	F
	,		10-100	rs1799724 (TNF_857)	0.002	55.55	5170	0.07	•
African	CiveT	1	302	0.41 [0.23, 0.72]	0.002	NΔ	NΔ	NΔ	R
/ inicali		1	136	3 08 [0 15 65 52]	0.002	ΝΔ	NA	ΝΔ	F
		1	10/		<0.00001				D
		1	194	4 61 [0 22 07 10]	0.22	N/A N/A	NA	NA NA	F
		1	106		0.00				- ' -
Caucasian		1	190		0.33			N/A N/A	P
Caucasian	0 /5 1		920	0.91[0.40, 1.71]	0.70	INA	INA	INA	71

Table 4: Meta-analysis of the genetic polymorphisms of the TNF-α gene and susceptibility to TB by ethnicity and overall cohort.

	CC vs TT	1	442	1.10 [0.39, 3.11]	0.85	NA	NA	NA	F
	CC vs CT	1	443	0.55 [0.16, 1.91]	0.35	NA	NA	NA	R
	CC+CT vs TT	1	463	1.13 [0.40, 3.18]	0.82	NA	NA	NA	F
	TT vs CT+CC	1	463	0.89 [0.31, 2.50]	0.82	NA	NA	NA	F
Asian	C vs T	8	7406	0.99 [0.68, 1.44]	0.95	57.08	88%	<0.00001	R
	CC vs TT	8	2638	2.21 [1.02, 4.79]	0.04	14.70	52%	0.04	R
	CC vs CT	8	3614	0.91 [0.58, 1.42]	0.67	57.83	88%	<0.00001	R
	CC+CT vs TT	8	3703	2.05 [1.33,3.16]	0.001	13.65	49%	0.06	F
	TT vs CT+CC	8	3703	0.49 [0.32, 0.75]	0.001	13.65	49%	0.06	F
Total	C vs T	10	8724	0.91 [0.64, 1.28]	0.58	67.99	87%	<0.00001	R
	CC vs TT	10	3216	1.96 [1.32, 2.91]	0.0008	16.16	44%	0.06	F
	CC vs CT	10	4251	0.78 [0.50, 1.21]	0.27	72.68	88%	<0.00001	R
	CC+CT vs TT	10	4362	1.92 [1.30, 2.84]	0.001	15.03	40%	0.09	F
	TT vs CT+CC	10	4362	0.52 [0.35, 0.77]	0.001	15.03	40%	0.09	F
				rs1800630 (TNF-863)					
African	C vs A	1	1164	1.29 [0.88, 1.90]	0.19	NA	NA	NA	R
	CC vs AA	1	440	1.00 [0.25, 3.93]	1	NA	NA	NA	R
	CC vs CA	1	572	1.42 [0.91, 2.20]	0.12	NA	NA	NA	R
	CC+CA vs AA	1	582	0.92 [0.24, 3.61]	0.91	NA	NA	NA	R
	AA vs CA+CC	1	582	1.08 [0.28, 4.25]	0.91	NA	NA	NA	R
Caucasian	C vs A	1	924	1.18 [0.86, 1.64]	0.31	NA	NA	NA	R
	CC vs AA	1	266	1.54 [0.78, 3.06]	0.22	NA	NA	NA	R
	CC vs CA	1	412	1.04 [0.65, 1.66]	0.87	NA	NA	NA	R
	CC+CA vs AA	1	462	1.51 [0.79, 2.89]	0.21	NA	NA	NA	R
	AA vs CA+CC	1	462	0.66 [0.35, 1.26]	0.21	NA	NA	NA	R
Asian	C vs A	8	6460	0.87 [0.67, 1.13]	0.31	20.58	66%	0.004	R
	CC vs AA	8	2315	0.62 [0.28, 1.35]	0.23	14.27	51%	0.05	R
	CC vs CA	8	3118	0.93 [0.68, 1.27]	0.65	20.41	66%	0.005	R
	CC+CA vs AA	8	3230	0.64 [0.29, 1.41]	0.27	14.80	53%	0.04	R
	AA vs CA+CC	8	3230	1.56 [0.71, 3.46]	0.27	14.80	53%	0.04	R
Total	C vs A	10	8548	0.95 [0.76, 1.19]	0.64	27.54	67%	0.001	R
	CC vs AA	10	3021	0.77 [0.41, 1.45]	0.42	19.53	54%	0.02	R
	CC vs CA	10	4102	0.99 [0.76, 1.27]	0.91	23.91	62%	0.004	R
	CC+CA vs AA	10	4274	0.79 [0.42, 1.46]	0.44	19.71	54%	0.02	R
	AA vs CA+CC	10	4274	1.27 [0.69, 2.37]	0.44	19.71	54%	0.02	R

a: SNP=Single Nucleotide Polymorphism.

