Review

Common Variants of Vitamin D Receptor Gene Polymorphisms and Susceptibility to Coronary Artery Disease: A Systematic Review and Meta-Analysis

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Keywords

Vitamin D receptor · Polymorphism · Coronary artery disease · Meta-analysis

Abstract

Background and Aims: *ApaI*, *FokI*, *TaqI*, and *BsmI* polymorphisms in the vitamin D receptor (*VDR*) gene have been reported to be associated with the risk of coronary artery disease (CAD), although the results of previous studies have been inconsistent. The aim of this study was to explore whether these polymorphisms play a role in the genetic susceptibility to CAD.

Methods: A comprehensive search of Medline and Embase databases was conducted for studies evaluating the association between the *VDR* polymorphisms and CAD risk. Odds ratios with 95% confidence intervals were calculated to assess the strength of association in the dominant model, recessive model, allelic model, and genotypes contrast. **Results:** Nine studies involving a total of 5,259 cases and 1,981 controls were finally included in this meta-analysis. Overall, no significant associations were found between *ApaI*, *FokI*, *TaqI*, and *BsmI* polymorphisms and the risk of CAD in any of the genetic models (all $p > 0.05$). Moreover, a subgroup analysis by ethnicity did not reveal a significant relationship between any of the examined polymorphisms and CAD risk in Caucasians and East-Asians for any model (all $p > 0.05$). **Conclusion:** Current evidence suggests that the *ApaI*, *FokI*, *TaqI*, and *BsmI* polymorphisms of the *VDR* gene might not be associated with genetic susceptibility to CAD. Further well-designed studies with large sample sizes are needed to confirm our results.

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Introduction

Coronary artery disease (CAD) is the most prevalent cardiovascular disease [1] and is the major cause of morbidity and mortality worldwide [2, 3]. CAD is caused by a thrombotic occlusion of coronary arteries triggered by atherosclerotic plaque disruption, resulting in an activation of coagulation processes [4]. It is a complex, multifactorial, and polygenic disorder that involves an interaction between genetic predisposition and environmental factors [5]. It has been shown that traditional risk factors, including diet, obesity, diabetes, hypertension, dyslipidemia, inflammation, smoking, and alcohol consumption, allow the prediction of only about 50% of the absolute risk of a cardiovascular event in individual patients [6, 7], and the remaining risk is attributed to genetic influences [8]. Genetic susceptibility may be caused by mutations and polymorphisms in a variety of genes mostly involved in blood coagulation, regulation of blood pressure, and metabolism of glucose, lipids, or homocysteine [7].

Various association studies have attempted to identify genetic variants that contribute to CAD; among them, the vitamin D receptor (*VDR*) gene has received special attention and has been reported as one of the possible candidates for cardiovascular disorders [9]. A recent meta-analysis demonstrated a linear, inverse association between circulating 25-hydroxyvitamin D and risk of cardiovascular disease [10]. The genomic effects of 1,25-dihydroxyvitamin D in a wide variety of tissues are mediated by *VDR* [11]. The *VDR* gene is located on the long arm of chromosome 12 (12q12–14) and consists of at least 5 promoter regions, 8 protein-coding exons, and 6 untranslated exons, which are alternatively spliced [11–13]. More than 470 *VDR* single-nucleotide polymorphisms have been determined so far; among them, *FokI* (rs2228570), *Apal* (rs7975232), *BsmI* (rs1544410), and *TaqI* (rs731236) have been thoroughly studied for their effects on various physiological and pathological phenotypes, such as cancer, diabetes, myocardial infarction, and CAD [13–15].

Molecular epidemiological studies have presented seemingly contradictory results concerning a potential role of the *VDR* gene polymorphisms in CAD susceptibility. A single study may have low statistical power due to a small sample size and other limitations. Therefore, in order to decisively draw conclusions, the present meta-analysis was conducted to overcome the limitations of individual studies and to resolve these controversial results, as well as to decrease the uncertainty of the effect size of estimated risk.

