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Original Article

Association between Vitamin D Receptor polymorphisms and rheumatoid arthritis risk: a meta-analysis

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Abstract: The aim of this study was to identify whether vitamin D receptor (VDR) variants were implicated in Rheumatoid arthritis (RA) pathogenesis. Relevant case-control studies published between 2000 and 2016 were searched in electronic databases. Odds ratio (OR) with its corresponding 95% confidence interval (CI) were employed to calculate extracted data. Total fourteen studies were screened out, including 2359 patients and 2764 controls, and focusing on four genetic variants (TaqI, BsmI, FokI and ApaI). Our results found that T allele of TaqI (T vs. t: OR=1.40, 95% CI=1.08-1.82, P=0.01), B allele of BsmI (B vs. b: OR=0.84, 95% CI=0.75-0.94, P=0.003), and F allele of FokI (F vs. f: OR=1.2495% CI=1.05-1.47, P=0.01) polymorphisms were associated with increased the risk of RA in total populations. This significant association was also found in TT genotype of TaqI, BB genotype and Bb genotyps of BsmI, and FF and Ff genotypes of FokI. Subgroup analysis found that BsmI variant among Africans, FokI variant among Asians and Caucasians were significantly increased the risk of RA. No relationship was found between ApaI variant and Ra risk. Our results demonstrated that polymorphisms of TaqI, BsmI, FokI, not ApaI in VDR gene might be involved in the development of RA.

Keywords: Rheumatoid arthritis, vitamin D receptor, polymorphism, meta-analysis

Introduction

Rheumatoid arthritis (RA) is the most common autoimmune disease worldwide, and is an important public health concern [1], associating with early death and systemic complications [2]. The characteristic of RA is muscular weakness around the affected joints, and symmetric joint inflammation, stiffness and pain [3]. It is the most severe form of arthritis, approximately affecting 0.5% to 1% of total population [4]. The incidence and prevalence of RA in populations vary substantially between geographic areas, relating with increased cardiovascular morbidity and mortality [5-7]. Smoking, diabetes mellitus, citrullination and genetic variability were shown to be involved in the immunopathogenesis of RA and might contribute to the prevalent [8-10]. Although major progress has been made in treating RA, many patients still experience premature work disability and co-morbidities. Therefore, there is an urgent need to explore new risk factors in helping early identification and treatment of the disease.

About 60% of RA risk is thought to be genetic. Studies have shown that identification of new genes associated with this disease might be useful in finding potential biomarkers for early detection and treatment [11]. Vitamin D, as an immunoregulatory hormone, is central to the control of bone and calcium homeostasis. The deficiency of vitamin D was shown increased the risk of cancer and adding vitamin D supplements might reduce cancer incidence and improve cancer prognosis and outcome [12]. Previous meta-analysis showed that low vitamin D intake was associated with an elevated risk of RA development [13]. Greater intake of vitamin D was associated with a lower risk of RA, as well as a significant clinical improvement was strongly correlated with the immunomodulating potential in vitamin D-treated RA patients

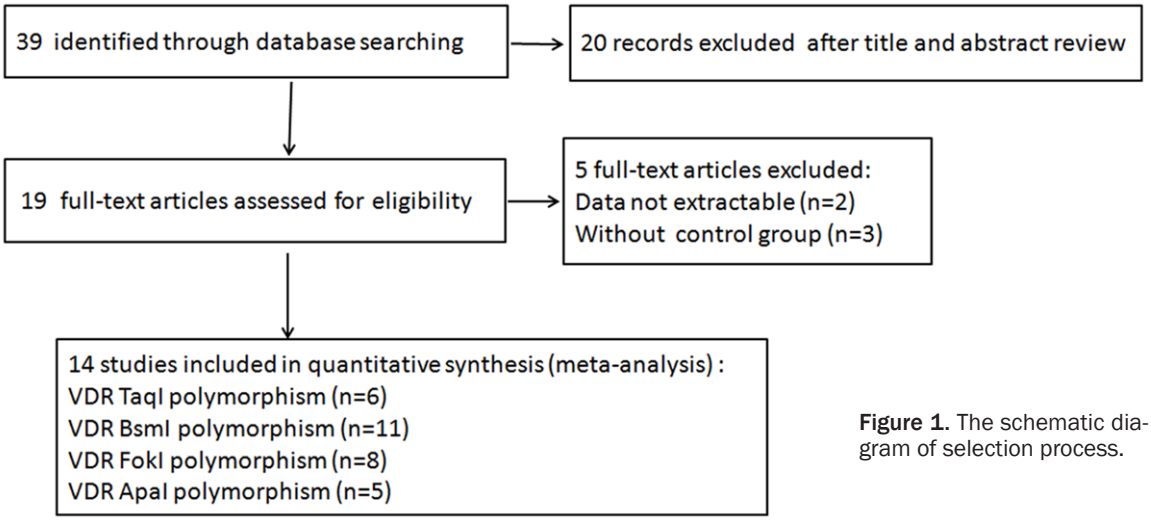


Figure 1. The schematic diagram of selection process.

Table 1. Main characteristics of included studies

First author	Year	Country	Ethnicity	Mean Age		Sample size		SNP	Genotype methods
				Cases	Controls	Cases	Controls		
Garcia-Lozano	2001	Spain	Caucasian	-	-	120	200	Taq I, Bsm I, Apa I	PCR-RFLP
Lee CK	2001	Korea	Asian	16-82	16-82	157	211	Taq I, Bsm I	PCR-RFLP
Goertz B	2003	Germany	Caucasian	57.4±14.8	52.8±15.5	62	40	Taq I, Bsm I, Fok I	PCR
Maalej A-a	2005	France	Caucasian	-	-	100	100	Taq I, Bsm I, Fok I	PCR-RFLP
Maalej A-b	2005	France	Caucasian	-	-	100	100	Fok I	PCR-RFLP
Rass P	2006	Hungary	Caucasian	51.2±23.2	46.7±19.4	64	40	Bsm I	PCR
Ghelani AM-a	2011	UK	Asian	-	-	134	149	Fok I, Bsm I	PCR-RFLP
Ghelani AM-b	2011	UK	Caucasian	29-75	-	137	150	Fok I, Bsm I	PCR-RFLP
Hitchon CA	2012	USA	Caucasian	47±15	35±12	448	704	Fok I	Sequenom
Karray EF	2012	Tunisia	African	39.5±13.4	41.3±9	135	152	Fok I, Bsm I	PCR-RFLP
Huang Y	2013	China	Asian	21-76	21-68	236	220	Bsm I, Fok I, Apa I	PCR-MassARRAY AnalyzerCompac
Hussien YM	2013	Egypt	African	57.3±3.9	57.1±3.8	200	150	Bsm I	PCR-RFLP
Li CH	2013	China	Asian	44±10	46±11	120	120	Bsm I, Apa I	PCR-RFLP
Mosaad Y	2014	Egypt	African	46.91±11.73	40±15.83	128	150	Taq I, Bsm I, Fok I, Apa I	PCR-RFLP
Shukla S	2014	India	Asian	-	-	112	125	Fok I	PCR-RFLP
Tizaoui K	2014	Tunisia	Caucasian	51.66±5.70	44.64±7.93	106	153	Taq I, Apa I	PCR

-, not available; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SNP, single nucleotide polymorphism.

