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META-ANALYSIS

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Vitamin D Receptor Polymorphisms Associated with Susceptibility to Obesity: A Meta-Analysis

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Background: Obesity has become a global public health problem. Obesity increases the risk of several lethal diseases. This study aimed to assess whether the obesity susceptibility was associated with genetic variation in vitamin D receptor (VDR) gene by conducting a meta-analysis.

Material/Methods: PubMed, EMBASE and Cochrane Library databases were screened for all relevant articles published up to October 2018. The pooled odds ratios (OR) were calculated using STATA 13.0 software for 4 polymorphisms in the VDR gene (ApaI, BsmI, FokI and TaqI).

Results: Seven case-control studies, including 1188 obese patients and 1657 healthy controls, were recruited. The pooled findings showed that there were no associations between obesity risk and the VDR polymorphisms in ApaI, BsmI and TaqI *loci* overall. However, VDR TaqI polymorphism was associated with the risk of obesity in Asian under homozygous [TT versus tt: odds ratio (OR)=0.26, 95% confidence interval (CI)=0.14–0.49; *P*<0.001], heterozygous (Tt versus tt: OR=0.34, 95% CI=0.18–0.64; *P*=0.001), and dominant (TT+Tt versus tt: OR=0.30, 95% CI=0.17–0.52; *P*<0.001) models; FokI variant was related with increased risk of obesity only under dominant model (FF+Ff versus ff: OR=1.54, 95% CI=1.15–2.06; *P*=0.004).

Conclusions: Our meta-analysis results suggest that the T allele of TaqI may have a protective effect, while the F allele of FokI is proposed as a risk factor related to obesity.

MeSH Keywords: Obesity • Polymorphism, Single Nucleotide • Receptors, Calcitriol

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/915678

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Background

Obesity, defined by some experts as a body mass index (BMI) of ≥30 kg/m^2 and by other experts as ≥28 kg/m^2, is currently a very common health problem globally, with an estimated age-standardized prevalence of approximately 35% [1–3]. Obesity is associated with an increased risk for the development of several disorders, such as diabetes, hypertension, hyperlipidemia, cardiovascular, cerebrovascular diseases and cancer, which may seriously influence the quality of life of patients [4], impose a significant economic burden on family and society [5], and even result in sudden death [6]. Therefore, it is of importance to investigate the risk factors of obesity for identifying high-risk obese individuals timely.

Although the pathogenesis of obesity is complex, recent evidence suggests that genetic variants, especially functional single nucleotide polymorphisms (SNPs) in genes contribute to interindividual variability in susceptibility to obesity [7–9]. Vitamin D receptor (VDR) is a gene that encodes a nuclear receptor to mediate the inhibitory effects of vitamin D3 on adipogenesis [10,11]. Thus, SNPs that could cause the lower expression of VDR mRNA and protein (such as BsmI bb [12] and TaqI tt [13]) may be correlated with an increased susceptibility to obesity. This hypothesis has been proven in some studies. For example, the study of Al-Hazmi et al. demonstrated that polymorphisms in BsmI and TaqI *loci* of the VDR gene, were closely associated with the susceptibility of obesity, with significantly higher frequency in allele b (P=0.044)/t (P=0.041) or genotype bb (P=0.042)/tt (P=0.021) of the obese group than those in the control group [9]. These conclusions for BsmI and TaqI polymorphisms in VDR were also confirmed in the studies of Speer et al. [14] and Bienertova-Vasku et al. [15], respectively. However, Morteza et al. [16] and Bienertova-Vasku et al. [15] observed that no significant differences in allele and genotype frequencies of BsmI polymorphism between obesity and control groups. Fan et al. oppositely detected the higher frequency in allele T (P=0.041) or genotype TT (P=0.021) of TaqI polymorphism in the obese group compared with the control group [17]. Thus, the possible role of the VDR polymorphisms in obesity still remains inconclusive. These controversial conclusions might be partially a result of the small sample size of the individual studies. Therefore, there is an essential need to reevaluate the true association between the polymorphisms of VDR gene and the risk of obesity.

The goal of this study was to investigate the relation of obesity with all included VDR gene polymorphisms (BsmI, TaqI, FokI, and ApaI) in the accumulated evidence by performing a meta-analysis, which, to our knowledge, has not been reported previously.