Materials and Methods

Publication Search

All studies reporting on the association between the *FokI*, *BsmI*, *TaqI*, and *Apal* polymorphisms of the *VDR* gene and susceptibility to CAD published in English before January 2016 were identified by comprehensive computer-based searches of Medline and Embase databases. The following keywords were used for searching: (vitamin D receptor OR *VDR*) AND (polymorphism* OR variant* OR mutation) AND (cardiovascular diseases OR coronary artery disease OR coronary heart disease OR ischemic heart disease OR myocardial infarction OR angina). Google scholar and cross-references within both original and review articles were searched for additional literature. The search was restricted to articles in English.

Inclusion Criteria

Two investigators reviewed all identified studies independently to determine whether an individual study was eligible for inclusion. The selection criteria for studies to be considered for this meta-analysis were as follows: (1) assessing the *FokI*, *BsmI*, *TaqI*, and *Apal* polymorphisms of the *VDR* gene and risk of CAD; (2) applying cohort studies, case-control studies, or nested case-control studies; (3) supplying the number of individual genotypes for the mentioned polymorphisms in cases and controls; and (4) appropriate CAD diagnosis criteria. Cross-sectional studies, reviews, case reports, and animal studies were excluded. Furthermore, studies were excluded if the information could not be extracted.

Data Extraction and Quality Assessment

The following information was collected from each study: the authors' names, journal and year of publication, country of origin, ethnicity, gender, mean or range of age, sample size of cases and controls, and number of cases and controls for each genotype. Data were extracted independently by 2 investigators, and disagreements during the data extraction were resolved by discussion among all reviewers. Furthermore, the quality of the studies was assessed by the Newcastle-Ottawa Scale (NOS) [16]. This quality assessment tool judges studies on the basis of a star system, ranging from 0 to 9 stars and comprising the areas selection, comparability, and outcome. Reports scoring 7–9 were classified as "high quality."

Statistical Analyses

Deviation from Hardy-Weinberg equilibrium (HWE) for the distribution of the allele frequencies was analyzed by Fisher exact test in control groups [17]. Odds ratios (ORs) corresponding to a 95% confidence interval (CI) were applied to evaluate the strength of association of *VDR* polymorphisms with CAD risk; ORs were calculated according to the method of Woolf [18]. The pooled ORs were performed for the dominant model, recessive model, allelic model, homozygote model, and heterozygote contrast, respectively. For each genetic contrast, a subgroup analysis according to ethnicity was applied to evaluate ethnicity-specific effects. Heterogeneity among the studies was assessed by the Cochran Q test and the I^2 statistic ($I^2 = (Q - df)/Q \times 100\%$; $I^2 < 25\%$, no heterogeneity; $I^2 = 25\text{--}50\%$, moderate heterogeneity; $I^2 = 50\text{--}75\%$, large heterogeneity; $I^2 > 75\%$, extreme heterogeneity [19, 20]. The heterogeneity was considered significant if either the Q statistic had $p < 0.1$ or if $I^2 > 50\%$. When heterogeneity was considered significant, the random-effects model (DerSimonian-Laird approach) was applied. Otherwise, the fixed-effects model (Mantel-Haenszel approach) was applied [21, 22]. Begg's and Egger's [23] tests were performed to assess the publication bias of the studies. All statistical tests for this meta-analysis were performed with STATA software (version 14.0; Stata Corporation, College Station, TX, USA).