[14]. Vitamin D initiates biological responses via binding to the vitamin D receptor (VDR) [15], which is a member of the steroid hormone receptor superfamily located on chromosome 12 (12q12-q14) that regulates gene expression in a ligand dependent manner [16]. VDR is active in almost all tissues that are necessary for the effects of vitamin D. Several genetic variations have been identified in the VDR gene. Among which, TaqI (rs731236 in exon 9), BsmI (rs1544410 in intron 8), ApaI (rs7975232 in intron 8) at the 3'-end, and FokI (rs2228570 in exon 2) at the 5'-end of this gene were the most studied. These polymorphisms were shown to modulate the risk of some cancer sites [17], and associated with human diseases. FokI polymorphism was found to have an overall significant association with prostate cancer, breast cancer, colorectal cancer, skin cancer and ovary cancer [18]. The t allele of TaqI variant might be a risk factor for severe stone disease and recurrent stones [19]. ApaI variant involved in the clinical presentation of patients with calcium urolithiasis [20].

Although several studies reported the role of VDR polymorphisms in RA risk, the results remain inconclusive. This may due to the non-

Table 2. Alleles and genotypes distribution for each polymorphism in RA patients and controls of included studies

First author	Cases					Control				
TaqI	TT	Tt	tt	T	t	TT	Tt	tt	T	t
Garcia-Lozano	57	47	16	161	79	79	94	27	252	148
Lee CK	147	10	0	304	10	109	9	2	227	13
Goertz B	24	34	4	82	42	16	14	10	46	34
Maalej A-a	42	35	18	119	71	33	49	13	115	75
Mosaad Y	64	51	13	179	77	39	74	37	152	148
Tizaoui K	44	52	10	140	72	56	80	17	192	114
BsmI	BB	Bb	bb	B	b	BB	Bb	bb	B	b
Garcia-Lozano	23	43	54	89	151	29	94	77	152	248
Lee CK	1	8	148	10	304	3	17	191	23	399
Goertz B	9	43	10	61	63	12	17	11	41	39
Maalej A-a	19	35	42	73	119	13	48	35	74	118
Rass P	13	26	25	52	76	11	16	13	38	42
Ghelani AM-a	62	30	29	154	88	49	73	24	171	121
Ghelani AM-b	35	51	34	121	119	43	53	33	139	119
Karray EF	21	47	40	89	127	35	64	53	134	170
Huang Y	0	30	206	30	442	0	29	191	29	411
Hussien YM	53	78	69	184	216	48	60	42	156	144
Li CH	32	43	45	107	133	40	36	44	116	124
Mosaad Y	13	52	63	78	178	36	74	40	146	154
FokI	FF	Ff	ff	F	f	FF	Ff	ff	F	f
Goertz B	34	23	5	91	33	14	23	3	51	29
Maalej A-a	45	43	12	133	67	30	48	22	108	92
Maalej A-b	48	40	12	136	64	37	50	13	124	76
Ghelani AM-a	86	35	9	207	53	88	48	10	224	68
Ghelani AM-b	45	64	23	154	110	57	62	25	176	112
Hitchon CA	90	243	115	423	473	156	308	241	620	790
Karray EF	49	49	10	147	69	46	72	34	164	140
Huang Y	109	83	44	301	171	77	89	54	243	197
Mosaad Y	69	51	8	189	67	93	55	2	241	59
Shukla S	58	50	4	166	58	54	63	8	171	79
ApaI	AA	Aa	aa	A	a	AA	Aa	aa	A	a
Garcia-Lozano	37	49	34	123	117	53	102	45	208	192
Huang Y	119	90	27	328	144	108	81	31	297	143
Li CH	44	60	16	148	92	12	44	64	68	172
Mosaad Y	56	46	26	158	98	69	71	10	209	91
Tizaoui K	39	53	14	131	81	49	78	26	176	130

equilibrium distribution of RA incidences and VDR polymorphisms. Furthermore, differential VDR expression relates to ethnicity [21], and may affects the genetic associations in RA [22]. Therefore, we conducted this meta-analysis to identify the exact association between VDR polymorphisms and RA risk in total and subgroup analysis by ethnicity.

Materials and methods

Study identification

We conducted a literature search on online electronic databases of PubMed, Embase, Medline to retrieve relevant studies published between January 2000 and November 2016. The following medical subject heading (MeSH): "rheumatoid arthritis or arthritis", "vitamin D receptor or VDR", "polymorphism or mutation or variant" as well as their combinations were used. References of included studies were also searched manually.

Inclusion criteria

Studies included must met the following criteria: 1) case-control studies; 2) evaluating the role of VDR polymorphisms in RA risk; 3) RA patients should be confirmed and met American College of Rheumatology criteria for RA [23], controls should be unrelated ethnically matched individual; 4) the results were presented in odds ratio (OR) with its 95% corresponding confidence intervals (CI); and 5) genotype information in patients and controls was available to extract.

Data extraction

Two authors independently assessed the information of each included study to reach a consensus. The following information was extracted: first author, published year, country, ethnicity, mean age, sample size, genotype methods and genotype distribution.

Statistical analysis

The association between VDR polymorphisms and RA risk was measured by pooled OR with

Table 3. Meta-analysis of VDR polymorphisms and RA risk in total and subgroup analysis by ethnicity

