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ORIGINAL ARTICLE

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

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ABSTRACT

Objective: Numerous studies already investigated potential associations between vitamin D receptor (VDR) genetic variants and periodontitis. However, the results of these studies were not consistent. Previous studies failed to reach a consensus regarding associations between *VDR* variants and periodontitis partially because of their relatively small sample sizes. Thus, we performed the present meta-analysis to explore the relationship between *VDR* variants and periodontitis in a larger pooled sample size.

Material and methods: Systematic literature research was conducted in PubMed, Web of Science, Embase and CNKI to identify eligible case-control studies on associations between *VDR* variants and periodontitis. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) to estimate the strength of associations in all possible genetic models, and p values $\leq .05$ were considered to be statistically significant.

Results: Totally 30 studies were enrolled for analyses. Pooled analyses suggested that *VDR* rs2228570 variant was significantly associated with the susceptibility to periodontitis under dominant genetic model in the overall population ($p = .03$, OR = 0.82, 95%CI: 0.69–0.98, $I^2 = 0$). Further subgroup analyses yielded similar positive results for rs2228570 variant in East Asians and patients with chronic periodontitis. Nevertheless, no any other positive findings were observed in overall and subgroup analyses.

Conclusions: Our meta-analysis supported that *VDR* rs2228570 variant might serve as a genetic biomarker of periodontitis. However, further well-designed studies are still warranted to confirm our findings.

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Vitamin D receptor (VDR); gene variants; periodontitis; meta-analysis

Introduction

Periodontitis, characterized by inflammation in the periodontal connective tissue and destruction of alveolar bone, is the primary cause of tooth loss in adults [1,2]. The course of periodontitis depends on a complex interaction of bacteria associated with periodontitis, host and environmental factors, and the fact that the odds of developing periodontitis in subjects exposed to similar bacteria and environmental factors were different suggested that host genetic background might play a crucial role in its occurrence and development [3,4].

Some evidence supported that vitamin D metabolic pathway might be involved in the pathogenesis of periodontitis. First, previous experimental studies showed that vitamin D had profound effects on tooth mineral density, and serum vitamin D level was reversely correlated with disease severity of periodontitis [5–7]. Second, several lines of investigations also demonstrated that vitamin D had vital immune-regulatory function and it could promote microbial eradication [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 genetic variations of the *VDR* gene, which may lead to alternations in gene expression or changes in VDR protein structure, may also affect biological functions of vitamin D and ultimately impact individual susceptibility to periodontitis.

To date, some pilot studies already investigated potential associations between *VDR* variants and periodontitis. But the results of these studies were not consistent, especially when they were conducted in different populations. Previous studies failed to reach a consensus regarding associations between *VDR* variants and periodontitis partially because of their relatively small sample sizes. Thus, we performed the present meta-analysis to explore the relationship between *VDR* variants and periodontitis in a larger pooled sample size.

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Materials and methods

Literature search and inclusion criteria

This meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [11]. Potentially relevant studies published before February 2019 were retrieved from PubMed, Web of Science, Embase and CNKI using the following searching strategy: (Vitamin D receptor OR VDR) AND (polymorphism OR variant OR mutation OR genotype OR allele) AND periodontitis. 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 periodontitis; (2) provide genotypic frequency of investigated *VDR* variants in cases and controls; (3) full text in English or Chinese available. Studies were excluded if one of the following criteria was fulfilled: (1) not relevant to *VDR* variants and periodontitis; (2) case reports or case series; (3) abstracts,

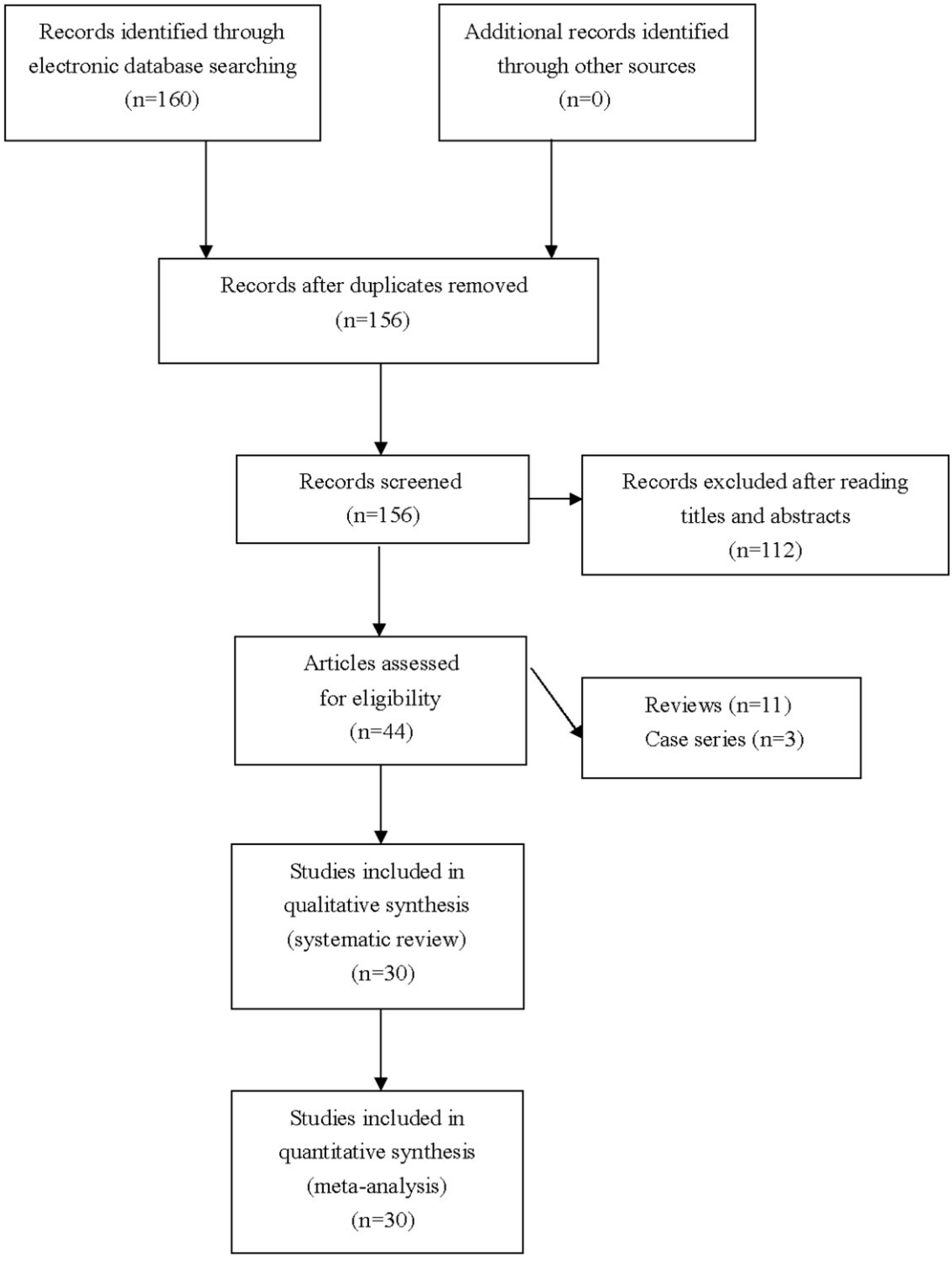


Figure 1. Flowchart of study selection for the present study.

