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REVIEW ARTICLE

Vitamin D receptor (VDR) gene polymorphism and risk of rheumatoid arthritis (RA): systematic review and meta-analysis

Zahra Bagheri-Hosseinabadi[1,2] · Danyal Imani[3] · Hassan Yousefi[4] · Mitra Abbasifard[2,5]

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Abstract

Vitamin D is involved in immune system modulation as well as in calcium and bone homeostasis, hence plays a role in rheumatoid arthritis (RA) etiopathogenesis. A bulk of studies in different populations have assessed the association between the vitamin D receptor (*VDR*) gene polymorphisms and the risk of RA, reporting conflicting results. Therefore, we designed a meta-analysis to comprehensively evaluate the association of *VDR* gene polymorphisms and RA risk. All potential studies reporting the association between *VDR* gene polymorphisms and susceptibility to RA published till February 2020 were retrieved through systematic search of database, including Scopus and MEDLINE. Strength of pooled association was determined through calculating the pooled odds ratios (ORs) and 95% confidence intervals (CIs). Subgroup analysis was performed by stratifying the studies by population type. This meta-analysis included 23 eligible studies (21 articles) overall. We noticed that *FokI* SNP had a significant protective association with susceptibility to RA in the overall analysis as well as in Europeans and Asians. *TaqI* SNP decreased the RA risk in Africans and Arabs, but not in the overall analysis. Likewise, *BsmI* SNP and RA risk in the overall population analysis was not significant. Interestingly, *BsmI* polymorphism increased RA risk in Africans. This meta-analysis offers a significant association between *VDR* gene polymorphism and susceptibility to RA in both overall and ethnic-specific analysis. However, different polymorphisms acted inversely in increasing or decreasing RA risk in different populations.

Keywords Meta-analysis · Polymorphism · Rheumatoid arthritis · Systematic review · Vitamin D receptor

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disorder, which is characterized by production of autoantibody, chronic synovial inflammation, and progressive destruction and deformity of joint [1–3]. RA is a devastating and common autoimmune disease that has a prevalence of approximately 0.3% to 1% of the total population and more frequently occurs in women than in men (3:1 ratio) [4, 5]. While the main etiology of RA is yet unknown, several population base studies have reported that genetic susceptibility and environmental factors play a principal role in the onset and progression of the disorder [6]. Early investigations proposed that genetic factors contribute to about 50–65% of the RA developing risk [7]. *Human leukocyte antigen* (*HLA*) is one of the common significant genetic loci for RA susceptibility [8, 9]. However, family studies recommend that the *HLA* region is attributed to only about 30% of genetic susceptibility and that non-HLA loci, such as *Cytotoxic T lymphocyte-associated protein 4* (*CTLA4*), *Peptidyl arginine deiminase 4* (*PADI4*), *Methylenetetrahydrofolate reductase* (*MTHFR*), *TIM (T cell/transmembrane, immunoglobulin, and mucin) gene family*, and *Tumor necrosis factor alpha-induced protein 3* (*TNFAIP3*), have also been associated with RA predisposition [10–16].

Vitamin D is a steroid-like hormone that acts by binding to vitamin D receptor (VDR), belonging to the nuclear hormone

✉ Mitra Abbasifard
Rh.abbasi70@gmail.com

1 Department of Clinical Biochemistry, Faculty of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

2 Molecular Medicine Research Center,Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

3 Department of Immunology, School of Public Health, Tehran University of Medical Sciences (TUMS), Tehran, Iran

4 Department of Biochemistry and Molecular Biology, School of Medicine, LSUHSC, New Orleans, LA, USA

5 Department of internal Medicine, Ali-Ibn Abi-Talib hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

receptor superfamily. Vitamin D/VDR signaling plays an important role in the regulation of immune cell proliferation and differentiations, lymphocyte activation, and cytokine production, probably contributing to autoimmunity [17, 18]. Other than its critical function in the calcium metabolism and bone homeostasis, vitamin D plays an immunomodulatory role [19]. It also exhibits anti-inflammatory and anti-infection characteristics [20, 21]. Several studies have suggested that VDR signaling plays a critical function in T-cell differentiation and function. Widespread investigations have demonstrated the involvement of T cells in the etiopathogenesis of RA [22]. Genetic variation of the VDR gene and abnormal levels of vitamin D could result in the initiation and perpetuation of multiple autoinflammatory disorders like RA [23, 24].

It has been demonstrated that the biological function of vitamin D can be affected by single-nucleotide polymorphisms (SNPs) of the *VDR* gene [25]. Recently, *VDR* gene SNPs have become the focus of association studies in searching for genetic factors involved in the RA risk. On the other side, although the functional significances of VDR polymorphisms remain obscure, these *VDR* gene polymorphisms have been associated with an increased risk of several autoimmune and inflammatory diseases, such as type 1 diabetes (T1D), multiple sclerosis (MS), and asthma [26–28]. The four commonly studied VDR polymorphisms sites are *BsmI*, *ApaI*, *FokI*, and *TaqI*. *BsmI* and *ApaI* polymorphisms are located near the 3′ end of the *VDR* gene in the intron between exons 8 and 9, and *TaqI* is located in exon 9. These polymorphisms result in silent codon mutations associated with raised VDR mRNA stability [29]. *FokI* polymorphism is located in exon 2 and leads to the production of a protein with different sizes; the smaller form of the protein (424 amino acids) is more effective than the long form (427 amino acids) [30].

Association studies between *VDR* gene polymorphisms and risk of RA conducted in multiple populations have yielded conflicting results; some revealed significant correlation while other studies failed to reach statistical significance [31–33]. The causes for this discrepancy may be due to low statistical power, sample sizes and/or clinical heterogeneity. To offset these limitations, we conducted this most up-to-date meta-analysis to evaluate whether *VDR* gene polymorphisms are associated with RA susceptibility.

Methods

The current meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [34]. No ethics committee approval was necessary for this meta-analysis, which does not contain any studies with human participants or animals performed by any of the authors.

Literature search

A comprehensive systematic search was conducted in Scopus and MEDLINE databases and retrieved all relevant publications till February 2020 (the search was also updated before submission). The applied key words for search were as follows: ("Rheumatoid Arthritis" OR "Arthritis" OR "RA") AND ("VDR" OR "vitamin D receptor") AND ("single nucleotide polymorphism" OR "SNP" OR "polymorphisms" OR "mutation" OR "variation"). The reference list of all studies was cross-checked to find other potential studies which might have been missed during initial search.

Study selection criteria

Our initial search strategy yields 233 studies that were exported to EndNote X8. The title and abstract of all studies were scanned by two authors and irrelevant studies were excluded. Full-text verification was performed if we could not categorize studies based on their title and abstract. Any disagreements during study selection was discussed and resolved by consensus.

Inclusion and exclusion criteria

The primary search results were transported to the EndNote and publications were screened based on the following criteria: (1) all publications considering the association between VDR gene polymorphisms (FokI (rs2228570) or/and TaqI (rs731236) or/and BsmI (rs1544410) or/and ApaI (rs7975232)) and RA risk; (2) all observational studies (cohort or case–control design); (3) publications with sufficient data to extract or calculate odds ratios (ORs) and 95% confidence intervals (CIs); (4) publications that report genotype or allele frequencies in RA patients and healthy individuals. Reviews, meta-analysis, case reports, book chapters, letters to the editor, conference abstracts, as well as duplicates were all excluded. The application of these criteria recognized 15, 11, 17, and 9 eligible studies for *FokI*, *TaqI*, *BsmI*, and *ApaI* polymorphisms, respectively.

Data extraction and quality assessment

All required data were extracted conforming to the standardized extraction checklist for the following data: the first author's name, journal and year of publication, country of origin, ethnicity, number of subjects in the case and control groups, mean or range of age, genotyping method, and genotype counts in the case and control group. In order to improve the accuracy of our data, two authors independently extract data and possible discrepancies were solved by consensus. In the current meta-analysis, we exploited the Newcastle–Ottawa Scale (NOS) to assess methodological quality of included

studies [35]. Collectively, we divided publications into three groups: higher quality score ≥ 7; moderate quality 4 ≤ score < 7; low quality score < 4.