SNP	Group	Comparison	Number	Test of association		Test of heterogeneity		
				OR (95% CI)	P	Ph	I^2	Model
TaqI	Total	T vs. t	6	1.40 (1.08, 1.82)	0.01	0.06	54%	R
		TT vs. tt	6	7.48 (5.40, 10.36)	<0.00001	0.19	32%	F
		Tt vs. tt	6	1.35 (0.70, 2.61)	0.37	0.02	63%	R
		TT+Tt vs. tt	6	1.60 (0.86, 2.98)	0.14	0.02	63%	R
		TT vs. Tt+tt	6	1.56 (1.23, 1.96)	0.0002	0.15	38%	F
	Caucasian	T vs. t	4	1.19 (0.97, 1.45)	0.10	0.89	0%	F
		TT vs. tt	4	5.88 (4.04, 8.55)	<0.00001	0.65	0%	F
		Tt vs. tt	4	1.15 (0.51, 2.59)	0.74	0.02	70%	R
		TT+Tt vs. tt	4	1.24 (0.65, 2.36)	0.52	0.07	57%	R
		TT vs. Tt+tt	4	1.30 (0.99, 1.71)	0.06	0.82	0%	F
	Asian	T vs. t	1	1.74 (0.75, 4.04)	0.20	NA	NA	NA
		TT vs. tt	1	30.98 (1.81, 531.44)	0.02	NA	NA	NA
		Tt vs. tt	1	5.53 (0.23, 130.34)	0.29	NA	NA	NA
		TT+Tt vs. tt	1	6.65 (0.32, 139.72)	0.22	NA	NA	NA
		TT vs. Tt+tt	1	1.48 (0.61, 3.62)	0.39	NA	NA	NA
	African	T vs. t	1	2.26 (1.59, 3.21)	<0.00001	NA	NA	NA
		TT vs. tt	1	14.01 (6.96, 28.19)	<0.00001	NA	NA	NA
		Tt vs. tt	1	1.96 (0.95, 4.05)	0.07	NA	NA	NA
		TT+Tt vs. tt	1	2.90 (1.46, 5.74)	0.002	NA	NA	NA
		TT vs. Tt+tt	1	2.85 (1.72, 4.71)	<0.00001	NA	NA	NA
BsmI	Total	B vs. b	12	0.84 (0.75, 0.94)	0.003	0.06	42%	F
		BB vs. bb	11	0.75 (0.60, 0.93)	0.009	0.17	29%	F
		Bb vs. bb	12	0.75 (0.63, 0.90)	0.002	0.04	46%	F
		BB+Bb vs. bb	12	0.75 (0.64, 0.89)	0.0007	0.21	24%	F
		BB vs. Bb+bb	11	0.86 (0.62, 1.20)	0.36	0.003	63%	R
	Caucasian	B vs. b	5	0.91 (0.76, 1.10)	0.32	0.95	0%	F
		BB vs. bb	5	0.93 (0.65, 1.33)	0.70	0.80	0%	F
		Bb vs. bb	5	0.81 (0.60, 1.09)	0.17	0.12	45%	F
		BB+Bb vs. bb	5	0.84 (0.64, 1.11)	0.22	0.49	0%	F
		BB vs. Bb+bb	5	0.96 (0.70, 1.31)	0.80	0.13	44%	F
	Asian	B vs. b	4	0.97 (0.78, 1.21)	0.79	0.24	28%	F
		BB vs. bb	3	0.87 (0.56, 1.35)	0.53	0.68	0%	F
		Bb vs. bb	4	0.72 (0.41, 1.24)	0.23	0.04	63%	R
		BB+Bb vs. bb	4	0.81 (0.60, 1.09)	0.16	0.54	0%	F
		BB vs. Bb+bb	3	1.09 (0.43, 2.75)	0.85	0.01	77%	R
	African	B vs. b	3	0.69 (0.47, 1.01)	0.05	0.02	74%	R
		BB vs. bb	3	0.51 (0.25, 1.03)	0.06	0.03	71%	R
		Bb vs. bb	3	0.70 (0.44, 1.10)	0.12	0.12	54%	R
		BB+Bb vs. bb	3	0.63 (0.38, 1.06)	0.08	0.04	69%	R
		BB vs. Bb+bb	3	0.65 (0.47, 0.89)	0.008	0.14	48%	F
FokI	Total	F vs. f	10	1.24 (1.05, 1.47)	0.01	0.01	57%	R
		FF vs ff	10	1.45 (1.02, 2.07)	0.04	0.03	50%	R
		Ff vs. ff	10	1.38 (1.13, 1.67)	0.001	0.19	28%	F
		FF+Ff vs. ff	10	1.42 (1.19, 1.71)	0.0001	0.17	30%	F
		FF vs. Ff+ff	10	1.28 (1.01, 1.64)	0.05	0.007	61%	R
	Caucasian	F vs. f	6	1.19 (1.05, 1.35)	0.006	0.21	30%	F

		FF vs ff	6	1.31 (1.01, 1.70)	0.05	0.38	5%	F
		Ff vs. ff	6	1.48 (1.17, 1.86)	0.0009	0.54	0%	F
		FF+Ff vs. ff	6	1.37 (1.13, 1.68)	0.001	0.25	23%	F
		FF vs. Ff+ff	6	1.28 (0.92, 1.78)	0.15	0.03	60%	R
	Asian	F vs. f	2	1.35 (1.08, 1.69)	0.008	0.45	0%	F
		FF vs ff	2	1.57 (1.01, 2.43)	0.04	0.39	0%	F
		Ff vs. ff	2	1.07 (0.68, 1.67)	0.77	0.54	0%	F
		FF+Ff vs. ff	2	1.33 (0.89, 1.99)	0.17	0.49	0%	F
		FF vs. Ff+ff	2	1.47 (1.09, 1.99)	0.01	0.50	0%	F
	African	F vs. f	2	1.12 (0.44, 2.90)	0.81	0.0004	92%	R
		FF vs ff	2	0.89 (0.05, 16.63)	0.94	0.001	91%	R
		Ff vs. ff	2	0.82 (0.09, 7.77)	0.86	0.01	85%	R
		FF+Ff vs. ff	2	0.83 (0.06, 11.03)	0.89	0.003	89%	R
		FF vs. Ff+ff	2	1.17 (0.45, 3.05)	0.75	0.006	87%	R
ApaI	Total	A vs. a	5	1.29 (0.76, 2.19)	0.35	<0.00001	92%	R
		AA vs. aa	5	1.50 (0.52, 4.33)	0.46	0.0001	91%	R
		Aa vs. aa	5	1.08 (0.43, 2.72)	0.87	0.0001	90%	
		AA+Aa vs. aa	5	1.22 (0.46, 3.23)	0.69	0.0001	92%	R
		AA vs. Aa+aa	5	1.42 (0.88, 2.29)	0.15	0.001	78%	R
	Caucasian	A vs. a	2	1.06 (0.84, 1.35)	0.61	0.40	0%	F
		AA vs. aa	2	1.11 (0.69, 1.79)	0.67	0.35	0%	F
		Aa vs. aa	2	0.86 (0.44, 1.67)	0.65	0.15	52%	R
		AA+Aa vs. aa	2	0.91 (0.60, 1.38)	0.67	0.17	46%	F
		AA vs. Aa+aa	2	1.24 (0.86, 1.77)	0.25	1.00	0%	F
	Asian	A vs. a	2	2.10 (0.58, 7.58)	0.26	<0.00001	97%	R
		AA vs. aa	2	4.22 (0.38, 46.67)	0.24	0.0001	95%	R
		Aa vs. aa	2	2.62 (0.63, 10.87)	0.19	0.002	95%	R
		AA+Aa vs. aa	2	3.05 (0.54, 17.24)	0.21	0.0001	94%	R
		AA vs. Aa+aa	2	2.28 (0.47, 10.93)	0.30	0.0001	94%	R
	African	A vs. a	1	0.70 (0.49, 1.00)	0.05	NA	NA	NA
		AA vs. aa	1	0.31 (0.14, 0.70)	0.005	NA	NA	NA
		Aa vs. aa	1	0.25 (0.11, 0.56)	0.0009	NA	NA	NA
		AA+Aa vs. aa	1	0.28 (0.13, 0.61)	0.001	NA	NA	NA
		AA vs. Aa+aa	1	0.91 (0.57, 1.47)	0.71	NA	NA	NA

