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REVIEW ARTICLE

Vitamin D Receptor gene polymorphisms and susceptibility to type 2 diabetes: evidence from a meta-regression and meta-analysis based on 47 studies

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Abstract

Background Evidence from various studies suggest that vitamin D receptor (VDR) gene polymorphisms are associated with type 2 diabetes (T2D); However, these results have been disputable. Here we conducted a meta-analysis to comprehensively evaluate the effect of *VDR* gene polymorphisms and susceptibility to T2D.

Methods All relevant studies reporting the association between *VDR* gene polymorphisms and susceptibility to T2D published up to August 2020 were identified by comprehensive systematic database search in web of science, Scopus, and Medline. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to measure strength of association. The methodological quality of each study was assessed according to the Newcastle–Ottawa Scale. Subgroup and meta-regression analysis were also performed.

Results A total of 47 case–control studies were included in this meta-analysis. The overall population results revealed a significant association between *FokI,* and *BsmI* (heterozygote model) polymorphisms and T2D in the overall analysis. However, no association was found with the *TaqI* and *ApaI* polymorphisms. Moreover, the pooled results of subgroup analysis by ethnicity suggested significant association between *FokI, TaqI*, and *BsmI* polymorphisms and T2D in some subgroups. Meta-regression analyses indicated that none of the publication year, ethnicity, and genotyping method were the source of heterogenicity in all four polymorphisms.

Conclusions This meta-analysis suggested a significant association between *VDR* gene *FokI*, and *BsmI* (heterozygote model) polymorphisms and T2D susceptibility in overall population and ethnic-specific analysis.

Keywords Vitamin D receptor · Type 2 diabetes mellitus · Polymorphism · Meta-analysis · Meta-regression

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Abbreviations

T2DM	Type 2 diabetes mellitus
VDR	Vitamin D receptor
VitD	Vitamin D,
SNP	Single nucleotide polymorphisms
IL	Interleukin
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
NOS	Newcastle-Ottawa Scale
UVR	Ultraviolet radiation
Th	T helper
TNF	Tumor necrosis factor
IFN	Interferon; HWE, Hardy–Weinberg equilibrium
PCR- RFLP	Polymerase chain reaction-restriction fragment length polymorphism.

Background

Type 2 diabetes mellitus (T2D) is recognized as chronic metabolic disease with progressive reduction in pancreatic β-cell secretion, glucose intolerance, and hyperglycemia [1]. According to the latest report released by International Diabetes Federation (IDF), it is estimated that 424.9 million people in the world were diagnosed with diabetes in 2017, and predictions demonstrate excision of this number from 628.6 million by 2045 [2–4]. Specifically, T2D which is the most prevalent form of diabetes worldwide account for 90 to 95% of all types of diabetes [5]. Although the exact etiologies underlying T2D is not clear, however subclinical inflammation and immune system are among effective factors in the development of T2D and subsequent disorders such as retinopathy, neuropathy, nephropathy and cardiovascular abnormality [6, 7]. From pathophysiological perspective, T2D is characterized as a polygenic and multi-factorial disease which necessitate deeper investigation of genetic factors besides of life style, and environmental agents. In this regard, researches on polymorphisms of possible effective genes in development of T2D become one of the most popular areas in recent years and some studies revealed potential roles of SNPs in development of T2D [8, 9].

Parallel with mentioned reasons in etiology of T2D, diet also must consider as effective factor. With knowledge to substantial roles of Vitamin D (VD) in control of insulin secretion by regulation of calcium concentration and different other roles, any genetic polymorphism which change VD absorption or VD receptor functions, directly influence etiology of T2D [10, 11]. Other potential roles for VD are regulation of the insulin receptor gene and increasing insulin sensitivity in muscle and adipose tissues by activation of PPAR-δ (transcriptional factor) [12]. It is noteworthy that VD regulate about 3% of human genome and mostly these function exert by its receptor (VDR) [13]. *VDR* is a member of the nuclear hormone receptors superfamily with a DNA binding domain and its gene is located on chromosome 12q13.1 consist of 11 exons [14, 15]. Four common single nucleotide polymorphisms (SNPs) of *VDR* gene are *FokI* (rs2228570), *TaqI* (rs731236), *BsmI* (rs1544410), and *ApaI*(rs7975232) [16, 17]. Of them, polymorphisms of *ApaI, BsmI*, and *TaqI* are located in the 3′-end of *VDR* gene which lead to silent mutation associated with increased *VDR* mRNA stability. In contrast, *FokI* SNP is located in the start codon resulting protein with shorter size, the shorter form of the protein (424amino acid) is more active than the long form (427amino acid) [18–21]. So far, several studies investigated the potential roles of these common SNPs in T2D but results are conflicting; therefore, here we conducted an updated meta-analysis with the aim of providing a much more reliable conclusion on the significance of the associations.

Methods and analysis

This study adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses(PRISMA) guidelines, including; literature retrieval, inclusion and exclusion criteria, data extraction, quality assessment, and statistical analysis [22]. Since we did not any experiment on human participants or animals, therefore no ethical approval was needed.

Literature retrieval

A systematic search in Medline, Scopus, and Web of Science databases was carried out to retrieve all articles considering polymorphisms of *VDR* (*FokI*(rs2228570)or/and*TaqI*(rs731236)or/and*BsmI* (rs1544410) or/and*ApaI*(rs7975232) and T2D. Search time interval was range from the register to August 2020. The major key words and Medical Subject Headings (Mesh) were as follow: ("T2D" OR "type 2 diabetes" OR "diabetes") AND (VDR" OR "vitamin D receptor") AND ("polymorphisms" OR "single nucleotide polymorphism" OR "SNP" OR "variation"). These studies used Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) and allelic discrimination technique by Taq-Man Real-time PCR for genotyping the four *VDR* polymorphisms. In addition, cross references within both original and review articles were searched for possible publications.

Inclusion and exclusion criteria

To find desirable articles, the following criteria were considered: 1) observational studies (case–control and cohort) considering the association between *VDR* gene polymorphisms and T2D as the main outcome; 2) Studies with calculable or

extractable data for odds ratio (OR) and 95% confidence intervals (CIs); 3) studies providing detailed genotype frequencies and the total number of cases and controls. Other studies including reviews, book chapters, duplicates and irrelevant publications were excluded. Finally, 47 case–control studies finalized for analysis.

Data extraction

The following items were recorded from all 47 eligible studies: the first author's name,, mean or range of age, year of publication, total sample size of cases and controls, ethnicity, country of origin, genotyping method, allele frequency of cases and controls, and the number of cases and controls for each genotype. The ethnicity classification of the included studies was determined by direct statement of the authors in the method section of the articles. Any possible controversy about extracted items were resolved by consensus.

Quality assessment

In order to assess methodological quality of included studies Newcastle-Ottawa Scale (NOS) was applied by two reviewers. The NOS consists of three aspects (Selection, Comparability, and Exposure) with nine items in total. The final score ranges from zero star to nine stars and studies with scores 0–3, 4–6 or 7–9 were of low, moderate or high-quality, respectively [23].

Statistical analysis

χ2-test in control group was utilized to recognize deviation from Hardy–Weinberg equilibrium (HWE). The effect size of the association between *VDR* gene polymorphisms and T2D was assessed by ORs and its 95% CI. Different comparison models for *FokI, TaqI, BsmI, ApaI* were as follow: ***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 potential between study heterogeneity was estimated by Cochran's Q-statistic (*P* value<0.10 was considered as statistically significant) and I-squared (I^2) tests [24].Accordingly, the fixed-effected model (FEM) was used if $P_{Q\text{-statistic}} > 0.10$ or I^2 was<50%; otherwise, the random-effected model (REM) was applied [25, 26]. To identify predefined sources of heterogeneity among included studies, subgroup analysis and meta-regression analysis based on years of population, ethnicity, and genotyping method were performed. Additionally, we evaluate the conclusiveness and robustness of results by excluding each of the studies from the pooled estimate and analyzing the rest of them. This method enables the assessment of whether the pooled estimates were affected by any individual studies. To discover the risk of publication bias and the small-study effect, Begg's funnel plots and Egger's regression test were estimated (*P* value<0.05 considered statistically significant) [27, 28]. The data analyses were carried out using STATA (version 14.0; Stata Corporation, College Station, TX) and SPSS (version 23.0; SPSS, Inc. Chicago, IL).

Results

Study characteristics

The four-phase search and screening process based on the PRISMA statement is outlined in Fig. 1. After the removal of duplicates, 855 publications were remained. Of these, 744 publications were excluded based on title & abstract and 64 publications excluded by full text evaluation. Ultimately, 47 eligible studies were included in final analysis. All eligible studies were published between 1999 to 2020 and had an overall good methodological quality with NOS scores ranging from 6 to 8. Tables 1 and 2 summarized the characteristics and genotype frequency of the included studies.

Quantitative synthesis

Meta-analysis of FokI (rs2228570) polymorphism

A total of 29 case-control studies with 7260 patients and 7771 controls were included in overall analysis. Of them, 3 publications were performed in European countries [29–31], 17 publications were in Asian countries [32–48], 4 publications in African countries [49–52], and 5 publications in American countries [53–57]. The pooled results of overall analysis demonstrated a significant positive association between the *FokI* gene polymorphism and T2D under all five genotype models; dominant model (OR = 1.37, 95% CI = 1.11–1.68, $P < 0.001$), recessive model (OR = 1.10, 95% CI = 0.99–1.21, $P = 0.06$), allelic model (OR = 1.24, 95% CI = 1.09–1.42, $P < 0.001$), ff vs. FF model (OR = 1.36, 95% CI = 1.09–1.70, $P < 0.001$), and Ff vs. FF model (OR = 1.34, 95% CI = 1.09–1.66, $P < 0.001$) (Fig. 2). Moreover, subgroup analysis by ethnicity detected an increased susceptibility of T2D in Asian population across all five genotype models (Fig. 3). No significant association were found in African, European and people with mixed ethnicity (mostly composed of Caucasians, Latins, and American-Africans).