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			
Chantarangsu 2016	Thailand	East Asian	Chronic periodontitis	1090/370	474/487/129	177/146/47	.055	8
El Jilani 2015	Libya	Mixed	Chronic periodontitis	61/45	10/43/8	7/33/5	.002	8
Gunes 2008	Turkey	Caucasian	Chronic periodontitis	72/102	33/23/16	40/43/19	.227	8
Karasneh 2013	Jordan	South Asian	Chronic periodontitis	99/126	35/47/17	52/56/18	.643	8
Karasneh 2013	Jordan	South Asian	Aggressive periodontitis	62/126	21/34/7	52/56/18	.643	8
Li 2008	China	East Asian	Aggressive periodontitis	51/53	15/25/11	16/29/8	.383	8
Li 2010	China	East Asian	Aggressive periodontitis	36/50	11/17/8	14/29/7	.195	7
Naito 2007	Japan	East Asian	Chronic periodontitis	17/80	12/3/2	38/33/9	.654	7
Nazemisalman 2018	Iran	Mixed	Chronic periodontitis	57/78	24/32/1	31/46/1	<.001	8
Tobón-Arroyave 2017	Colombia	Mixed	Chronic periodontitis	110/50	27/64/19	20/25/5	.484	7
Wang 2009	China	East Asian	Chronic periodontitis	107/121	45/51/11	55/46/20	.061	8
BsmI rs1544410					AA/AT/TT			
Cao 2015	China	East Asian	Chronic periodontitis	85/105	71/14/0	100/5/0	.803	7
Chantarangsu 2016	Thailand	East Asian	Chronic periodontitis	1090/370	880/210/0	303/67/0	.055	8
de Brito Júnior 2004	Brazil	Mixed	Chronic periodontitis	69/44	16/43/10	18/18/8	.363	8
de Souza 2007	Brazil	Mixed	Periodontitis	50/59	21/22/7	22/22/15	.061	7
El Jilani 2015	Libya	Mixed	Chronic periodontitis	75/47	21/47/7	18/26/3	.112	8
Gunes 2008	Turkey	Caucasian	Chronic periodontitis	72/102	29/33/10	42/51/9	.238	8
Karasneh 2013	Jordan	South Asian	Chronic periodontitis	94/123	34/45/15	37/56/30	.338	8
Karasneh 2013	Jordan	South Asian	Aggressive periodontitis	60/123	21/28/11	37/56/30	.338	8
Li 2008	China	East Asian	Aggressive periodontitis	51/53	48/3/0	49/4/0	.775	8
Li 2010	China	East Asian	Aggressive periodontitis	36/50	34/2/0	48/2/0	.885	7
Naito 2007	Japan	East Asian	Chronic periodontitis	17/80	13/4/0	65/15/0	.355	7
Park 2006	Korea	East Asian	Aggressive periodontitis	93/143	87/6/0	134/9/0	.698	8
Tobón-Arroyave 2017	Colombia	Mixed	Chronic periodontitis	110/50	50/45/15	18/23/9	.728	7
Wang 2008	China	East Asian	Chronic periodontitis	106/80	95/11/0	72/8/0	.638	8
Wang 2009	China	East Asian	Chronic periodontitis	107/121	92/15/0	110/11/0	.600	8
Wu 2015	China	Mixed	Chronic periodontitis	95/90	12/25/58	19/35/36	.066	8
Yoshihara 2001	Japan	East Asian	Periodontitis	94/55	76/17/1	44/11/0	.410	7
FokI rs2228570					TT/TA/AA			
Chantarangsu 2016	Thailand	East Asian	Chronic periodontitis	1090/370	324/534/232	111/153/106	<.001	8
El Jilani 2015	Libya	Mixed	Chronic periodontitis	66/37	38/27/1	21/13/3	.629	8
Li 2008	China	East Asian	Aggressive periodontitis	51/53	19/23/9	17/27/9	.756	8
Naito 2007	Japan	East Asian	Chronic periodontitis	17/80	9/4/4	25/40/15	.887	7
Park 2006	Korea	East Asian	Aggressive periodontitis	93/143	41/38/14	43/75/25	.431	8
Pinho 2018	Brazil	Mixed	Chronic periodontitis	210/69	102/93/15	39/24/6	.415	8
Tachi 2003	Japan	East Asian	Chronic periodontitis	76/92	28/35/13	43/38/11	.564	8
Tobón-Arroyave 2017	Colombia	Mixed	Chronic periodontitis	110/50	42/54/14	16/28/6	.239	7
Wang 2009	China	East Asian	Chronic periodontitis	107/121	29/62/16	37/65/19	.278	8
Wang 2015	China	Mixed	Chronic periodontitis	440/324	127/218/95	91/161/74	.863	8
TaqI rs731236					AA/AG/GG			
Baldini 2013	Italy	Caucasian	Chronic periodontitis	42/39	14/26/2	23/13/3	.551	7
Borges 2009	Brazil	Mixed	Chronic periodontitis	30/30	7/18/5	16/9/5	.093	8
Brett 2005	UK	Caucasian	Chronic periodontitis	55/98	28/19/8	27/56/15	.113	7
Brett 2005	UK	Caucasian	Aggressive periodontitis	49/98	19/24/6	27/56/15	.113	7
Cao 2015	China	East Asian	Chronic periodontitis	85/104	70/14/1	99/5/0	.802	7
Chantarangsu 2016	Thailand	East Asian	Chronic periodontitis	1090/370	915/164/11	314/53/3	.646	8
de Brito Júnior 2004	Brazil	Mixed	Chronic periodontitis	69/44	23/41/5	24/14/6	.118	8
de Souza 2007	Brazil	Mixed	Periodontitis	50/59	20/24/6	23/29/7	.639	7
Gunes 2008	Turkey	Caucasian	Chronic periodontitis	72/102	36/28/8	48/47/7	.317	8
Hennig 1999	UK	Caucasian	Periodontitis	69/72	30/27/12	31/36/5	.203	7
Kaarthikeyan 2013	India	South Asian	Chronic periodontitis	60/60	23/26/11	37/19/4	.476	8
Karasneh 2013	Jordan	South Asian	Chronic periodontitis	99/126	40/44/15	41/60/25	.719	8
Karasneh 2013	Jordan	South Asian	Aggressive periodontitis	62/126	20/33/9	41/60/25	.719	8
Li 2008	China	East Asian	Aggressive periodontitis	51/53	45/6/0	46/7/0	.607	8
Martelli 2011	Italy	Caucasian	Chronic periodontitis	115/65	14/60/41	20/30/15	.565	8
Martelli 2011	Italy	Caucasian	Aggressive periodontitis	43/65	12/10/21	20/30/15	.565	8
Nazemisalman 2018	Iran	Mixed	Chronic periodontitis	63/78	18/39/6	29/45/4	.011	8
Nibali 2008	UK	Caucasian	Periodontitis	303/231	134/129/40	90/96/45	.039	8
Park 2006	Korea	East Asian	Aggressive periodontitis	93/143	86/7/0	133/10/0	.665	8
Ratheesh 2018	India	South Asian	Chronic periodontitis	70/70	28/30/12	28/33/9	.881	8
Sun 2002	China	East Asian	Periodontitis	61/39	51/10/0	37/2/0	.869	7
Tachi 2003	Japan	East Asian	Chronic periodontitis	74/94	66/8/0	72/22/0	.198	7
Tobón-Arroyave 2017	Colombia	Mixed	Chronic periodontitis	110/50	27/64/9	20/25/5	.484	7
Wang 2009	China	East Asian	Chronic periodontitis	107/121	99/7/1	99/22/0	.271	8
Wu 2015	China	Mixed	Chronic periodontitis	49/47	41/8/0	36/11/0	.364	8
Zhang 2010	China	East Asian	Chronic periodontitis	34/91	33/1/0	84/7/0	.703	8
Zhang 2010	China	East Asian	Aggressive periodontitis	90/91	75/15/0	84/7/0	.703	8

