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ORIGINAL ARTICLE

Association between polymorphisms in vitamin D receptor gene and adolescent idiopathic scoliosis: a meta-analysis

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Abstract

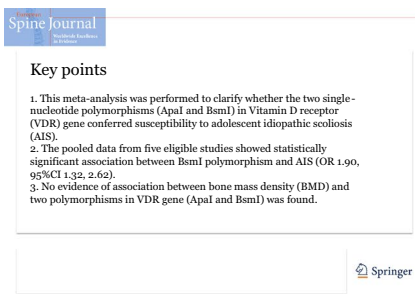
Purpose This meta-analysis was performed to clarify whether the two single nucleotide polymorphisms (*ApaI* and *BsmI*) in vitamin D receptor (VDR) gene conferred susceptibility to adolescent idiopathic scoliosis (AIS).

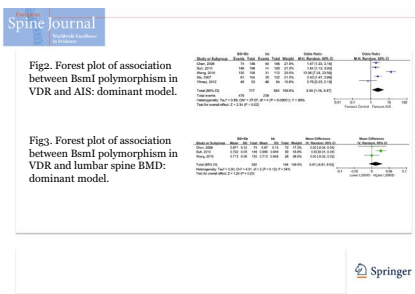
Methods A comprehensive literature search in five online databases (PubMed, EMBASE, ISI Web of Science, CNKI, and Wanfang) was performed to identify studies that analyzed the association between VDR gene polymorphisms and risk of AIS. Observational studies met the predetermined inclusion criteria were selected for meta-analysis. The most appropriate genetic model was identified using a genetic model-free approach. Meta-analysis was performed using RevMan 5.3 software.

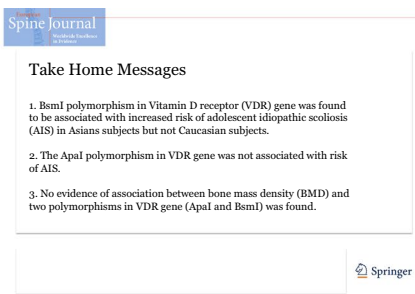
Results Five eligible studies were included in this meta-analysis, which involved a total of 717 cases and 554 controls. A statistically significant association was observed between *BsmI* polymorphism and AIS (OR 1.90, 95% CI 1.32, 2.62). In subgroup analysis by ethnicity, the association between *BsmI* polymorphism and AIS was significant in Asians (OR 2.06, 95% CI 1.56, 2.73) but not in Caucasians (OR 0.70, 95% CI 0.23, 2.19). However, the *ApaI* polymorphism was not associated with AIS. Moreover, no evidence of association between BMD and the two VDR gene polymorphisms was detected.

Conclusions Meta-analysis of existing data suggested that *BsmI* was associated with increased risk of AIS in Asian populations. Nevertheless, further studies with rigorous design and more ethnic groups are encouraged to validate our findings.

Graphical abstract These slides can be retrieved under Electronic Supplementary Material.







Keywords Adolescent idiopathic scoliosis · Polymorphism · Vitamin D receptor · Bone mineral density · Meta-analysis

Introduction

Adolescent idiopathic scoliosis (AIS), a disorder that usually begins in early puberty and affects about 1–4% of the overall population, is the most common type of scoliosis [1]. Compared with neuromuscular, degenerative, congenital, and other types of scoliosis which have better understood fundamental mechanisms, the etiopathogenesis

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Extended author information available on the last page of the article

of AIS remains indeterminate although hypothesis such as hormonal imbalances, neurological abnormalities, spinal growth disturbance, as with biochemical factors that have been proposed to elucidate the condition [2, 3]. Studies have noted the familial aggregation phenomenon of AIS patients [4]. In addition, an autosomal-dominant mode of inheritance [5] as well as abnormal expression of lncRNAs and mRNAs among AIS population also has been reported [6]. Supported by pile of concrete evidence, genetic factors have been widely acknowledged to be associated with the occurrence and development of AIS [7–10].