Material and Methods

Search strategy

All related literatures were identified by an electronic search from online PubMed, EMBASE, and the Cochrane Library databases with the keywords as follows: vitamin D receptor (OR VDR) AND obesity (OR obese OR overweight OR body mass index OR adiposity) AND polymorphism (OR polymorphisms OR SNP OR variant OR mutation) up to October, 2018. Furthermore, the references of retrieved articles were also manually searched for identifying additional relevant studies.

This search followed the Guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. All results and analyses were from previous published studies; thus, no ethical approval and patient consent are required.

Selection criteria

All the articles were selected based on the inclusion criteria: 1) human case-control studies; 2) investigation of the association between VDR polymorphisms and obesity; 3) obesity in a study was defined according to BMI >28 or 30 kg/m^2; 4) study provided available genotype frequencies for calculating the odds ratio (OR) with 95% confidence interval (CI); 5) genotype distribution of control groups conformed to the assumptions of the Hardy-Weinberg equilibrium (HWE); and 6) published in the English language. Studies were excluded it they met the exclusion criteria as follows: 1) duplicated data; 2) abstracts, case reports/series, reviews, comments or editorial articles that did not have related raw data; and 3) without genotype frequencies.

Data extraction

Two investigators extracted the following data independently: first author, publication year, country, sample size (cases and controls), obesity definition, age group of the population, genotyping method, the source of controls, HWE test, and polymorphism *loci*. A, B, F and T were respectively designated to define the genotypes for 4 VDR gene polymorphisms (ApaI, BsmI, FokI, or TaqI) if the restriction sites for corresponding enzymes was absent; otherwise, a, b, f and t were used. The labels of ApaI (A/C) corresponds to ApaI (A/a), BsmI [A (or T)/G (or C)] corresponds to BsmI (B/b), FokI (C/T) corresponds to FokI (F/f), and TaqI (A/G) corresponds to TaqI (T/t). Any disagreement was resolved by discussion and consultation with the third author.

Quality assessment

The quality of included studies was assessed by 2 independent reviewers using the Newcastle-Ottawa Scale (NOS) [18]

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according to indicators of 3 aspects: selection, comparability and exposure/outcome. A study that scored >6 stars (total is 9 stars) was considered to have high quality.

Statistical analysis

The statistical analyses were conducted via the STATA software (version 13.0; STATA Corporation, College Station, TX, USA). The associations between VDR polymorphisms and obesity risk were determined by computing the crude OR and 95% CI under allelic model (e.g., B versus b), homozygous model (e.g., BB versus bb), heterozygous model (e.g., Bb versus bb), recessive model (e.g., BB versus Bb+bb), and dominant model (e.g., BB+Bb versus bb), respectively. The statistical significance of the pooled OR was tested by the Z test, with $P<0.05$ defined as the threshold value. Furthermore, the subgroup meta-analyses were also done with stratifications by ethnicity (Asian or European), sample size (≤100 or >100), genotyping method (PCR-RFLP or others) and control source (hospital-based or population-based). Heterogeneity among studies was quantified using Cochran's Q (chi-squared) statistic and the I^2 statistic. A random-effects (heterogeneous, $P<0.10$ and $I^2>50\%$) or fixed-effects (homogeneous, $P>0.10$ and $I^2<50\%$) model was used to estimate the pooled effects. Egger's or Begger's test linear regression test was applied to diagnose potential publication bias ($P<0.05$). Sensitivity analysis was utilized to evaluate whether the results were substantially influenced by any individual study via removing each study at a time.