HWE: Hardy-Weinberg equilibrium; NOS: Newcastle-Ottawa scale; NA: Not available.

Table 2. Results of overall and subgroup analyses.

			Dominant comparison		Recessive comparison		Over-dominant comparison		Allele comparison	
Polymorphisms	Population	Sample size	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)
ApaI rs7975232	Overall	1762/1201	.25	0.91 (0.77–1.07)	.76	1.04 (0.82–1.31)	.20	1.11 (0.95–1.30)	.22	0.93 (0.83–1.04)
	South Asian	161/252	.68	0.92 (0.60–1.39)	.92	1.03 (0.59–1.81)	.22	1.28 (0.86–1.91)	.32	0.86 (0.65–1.15)
	East Asian	1301/674	.29	0.90 (0.73–1.10)	.71	0.95 (0.71–1.27)	.19	1.14 (0.94–1.40)	.55	0.96 (0.83–1.11)
	Chronic periodontitis	1613/972	.33	0.92 (0.77–1.09)	.96	1.01 (0.78–1.30)	.19	1.12 (0.95–1.33)	.31	0.94 (0.83–1.06)
	Aggressive periodontitis	149/229	.54	0.87 (0.56–1.36)	.53	1.20 (0.68–2.13)	.90	1.03 (0.68–1.55)	.45	0.89 (0.66–1.20)
BsmI rs1544410	Overall	2304/1695	.22	0.90 (0.76–1.07)	.95	1.01 (0.76–1.34)	.25	1.10 (0.93–1.30)	.32	0.93 (0.82–1.07)
	South Asian	154/246	.25	1.29 (0.84–1.98)	.08	0.63 (0.38–1.06)	.72	1.08 (0.72–1.62)	.07	1.30 (0.97–1.74)
	East Asian	1679/1057	.15	0.84 (0.67–1.07)	.73	1.78 (0.07–44.47)	.17	1.18 (0.93–1.50)	.16	0.85 (0.68–1.07)
	Chronic periodontitis	1920/1212	.09	0.85 (0.70–1.02)	.69	1.12 (0.65–1.92)	.26	1.11 (0.93–1.33)	.07	0.87 (0.75–1.01)
	Aggressive periodontitis	240/369	.60	1.14 (0.69–1.91)	.36	0.70 (0.32–1.51)	.82	1.06 (0.63–1.78)	.39	1.19 (0.81–1.74)
FokI rs2228570	Overall	2260/1339	**.03**	**0.82 (0.69–0.98)**	.70	1.03 (0.89–1.20)	.21	1.10 (0.95–1.26)	.15	0.93 (0.84–1.03)
	East Asian	1434/859	**.03**	**0.78 (0.63–0.98)**	.59	1.05 (0.87–1.28)	.78	0.95 (0.67–1.36)	.11	0.90 (0.79–1.02)
	Chronic periodontitis	1999/1217	**.03**	**0.81 (0.68–0.98)**	.52	1.05 (0.90–1.24)	.29	1.08 (0.93–1.26)	.11	0.92 (0.82–1.02)
	Aggressive periodontitis	261/122	.82	0.92 (0.45–1.87)	.52	0.86 (0.55–1.36)	.43	1.20 (0.76–1.88)	.71	0.94 (0.67–1.32)
TaqI rs731236	Overall	3095/2566	.22	0.86 (0.68–1.10)	.37	1.10 (0.89–1.36)	.74	1.04 (0.83–1.30)	.16	0.88 (0.74–1.05)
	South Asian	291/382	.65	0.89 (0.53–1.49)	.97	1.01 (0.66–1.53)	.68	1.07 (0.78–1.45)	.58	0.88 (0.55–1.40)
	East Asian	1685/1106	.80	0.93 (0.55–1.59)	.39	1.64 (0.54–5.02)	.88	1.04 (0.61–1.79)	.73	0.92 (0.56–1.50)
	Caucasian	748/770	.94	0.98 (0.63–1.52)	.29	1.32 (0.79–2.18)	.31	0.82 (0.55–1.21)	.55	0.91 (0.67–1.24)
	Chronic periodontitis	2224/1589	.25	0.81 (0.57–1.16)	.17	1.22 (0.92–1.63)	.62	1.08 (0.79–1.48)	.23	0.86 (0.68–1.10)
	Aggressive periodontitis	388/576	.84	0.97 (0.69–1.36)	.71	1.21 (0.44–3.31)	.80	0.94 (0.57–1.54)	.55	0.93 (0.72–1.19)

OR: Odds ratio; CI: Confidence interval; NA: Not available.
The values in bold represent there are statistically significant differences between cases and controls.

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 distribution of *VDR* variants in cases and controls. The probability value (*p* value) of 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 [12]. This scale has a score range of zero to nine, and studies with a score of more than seven 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 the strength of associations in all possible genetic models, and *p* values $\leq$.05 were considered to be statistically significant. I^2 statistics were employed to assess between-study heterogeneities. If I^2 was greater than 50%, random-effect models (REMs) would be used to pool the data. Otherwise, fixed-effect models (FEMs) would be 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

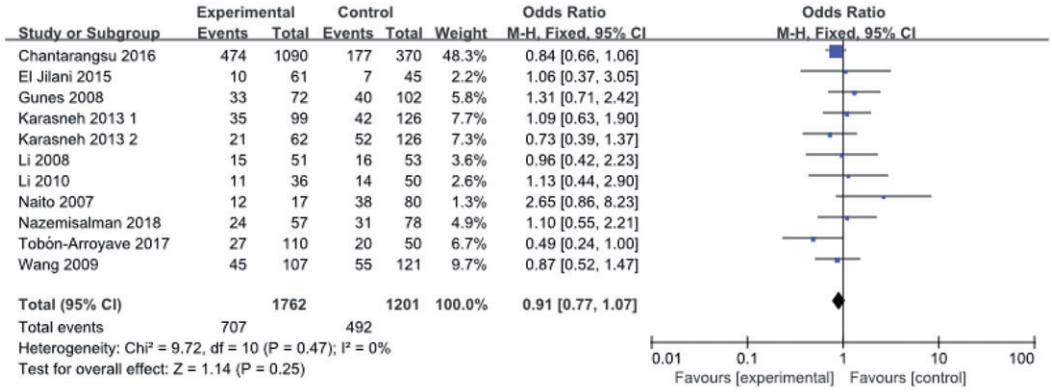
We found 160 potentially relevant articles. Among these articles, totally 30 eligible studies were finally included for pooled analyses (see Figure 1). The NOS score of eligible articles ranged from 7 to 8, which indicated that all included studies were of high quality. Baseline characteristics of the included studies were summarized in Table 1.