Number, number of included studies; OR, odds ratio; 95% CI, 95% confidence intervals; F, fixed-effect model; R, random-effect model; NA, not applicable.

95% CI. The significance of the pooled OR was determined by the Z test, and a *P* value less than 0.05 was considered significant. The allelic model (M vs. m), homozygote model (MM vs. mm), heterozygote model (Mm vs. mm), dominant model (MM+Mm vs. mm) and recessive model (MM vs. Mm+mm) were examined to evaluate the strength of association. The I^2 test and the Q-statistic test were used to calculate the between-study heterogeneity. The fixed-effect model was used when the effects are assumed to be homogenous (a *P*-value more than 0.10 for the Q-test and I^2 less than 50%), otherwise, the random-effect model was employed. Funnel plot asymmetry was used to assess the publication bias. Analyses were performed using the software Review Manange5 (Oxford, England, UK). All *p*-values were two-sided.

Results

Characteristics of included studies

Figure 1 showed the selection process of search. Finally, we screened out fourteen case-control studies (twelve in English and two in Chinese) [22, 24-36] that reporting the association between VDR polymorphisms and RA risk,

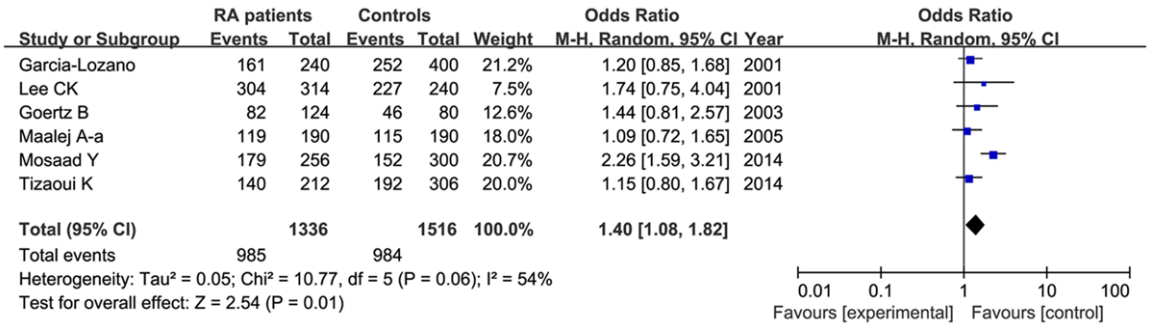


Figure 2. Forest plot of the association between TaqI variant and RA risk in allele model (T vs. t) in total population.

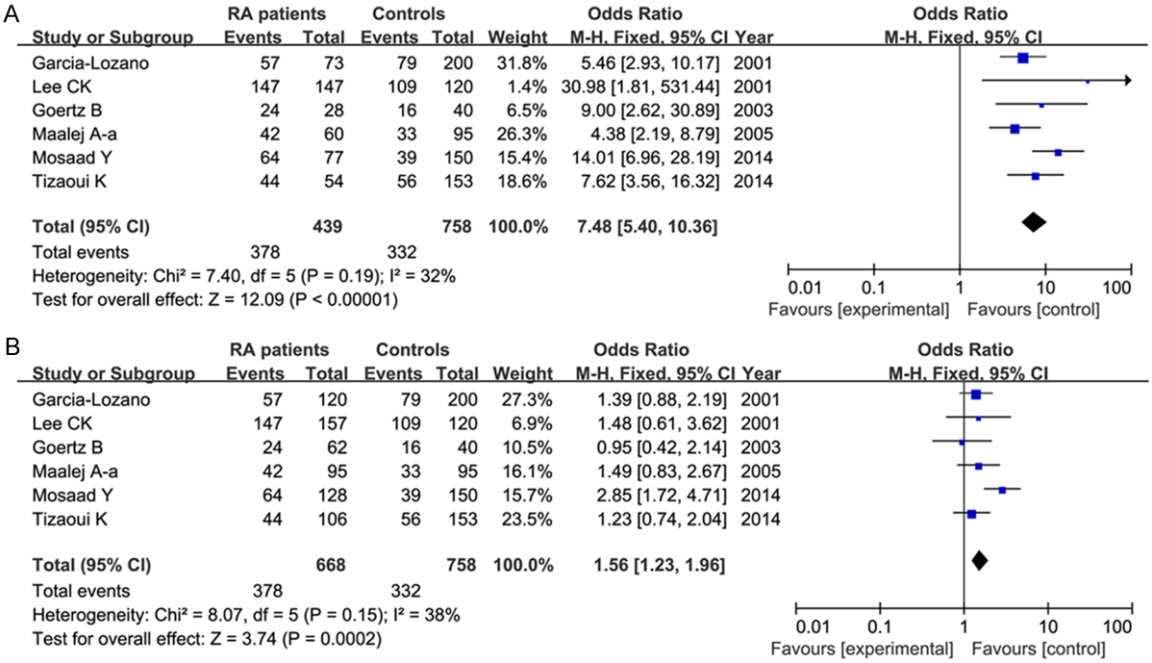


Figure 3. Forest plot of the association between TaqI variant and RA risk in homozygote model (TT vs. tt, A) and recessive model (TT vs. Tt+tt, B) in a fixed-effect model.

including 2359 patients and 2764 controls. Among which, two articles involved two study population [22, 28]. Four VDR polymorphisms were concerned (TaqI, BsmI, FokI, and ApaI). Eight studies were the Caucasians, five were the Asians, and three were the Africans. The sample size ranged from 102 to 1152. **Table 1** listed the main characteristics of included studies in this meta-analysis. **Table 2** showed the distribution information of alleles and genotypes for each polymorphism.