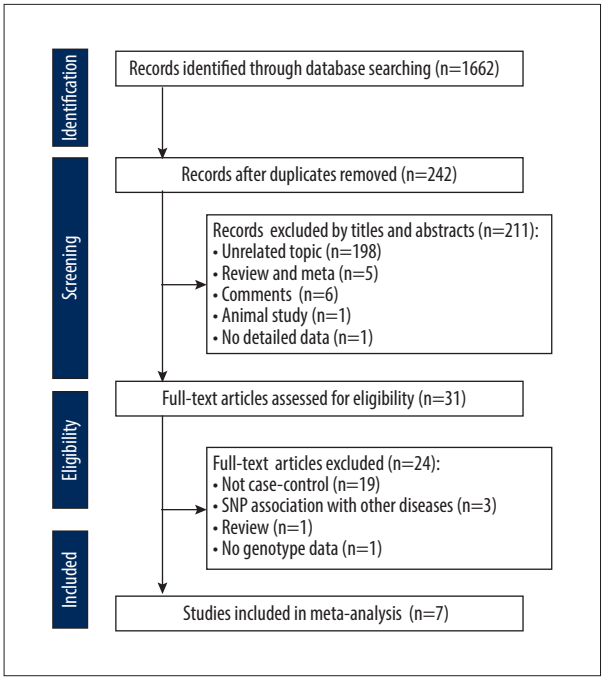

Figure 1. Flow diagram of study identification.

Results

Characteristics of eligible studies

The detailed flow chart for the study selection is displayed in Figure 1. Seven case-control studies, including 1188 obese patients and 1657 healthy controls, were recruited for this meta-analysis according to the inclusion and exclusion

Table 1. Study characteristics of each article included in the meta-analysis.

First author	Year	Country	Sample size (case/control)	Population	Genotype method	Control source	Gene polymorphism	HWE	NOS
Al-Hazmi et al. [9]	2017	Saudi Arabia	100/200	Adult	PCR-RFLP	Unclear	ApaI, TaqI, BsmI	Yes	7
Bagheri et al. [16]	2017	Iran	38/27	Adult	Direct sequencing	PB	BsmI	Yes	7
Bienertová-Vašků et al. [15]	2017	Czech	511/371	Adult	PCR-RFLP	PB	BsmI, ApaI, TaqI, FokI	Yes	6
Rahmadhani et al. [19]	2017	Malaysia	183/535	Juveniles	Massarray	PB	BsmI	Yes	6
Yiannis et al. [20]	2016	Greece	82/102	Adult	PCR-RFLP	PB	TaqI	Yes	6
Fan et al. [17]	2015	China	245/284	Adult	PCR-RFLP	PB	ApaI, TaqI, FokI	Partial	6
Speer et al. [14]	2001	Hungary	29/138	Adult	PCR-RFLP	HB	BsmI	Yes	7

HB – hospital-based; PB – population-based; HWE – Hardy-Weinberg equilibrium; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism; NOS – Newcastle-Ottawa Scale.

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Table 2. Overall meta-analysis of polymorphisms in vitamin D receptor gene.

SNP	Comparison	Qualified studies	Test of association			Test of heterogeneity		Egger's or Begger's test
			OR (95% CI)	P_z	Model	*P*-value	I^2 (%)	*P*-value
ApaI	A *vs.* a	3	1.02 (0.88–1.19)	0.770	F	0.193	39.2	0.256
	AA *vs.* aa		1.09 (0.81–1.47)	0.568	F	0.341	7.1	0.243
	AA *vs.* Aa		1.10 (0.85–1.43)	0.482	F	0.953	0.0	0.749
	Aa *vs.* aa		0.95 (0.74–1.21)	0.681	F	0.244	29.0	0.622
	AA+Aa *vs.* aa		0.98 (0.78–1.23)	0.840	F	0.168	44.0	0.268
	AA *vs.* Aa+aa		1.25 (0.632–2.48)	0.519	R	0.001	86.3	0.599
BsmI	B *vs.* b	5	0.93 (0.67–1.28)	0.644	R	0.004	73.7	0.483
	BB *vs.* bb		0.90 (0.45–1.78)	0.755	R	0.010	70.0	0.173
	BB *vs.* Bb		1.02 (0.77–1.36)	0.894	F	0.168	37.9	0.083
	Bb *vs.* bb		0.94 (0.76–1.17)	0.572	F	0.102	48.2	0.818
	BB+Bb *vs.* bb		0.82 (0.53–1.28)	0.387	R	0.018	66.5	0.626
	BB *vs.* Bb+bb		1.05 (0.64–1.71)	0.857	R	0.034	61.5	0.138
FokI	F *vs.* f	2	1.05 (0.77–1.44)	0.753	R	0.054	73.0	0.317
	FF *vs.* ff		1.21 (0.71–2.06)	0.493	R	0.107	61.4	0.317
	FF *vs.* Ff		0.92 (0.72–1.18)	0.515	F	0.190	41.7	0.317
	Ff *vs.* ff		1.35 (0.99–1.83)	0.061	F	0.511	0.0	0.317
	FF+Ff *vs.* ff		1.54 (1.15–2.06)	0.004	F	0.750	0.0	0.317
	FF *vs.* Ff+ff		0.98 (0.66–1.44)	0.914	R	0.092	64.8	0.317
TaqI	T *vs.* t	4	1.07 (0.55–2.08)	0.843	R	0.000	93.2	0.362
	TT *vs.* tt		0.63 (0.25–1.60)	0.330	R	0.003	82.9	0.846
	TT *vs.* Tt		1.37 (0.65–2.88)	0.413	R	0.000	89.3	0.645
	Tt *vs.* tt		0.62 (0.33–1.17)	0.138	R	0.058	64.8	0.406
	TT+Tt *vs.* tt		0.61 (0.29–1.28)	0.189	R	0.011	77.8	0.583
	TT *vs.* Tt+tt		1.21 (0.53–2.72)	0.654	R	0.000	92.0	0.751