Vitamin D receptor (VDR) gene, which is located on chromosome 12q13 [11], is a member of human transcription factors [12, 13] and mediates various biological effects of 1, 25-dihydroxycholecalciferol ($1,25(OH)_2D_3$) [14, 15]. In bone tissue, VDR can mediate the function of vitamin D and has a critical effect on normal bone remodeling and mineralization, as numerous studies have demonstrated [16, 17]. By means of binding to $1,25(OH)_2D_3$, VDR regulates gene transcription by forming a heterodimer with retinoid X receptor (RXR) [18]. When occupied by $1,25(OH)_2D_3$, the heterodimer formed by VDR and RXR binds to vitamin D responsive elements in the region of genes directly regulated by $1,25(OH)_2D_3$ [19]. Meanwhile, VDR could mediate rapid non-genomic effects [20]. When binding to $1,25(OH)_2D_3$ in the cellular membrane, VDR triggers a series of downstream effects within seconds to minutes such as opening of ion channels, induction of second messengers, insulin secretion, which cannot be blocked by inhibitors of transcription and translation [19, 21]. In recent years, several genetic association studies has identified VDR gene as being closely associated with thoracic curve severity [22–24]. Therefore, VDR gene is regarded as one of the candidate genes potentially related to AIS and has been studied in several populations.

To date, several epidemiologic studies have been conducted to examine the association between two widely known VDR gene polymorphisms (*ApaI* and *BsmI*) and risk of AIS. However, the results are still unable to reach a consensus, particularly owing to the small numbers and varying ethnic groups of the published studies. In order to overcome this contradictory, a meta-analysis by combining all currently available samples was employed to investigate the associations between VDR gene polymorphisms and the risk of AIS.

Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature search strategy

To identify potentially eligible articles on the association between VDR gene polymorphisms and AIS, we searched five online databases including PubMed, EMBASE, ISI Web of Science, CNKI, and Wanfang. A combination of free text terms and Medical Subject Headings (MeSH) was used to retrieve all the potentially relevant articles; MeSH was slightly modified according to the specification of each database. No restriction on language was imposed. Studies published before June 1, 2017, were searched using the following search strategy: (Single Nucleotide Polymorphism or SNP or SNPs or "Polymorphism, Single Nucleotide"[Mesh]) and (VDR or Vitamin D receptor) and ("Scoliosis"[Mesh] or scoliosis or scolioses). For Chinese databases, the search strategy was as follows: "VDR" and "jizhu cewan" and "duotaixing." The reference sections of relevant reviews were also manually searched to identify additional related studies.

Inclusion and exclusion criteria

Studies that met the following criteria were included: (1) Enrolled cases should be adolescents diagnosed as AIS based on well-established diagnostic criteria such as SRS criteria; (2) subjects in control groups should be healthy adolescents without any history of scoliosis; (3) case–control studies or cohort studies on humans that analyzed *ApaI* or *BsmI* polymorphisms in VDR gene; (4) included studies should provide sufficient data for the calculation of odds ratio (OR) and 95% confidence interval (95% CI).

Studies were excluded for following reasons: (1) animal studies, case report or case series, expert opinion; (2) studies that failed to provide sufficient data to calculate OR and the associated 95% CI; (3) studies that are duplicated for retrieval. The most complete study was selected if data reported were duplicated or had been reported for more than once.

Data extraction and quality assessment

Two reviewers screened each article independently and were blinded to the findings of the other reviewer. According to the predetermined inclusion criteria, two reviewers conducted a strict screening to identify qualified articles independently, and they extracted data from these eligible papers using a standardized data collection form, which included first author, year of the publication, country, ethnicity of enrolled subjects, sample size, source of cases, genotypes distribution of cases and controls, and Hardy–Weinberg equilibrium (HWE), which is a critical tool to detect the

population structure [25]. Under HWE, alleles segregate in the population randomly, allowing expected genotype frequencies to be calculated based on allele frequencies [25, 26]. Any discrepancy between the two reviewers was resolved through discussion until a consensus could be reached.

The Newcastle–Ottawa Scale (NOS) for the assessment of observational studies was employed to assess the methodological quality of eligible studies [27]. Three broad perspectives including selection of cases and controls, comparability of the groups, and ascertainment of outcome of interest were evaluated using the Star system. Two investigators assessed the methodological qualities of included studies independently, and the results of risk of bias judgment were compared afterward.