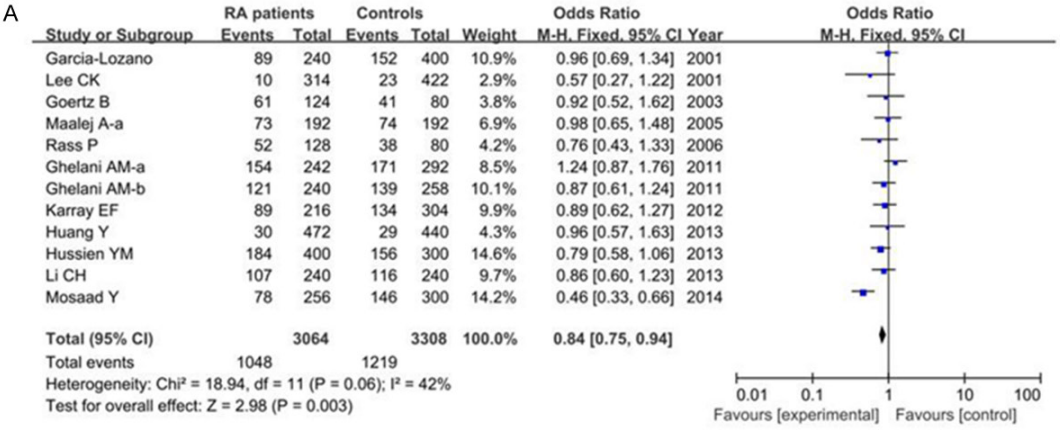
Association between VDR polymorphisms and RA incidence

Table 3 displayed the results of this meta-analysis of the associations between VDR polymorphisms and Ra risk.

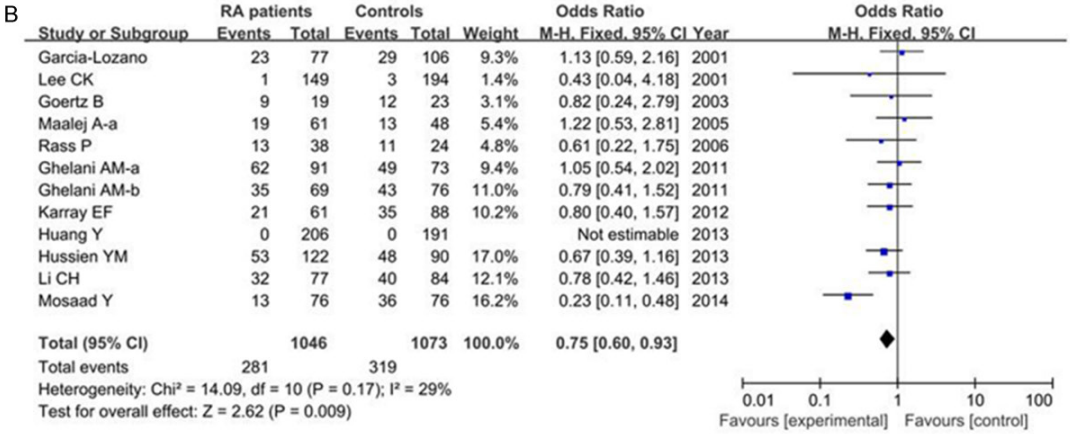
TaqI polymorphism

Six studies included 668 cases and 758 controls. Between-study heterogeneity was calculated, and the fixed- or random- effect model was used. Overall, the T allele was shown to be higher in RA patients than that in controls (73.7% vs. 64.9%), indicting the T allele significantly increased the risk of RA compared to the t allele (T vs. t: OR=1.40, 95% CI=1.08-1.82, P=0.01) in a random-effect model as shown in **Figure 2**. This significant relationship was also found in homozygous model (TT vs. tt: OR=7.48, 95% CI=5.40-10.36, P<0.00001) and recessive model (TT vs. Tt+tt: OR=1.56, 95% CI=1.23-1.96, P=0.0002) in a fixed-effect model as shown in **Figure 3**. However, no association was

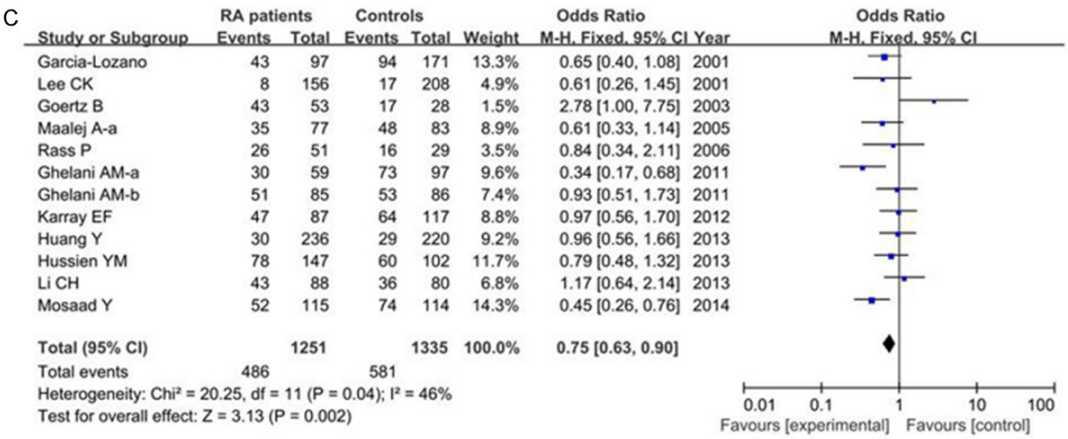
A


RA patients
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Garcia-Lozano 89 240 152 400 10.9% 0.96 [0.69, 1.34] 2001
Lee CK 10 314 23 422 2.9% 0.57 [0.27, 1.22] 2001
Goertz B 61 124 41 80 3.8% 0.92 [0.52, 1.62] 2003
Maalej A-a 73 192 74 192 6.9% 0.98 [0.65, 1.48] 2005
Rass P 52 128 38 80 4.2% 0.76 [0.43, 1.33] 2006
Ghelani AM-a 154 242 171 292 8.5% 1.24 [0.87, 1.76] 2011
Ghelani AM-b 121 240 139 258 10.1% 0.87 [0.61, 1.24] 2011
Karray EF 89 216 134 304 9.9% 0.89 [0.62, 1.27] 2012
Huang Y 30 472 29 440 4.3% 0.96 [0.57, 1.63] 2013
Hussien YM 184 400 156 300 14.6% 0.79 [0.58, 1.06] 2013
Li CH 107 240 116 240 9.7% 0.86 [0.60, 1.23] 2013
Mosaad Y 78 256 146 300 14.2% 0.46 [0.33, 0.66] 2014
Total (95% CI) 3064 3308 100.0% 0.84 [0.75, 0.94]
Total events 1048 1219
Heterogeneity: Chi² = 18.94, df = 11 (P = 0.06); I² = 42%
Test for overall effect: Z = 2.98 (P = 0.003)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