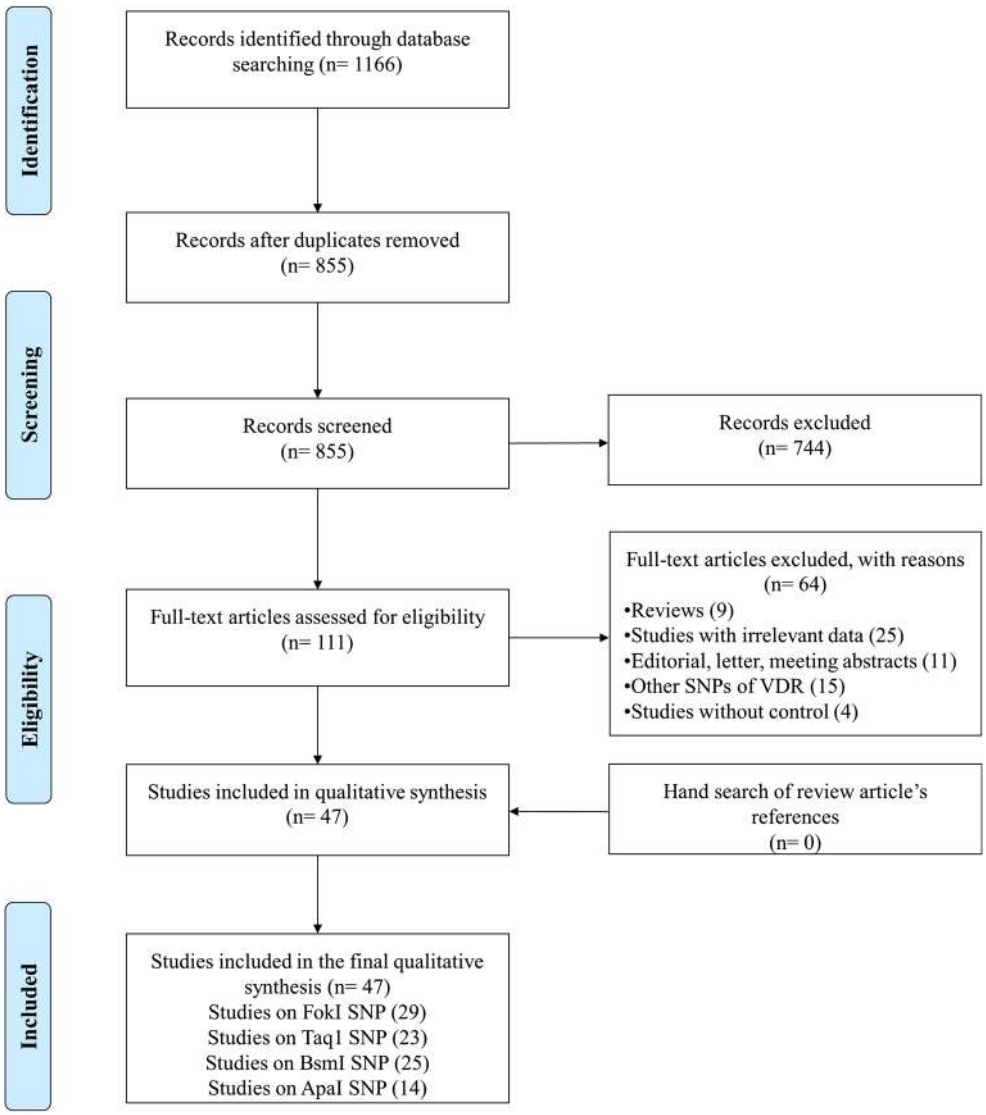

Fig. 1 Flow diagram of study selection process

Meta-analysis of TaqI (rs731236) polymorphism

Twenty-three case-control studies containing 4579 patients and 4815 controls were identified eligible for quantitative synthesis. Qualified studies were conducted in different countries including Asian countries [32–36, 40, 44, 46, 58–62], American countries [54, 56, 63, 64], European countries [29, 65–67] and African countries [49]. There was no association between *TaqI* SNP and T2D in overall analysis. However, subgroup analysis by ethnicity revealed increased susceptibility of T2D in Asian population in recessive model (OR = 1.17, 95% CI = 1–1.37, $P = 0.05$) and tt vs. TT model (OR = 1.21, 95% CI, 1.01–1.45, $P = 0.03$), but not other models and decreased susceptibility of T2D in European population in dominant model (OR = 0.77, 95% CI = 0.61–0.97, $P = 0.02$) and Tt vs. TT model (OR = 0.78, 95% CI, 0.61–0.99, $P = 0.04$), but not other models. Moreover, no significant association was detected for mixed ethnicity (Fig. 3).

Meta-analysis of BsmI (rs1544410) polymorphism

Herein, 25 studies provided data on *BsmI* gene polymorphism. A total of 5334 patients and 6015 controls were included in the analysis. Most of included studies were performed in Asian countries [32–34, 36, 37, 39, 40, 42, 44, 46, 58, 61, 68, 69] and other studies were in Europe [29, 30, 65, 70], America [55, 56, 63] and Africa [49, 50, 52]. No significant association was found for both overall and ethnic-specific subgroup analysis except Bb vs. BB model in overall analysis (OR = 1.17, 95% CI, 1.05–1.31, $P < 0.001$) and Asians (OR = 1.24, 95% CI, 1.09–1.41, $P < 0.001$).

Table 1 Characteristics of studies included in meta-analysis of overall T2D

Study author	Year	Country	Ethnicity	Total cases/control	Age case/control (Mean)	Genotyping method	Quality score
FokI (rs2228570)							
Malecki et al.	2003	Poland	European	308 /239	59.8±9.2 / 54.0±15.1	RFLP-PCR	7
Bid et al.	2009	India	Asian	100 /160	49.32±10.97 / NR	RFLP-PCR	6
Dong et al.	2010	China	Asian	180 /96	59.7±8.7 / 57.9±8.1	Taq-Man	5
Al-Daghri et al.	2012	Saudi Arabia	Asian	368 /259	51.5±8.6 / 44.1±9.9	Taq-Man	7
Vedralova et al.	2012	Czech	European	116 /113	67.2±12.44 /45.0±7.31	RFLP-PCR	6
Mackawy et al.	2014	Egypt	African	130 /60	47.96±5.61 /47.90±7.1	RFLP-PCR	5
Jia et al.	2015	China	Asian	668 /1960	NR / NR	Taq-Man	8
Shab-Bidar et al.	2015	Iran	Asian	358 /372	45.6±7.6 /44.7±8.5	RFLP-PCR	7
Zhong et al.	2015	China	Asian	204 /116	45.6±7.6/ 58.11±10.7	RFLP-PCR	6
Angel et al.	2016	Chile	Mixed	160 /160	69.4±6.9 / 45.6±7.6	RFLP-PCR	6
Mahjoubi et al.	2016	Tunisia	African	439 /302	55.96±9.6 /9.3±9.63	RFLP-PCR	7
Maia et al.	2016	Brazil	Mixed	100 /100	65.7±7.8 /65.1±9.8	Taq-Man	6
Soroush et al.	2016	Iran	Asian	105 /107	55.96±7.8 /55.88±6.6	RFLP-PCR	6
Yu et al.	2016	China	Asian	397 /775	59.53±11.9 /59.54±11.9	Sequenom Mass Array SNP assay	8
Bertoccini et al.	2017	Italy	European	883 /830	NR / NR	Taq-Man	8
Rasheed et al.	2017	Egypt	African	180 /150	43.2±6.5 /44.3±4.1	Taq-Man	6
Taneja et al.	2017	India	Asian	100 /100	46.8±11.33 /39.34±11.1	RFLP-PCR	6
Xia et al.	2017	China	Asian	242 /100	76.8±11.8 / 75.8±11.2	RFLP-PCR	6
Angel et al.	2018	Chile	Mixed	138 / 172	60–79 /60–79	RFLP-PCR	6
Gendy et al.	2018	Egypt	African	50 /50	51.0±8.2 /52.4±6.55	RFLP-PCR	5
Safar et al.	2018	United Arab Emirates	Asian	261 /90	60.5±11.59 /48.21±12.1	Taq-Man	6
Sarma et al.	2018	India	Asian	40 /20	49.65±9.78/ 48.45±8.7	RFLP-PCR	5
Gnanaprakash et al.	2019	India	Asian	159 /147	50.9±8.1 /48.8±8.2	RFLP-PCR	6
Hadi et al.	2019	Iraq	Asian	94 /101	47.59±10.8 /45.4±13.6	ARMS-PCR	5
Pinho et al.	2019	Brazil	Mixed	115 /69	58.2±9.7 /49.6±10.7	Taq-Man	5
Rodrigues et al.	2019	Brazil	Mixed	101 /62	56/ 53	RFLP-PCR	5
Ma et al.	2019	China	Asian	674 /521	61.9 /62.4±3.3	RFLP-PCR	8
Saxena et al.	2020	Saudi Arabia	Asian	440 /440	48.10±8.2 /45.68±9.1	RFLP-PCR	7
Sattar et al.	2020	Pakistan	Asian	150 /100	47.5±5.0 /48.3±5.4	RFLP-PCR	6
TaqI (rs731236)							
Sanchis et al.	1999	India	Asian	89 / 100	53.1±9.80 / 48.9±9.6	RFLP-PCR	5
Ye et al.	2001	France	European	305 / 143	62±12 / 61±16	RFLP-PCR	6
Oh et al.	2002	USA	Mixed	242 / 1303	71.7±8.6 / 68.8±9.2	RFLP-PCR	8
Malecki et al.	2003	Poland	European	308 / 240	59.8±9.2 / 54.0±15.1	RFLP-PCR	7

Table 1 (continued)

