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Associations between vitamin D receptor genetic variants and tuberculosis: a meta-analysis

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Abstract

We performed a meta-analysis to evaluate potential associations between vitamin D receptor (*VDR*) genetic variants and tuberculosis (TB). Systematic literature research was conducted in PubMed, Web of Science, and Embase. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) to estimate strength of associations in all possible genetic models, and *P* values ≤ 0.05 were considered to be statistically significant. In total, 42 studies were enrolled for analyses. Pooled overall analyses suggested that *VDR* rs1544410 (dominant model: $P = 0.02$; allele model: $P = 0.03$) and rs731236 (dominant model: $P = 0.04$; recessive model: $P = 0.02$; allele model: $P = 0.01$) variants were significantly associated with TB. Further subgroup analyses by ethnicity revealed that rs1544410 (dominant and allele models) and rs731236 (dominant, recessive, and allele models) variants were both significantly associated with TB in South Asians. When we stratified data by type of disease, positive results were detected for rs7975232 variant in EPTB (dominant, recessive, over-dominant, and allele models) subgroup, and for rs2228570 variant in PTB (dominant, recessive, and allele models) and EPTB (dominant, recessive, over-dominant, and allele models) subgroups. Our meta-analysis supported that rs7975232, rs1544410, rs2228570, and rs731236 variants might serve as genetic biomarkers of certain types of TB.

Keywords

Vitamin D receptor, gene variants, tuberculosis, pulmonary tuberculosis, extrapulmonary tuberculosis, meta-analysis

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Introduction

Tuberculosis (TB) is a commonly seen chronic infectious disorder which includes pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB).[1] In spite of rapid advancements achieved in early diagnosis and pharmacological therapy over the past few decades, TB remains a serious public health problem. According to a recent investigation, over 30% of the general population is infected with *Mycobacterium tuberculosis* (MTB), and around 5–10% of these infected individuals will eventually develop active TB.[2] The course of MTB infection depends on a complex interaction of pathogen, host, and environmental factors, and the fact that only a small portion of infected individuals finally develop active TB suggests that host genetic background may play a crucial role in its development.[3,4]

Recently, it became evident that the vitamin D metabolic pathway might be involved in the pathogenesis of TB. First, previous epidemical investigations showed that vitamin D deficiency was much more prevalent in patients with TB, and the serum level of vitamin D was reversely correlated with disease severity.[5–7] Second, several experimental studies demonstrated that vitamin D could activate macrophages and promote elimination of MTB.[8–10] It is well acknowledged that vitamin D exerts its biological functions by binding with vitamin D receptor (VDR). Therefore, it is possible that *VDR* variants, which may result in diminished function of vitamin D, might also be involved in the development of TB.

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To date, numerous studies already investigated potential associations between *VDR* variants and TB. But the results of these studies were not consistent.[11–52] Thus, we performed the present meta-analysis to obtain a more conclusive result.