b: The statistical method used in Test of association is Mantel-Haenszel method. OR=Odds Ratio, CI=Confidence Interval.

c: Pheterogeneity=P value of heterogeneity.

d: R=Random-effect model, F=Fixed-effect model. The effect model used in test of heterogeneity was determined by the I² and Pheterogeneity value of total.

genetic model and the dominant genetic model, but a decreased TB susceptibility considerably under the recessive genetic model in PTB type. Furthermore, a reduced TB risk was observed in other TB types under the allele genetic model and the heterozygote genetic model. For the rs1800630 polymorphism, only a significantly increased TB risk was found in the other TB types under the heterozygote genetic model.

HIV status

For the rs361525 polymorphism, decreased TB risk was observed in the HIV negative population under the allele model and the heterozygote model. In addition, we also found a decreased TB risk under the dominant genetic model, and an increased TB risk under the recessive genetic model in HIV NA population. For the rs1800629 polymorphism, a decreased TB risk was found in the HIV negative population under the homozygote genetic model and the dominant genetic model, but an increased TB risk under the recessive genetic model. For rs1799724 polymorphism, opposite results were observed in the HIV NA population under the homozygote genetic model, the dominant genetic model, and the recessive genetic model.

Sensitivity analysis and potential publication bias

To determine the robustness of the pooled results, we conducted a sensitivity analysis by sequentially removing each study. In our present meta-analysis, there was statistically significant heterogeneity in all 4 SNPs. First, for rs361525 polymorphism, significant heterogeneity was observed under the allele genetic model, the homozygote genetic model, and the heterozygote model, and sensitivity analysis showed that there were four studies [25,26,30,54] respectively influencing the result of the I² values and Pheterogeneity. Second, for rs1800629 polymorphism, significant heterogeneity was observed under the allele genetic model, and the heterozygote genetic model and the heterozygote genetic model, the I² values