Statistical analysis

Deviation from Hardy–Weinberg equilibrium (HWE) for distribution of the allele frequencies was analyzed by χ^2-test in control groups. The association between *VDR* gene polymorphism and RA was assessed by estimating ORs and their corresponding 95% CIs. For each SNP, the dominant model, recessive model, allelic model, homozygous model, and heterozygous model were examined to estimate its effect. In detail, defined models for *FokI*, *TaqI*, *BsmI*, and *ApaI* SNPs are as follows: **FokI**—dominant model (ff + Ff vs. FF), recessive model (ff vs. Ff + FF), allelic model (f vs. F), homozygote (ff vs. FF), and heterozygote (Ff vs. FF); **TaqI**—dominant model (tt + Tt vs. TT), recessive model (tt vs. Tt + TT), allelic model (t vs. T), homozygote (tt vs. TT), and heterozygote (Tt vs. TT); **BsmI**—dominant model (bb + Bb vs. BB), recessive model (bb vs. Bb + BB), allelic model (b vs. B), homozygote (bb vs. BB), and heterozygote (Bb vs. BB); **ApaI**—dominant model (aa + Aa vs. AA), recessive model (aa vs. Aa + AA), allelic model (a vs. A), homozygote (aa vs. AA), and heterozygote (Aa vs. AA). The heterogeneity among studies was measured by the χ^2 test–based Q and I^2 value which quantify the degree of heterogeneity [36]. In the case of heterogeneity (Q statistic with a P value less than 0.1 and I^2 exceeding 50%), random-effects model (REM) was employed [37]; otherwise, fixed-effect model was exploited [38]. Potential publication bias was estimated by Egger's linear regression test, and Begg's test (P value < 0.05 considered statistically significant) [39]. Finally, we utilized sensitivity analysis to show the stability of our results. All statistical tests for this meta-analysis were performed with Stata statistical software (version 14.0; Stata Corporation, College Station, TX, USA) and SPSS (version 23.0; SPSS, Inc. Chicago, IL, USA).

Results

Study characteristics

The four-phase process of study selection based on the PRISMA statement is outlined in Fig. 1. After the removal of duplicates (50 publications), 183 publications remained. Of these, 124 publications were excluded based on the title and abstract screening, and 36 publications were excluded by full-text evaluation. Ultimately, 23 eligible studies (21 articles) were included in final analysis [31–33, 40–57]. The references of all eligible publications were cross-checked and no more study was found. The studies were published between 2001 and 2019 and had an overall good methodological quality with NOS scores ranging from 6 to 8. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and TaqMan were used by majority of the included studies as genotyping method. Tables 1 and 2 summarize the characteristics and genotype frequency of the included studies.

Quantitative synthesis

In the current meta-analysis, FF for *FokI* SNP, TT for *TaqI* SNP, BB for *BsmI* SNP, and AA for *ApaI* SNP were used as the reference category.

Meta-analysis of *FokI* (rs2228570) SNP and RA risk

For *FokI* SNP, 15 case–control studies (13 articles) with 2170 cases and 2452 controls were included in quantitative analysis [31–33, 42, 44, 46, 47, 49, 52–54, 56, 57]. Of them, seven studies were performed in Europe, four studies were in Asia, three studies were in Africa, and only one study was carried out in the USA. The pooled OR of overall population detected a significant protective association between *FokI* SNP and susceptibility to RA under the dominant model (OR = 0.74, 95% CI = 0.60–0.92, $P < 0.001$), the ff versus FF model (OR = 0.66, 95% CI = 0.54–0.81, $P < 0.001$), and the Ff versus FF model (OR = 0.85, 95% CI = 0.73–0.98, $P < 0.001$), but not the allelic model (OR = 0.96, 95% CI = 0.42–1.14, $P = 0.14$) and the recessive model (OR = 0.54, 95% CI = 0.29–1.04, $P = 0.06$) (Fig. 2). For more clarifications, subgroup analysis by ethnicity was performed. The analyses showed a remarkable decreased risk of RA in Europeans across all genotype models (Fig. 3). In addition, Asians showed a decreased risk of RA under the dominant (OR = 0.65, 95% CI = 0.48–0.89, $P < 0.001$), Ff versus FF (OR = 0.56, 95% CI = 0.35–0.89, $P = 0.01$), and Ff versus FF (OR = 0.69, 95% CI = 0.50–0.96, $P = 0.02$) models, but not the recessive and allelic models. No significant associations were found in Africans and Arabs (Table 3).

Meta-analysis of *TaqI* (rs731236) SNP and RA risk

There were 11 case–control studies containing 1334 cases and 1560 controls concerning *TaqI* polymorphism and RA risk [31, 32, 40–42, 50, 52–56]. Of those, four studies were conducted in Europeans, four studies were in Asians, and three studies were in Africans. There was no evidence of significant association between *TaqI* polymorphism and RA risk in the pooled results. However, subgroup analyses indicated interesting results. In this regard, our analysis revealed a protective role of TaqI polymorphism in Africans and Arabs. In Africans, all of the genetic models, including the dominant (OR = 0.50, 95% CI = 0.29–0.85, $P = 0.01$), recessive (OR = 0.44, 95% CI = 0.25–0.79, $P < 0.001$), allelic (OR = 0.57,

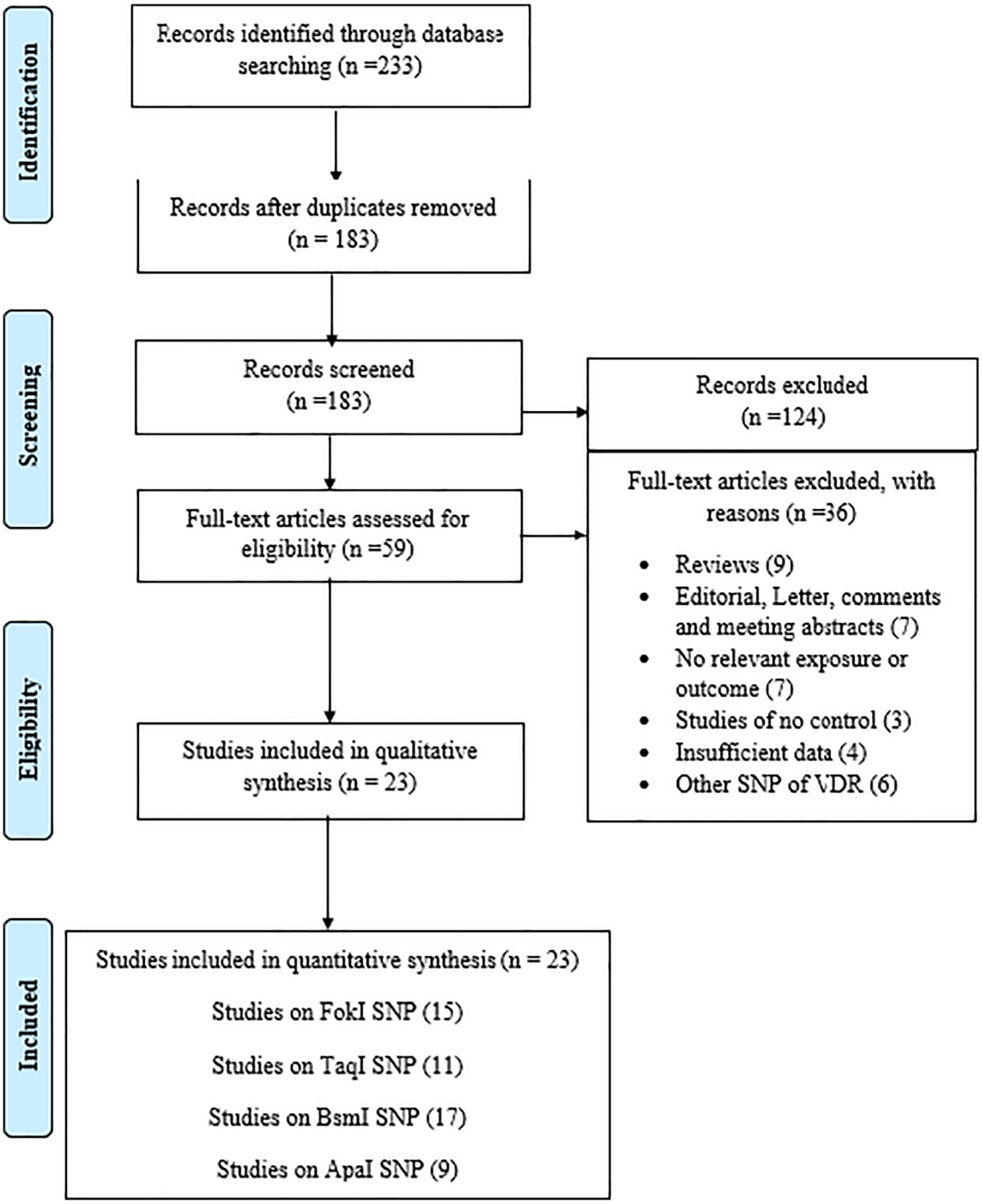

Fig. 1 Flow diagram of study selection process

95% CI = 0.37–0.88, $P = 0.01$), tt versus TT (OR = 0.32, 95% CI = 0.15–0.72, $P < 0.001$), and Tt versus TT (OR = 0.57, 95% CI = 0.38–0.87, $P < 0.001$) models were associated with decreased risk of RA. Furthermore, statistically significant and protective association of the recessive (OR = 0.53, 95% CI = 0.32–0.87, $P = 0.01$) and tt versus TT (OR = 0.43, 95% CI = 0.20–0.94, $P = 0.03$) models were detected in Arabs. No significant association was detected for Europeans and Asians (Table 3).