Materials and methods

Literature search and inclusion criteria

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses

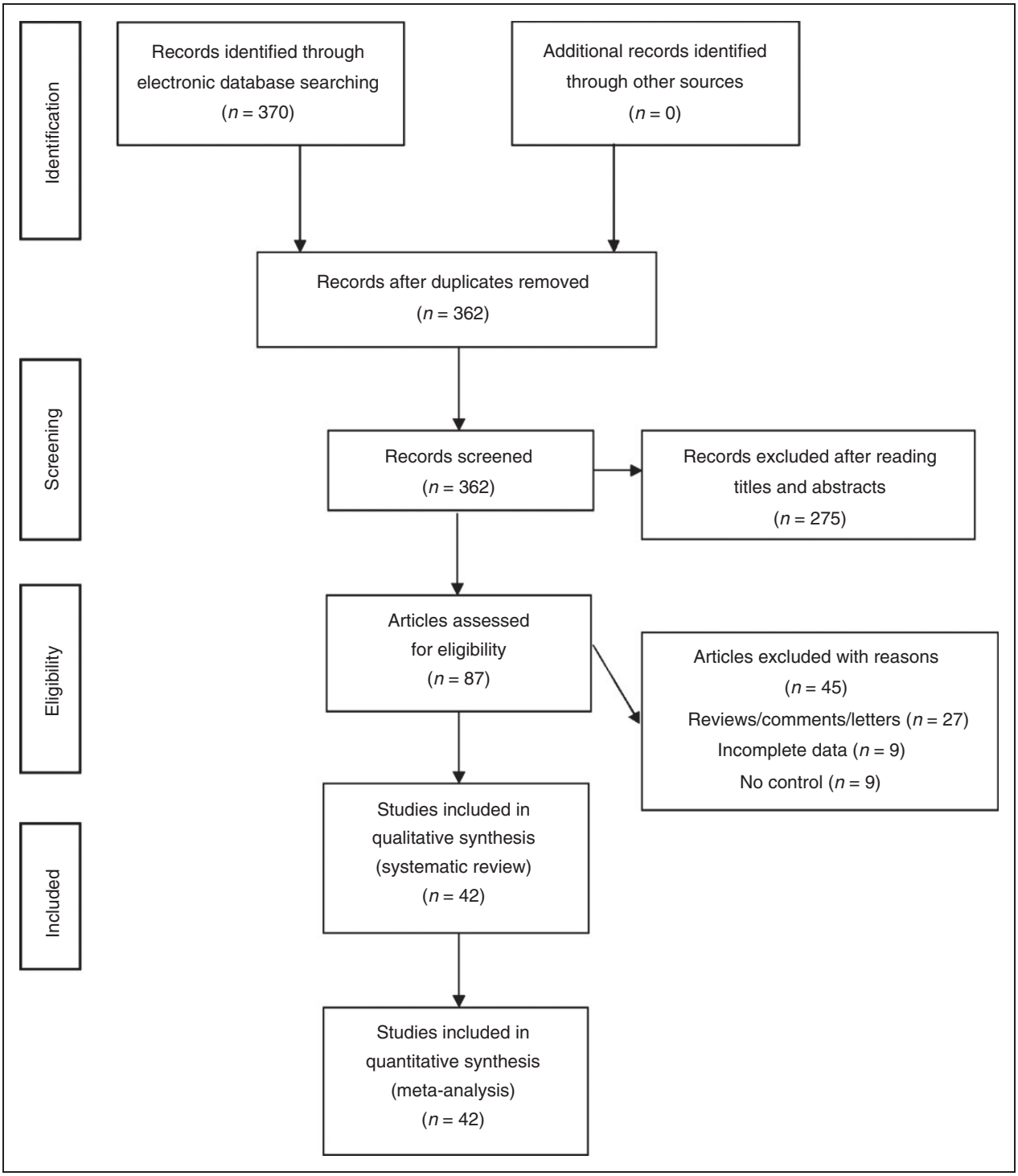

Figure 1. PRISMA diagram for the selection of studies of the present meta-analysis.

Table 1. The characteristics of included studies.

