Original Article

The genetic polymorphisms in vitamin D receptor and the risk of type 2 diabetes mellitus: an updated meta-analysis

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Background and Objectives: Vitamin D receptor (VDR) genetic polymorphisms are considered to be associated with type 2 diabetes mellitus (T2DM), but this is inconclusive. The aim of this study is to quantify the association between polymorphisms of *Bsm*I and *Fok*I in the VDR gene and T2DM risk through literature review. **Methods and Study Design:** Original articles published from 1999 to June 2014 were discovered through PubMed, ISI Web of Science, China National Knowledge Infrastructure, Chinese Wanfang Database, and the Chinese Biomedical Literature Database. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated with software STATA version 12.0. **Results**: Twenty-three articles containing 30 case-control studies were included. The association between the *Bsm*I polymorphism and T2DM was weak in two genetic models (Bb vs bb and BB+Bb vs bb). The subgroup analysis showed that this association was only found in the studies with a small sample size (<200). A strong association between *Fok*I polymorphism and T2DM indicated that this gene polymorphism was possibly a risk factor for T2DM (ff vs FF: OR=1.57, 95% CI: 1.28-1.93, p<0.001; Ff vs FF: OR=1.54, 95% CI: 1.31-1.81, p<0.001; ff+Ff vs FF: OR=1.57, 95% CI: 1.35-1.83, p<0.001), especially in Chinese populations. **Conclusion:** More reliable conclusions about associations between VDR genetic polymorphisms and T2DM will depend on studies with larger sample size and by ethnicity.

Key Words: vitamin D receptor, type 2 diabetes mellitus, genetic polymorphism, association, meta-analysis

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies caused by defects in insulin secretion and insulin action. Diabetes mellitus, especially type 2 diabetes mellitus (T2DM) is one of the most prevalent endocrine diseases. More than 415 million people worldwide suffer from type 2 diabetes mellitus.[1] Along with the disease progress, T2DM could induce many chronic complications such as retinopathy, renal failure, diabetic foot, nerve damage and cardiovascular disease.

Many investigations indicate that genetic predisposition plays a crucial role in the development of T2DM[2] although its manifestation is highly dependent on environmental factors. Many genes have been associated with T2DM, including TCF7L2,[3] CD36,[4] and WFS1.[5] Epidemiological studies indicate that vitamin D deficiency is widespread in those with diabetes.[6] Vitamin D supplements in early life lowers the risk of T2DM in adulthood.[7] The activated form of vitamin D, 1, 25-$(OH)_2D_3$, can enhance pancreatic β-cell function, protect β-cell from detrimental immune attack, improve insulin receptor sensitivity, and diminish insulin resistance. For these functions, active vitamin D needs to bind with the intracellular vitamin D receptor (VDR). Therefore, the expression of the VDR gene might be involved in the pathogenesis and progression of T2DM.

Frequent VDR gene polymorphisms have been reported to be associated with a variety of physiological and pathological phenotypes in many populations. Up to present, *Fok*I (rs10735810, in exon 2) and *Bsm*I (rs1544410, in intron 8) the two single nucleotide polymorphisms (SNPs) have been widely investigated and been found associated with T2DM in different ethnic populations. However, the published results are not consistent. Considering the isolated individual studies may have not enough statistical power to ascertain the association between VDR polymorphisms and T2DM, several meta-analyses have been performed to reveal the association between allelic variants of VDR and T2DM. However, the terminology describing the genotype of VDR in different papers is confusing because of the different methods applied on SNP analysis. Misnomers will lead to

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misunderstanding and erroneous interpretation on data. Therefore, it is crucial to have a unified expression of the allelic gene before a meta-analysis.

In this article, we selected the two most controversial VDR gene loci, namely *Bsm*I and *Fok*I sites, using the initial letter of the restriction enzyme to name the different alleles, the capital letter for absence of the restriction enzyme site, whereas a lower case letter indicates its presence. Then, the data were gathered from the different studies, and a comprehensive meta-analysis was carried out to evaluate the association between T2DM susceptibility and the genetic polymorphisms of VDR.

METHODS

Literature and search strategy

All the original literature from 1999 to June 2014 on the association of VDR and T2DM were identified through computer-based searches from the following databases, PubMed, ISI Web of Science, CNKI (China National Knowledge Infrastructure), Chinese Wanfang Database, and Chinese Biomedical Literature Database. The searching keywords were as follows: vitamin D receptor, VDR, *Fok*I, *Bsm*I, T2DM, NIDDM, polymorphism, genotype. Besides, the references of the original literatures and the related articles were also searched for potential complementary studies.

Inclusion criteria and exclusion criterion

The studies involved in this meta-analysis all met the following criteria: (1) original article about the association of VDR polymorphisms (*Fok*I and *Bsm*I) with T2DM risk, (2) case-control study, (3) performed in a human population, (4) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); (5) published in Chinese and English. Accordingly, the following exclusion criteria were also considered: (1) without healthy population as control subjects, (2) abstracts, reviews, and repeated publications, (3) no exact genotype frequency, (4) apart from T2DM, the cases also suffered from other diseases (such as cardiovascular diseases, osteoporosis, psoriasis and so on).

Data extraction and quality assessment

In our study, the contents and quality of the included studies were checked and assessed by two independent authors (Fei Yu and Lingling Cui) using the method reported by Xu et al[8] and reached conformity on all items through consultation. According to the recommendations of the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines[8] and other relevant meta-analytic papers, the following information was extracted from the selected literatures: year of publication, name of first author, region/country where the study was performed, ethnicity and region of population, gender ratios, mean age with standard deviation or age range of subjects, the source of the controls, genotype distribution in cases and controls, genotyping methods and diagnostic criteria. If the same study data was used by more than one publication, the data were only collected from the largest sample size or a more authoritative scientific journal. According to the "extended quality score" developed by Xu[8] et al each of the included studies was categorized as 'high', 'median' or 'poor' quality on the basis of its scores of eleven items such as the type of study design, sample size, disease-diagnostic criteria, and so on.