Meta-analysis of *BsmI* (rs1544410) SNP and RA risk

For *BsmI* SNP, 17 case–control studies (16 articles) encapsulating 2153 cases and 2326 controls subjects examined the association between *BsmI* polymorphism and RA risk [31–33, 40–43, 45–48, 51–54, 56]. Among included studies, seven studies were conducted in Europeans, six studies were in Asians, and four studies were in Africans. Our findings did not indicate any association between *BsmI* SNP and RA risk

Table 1 Characteristics of studies included in meta-analysis of overall RA

Study author	Year	Country	Ethnicity	Total cases/controls	Age case/control (mean)	Genotyping method	Quality score
FokI (rs2228570)							
Goertz et al.	2003	Germany	European	62/40	57.4 ± 14.8/52.8 ± 15.5	PCR	5
Maalej et al. (i)	2005	France	European	100/100	NR/NR	PCR-RFLP	6
Maalej et al. (ii)	2005	France	European	100/100	NR/NR	PCR-RFLP	6
Ghelani et al. (i)	2011	UK	European	100/100	NR/NR	PCR-RFLP	6
Ghelani et al. (ii)	2011	UK	European	100/100	29–75/NR	PCR-RFLP	6
Hitchon et al.	2012	USA	American	448/705	47 ± 15/35 ± 12	Sequenom	8
Karray et al.	2012	Tunisia	African	108/152	39.5 ± 13.4/41.3 ± 9	PCR-RFLP	6
Huang et al.	2013	China	Asian	236/220	21–76/21–68	PCR-MassARRAY	7
Mosaad et al.	2014	Egypt	African	128/150	46.91 ± 11.73/40 ± 15.83	PCR-RFLP	6
Shukla et al.	2014	India	Asian	112/125	NR/NR	PCR-RFLP	6
Saad et al.	2015	Egypt	African	105/80	42.71 ± 12.07/NR	PCR-RFLP	6
Spinga et al.	2016	Italy	European	40/40	40.3 ± 11.3/NR	PCR-RFLP	5
Khoja et al.	2018	Saudi Arabia	Asian	37/40	49.4 ± 13.1/45.1 ± 12.6	PCR-RFLP	5
Mukhtar et al.	2019	Pakistan	Asian	300/412	NR/NR	PCR-RFLP	8
Rodriguez et al.	2019	Spain	European	194/88	53.87/53.25	TaqMan	7
							TaqI (rs731236)
Garcia et al.	2001	Spain	European	120/200	NR/NR	PCR-RFLP	7
Lee et al.	2001	Korea	Asian	157/120	16–82/16–82	PCR-RFLP	6
Goertz et al.	2003	Germany	European	62/70	57.4 ± 14.8/52.8 ± 15.5	PCR	5
Maalej et al. (i)	2005	France	European	95/95	NR/NR	PCR-RFLP	5
Mosaad et al.	2014	Egypt	African	128/150	46.91 ± 11.73/40 ± 15.83	PCR-RFLP	6
Tizaoui et al.	2014	Tunisia	African	106/153	51.66 ± 5.70/44.64 ± 7.93	PCR	6
Saad et al.	2015	Egypt	African	105/80	42.71 ± 12.07/NR	PCR-RFLP	6
Spinga et al.	2016	Italy	European	40/40	40.3 ± 11.3/NR	PCR-RFLP	5
Khoja et al.	2018	Saudi Arabia	Asian	37/40	49.4 ± 13.1/45.1 ± 12.6	PCR-RFLP	5
Mahmoud et al.	2018	Jordan	Asian	184/200	NR/NR	PCR-RFLP	7
Mukhtar et al.	2019	Pakistan	Asian	300/412	NR/NR	PCR-RFLP	8
BsmI (rs1544410)							
Garcia et al.	2001	Spain	European	120/200	NR/NR	PCR-RFLP	7
Lee et al.	2001	Korea	Asian	167/211	16–82/16–82	PCR-RFLP	6
Goertz et al.	2003	Germany	European	62/40	57.4 ± 14.8/52.8 ± 15.5	PCR	5
Maalej et al. (i)	2005	France	European	96/96	NR/NR	PCR-RFLP	5
Rass et al.	2006	Hungary	European	64/40	51.2 ± 23.2/46.7 ± 19.4	PCR	5
Ghelani et al. (i)	2011	UK	European	121/146	NR/NR	PCR-RFLP	6
Ghelani et al. (ii)	2011	UK	European	120/129	29–75/NR	PCR-RFLP	6
Karray et al.	2012	Tunisia	African	108/152	39.5 ± 13.4/41.3 ± 9	PCR-RFLP	6
Huang et al.	2013	China	Asian	236/220	21–76/21–68	PCR-MassARRAY	7
Hussien et al.	2013	Egypt	African	200/150	57.3 ± 3.9/57.1 ± 3.8	PCR-RFLP	7
Li et al.	2013	China	Asian	120/120	44 ± 10/46 ± 11	PCR-RFLP	6
Mosaad et al.	2014	Egypt	African	128/150	46.91 ± 11.73/40 ± 15.83	PCR-RFLP	6
John et al.	2015	Pakistan	Asian	100/100	44.2/43	ARMS-PCR	5
Saad et al.	2015	Egypt	African	105/80	42.71 ± 12.07/NR	PCR-RFLP	5
Spinga et al.	2016	Italy	European	40/40	40.3 ± 11.3/NR	PCR-RFLP	5
Khoja et al.	2018	Saudi Arabia	Asian	36/40	49.4 ± 13.1/45.1 ± 12.6	PCR-RFLP	5
Mukhtar et al.	2019	Pakistan	Asian	300/412	NR/NR	PCR-RFLP	8
ApaI (rs7975232)							
Garcia et al.	2001	Spain	European	120/200	NR/NR	PCR-RFLP	7
Huang et al.	2013	China	Asian	236/220	21–76/21–68	PCR-MassARRAY	7

Table 1 (continued)

Study author	Year	Country	Ethnicity	Total cases/controls	Age case/control (mean)	Genotyping method	Quality score
Li et al.	2013	China	Asian	120/120	44 ± 10/46 ± 11	PCR-RFLP	6
Mosaad et al.	2014	Egypt	African	128/150	46.91 ± 11.73/40 ± 15.83	PCR-RFLP	6
Tizaoui et al.	2014	Tunisia	African	106/153	51.66 ± 5.70/44.64 ± 7.93	PCR	5
Saad et al.	2015	Egypt	African	105/80	42.71 ± 12.07/NR	PCR-RFLP	5
Spinga et al.	2016	Italy	European	40/40	40.3 ± 11.3/NR	PCR-RFLP	5
Khoja et al.	2018	Saudi Arabia	Asian	36/40	49.4 ± 13.1/45.1 ± 12.6	PCR-RFLP	5
Mukhtar et al.	2019	Pakistan	Asian	300/412	NR/NR	PCR-RFLP	8

Bold values have a significant association. *NR* not reported

in the overall population analysis. Nonetheless, subgroup analysis found a significant positive association between *BsmI* SNP and RA risk in Africans under all genetic models: the dominant model (OR = 1.82, 95% CI = 1.14–2.88 2, P = 0.01), the recessive model (OR = 1.77, 95% CI = 1.13–2.78, P = 0.01), the allelic model (OR = 1.59, 95% CI = 1.14–2.23, P < 0.001), the bb versus BB model (OR = 2.40, 95% CI = 1.22–4.71, P = 0.01), and the Bb versus BB model (OR = 1.45, 95% CI = 1.04–2.01, P = 0.02) (Fig. 3). No significant association was detected for Europeans, Asians, and Arabs (Table 3).

Meta-analysis of *ApaI* (rs7975232) SNP and RA risk

Herein, nine studies were found providing data about *ApaI* polymorphism and RA risk [32, 40, 47, 48, 50, 52–54, 56]. A total of 1191 cases and 1415 controls were included in the quantitative analysis. Of eligible studies, four studies were performed in Asians, three studies were in Africans, and two studies were in Europeans. The analyses revealed no association between *ApaI* SNP and RA risk across all models in both overall population and subgroups. However, this polymorphism was significantly associated with RA risk under the Aa versus AA model in the overall analysis (OR = 0.76, 95% CI = 0.61–0.94, P = 0.01) (Table 3).