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P* Value for HWE	NOS score
					Cases	Controls		
ApaI rs7975232					AA/AC/CC			
Alagarasu,[12] 2009	India	South Asian	PTB	185/146	77/79/29	44/81/21	0.096	7
Babb,[14] 2007	South Africa	African	PTB	249/352	101/108/40	116/173/63	0.914	7
Bornman,[17] 2004	UK	African	PTB	343/634	152/153/38	266/292/76	0.762	8
Devi,[19] 2018	India	South Asian	PTB	169/227	50/83/36	75/103/49	0.225	8
Fernández-Mestre,[20] 2015	Venezuela	African	PTB	89/101	27/42/20	29/54/18	0.062	7
Fitness,[21] 2004	UK	African	PTB	328/543	150/145/33	287/210/46	0.391	7
Hu,[23] 2016	China	East Asian	PTB	217/383	NA	NA	NA	7
Jafari,[24] 2016	Iran	South Asian	PTB	96/122	33/44/19	36/55/31	0.285	7
Lee,[28] 2016	Taiwan	East Asian	PTB	198/170	103/78/17	89/65/16	0.416	8
Lombard,[29] 2006	South Africa	African	PTB	95/117	78/16/1	84/29/4	0.455	7
Olesen,[32] 2007	Gambia	African	PTB	320/345	150/145/25	161/150/34	0.913	8
Panwar,[33] 2016	India	South Asian	PTB	106/106	74/23/9	88/15/3	0.033	8
Panwar,[33] 2016	India	South Asian	EPTB	106/106	47/43/16	88/15/3	0.033	8
Rashedi,[34] 2014	Iran	South Asian	TB	84/90	29/42/13	30/48/12	0.292	8
Rizvi,[36] 2016	India	South Asian	PTB	130/130	96/25/9	102/23/5	0.021	7
Rizvi,[36] 2016	India	South Asian	EPTB	130/130	69/44/17	102/23/5	0.021	7
Selvaraj,[39] 2004	India	South Asian	EPTB	64/103	20/35/9	39/49/15	0.951	7
Selvaraj,[41] 2009	India	South Asian	PTB	65/60	25/29/11	23/25/12	0.286	7
Sharma,[42] 2011	India	South Asian	PTB	478/857	191/255/32	395/401/61	0.002	7
Søborg,[45] 2007	Tanzania	African	PTB	438/426	224/186/28	211/170/45	0.223	7
Vidyarani,[46] 2009	India	South Asian	PTB	40/49	17/16/7	14/25/10	0.849	8
Zhang,[52] 2018	China	East Asian	PTB	180/59	94/67/19	36/21/2	0.613	8
BsmI rs1544410					AA/AT/TT			
Alagarasu,[12] 2009	India	South Asian	PTB	179/146	42/73/64	45/62/39	0.071	7
Ates,[13] 2011	Turkey	Caucasian	TB	128/80	32/68/28	37/38/5	0.241	7
Banoei,[15] 2010	Iran	South Asian	PTB	60/62	13/27/20	31/26/5	0.889	8
Bornman,[17] 2004	UK	African	PTB	343/634	215/108/20	387/208/39	0.125	8
Devi,[19] 2018	India	South Asian	PTB	169/227	45/100/24	58/113/56	0.948	8
Fitness,[21] 2004	UK	African	PTB	345/545	212/123/10	314/192/39	0.201	7
Jafari,[24] 2016	Iran	South Asian	PTB	96/122	43/42/11	55/52/15	0.620	7
Joshi,[26] 2014	India	South Asian	PTB	110/115	35/58/17	55/37/23	0.001	8
Kang,[27] 2011	Korea	East Asian	PTB	150/83	135/13/2	75/8/0	0.644	8
Lee,[28] 2016	Taiwan	East Asian	PTB	198/170	183/14/1	146/24/0	0.322	8
Lombard,[29] 2006	South Africa	African	PTB	95/117	55/35/5	76/32/9	0.044	7
Merza,[31] 2009	Iran	South Asian	PTB	117/60	43/67/7	26/21/13	0.039	7
Olesen,[32] 2007	Gambia	African	PTB	320/342	146/141/33	152/152/38	1.000	8
Rashedi,[34] 2014	Iran	South Asian	TB	84/90	30/27/27	33/31/26	0.004	8
Rathored,[35] 2012	India	South Asian	PTB	692/205	192/346/154	51/108/46	0.437	8
Salimi,[38] 2015	Iran	South Asian	PTB	120/131	31/66/23	39/70/22	0.319	8
Selvaraj,[39] 2004	India	South Asian	EPTB	64/103	15/36/13	40/38/25	0.012	7
Selvaraj,[41] 2009	India	South Asian	PTB	51/60	12/16/23	27/17/16	0.001	7
Sharma,[42] 2011	India	South Asian	PTB	488/1062	144/215/129	274/577/211	0.003	7
Sinaga,[43] 2014	Indonesia	South Asian	PTB	76/76	24/52/0	56/18/2	0.705	8
Singh,[44] 2011	India	South Asian	PTB	101/225	32/52/17	57/134/34	0.002	7
Vidyarani,[46] 2009	India	South Asian	PTB	40/49	10/14/16	21/13/15	0.001	8
Zhang,[52] 2018	China	East Asian	PTB	180/59	159/19/2	54/4/1	0.022	8
FokI rs2228570					TT/TA/AA			
Acen,[11] 2016	Uganda	African	PTB	41/41	36/3/2	38/2/1	0.002	7
Alagarasu,[12] 2009	India	South Asian	PTB	187/144	116/58/13	81/59/4	0.077	7
Ates,[13] 2011	Turkey	Caucasian	TB	128/80	58/60/10	35/37/8	0.695	7
Babb,[14] 2007	South Africa	African	PTB	248/352	132/103/13	203/129/20	0.934	7