Results

Studies' Characteristics

A total of 281 studies were identified by the literature search. The flow diagram describing the process of screening and excluding articles for specific reasons is shown in Figure 1. Of the 272 excluded studies, 44 were duplicate publications; 196 were not relevant to *VDR* gene polymorphisms and CAD risk; 12 were reviews, editorials, or comments; 4 were case reports; 5 were studies that reported on the association between other polymorphisms of the *VDR* gene and CAD risk; 4 were on patients with diabetes or kidney disorders; 2 were studies without any control group; and 8 were other irrelevant articles. A total of 8 relevant studies (cases, 5,259; controls, 1,981) were finally included based on the inclusion criteria for CAD susceptibility related to the *FokI*, *BsmI*, *TaqI*, and *Apal* polymorphisms [24–32]. Of these, 7 studies were performed in Caucasians [24–27, 29, 30, 32], and 2 studies [28, 31] were performed in East-Asians. Studies' characteristics are summarized in Table 1. Moreover, genotype and allele distributions for each study are shown in Table 2.

Meta-Analysis of BsmI Polymorphism (rs1544410)

There were 4 studies (cases, 2,574; controls, 1,297) concerning the *BsmI* polymorphism and CAD risk (Tables 1, 2). Of these, 3 studies were performed in Caucasian populations [24, 25, 29], and 1 study was performed in East-Asians [31]. For this polymorphism, the study by Ortlepp et al. [25] deviated from HWE. In the overall population, when all eligible studies were pooled, the analysis revealed no significant association between the *BsmI* polymorphism and risk of CAD in all defined models, including the dominant model (OR = 1.02, 95% CI = 0.87–1.19), recessive model (OR = 1.53, 95% CI = 0.88–2.68), allelic model (OR = 1.17, 95% CI = 0.87–1.58), homozygote model (OR = 1.61, 95% CI = 1.82–3.17), and heterozygote contrast (Aa vs. AA, OR = 0.97, 95% CI = 0.82–1.14) (Table 3). Subgroup analysis by ethnicity

Table 1. Characteristics of the studies included in the meta-analysis

First author [ref.]	Year	Country	Ethnicity	Sex	Cases/ controls	Case/control age, years ^a	Genotype method	Polymorphism	Quality score
Ortlepp [24]	2001	Germany	Caucasian	M/F	217/273	61.5±9.9/61.5±9.9	PCR-RFLP	<i>BsmI</i>	7
Ortlepp [25]	2003	Germany	Caucasian	M/F	2,087/775	59.8±7.1/56.5±11.2	PCR-RFLP	<i>BsmI</i>	7
O'Halloran [27]	2006	Ireland	Caucasian	M/F	1,598/386	NR/NR	PCR-RFLP	<i>ApaI</i> , <i>FokI</i>	7
Pan [31]	2009	China	Asian	M/F	152/212	59.2±11.3/58.6±11.1	PCR-RFLP	<i>FokI</i> , <i>BsmI</i>	8
Hossein-Nezhad [26]	2014	Iran	Caucasian	M/F	642/118	57.93±16/57.46±10	PCR-RFLP	<i>FokI</i>	6
Abu el Maaty [32]	2016	Egypt	Caucasian	M	137/58	35–50/35–50	PCR-RFLP	<i>TaqI</i> , <i>ApaI</i>	8
He [28]	2015	China	Asian	M/F	215/67	62.1±9.4/59.6±13.3	PCR-RFLP	<i>Tru9I</i> , <i>ApaI</i> , <i>TaqI</i> , <i>FokI</i>	9
Garbuzova [29]	2015	Ukraine	Caucasian	M/F	118/234	55.9±0.8/66.0±0.9	PCR-RFLP	<i>ApaI</i> , <i>FokI</i> , <i>BsmI</i> , <i>TaqI</i>	8

NR, not reported; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism. ^a Age is reported as mean ± standard deviation or range.

Fig. 1. Flow diagram describing the process of screening and excluded articles.

did not show a significant association between the *BsmI* polymorphism and CAD risk in Caucasians in any of the genetic models. Since there was only 1 study on an East-Asian population, a subgroup analysis by ethnicity could not be performed for this population.