Sub	Sub Case/ Allele model					Homozygote model		Heterozygote model		Dominant model			I	Recessive model			I					
group	Studies	control	OR (95%	Р	²	P	OR (95%	Р	²	P	OR (95%	Р	1 ²	P	OR (95%	Р	²	P	OR (95%	Р	1 ²	P
			CI) ^a			neterogeneity	CI)			rs36152	CI) 5 (TNF-238)		neterogeneity	CI)			neterogeneity	CI)			neterogeneity
									N	umber of bo	spitals or ce	nters ^c										
			0.64 [0.42,				0.27				0.59			<	0.34	<			2.92	<		
1	1/	1989/2416	0.98]	0.04	0.8	< 0.00001	[0.10, 0.70] 1.22	0.007	0.59	0.02	[0.36, 0.97] 0.85	0.04	0.77	0.00001	[0.23, 0.50] 1.16	0.00001	0.04	0.4	[1.98, 4.32] 0.86	0.00001	0.04	0.4
≥2	7	1442/1518	0.89 [0.61, 1.29]	0.54	0.28	0.22	[0.42, 3.55]	0.71	0	0.73	[0.60, 1.22]	0.38	0.09	0.36	[0.43, 3.12]	0.77	0	0.74	[0.32, 2.33]	0.77	0	0.74
										TB	types											
PTB	16	2220/2569	0.73 [0.48,	0.15	0.82	< 0.00001	0.37 [0.15,	0.03	0.56	0.02	0.70 [0.44,	0.14	0.76	< 0.00001	0.36 [0.24,	< 0.00001	0.02	0.42	2.80 [1.91,	< 0.00001	0.02	0.42
Others	9	1311/1559	0.70 [0.44,	0.12	0.37	0.12	0.93] 0.91 [0.30	0.86	0	0.39	1.12] 0.61 [0.34	0.09	0.5	0.04	0.52]	0.92	0	0.38	4.10] 0.95 [0.32	0.92	0	0.38
		1011/1000	1.10]	0.12	0.07	0.12	2.76]	0.00		0.00	1.08]	0.00	0.0	0.01	3.09]	0.02		0.00	2.78]	0.02		0.00
							0.70			HIV	status											
HIV Negative	8	1133/1615	0.63 [0.45, 0.89]	0.009	0.48	0.06	[0.28, 2.06]	0.59	0	0.7	0.57 [0.35, 0.91]	0.02	0.64	0.007	0.85 [0.33, 2.17]	0.73	0	0.67	1.18 [0.46, 3.01]	0.73	0	0.67
HIV NA	16	2298/2319	0.82 [0.50, 1.36]	0.44	0.84	< 0.00001	0.46 [0.16,	0.14	0.65	0.004	0.79	0.33	0.71	< 0.00001	0.37	< 0.00001	0.24	0.23	2.69 [1.83,	< 0.00001	0.24	0.23
	I			I			1.29]	I		rs180062	9 (TNF-308	;)		1	0.55]	I		1	3.95	I		I
									N	umber of ho	spitals or ce	enters										
1	25	2803/3106	0.84 [0.64,	0.21	0.7	< 0.00001	0.82 [0.53,	0.35	0	0.85	0.81	0.17	0.7	<	0.86 [0.56,	0.51	0	0.92	1.16 [0.75,	0.51	0	0.92
~~~	14	4057/0400	1.10] 0.77 [0.60,	0.04	0.00	0.004	1.25]	<	0.40	0.05	1.10] 0.80	0.04	0.00	0.00001	1.33] 0.43	0.0002	0.44	0.00	1.78]	0.0000	0.44	0.00
		1957/2432	0.98]	0.04	0.00	0.001	0.63]	0.0001	0.40	0.05	[0.03, 0.99]	0.04	0.30	0.11	0.67]	0.0003	0.41	0.08	3.72]	0.0003	0.41	0.06
			0.91 [0.62				0.48				0.84				0.51				1.94			
РТВ	23	3105/3617	1.03]	0.08	75%	< 0.00001	[0.34, 0.69]	< 0.0001	12%	0.3	[0.65, 1.09]	0.19	70%	< 0.00001	[0.36, 0.74]	0.0003	0%	0.47	[1.36, 2.78]	0.0003	0%	0.47
Others	15	1886/2210	0.86 [0.66, 1.13]	0.29	52%	0.01	[0.55, 2.03]	0.88	4%	0.4	[0.60, [0.66]	0.12	47%	0.02	[0.58, 2.16]	0.73	0%	0.45	[0.46, 1.71]	0.73	0%	0.45
										HIV	status											
HIV Negative	14	2050/2622	0.80 [0.59, 1.08]	0.15	72%	< 0.00001	0.50 [0.32,	0.002	49%	0.03	0.81 [0.59,	0.18	59%	0.006	0.52 [0.33,	0.004	43%	0.05	1.93 [1.24, 3.02]	0.004	43%	0.05
HIV NA	24	2895/3061	0.87 [0.69, 1.10]	0.24	67%	< 0.00001	0.67	0.07	0%	0.79	0.87	0.29	68%	< 0.00001	0.72	0.14	0%	0.85	1.39 [0.90,	0.14	0%	0.85
							1.03]			rs179972	1.13] 4 (TNF-857	·)			1.11]				2.15			
									N	umber of ho	spitals or ce	enters										
1	6	1319/784	0.86 [0.50, 1.48]	0.59	89%%	< 0.00001	1.72 [1.04,	0.04	0.27	0.24	0.74 [0.36,	0.42	0.89	< 0.00001	1.68	0.04	0.12	0.34	0.60	0.04	0.12	0.34
≥2	4	1127/1082	0.98 [0.61,	0.92	85%%	0.0002	2.84] 2.38 [1.25,	0.008	0.69	0.02	1.52] 0.85 [0.49,	0.56	0.85	0.0002	2.76] 2.35 [1.24,	0.009	0.69	0.02	0.98]	0.009	0.69	0.02
			1.00]				4.52]			тр	1.46]				4.45]				0.81]			
							1.91				0.95				1.84				0.54			
PTB	9	2206/1716	1.05 [0.80, 1.37]	0.75	0.75	< 0.0001	[1.28, 2.84]	0.001	0.49	0.05	[0.70, 1.30]	0.77	0.71	0.0005	[1.24, 2.73]	0.003	0.43	0.08	[0.37, 0.81]	0.003	0.43	0.08
Others	1	240/150	0.30 [0.20, 0.45]	< 0.00001	NA °	NA	5.38 [0.28, 105.00]	0.27	NA	NA	0.18	< 0.00001	NA	NA	8.48 [0.44, 165.17]	0.16	NA	NA	0.12	0.16	NA	NA
							105.00]			HIV	status			1	103.17]				2.30			
HIV			0.76 [0.39,				1.71				0.57			<	1.83				0.55			