(continued)

Table 1. Continued

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P* Value for HWE	NOS score
					Cases	Controls		
Banoei,[15] 2010	Iran	South Asian	PTB	60/62	30/21/9	29/27/6	0.938	8
Bornman,[17] 2004	UK	African	PTB	416/718	258/138/20	444/242/32	0.893	8
Devi,[19] 2018	India	South Asian	PTB	169/227	59/106/4	119/90/18	0.865	8
Fernández-Mestre,[20] 2015	Venezuela	African	PTB	93/102	34/47/12	26/60/16	0.058	7
Jafari,[24] 2016	Iran	South Asian	PTB	96/121	41/50/5	55/61/5	0.018	7
Jin,[25] 2017	China	East Asian	PTB	180/100	51/104/25	42/51/7	0.104	8
Joshi,[26] 2014	India	South Asian	PTB	110/115	51/46/13	63/41/11	0.266	8
Kang,[27] 2011	Korea	East Asian	PTB	103/105	30/58/15	41/43/21	0.124	8
Lee,[28] 2016	Taiwan	East Asian	PTB	198/170	44/104/50	51/87/32	0.634	8
Lombard,[29] 2006	South Africa	African	PTB	95/117	62/30/3	90/24/3	0.373	7
Medapati,[30] 2017	India	South Asian	PTB	89/83	5/76/8	12/61/10	<0.001	7
Merza,[31] 2009	Iran	South Asian	PTB	117/60	67/46/4	35/25/0	0.042	7
Olesen,[32] 2007	Gambia	African	PTB	320/344	198/106/16	207/118/19	0.686	8
Rashedi,[34] 2014	Iran	South Asian	TB	84/90	44/33/7	50/32/8	0.388	8
Rathored,[35] 2012	India	South Asian	PTB	692/205	319/298/75	118/80/7	0.136	8
Roth,[37] 2004	Peru	African	PTB	200/201	119/60/21	109/78/14	0.993	7
Salimi,[38] 2015	Iran	South Asian	PTB	120/131	65/44/11	93/31/7	0.054	8
Selvaraj,[39] 2004	India	South Asian	EPTB	64/103	47/15/2	55/39/9	0.583	7
Selvaraj,[41] 2009	India	South Asian	PTB	65/60	33/29/3	33/26/1	0.102	7
Sharma,[42] 2011	India	South Asian	PTB	258/924	133/95/30	585/311/28	0.081	7
Sinaga,[43] 2014	Indonesia	South Asian	PTB	76/80	27/42/7	30/34/12	0.650	8
Singh,[44] 2011	India	South Asian	PTB	101/225	55/40/6	96/110/19	0.107	7
Søborg,[45] 2007	Tanzania	African	PTB	435/416	288/128/19	267/128/21	0.273	7
Vidyarani,[46] 2009	India	South Asian	PTB	40/49	23/14/3	20/29/0	0.003	8
Wang,[47] 2017	China	East Asian	EPTB	150/149	75/53/22	42/68/39	0.289	8
Wilbur,[48] 2007	USA	African	PTB	91/290	64/26/1	165/120/5	0.001	7
Wilkinson,[49] 2000	USA	South Asian	PTB	91/116	52/31/8	74/39/3	0.418	8
Wu,[50] 2015	China	East Asian	PTB	151/453	57/70/24	226/181/46	0.277	8
Zhang,[51] 2010	China	East Asian	EPTB	110/102	51/43/16	29/47/26	0.433	7
Zhang,[52] 2018	China	East Asian	PTB	180/59	21/80/79	21/25/13	0.294	8
TaqI rs731236					AA/AG/GG			
Alagarasu,[12] 2009	India	South Asian	PTB	184/146	71/80/33	70/62/14	0.960	7
Ates,[13] 2011	Turkey	Caucasian	TB	128/80	49/65/14	30/39/11	0.766	7
Babb,[14] 2007	South Africa	African	PTB	249/356	136/94/19	190/144/22	0.442	7
Banoei,[15] 2010	Iran	South Asian	PTB	60/62	8/33/19	33/24/5	0.829	8
Bellamy,[16] 2000	UK	African	PTB	408/414	204/177/27	188/177/49	0.460	7
Bornman,[17] 2004	UK	African	PTB	343/634	174/132/37	331/253/50	0.864	8
Delgado,[18] 2002	USA	East Asian	PTB	358/106	325/30/3	96/10/0	0.610	7
Devi,[19] 2018	India	South Asian	PTB	169/227	86/73/10	116/86/25	0.143	8
Fernández-Mestre,[20] 2015	Venezuela	African	PTB	86/97	51/33/2	58/38/1	0.053	7
Fitness,[21] 2004	UK	African	PTB	397/672	261/118/18	384/241/47	0.279	7
Harishankar,[22] 2016	India	South Asian	PTB	90/89	36/39/15	42/39/8	0.805	7
Jafari,[24] 2016	Iran	South Asian	PTB	96/120	38/46/12	56/58/6	0.063	7
Kang,[27] 2011	Korea	East Asian	PTB	149/94	134/14/1	85/8/1	0.133	8
Lee,[28] 2016	Taiwan	East Asian	PTB	198/170	186/12/0	149/20/1	0.715	8
Lombard,[29] 2006	South Africa	African	PTB	95/117	56/33/6	67/49/1	0.013	7
Medapati,[30] 2017	India	South Asian	PTB	91/85	27/56/8	5/74/6	<0.001	7
Olesen,[32] 2007	Gambia	African	PTB	320/345	150/145/25	161/150/34	0.913	8
Panwar,[33] 2016	India	South Asian	PTB	106/106	66/28/12	90/14/2	0.122	8
Panwar,[33] 2016	India	South Asian	EPTB	106/106	58/34/14	90/14/2	0.122	8
Rashedi,[34] 2014	Iran	South Asian	TB	84/90	44/33/7	50/32/8	0.388	8