Evaluation of heterogeneity and publication bias

The degree of heterogeneity was measured for all five genetic models among intended genes. Collectively, significant heterogeneity was observed for *FokI*, *TaqI*, *BsmI*, and *ApaI* genes and subsequently random-effect model was used (Table 3). The Egger regression, Begg rank correlation analysis, and funnel plot according to quantitative analysis demonstrated no statistical significance (Table 3, Fig. 4).

Sensitivity analysis

Sensitivity analysis was performed by removing a single study at a time to evaluate the robustness of the results. Accordingly, the significance of the pooled ORs was not affected by any single study in the dominant model for *FokI*, *TaqI*, *BsmI*, and *ApaI* SNPs (Fig. 5).

Discussion

In the current most up-to-date systematic review and meta-analysis study, we intended to obtain a conclusive and exact estimation of the associations between the polymorphisms located on the *VDR* gene, including *FokI* (rs2228570), *BsmI* (rs1544410), *TaqI* (rs731236), and *ApaI* (rs7975232) and risk of RA predisposition. The results of the meta-analysis on 23 eligible studies (21 articles) unraveled that *FokI* and *TaqI* polymorphisms in the overall and subgroup analysis, respectively, had significant association with RA risk.

During the past years, numerous investigations have evaluated the association of *VDR* gene polymorphisms and risk of RA throughout different populations. That notwithstanding, these studies sometimes confirmed findings in different populations, but sometimes not. The conflict among these studies may be due to differences in the genotyping methods, clinical heterogeneity of the patients, variations in the diagnosis of patients, small sample sizes, lack of statistical power, and the interactions between genetic content and environmental risk factors offered by different geographic regions. As a result, three previous meta-analyses have tried to settle the issue [58–60]. That notwithstanding, several original association studies investigated the association of *VDR* gene polymorphisms and RA risk, after the latest meta-analysis published in 2016. As a consequence, it seems paramount to perform an up-to-date meta-analysis to achieve more valid and comprehensive pooled approximation on the association of *VDR* gene SNPs and RA risk.

Table 2 Distribution of genotype and allele among RA patients and controls

Study author	RA cases					Healthy control					P-HWE	MAF
	FF	Ff	ff	F	f	FF	Ff	ff	F	f		
FokI (rs2228570)												
Goertz et al.	34	23	5	91	33	14	23	3	51	29	0/122	0/363
Maalej et al. (i)	45	43	12	133	67	30	48	22	108	92	0/735	0/46
Maalej et al. (ii)	48	40	12	136	64	37	50	13	124	76	0/541	0/38
Ghelani et al. (i)	45	43	12	133	67	30	48	22	108	92	0/735	0/46
Ghelani et al. (ii)	48	40	12	136	64	37	50	13	124	76	0/541	0/38
Hitchon et al.	90	243	115	423	473	156	308	241	620	790	0/002	0/56
Karray et al.	49	49	10	147	69	46	72	34	164	140	0/564	0/461
Huang et al.	109	83	44	301	171	77	89	54	243	197	0/006	0/448
Mosaad et al.	69	51	8	189	67	93	55	2	241	59	0/049	0/197
Shukla et al.	58	50	4	166	58	54	63	8	171	79	0/063	0/316
Saad et al.	61	38	6	160	50	50	29	1	129	31	0/151	0/194
Spinga et al.	24	13	3	61	19	18	18	4	54	26	0/871	0/325
Khoja et al.	0	8	29	8	66	16	24	0	56	24	0/006	0/3
Mukhtar et al.	161	112	27	434	166	0	15	397	15	809	0/706	0/982
Rodriguez et al.	71	93	30	235	153	32	40	16	104	72	0/574	0/409
Study author	**RA cases**					**Healthy control**					**P-HWE**	**MAF**
	TT	**Tt**	**tt**	**T**	**t**	**TT**	**Tt**	**tt**	**T**	**t**		
TaqI (rs731236)												
Garcia et al.	57	47	16	161	79	79	94	27	252	148	0/908	0/37
Lee et al.	147	10	0	304	10	109	9	2	227	13	0/003	0/054
Goertz et al.	24	34	4	82	42	14	10	46	38	102	0	0/729
Maalej et al. (i)	42	35	18	119	71	33	49	13	115	75	0/438	0/395
Mosaad et al.	64	51	13	179	77	39	74	37	152	148	0/871	0/493
Tizaoui et al.	44	52	10	140	72	56	80	17	192	114	0/142	0/373
Saad et al.	48	47	10	143	67	21	39	20	81	79	0/824	0/494
Spinga et al.	16	18	6	50	30	34	5	1	73	7	0/169	0/088
Khoja et al.	12	11	14	35	39	40	0	0	80	0	0	0
Mahmoud et al.	73	87	24	233	135	87	81	32	255	145	0/080	0/363
Mukhtar et al.	159	129	12	447	153	412	0	0	824	0	0	0
Study author	**RA cases**					**Healthy control**					**P-HWE**	**MAF**
	BB	**Bb**	**bb**	**B**	**b**	**BB**	**Bb**	**bb**	**B**	**b**		
BsmI (rs1544410)												
Garcia et al.	23	43	54	89	151	29	94	77	152	248	0/971	0/62
Lee et al.	1	18	148	20	314	3	17	191	23	399	0/001	0/945
Goertz et al.	9	43	10	61	63	12	17	11	41	39	0/344	0/488
Maalej et al. (i)	19	35	42	73	119	13	48	35	74	118	0/587	0/615
Rass et al.	13	26	25	52	76	11	16	13	38	42	0/210	0/525
Ghelani et al.	62	30	29	154	88	49	73	24	171	121	0/715	0/414
Ghelani et al.	35	51	34	121	119	43	53	33	139	119	0/048	0/461
Karray et al.	21	47	40	89	127	35	64	53	134	170	0/072	0/559
Huang et al.	0	30	206	30	502	0	29	191	29	411	0/295	0/934
Hussien et al.	53	78	69	184	216	48	60	42	156	144	0/014	0/48
Li et al.	32	43	45	107	133	40	36	44	116	124	0	0/517
Mosaad et al.	13	52	63	78	178	36	74	40	146	154	0/877	0/513
John et al.	19	50	31	88	112	8	52	40	68	132	0/112	0/66
Saad et al.	10	47	48	67	143	20	41	19	81	79	0/821	0/494

Table 2 (continued)

Study author	RA cases					Healthy control					P-HWE	MAF
	FF	Ff	ff	F	f	FF	Ff	ff	F	f		
Spinga et al.	6	16	18	28	52	3	20	17	26	54	0/377	0/675
Khoja et al.	10	15	11	35	37	3	16	21	22	58	0/984	0/725
Mukhtar et al.	27	64	209	118	482	412	0	0	824	0	0	0
Study author	**RA cases**					**Healthy control**					**P-HWE**	**MAF**
	AA	**Aa**	**aa**	**A**	**a**	**AA**	**Aa**	**aa**	**A**	**A**		
ApaI (rs7975232)												
Garcia et al.	37	49	34	123	117	53	102	45	208	192	0/759	0/48
Huang et al.	119	90	27	328	144	108	81	31	297	143	0/017	0/325
Li et al.	44	60	16	148	92	12	44	64	68	172	0/287	0/717
Mosaad et al.	56	46	26	158	98	69	71	10	209	91	0/141	0/303
Tizaoui et al.	39	53	14	131	81	49	78	26	176	130	0/593	0/425
Saad et al.	47	38	20	132	78	36	40	4	112	48	0/088	0/3
Spinga et al.	36	3	1	75	5	34	5	1	73	7	0/169	0/088
Khoja et al.	11	12	13	34	38	3	14	23	20	60	0/673	0/75
Mukhtar et al.	126	159	15	411	189	412	0	0	824	0	0	0

Bold values have a significant association. *P-HWE P* value for Hardy–Weinberg equilibrium, *MAF* minor allele frequency of control group