Statistical analysis

The combined odds ratios (ORs) together with their corresponding 95% confidence intervals (95% CIs) were calculated to assess the strength of association between the polymorphism of VDR gene and T2DM risk for two polymorphisms. For the polymorphism *Fok*I, the codominant model (ff vs FF, Ff vs FF), the dominant model (ff+Ff vs FF) and the recessive model (ff vs FF+Ff) were estimated. Similarly, for the polymorphism BsmI, the codominant model (BB vs bb, Bb vs bb), the dominant model (BB+Bb vs bb) and the recessive model (BB vs Bb+bb) were estimated. To find out the possible confounding factors which might impact the results of the published reports, we performed further analysis by Meta-regression and subgroup analysis based on ethnicity, sample size (the sum of the case and control), match (by age, gender, region, and ethnicity), Hardy Weinberg equilibrium (HWE) and quality of the articles.

Heterogeneity assumption was examined by the chi-square based on *Q*-test. The pooled OR estimation of each study was calculated with a random-effect model using the DerSimonian and Laird method when $p<0.10$, otherwise with a fixed-effect model using the Mantel–Haenszel method.[9] Publication bias was evaluated through the Begg's test, the Egger's Asymmetry test, and visual inspection of funnel plots, in which the standard error was plotted against the Log (OR) to form a simple scatterplot. The distribution of genotypes in controls of each individual population was tested for a departure from HWE by using online software (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The sensitive analysis was performed by omitting one study at a time to assess the stability of the meta-analysis results. The unchanged pooled OR implies the stable result.

The statistical analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX). All the p values were for a two-sided test and $p<0.05$ was considered as statistically significant.

RESULTS

Characteristics of the eligible studies

A total of 294 publications were chosen from the five electronic databases. Then, 240 reports were excluded as they were not related to the association of VDR polymorphisms and type 2 diabetes mellitus by screening the titles and reading the abstracts. Examined the full-text of the remaining 54 potential articles, there were 4 duplicated results,[10-13] 10 reviews or comments and 6 articles studied on *Apa*I and *Taq*I were excluded. In the remaining 34 articles, 3 articles were excluded for omitting healthy control group,[14-16] 1 article was about the early-onset T2MD,[17] and another 7 articles were excluded because of the cases were combined with other diseases. Therefore, only 23 eligible articles (8 in English and 15 in Chinese) involving 30 independent case-control studies were qualified for this meta-analysis on the association between VDR polymorphism (*Bsm*I and *Fok*I) and T2DM risk. The detailed steps of literature search are shown in Fig-

ure 1.

There were 18 articles studied on the *Bsm*I polymorphisms including 2757 cases and 3517 controls, and 12 articles studied on the *Fok*I polymorphisms including 2218 cases and 1859 controls. In the 18 articles on the *Bsm*I polymorphisms, there were two "high" quality studies, two "poor" quality studies, and fourteen "middle" quality studies. One study was considered as "high" quality, while all other studies on the *Fok*I polymorphisms were categorized as "middle" quality. The detailed characteristic and genotype allele distributions for each case-control study were listed in Table 1 & 2, including first author, publication year, reference, original country, ethnicity, gender, age, genotype distribution, HWE test of controls and the quality level of studies.

Overall and subgroup meta-analysis results

*Bsm*I

Overall, marginal significant associations with T2DM risk were found for Bb vs bb (OR=1.36, 95% CI: 1.02-1.83, p=0.038) and BB+Bb vs bb (OR=1.36, 95% CI: 1.00-1.84, p=0.049). Whereas no significant associations were observed for BB vs bb (OR=1.01, 95% CI: 0.67-1.52, p=0.956) and BB vs Bb+bb (OR=0.93, 95% CI: 0.65-1.33, p=0.692) (Table 4, Figure 2). Because of significant heterogeneity between studies for all contrast model (p<0.05), a random-effect model was used (Figure 2). The meta-regression was performed to search the source of heterogeneity focusing on the possible factors, such as ethnicity, sample size, matching, HWE and quality of the articles. The results of meta-regression showed that ethnicity and sample size were the possible factors of the heterogeneity (p<0.05, Table 3). Thus, a further analysis was performed on data stratified by ethnicity and sample size, in which Indian subjects were classified as Caucasians. Significantly increased susceptibility of T2DM was only found for VDR *Bsm*I polymorphism among the studies with small sample size (n<200) in 2 genetic models (Bb vs bb: OR=2.12, 95% CI: 1.24-3.62, p=0.006; BB+Bb vs bb: OR=2.38, 95% CI: 1.33-4.25, p=0.003, respectively). However, we failed to detect any association between the VDR *Bsm*I polymorphism and T2MD in the subgroup analysis by ethnicity in all genetic models (Table 4, Figure 2).

*Fok*I

Significant associations between gene models and T2DM were detected for three genetic models (ff vs FF: OR=1.57, 95% CI: 1.28-1.93, p<0.001; Ff vs FF: OR=1.54, 95% CI: 1.31-1.81, p<0.001; ff+Ff vs FF: OR=1.57, 95% CI: 1.35-1.83, p<0.001, respectively), and marginal significant association were found for ff vs FF+Ff (OR=1.16, 95% CI: 1.00-1.36, p=0.055) (Table 4, Figure 3). Due to the lack of heterogeneity among the included studies for all contrast model (p>0.05), a fixed-effect model was used (Figure 3). Further analysis by meta-regression revealed that ethnicity and sample size might affect the overall results (Table 3). Interestingly, a significantly increased susceptibility was only found in T2DM patients among Chinese for all genetic models (ff