ApaI Polymorphism (rs7975232)

Four studies including 2,068 cases and 745 controls addressed this issue [27–30] (Tables 1, 2). Of these, 3 studies were performed in Caucasians (cases, 1,853; controls, 678) [27, 29, 30], and 1 study was performed in East-Asians (cases, 215; controls, 67) [28]. The results of pooled ORs in different analysis models are shown in Table 3. No significant association was found between the *ApaI* polymorphism and the risk of CAD in the dominant model (OR = 1.05, 95% CI = 0.83–1.27), recessive model (OR = 1.02, 95% CI = 0.78–1.27), allelic model (OR =

Table 2. Distribution of *VDR* genotypes and alleles in CAD patients and controls

First author [ref.]	CAD cases					Healthy controls					P-HWE	MAF
	<i>BsmI</i>	<i>BsmI</i>	<i>BsmI</i>	<i>BsmI</i>	<i>BsmI</i>	<i>BsmI</i>	<i>BsmI</i>	<i>BsmI</i>	<i>BsmI</i>	<i>BsmI</i>		
	bb	bB	BB	b	B	bb	bB	BB	b	B		
Ortlepp [24]	51	110	56	212	220	77	152	64	306	280	0.497	0.47
Ortlepp [25]	643	1,093	351	2,379	2,186	232	419	124	883	667	0.004*	0.43
Pan [31]	129	21	2	279	25	170	38	4	378	46	0.285	0.11
Garbuzova [29]	44	52	22	140	104	105	104	25	314	154	0.92	0.33

	CAD cases					Healthy controls					P-HWE	MAF
	<i>ApaI</i>	<i>ApaI</i>	<i>ApaI</i>	<i>ApaI</i>	<i>ApaI</i>	<i>ApaI</i>	<i>ApaI</i>	<i>ApaI</i>	<i>ApaI</i>	<i>ApaI</i>		
	AA	Aa	aa	A	a	AA	Aa	aa	A	a		
O'Halloran [27]	443	797	358	1,683	1,513	109	195	82	413	359	0.767	0.46
Abu el Maaty [32]	38	63	36	139	135	22	22	14	66	50	0.084	0.43
He [28]	104	93	18	301	129	31	29	7	91	43	0.954	0.32
Garbuzova [29]	34	58	26	126	110	77	102	55	256	212	0.065	0.45

	CAD cases					Healthy controls					P-HWE	MAF
	<i>FokI</i>	<i>FokI</i>	<i>FokI</i>	<i>FokI</i>	<i>FokI</i>	<i>FokI</i>	<i>FokI</i>	<i>FokI</i>	<i>FokI</i>	<i>FokI</i>		
	FF	Ff	ff	F	f	FF	Ff	ff	F	f		
O'Halloran [27]	615	756	227	1,986	1,210	131	207	48	469	303	0.014*	0.39
Hossein-Nezhad [26]	338	254	50	930	354	76	34	8	186	50	0.136	0.21
Pan [31]	47	65	40	159	145	68	97	47	233	191	0.269	0.45
He [28]	61	103	53	225	209	28	27	12	83	51	0.234	0.38
Garbuzova [29]	32	61	25	125	111	67	115	52	249	219	0.841	0.47

	CAD cases					Healthy controls					P-HWE	MAF
	<i>TaqI</i>	<i>TaqI</i>	<i>TaqI</i>	<i>TaqI</i>	<i>TaqI</i>	<i>TaqI</i>	<i>TaqI</i>	<i>TaqI</i>	<i>TaqI</i>	<i>TaqI</i>		
	TT	TC	CC	T	C	TT	TC	CC	T	C		
Abu el Maaty [32]	36	60	41	132	142	18	27	13	63	53	0.636	0.46
He [28]	195	20	0	410	20	63	4	0	130	4	0.801	0.03
Garbuzova [29]	44	57	17	145	91	103	108	23	314	154	0.488	0.33

CAD, coronary artery disease; P-HWE, *p* value for Hardy-Weinberg equilibrium; MAF, minor allele frequency of control group. * Indicates statistical significance.