Negative	4	1085/713	1.48]	0.42	0.88	< 0.00001	[0.84, 3.44] 2.09	0.14	0	0.58	[0.23, 1.43] 0.96	0.23	0.91	0.00001	[U.91, 3.68] 1.96	0.09	0	0.48	[0.27, 1.09] 0.51	0.09	0	0.48
HIV NA	6	1361/1153	1.03 [0.70, 1.51]	0.88	0.83	< 0.0001	[1.30, 3.37]	0.002	0.64	0.02	[0.63, 1.48]	0.87	0.8	0.0001	[1.22, 3.14]	0.005	0.6	0.03	[0.32, 0.82]	0.005	0.6	0.03
										rs180063	0 (TNF-863	•)										
					1		4.00		N	umber of ho	spitals or ce	enters			4.0.1				0.71			
1	6	1167/1032	1.15 [0.95, 1.38]	0.15	0%%	0.83	1.39 [0.76, 2.53]	0.28	0.05	0.39	1.18 [0.94, 1.47]	0.16	0	0.63	1.34 [0.71, 2.55]	0.37	0.11	0.35	0.74 [0.39, 1.41]	0.37	0.11	0.35
≥2	4	1127/1082	0.75 [0.51, 1.12]	0.16	81%%	0.001	0.46 [0.19,	0.09	0.61	0.05	0.81 [0.50,	0.4	0.81	0.001	0.49 [0.20, 1.181	0.11	0.63	0.04	2.06 [0.84, 5.03]	0.11	0.63	0.04
			1	1		1	1.14]	1		тв	types	1		1	1.10]	1		1	0.00]	1		1
PTB	7	1753/1331	0.88 [0.67,	0.38	0.74	0.0009	0.80 [0.38,	0.57	0.65	0.009	0.87 [0.64,	0.38	0.65	0.008	0.83 [0.40,	0.63	0.65	0.009	1.20 [0.58,	0.63	0.65	0.009
			1.17]				1.70]				1.18]				1.73]				2.50]			

## Table 5: Results of subgroup analysis by number of hospitals or centers, TB types, and HIV status.

			4 45 10 07				0.65				1.38				0.61				1.65			
Others	3	541/783	1.15[0.87,	0.32	0	0.45	[0.16,	0.55	0.23	0.27	[1.01,	0.05	0	0.82	[0.15,	0.49	0.23	0.27	[0.40,	0.49	0.23	0.27
			1.51]				2.66]				1.89]				2.50]				6.78]			
										1.115.4												
										HIV	status											
1107			4 44 50 00				1.21				1.16				1.23				0.81			
HIV	5	1084/1044	1.11[0.93,	0.23	0	0.71	[0.77,	0.41	0	0.44	[0.92,	0.2	0	0.55	[0.79,	0.36	0	0.41	[0.52,	0.36	0	0.41
Negative			1.33]				1.92]				1.45]				1.91]				1.26]			
			0.04 [0.55				0.55				0.84				0.58				1.73			
HIV NA	5	1210/1070	0.81 [0.55,	0.27	0.76	0.002	[0.18,	0.29	0.52	0.08	[0.54,	0.45	0.76	0.002	[0.20,	0.32	0.51	0.09	[0.59,	0.32	0.51	0.09
			1.10]				1.67]				1.31]				1.70]				5.10]			

a: The statistical method used in Test of association is Mantel-Haenszel method. OR=Odds Ratio, CI=Confidence Interval.

b:  $P_{\text{heterogeneity}} = P$  value of heterogeneity.

c: Number of hospitals or centers were obtained from each full article, the number in each form represent the number of hospitals or centers registered by TB patients. d: Others, the other TB types including EPTB, STB, OATB, and NA.

e: NA=Not Applicable.

Table 6: Begg's and Egger's tests for the evaluation of potential publication bias under allele genetic model.

SNP Groups		Number of studies	Begg's regression analysis	Egger's regression analysis					
SNP	Groups	Number of studies	P-value	Intercept [95% confidence interval]	P-value	t-value			
	Pooled	24	0.000	2.852263 [-1.438772, 7.143298]	0.181	1.38			
	African	1	NA	NA	NA	NA			
18361525	Caucasian	3	0.296	-0.1117765 [-1.270911, 1.047358]	0.436	-1.23			
	Asian	20	0.013	6.270712 [1.051285, 11.49014]	0.021	2.53			
	Pooled	38	0.943	0.0303175 [-0.03660599, 0.4266949]	0.877	0.16			
ro1800600	African	3	0.296	1.509799 [-6.030845, 9.050444]	0.238	2.54			
151600629	Caucasian	8	0.902	-0.1145969 [-1.79884, 1.569646]	0.873	-0.17			
	Asian	27	0.575	-0.1341091 [-0.5513733, 0.2831551]	0.513	-0.66			
	Pooled	10	0.128	-0.8502204 [-2.69953, 0.9990891]	0.320	-1.06			
ro1700704	African	1	NA	NA	NA	NA			
151799724	Caucasian	1	NA	NA	NA	NA			
	Asian	8	0.621	-0.4462863 [-3.165534, 2.272961]	0.702	-0.40			
	Pooled	10	0.592	-0.1729943 [-1.028426, 0.6824379]	0.653	-0.47			
ro1800620	African	1	NA	NA	NA	NA			
151000030	Caucasian	1	NA	NA	NA	NA			
	Asian	8	0.711	-0.1642557 [-1.005393, 0.6768819]	0.650	-0.48			

NA=Not Applicable

were less than 50%, and Pheterogeneity was higher than 0.01 after removing two studies [23,36]. Third, for rs1799724 polymorphism, there was significant heterogeneity under the allele genetic model and the heterozygote genetic model, and the heterogeneity disappeared after excluding three studies [20,41,49]. Finally, for rs1800630 polymorphism, the I² values and Pheterogeneity in the allele genetic model and the heterozygote genetic model were changed by removing three studies [22,28,29].