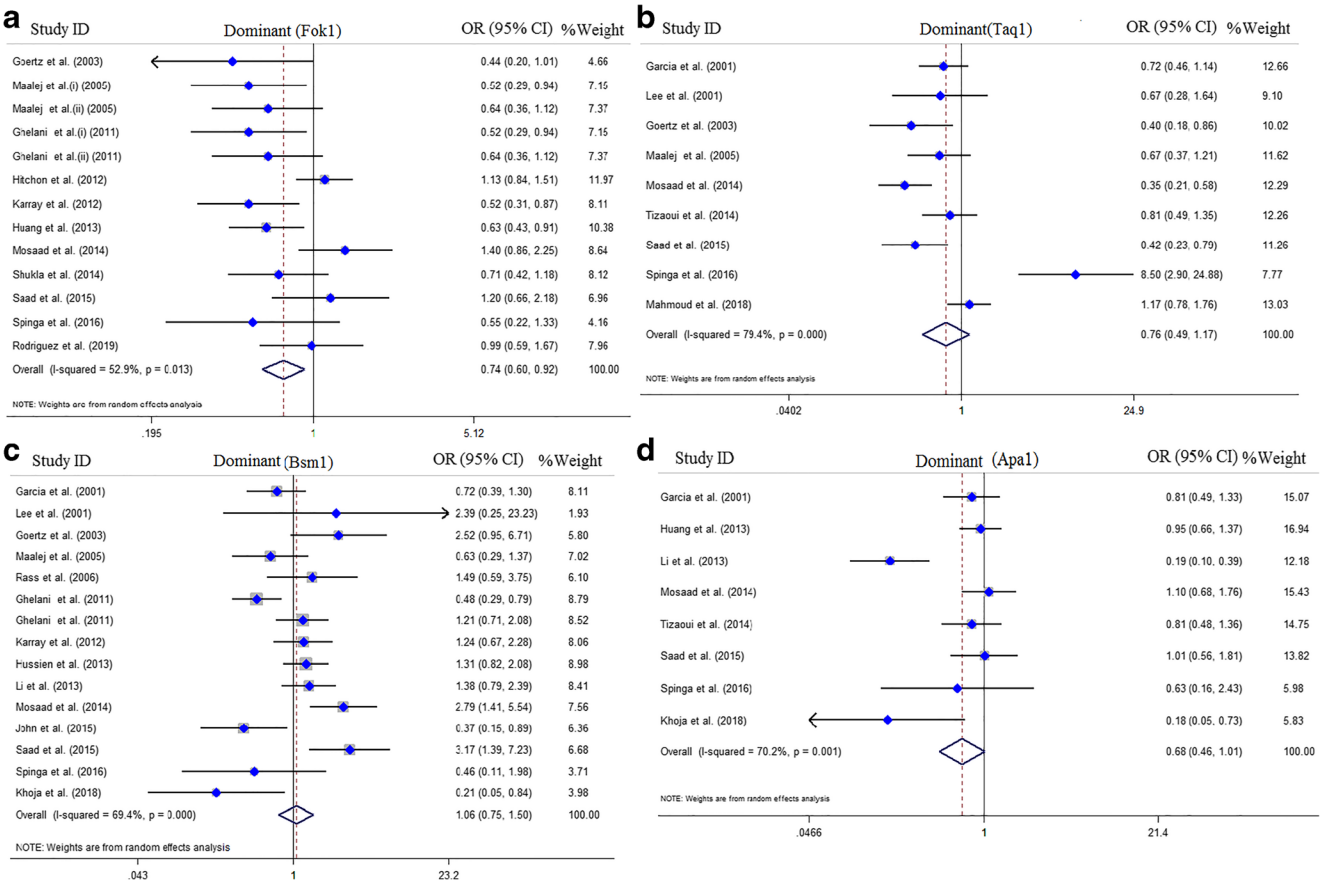

Fig. 2 Pooled odds ratio (OR) and 95% confidence interval (CI) of individual studies and pooled data for the association between *VDR* gene polymorphism and RA risk in overall analysis. (**a**) Dominant model for *FokI*, (**b**) dominant model for *TaqI*, (**c**) dominant model for *BsmI*, (**d**) dominant model for *ApaI*

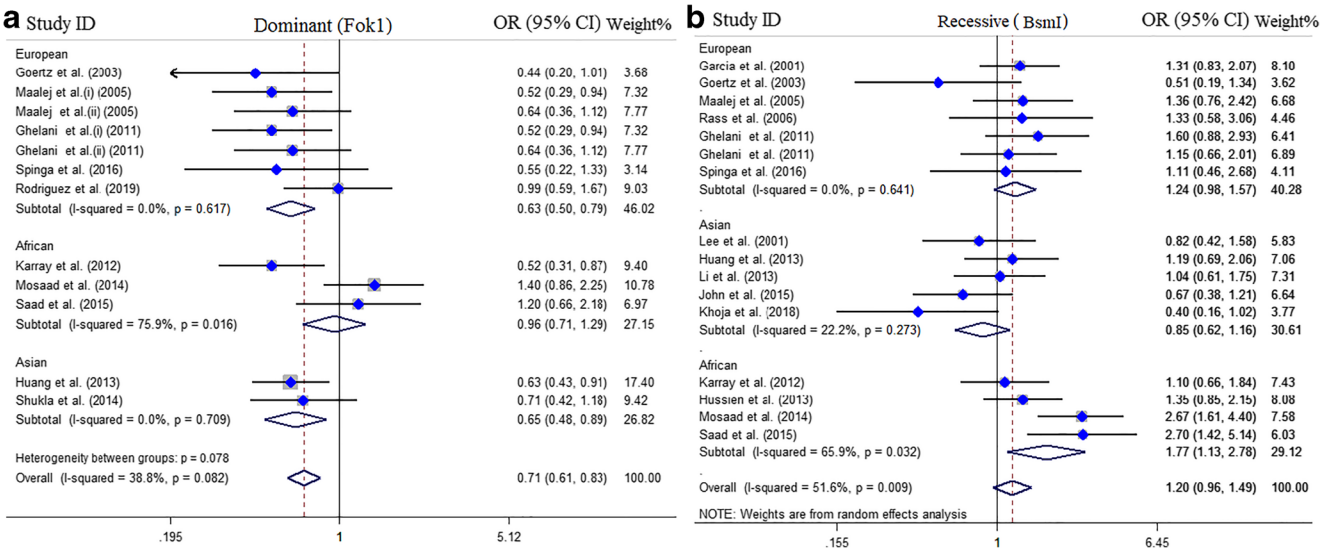

Fig. 3 Pooled odds ratio (OR) and 95% confidence interval (CI) of individual studies and pooled data for the association between *FokI and BsmI* polymorphisms and RA risk in different ethnicity subgroups. (**a**) Dominant model (*FokI*), (**b**) recessive model (*BsmI*)

The meta-analysis was performed by Tizaoui et al. in 2015 [59]; 12 case–control studies, involving 1703 cases and 2635 controls, were included. This analysis indicated a significant association between TaqI polymorphism and RA disease in homozygous, codominant, and allele contrast models. Association between BsmI polymorphism and RA risk was marginal in the dominant, codominant, and allele contrast models. The association between FokI polymorphism and RA risk was significant in the recessive, dominant, and allele contrast models. Subgroup analysis indicated that publication year, ethnicity, age, latitude, and estimated 25(OH)D levels influenced significantly the association between VDR polymorphisms and RA risk. Therefore, study characteristics impressed the association between *VDR* gene polymorphisms and RA disease. This meta-analysis suggested that VDR gene *TaqI* and *FokI* polymorphisms are involved in RA risk. On the other side, in the last meta-analysis conducted by Song et al. in 2016, seven studies containing a total of 923 patients and 912 controls were included in the meta-analysis, and three of the VDR gene SNPs, FokI, BsmI, and TaqI, were considered [60]. This study found no association between FokI, BsmI, and TaqI polymorphisms and risk of RA in the overall analysis. However, FokI SNP was associated with increased risk of RA in Europeans (OR = 1.40). Our most up-to-date meta-analysis included 23 eligible studies (21 articles) in total, 15 case–control studies (13 articles) with 2170 cases and 2452 controls for *FokI* SNP, 11 case–control studies containing 1334 cases and 1560 controls for *TaqI* polymorphism, 17 case–control studies (16 articles) involving 2153 cases and 2326 controls for *BsmI* SNP, and 9 studies containing 1191 cases and 1415 controls for *ApaI* polymorphism. We indicated that *FokI* SNP had a significant association with susceptibility to RA and was protective under the dominant model (OR = 0.74), the ff versus FF model (OR = 0.66), and the Ff versus FF model (OR = 0.85). Moreover, this polymorphism decreased the RA risk in Europeans in all models and also was protective in Asians under the dominant, Ff versus FF, and Ff versus FF models. On the other hand, although we did not detect a significant association of *TaqI* SNP and RA risk in the overall analysis, this polymorphism decreased the RA risk in Africans and Arabs. As such, *BsmI* SNP and RA risk in the overall population analysis was not significant. Nonetheless, this polymorphism increased RA risk in Africans under all genetic models. Finally, neither overall nor subgroup analyses indicated association of *ApaI* SNP with RA risk. The differences in the findings of the current meta-analysis with the previous ones may stem from the difference in the sample size and ethnicity, as our meta-analysis included further studies with diverse populations.