Statistical analysis

The goodness of fit of HWE was evaluated using the Chi-square test in control subjects of each included study. The association between *ApaI* and *BsmI* in VDR gene and risk of AIS was expressed using odds ratio (OR) and 95% confidence interval (95% CI). The estimated difference of BMD between different genotypes was assessed using mean difference (MD) along with the associated 95% CI. In order to identify the most appropriate inheritance model for VDR gene polymorphisms in the association of BMD and risk of AIS, we used a genetic model-free approach [28]. Briefly, no prior assumptions regarding the genetic model for meta-analysis were made, and we allowed the data available to "dictate" the best-matching genetic model. If the alleles of the gene of interest were A and a, and A was the allele causing an effect, then OR1, OR2, and OR3 were calculated for genotypes AA versus aa, Aa versus aa, and AA versus Aa for each polymorphism that is selected for meta-analysis to capture the magnitude of genetic effect. For continuous variables, data from each included study were extracted and expressed as mean and standard difference (SD) for each genotype (AA, Aa, aa). We further defined the combined difference of means value between groups AA and aa (D1), groups Aa and aa (D2), and groups AA and Aa (D3). The best-matching genetic model was then determined according to the relationships between the following three pairwise comparisons:

(1) Recessive model: if $OR1 = OR3 \neq 1$ and $OR2 = 1$, or $D1 = D3 \neq 0$ and $D2 = 0$;
(2) Dominant model: if $OR1 = OR2 \neq 1$ and $OR3 = 1$, or $D1 = D2 \neq 0$ and $D3 = 0$;
(3) Complete over-dominant model: if $OR1 = 1$, $OR2 = 1/OR3 \neq 1$, or $D2 = -D3 \neq 0$ and $D1 = 0$;
(4) Codominant model: if $OR1 > OR2 > 1$ and $OR1 > OR3 > 1$ (or $OR1 < OR2 < 1$ and $OR1 < OR3 < 1$), or $D1 > D2 > 0$ and $D1 > D3 > 0$ (or $D1 < D2 < 0$ and $D1 < D3 < 0$).

The homogeneity among studies was evaluated using the Q-statistical test and I^2 test. The random-effect model and fixed-effect model were used for meta-analysis in the presence ($P < 0.1$, $I^2 > 50\%$) or absence of heterogeneity ($P > 0.1$, $I^2 < 50\%$ indicates acceptable heterogeneity), respectively. If statistically significant heterogeneity across studies existed, subgroup analysis by ethnicity (Asian/Caucasian) was performed to test whether there was an ethnicity-dependent effect. Egger's regression test and Begg's rank correlation test were employed to estimate the potential publication bias (Stata version 12.0, Stata Corp LP, USA). Funnel plots were generated using RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Sensitivity analysis was performed by omitting each study at a time and reevaluating the resulting effect on the overall effect.

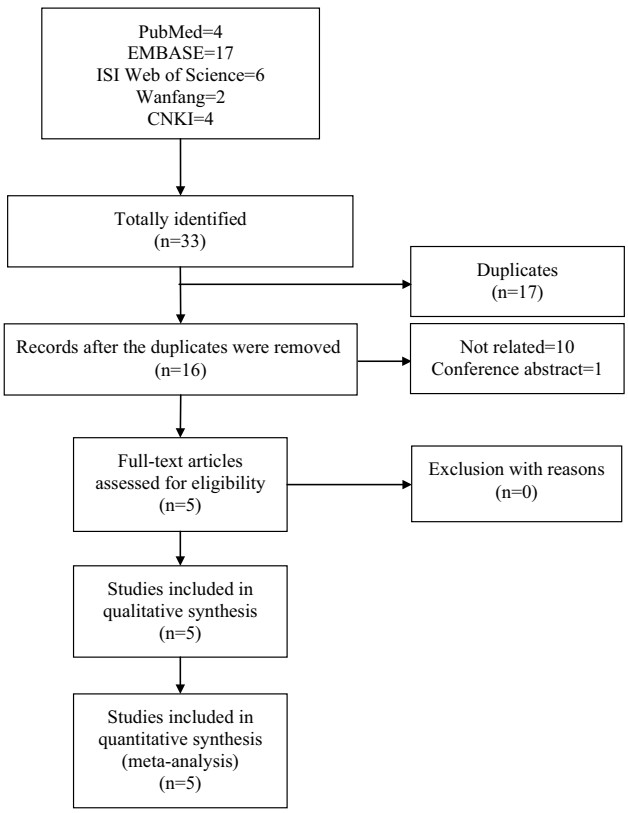

Fig. 1 Flowchart of literature selection

Results

Study characteristics

The process of literature selection is given in Fig. 1. We initially identified 33 articles according to the search strategy (PubMed: 4, EMBASE: 17, ISI Web of Science: 6, Wanfang: 2, CNKI: 4), and after the removal of 17 duplicated records, 16 studies were screened with titles and abstracts. Among these studies, 10 were excluded for irrelevance, and one was removed because it was a conference abstract. Finally, five case–control studies [22–24, 29, 30] including 717 adolescents with AIS and 554 healthy controls were deemed eligible for inclusion for meta-analysis.