Moreover, to evaluate the publication bias of the included studies in our meta-analysis, Begg's test, Egger's test, and funnel plots were performed under the allele genetic model of each SNP by pooled (Figure 5 and Table 6) and ethnicity subgroups (Figure S1-S4, Table 6). The results showed that the funnel plots of rs1799724, rs1800629 and rs1800630 did not reveal apparent asymmetry under the allele model by pooled (Figure 5) or subgroups, and the results of Egger's test and Begg's test also showed no publication bias (Table 6). However, the funnel plot of rs361525 revealed evident asymmetry under the allele genetic model in the pooled population (Figure 5A), and the publication bias is derived from the Asian population (Figure S1B). The same results were showed by Begg's test (Table 6, *P*=0.013) and Egger's test (Table 6, P=0.021). The potential sources of the bias in rs361525 might be contributed by following factors: (1) The quality of two included studies [25,26] is questionable because they both came from the same research institute and their genotype distribution was significantly inconsistent with other studies. Furthermore, we found that publication bias disappeared when we removed them; (2) Ten included studies have high risk of bias (showed as solid circles in Figure 2-4) in sample size [40,47,50,54,60], the ratio of case and control [27,30,40,49,50,54,56,57], TB combined with other diseases [33,50-52,55], SNP genotyping method was not given [29,58], and others mistakes [36,37,41], which might induce the publication biases; (3) Studies with null results should have the same scientific value as studies with significant results, but statistically significant results are three times more likely to be published than papers with invalid results [63].

### Discussion

TB has existed for thousands of years and is a major global health problem. Prevention of new *M. tuberculosis* infection and its progression to TB are critical to reducing the burden of disease and death caused by TB. For the past few years, accumulating evidence has indicated that the genetic background of the host influences the outcome of some infectious diseases [64,65], including TB. Genome-Wide Association Studies (GWAS) and meta-analyses have been used to analyze the genetic basis of TB, and some susceptibility genes and SNPs have been identified [21,66-70].

The TNF gene, a locus on the human chromosome 6 and mouse chromosome 17, is well known as encoding cytokine TNF- $\alpha$  for

granuloma formation in a TB infection. Previous studies have proven that deficiency of TNF in a mouse model could result in failing to form organized granulomas and accelerating the death of *M. tuberculosis*infected mice [71], which indicated that TNF played a key role in formation and maintenance of granuloma as well as inhibiting M. tuberculosis dissemination in an animal model. Subsequently, similar evidence was observed in human beings [72]. With the development of genetics and molecular biology, the accumulated data showed that several polymorphisms of TNF gene were associated with TB in different populations, including TNF +488G>A) [32], TNF -224G>A [20], rs361525 [20,22-32], rs673 [28], rs1800629 [20,22-32,34-40], rs1800750 [31], rs1799724 [20,22,25,26,28,29,41], rs1800630 [20,22,24,25,28,29,41], and rs1799964 [22]. However, the results of these studies were always inconsistent. Several factors may explain the discrepancy between the results of different studies: 1) Differences in ethnic genetic background led to differences in the results of these studies; 2) Other confounders, such as the number of cases and controls, patient selection criteria, SNP detection method, and HIV status, may have affected the consistency and reliability of the results; 3) Environmental factors might play an important role in TB infection and disease development.