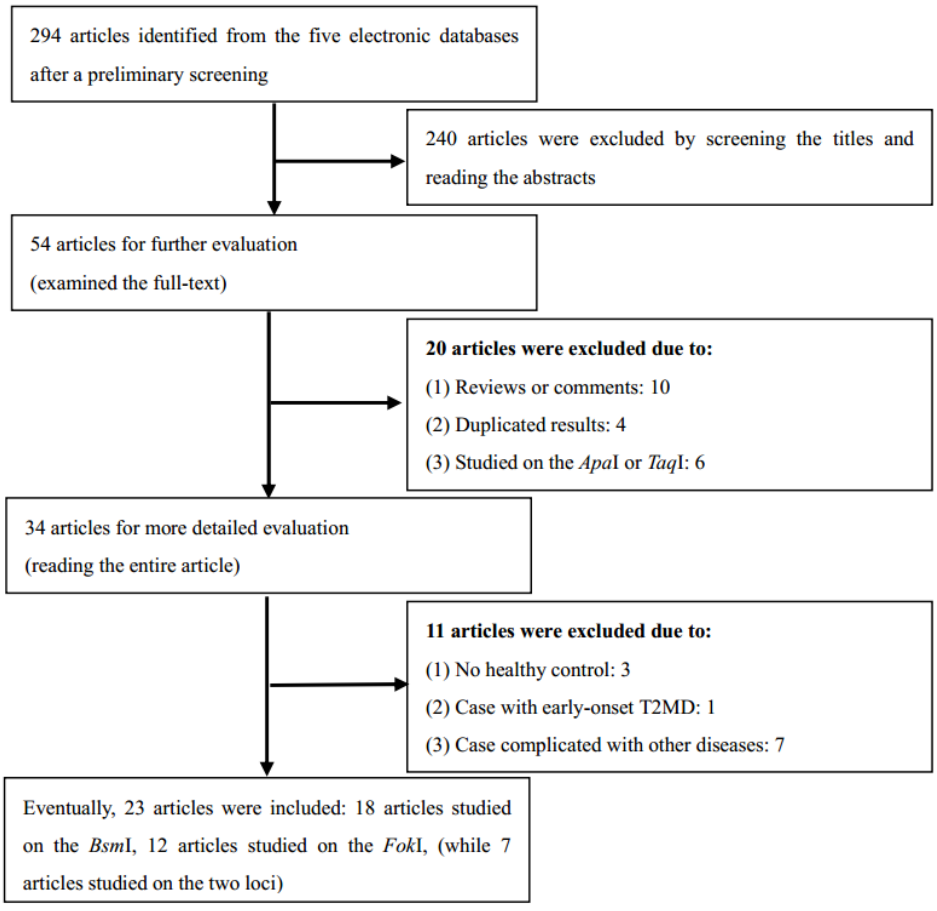

Figure 1. Diagram for selection of studies and specific reasons for exclusion

Table 1. Main characteristic of included studies about *Bsm*I genotype polymorphism in the meta-analysis

First author/Year (Reference)	Country	Ethnicity	Gender (Women/men)		Age		Genotype distribution (case/control)			HWE(p)*	Quality level
			Case	Control	Case	Control	bb	Bb	BB		
Speer G, 2001[18]	Hungary	Caucasian	27/22	66/72	57(29-77)	63(23-83)	20/46	22/66	7/26	0.787	Poor
Ye WZ, 2001[19]	France	Caucasian	130/179	72/71	62±12	61±16	119/54	135/65	52/24	0.557	High
Oh JY, 2002[20]	USA	Caucasian	NR	NR	71.7±8.6	68.8±9.26	86/460	107/590	49/253	0.010	Medium
Malecki MT, 2003[21]	Poland	Caucasian	165/143	142/98	59.8±9.2	54.0±15.1	131/92	142/116	35/32	0.630	High
Shen BS, 2004[22]	China	Chinese	40/56	21/31	65.6±10.5	36.0±4.9	59/45	34/7	3/0	0.603	Medium
Shi YJ, 2007[23]	China	Chinese	65/92	67/129	58±11	NR	139/177	17/18	1/1	0.470	Medium
Xu JR, 2007[24]	China	Chinese	61/45	60/42	62±11	58±10	19/6	46/28	41/68	0.192	Medium
Zhang P, 2008[25]	China	Chinese	50/66	51/61	55.6±10.5	56.0±8.9	71/97	41/15	4/0	0.448	Medium
Bid HK, 2009[26]	India	Caucasian	NR	NR	49.3±11.0	NR	30/60	52/77	18/23	0.831	Medium
Ding HG, 2009[27]	China	Chinese	15/17	14/16	42±8	40±6	19/26	13/4	0/0	0.696	Poor
Lan XC, 2009[28]	China	Chinese	34/32	41/39	53.0±14.1	51.3±13.3	48/75	13/5	5/0	0.773	Medium
Wang CX, 2009[29]	China	Caucasian	40/24	83/38	48.7±8.54	48.0±8.56	56/110	8/11	0/0	0.600	Medium
Mukhopadhyaya PN, 2010[30]	India	Caucasian	21/19	21/19	47.3±12.2	42.5±12.1	17/26	9/10	14/4	0.073	Medium
Su BC, 2011[31]	China	Chinese	129/159	63/76	53.8±11.9	54.0±11.6	264/118	21/15	3/6	<0.001	Medium
Zhao Y, 2011[32]	China	Chinese	45/51	40/43	55.7±11.4	55.7±11.7	67/71	29/11	0/1	0.455	Medium
Al-Daghri NM, 2012[33]	Saudi Arabia	Caucasian	NR	NR	51.5±8.6	44.1±9.9	105/114	201/95	62/50	<0.001	Medium
Xu JR, 2012[34]	China	Chinese	77/124	131/88	NR	NR	176/172	24/47	1/0	0.075	Medium
Zhang H, 2012[35]	China	Chinese	54/68	47/53	57.0±10.8	55.3±8.8	96/85	26/14	0/1	0.625	Medium

*p value for HardyeWeinberg equilibrium in control group. NR: not reported.