B


RA patients
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Garcia-Lozano 23 77 29 106 9.3% 1.13 [0.59, 2.16] 2001
Lee CK 1 149 3 194 1.4% 0.43 [0.04, 4.18] 2001
Goertz B 9 19 12 23 3.1% 0.82 [0.24, 2.79] 2003
Maalej A-a 19 61 13 48 5.4% 1.22 [0.53, 2.81] 2005
Rass P 13 38 11 24 4.8% 0.61 [0.22, 1.75] 2006
Ghelani AM-a 62 91 49 73 9.4% 1.05 [0.54, 2.02] 2011
Ghelani AM-b 35 69 43 76 11.0% 0.79 [0.41, 1.52] 2011
Karray EF 21 61 35 88 10.2% 0.80 [0.40, 1.57] 2012
Huang Y 0 206 0 191 Not estimable 2013
Hussien YM 53 122 48 90 17.0% 0.67 [0.39, 1.16] 2013
Li CH 32 77 40 84 12.1% 0.78 [0.42, 1.46] 2013
Mosaad Y 13 76 36 76 16.2% 0.23 [0.11, 0.48] 2014
Total (95% CI) 1046 1073 100.0% 0.75 [0.60, 0.93]
Total events 281 319
Heterogeneity: Chi² = 14.09, df = 10 (P = 0.17); I² = 29%
Test for overall effect: Z = 2.62 (P = 0.009)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

C


RA patients
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Garcia-Lozano 43 97 94 171 13.3% 0.65 [0.40, 1.08] 2001
Lee CK 8 156 17 208 4.9% 0.61 [0.26, 1.45] 2001
Goertz B 43 53 17 28 1.5% 2.78 [1.00, 7.75] 2003
Maalej A-a 35 77 48 83 8.9% 0.61 [0.33, 1.14] 2005
Rass P 26 51 16 29 3.5% 0.84 [0.34, 2.11] 2006
Ghelani AM-a 30 59 73 97 9.6% 0.34 [0.17, 0.68] 2011
Ghelani AM-b 51 85 53 86 7.4% 0.93 [0.51, 1.73] 2011
Karray EF 47 87 64 117 8.8% 0.97 [0.56, 1.70] 2012
Huang Y 30 236 29 220 9.2% 0.96 [0.56, 1.66] 2013
Hussien YM 78 147 60 102 11.7% 0.79 [0.48, 1.32] 2013
Li CH 43 88 36 80 6.8% 1.17 [0.64, 2.14] 2013
Mosaad Y 52 115 74 114 14.3% 0.45 [0.26, 0.76] 2014
Total (95% CI) 1251 1335 100.0% 0.75 [0.63, 0.90]
Total events 486 581
Heterogeneity: Chi² = 20.25, df = 11 (P = 0.04); I² = 46%
Test for overall effect: Z = 3.13 (P = 0.002)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

D

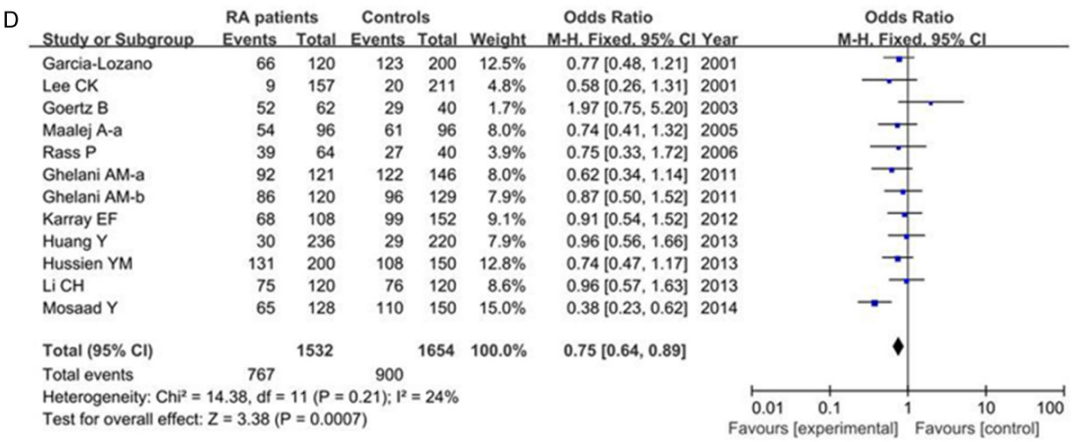

RA patients
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Garcia-Lozano 66 120 123 200 12.5% 0.77 [0.48, 1.21] 2001
Lee CK 9 157 20 211 4.8% 0.58 [0.26, 1.31] 2001
Goertz B 52 62 29 40 1.7% 1.97 [0.75, 5.20] 2003
Maalej A-a 54 96 61 96 8.0% 0.74 [0.41, 1.32] 2005
Rass P 39 64 27 40 3.9% 0.75 [0.33, 1.72] 2006
Ghelani AM-a 92 121 122 146 8.0% 0.62 [0.34, 1.14] 2011
Ghelani AM-b 86 120 96 129 7.9% 0.87 [0.50, 1.52] 2011
Karray EF 68 108 99 152 9.1% 0.91 [0.54, 1.52] 2012
Huang Y 30 236 29 220 7.9% 0.96 [0.56, 1.66] 2013
Hussien YM 131 200 108 150 12.8% 0.74 [0.47, 1.17] 2013
Li CH 75 120 76 120 8.6% 0.96 [0.57, 1.63] 2013
Mosaad Y 65 128 110 150 15.0% 0.38 [0.23, 0.62] 2014
Total (95% CI) 1532 1654 100.0% 0.75 [0.64, 0.89]
Total events 767 900
Heterogeneity: Chi² = 14.38, df = 11 (P = 0.21); I² = 24%
Test for overall effect: Z = 3.38 (P = 0.0007)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

Figure 4. Forest plot of the association between BsmI variant and RA risk in four genetic models (A: B vs. b; B: BB vs. bb; C: Bb vs. bb; D: BB+Bb vs. bb) in a fixed-effect model.

found in heterozygous model (Tt vs. tt: OR=1.35, 95% CI=0.70-2.61, P=0.37) and dominant model (TT+Tt vs. tt: OR=1.60, 95% CI=0.86-2.98, P=0.14). Subgroup analysis by ethnicity showed that only TT genotype in heterozygous model was associated with RA susceptibility among Caucasians (TT vs. tt: OR=5.88, 95% CI=4.04-8.55, P<0.00001). Only one study was conducted in Asians and Africans, and the findings were negative and positive, respectively.