Overall and subgroup analyses

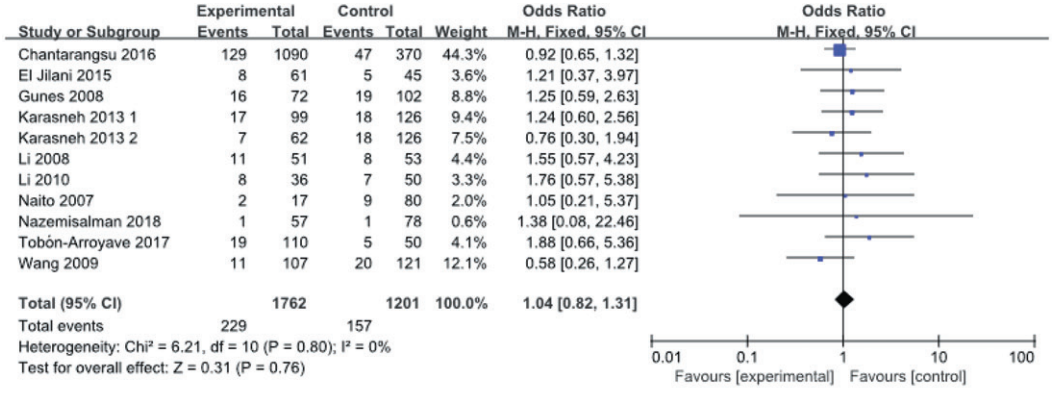
To analyze potential associations between *VDR* variants and periodontitis, 1762 cases and 1201 controls about rs7975232 variant, 2304 cases and 1695 controls about rs1544410 variant, 2260 cases and 1339 controls about rs2228570 variant, and 3095 cases and 2566 controls about rs731236 variant were enrolled for analyses. Pooled analyses suggested that *VDR* rs2228570 variant was significantly associated with the susceptibility to periodontitis under dominant genetic model ($p = .03$, OR = 0.82, 95%CI: 0.69–0.98, $I^2 = 0$) in the overall population. Further subgroup analyses yielded similar positive results for rs2228570 variant in East Asians and patients with chronic periodontitis. Nevertheless, no any other positive findings were observed in overall and subgroup analyses (see Table 2 and Figure 2).

Sensitivity analyses

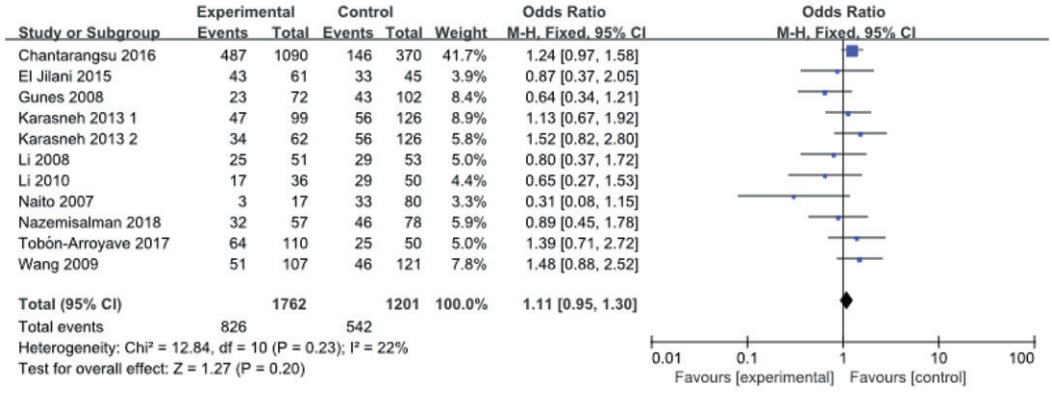
We performed sensitivity analyses to test the stabilities of pooled results by excluding studies that violated HWE. No any altered results were observed in overall and subgroup