(continued)

Table 1. Continued

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P* Value for HWE	NOS score
					Cases	Controls		
Rathored,[35] 2012	India	South Asian	PTB	692/205	319/298/75	118/80/7	0.135	8
Rizvi,[36] 2016	India	South Asian	PTB	130/130	92/27/11	104/22/4	0.051	7
Rizvi,[36] 2016	India	South Asian	EPTB	130/130	66/49/15	104/22/4	0.051	7
Roth,[37] 2004	Peru	African	PTB	200/201	119/60/21	109/78/14	0.993	7
Salimi,[38] 2015	Iran	South Asian	PTB	120/131	52/54/14	67/50/14	0.318	8
Selvaraj,[39] 2004	India	South Asian	EPTB	64/102	27/28/9	40/48/14	0.947	7
Selvaraj,[40] 2008	India	South Asian	PTB	65/60	24/33/8	27/21/12	0.050	7
Sharma,[42] 2011	India	South Asian	PTB	275/659	138/95/42	358/275/26	0.002	7
Singh,[44] 2011	India	South Asian	PTB	101/225	61/30/10	132/60/33	<0.001	7
Søborg,[45] 2007	Tanzania	African	PTB	438/425	247/172/19	233/162/30	0.799	7
Vidyarani,[46] 2009	India	South Asian	PTB	40/49	15/18/7	27/18/4	0.686	8
Wilbur,[48] 2007	USA	African	PTB	156/496	61/85/10	251/218/27	0.020	7
Wilkinson,[49] 2000	USA	South Asian	PTB	91/116	39/46/6	45/58/13	0.375	8
Wu,[50] 2015	China	East Asian	PTB	151/453	138/13/0	403/50/0	0.213	8
Zhang,[52] 2018	China	East Asian	PTB	180/59	160/19/1	52/7/0	0.628	8

TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; HWE, Hardy–Weinberg equilibrium; NOS, Newcastle–Ottawa scale; NA, not available.

(PRISMA) guideline.[53] Potentially relevant literature published before January 2019 was retrieved from PubMed, Web of Science, and Embase using the following searching strategy: (vitamin D receptor OR VDR) AND (polymorphism OR variant OR mutation OR genotype OR allele) AND (tuberculosis OR TB). We also checked the references of enrolled articles to identify other potentially related studies.

To test the research hypothesis of this meta-analysis, included studies must meet all the following criteria: (1) case-control study on associations between *VDR* variants and TB; (2) provide genotypic/allelic frequency of investigated *VDR* variants in cases and controls; (3) full text in English available. Studies were excluded if one of the following criteria was fulfilled: (1) not relevant to *VDR* variants and TB; (2) case reports or case series; (3) abstracts, reviews, comments, letters, and conference presentations. For repeated reports, we only included the study with the largest sample size for analyses.

Data extraction and quality assessment

We extracted following data from included studies: (1) the name of the first author; (2) publication time; (3) country and ethnicity; (4) sample size; and (5) genotypic/allelic distribution of *VDR* variants in cases and controls. The *P* value of the Hardy–Weinberg equilibrium (HWE) was also calculated. When necessary, we wrote to the corresponding authors for extra information. We used the Newcastle–Ottawa scale (NOS) to assess the quality of eligible studies.[54] This scale has a score range of 0–9, and studies with a score of more than 7 were thought to be of high quality. Data extraction and quality assessment were performed by two independent reviewers. Any disagreement between two reviewers was solved by discussion until a consensus was reached.

Statistical analyses

We used Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update) to conduct statistical analyses. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) to estimate strength of associations in all possible genetic models, and *P* values ≤ 0.05 were considered to be statistically significant. Q test and I^2 statistic were employed to assess between-study heterogeneities. If the *P* value of Q test was less than 0.1 or I^2 was greater than 50%, random-effect models (REMs) were used to pool the data. Otherwise, fixed-effect models (FEMs) were applied for synthetic analyses. Subgroup analyses by ethnicity of participants and type of disease were performed. Stabilities of synthetic results were evaluated with sensitivity analyses, and publication biases were evaluated with funnel plots.

Results

Characteristics of included studies

We found 370 potentially relevant articles. Among these articles, 42 eligible studies were finally included for pooled analyses (see Figure 1). The NOS score of eligible articles ranged from 7 to 8, which indicated that all

Table 2. Results of overall and subgroup analyses.