1.03, 95% CI = 0.90–1.17), homozygote model (OR = 1.06, 95% CI = 0.75–1.37), and heterozygote contrast (Aa vs. AA, OR = 1.05, 95% CI = 0.81–1.28) in the overall population. Subgroup analysis by ethnicity did not show any significant association between *ApaI* polymorphism and CAD risk in Caucasians in any of the genetic models. Subgroup analysis by ethnicity could not be performed in East-Asians due to insufficient data.

FokI Polymorphism (rs2228570)

There were 6 studies [26–29, 31, 32] with 2,823 cases and 1,072 controls concerning the *FokI* polymorphism and CAD risk; among them, 4 studies were performed in Caucasians [26, 27, 29, 32], and 2 studies were performed in East-Asians [28, 31] (Tables 1, 2). For this polymorphism, the studies by O'Halloran et al. [27] and Abu el Maaty et al. [32] deviated from HWE. We did not find a statistically significant association between the *FokI* polymorphism and CAD risk under the dominant model (OR = 0.91, 95% CI = 0.75–1.07), recessive model (OR = 1.08, 95% CI = 0.86–1.35), allelic model (OR = 1.05, 95% CI = 0.85–1.30), homozygote model (OR = 0.83, 95% CI = 0.58–1.08), and heterozygote contrast (TC vs. TT, OR = 1.13, 95%

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Table 3. Main results of the pooled ORs in different genetic models

	Case/ control	Dominant model		Recessive model		Allelic model		Heterozygote contrast		Homozygote contrast	
		OR (95% CI)	<i>p</i> ^a	OR (95% CI)	<i>p</i> ^a	OR (95% CI)	<i>p</i> ^a	OR (95% CI)	<i>p</i> ^a	OR (95% CI)	<i>p</i> ^a
<i>BsmI</i>											
Overall	2,574/1,494	1.07 (0.82–1.31)	0.02	1.11 (0.88–1.33)	0.61	1.15 (0.93–1.37)	0.10	0.95 (0.79–1.10)	0.65	1.20 (1.02–1.38)	0.26
Caucasians	2,422/1,282	1.14 (0.89–1.38)	0.04	1.11 (0.89–1.34)	0.43	1.22 (1.09–1.35)	0.45	0.97 (0.81–1.14)	0.68	1.20 (1.02–1.38)	0.15
<i>ApaI</i>											
Overall	2,068/745	1.05 (0.83–1.27)	0.74	1.02 (0.78–1.27)	0.92	1.03 (0.90–1.17)	0.80	1.05 (0.81–1.28)	0.73	1.06 (0.75–1.37)	0.89
Caucasians	1,853/678	1.08 (0.84–1.32)	0.61	1.04 (0.78–1.30)	0.88	1.05 (0.90–1.19)	0.74	1.06 (0.81–1.31)	0.54	1.09 (0.77–1.41)	0.86
<i>FokI</i>											
Overall	2,725/1,017	0.93 (0.76–1.10)	0.11	1.14 (0.86–1.43)	0.92	1.00 (0.88–1.12)	0.49	0.88 (0.71–1.06)	0.13	1.06 (0.77–1.35)	0.87
Caucasians	2,358/738	0.90 (0.71–1.08)	0.08	1.10 (0.77–1.42)	0.81	0.96 (0.83–1.09)	0.89	0.85 (0.67–1.04)	0.08	1.01 (0.69–1.32)	1.00
Asians	367/279	1.18 (0.70–1.65)	0.23	1.30 (0.71–1.89)	0.75	1.20 (0.89–1.50)	0.28	1.09 (0.60–1.57)	0.25	1.34 (0.61–2.07)	0.46
<i>TaqI</i>											
Overall	470/359	1.31 (0.77–1.85)	0.97	1.51 (0.62–2.40)	0.94	1.28 (0.93–1.64)	0.98	1.21 (0.68–1.74)	0.94	1.66 (0.55–2.78)	0.89
Caucasians	255/292	1.30 (0.75–1.85)	0.92	1.51 (0.62–2.40)	0.94	1.28 (0.92–1.64)	1.0	1.20 (0.66–1.74)	0.82	1.66 (0.55–2.78)	0.89
OR, odds ratio; CI, confidence interval. ^a <i>p</i> value for heterogeneity.											