2.1 Forest plot of **ApaI rs7975232** polymorphism and PD under dominant comparison

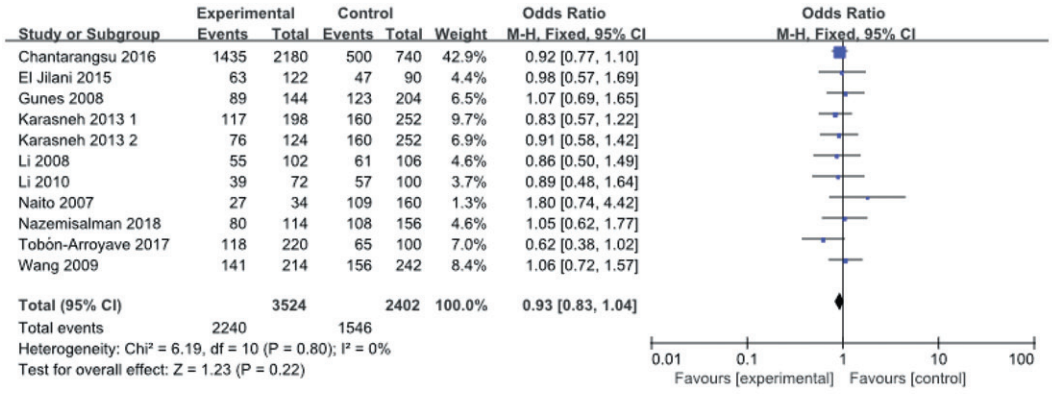


2.2 Forest plot of **ApaI rs7975232** polymorphism and PD under recessive comparison

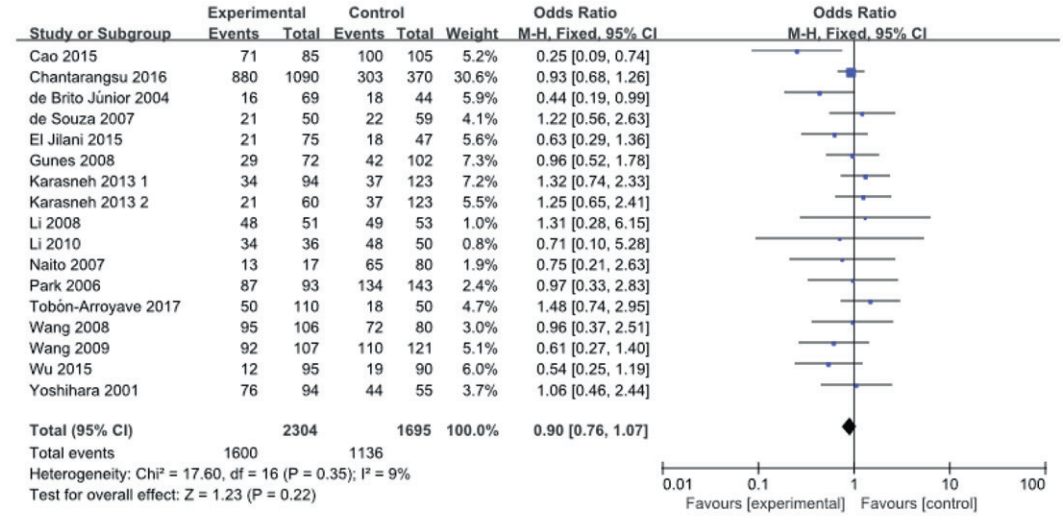


2.3 Forest plot of **ApaI rs7975232** polymorphism and PD under over-dominant comparison

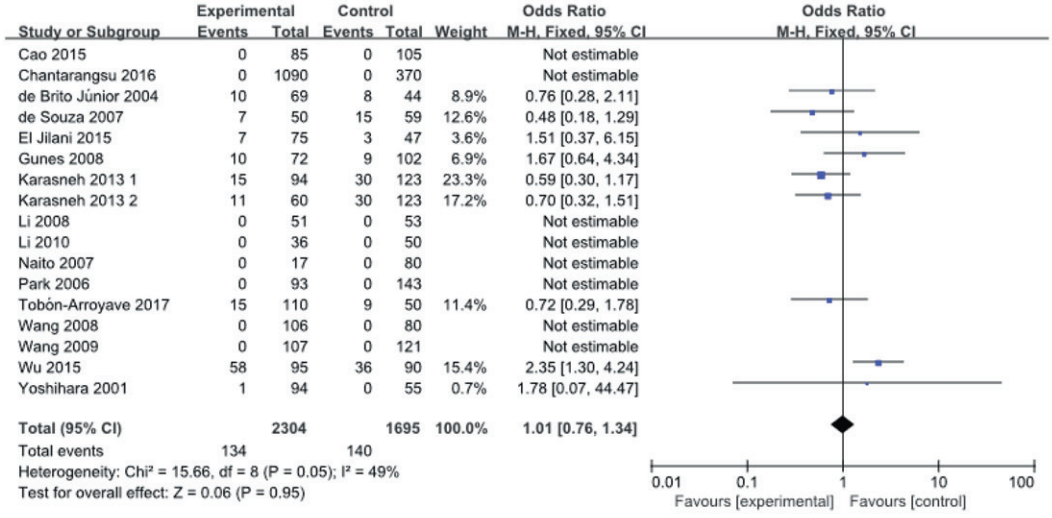
Figure 2. Forest plots of investigated polymorphisms.
2.1. Forest plot of ApaI rs7975232 polymorphism and PD under dominant comparison.
2.2. Forest plot of ApaI rs7975232 polymorphism and PD under recessive comparison.
2.3. Forest plot of ApaI rs7975232 polymorphism and PD under over-dominant comparison.
2.4. Forest plot of ApaI rs7975232 polymorphism and PD under allele comparison.
2.5. Forest plot of BsmI rs1544410 polymorphism and PD under dominant comparison
2.6. Forest plot of BsmI rs1544410 polymorphism and PD under recessive comparison
2.7. Forest plot of BsmI rs1544410 polymorphism and PD under over-dominant comparison
2.8. Forest plot of BsmI rs1544410 polymorphism and PD under allele comparison
2.9. Forest plot of FokI rs2228570 polymorphism and PD under dominant comparison
2.10. Forest plot of FokI rs2228570 polymorphism and PD under recessive comparison
2.11. Forest plot of FokI rs2228570 polymorphism and PD under over-dominant comparison
2.12. Forest plot of FokI rs2228570 polymorphism and PD under allele comparison
2.13. Forest plot of TaqI rs731236 polymorphism and PD under dominant comparison
2.14. Forest plot of TaqI rs731236 polymorphism and PD under recessive comparison
2.15. Forest plot of TaqI rs731236 polymorphism and PD under over-dominant comparison
2.16. Forest plot of TaqI rs731236 polymorphism and PD under allele comparison (see Figure 2)