OR – odds ratio; CI – confidence interval; R – random-effects; F – fixed-effects. Begger's test was performed only for FokI.

Table 3. Subgroup analysis for ApaI polymorphism in vitamin D receptor gene.

Study		A *vs.* a		AA *vs.* aa		Aa *vs.* aa		AA+Aa *vs.* aa		AA *vs.* Aa+aa	
	N	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Ethnicity											
Asian	2	0.92 (0.75–1.13)	0.416	0.91 (0.61–1.37)	0.659	0.82 (0.59–1.13)	0.225	0.84 (0.62–1.13)	0.241	0.90 (0.63–1.27)	0.539
European	1	1.15 (0.93–1.43)	0.197	1.33 (0.86–2.06)	0.194	1.17 (0.80–1.70)	0.428	1.22 (0.85–1.74)	0.276	2.31 (1.65–3.23)	0.000

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Table 3 continued. Subgroup analysis for ApaI polymorphism in vitamin D receptor gene.

Study		A *vs.* a		AA *vs.* aa		Aa *vs.* aa		AA+Aa *vs.* aa		AA *vs.* Aa+aa	
	N	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Population											
Adult	3	1.02 (0.88–1.19)	0.770	1.09 (0.81–1.47)	0.568	0.95 (0.74–1.21)	0.681	0.98 (0.78–1.23)	0.840	1.25 (0.63–2.48)	0.519
Juveniles	0										
Sample size											
≤100	1	1.06 (0.75–1.50)	0.725	1.12 (0.58–2.19)	0.735	1.08 (0.56–2.08)	0.821	1.10 (0.60–2.02)	0.760	0.85 (0.52–1.41)	0.532
>100	2	1.01 (0.86–1.19)	0.875	1.08 (0.78–1.51)	0.639	0.93 (0.71–1.21)	0.593	0.96 (0.75–1.23)	0.730	1.50 (0.62–3.61)	0.367
Genotyping											
PCR-RFLP	3	1.02 (0.88–1.19)	0.770	1.09 (0.81–1.47)	0.568	0.95 (0.74–1.21)	0.681	0.98 (0.78–1.23)	0.840	1.25 (0.63–2.48)	0.519
Other	0										
Control											
PB	2	1.01 (0.86–1.19)	0.875	1.08 (0.78–1.51)	0.639	0.93 (0.71–1.21)	0.593	0.96 (0.75–1.23)	0.730	1.50 (0.62–3.61)	0.367
Other	1	1.06 (0.75–1.50)	0.725	1.12 (0.58–2.19)	0.735	1.08 (0.56–2.08)	0.821	1.10 (0.60–2.02)	0.760	0.85 (0.52–1.41)	0.532

PB – population-based; OR – odds ratio; CI – confidence interval; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism.

Table 4. Subgroup analysis for BsmI polymorphism in vitamin D receptor gene.