The interaction of common polymorphisms might be involved in determining the genetic etiopathogenesis of the multifactorial diseases. SNPs have been reported to cause little, but rarely significant, biological impact on the protein they are encoding [61]. *VDR* gene polymorphisms, such as *ApaI*, *BsmI*, and *TaqI*, have been suggested to lack considerable influence on the protein structure of VDR. Nevertheless, these SNPs may modulate the VDR protein stability, translation quality, or splicing of the corresponding mRNA. Interestingly, *FokI* SNP has been reported to modify the VDR protein structure and the efficacy of mRNA transcription [62]. Hence, VDR gene *ApaI*, *BsmI*, and *TaqI* SNPs may be associated with diseases pathogenesis during the linkage disequilibrium with the real disease-associating genes [63]. Environmental interactions and ethnicity of the population may be critical in determining the function and expression of VDR [64],

Table 3 Main results of pooled ORs in meta-analysis of *VDR* gene polymorphisms in association with RA risk

Subgroup		Sample size	Test of association		Test of heterogeneity		Test of publication bias (Begg's test)		Test of publication bias (Egger's test)	
	Genetic model	Case/control	OR	95% CI (*P* value)	I^2 (%)	*P*	*Z*	*P*	*T*	*P*
FokI (rs2228570)										
Overall	Dominant model	2170/2452	**0.74**	**0.60–0.92 (< 0.001)**	52.9	0.01	0.81	0.41	0.44	0.66
	Recessive model	2170/2452	0.54	0.29–1.04 (0.06)	90.1	< 0.001	0.19	0.85	0.24	0.81
	Allelic model	2170/2452	0.96	0.42–1.14 (0.14)	96.1	< 0.001	0.44	0.66	0.32	0.75
	ff vs. FF	2170/2452	**0.66**	**0.54–0.81 (< 0.001)**	43.4	0.04	0.06	0.95	0.35	0.73
	Ff vs. FF	2170/2452	**0.85**	**0.73–0.98 (0.02)**	49.4	0.02	0.46	0.64	0.39	0.69
Subgroup										
European	Dominant model	696/568	**0.63**	**0.50–0.79 (< 0.001)**	0	0.61	− 0.52	0.60	− 0.55	0.68
	Recessive model	696/568	**0.71**	**0.51–0.98 (0.03)**	0	0.79	0.52	0.60	0.60	0.65
	Allelic model	696/568	**0.72**	**0.61–0.85 (< 0.001)**	0	0.63	− 0.94	0.34	− 0.43	0.67
	ff vs. FF	696/568	**0.58**	**0.40–0.82 (< 0.001)**	0	0.70	− 1.57	0.11	− 2.63	0.23
	Ff vs. FF	696/568	**0.65**	**0.51–0.83 (< 0.001)**	0	0.64	− 0.52	0.60	− 0.49	0.70
African	Dominant model	341/382	0.96	0.71–1.29 (0.76)	75.9	0.01	− 0.15	0.88	− 0.41	0.68
	Recessive model	341/382	1.76	0.23–13.63 (0.58)	83.6	< 0.001	− 0.35	0.72	− 0.41	0.68
	Allelic model	341/382	1	0.52–1.92 (0.99)	86.1	< 0.001	0.44	0.66	0.32	0.75
	ff vs. FF	341/382	0.65	0.33–1.28 (0.21)	86.3	< 0.001	− 0.35	0.72	− 0.34	0.73
	Ff vs. FF	341/382	0.96	0.70–1.31 (0.80)	41.2	0.18	− 0.49	0.62	− 0.61	0.55
Asian	Dominant model	685/797	**0.65**	**0.48–0.89 (< 0.001)**	0	0.70	− 1.48	0.13	− 1.88	0.11
	Recessive model	685/797	0.11	0.01–3.46 (0.20)	98	< 0.001	− 1.24	0.21	− 0.95	0.38
	Allelic model	685/797	0.51	0.05–5.02 (0.56)	99	< 0.001	− 1.73	0.08	− 1.27	0.25
	ff vs. FF	685/797	**0.56**	**0.35–0.89 (0.01)**	0	0.75	− 1.73	0.08	− 1.68	0.14
	Ff vs. FF	685/797	**0.69**	**0.50–0.96 (0.02)**	0	0.13	− 0.99	0.32	− 1.10	0.31
Arab	Dominant model	378/422	0.96	0.71–1.29 (0.76)	75.9	0.01	0	1	− 1.08	0.31
	Recessive model	378/422	0.71	0.37–1.35 (0.29)	83.6	< 0.001	− 2.44	0.01	− 3.55	0.02
	Allelic model	378/422	1.97	0.69–5.64 (0.20)	94.7	< 0.001	0	1	− 0.75	0.45
	ff vs. FF	378/422	0.65	0.33–1.28 (0.21)	86.3	< 0.001	− 1.69	0.09	− 3.10	0.03
	Ff vs. FF	378/422	0.96	0.70–1.31 (0.80)	41.2	0.18	− 0.83	0.40	− 0.77	0.46
TaqI (rs731236)										
Overall	Dominant model	1334/1560	0.76	0.49–1.17 (0.20)	79.4	< 0.001	− 0.25	0.80	0.89	0.39
	Recessive model	1334/1560	0.57	0.28–1.17 (0.12)	83.5	< 0.001	− 0.25	0.80	− 0.63	0.54
	Allelic model	1334/1560	0.73	0.49–1.11 (0.13)	87.9	< 0.001	− 0.35	0.72	− 0.75	0.46
	tt vs. TT	1334/1560	0.52	0.25–1.10 (0.08)	82.1	< 0.001	0.05	0.96	− 0.57	0.57
	Tt vs. TT	1334/1560	0.90	0.59–1.38 (0.64)	74.3	< 0.001	− 0.45	0.65	− 0.99	0.34
Subgroup										
European	Dominant model	317/405	1.03	0.41–2.58 (0.95)	86.5	0.58	0.04	0.11	1.14	0.09
	Recessive model	317/405	0.69	0.12–3.83 (0.67)	91.5	< 0.001	0.76	0.60	0.38	0.76
	Allelic model	317/405	0.92	0.35–2.45(0.86)	93.8	< 0.001	0.57	0.60	0.80	0.57
	tt vs. TT	317/405	0.73	0.15–3.52 (0.69)	88.4	< 0.001	0.96	0.60	0.06	0.96
	Tt vs. TT	317/405	1.39	0.54–3.57 (0.49)	84.2	< 0.001	0.36	0.60	1.56	0.36
African	Dominant model	339/383	**0.50**	**0.29–0.85 (0.01)**	64.9	0.05	0.90	0.60	− 0.15	0.90
	Recessive model	339/383	**0.44**	**0.25–0.79 (< 0.001)**	41.4	0.18	0.23	0.31	0.18	0.23
	Allelic model	339/383	**0.57**	**0.37–0.88 (0.01)**	73.9	0.02	0.96	0.60	0.05	0.96
	tt vs. TT	339/383	**0.32**	**0.15–0.72 (< 0.001)**	62.9	0.06	0.35	0.31	0.15	0.35
	Tt vs. TT	339/383	**0.57**	**0.38–0.87 (< 0.001)**	37.9	0.20	0.89	0.60	− 0.16	0.89
Asian	Dominant model	678/772	1.03	0.65–1.63 (0.89)	18	0.27	1.70	0.08	0.90	0.39
	Recessive model	678/772	0.79	0.44–1.40 (0.41)	0	0.68	1.88	0.06	1.26	0.24
	Allelic model	678/772	0.88	0.54–1.44 (0.61)	37	0.20	1.34	0.18	1.69	0.13

Table 3 (continued)