Polymorphisms	Population	Sample size	Dominant comparison *P* Value OR (95% CI)	Recessive comparison *P* Value OR (95% CI)	Over-dominant comparison *P* Value OR (95% CI)	Allele comparison *P* Value OR (95% CI)
ApaI rs7975232	Overall	3893/4873	0.20 0.88 (0.73–1.07)	0.85 1.01 (0.88–1.16)	0.23 1.09 (0.94–1.27)	0.14 0.89 (0.77–1.04)
	South Asian	1653/2126	0.10 0.75 (0.54–1.06)	0.17 1.16 (0.94–1.42)	0.12 1.24 (0.95–1.61)	0.06 0.78 (0.60–1.01)
	East Asian	378/229	0.47 0.88 (0.63–1.24)	0.46 1.26 (0.68–2.34)	0.75 1.06 (0.75–1.50)	0.37 0.88 (0.68–1.16)
	African	1862/2518	0.46 1.05 (0.93–1.18)	0.20 0.88 (0.72–1.07)	0.94 1.00 (0.89–1.14)	0.25 1.06 (0.96–1.16)
	PTB	3509/4444	0.65 0.98 (0.89–1.07)	0.43 1.06 (0.92–1.23)	0.35 1.05 (0.95–1.15)	0.97 1.00 (0.93–1.07)
	EPTB	300/339	**0.008 0.33 (0.15–0.75)**	0.09 2.64 (0.85–8.17)	**0.007 2.34 (1.26–4.34)**	**0.03 0.39 (0.17–0.91)**
BsmI rs1544410	Overall	4206/4763	**0.02 0.79 (0.65–0.96)**	0.82 1.03 (0.81–1.30)	0.09 1.18 (0.97–1.43)	**0.03 0.86 (0.75–0.99)**
	South Asian	2447/2733	**0.01 0.70 (0.53–0.92)**	0.71 1.05 (0.81–1.37)	0.07 1.31 (0.98–1.75)	**0.02 0.81 (0.68–0.96)**
	East Asian	528/312	0.29 0.78 (0.49–1.23)	0.59 1.56 (0.32–7.64)	0.19 0.73 (0.45–1.17)	0.43 0.84 (0.54–1.30)
	African	1103/1638	0.42 1.07 (0.91–1.25)	0.06 0.74 (0.55–1.01)	0.85 1.02 (0.87–1.19)	0.15 1.10 (0.97–1.24)
	PTB	3930/4490	0.06 0.83 (0.68–1.01)	0.88 1.02 (0.79–1.30)	0.16 1.16 (0.94–1.43)	0.11 0.89 (0.77–1.03)
FokI rs2228570	Overall	5378/6494	0.35 0.93 (0.79–1.09)	0.23 1.16 (0.91–1.50)	0.67 1.03 (0.90–1.17)	0.22 0.91 (0.79–1.05)
	South Asian	2419/2795	0.18 0.86 (0.69–1.07)	0.15 1.40 (0.89–2.20)	0.50 1.08 (0.86–1.34)	0.13 0.88 (0.74–1.04)
	East Asian	892/1038	0.62 0.85 (0.45–1.62)	0.92 1.03 (0.59–1.79)	0.73 1.05 (0.79–1.40)	0.78 0.93 (0.59–1.49)
	African	1739/2380	0.66 0.94 (0.70–1.25)	0.56 1.04 (0.91–1.18)	0.70 0.97 (0.85–1.11)	0.56 0.90 (0.65–1.27)
	PTB	4842/5970	**0.03 0.84 (0.72–0.98)**	**0.03 1.33 (1.03–1.72)**	0.32 1.07 (0.93–1.23)	**0.01 0.83 (0.73–0.96)**
	EPTB	324/354	**0.0006 0.47 (0.31–0.73)**	**<0.0001 2.39 (1.73–3.30)**	**0.007 0.65 (0.47–0.89)**	**<0.0001 0.51 (0.40–0.64)**
TaqI rs731236	Overall	6550/7557	**0.04 0.85 (0.73–1.00)**	**0.02 1.38 (1.05–1.82)**	0.39 1.06 (0.93–1.19)	**0.01 0.84 (0.74–0.97)**
	South Asian	2924/2938	**0.002 0.68 (0.53–0.87)**	**0.004 1.79 (1.20–2.65)**	0.07 1.22 (0.99–1.51)	**0.0005 0.69 (0.55–0.85)**
	East Asian	1036/882	0.78 0.82 (0.21–3.26)	0.13 1.29 (0.92–1.81)	0.12 0.76 (0.54–1.07)	0.16 0.79 (0.57–1.10)
	African	2692/3757	0.19 1.07 (0.97–1.18)	0.79 0.96 (0.69–1.32)	0.40 0.96 (0.86–1.06)	0.50 1.04 (0.92–1.17)
	PTB	6038/7049	0.21 0.91 (0.79–1.05)	0.05 1.35 (1.00–1.82)	0.68 0.98 (0.91–1.06)	0.08 0.89 (0.78–1.01)
	EPTB	300/338	0.07 0.40 (0.15–1.08)	0.09 2.91 (0.85–9.98)	0.10 2.00 (0.89–4.52)	0.07 0.42 (0.16–1.08)