Study author	Year	Country	Ethnicity	Total cases/control	Age case/control (Mean)	Genotyping method	Quality score
Bid et al.	2009	India	Asian	100 / 160	49.32±10.97 / NR	RFLP-PCR	6
Dilmec et al.	2010	Turkey	European	72 / 169	57.1±10.8 / 56.1±6.8	RFLP-PCR	6
Mukhopadhyaya et al.	2010	India	Asian	40 / 40	47.2±12.0 / 43.2±10.12	RFLP-PCR	5
Al-Daghri et al.	2012	Saudi Arabia	Asian	368 / 259	51.5±8.6 / 44.1±9.9	Taq-Man genotyping	7
Vural et al.	2012	Turkey	European	100 / 100	NR / NR	Real-time qPCR	6
Leon et al.	2015	Mexico	Mixed	125 / 125	50.8±7.3 / 44.5±8.2	RFLP-PCR	6
Shab-Bidar et al.	2015	Iran	Asian	358 / 372	45.6±7.6 / 44.7±8.5	RFLP-PCR	7
Maia et al.	2016	Brazil	Mixed	100 / 100	65.7±7.8 / 65.1±9.8	Taq-Man genotyping	6
Taneja et al.	2016	India	Asian	100 / 100	46.8±11.3 / 39.34±11.1	RFLP-PCR	6
Darraji et al.	2017	Iraq	Asian	200 / 75	NR / NR	RFLP-PCR	6
Malik et al.	2017	India	Asian	101 / 100	51.2±8.79 / 45.02±11	RFLP-PCR	6
Xia et al.	2017	China	Asian	242 / 100	76.8±11.8 / 75.8±11.2	RFLP-PCR	6
Gendy et al.	2018	Egypt	African	50 / 50	51.0±8.2 / 52.4±6.55	RFLP-PCR	5
Safar et al.	2018	United Arab Emirates	Asian	262 / 91	60.5±11.5 / 48.21±12.1	Taq-Man	6
Sarma et al.	2018	India	Asian	40 / 20	49.65±9.78 / 48.45±8.7	RFLP-PCR	5
Gnanaprakash et al.	2019	India	Asian	162 / 145	50.9±8.1 / 48.8±8.2	RFLP-PCR	6
Rodrigues et al.	2019	Brazil	Mixed	101 / 62	56 /53	RFLP-PCR	5
Ma et al.	2019	China	Asian	674 / 521	61.9 / 62.4±3.3	RFLP-PCR	8
Saxena et al.	2020	Saudi Arabia	Asian	440 / 440	48.10±8. / 45.68±9	RFLP-PCR	7
BsmI (rs1544410)							
Speer et al.	2001	Hungary	European	49 / 138	29–77 / 23–83	RFLP-PCR	5
Ye et al.	2001	France	European	306 / 143	62±12 / 61±16	RFLP-PCR	6
Oh et al.	2002	USA	Mixed	242 / 1303	71.7±8.6 / 68.8±9.2	RFLP-PCR	8
Malecki et al.	2003	Poland	European	308 / 240	59.8±9.2 / 54.0±15.1	RFLP-PCR	7
Bid et al.	2009	India	Asian	100 / 160	49.32±10.97 / NR	RFLP-PCR	6
Mukhopadhyaya et al.	2010	India	Asian	40 / 40	47.2±12.0 / 43.2±10.12	RFLP-PCR	5
Al-Daghri et al.	2012	Saudi Arabia	Asian	368 / 259	51.5±8.6 / 44.1±9.9	Taq-Man	7
Zhang et al.	2012	China	Asian	304 / 100	55.3±8.8 / 56.5±12.2	Sequencing	6
Mackawy et al.	2014	Egypt	African	130 / 60	47.96±5.61 / 47.90±7.1	RFLP-PCR	5
Shab-Bidar et al.	2015	Iran	Asian	358 / 372	45.6±7.6 / 44.7±8.5	RFLP-PCR	7
Shah et al.	2015	India	Asian	34/ 23	NR / NR	RFLP-PCR	5
Zhong et al.	2015	China	Asian	204 / 116	45.6±7.6 / 58.11±10.7	RFLP-PCR	6
Taneja et al.	2016	India	Asian	100 / 100	46.8±11.3 /39.34±11.12	RFLP-PCR	6
Yu et al.	2016	China	Asian	397 / 776	59.53±11.9 /59.54±11.9	Sequenom Mass Array SNP assay	8
Malik et al.	2017	India	Asian	100 / 100	51.2±8.79 / 45.02±11.0	RFLP-PCR	6
Rahmadhani et al.	2017	Malaysia	Asian	248 / 432	NR / NR	Mass spectrometry	7

Table 1 (continued)

Study author	Year	Country	Ethnicity	Total cases/control	Age case/control (Mean)	Genotyping method	Quality score
Rasheed et al.	2017	Egypt	African	180 / 150	43.2±6.5 / 44.3±4.1	Taq-Man	6
Angel et al.	2018	Chile	Mixed	138 / 172	60–79 / 60–79	RFLP-PCR	6
Gendy et al.	2018	Egypt	African	50 / 50	51.0±8.2 / 52.4±6.55	RFLP-PCR	5
Safar et al.	2018	United Arab Emirates	Asian	263 / 91	60.5±11.5 / 48.21±12.1	Taq-Man	6
Sarma et al.	2018	India	Asian	40 / 20	49.65±9.78 / 48.45±8.7	RFLP-PCR	5
Gnanaprakash et al.	2019	India	Asian	160 / 147	50.9±8.1 / 48.8±8.2	RFLP-PCR	6
Rodrigues et al.	2019	Brazil	Mixed	101 / 62	56 / 53	RFLP-PCR	5
Ma et al.	2019	China	Mixed	674 / 521	61.9 / 62.4±3.3	RFLP-PCR	8
Saxena et al.	2020	Saudi Arabia	Asian	440 / 440	48.10±8 / 45.68±9	RFLP-PCR	7
ApaI (rs7975232)							
Sanchis et al.	1999	India	Asian	89 / 100	53.1±9.80 / 48.9±9.6	RFLP-PCR	5
Ye et al.	2001	France	European	305 / 143	62±12 / 61±16	RFLP-PCR	6
Oh et al.	2002	USA	Mixed	242 / 1303	71.7±8. 6 / 68.8±9.2	RFLP-PCR	8
Malecki et al.	2003	Poland	European	308 / 240	59.8±9.2 / 54.0±15.1	RFLP-PCR	7
Dilmec et al.	2010	Turkey	European	72 / 169	57.1±10.8 / 56.1±6.8	RFLP-PCR	6
Al-Daghri et al.	2012	Saudi Arabia	Asian	368 / 259	51.5±8.6 / 44.1±9.9	Taq-Man	7
Leon et al.	2015	Mexico	Mixed	125 / 125	50.8±7.3 / 44.5±8.2	RFLP-PCR	6
Shab-Bidar et al.	2015	Iran	Asian	348 / 372	45.6±7.6 / 44.7±8.5	RFLP-PCR	7
Zhong et al.	2015	China	Asian	204 / 116	45.6±7.6 / 58.11±10.7	RFLP-PCR	6
Taneja et al.	2017	India	Asian	100/ 100	46.8±11.3 / 39.34±11.1	RFLP-PCR	6
Xia et al.	2017	China	Asian	242 / 100	76.8±11.8 / 75.8±11.2	RFLP-PCR	6
Rodrigues et al.	2019	Brazil	Mixed	101 / 62	56 / 53	RFLP-PCR	5
Ma et al.	2019	China	Asian	674 / 521	61.9 / 62.4±3.3	RFLP-PCR	8
Yasmeen et al.	2020	Pakistan	Asian	150 / 100	NR / NR	RFLP-PCR	6

NR, not reported; M, male; F, female;

Table 2 Distribution of genotype and allele among T2D patients and controls

Study author	T2D cases					Healthy control					P-HWE	MAF
	FF	Ff	ff	F	f	FF	Ff	Ff	F	f		
FokI (rs2228570)												
Malecki et al.	85	159	64	329	287	77	110	52	264	214	0/28	0/447
Bid et al.	38	60	2	136	64	80	79	1	239	81	≤0.001	0/253
Dong et al.	44	97	39	185	175	31	45	20	107	85	0/62	0/442
Al-Daghri et al.	213	133	22	559	177	129	111	19	369	149	0/46	0/287
Vedralova et al.	38	60	18	136	96	25	76	12	126	100	≤0.001	0/442
Mackawy et al.	66	30	34	162	98	44	11	5	99	21	≤0.001	0/175
Jia et al.	212	336	120	760	576	579	973	408	2131	1789	0/98	0/456
Shab-Bidar et al.	169	118	71	456	260	191	119	62	501	243	0	0/326
Zhong et al.	46	114	44	206	202	40	58	18	138	94	0/68	0/405
Angel et al.	24	96	40	144	176	53	75	32	181	139	0/56	0/434
Mahjoubi et al.	231	180	28	642	236	168	117	17	453	151	0/56	0/25
Maia et al.	46	42	12	134	66	38	47	15	123	77	0/94	0/385
Soroush et al.	49	44	12	142	68	65	36	6	166	48	0/73	0/224
Yu et al.	80	205	112	365	429	147	405	223	699	851	0/12	0/549
Bertoccini et al.	395	379	109	1169	597	378	359	93	1115	545	0/57	0/328
Rasheed et al.	17	57	106	91	269	11	47	92	69	231	0/15	0/77
Taneja et al.	3	36	61	42	158	29	39	32	97	103	0/02	0/515
Xia et al.	129	94	19	352	132	38	50	12	126	74	0/46	0/37
Angel et al.	28	86	24	142	134	53	81	38	187	157	0/5	0/456
Gendy et al.	16	26	8	58	42	32	15	3	79	21	0/49	0/21
Safar et al.	20	94	147	134	388	18	34	38	70	110	0/05	0/611
Sarma et al.	32	0	8	64	16	15	3	2	33	7	0/03	0/175
Gnanaprakash et al.	77	76	6	230	88	84	54	9	222	72	0/93	0/244
Hadi et al.	7	36	51	50	138	10	60	31	80	122	0/01	0/603
Pinho et al.	50	57	8	157	73	39	24	6	102	36	0/41	0/26
Rodrigues et al.	61	31	9	153	49	31	24	7	86	38	0/48	0/306
Ma et al.	237	394	43	868	480	344	161	16	849	193	0/58	0/185
Saxena et al.	74	270	96	418	462	86	259	95	431	449	≤0.001	0/51
Sattar et al.	46	91	13	183	117	53	36	11	142	58	0/2	0/29
Study author	**T2D cases**					**Healthy control**					**P-HWE**	**MAF**
	TT	**Tt**	**tt**	**T**	**t**	**TT**	**Tt**	**tt**	**T**	**t**		
TaqI (rs731236)												
Sanchis et al.	8	33	48	49	129	17	39	44	73	127	0/11	0/635

Table 2 (continued)