2.4 Forest plot of **ApaI rs7975232** polymorphism and PD under allele comparison

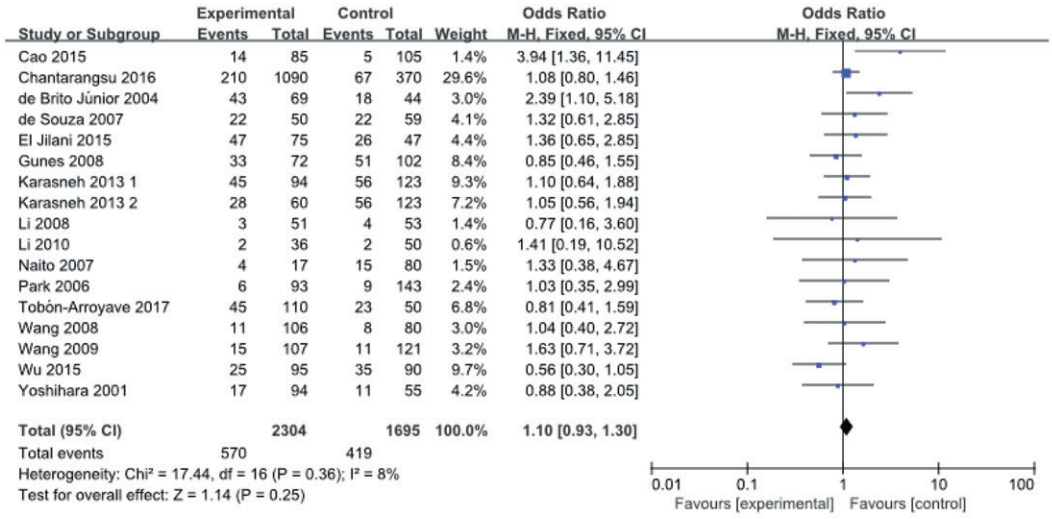


2.5 Forest plot of **BsmI rs1544410** polymorphism and PD under dominant comparison

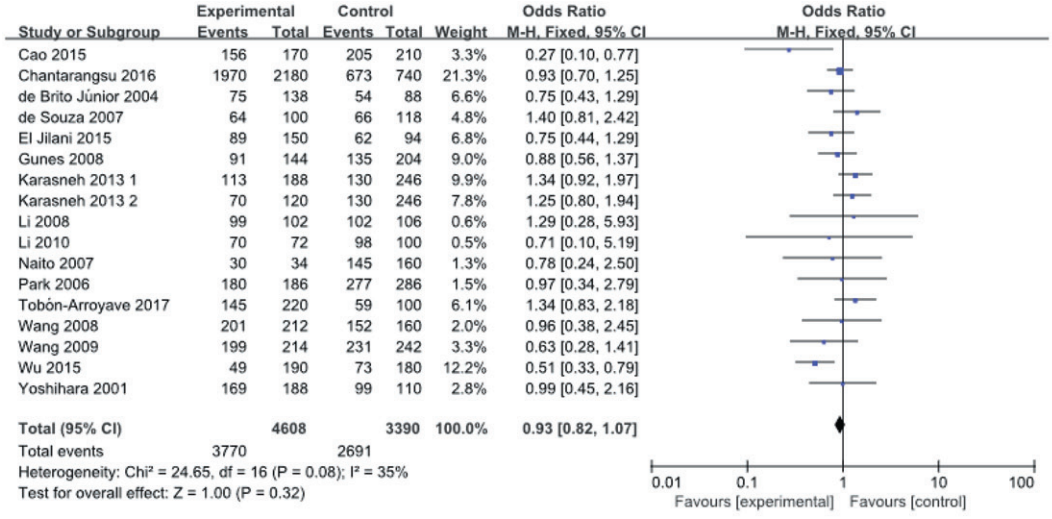


2.6 Forest plot of **BsmI rs1544410** polymorphism and PD under recessive comparison

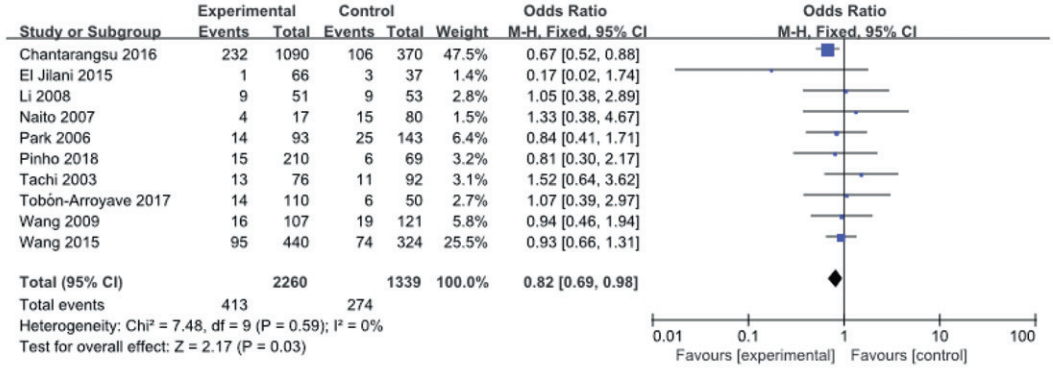
Figure 2. Continued



2.7 Forest plot of **BsmI rs1544410** polymorphism and PD under over-dominant comparison

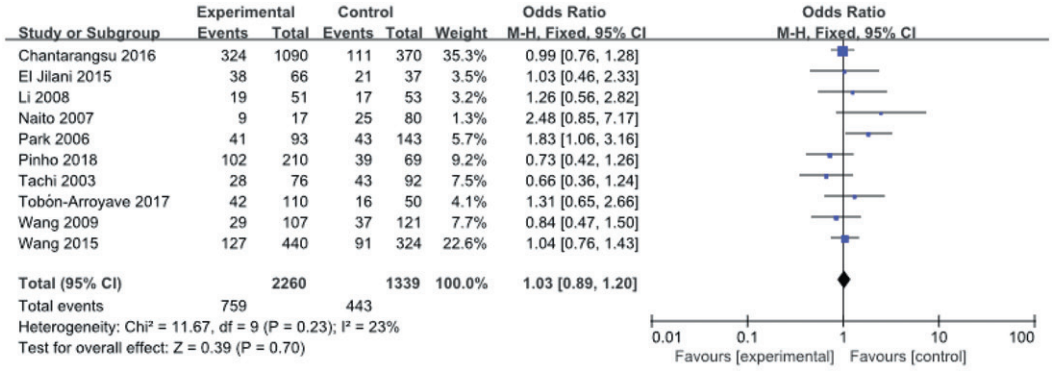


2.8 Forest plot of **BsmI rs1544410** polymorphism and PD under allele comparison

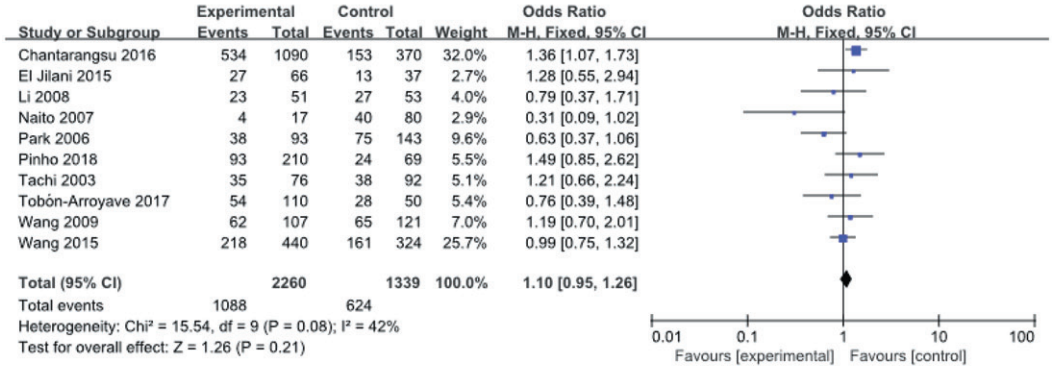


2.9 Forest plot of **FokI rs2228570** polymorphism and PD under dominant comparison

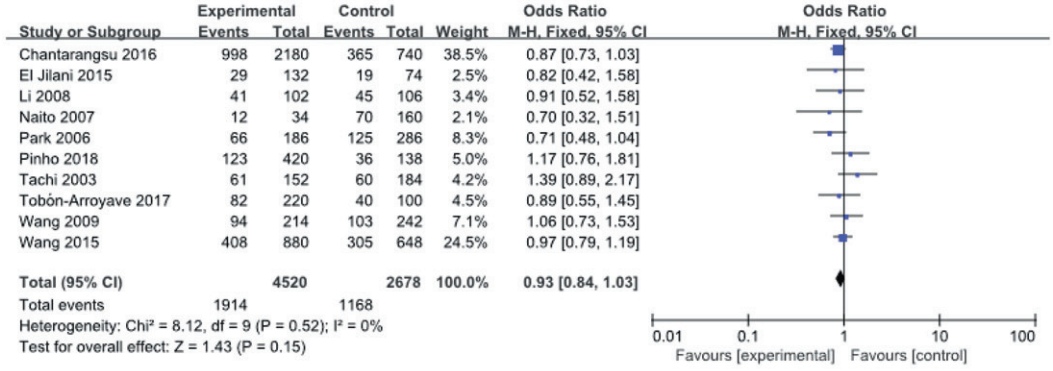
Figure 2. Continued



2.10 Forest plot of **FokI rs2228570** polymorphism and PD under recessive comparison



2.11 Forest plot of **FokI rs2228570** polymorphism and PD under over-dominant comparison



2.12 Forest plot of **FokI rs2228570** polymorphism and PD under allele comparison

Figure 2. Continued

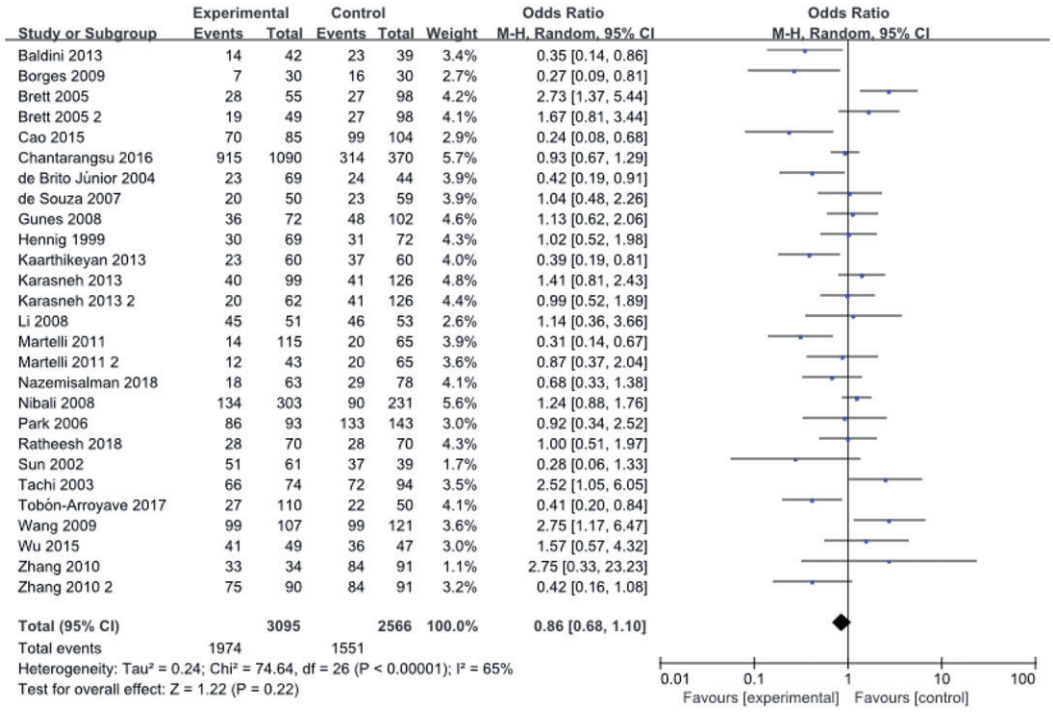
comparisons, which indicated that our findings were statistically stable.

Publication biases