Study		B *vs.* b		BB *vs.* bb		Bb *vs.* bb		BB+Bb *vs.* bb		BB *vs.* Bb+bb	
	N	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Ethnicity											
Asian	3	0.78 (0.43–1.42)	0.422	0.63 (0.17–2.27)	0.478	0.89 (0.64–1.23)	0.477	0.56 (0.20–1.55)	0.264	0.90 (0.40–2.02)	0.797
European	2	1.08 (0.89–1.31)	0.442	1.24 (0.82–1.88)	0.313	0.98 (0.73–1.32)	0.905	1.04 (0.79–1.37)	0.807	1.26 (0.86–1.84)	0.242
Population											
Adult	4	0.86 (0.56–1.32)	0.481	0.78 (0.31–1.93)	0.583	0.85 (0.65–1.11)	0.230	0.68 (0.35–1.32)	0.255	0.99 (0.54–1.81)	0.969
Juveniles	1	1.19 (0.89–1.59)	0.247	1.43 (0.70–2.93)	0.325	1.14 (0.79–1.66)	0.479	1.19 (0.84–1.68)	0.339	1.37 (0.68–2.78)	0.378
Sample size											
≤100	3	0.79 (0.43–1.44)	0.436	0.65 (0.17–2.52)	0.531	0.56 (0.32–0.97)	0.037	0.54 (0.21–1.41)	0.209	0.95 (0.38–2.35)	0.909
>100	2	1.09 (0.92–1.30)	0.300	1.24 (0.84–1.81)	0.276	1.04 (0.82–1.31)	0.774	1.08 (0.86–1.35)	0.510	1.23 (0.86–1.77)	0.254

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Table 4 continued. Subgroup analysis for BsmI polymorphism in vitamin D receptor gene.

Study	N	B *vs.* b		BB *vs.* bb		Bb *vs.* bb		BB+Bb *vs.* bb		BB *vs.* Bb+bb	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Genotyping											
PCR-RFLP	2	0.75 (0.38–1.49)	0.414	0.56 (0.12–2.58)	0.453	0.88 (0.66–1.17)	0.364	0.59 (0.18–1.89)	0.376	0.78 (0.34–1.81)	0.563
Other	3	1.15 (0.90–1.47)	0.258	1.41 (0.80–2.48)	0.237	1.03 (0.74–1.44)	0.855	1.01 (0.58–1.74)	0.976	1.47 (0.87–2.48)	0.148
Control											
PB	3	0.81 (0.32–2.05)	0.408	1.21 (0.83–1.75)	0.326	0.99 (0.78–1.25)	0.927	1.01 (0.74–1.40)	0.939	1.25 (0.88–1.77)	0.217
Other	2	1.07 (0.91–1.26)	0.661	0.64 (0.09–4.45)	0.648	0.64 (0.35–1.20)	0.165	0.63 (0.15–2.61)	0.521	0.85 (0.27–2.69)	0.782

PB – population-based; OR – odds ratio; CI – confidence interval; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism.polymorphism.