CI = 0.83–1.55) in the overall population (Table 3). We also did not find any association in the subgroup analysis of Caucasians and East-Asians in any of the genetic models.

TaqI Polymorphism (rs731236)

The *TaqI* polymorphism was investigated in 3 studies [28–30], including 470 cases and 359 controls; among them, 2 studies were performed in Caucasians [29, 30], and 1 study was performed in East-Asians [28] (Tables 1, 2). No significant association was found between this polymorphism and the risk of CAD in the dominant model (OR = 1.31, 95% CI = 0.77–1.85), recessive model (OR = 1.51, 95% CI = 0.62–2.40), allelic model (OR = 1.28, 95% CI = 0.93–1.64), homozygote model (OR = 1.66, 95% CI = 0.91–3.03), and heterozygote contrast (Ff vs. FF, OR = 1.21, 95% CI = 0.68–1.74) in the overall population. Furthermore, no significant association was observed in the subgroup analysis of Caucasians in any of the genetic models (Table 3). We could not evaluate this polymorphism in East-Asians because there was only 1 study.

Heterogeneity and Publication Bias

Heterogeneity of the included studies is reported in Table 3. For the *BsmI* polymorphism, in the overall analysis, there was a significant moderate heterogeneity in the recessive ($I^2 = 54.1\%$, $p = 0.06$), allelic ($I^2 = 71.6\%$, $p = 0.01$), and homozygote ($I^2 = 65.9\%$, $p = 0.03$) models. Moreover, a statistically significant heterogeneity was detected for *FokI* polymorphism in the dominant ($I^2 = 62.0\%$, $p = 0.02$), allelic ($I^2 = 62.6\%$, $p = 0.02$), and heterozygote ($I^2 = 56.3\%$, $p = 0.04$) models. No significant heterogeneity was found in any of the other models in the overall analysis. Because the number of included studies for our meta-analysis was small, the test for publication bias was only conducted for the *FokI* polymorphism (including 6 studies). Begg's and Egger's tests found no evidence of a publication bias in any of the genetic models for the *FokI* polymorphism (data not shown).

Sensitivity Analyses

We removed the study by Ortlepp et al. [25], Abu el Maaty et al. [32], and O'Halloran et al. [27] in the meta-analysis due to the genotype distribution in the control groups, since *BsmI* and *FokI* polymorphisms deviated from HWE, respectively. We found that the corresponding pooled ORs were not substantially altered, which points to the reliability of our results.

Discussion

FokI, *BsmI*, *TaqI*, and *ApaI* polymorphisms in the *VDR* gene have been suggested as potential genetic factors for CAD susceptibility. However, the results from published studies are still inconclusive. Thus, the present meta-analysis was performed to comprehensively analyze these associations. The results of our meta-analysis do not provide evidence for an association between the *VDR FokI*, *BsmI*, *TaqI*, and *ApaI* polymorphisms and the risk of CAD. These findings suggest that these polymorphisms may not be involved in CAD pathogenesis and, thus, could not explain individual differences in genetic susceptibility to CAD. Since ethnic background can influence the results [33], we also conducted subgroup analyses by ethnicity for these polymorphisms but again found no relation in stratified analyses.

Consistent with our results, results of a recently published study with a Mendelian randomization design in the Copenhagen City Heart showed that there is no causal relationship between lower serum vitamin D and increased risk of ischemic heart disease or myocardial infarction, and the genetic variants were not associated with increased risk of ischemic heart disease [34].