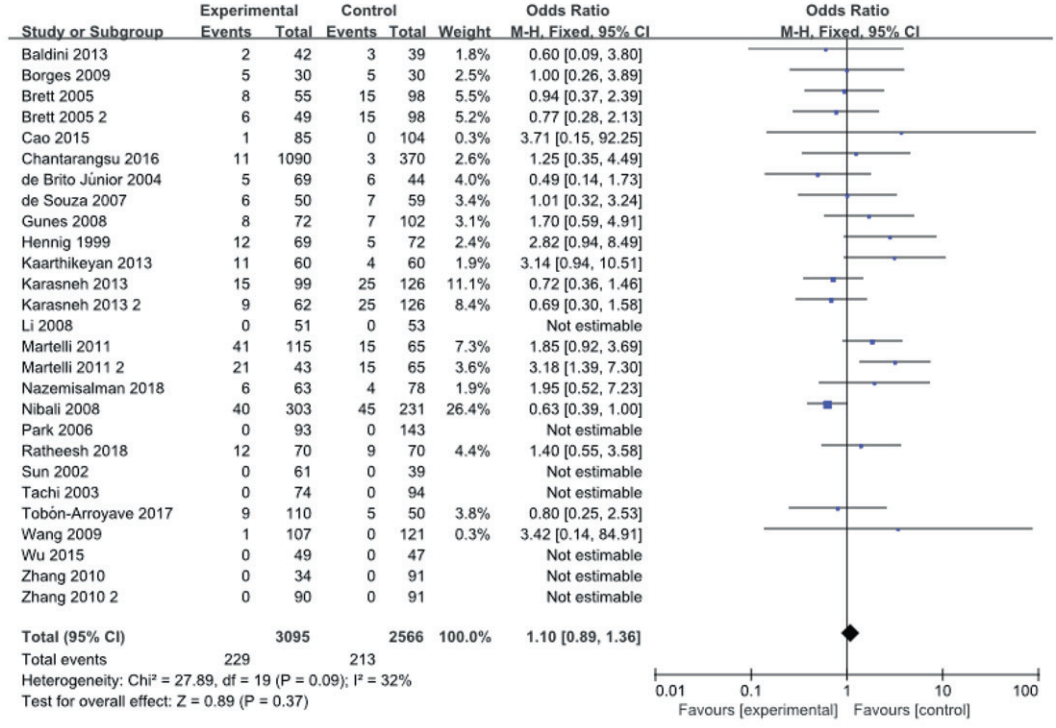
We used funnel plots to assess publication biases. We did not find obvious asymmetry of funnel plots in any comparisons, which suggested that our findings were unlikely to be impacted by severe publication biases.

Discussion

As far as we know, this is so far the most comprehensive meta-analysis on roles of *VDR* variants in periodontitis, and our pooled analyses suggested that *VDR* rs2228570 variant was significantly associated with individual susceptibility to periodontitis. The stabilities of synthetic results were subsequently evaluated in sensitivity analyses, and no changes of results were observed in any comparisons, which indicated that our findings were statistically stable. As for the evaluation of heterogeneities, only trivial heterogeneities were detected for rs7975232, rs1544410 and rs2228570 variants, thus all analyses were performed with FEMs. For rs731236 variant, significant between-study heterogeneities were found for dominant, over-dominant and allele genetic models in overall analyses, but in further subgroup analyses by ethnicity, studies of South Asian and Caucasian origins were found to be homogenous, which indicated that ethnic