BsmI polymorphism

Total eleven studies (one study contained two study population) were screened out, involving 1532 patients and 1654 controls. Overall, our result found that BsmI polymorphism of VDR was associated with increased the risk of RA under four genetic models (B vs. b: OR=0.84, 95% CI=0.75-0.94, P=0.003; BB vs. bb: OR=0.75, 95% CI=0.60-0.93, P=0.009; Bb vs. bb: OR=0.75, 95% CI=0.63-0.90, P=0.002; BB+Bb vs. bb: OR=0.75, 95% CI=0.64-0.89, P=0.0007) in a fixed-effect model as shown in **Figure 4**. No significant association was found in recessive model (BB vs. Bb+bb: OR=0.86, 95% CI=0.62-1.20, P=0.36) in a random-effect model. Subgroup analysis by ethnicity showed that this polymorphism was associated with RA incidence only in allele model (B vs. b: OR=0.69, 95% CI=0.47-1.01, P=0.05) and recessive model (BB vs. Bb+bb: OR=0.65, 95% CI=0.47-0.89, P=0.008) among Africans. No significant association between BsmI polymorphism and RA among Asians and Caucasians was found.

FokI polymorphism

Eight studies were identified (ten comparisons), containing 1556 cases and 1882 controls. We found the frequency of F allele was higher in cases than that in controls (62.6% vs. 56.4%). The results demonstrated a positive relationship between FokI polymorphism of VDR and RA risk under all five genetic models (F vs. f: OR=1.24, 95% CI=1.05-1.47, P=0.01; FF vs ff: OR=1.45, 95% CI=1.02-2.07, P=0.04; Ff vs. ff: OR=1.38, 95% CI=1.13-1.67, P=0.001; FF+Ff vs. ff: OR=1.42, 95% CI=1.19-1.71, P=0.0001; FF vs. Ff+ff: OR=1.28, 95% CI=1.01-1.64, P=0.05) as shown in **Figure 5**. Subgroup analysis shown that four genetic models were associated with RA among Caucasians (F vs. f: OR=1.19, 95% CI=1.05-1.35, P=0.006; FF vs ff: OR=1.31, 95% CI=1.01-1.70, P=0.05; Ff vs. ff: OR=1.48, 95% CI=1.17-1.86, P=0.0009; FF+Ff vs. ff: OR=1.37, 95% CI=1.13-1.68, P=0.001), three genetic models among Asians (F vs. f: OR=1.35, 95% CI=1.08-1.69, P=0.008; FF vs ff: OR=1.57, 95% CI=1.01-2.43, P=0.04; FF vs. Ff+ff: OR=1.47, 95% CI=1.09-1.99, P=0.01), no genetic models among Africans.

ApaI polymorphism

Five studies were obtained, including 710 cases and 843 controls. Higher between-study heterogeneity was found and the random-effect model was employed to calculate the pooled ORs. Finally, our results found no significant association between ApaI polymorphism and RA risk under all genetic modes (A vs. a: OR=1.29, 95% CI=0.76-2.19, P=0.35; AA vs. aa: OR=1.50, 95% CI=0.52-4.33, P=0.46; Aa vs. a: OR=1.08, 95% CI=0.43-2.72, P=0.87; AA+Aa vs. aa: OR=1.22, 95% CI=0.46-3.23, P=0.69; AA vs. Aa+aa: OR=1.42, 95% CI=0.88-2.29, P=0.15). No relationship was found among Asians and Caucasians.

Publication bias

As shown in **Figure 6**, no obvious asymmetry was presented, indicating no possible bias was existed.

Discussion

We conducted this study to evaluate whether VDR polymorphisms (the 5' FokI and 3' BsmI, ApaI and TaqI regions) were associated with RA risk. Totally, 14 studies were eligible for this study based on the selection criteria employed. Overall, our results found that the alleles of TaqI, BsmI and FokI polymorphisms were associated with RA susceptibility in total population. Subgroup analysis by ethnicity showed that BsmI variant among Africans, FokI variant among Asians and Caucasians were significantly increased the risk of RA. No association was found between ApaI variant and RA risk. Our results were not consistence with previous meta-analysis conducted by Lee et al. [37].