Study author	T2D cases					Healthy control					P-HWE	MAF
	FF	Ff	ff	F	f	FF	Ff	Ff	F	f		
Ye et al.	120	136	49	376	234	54	66	23	174	112	0/7	0/391
Oh et al.	93	108	41	294	190	503	581	219	1587	1019	0/02	0/391
Malecki et al.	138	140	30	416	200	92	117	31	301	179	0/51	0/372
Bid et al.	36	49	15	121	79	67	65	28	199	121	0/08	0/378
Dilmec et al.	33	25	14	91	53	69	81	19	219	119	0/51	0/352
Mukhopadhyaya et al.	23	12	5	58	22	7	25	8	39	41	0/11	0/512
Al-Daghri et al.	108	65	195	281	455	95	50	114	240	278	≤0.001	0/536
Vural et al.	51	46	3	148	52	35	49	16	119	81	0/86	0/405
Leon et al.	38	62	25	138	112	34	72	19	140	110	0/05	0/44
Shab-Bidar et al.	127	160	71	414	302	158	139	75	455	289	≤0.001	0/388
Maia et al.	45	46	9	136	64	49	39	12	137	63	0/33	0/315
Taneja et al.	36	54	10	126	74	50	37	13	137	63	0/15	0/315
Darraji et al.	78	95	27	251	149	15	44	16	74	76	0/13	0/506
Malik et al.	37	45	19	119	83	46	39	15	131	69	0/17	0/345
Xia et al.	224	18	0	466	18	86	14	0	186	14	0/45	0/07
Gendy et al.	19	24	7	62	38	23	20	7	66	34	0/44	0/34
Safar et al.	108	111	43	327	197	37	38	16	112	70	0/26	0/384
Sarma et al.	22	10	8	54	26	14	4	2	32	8	0/09	0/2
Gnanaprakash et al.	76	75	11	227	97	53	73	19	179	111	0/43	0/382
Rodrigues et al.	10	47	44	67	135	9	32	21	50	74	0/56	0/596
Ma et al.	269	372	33	910	438	333	172	16	838	204	0/26	0/195
Saxena et al.	146	196	98	488	392	134	237	69	505	375	0/03	0/426
Study author	**T2D cases**					**Healthy control**					**P-HWE**	**MAF**
	BB	**Bb**	**bb**	**B**	**b**	**BB**	**Bb**	**bb**	**B**	**b**		
BsmI (rs1544410)												
Speer et al.	7	22	20	36	62	26	66	46	118	158	0/78	0/572
Ye et al.	52	135	119	239	373	24	65	54	113	173	0/55	0/604
Oh et al.	49	107	86	205	279	253	590	460	1096	1510	0/01	0/579
Malecki et al.	35	142	131	212	404	32	116	92	180	300	0/62	0/625
Bid et al.	30	52	18	112	88	60	77	23	197	123	0/83	0/384
Mukhopadhyaya et al.	17	9	14	43	37	26	10	4	62	18	0/07	0/225
Al-Daghri et al.	105	201	62	411	325	114	95	50	323	195	≤0.001	0/376
Zhang et al.	3	83	218	89	519	1	14	85	16	184	0/62	0/92
Mackawy et al.	80	33	17	193	67	40	14	6	94	26	0/01	0/216

Table 2 (continued)

Study author	T2D cases					Healthy control					P-HWE	MAF
	FF	Ff	ff	F	f	FF	Ff	Ff	F	f		
Shab-Bidar et al.	106	211	41	423	293	146	189	37	481	263	0/03	0/353
Shah et al.	10	9	15	29	39	2	10	11	14	32	0/89	0/695
Zhong et al.	11	54	139	76	332	2	18	96	22	210	0/3	0/905
Taneja et al.	20	56	24	96	104	9	77	14	95	105	≤0.001	0/525
Yu et al.	354	43	0	751	43	698	75	3	1471	81	0/52	0/052
Malik et al.	79	16	5	174	26	40	22	38	102	98	≤0.001	0/49
Rahmadhani et al.	158	72	18	388	108	297	118	17	712	152	0/22	0/175
Rasheed et al.	72	74	34	218	142	57	52	41	166	134	≤0.001	0/446
Angel et al.	77	36	25	190	86	97	49	26	243	101	≤0.001	0/293
Gendy et al.	15	25	10	55	45	21	24	5	66	34	0/62	0/34
Safar et al.	67	118	78	252	274	33	38	20	104	78	0/15	0/428
Sarma et al.	12	23	5	47	33	10	6	4	26	14	0/12	0/35
Gnanaprakash et al.	70	62	28	202	118	52	73	22	177	117	0/65	0/397
Rodrigues et al.	16	49	36	81	121	9	33	20	51	73	0/43	0/588
Ma et al.	533	110	31	1176	172	443	63	15	949	93	≤0.001	0/089
Saxena et al.	320	94	26	734	146	317	89	34	723	157	≤0.001	0/178
Study author	**T2D cases**					**Healthy control**					**P-HWE**	**MAF**
	AA	**Aa**	**aa**	**A**	**a**	**AA**	**Aa**	**aa**	**A**	**a**		
ApaI (rs7975232)												
Sanchis et al.	22	42	25	86	92	22	47	31	91	109	0/6	0/545
Ye et al.	98	142	65	338	272	35	78	30	148	138	0/26	0/482
Oh et al.	84	92	66	260	224	487	552	264	1526	1080	≤0.001	0/414
Malecki et al.	71	153	84	295	321	60	124	56	244	236	0/6	0/491
Dilmec et al.	7	38	27	52	92	26	82	61	134	204	0/85	0/603
Al-Daghri et al.	148	172	48	468	268	101	106	52	308	210	0/01	0/405
Leon et al.	47	64	14	158	92	31	78	16	140	110	≤0.001	0/44
Shab-Bidar et al.	126	166	56	418	278	119	210	43	448	296	≤0.001	0/397
Zhong et al.	61	114	29	236	172	29	59	28	117	115	0/85	0/495
Taneja et al.	2	40	58	44	156	10	46	44	66	134	0/68	0/67
Xia et al.	19	92	131	130	354	13	38	49	64	136	0/2	0/68
Rodrigues et al.	60	33	8	153	49	38	22	2	98	26	0/57	0/209
Ma et al.	283	291	100	857	491	203	224	94	630	412	0/02	0/395
Yasmeen et al.	85	61	4	231	69	42	54	4	138	62	≤0.001	0/31

P-HWE, p value for Hardy–Weinberg equilibrium; MAF, minor allele frequency of control group

Meta-analysis of ApaI (rs7975232) polymorphism

There were 14 case-control studies with 3328 patients and 3710 controls regarding *ApaI* gene polymorphism and T2D. Three studies were conducted in Europe [29, 65, 67], eight studies were in Asia [35, 36, 39, 40, 44, 59, 71], and three studies were in American population [56, 63, 64]. The pooled results rejected any significant association in overall and subgroup analysis. The results of pooled ORs, heterogeneity and publication bias tests in different analysis models are shown in Table 3.

Evaluation of heterogeneity and publication bias

During the meta-analysis of *VDR* gene polymorphisms, evidence of substantial to moderate heterogeneity were detected. However, partial heterogeneity was resolved while the data were stratified by ethnicity. Publication bias was evaluated by funnel plot, Begg's test and Egger's test. Subsequently, there was no obvious evidence of asymmetry from the shapes of the funnel plots (Fig. 4), and all *P* values of Begg's test and Egger's test were > 0.05, which showed no evidences of publication biases.

Sensitivity analysis

The leave-one-out method was used in the sensitivity analysis to explore the effect of individual data on the pooled ORs. The significance of ORs was not altered through omitting any single study in the dominant model for *FokI, TaqI, BsmI* and *ApaI* SNPs, indicating that our results were statistically robust (Fig. 5).

Meta-regression analyses

We applied meta-regression analyses to find potential sources of heterogeneity among eligible publications according to years of population, ethnicity, and genotyping method (Table 4). The findings revealed that none of the expected heterogeneity parameters were the source of heterogeneity (Fig. 6).

Discussion

Here in this systematic review and meta-analysis study, we intended to attain with a clear and valid estimation of the associations between the *VDR* gene polymorphisms of *FokI* (rs2228570), *TaqI* (rs731236), *BsmI* (rs1544410), and *ApaI*(rs7975232) and T2D. The findings of meta-analysis on 47 case–control studies in the overall population indicated a significant association between *FokI,* and *BsmI* (only heterozygote model) polymorphisms and T2D, but not *TaqI* and *ApaI* polymorphisms. Moreover, the pooled results of subgroup analysis by ethnicity revealed significant associations between *FokI, TaqI*, and *BsmI* (heterozygote model in Asians) and *ApaI* (recessive model in mixed ethnicity) polymorphisms and T2D.

VDR has been established to be critically involved in the regulation of the endocrine system. As a consequence, it is a potential candidate gene for genetic evaluations of metabolic disorders. The function of the VD in the endocrine system is modulated through both genomic and non-genomic approaches [72]. In the genomic context, ligation of 1,25-dihydroxy vitamin D3 (1,25-(OH)2D3) to the cytosolic/nuclear*VDR*, which is a member of the steroid/thyroidhormone-receptor superfamily, leads to activation of other transcription factors that allow transcription of the corresponding genes [73]. Several studies have revealed that pancreatic β-cells express *VDR* on themselves [74]. On the other side, the non-genomic pathway is activated through a putative membrane *VDR*, which seems to account for the immediate effects of VD [75]. *VDR* gene is found on chromosome 12q13.11 and contains 14 exons. This gene possesses a large promoter region, enabling it to produce several tissue-specific transcripts [14, 76]. *VDR* has been shown to be expressed in various tissues, such as tissues that participate in the modulation of glucose metabolism like pancreatic cells and muscle [77, 78]. A number of SNPs, such as rs11574129 and rs739837, are found at the 3′-untranslated region (UTR) of *VDR* gene, a region involved in the controlling of gene expression, especially by the modification of mRNA stability. The *FokI* polymorphism is found within the 5′-end of the *VDR* gene and leads to T > C variation at translation start codon in exon 2 [79]. Moreover, *FokI, BsmI, ApaI* and *TaqI*, have been reported to influence on the insulin secretion [80] and sensitivity [81]. Therefore, *VDR* gene polymorphisms might be involved in the pathogenesis of T2D through modulating the secretory capacity of β-cells in the pancreas [70].