Table 2. Main characteristics of included studies about *Fok*I genotype polymorphism in the meta-analysis

First author/Year (Reference)	Country	Ethnicity	Gender (Women/men)		Age		Genotype distribution (case/control)			HWE(p)*	Quality level
			Case	Control	Case	Control	ff	Ff	FF		
Malecki MT, 2003[21]	Poland	Caucasian	165/143	142/98	59.8±9.2	54.0±15.1	64/52	159/110	85/77	0.284	High
Shen BS, 2004[22]	China	Chinese	40/56	21/31	65.6±10.5	36.0±4.9	19/10	53/24	24/18	0.694	Medium
Li HM, 2005[36]	China	Chinese	34/21	42/35	54.6±9.9	59.5±9.6	5/6	22/28	28/43	0.633	Medium
Li HM, 2005[37]	China	Chinese	63/41	42/35	61.9±11.0	59.5±9.6	19/6	46/28	39/43	0.633	Medium
Liao L, 2005[38]	China	Chinese	68/72	62/104	53.5±8.6	61.8±10.8	27/28	83/74	30/64	0.406	Medium
Du T, 2008[39]	China	Chinese	202/271	119/261	54.5±9.2	61.4±9.8	95/68	264/189	114/123	0.755	Medium
Zhang P, 2008[25]	China	Chinese	50/66	51/61	55.6±10.5	56.0±8.9	23/21	64/52	29/39	0.620	Medium
Bai R, 2009[40]	China	Chinese	50/56	35/42	52.0±8.0	58.0±12	22/7	50/26	34/44	0.286	Medium
Bid HK, 2009[26]	India	Caucasian	NR	NR	49.3±11.0	NR	38/80	60/79	2/1	<0.001	Medium
Wang CX, 2009[29]	China	Chinese	40/24	83/38	48.7±8.54	48.0±8.56	15/19	29/65	20/37	0.278	Medium
Su BC, 2011[31]	China	Chinese	129/159	63/76	53.8±11.9	54.0±11.6	34/16	221/95	33/28	<0.001	Medium
Al-Daghri NM, 2012[33]	Saudi Arabia	Caucasian	NR	NR	51.5±8.6	44.1±9.9	213/129	133/111	22/19	0.461	Medium

*p value for HardyeWeinberg equilibrium in control group. NR: not reported.

Table 3. Results of meta-regression (*p* value)

Locus	Models	Ethnicity	Sample size	Match	HWE	Quality
*Bsm*I	BB vs bb	0.036	0.511	0.993	0.897	0.999
	Bb vs bb	0.229	0.055	0.387	0.454	0.461
	BB+Bb vs bb	0.285	0.031	0.371	0.258	0.493
	BB vs Bb+bb	0.013	0.306	0.850	0.689	0.823
*Fok*I	ff vs FF	0.003	0.071	0.547	0.304	0.535
	Ff vs FF	0.003	0.412	0.703	0.241	0.888
	ff+Ff vs FF	0.003	0.232	0.575	0.273	0.714
	ff vs FF+Ff	0.169	0.066	0.746	0.033	0.497

Table 4. Results of meta-analysis for the association between VDR *Bsm*I and *Fok*I polymorphisms and T2DM

Locus	Groups	Case/control	Codominant model				Dominant model		Recessive model	
			BB vs bb		Bb vs bb		BB+Bb vs bb		BB vs Bb+bb	
			p	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)
*Bsm*I	Total	2757/3517	0.956	1.01 (0.67, 1.52)	0.038	1.36 (1.02, 1.83)	0.049	1.36 (1.00, 1.84)	0.692	0.93 (0.65, 1.33)
	Ethnicity									
	Chinese	1413/2283	0.940	1.05 (0.30, 3.65)	0.068	1.62 (0.97, 2.72)	0.130	1.57 (0.88, 2.80)	0.881	0.92 (0.32, 2.66)
	Caucasians	1344/1234	0.447	1.13 (0.83, 1.54)	0.414	1.15 (0.83, 1.59)	0.309	1.17 (0.86, 1.89)	0.874	1.02 (0.79, 1.32)
	Sample size									
	<200	443/544	0.256	2.31 (0.55, 9.80)	0.006	2.12 (1.24, 3.62)	0.003	2.38 (1.33, 4.25)	0.272	2.09 (0.56, 7.80)
	≥200	2314/2973	0.527	0.88 (0.59, 1.31)	0.498	1.12 (0.80, 1.57)	0.786	1.05 (0.75, 1.47)	0.234	0.81 (0.57, 1.15)
			ff vs FF		Ff vs FF		ff+Ff vs FF		ff vs FF+Ff	
			p	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)
*Fok*I	Total	2218/1859	<0.001	1.57 (1.28, 1.93)	<0.001	1.54 (1.31, 1.81)	<0.001	1.57 (1.35, 1.83)	0.055	1.16 (1.00, 1.36)
	Ethnicity									
	Chinese	1446/1201	<0.001	1.78 (1.40, 2.27)	<0.001	1.66 (1.38, 1.99)	<0.001	1.70 (1.43, 2.02)	0.025	1.27 (1.03, 1.57)
	Caucasians	772/658	0.440	1.16 (0.79, 1.70)	0.281	1.20 (0.86, 1.68)	0.229	1.21 (0.89, 1.66)	0.682	1.05 (0.84, 1.31)
	Sample size									
	<200	425/404	0.001	2.16 (1.40, 3.33)	<0.001	1.53 (1.31, 1.81)	<0.001	1.68 (1.25, 2.24)	0.007	1.74 (1.16, 2.60)
	≥200	1793/1455	0.002	1.44 (1.14, 1.81)	<0.001	1.55 (1.28, 1.86)	<0.001	1.53 (1.28, 1.83)	0.354	1.08 (0.92, 1.28)