To avoid these disadvantages of individual study, we performed this meta-analysis to evaluate the associations between TNF polymorphism and TB susceptibility. In the overall analysis, no significant association was observed between the rs1800630 polymorphism and TB risk under any genetic models. However, significant associations were found between rs361525, rs1800629, as well as rs1799724 polymorphisms and TB risk. Furthermore, in the stratified analysis by ethnicity, our meta-analysis demonstrated that these three SNPs were associated with TB risk in the Asian population and African population, especially in the Asian population. Our metaanalysis was consistent with three previous meta-analyses [21,69,70], but was contrary to 3 other previous meta-analyses conducted by Pacheco et al., [73], Zhang et al., [74], and Wang et al., [75]. These meta-analyses did not find any association between TNFSNPs rs361525 and rs1800629 and TB susceptibility. The possible reasons for this inconsistency may be the following aspects: inclusion of small sample size in the previous meta-analyses, non-uniformly defined cases, and different ethnic sub-groups among various studies.

Comparing with previous meta-analyses, this meta-analysis has several advantages: 1) The candidate studies were retrieved from 6 databases, and the number of finally included studies was more than any those in the previous meta-analysis, which enhanced the reliability and integrity of our research; 2) More than ten newly published articles were included in this meta-analysis, which provided a more accurate overview for the relationship between TNF SNPs and TB risk; 3) We were the first to detect the association between SNPs rs361525, rs1800629, rs1799724, and rs1800630 and TB risk under five genetic models; 4) crucial several confounding factors including TB types, number of hospitals or centers, and HIV status were included in this meta-analysis. However, there were several limitations in this meta-analysis: 1) The number of included studies in the African population was only three, which might reduce the accuracy and reliability of this meta-analysis; 2) Only articles written in English and Chinese were included in our meta-analysis; other language articles and unpublished data were omitted, which might cause publication bias and data inaccuracy; 3) Cohort studies were not included in the meta-analysis, cohort studies will allow the evaluation of a causal relationship between the SNPs and TB risk; 4) The relationship between TNFSNPs and other confounders such as age, gender, BMI (Body Mass Index), and environmental factors were not discussed in this study.

## Conclusion

In summary, this meta-analysis suggested that TNFSNPs rs361525, rs1800629, and rs1799724rather than rs1800630were significantly associated with TB susceptibility, especially in Asians. Additionally, the essential confounding factors, such as TB types, number of hospitals or centers, and HIV status, might play an important role in TB susceptibility. These findings provide new insights into the association of SNPs in the inflammation and immune-related TNF with susceptibility to TB. It is necessary to confirm our results by performing further studies with a large sample size, different ethnic groups, and potential confounder factors in the future.

### Acknowledgments

This study was supported by grants from the National Natural Science Foundation of China (81801643), the Beijing Municipal Science & Technology Commission (Z181100001718005 and 19L2065), and the Chinese PLA General Hospital (QNC19047).

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