A vast majority of investigations has attempted to disclose the association between *VDR* gene polymorphisms and susceptibility to T2D in different ethnicities and populations. Nonetheless, the findings were in discrepancy with each other. Such conflicting results might be due to differences in experimental approaches, variations in diagnostic criterions of the patients, clinical heterogeneity, little statistical power, small sample sizes, and interactions between genetic background and environmental stimuli based on geographic differences. The previous meta-analysis published by Yu et al. in 2016 (in Chinese language) included 30 case-control studies and demonstrated that the *BsmI* polymorphism was associated with T2D weakly in two genetic models of Bb vs. bb and BB + Bb vs. bb. The subgroup analysis also resulted in finding associations. However, a strong association between *FokI* polymorphism and T2D was recognized, especially in Chinese population [82]. That notwithstanding, the necessity

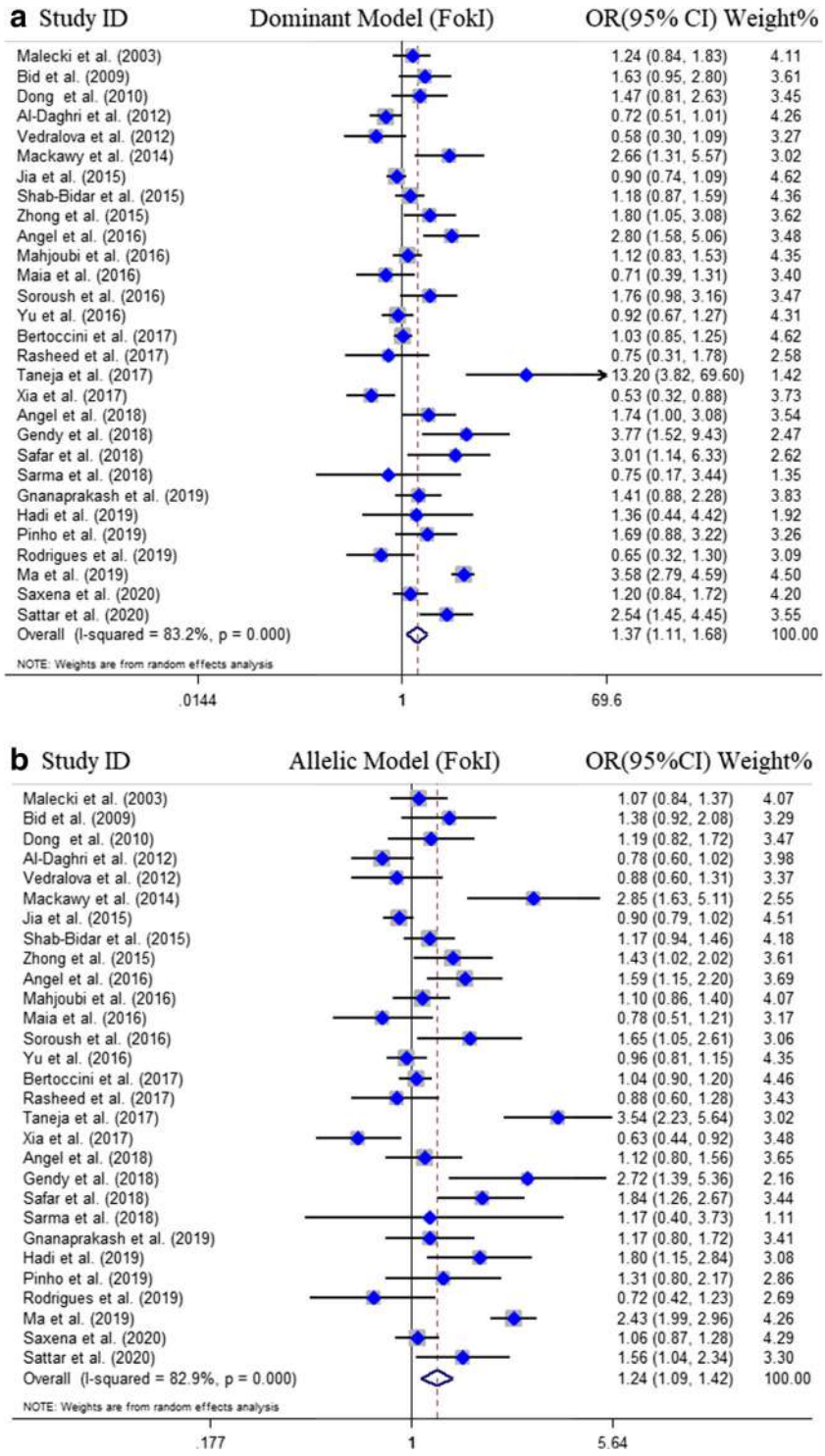

Fig. 2 Pooled OR and 95% CI of individual studies and pooled data for the association between *FokI* gene polymorphism and T2D in: A; dominant model and, B; allelic Model

was felt to perform a meta-analysis by including further original works to reach more valid and comprehensive approximation of *VDR* genetic polymorphisms and T2D risk. Our meta-analysis, however, included 47 publications in the final meta-analysis, involving 29 studies containing 7260 patients and 7771 controls for *FokI* polymorphism, 23 studies containing 4579 patients and 4815 controls for *TaqI* polymorphism, 25 studies containing 5334 patients and 6015 controls for *BsmI* polymorphism, and 14 studies containing 3328 patients and 3710 controls for *ApaI* polymorphism. It was found that *FokI* polymorphism in the overall analysis increased the susceptibility of T2D according to the dominant model (OR = 1.37), recessive model (OR = 1.10), allelic model (OR = 1.24), ff vs. FF model (OR = 1.36), and Ff vs. FF model

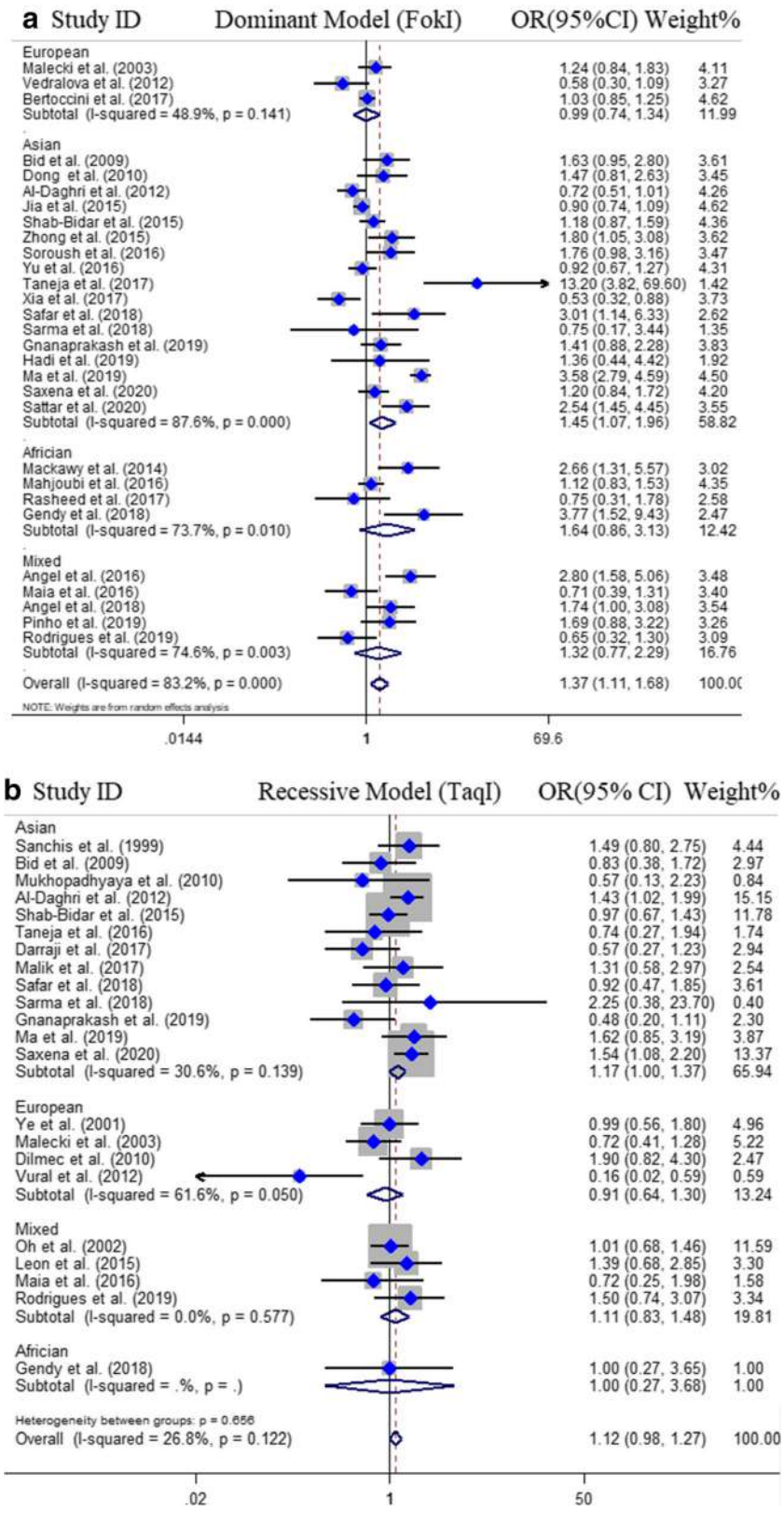

Fig. 3 Pooled odds ratio (OR) and 95% confidence interval of individual studies and pooled data for the association between *FokI, TaqI* genes polymorphisms and T2D in different ethnicity subgroups for A; dominant model (*FokI*), B; recessive model (*TaqI*)

(OR = 1.34). In addition, the heterozygote genotype of *BsmI* polymorphism increased the susceptibility of T2D. However, the overall analysis indicated that *TaqI* and *ApaI* were not genetic risk factors for T2D. Interestingly, a meta-analysis in 2016 indicated that *ApaI* (in the heterozygote model) was associated with

Table 3 Main results of pooled ORs in meta-analysis of Vitamin D Receptor gene polymorphisms in T2D patients