2.13 Forest plot of **TaqI rs731236** polymorphism and PD under dominant comparison

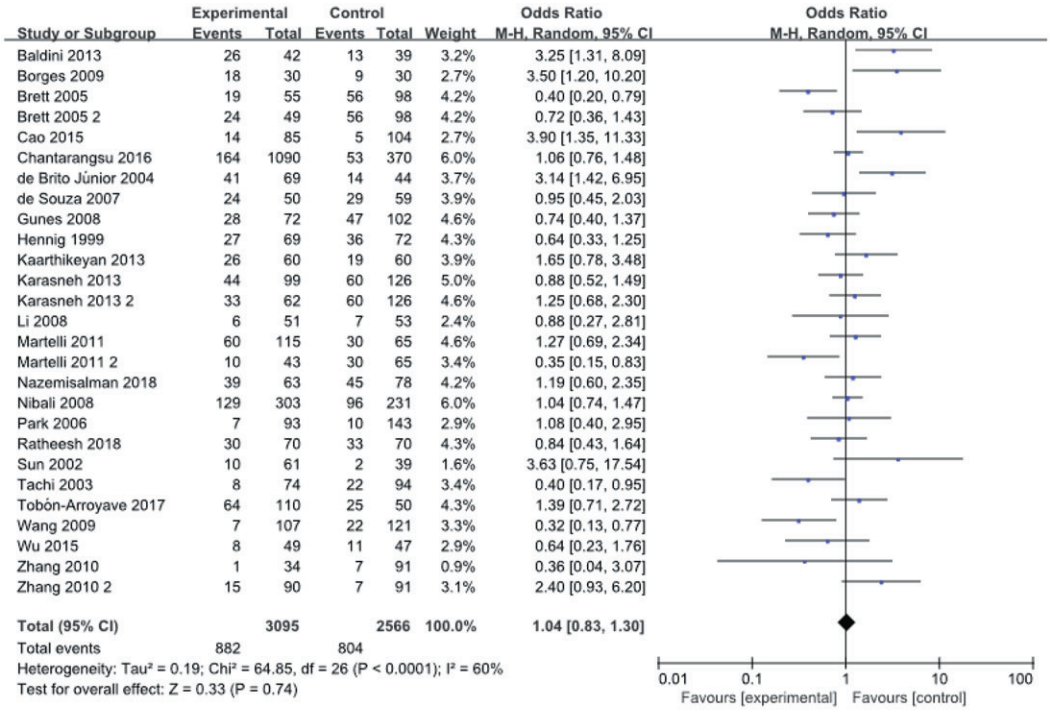


2.14 Forest plot of **TaqI rs731236** polymorphism and PD under recessive comparison

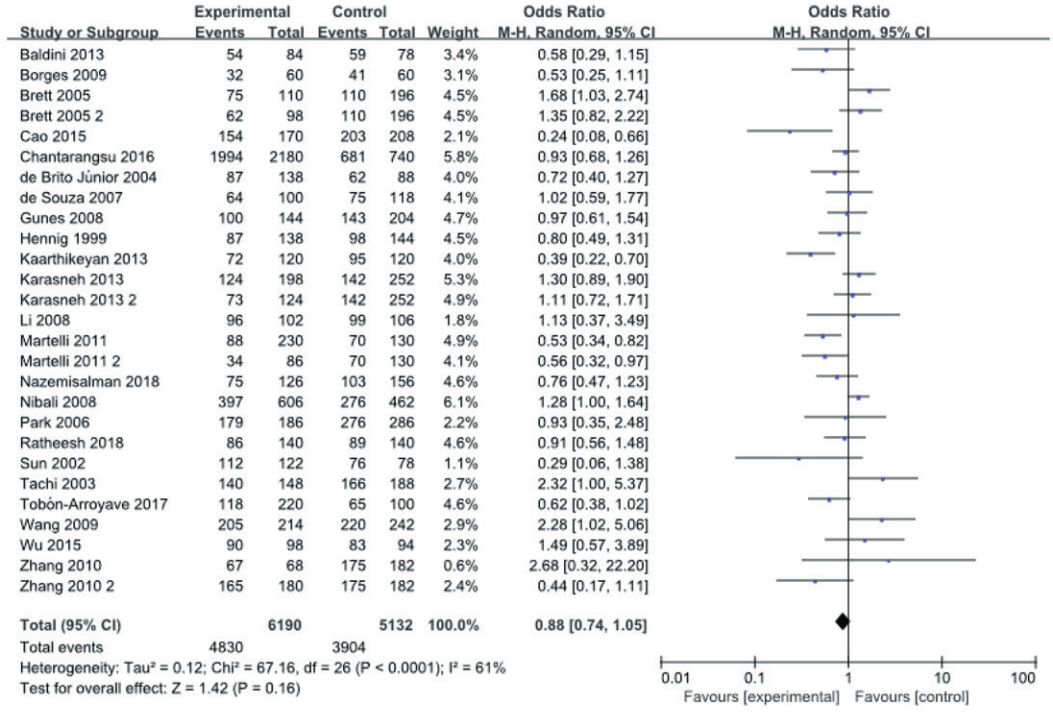
Figure 2. Continued

differences could largely explain observed heterogeneities between studies.

There are several points that need to be addressed about this meta-analysis. Firstly, although the investigated *VDR* variants were intensively analyzed with regard to their potential associations with periodontitis, the functional significances of these variants were still undetermined [13,14], and thus future investigations still need to explore the underlying molecular mechanisms of our positive finding about rs2228570 variant and periodontitis. Secondly, the



2.15 Forest plot of **TaqI rs731236** polymorphism and PD under over-dominant comparison



2.16 Forest plot of **TaqI rs731236** polymorphism and PD under allele comparison

Figure 2. Continued

pathogenic mechanism of periodontitis 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 periodontitis, we strongly recommend further studies to perform haplotype analyses and explore potential gene-gene interactions. Thirdly, it is noteworthy that the sample sizes of pooled analyses are still relatively small, so maybe our study is still not statistically adequate to detect the actual associations between other investigated *VDR* variants and

periodontitis. Therefore, further studies with larger sample sizes are still needed to test the associations between investigated *VDR* variants and periodontitis. Fourth, previous experimental studies found that matrix metalloproteinase 8 (MMP8), a collagenolytic enzyme, could cause periodontal tissue destruction, and pathological elevation of the levels and activation of MMP8 in oral fluids was also verified to be one of the main characteristics of active periodontal diseases [15–18]. Therefore, future studies are warranted to explore the potential associations of investigated *VDR* variants with levels and activation of MMP8. Moreover, whether *VDR* variants were linked with *MMP8* variants or not is also worth investigating.

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 the lack of further adjusted analyses for potential confounding factors might impact the reliability of our findings [19]. Second, associations between *VDR* variants and periodontitis might also be modified by gene-environmental interactions. However, most eligible studies ignore these potential interactions, which impeded us to perform relevant analyses accordingly [20,21]. Third, grey literatures like abstracts and other research materials that were not formally published in academic journals were not considered to be eligible for analyses in this meta-analysis since it is hard to determine their quality. However, since grey literatures were not analyzed, although funnel plots suggested that severe publication biases were unlikely to be existed in the current meta-analysis, it is still possible that our findings may be impacted by potential publication biases [22]. On account of the above mentioned limitations, our findings should be cautiously interpreted.

In conclusion, our meta-analysis suggested that *VDR* rs2228570 variant might serve as a genetic biomarker of periodontitis. However, further well-designed studies are still warranted to confirm our findings. Moreover, future investigations also need to explore the exact underlying molecular mechanisms of our positive findings.

Disclosure statement

No potential conflict of interest was reported by the authors.

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