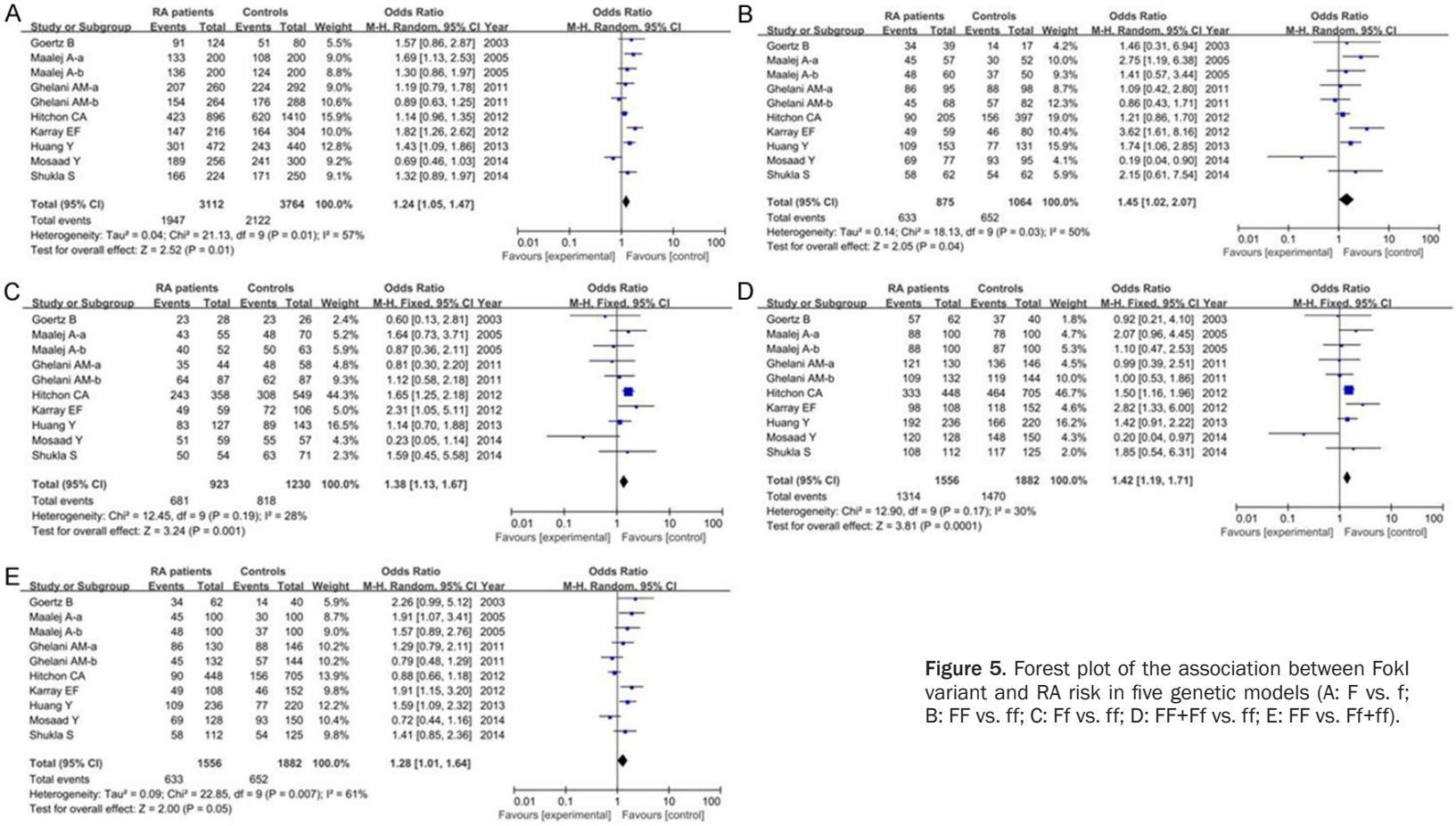


Figure 5. Forest plot of the association between FokI variant and RA risk in five genetic models (A: F vs. f; B: FF vs. ff; C: Ff vs. ff; D: FF+Ff vs. ff; E: FF vs. Ff+ff).

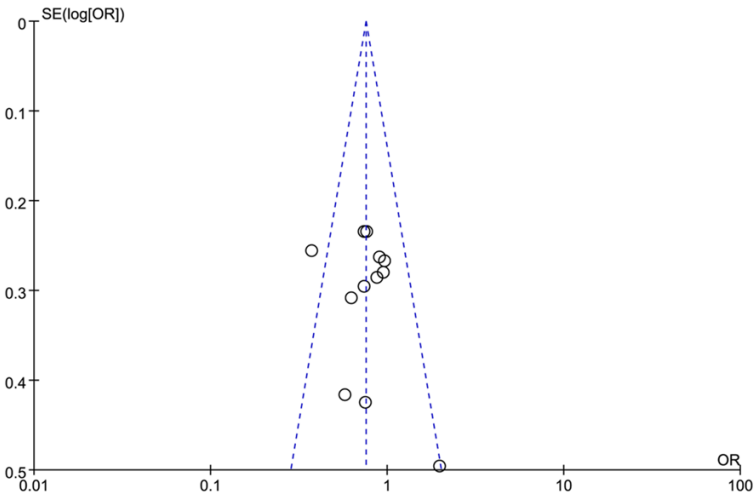


Figure 6. Funnel plot of publication bias between studies of BsmI variant in dominant model (BB+Bb vs. bb).

The VDR gene, an important regulator involving in the vitamin D pathway, belongs to the family of trans-acting transcriptional regulatory factors. It encodes the nuclear hormone receptor for vitamin D3 [38], and plays an important role in regulating cell differentiation, proliferation, and the induction of apoptosis [39]. The level of VDR mRNA was varied in different tumors, it was modestly down-regulated in colon, breast and lung tumors, but highly up-regulated in ovarian tumors [40]. VDR target gene expression is modulated by 1,25(OH)2D3. Studies have shown that 1,25(OH)2D3 regulated the expression level of VDR mRNA which in turn might be regulated by VDR microRNAs or epigenetic modulating drugs [41]. High VDR expression may be associated with a reduced risk of lethal cancer such as prostate cancer [42], and improved survival of patients with lung adenocarcinoma [43], suggesting that VDR is essential for vitamin D-mediated cancer prevention.

VDR polymorphisms may be altered gene expression or gene function through physiologic and pathologic phenotypes [44]. VDR polymorphisms and vitamin D status may influence osteoarthritis and intervertebral disc degeneration [45]. Vitamin D status could influence the impact of VDR variants on VDR function and associated disease risk. These polymorphisms were associated with numerous human diseases. Sarkissyan et al. demonstrated that FokI polymorphism of VDR might influence the risk of colorectal cancer, particularly in African American cohorts [46]. Grant et al. firstly reported that VDR variants associated with ovarian cancer risk in African American women [47]. Qin et al. identified that BsmI variant of VDR gene might be a moderate risk factor in the development of ovarian cancer among the European population instead of North America or Asian population [48]. Kolahi et al. found that f allele and ff genotype of FokI variant in VDR gene were associated with Behçet's disease among the Iranian Azari population [49]. However, BsmI B allele was shown to have a weak effect in reducing cancer risk, especially of the skin [50]. The VDR polymorphism could improve the ability to predict Ca absorption under a variety of conditions and may influence dietary Ca requirements [51].

Among patients with RA, the results remain unclearly in different populations. Vitamin D serum concentration and BsmI variant of VDR gene might show some correlation with RA activity and progression [52]. Gómez-Vaquero et al. showed that the bb genotype of the BsmI polymorphism of the VDR gene was associated with less severe disease [53]. Of the included studies, Mosaad et al. proved that the ApaI, BsmI and TaqI polymorphisms might be a susceptibility risk factors for RA and the Ff genotype may be responsible for development of osteoporosis in RA Egyptian patients [33]. Hussien et al. showed that BsmI variant was an important candidate for osteoporosis in RA patients [31]. Hitchon et al. demonstrated that FokI might contribute to the high prevalence of RA in north American natives populations [30]. While Shukla et al. the found that FokI variant of VDR polymorphism was not associated with RA susceptibility [32]. Tizaoui et al. identified no association between TaqI and ApaI polymorphisms and RA pathogenesis [26].

Several limitations were presented in this meta-analysis. Firstly, the association (or co-occurrence) of alleles of adjacent polymorphisms with each other existed linkage disequi-

librium, which may influence the role of each variant in RA risk [54]. Secondly, the number of included studies for subgroup analysis was little for a certain polymorphism. Thirdly, for ApaI polymorphism, between-study heterogeneity was very high, which may affect the reliability. Lastly, RA involves a complex interplay among genotype, environmental triggers, and chance [55], other risk factors, such as sex, the stage of disease, and gene-environment interactions should be considered.

In conclusion, our results demonstrated that the alleles of TaqI, BsmI and FokI polymorphisms were associated with RA susceptibility in total population. Subgroup analysis by ethnicity showed that BsmI variant among Africans, FokI variant among Asians and Caucasians were significantly increased the risk of RA. No relationship was found between ApaI polymorphism and RA risk. These data may provide information that could lead to the development of biomarkers for RA risk.

Disclosure of conflict of interest

None.

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