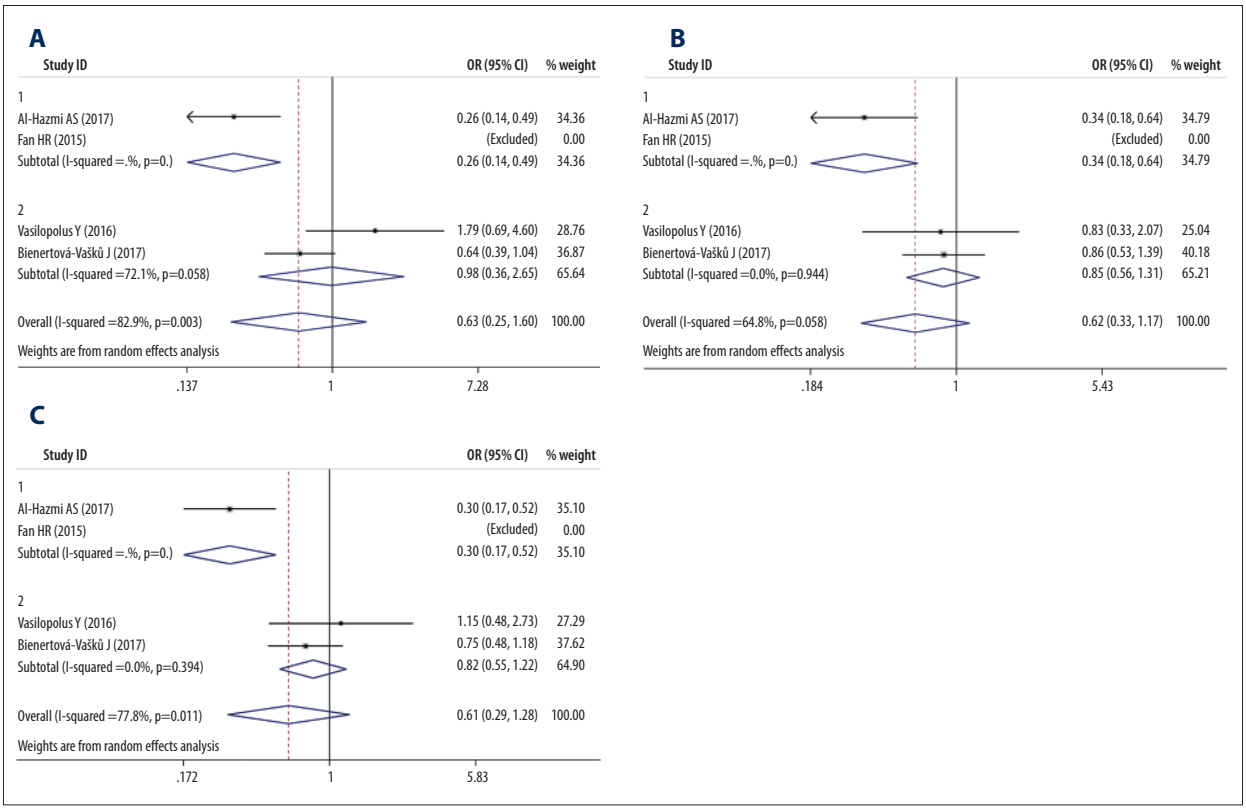

Figure 2. Forest plots of the association of VDR TaqI polymorphism and obesity risk under allele model overall and in Asian. Squares indicate odds ratio (OR); horizontal lines indicate 95% confidence intervals (CI); hollow diamond indicates the pooled OR and its 95% CI. (**A**) T versus t; (**B**) Tt versus tt; (**C**) TT+Tt versus tt.

criteria (Table 1) [9,14–17,19,20]. Among them, the association of the VDR ApaI polymorphism with obesity risk was examined by 3 studies [9,15,17], the VDR BsmI polymorphism by 5 [9,14–16,19], FokI polymorphism by 2 [15,17] and the TaqI polymorphism by 4 [9,15,17,20]. The related characteristics of these included articles are summarized in Table 1. According to the NOS criteria, most of the included studies had high quality (Table 1).

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Table 5. Subgroup analysis for TaqI polymorphism in vitamin D receptor gene.

Study	T *vs.* t		TT *vs.* tt		Tt *vs.* tt		TT+Tt *vs.* tt		TT *vs.* Tt+tt	
	N	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Ethnicity											
Asian	2	1.10 (0.19–6.21)	0.918	0.26 (0.14–0.49)	**0.000**	0.34 (0.18–0.64)	**0.001**	0.30 (0.17–0.52)	**0.000**	1.22 (0.21–7.10)	0.825
European	2	1.04 (0.56–1.94)	0.892	0.98 (0.36–2.65)	0.973	0.86 (0.56–1.31)	0.469	0.82 (0.55–1.23)	0.331	1.18 (0.42–3.32)	0.757
Population											
Adult	4	1.07 (0.55–2.08)	0.843	0.63 (0.25–1.60)	0.330	0.62 (0.33–1.17)	0.138	0.61 (0.29–1.28)	0.189	1.21 (0.53–2.72)	0.654
Juveniles	0										
Sample size											
≤100	2	0.81 (0.26–2.57)	0.725	0.66 (0.10–4.36)	0.665	0.50 (0.21–1.18)	0.113	0.56 (0.15–2.09)	0.388	1.00 (0.25–4.07)	0.997
>100	2	1.42 (0.43–4.74)	0.569	0.64 (0.39–1.04)	0.071	0.86 (0.53–1.39)	0.543	0.75 (0.48–1.18)	0.209	1.45 (0.36–5.87)	0.605
Genotyping											
PCR-RFLP	4	1.07 (0.55–2.08)	0.843	0.63 (0.25–1.60)	0.330	0.62 (0.33–1.17)	0.138	0.61 (0.29–1.28)	0.189	1.21 (0.53–2.72)	0.654
Other	0										
Control											
PB	3	1.43 (0.68–3.00)	0.351	0.98 (0.36–2.65)	0.973	0.86 (0.56–1.31)	0.469	0.82 (0.55–1.23)	0.331	1.62 (0.61–4.29)	0.336
Other	1	0.46 (0.32–0.64)	0.000	0.26 (0.14–0.49)	0.000	0.34 (0.18–0.64)	0.001	0.30 (0.17–0.52)	0.000	0.50 (0.30–0.83)	0.008