All the cases were corresponded with the definition of AIS, with the diagnosis confirmed by normal standing whole-spine anterior–posterior radiographs. Each included study focused on the association between *BsmI* polymorphism of VDR gene and risk of AIS, three studies additionally analyzed the association between *ApaI* and AIS. Among the selected studies, four were conducted in Asian population, whereas another study was performed in Caucasian population. Four studies recruited only female adolescents while one study recruited patients of both genders. All the studies had genotype frequencies in control groups consist with HWE. The genotype distributions of VDR gene polymorphisms in cases and controls are summarized in Table 1.

Quality assessment

In the assessment of methodological quality, included studies achieved an average of 6.2 stars. All the included studies reported adequate definition of AIS, but none of them recruited consecutive patients or used random sampling method to ensure the representativeness of cases. The control groups were comprised of adolescents without any history of AIS, thus all studies gained one star in "Definition of control subjects." With regard to "Control for important factor or additional factor," three studies were given one star because they controlled gender for cases and controls, one

Table 1 Main characteristics and genotypes distribution of VDR polymorphisms in cases and controls

Study	Country	Ethnicity	Sample size	Source of cases	Case			Control			HWE
ApaI					AA	Aa	aa	AA	Aa	aa	
Chen et al. [28]	China	Asian	146/146	Female AIS	14	49	83	8	59	79	0.779
Wang et al. [23]	China	Asian	156/112	Female AIS	12	51	93	5	46	61	0.602
Xia et al. [30]	China	Asian	164/122	Female AIS	15	56	93	6	50	66	0.669
BsmI					BB	Bb	bb	BB	Bb	bb	
Chen et al. [28]	China	Asian	146/146	Female AIS	7	67	72	6	44	96	0.945
Suh et al. [22]	Korea	Asian	198/120	Female AIS	46	102	50	13	61	46	0.550
Wang et al. [23]	China	Asian	156/112	Female AIS	43	87	26	3	28	81	0.954
Xia et al. [30]	China	Asian	164/122	Female AIS	8	73	83	6	29	87	0.254
Yilmaz et al. [24]	Turkey	Caucasian	53/54	AIS of both gender	19	26	8	22	26	6	0.920

AIS adolescent idiopathic scoliosis, *VDR* vitamin D receptor, *NA* not available, *HWE* Hardy–Weinberg equilibrium

Table 2 Quality assessment of included studies

Item/study	Chen et al. [28]	Suh et al. [22]	Wang et al. [23]	Xia et al. [30]	Yilmaz et al. [24]
Adequate definition of cases	*	*	*	*	*
Representativeness of cases	–	–	–	–	–
Selection of control subjects	*	–	–	–	–
Definition of control subjects	*	*	*	*	*
Control for important factor or additional factor	*	**	*	*	–
Exposure assessment	*	*	*	*	*
Same method of ascertainment for all subjects	*	*	*	*	*
Non-response rate	*	*	*	*	*

A study could be awarded a maximum of one star for each item except for the item "Control for important factor or additional factor". The definition/explanation of each column of the Newcastle–Ottawa Scale is available from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

study was allotted two stars because gender and age-matched cases were recruited in their study. The detailed information of quality assessment is given in Table 2.

Risk of AIS and VDR gene polymorphisms

The association between VDR gene polymorphisms and risk of AIS was indicated as OR and 95% CI. For association between *ApaI* and risk of AIS, the estimated OR1 (AA vs. aa), OR2 (Aa vs. aa), OR3 (AA vs. Aa) were 1.67 (95% CI 0.94, 2.98; $P=0.08$), 0.77 (95% CI 0.58, 1.03; $P=0.08$) and 2.17 (95% CI 1.20, 3.91; $P=0.01$), respectively. The estimated OR3 was statistically significant while OR1 and OR2 were not significant, and thus no association was found between *ApaI* and risk of AIS.

For another polymorphism in VDR gene, *BsmI*, estimated OR1 (BB vs. bb), OR2 (Bb vs. bb), OR3 (BB vs. Bb) were 3.54 (95% CI 2.36, 5.31; $P<0.00001$), 2.57 (95% CI 2.00, 3.00; $P<0.00001$), 1.44 (0.97, 2.15; $P=0.07$), respectively. The pooled results indicated that OR1 and OR2 were significant, whereas OR3 was not significant, and thus the genetic model was most likely to be dominant model. Using a dominant model, data for BB and Bb were collapsed and compared to bb group, the estimated OR was 2.55 (95% CI 1.16, 5.57; $P=0.02$), as shown in Fig. 2. Since substantial between-study heterogeneity existed, the random-effect model was applied for meta-analysis. Further sources of heterogeneity should be identified before accepting the estimate.