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	7260 / 7771	**1.37**	**1.11–1.68 (≤0.001)**	83.2	≤0.001	0.81	0.41	0.44	0.66
	Recessive model	7260 / 7771	**1.10**	**0.99–1.21 (0.06)**	46.5	0.004	0.19	0.85	0.24	0.81
	Allelic model	7260 / 7771	**1.24**	**1.09–1.42 (≤0.001)**	82.9	≤0.001	0.44	0.66	0.32	0.75
	ff VS. FF	7260 / 7771	**1.36**	**1.09–1.70 (≤0.001)**	61.8	≤0.001	0.06	0.95	0.35	0.73
	Ff vs. FF	7260 / 7771	**1.34**	**1.09–1.66 (≤0.001)**	81.8	≤0.001	0.46	0.64	0.39	0.69
European	Dominant model	1307 / 1182	0.99	0.74–1.34 (0.97)	48.9	0.14	- 0.52	0.60	−0.55	0.68
	Recessive model	1307 / 1182	1.08	0.85–1.37 (0.52)	0	0.584	0.52	0.60	0.60	0.65
	Allelic model	1307 / 1182	1.03	0.92–1.16 (0.61)	0	0.693	- 0.94	0.34	- 0.43	0.67
	ff vs. FF	1307 / 1182	1.11	0.85–1.44 (0.44)	0	0.969	- 1.57	0.11	- 2.63	0.23
	Ff vs. FF	1307 / 1182	0.96	0.65–1.40 (0.81)	63.2	0.066	- 0.52	0.60	- 0.49	0.70
Asian	Dominant model	4540 / 5464	**1.45**	**1.07–1.95 (0.01)**	87.6	≤0.001	−0.15	0.88	- 0.41	0.68
	Recessive model	4540 / 5464	**1.11**	**0.99–1.26 (0.08)**	61	≤0.001	- 0.35	0.72	- 0.41	0.68
	Allelic model	4540 / 5464	**1.31**	**1.07–1.60 (≤0.001)**	87.8	≤0.001	0.44	0.66	0.32	0.75
	ff vs. FF	4540 / 5464	**1.47**	**1.06–2.04 (0.02)**	71.6	≤0.001	- 0.35	0.72	- 0.34	0.73
	Ff vs. FF	4540 / 5464	**1.43**	**1.05–1.94 (0.02)**	86.8	≤0.001	−0.49	0.62	- 0.61	0.55
Mixed	Dominant model	614 / 563	1.32	0.77–2.29 (0.31)	74.6	0.003	- 0.98	0.32	- 1.27	0.29
	Recessive model	614 / 563	0.93	0.66–1.32 (0.69)	0	0.655	0.49	0.62	- 0.98	0.4
	Allelic model	614 / 563	1.09	0.81–1.46 (0.57)	60.5	0.038	- 0.98	0.32	- 1.40	0.25
	ff vs. FF	614 / 563	1.19	066–2.12 (0.56)	46	0.116	- 0.98	0.32	- 1.50	0.23
	Ff vs. FF	614 / 563	1.40	0.80–2.46 (0.23)	73.1	0.005	- 0.98	0.32	−1.61	0.20
African	Dominant model	799 /562	1.64	0.86–3.13 (0.13)	73.7	0.01	2.04	0.04	3.34	0.07
	Recessive model	799 /562	1.17	0.82–1.67 (0.38)	55.4	0.08	1.36	0.17	1.98	0.18
	Allelic model	799 /562	1.55	0.92–2.60(0.09)	82.8	0.001	1.36	0.17	3.12	0.08
	ff vs. FF	799 /562	1.80	0.76–4.28(0.18)	63.9	0.04	1.36	0.17	2.72	0.11
	Ff vs. FF	799 /562	1.42	0.83–2.43 (0.19)	53.5	0.09	2.04	0.04	2.27	0.15
TaqI (rs731236)										
Overall	Dominant model	4579/4815	1.01	0.81–1.27 (0.93)	78.4	≤0.001	−0.60	0.54	−0.79	0.43
	Recessive model	4579/4815	1.12	0.98–1.27(0.08)	26.8	0.12	−1.49	0.13	−1.57	0.13
	Allelic model	4579/4815	1.02	0.88–1.18 (0.82)	76	≤0.001	0.24	0.80	−0.88	0.39
	tt vs. TT	4579/4815	1.11	0.96–1.29 (0.13)	48.8	0.006	−0.52	0.60	−1.40	0.17
	Tt vs.TT	4579/4815	0.99	0.78–1.26 (0.75)	77.3	≤0.001	−0.66	0.50	−0.81	0.42
European	Dominant model	785 / 652	**0.77**	**0.61–0.97 (0.02)**	0	0.469	−0.68	0.49	−0.73	0.54
	Recessive model	785 / 652	0.91	0.64–1.30 (0.60)	61.6	0.050	0	1	−0.64	0.58

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)	
	Genetic model	Case/Control	OR	95% CI (p value)	I^2 (%)	P	Z	P	T	P
	Allelic model	785 / 652	0.82	0.63–1.06 (0.13)	54.9	0.084	0	1	- 0.39	0.73
	tt vs. TT	785 / 652	0.79	0.54–1.16 (0.22)	63.4	0.042	0	1	- 0.86	0.48
	Tt VS.TT	785 / 652	**0.78**	**0.61–0.99 (0.04)**	0	0.751	−0.68	0.49	- 1.45	0.28
Asian	Dominant model	3176 / 2523	0.99	0.73–1.35 (0.71)	69.5	≤0.001	- 1.10	0.27	- 1.28	0.22
	Recessive model	3176 / 2523	**1.17**	**1–1.37 (0.05)**	30.6	0.13	- 1.48	0.13	−1.45	0.18
	Allelic model	3176 / 2523	1.05	0.85–1.30 (0.64)	81.2	≤0.001	0.14	0.89	−1.24	0.24
	tt vs. TT	3176 / 2523	**1.21**	**1.01–1.45 (0.03)**	58.4	≤0.001	- 0.54	0.58	- 1.31	0.22
	Tt vs.TT	3176 / 2523	1.03	0.72–1.48 (0.85)	83.8	≤0.001	−0.96	0.33	- 1.30	0.22
Mixed	Dominant model	568 / 1590	1.02	0.81–1.29 (0.84)	0	0.77	1.36	0.17	0.94	0.44
	Recessive model	568 / 1590	1.11	0.83–1.48 (0.49)	0	0.57	0	1	0.29	0.80
	Allelic model	568 / 1590	1.04	0.89–1.22 (0.59)	0	0.73	1.36	0.17	1.40	0.29
	tt vs. TT	568 / 1590	1.07	0.76–1.50 (0.71)	0	0.74	0.68	0.49	0.78	0.51
	Tt vs.TT	568 / 1590	1.01	0.79–1.30 (0.92)	0	0.68	0.68	0.49	0.41	0.71
BsmI (rs1544410)										
Overall	Dominant model	5334 / 6015	1.09	0.90–1.31 (0.39)	63.3	≤0.001	−0.67	0.50	−0.26	0.79
	Recessive model	5334 / 6015	1.02	0.83–1.25 (0.80)	56.5	≤0.001	−0.03	0.97	−0.55	0.59
	Allelic model	5334 / 6015	1.01	0.87–1.18 (0.88)	76.7	≤0.001	−0.69	0.48	−0.70	0.49
	bb vs. BB	5334 / 6015	1.15	0.98–1.34 (0.08)	42.2	0.01	−0.87	0.38	0.38	0.70
	Bb vs. BB	5334 / 6015	**1.17**	**1.05–1.31 (≤0.001)**	47.6	≤0.001	−0.50	0.62	0.29	0.77
European	Dominant model	663/ 521	1.12	0.78–1.62 (0.53)	0	0.80	−0.68	0.49	0.45	0.69
	Recessive model	663/ 521	1.15	0.89–1.49 (0.27)	0	0.79	1.36	0.17	3.34	0.7
	Allelic model	663/ 521	1.11	0.92–1.33 (0.27)	0	0.69	−0.68	0.49	−0.58	0.62
	bb vs. BB	663/ 521	1.20	0.81–1.80 (0.36)	0	0.72	−0.68	0.49	−0.42	0.71
	Bb vs. BB	663/ 521	1.06	0.71–1.56 (0.78)	0	0.89	0.68	0.49	1.01	0.41
Asian	Dominant model	3830 /3697	1.06	0.80–1.41 (0.66)	75.8	≤0.001	−1.21	0.22	−1.11	0.29
	Recessive model	3830 /3697	0.96	0.68–1.35 (0.81)	69.5	≤0.001	−1.21	0.22	−2.25	0.04
	Allelic model	3830 /3697	0.96	0.75–1.22 (0.71)	84.4	≤0.001	−1.37	0.17	−1.79	0.09
	bb vs. BB	3830 /3697	1.23	1–1.52 (0.05)	57.6	0.003	−1.34	0.18	−2.21	0.05
	Bb vs. BB	3830 /3697	**1.24**	**1.09–1.41 (≤0.001)**	64.2	≤0.001	−0.05	0.95	−0.44	0.66
Mixed	Dominant model	481 / 1537	0.96	0.73–1.27 (0.78)	0	0.95	0.52	0.60	0.93	0.52
	Recessive model	481 / 1537	1.06	0.82–1.37 (0.65)	0	0.82	1.57	0.11	2.05	0.28
	Allelic model	481 / 1537	1.01	0.85–1.19 (0.93)	0	0.89	0.52	0.60	2.61	0.23
	bb vs. BB	481 / 1537	1.02	0.73–1.42 (0.91)	0	0.84	0.52	0.60	1.48	0.37
	Bb vs. BB	481 / 1537	0.92	0.67–1.25 (0.58)	0	0.98	0.52	0.60	1.13	0.46

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)	
	Genetic model	Case/Control	OR	95% CI (p value)	I^2 (%)	P	Z	P	T	P
African	Dominant model	360 / 272	1.09	0.76–1.56 (0.64)	0	0.45	0.52	0.60	0.30	0.81
	Recessive model	360 / 272	1.03	0.347–2.27 (0.94)	50.5	0.13	0.52	0.60	0.34	0.79
	Allelic model	360 / 272	1.09	0.72–1.67 (0.67)	56.5	0.01	1.57	0.11	0.92	0.52
	bb vs. BB	360 / 272	0.91	0.54–1.51 (0.71)	49.8	0.13	1.57	0.11	1.30	0.41
	Bb vs. BB	360 / 272	1.18	0.79–1.77 (0.40)	0	0.89	−0.52	0.60	−0.16	0.90
ApaI (rs7975232)										
Overall	Dominant model	3328 / 3710	0.90	0.80–1.02 (0.09)	30.6	0.13	−0.14	0.89	−0.40	0.69
	Recessive model	3328 / 3710	1.05	0.91–1.20 (0.52)	48.8	0.02	−1.92	0.05	−1.98	0.07
	Allelic model	3328 / 3710	0.97	0.87–1.09 (0.64)	51.2	0.02	−1.65	1	−1.63	0.13
	aa vs. AA	3328 / 3710	0.98	0.83–1.15(0.60)	46.3	0.02	−0.81	0.42	−1.31	0.21
	Aa vs. AA	3328 / 3710	0.89	0.78–1.01 (0.06)	19.5	0.24	0.27	0.78	0.35	0.73
European	Dominant model	685/ 552	0.95	0.70–1.28 (0.73)	45.7	0.15	0.52	0.60	0.52	0.69
	Recessive model	685/ 552	1.12	0.85–1.50 (0.41)	0	0.83	−0.52	0.60	−1.48	0.37
	Allelic model	685/ 552	1.03	0.86–1.22 (0.77)	8.7	0.33	−0.52	0.60	0.10	0.93
	aa vs. AA	685/ 552	1.09	0.76–1.59 (0.63)	2.2	0.36	0.52	0.60	0.28	0.82
	Aa vs. AA	685/ 552	0.91	0.66–1.24 (0.54)	43.4	0.17	0.52	0.60	0.63	0.64
Asian	Dominant model	2175 / 1668	0.87	0.75–1.01 (0.06)	26.2	0.22	0.19	0.85	−0.25	0.81
	Recessive model	2175 / 1668	0.92	0.77–1.10 (0.34)	59.9	0.01	−1.32	0.18	−1.75	0.15
	Allelic model	2175 / 1668	0.93	0.79–1.09 (0.38)	55	0.03	−1.32	0.18	−1.38	0.23
	aa vs. AA	2175 / 1668	0.83	0.67–1.04 (0.10)	48.4	0.05	−1.32	0.18	−1.36	0.24
	Aa vs. AA	2175 / 1668	0.90	0.76–1.05 (0.17)	28.5	0.20	0.56	0.57	0.65	0.55
Mixed	Dominant model	468 / 1490	0.98	0.76–1.25 (0.85)	58.4	0.09	0.52	0.60	−0.73	0.60
	Recessive model	468 / 1490	1.39	1.03–1.87 (0.03)	0	0.45	−0.52	0.60	−0.28	0.82
	Allelic model	468 / 1490	1.03	0.74–1.44 (0.86)	60.9	0.01	−0.52	0.60	−0.54	0.68
	aa vs. AA	468 / 1490	1.30	0.92–1.83 (0.13)	44.7	0.16	−0.52	0.60	−0.29	0.81
	Aa vs. AA	468 / 1490	0.86	0.65–1.12 (0.25)	26.8	0.25	−0.52	0.60	−0.63	0.64