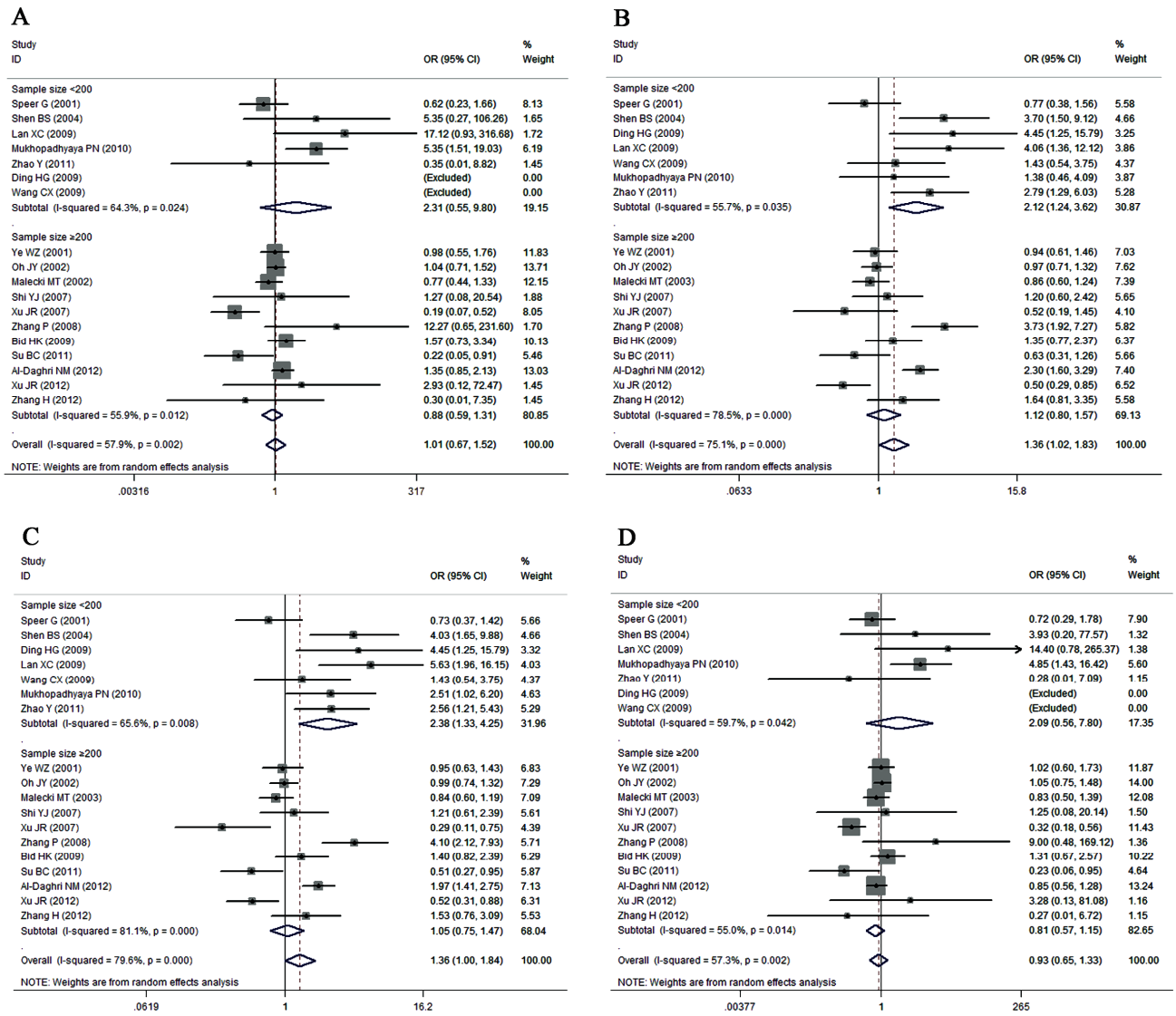

Figure 2. Forest plots for the overall association between VDR *Bsm*I polymorphism and T2DM risk. A: BB vs bb; B: Bb vs bb; C: BB+Bb vs bb; D: BB vs Bb+bb.

vs FF: OR=1.78, 95% CI: 1.40-2.27, $p<0.001$; Ff vs FF: OR=1.66, 95% CI: 1.38-1.99, $p<0.001$; ff+Ff vs FF: OR=1.70, 95% CI: 1.43-2.02, $p<0.001$; ff vs FF+Ff: OR=1.27, 95% CI: 1.03-1.57, $p=0.025$, respectively) (Table 4). In contrast, no significant association was observed among Caucasians in three studies ($p>0.05$). Subgroup analysis (by sample size) presented significantly increased susceptibility of T2DM for ff vs FF, Ff vs FF and ff+Ff vs FF ($p<0.01$) in both small and large sample size studies. However, significantly association was only observed in the studies with small sample size for ff vs FF+Ff (OR=1.74, 95% CI: 1.16-2.60, $p=0.007$), but not in those with large sample size for ff vs FF+Ff (OR=1.08, 95% CI: 0.92-1.28, $p=0.354$) (Table 4, Figure 3).

Sensitivity analyses and publication bias

The sensitivity analyses did not detect any individual study which affected the results using the exclusion method step by step (data not shown). Neither the Begg's test nor Egger's test provided any obvious evidence of publication bias (Table 5, $p\geq0.05$). The shapes of the funnel plots appeared to be symmetrical in all genetic models (see the supplementary Figure 1 and Figure 2).