PB – population-based; OR – odds ratio; CI – confidence interval; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism. Bold indicated the *P*-values to be significant by meta-analysis of at least 2 studies.

Association between the VDR ApaI polymorphism and the risk of obesity

The results about the associations between VDR ApaI polymorphism and susceptibility to obesity as well as the heterogeneity test are listed in Tables 2 and 3. Overall, the pooling results failed to show the association of ApaI polymorphism with the risk of obesity (Table 2). Subgroup analysis revealed that ApaI polymorphism was related with obesity risk in European ethnicity under recessive model (AA versus Aa+aa: OR=2.31, 95% CI=1.65–3.23; *P*<0.001), but this conclusion was obtained only in 1 study (Table 3).

Association between the VDR BsmI polymorphism and the risk of obesity

The results about the association between VDR BsmI polymorphism and susceptibility to obesity as well as the heterogeneity test are displayed in Tables 2 and 4. Our meta-analysis suggested that VDR BsmI polymorphism was not significantly correlated with obesity in all genetic models overall (Table 2) and in the subgroup analyses (Table 4).

Association between the VDR TaqI polymorphism and the risk of obesity

As shown in Table 2, no obvious association was observed between obesity risk and the VDR TaqI variant overall. However, in the subgroup analysis stratified by ethnicity, a positive association between VDR TaqI polymorphism and obesity risk was found in Asian population studies under a homozygous model (TT versus tt: OR=0.26, 95% CI=0.14–0.49; *P*<0.001) (Figure 2A), heterozygous model (Tt versus tt: OR=0.34, 95% CI=0.18–0.64; *P*=0.001) (Figure 2B), and dominant model (TT+Tt versus tt: OR=0.30, 95% CI=0.17–0.52; *P*<0.001) (Figure 2C, Table 5).

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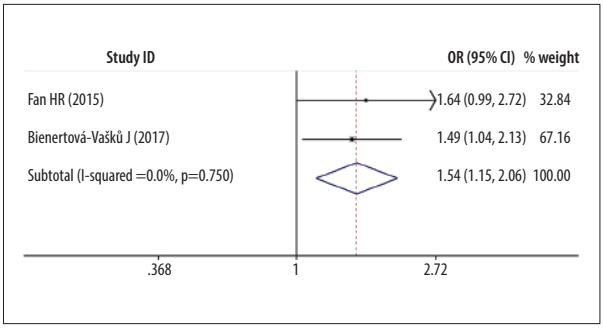

Figure 3. Forest plots of the association of FokI polymorphism and obesity risk in the dominant model (FF+Ff versus ff). Squares indicate odds ratio (OR); horizontal lines indicate 95% confidence interval (CI); hollow diamond indicates the pooled OR and its 95% CI.

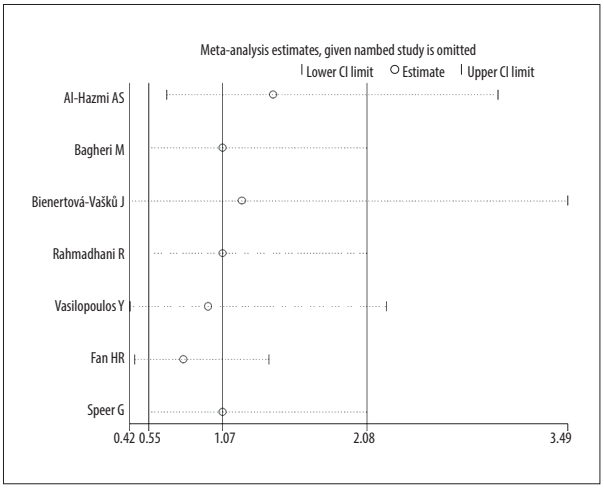

Figure 4. Sensitivity analysis for the assessment of influence of each study (TaqI polymorphism: T versus t). Every hollow round indicates the pooled OR. The broken line is 95% CI. The horizontal axis was ln(OR). OR – odds ratio; CI – confidence interval.