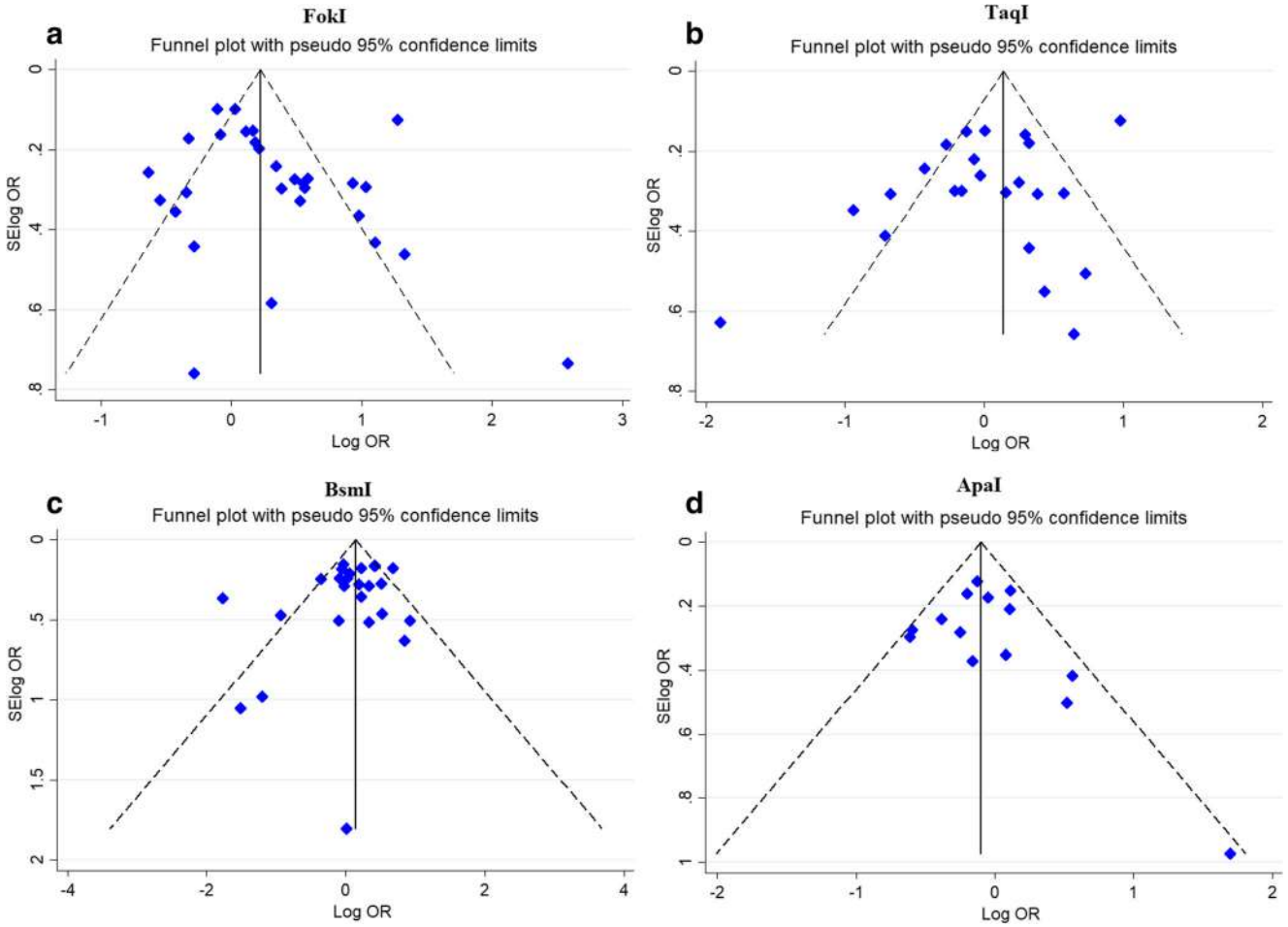

Fig. 4 Begg's funnel plot for publication bias test. A; Dominant Model *FokI*, B; Dominant Model *TaqI*, C; Dominant Model *BsmI,* D; Dominant Model *ApaI*. Each point represents a separate study for the indicated association

decreased risk of T2D in coronary artery disease patients [83].

We performed the subgroup analysis based on ethnicity of the patients in each study. *FokI* polymorphism was associated with increased T2D susceptibility only in Asians, but not Europeans and Africans. Even though *TaqI* polymorphism was not associated with T2D susceptibility in the overall analysis, but the subgroup analysis revealed that this polymorphism of *VDR* gene in some genetic models decrease and in some increase the susceptibility of T2D. The Bb vs. BB genotype of *BsmI* was only associated with T2D in Asian population. Meta-regression analyses indicated that ethnicity (as well as the publication year and genotyping method) was not the source of heterogenicity in all four polymorphisms.

This meta-analysis may subject to a number of limitations. First, we included English-written studies, hence it might subject to language bias. Second, little sample size did not allow a powerful conclusion of the results. Third, we did not evaluate a number of *VDR* gene SNPs that might act in interaction with environmental factors to determine the final outcome of T2D pathogenicity. Fourth, a degree of heterogenicity was observed among the studies that might stem largely from, ethnicity of participants, year of publication, genotyping methods which used for assessment of gene polymorphism, age, clinical heterogeneity (selection of patients, staging), unreported and unknown study characteristics and many other factors which we are not able to attenuate their impact on final analysis. Therefore, for finding any sources of heterogeneity and attenuating their effects, we conducted subgroup analysis and weighted meta-regression. Collectively, the results of meta-regression showed that none of the parameters, including publication year, ethnicity, and genotyping methods were the expected source of heterogeneity. However, subgroup analysis reduced heterogeneity and explained part of the observed heterogeneity in some subgroups. Furthermore, the other way of dealing with statistical heterogeneity, which we used in our analysis, was to incorporate "Random" term to account for it in a random-effects. Random effect model typically produces more conservative estimates of the significance of a result (a wider confidence interval). As it gives proportionately higher weights to smaller studies and lower weights to larger studies than fixed effect analysis.

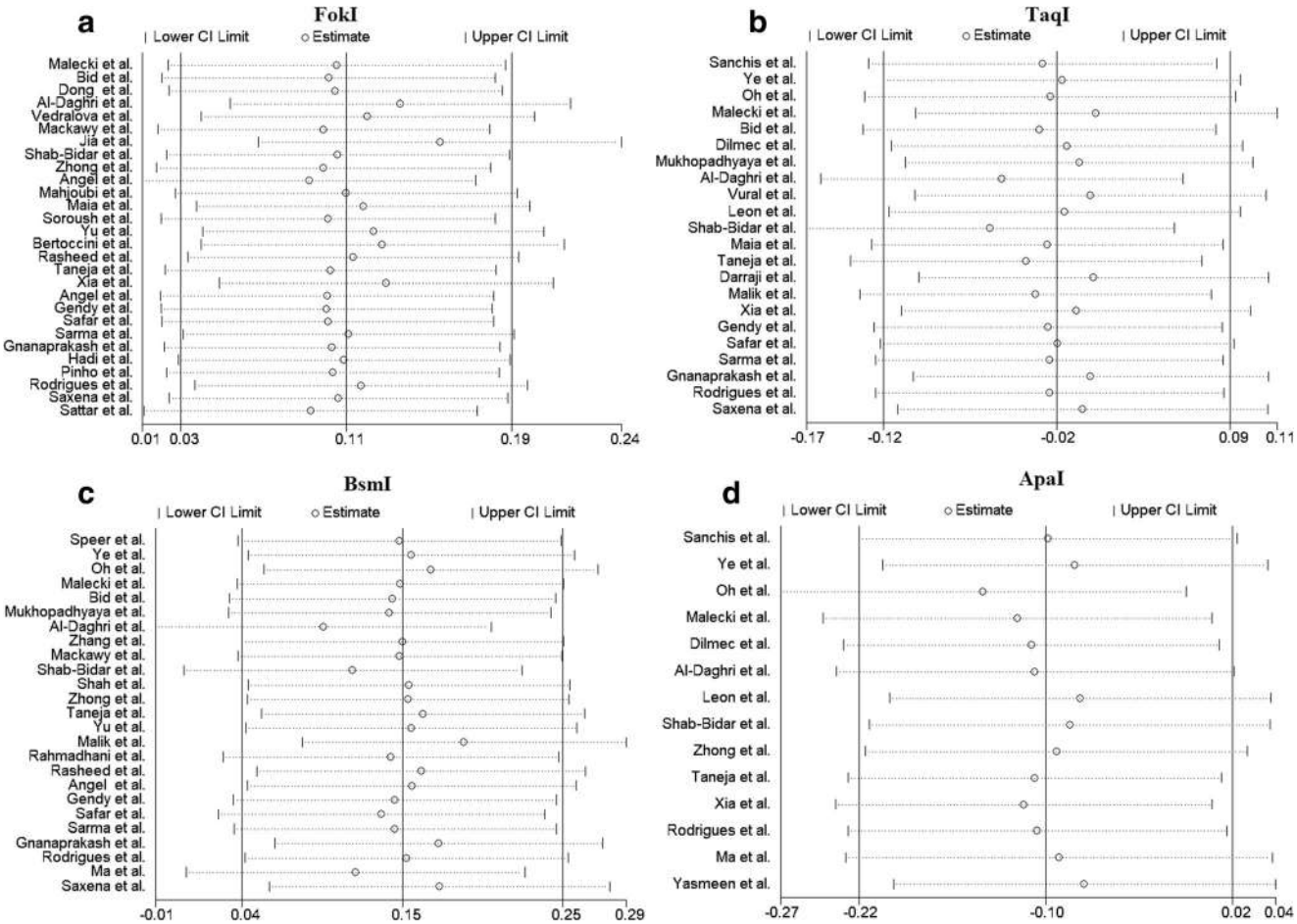

Fig. 5 Sensitivity analysis in present meta-analysis investigates the SNPs of *VDR* contribute to susceptibility of T2D (A, *FokI*; B, *TaqI*; C, *BsmI*; D, *ApaI*)

Conclusion

In consideration of all, this was a systematic review and meta-analysis of 47 case–control association studies to test for the exact estimation of the associations between the *VDR* gene SNPs and susceptibility of T2D. The results of the meta-analysis demonstrated that *FokI* polymorphism in the overall analysis increased the susceptibility of T2D according to the dominant model, recessive model, allelic model, homozygote model, and heterozygote model. In addition, the heterozygote genotype of *BsmI* polymorphism increased the susceptibility of T2D. However, the overall analysis indicated that *TaqI* and *ApaI* were not genetic risk factors for susceptibility of T2D.