OR, odds ratio; CI, confidence interval; NA, not available; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis.
The values in bold indicate that there are statistically significant differences between cases and controls.

included studies were of high quality. Baseline characteristics of included studies are summarized in Table 1.[11–52]

Overall and subgroup analyses

Pooled overall analyses suggested that *VDR* rs1544410 (dominant model: $P = 0.02$, OR = 0.79, 95% CI 0.65–0.96, $I^2 = 71\%$, REM; allele model: $P = 0.03$, OR = 0.86, 95% CI 0.75–0.99, $I^2 = 70\%$, REM) and rs731236 (dominant model: $P = 0.04$, OR = 0.85, 95% CI 0.73–1.00, $I^2 = 74\%$, REM; recessive model: $P = 0.02$, OR = 1.38, 95% CI 1.05–1.82, $I^2 = 69\%$, REM; allele model: $P = 0.01$, OR = 0.84, 95% CI 0.74–0.97, $I^2 = 79\%$, REM) variants were both significantly associated with TB.

Further subgroup analyses by ethnicity revealed that rs1544410 (dominant and allele models) and rs731236 (dominant, recessive, and allele models) variants were both significantly associated with TB in South Asians. When we stratified data by type of disease, positive results were detected for rs7975232 variant in EPTB (dominant, recessive, over-dominant, and allele models) subgroup, and for rs2228570 variant in PTB (dominant, recessive and allele models) and EPTB (dominant, recessive, over-dominant, and allele models) subgroups. No any other positive findings were observed in overall and subgroup analyses (see Table 2 and Supplemental Figure 1).

Sensitivity analyses

We performed sensitivity analyses to test stabilities of pooled results by excluding studies that violated HWE. No any altered results were observed in overall and subgroup comparisons, which indicated that our findings were statistically stable.

Publication biases

We used funnel plots to assess publication biases. We did not find obvious asymmetry of funnel plots in any comparisons, which suggested that our findings were unlikely to be impacted by severe publication biases.

Discussion

To the best of our knowledge, this is so far the most comprehensive meta-analysis on roles of VDR variants in TB, and our pooled analyses suggested that *VDR* rs7975232, rs1544410, rs2228570, and rs731236 variants were all significantly associated with certain types of TB.

There are several points that need to be addressed about this meta-analysis. First, although the investigated *VDR* variants were intensively analyzed with regard to their potential associations with TB, the functional significances of these variants were still undetermined,[55,56] and thus future investigations still need to explore the underlying molecular mechanisms of our positive findings. Second, the pathogenic mechanism of TB is highly complex, and therefore it is unlikely that a single genetic variant could significantly contribute to their development. So to better illustrate potential associations of certain genetic variants with TB, we strongly recommend further studies to perform haplotype analyses and explore potential gene-gene interactions.

As with all meta-analysis, this study certainly has some limitations. First, our results were based on unadjusted analyses, and we have to admit that lack of further adjusted analyses for potential confounding factors might impact the reliability of our findings.[57] Second, associations between *VDR* variants and TB might also be modified by gene–gene and gene–environmental interactions. However, most eligible studies ignore these potential interactions, which impeded us to perform relevant analyses accordingly.[58,59] Third, only retrospective case-control studies were included in this meta-analysis, and thus direct causal relation between investigated variants and TB could not be established.[60] On account of above mentioned limitations, our findings should be cautiously interpreted.

In conclusion, our meta-analysis suggested that *VDR* rs7975232, rs1544410, rs2228570, and rs731236 variants might serve as genetic biomarkers of certain types of TB. However, further well-designed studies are still warranted to confirm our findings. Moreover, future investigations also need to explore potential roles of other *VDR* variants in the development of TB.

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Supplemental material

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