Subgroup		Sample size	Test of association		Test of heterogeneity		Test of publication bias (Begg's test)		Test of publication bias (Egger's test)	
	tt vs. TT	678/772	0.89	0.48–1.65 (0.72)	0	0.73	1.34	0.18	0.23	0.82
	Tt vs. TT	678/772	1.18	0.80–1.75 (0.40)	0	0.40	1.46	0.14	1.35	0.22
Arab	Dominant model	560/623	0.63	0.35–1.12 (0.11)	81.4	< 0.001	− 1.36	0.17	− 1.69	0.22
	Recessive model	560/623	**0.53**	**0.32–0.87 (0.01)**	50.1	0.11	0	1	0.48	0.68
	Allelic model	560/623	0.66	0.43–1.02 (0.06)	82.6	< 0.001	− 0.68	0.49	− 0.85	0.48
	tt vs. TT	560/623	**0.43**	**0.20–0.94 (0.03)**	75.5	< 0.001	0.68	0.49	0.48	0.67
	Tt vs. TT	560/623	0.71	0.42–1.20 (0.20)	74	< 0.001	− 1.36	0.17	− 1.69	0.23
BsmI (rs1544410)										
Overall	Dominant model	2153/2326	1.06	0.75–1.50 (0.75)	69.4	< 0.001	− 1.70	0.09	− 1.32	0.21
	Recessive model	2153/2326	1.20	0.96–1.49 (0.10)	51.6	< 0.001	− 1.26	0.20	− 1.77	0.10
	Allelic model	2153/2326	1.10	0.92–1.32 (0.30)	66.3	< 0.001	− 1.37	0.17	− 2.18	0.05
	bb vs. BB	2153/2326	1.19	0.82–1.72 (0.35)	64.6	< 0.001	− 1.70	0.09	− 1.59	0.13
	Bb vs. BB	2153/2326	0.96	0.66–1.40 (0.85)	68.3	< 0.001	− 1.48	0.13	− 1.11	0.28
Subgroup										
European	Dominant model	623/691	0.88	0.57–1.35 (0.55)	58.4	0.02	− 2.41	0.01	− 2.68	0.02
	Recessive model	623/691	1.24	0.98–1.57 (0.08)	0	0.64	− 1.16	0.24	− 1.92	0.09
	Allelic model	623/691	1.02	0.87–1.19 (0.81)	0	0.78	− 1.88	0.06	− 3.02	0.01
	bb vs. BB	623/691	1.02	0.75–1.39 (0.91)	0	0.87	− 1.88	0.06	− 2.42	0.04
	Bb vs. BB	623/691	0.78	0.44–1.41 (0.41)	73	< 0.001	− 1.52	0.12	− 1.90	0.09
African	Dominant model	541/532	**1.82**	**1.14–2.88 (0.01)**	53.7	0.09	0	1	0.29	0.80
	Recessive model	541/532	**1.77**	**1.13–2.78 (0.01)**	65.9	< 0.001	0.68	0.49	− 0.41	0.72
	Allelic model	541/532	**1.59**	**1.14–2.23 (< 0.001)**	72.4	0.01	− 0.68	0.49	− 0.61	0.60
	bb vs. BB	541/532	**2.40**	**1.22–4.71 (0.01)**	72.3	0.01	0.68	0.49	0.33	0.77
	Bb vs. BB	541/532	**1.45**	**1.04–2.01 (0.02)**	0	0.46	0	1	0.44	0.70
Asian	Dominant model	989/1103	0.66	0.23–1.84 (0.42)	72.8	0.01	− 0.19	0.85	1.37	0.24
	Recessive model	989/1103	0.85	0.62–1.16 (0.31)	22.2	0.23	1.32	0.18	2.02	0.07
	Allelic model	989/1103	0.83	0.58–1.19 (0.31)	62.8	0.02	1.32	0.18	2.30	0.08
	bb vs. BB	989/1103	0.58	0.19–1.76 (0.33)	72.7	0.01	2.07	0.03	3.04	0.04
	Bb vs. BB	989/1103	0.77	0.29–2.05 (0.59)	66	0.03	− 0.94	0.34	1.13	0.32
Arab	Dominant model	577/572	1.45	0.79–2.68 (0.23)	72.9	< 0.001	− 0.21	0.83	0.70	0.50
	Recessive model	577/572	1.43	0.83–2.46 (0.19)	77	< 0.001	1.71	0.21	0.73	0.18
	Allelic model	577/572	1.29	0.83–2.01 (0.25)	84.2	< 0.001	1.88	0.06	2.44	0.04
	bb vs. BB	577/572	1.66	0.72–3.84 (0.23)	81.9	< 0.001	0.21	0.83	1.44	0.19
	Bb vs. BB	577/572	1.33	0.84–2.09 (0.22)	43.9	0.12	− 0.42	0.67	0.66	0.53
ApaI (rs7975232)										
Overall	Dominant model	1191/1415	0.68	0.46–1.01 (0.05)	70.2	< 0.001	0.27	0.78	− 0.07	0.94
	Recessive model	1191/1415	0.93	0.42–2.06 (0.85)	88.2	< 0.001	− 1.70	0.08	− 0.96	0.36
	Allelic model	1191/1415	0.77	0.50–1.18 (0.20)	88.4	< 0.001	− 0.63	0.53	− 0.47	0.65
	aa vs. AA	1191/1415	0.72	0.29–1.78 (0.47)	87.6	< 0.001	− 1.52	0.12	− 1.16	0.28
	Aa vs. AA	1191/1415	**0.76**	**0.61–0.94 (0.01)**	16.3	0.30	0.45	0.65	0.21	0.84
Subgroup										
European	Dominant model	160/240	0.78	0.49–1.25(0.31)	0	0.73	− 1.35	0.17	− 1.11	0.31
	Recessive model	160/240	1.35	0.81–2.24 (0.25)	38.6	0.14	0.45	0.65	0.97	0.37
	Allelic model	160/240	1.00	0.74–1.37 (0.98)	0	0.53	0.15	0.88	− 0.44	0.67
	aa vs. AA	160/240	1.08	0.59–1.96 (0.81)	0	0.92	0.45	0.65	0.54	0.61
	Aa vs. AA	160/240	0.67	0.40–1.12 (0.12)	0	0.81	− 0.45	0.65	− 0.86	0.43
African	Dominant model	339/383	0.97	0.72–1.31(0.83)	0	0.69	1.05	0.29	1.40	0.22
	Recessive model	339/383	2.18	0.67–7.10 (0.19)	82.8	< 0.001	− 0.45	0.65	0.24	0.82

Table 3 (continued)

Subgroup		Sample size	Test of association	Test of heterogeneity		Test of publication bias (Begg's test)		Test of publication bias (Egger's test)	
	Allelic model	339/383	1.17 0.82–1.66 (0.37)	60.7	0.07	0.45	0.65	1.15	0.30
	aa vs. AA	339/383	1.94 0.62–6.09 (0.25)	79.3	< 0.001	− 0.15	0.88	0.23	0.83
	Aa vs. AA	339/383	0.80 0.58–1.10 (0.16)	0	0.93	1.35	0..17	1.24	0.26
Asian	Dominant model	692/792	0.35 0.10–1.25 (0.10)	89.4	< 0.001	0.60	0.54	0.48	0.64
	Recessive model	692/792	0.35 0.11–1.12 (0.07)	88.2	< 0.001	1.81	0.07	1.53	0.15
	Allelic model	692/792	0.44 0.17–1.13 (0.08)	93.5	< 0.001	0.03	0.97	− 0.39	0.70
	aa vs. AA	692/792	0.21 0.04–1.21 (0.08)	91.4	< 0.001	1.37	0.17	1.18	0.26
	Aa vs. AA	692/792	0.76 0.54–1.07 (0.11)	74.5	0.02	− 0.16	0.87	− 0.01	0.99
Arab	Dominant model	375/423	0.83 0.53–1.31 (0.42)	50.7	0.10	0.48	0.62	0.68	0.50
	Recessive model	375/423	1.48 0.49–4.38 (0.49)	84.6	< 0.001	1.39	0.16	1.89	0.07
	Allelic model	375/423	0.94 0.58–1.52 (0.80)	79.5	< 0.001	0.02	0.98	− 0.23	0.81
	aa vs. AA	375/423	1.13 0.32–4.01 (0.84)	84.4	< 0.001	0.91	0.35	1.15	0.26
	Aa vs. AA	375/423	0.76 0.55–1.03 (0.07)	0	0.43	0.06	0.95	0.40	0.69

Bold values have a significant association

which are regarded as confounding factors during the association studies.

It should be noted that our meta-analysis was not bereft of limitations and caveats. First, we searched only English-