DISCUSSION

Vitamin D can modulate insulin secretion and also possesses pleiotropic effects on the pathogenesis of diabetes mellitus. It is feasible that genetic variants of the VDR gene may contribute to the development of T2DM. In recent years, many studies reported the links between body vitamin D status and T2DM in different ethnicities and regions. Through literature reviewing, we found that it was very confusing in describing the genotype of VDR. For example, Al-Daghri[33] and Dilmec[41] used the bases to describe the different alleles, while Bid,[26] Malecki,[21] Zhang,[35] Nosratabadi[11] applied the initial letter of the restriction enzyme to designate the different alleles; Nosratabadi and Bid employed a capital letter for the presence of the restriction enzyme site, while Malecki and Zhang employed a lowercase letter for its presence. The complicated description easily confuses readers. Therefore, there was an urgent need for a unified expression of the allelic gene before a meta-analysis.

The VDR gene is located on chromosome 12q13.1, which consists of 14 exons and has an extensive promoter region capable of generating multiple tissue-specific transcripts. The allele of the *Bsm*I polymorphism is located in

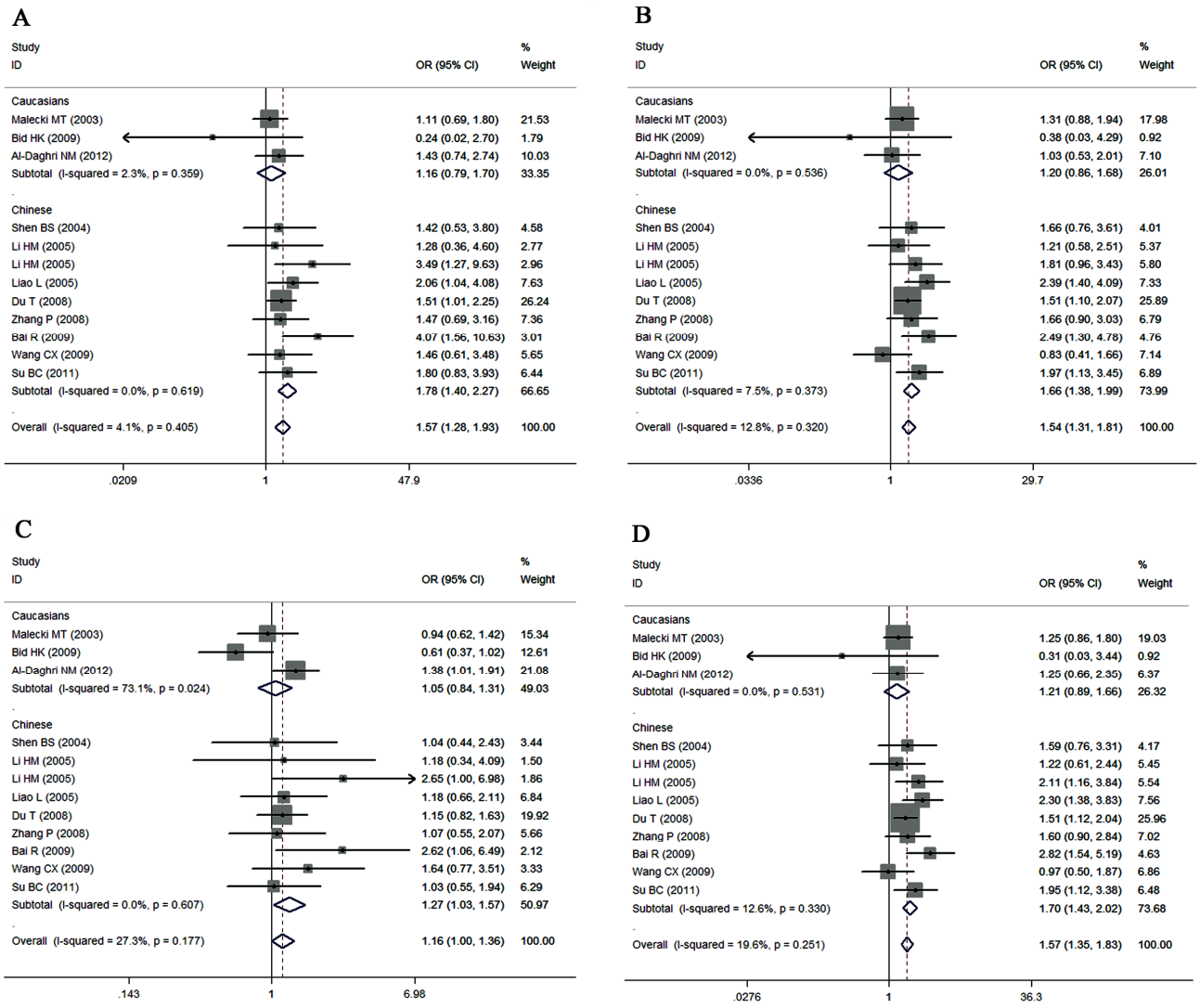

Figure 3. Forest plots for the overall association between VDR *Fok*I polymorphism and T2DM risk. A: ff vs FF; B: Ff vs FF; C: ff+Ff vs FF; D: ff vs FF+Ff.

Table 5. Results of Egger's test and Begg's test

Locus	Comparison	Egger's test			Begg's test	
		t	*p*	95% CI	*Z*	*p*
BsmI	BB vs bb	-0.61	0.557	-3.68, 2.13	0.54	0.59
	Bb vs bb	1.21	0.245	-1.07, 3.89	1.21	0.23
	BB vs Bb+bb	-0.03	0.973	-3.04, 2.95	0.36	0.72
	BB+Bb vs bb	1.28	0.220	-1.06, 4.27	1.44	0.15
FokI	ff vs FF	0.36	0.727	-1.51, 2.08	0.21	0.84
	Ff vs FF	-0.62	0.550	-2.52, 1.43	1.17	0.24
	ff vs FF+Ff	0.79	0.447	-1.29, 2.71	1.03	0.30
	ff+Ff vs FF	-0.35	0.731	-2.41, 1.75	0.75	0.45

intron 8 and near the 3' end of the VDR gene, which has been demonstrated to be associated with an increased risk of T1DM.[42] In our meta-analysis, marginal significant association between *Bsm*I polymorphism and T2DM risk was found for Bb vs bb and BB+Bb vs bb, which is similar with the results of another meta-analysis by Wang.[42] This implied that the allele B and the variant homozygote BB of *Bsm*I were the risk factors for T2DM. However, further subgroup analysis revealed significant associations between *Bsm*I polymorphism and T2DM among the studies with small sample size (n<200), and no association between them among large sample size studies. Therefore, the marginal significant associations might be induced by small sample size populations, and it could not reflect the genuine association between *Bsm*I polymorphism and T2DM risk. Therefore, further studies including larger sample sizes are necessary in different ethnicity to confirm the relationship between *Bsm*I polymorphism in the VDR gene and T2DM.