Association between the VDR FokI polymorphism and the risk of obesity

By pooling the data in 2 studies, a significant association between FokI polymorphism and obesity risk was observed in the dominant model (FF+Ff versus ff: OR=1.54, 95% CI=1.15–2.06; *P*=0.004) (Table 2, Figure 3).

Publication bias

Egger's or Begger's test was carried out to analyze the publication bias. The analysis outcomes showed that there was no obvious publication bias for all polymorphisms (Table 2).

Sensitivity analyses

As shown in Figure 4, although each study was successively removed, the overall results did not alter obviously, indicating the high stability of the meta-analysis results.

Discussion

This is the first meta-analysis to specially investigate the association between VDR polymorphisms and the risk of obesity based on 7 case control studies. The pooled findings showed that VDR TaqI polymorphism was statistically associated with susceptibility to obesity in an Asian population under homozygous, heterozygous and dominant models; FokI variant was related with increased risk of obesity only under a dominant model. No obesity risk associations were present for the VDR ApaI and BsmI polymorphisms.

Polymorphism TaqI and FokI are located in the 3' untranslated region of the VDR in exon 9 and 5' promoter region of the VDR in exon 2, respectively. There has been evidence to demonstrate that the mutation in these 2 *loci* affects VDR transcriptional activity and mRNA stability, thus altering the abundance of VDR protein. Low VDR protein levels have been detected from patients homozygous for the t allele [13] and heterozygous for F allele [21]. Furthermore, it had been reported that serum 25-hydroxyvitamin D levels were lower in patients with FokI FF genotype in comparison with patients carrying genotype of ff [22–24]. Also, a significant difference was present in 25-hydroxy vitamin D levels among different genotypes of TaqI, with tt genotype having the lowest vitamin D level, followed by the heterozygous (Tt) and then homozygous genotype (TT) [25]. Deficiency in vitamin D and its receptor VDR due to polymorphisms might contribute to the development of obesity via activating the inflammation in adipocytes through the NF-κB-IL-1 pathway [10,26], which may increase lipogenesis and reduce beta-oxidation [11,27,28]. In addition, lack of VDR was also reported to cause dysbiosis of the intestinal bacterial community, such as the decrease in the *Lactobacillus*, but increase in *Clostridium* and *Bacteroides*. These gut microbiomes may influence the glycolipid metabolism and lead to the obesity [29]. Vitamin D and VDR are common mediators for hormone secretion, including parathyroid hormone and insulin resistance, are important for regulating glucose tolerance [30]. In line with these studies, the "F" allele of FokI was also proposed as a risk factor (FF+Ff versus ff: OR=1.54) for obesity in our study. There was no significant association between TaqI polymorphism and obesity risk in the overall analysis. But, due to the presence of obvious heterogeneity as shown in Table 2, subgroup analyses were conducted. The results showed different ethnicities may be the main reason for heterogeneity. By stratification, we found "T" allele of TaqI may have a protective

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effect (TT versus tt: OR=0.26; Tt versus tt: OR=0.34; TT+Tt versus tt: OR=0.30) for the development of obesity in Asian, but not European. These suggested TaqI polymorphism might be only a crucial genetic factor for Asian population.

There are several limitations in this meta-analysis. First, the number of included studies was relatively small, which may result in lower statistical power to evaluate the associations between variants in the VDR gene and susceptibility to obesity. Second, we did not investigate the interactions between gene-gene and gene-environment due to missing the original data in the eligible studies. Thus, more original papers with large sample sizes were required to further confirm the associations between VDR gene polymorphisms and the risk of obesity.

Conclusions

This meta-analysis suggests that T allele of TaqI may have a protective effect, while the F allele of FokI is proposed as a risk factor for obesity.

Conflict of interests

None.

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