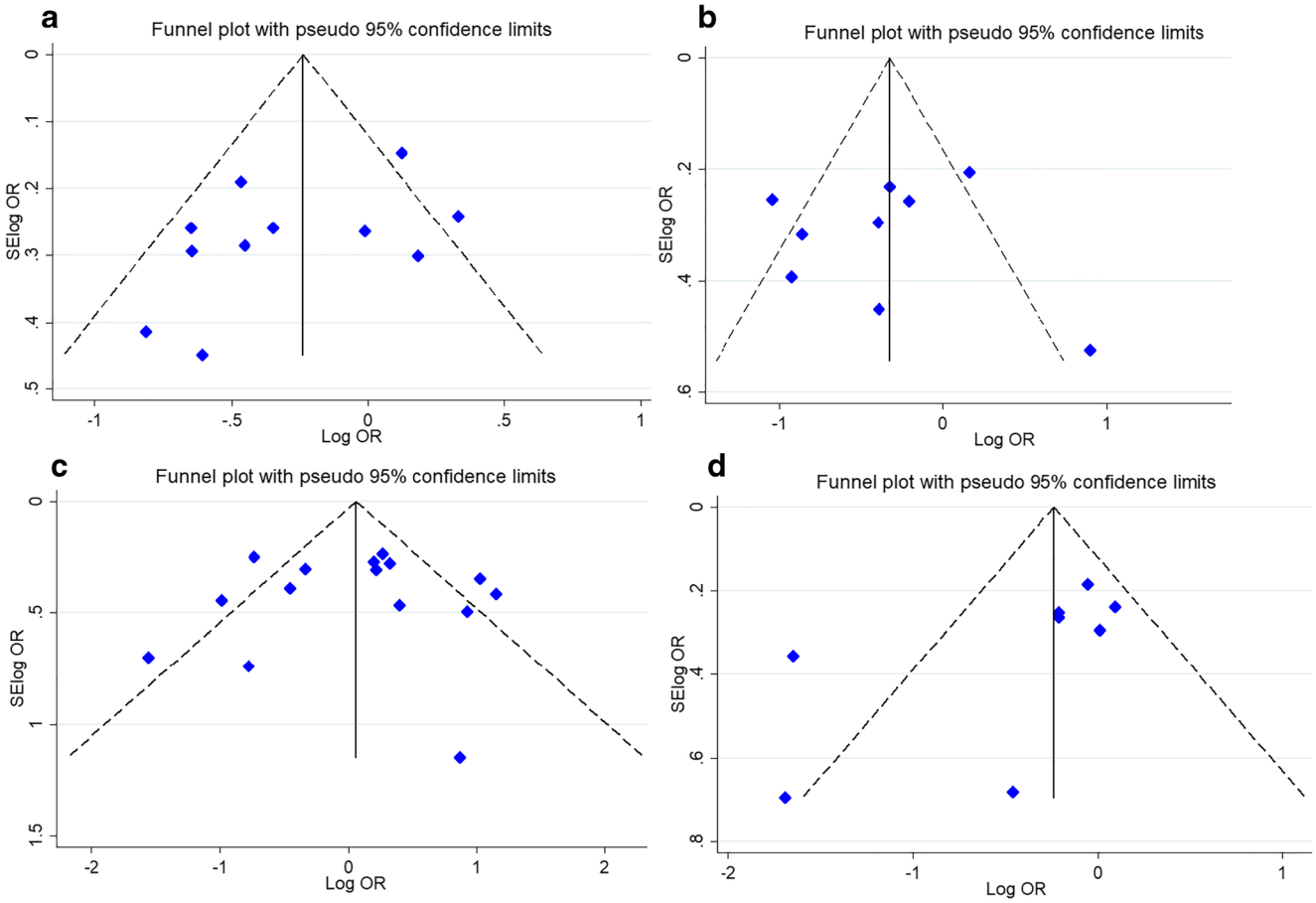

Fig. 4 Begg's funnel plot for publication bias test. (**a**) Dominant model for *FokI*, (**b**) dominant model for *TaqI*, (**c**) dominant model for *BsmI*, (**d**) dominant model for *ApaI*. Each point represents a separate study for the indicated association

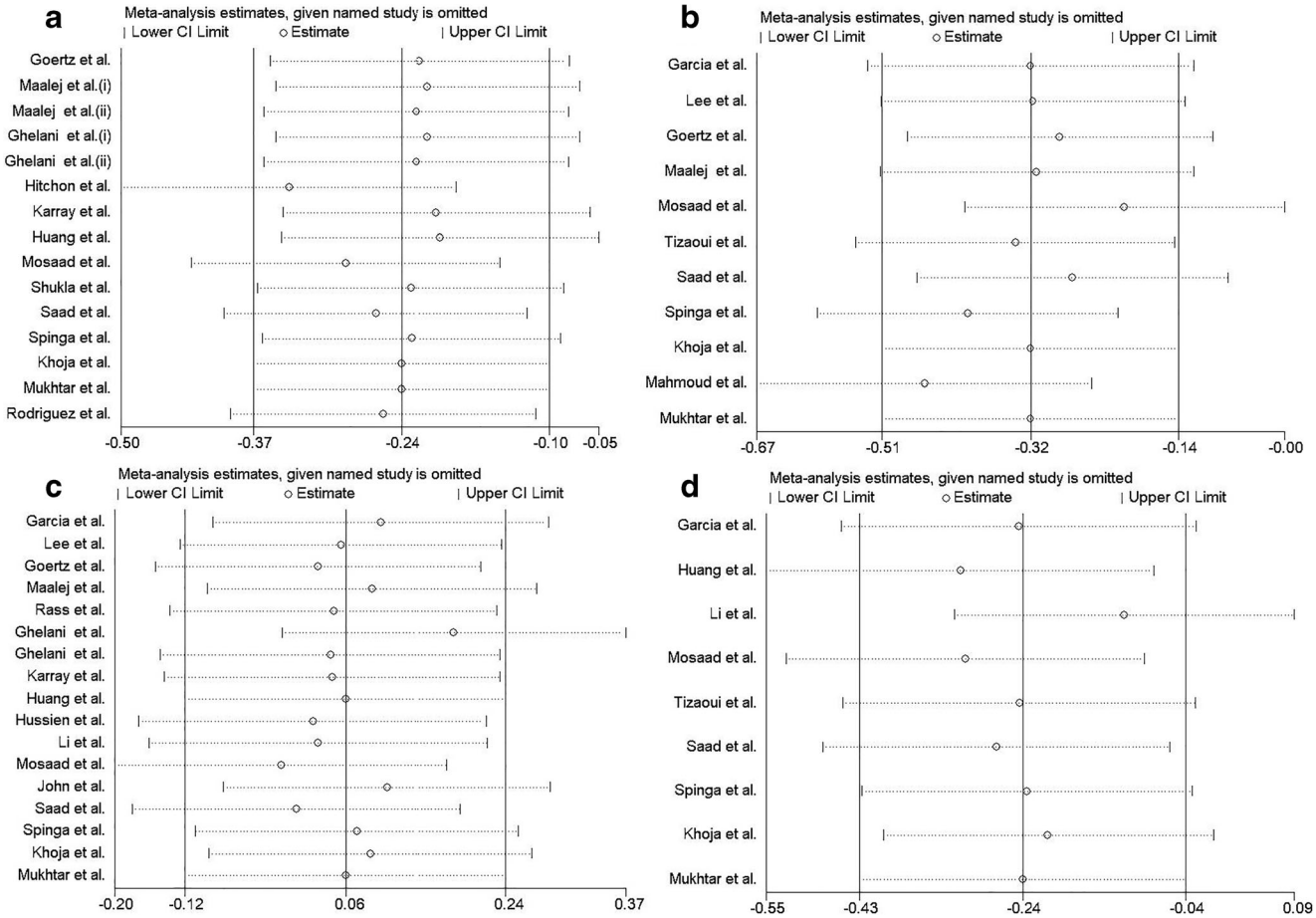

Fig. 5 Sensitivity analysis in the present meta-analysis investigates the SNPs of *VDR* gene in association with risk for RA susceptibility (**a**, *FokI*; **b**, *TaqI*; **c**, *BsmI*; **d**, *ApaI*)

written papers, which may raise the possibility of omission of potentially valuable studies. Second, we did not analyze the role and effect of age, lifestyle, gender, and other genetic SNPs as confounding factors on the association of VDR gene SNPs and RA risk. As a consequence, more investigations about the gene–environment and gene–gene interactions are still indispensable to attain an exhausted estimation of *VDR* gene polymorphism with RA risk. Third, we observed a significant heterogeneity among the studies for different genetic models in the SNPs, which may affect the way that the findings are interpreted. Finally, there are other polymorphisms in the VDR gene that have been studied in RA patients, but could not be involved in this meta-analysis because of insufficient amount of data. As a result, the results should be interpreted with caution.

Conclusion

All in all, this was the most up-to-date meta-analysis currently with respect to the association of *VDR* gene SNPs with RA risk. We evaluated 23 eligible studies (21 articles) to uncover the bona fide association of *VDR* gene FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232) polymorphisms with risk of RA susceptibility. We indicated that *FokI* SNP had a significant protective association with susceptibility to RA in the overall analysis as well as in Europeans and Asians. *TaqI* SNP decreased the RA risk in Africans and Arabs, but not in the overall analysis. As such, *BsmI* SNP and RA risk in the overall population analysis was not significant. Interestingly, *BsmI* polymorphism increased RA risk in Africans. Further studies on the VDR gene in RA patients other than the genetic as well as traditional risk factors may provide a possibility for recognizing the important susceptibility factors in the RA development, which might be used in the personalized medicine for better and optimized therapy of RA patients.

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Authors' contributions Z.B. generated the idea. D.I. analyzed and interpreted the data. Z.B. and H.Y. prepared the original draft. Z.B., H.Y., and M.A. critically revised the paper. M.A. supervised the project. All authors read and approved the final manuscript.

Compliance with ethical standards

Disclosures None.

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