In contrast to our results, in a cross-sectional study carried out by Ortlepp et al. [35] which covered 3,436 Caucasian subjects, the BB genotype of *VDR* was significantly associated with the presence of myocardial infarction in patients below 65 years (OR = 1.38, 95% CI = 1.07–1.79, $p = 0.016$). Unlike in the study by Ortlepp et al. [35], in a study by Van Schooten et al. [36], a marginally significant association was found, which indicated a higher incidence of CAD in carriers of the bb allele pair of *BsmI* *VDR* (OR = 4.2, 95% CI = 0.8–22.5, $p = 0.06$). This study was carried out in 41 Caucasian patients with documented CAD. Moreover, the DIAB-HYCAR prospective cohort study [37], including 3,137 patients with type 2 diabetes, also demonstrated an increased risk for incident cases of CAD among carriers of the B allele (hazard ratio = 1.16, 95% CI = 1.05–1.29, $p = 0.002$). Although the present meta-analysis did not find any associations between *FokI*, *TaqI*, *BsmI*, and *Apal* polymorphisms of the *VDR* gene and the risk of CAD in the overall population, in Caucasians, and in Asians, the results should be interpreted with caution.

For an evaluation of the investigated polymorphisms, there were limited published studies. Due to the relatively small sample size, it is not possible to draw a firm conclusion. Moreover, in the stratified analysis by ethnicity, the included studies involved only Caucasians and East-Asians, and data concerning other ethnicities, such as Africans, were not found. For East-Asians, only 2 published studies were analyzed. With a small sample size such as this, the ability to find a reliable association is limited. In addition, more than 30 polymorphisms of the human *VDR* gene have been identified [38], but only a modest amount of these polymorphisms has been examined in CAD patients.

As a result, our meta-analysis is restricted to 4 of the most studied polymorphisms. We are unable to exclude the likelihood that other polymorphisms of the *VDR* gene also contribute to the risk for CAD. Even if none of these single-nucleotide polymorphisms are associated with CAD, it is possible that *VDR*, as a gene mediating the action of vitamin D, might still play a role in CAD. Therefore, further studies are warranted to evaluate the effect of these polymorphisms on CAD risk in different ethnicities, especially in Africans and East-Asians.

The main aim of performing a meta-analysis was to increase statistical power and to obtain more compelling results by increasing the sample size. However, some limitations of the present study need to be discussed. First, because of the limited available published literature, the number of studies included in this meta-analysis was relatively small. Second, this meta-analysis focused only on papers published in the English language. Third, several studies have indicated the importance of age [39, 40], gene-environment interactions [41, 42], gene-gene interactions [43], and lifestyle factors [44] in CAD development. The present meta-analysis was based on crude estimates without adjusting by age, dietary vitamin D intake, and sun exposure, which is another potential limitation of our study. Fourth, statistically significant heterogeneity was observed for the *BsmI* and *FokI* polymorphisms when all the eligible studies were pooled. This heterogeneity can be due to genetic background, sample size, and the uniformity of cases and controls. After a stratified analysis by ethnicity, it was observed that the heterogeneity remarkably decreased in Caucasians, indicating that genetic background might be the source of heterogeneity.

In summary, the current meta-analysis provides pooled results of the available evidence for the association between the *VDR* polymorphisms and CAD risk. This gene-based analysis indicates that, based on current evidence from published studies, the *Apal*, *FokI*, *TaqI*, and *BsmI* polymorphisms of the *VDR* gene are not associated with CAD. Because of the paucity of the available data, additional large well-designed epidemiological studies are required to allow a more definitive conclusion. In addition, further studies should assess the influence of other *VDR* polymorphisms on CAD. Such studies should also take environmental factors into account, so as to gain a better and more comprehensive understanding of the relationship between *VDR* gene polymorphisms and CAD susceptibility.

Disclosure Statement

There are no conflicts of interest to declare.

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