In contrast to *Bsm*I polymorphisms, the *Fok*I polymorphism is located within the 5' end of the gene near the promoter region. *Fok*I polymorphism not only affects the function of the Vitamin D_3 but also interrupt the binding efficiency of vitamin D and VDR, impairing insulin func-

tion and leading to T2DM finally. In the meta-analysis of Wang[42] and Li,[43] the results indicated that *Fok*I polymorphism in the VDR gene was significantly associated with T2DM risk, and the allele f and variant homozygote ff of *Fok*I may be the risk factors for T2DM. We also found significant associations with T2DM for three genetic models. However, we found this significantly increased susceptibility only appeared in T2DM patients among Chinese for all genetic models. In contrast, no significant association was observed among Caucasians in three studies. So, we infer that the significant association between *Fok*I and T2DM obtained from overall analysis might arise from the Chinese population.

Strengths and limitations

In the present work, we clarified the definitions of the alleles in different papers to make sure that the data of genotype distribution were extracted exactly, and found that *Fok*I polymorphism in the VDR gene was significantly associated with T2DM risk in Chinese people, which were the highlight in the meta-analysis. Also, several studies conducted in India categorized the subjects as Caucasians, which was often classified as Asians in other previous studies.

Although the study was analyzed in detail, limitations still existed in this meta-analysis. Firstly, the source of the selected articles was only from those published in Chinese and English due to the limit of literature retrieval. Secondly, vitamin D status varies worldwide with area, season and diet. Without measuring an individual's serum vitamin D levels, it is perhaps not adequate to examine the relation between the VDR polymorphism and type 2 diabetes. Finally, the sample size may be an important factor that influences the results of case-control studies. Future larger sample size studies are needed to investigate the associations between VDR polymorphism and T2DM.

Conclusions

In conclusion, the results of our meta-analysis indicated that the evidence of significant association between the *Bsm*I polymorphism and T2DM was weak, the sample size was the main source of the heterogeneity. The *Fok*I polymorphism in the VDR gene was significantly associated with T2DM risk only in Chinese people, but not in Caucasians. Meanwhile, the sample size might be an important factor that influences the result of case-control studies. Future larger sample size studies are needed to investigate the associations between VDR polymorphism and T2DM. Besides, the gene-environment interactions and the molecular evidence of VDR polymorphism with T2DM should be studied.

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AUTHOR DISCLOSURES

The authors have declared that no competing interests exist.