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Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Table 4 Meta-regression analyses of potential source of heterogeneity

Heterogeneity Factor		Coefficient	SE	T	P value	95% CI	
						UL	LL
FokI (rs2228570)							
Publication Year	Dominant model	0.017	0.028	0.61	0.54	- 0.041	0.076
	Recessive model	0.014	0.022	0.65	0.52	−0.031	0.060
	Allelic model	0.018	0.020	0.93	0.35	−0.022	0.60
	ff vs. FF	0.022	0.034	0.64 64	0.52	−0.048	0.093
	Ff vs. FF	0.030	0.028	1.07	0.295	−0.027	0.088
Ethnicity	Dominant model	0.041	0.098	0.42	0.68	−0.161	0.244
	Recessive model	−0.038	0.080	−0.48	0.63	−0.204	0.127
	Allelic model	−0.004	0.070	−0.06	0.95	−0.148	0.139
	ff vs. FF	−0.011	0.122	−0.09	0.92	−0.262	0.239
	Ff vs. FF	−0.004	0.101	−0.05	0.96	−0.213	0.203
Genotyping Methods	Dominant model	−0.230	0.171	−1.34	0.19	−0.583	0.122
	Recessive model	−0.052	0.127	−0.42	0.68	−0.314	0.208
	Allelic model	−0.136	0.120	−1.13	0.26	−0.384	0.111
	ff vs. FF	−0.260	0.198	−1.31	0.20	−0.666	0.146
	Ff vs. FF	−0.299	0.171	−1.74	0.094	−0.652	0.054
TaqI (rs731236)							
Publication Year	Dominant model	0.007	0.018	0.41	0.68	−0.030	0.045
	Recessive model	0.005	0.0122	0.48	0.63	−0.019	0.031
	Allelic model	0.005	0.12	0.41	0.68	−0.020	0.030
	tt vs. TT	0.006	0.019	0.31	0.76	−0.035	0.047
	Tt vs.TT	0.008	0.018	0.47	0.64	−0.029	0.046
Ethnicity	Dominant model	−0.015	0.133	−0.12	0.90	−0.294	0.263
	Recessive model	−0.017	0.102	−0.17	0.866	−0.230	0.195
	Allelic model	−0.005	0.091	−0.05	0.95	−0.195	0.185
	tt vs. TT	−0.031	0.154	−0.20	0.84	−0.353	0.291
	Tt vs.TT	−0.009	0.134	−0.07	0.94	−0.288	0.270
Genotyping Methods	Dominant model	−0.141	0.225	−0.63	0.535	−0.609	0.326
	Recessive model	−0.148	0.212	−0.70	0.49	−0.591	0.293
	Allelic model	−0.159	0.156	−1.02	0.32	−0.484	0.165
	tt vs. TT	−0.331	0.295	−1.12	0.27	−0.947	0.284
	Tt vs.TT	−0.078	0.227	−0.35	0.73	−0.552	0.394
BsmI (rs1544410)							
Publication Year	Dominant model	−0.010	0.018	−0.55	0.58	−0.048	0.028
	Recessive model	−0.006	0.019	−0.35	0.72	−0.047	0.033
	Allelic model	−0.009	0.017	−0.56	0.58	−0.045	0.026
	bb vs. BB	−0.005	0.018	−0.31	0.75	−0.043	0.032
	Bb vs. BB	−0.003	0.014	−0.21	0.83	−0.034	0.027
Ethnicity	Dominant model	0.008	0.105	0.08	0.93	−0.210	0.226
	Recessive model	0.037	0.122	0.30	0.76	−0.217	0.291
	Allelic model	0.053	0.098	0.55	0.58	−0.149	0.256
	bb vs. BB	−0.083	0.105	−0.80	0.43	−0.302	0.134
	Bb vs. BB	−0.028	0.085	−0.33	0.74	−0.206	0.149
Genotyping Methods	Dominant model	0.098	0.134	0.73	0.47	−0.179	0.376
	Recessive model	−0.033	0.168	−0.20	0.84	−0.383	0.315
	Allelic model	0.009	0.129	0.08	0.94	−0.257	0.276
	bb vs. BB	0.156	0.161	0.97	0.34	−0.178	0.491
	Bb vs. BB	0.094	0.101	0.93	0.36	−0.115	0.304
ApaI (rs7975232)							
Publication Year	Dominant model	−0.009	0.010	−0.96	0.35	−0.031	0.012
	Recessive model	−0.008	0.015	−0.55	0.59	−0.041	0.024
	Allelic model	−0.005	0.009	−0.62	0.55	−0.025	0.014
	aa vs. AA	−0.010	0.018	−0.53	0.60	−0.051	0.031
	Aa vs. AA	−0.003	0.010	−0.35	0.73	−0.027	0.019
Ethnicity	Dominant model	0.061	0.088	0.70	0.49	−0.131	0.254
	Recessive model	0.178	0.130	1.37	0.19	−0.106	0.463
	Allelic model	0.064	0.080	0.80	0.44	−0.110	0.238
	aa vs. AA	0.181	0.156	1.16	0.27	−0.160	0.523
	Aa vs. AA	−0.025	0.095	−0.27	0.79	−0.233	0.182
Genotyping Methods	Dominant model	0.058	0.257	0.23	0.82	−0.502	0.619

Table 4 (continued)

Heterogeneity Factor		Coefficient	SE	T	P value	95% CI	
						UL	LL
	Recessive model	−0.615	0.331	−1.86	0.08	−1.338	0.106
	Allelic model	−0.175	0.220	−0.80	0.44	−0.656	0.304
	aa vs. AA	−0.508	0.407	−1.25	0.23	−1.39	0.379
	Aa vs. AA	0.240	0.221	1.09	0.29	−0.242	0.723

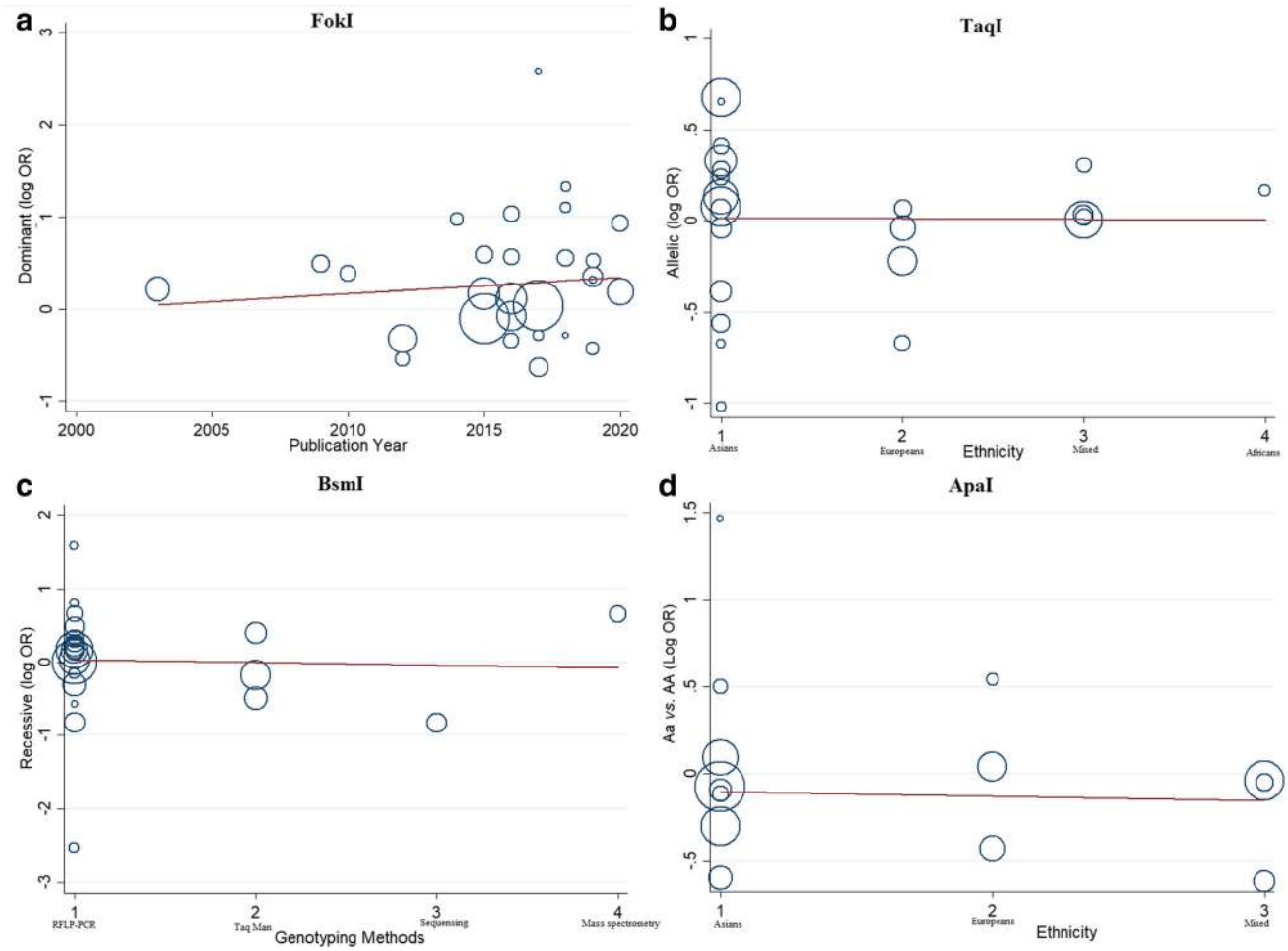

Fig. 6 Meta-regression plots of the association between *VDR* gene polymorphism and T2D based on; A: publication year, B: ethnicity, C: genotyping methods, D: ethnicity

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