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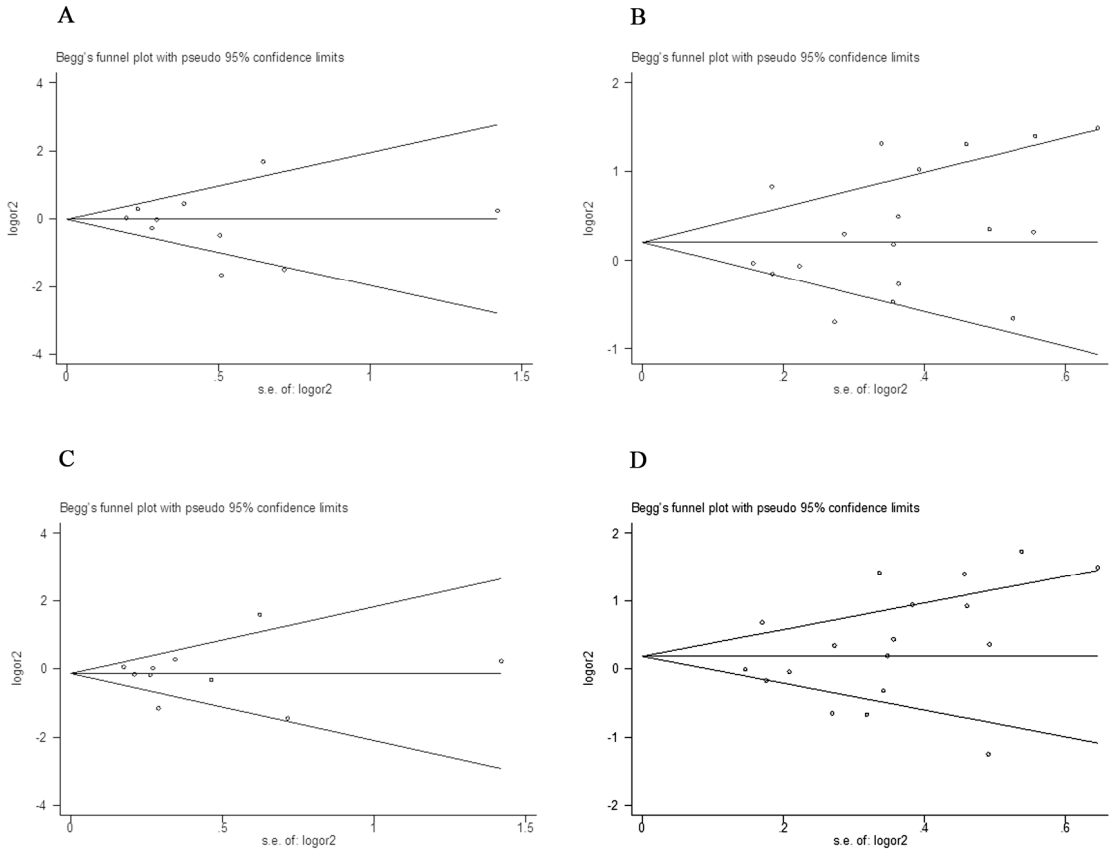
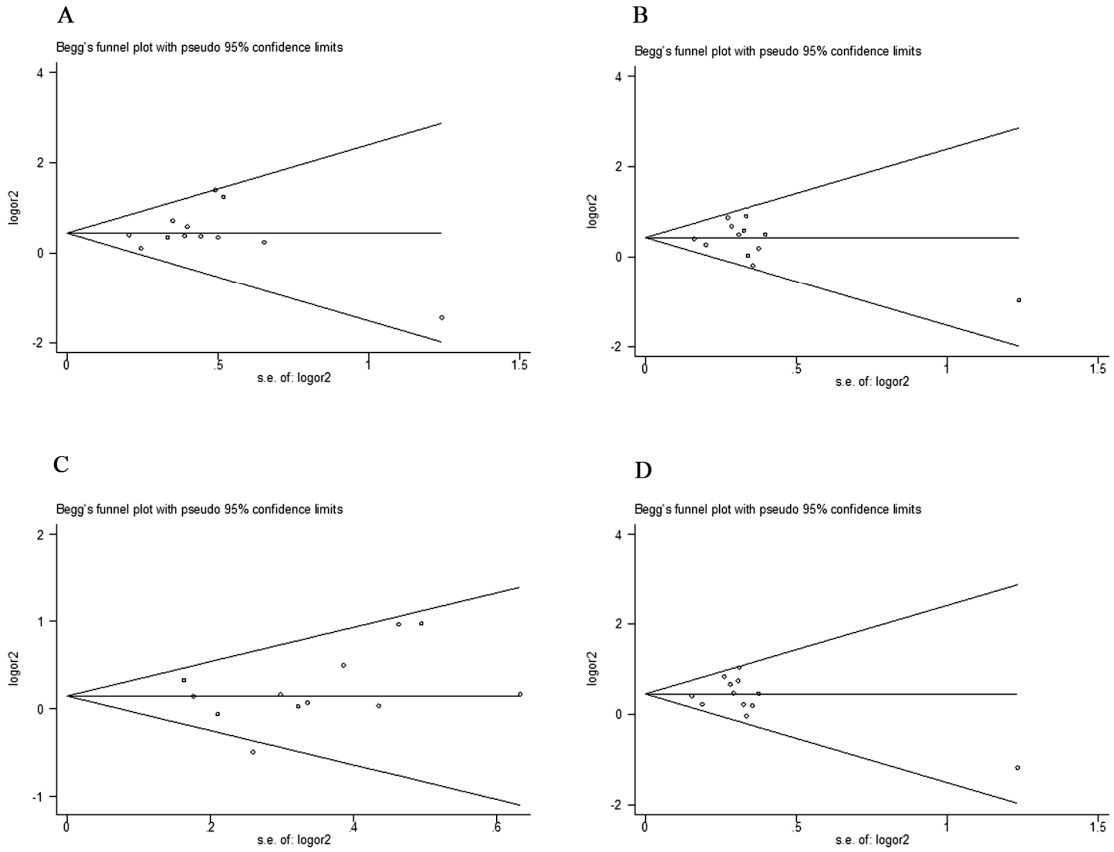
Appendix



Supplementary figure 1. Funnel plots for BsmI polymorphism of VDR in T2DM patients. A: BB vs bb; B: Bb vs bb; C: BB vs Bb+bb; D: BB+Bb vs bb.



Supplementary figure 2. Funnel plots for FokI polymorphism of VDR in T2DM patients. A: ff vs FF; B: Ff vs FF; C: ff vs Ff+FF; D: ff+Ff vs FF.

Original Article

The genetic polymorphisms in vitamin D receptor and the risk of type 2 diabetes mellitus: an updated meta-analysis

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维生素 D 受体基因多态性与 2 型糖尿病发病风险：一个更新的 meta 分析

背景与目的：研究发现维生素D受体（VDR）基因多态性与2型糖尿病（T2DM）的发病关系密切，但相关文献报道结论并不一致。本研究的目的是通过文献系统综述对VDR受体基因*Bsm*I和*Fok*I位点单核苷酸多态性与T2DM的关联性进行评价。**方法与研究设计：**于PubMed 、ISI Web of Science、中国期刊全文数据库（CNKI）、中国万方数据库和中国生物医学文献数据库（CBM）中检索1999年至2014年期间发表的所有相关文献。运用Stata 12.0软件，通过计算OR值和95% CI来评价位点*Bsm*I和*Fok*I变异与T2DM的关联性。**结果：**共23篇文献30个病例对照研究纳入本次meta分析中。分析结果显示*Bsm*I位点单核苷酸多态性与T2DM易患性在两种基因模型中（Bb vs bb 和 BB+Bb vs bb）存在弱的相关性。亚组分析显示这种弱的相关性主要出现在样本量较小的研究中（<200）。*Fok*I位点单核苷酸多态性与T2DM易患性（ff vs FF：OR=1.57，95% CI：1.28-1.93，p<0.001; Ff vs FF：OR=1.54，95% CI：1.31-1.81，p<0.001; ff+Ff vs FF：OR=1.57，95% CI：1.35-1.83，p<0.001）存在强的相关性，提示该位点基因突变是T2DM的危险因素，尤其是在中国汉族人群中。**结论：**有关VDR基因与T2DM的关联分析还需要大样本量和不同种族研究的支持。

关键词：维生素D受体、2型糖尿病、 基因多态性、关联、meta分析