BMD and VDR gene polymorphisms

Three studies [22, 23, 29] measured femoral neck BMD and lumbar spine BMD using dual-energy X-ray absorptiometry. In order to assess the association between VDR polymorphisms and BMD, mean and SD of BMD for different genotypes extracted from each included study are listed in Table 3. For *ApaI*, no significant association with femoral neck BMD was detected, because estimated D1 (0.00, 95 % CI −0.04, 0.04; $P=0.87$), D2 (0.01, 95% CI −0.01, 0.03; $P=0.28$), and D3 (−0.02, 95% CI −0.06, 0.02; $P=0.39$) were all nonsignificant, but still a negative correlation between *ApaI* and lumbar spine BMD was found for similar reason.

BsmI polymorphism in VDR was not related to femoral neck BMD since D1 (0.00, 95% CI −0.02, 0.01; $P=0.71$),

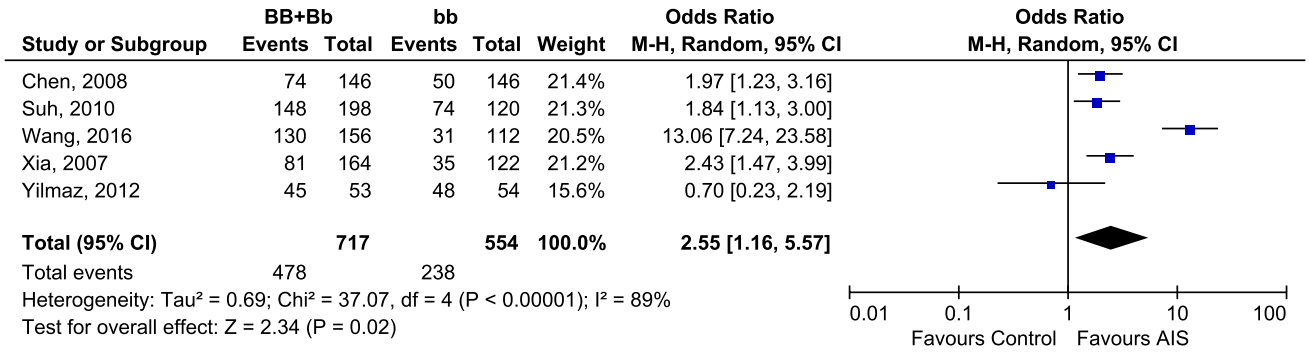

Fig. 2 Forest plot of association between *BsmI* polymorphism in VDR and AIS: dominant model

Table 3 Bone mineral densities in AIS patients with different genotypes

Study	*ApaI*			*P* value	*BsmI*			*P* value
	AA	Aa	aa		BB	Bb	bb	
FNBMD								
Chen et al. [28]	0.806 ± 0.080	0.840 ± 0.110	0.820 ± 0.110	0.440	0.860 ± 0.100	0.840 ± 0.100	0.830 ± 0.110	0.689
Suh et al. [22]	NA	NA	NA	NA	0.707 ± 0.047	0.701 ± 0.039	0.712 ± 0.052	0.330
Wang et al. [23]	0.715 ± 0.099	0.706 ± 0.072	0.698 ± 0.072	0.678	0.695 ± 0.078	0.706 ± 0.068	0.700 ± 0.088	0.723
LSBMD								
Chen et al. [28]	0.910 ± 0.130	0.880 ± 0.110	0.860 ± 0.130	0.401	0.880 ± 0.130	0.870 ± 0.120	0.870 ± 0.130	0.914
Suh et al. [22]	NA	NA	NA	NA	0.728 ± 0.054	0.720 ± 0.048	0.696 ± 0.048	0.005
Wang et al. [23]	0.718 ± 0.046	0.722 ± 0.067	0.707 ± 0.054	0.323	0.710 ± 0.061	0.715 ± 0.060	0.713 ± 0.048	0.890

FNBMD femoral neck bone mineral density, *LSBMD* lumbar spine bone mineral density, *NA* not available

P value was calculated based on intragroup comparison using ANOVA test

D2 (−0.01, 95% CI −0.02, 0.00; $P=0.44$), D3 (0.00, 95% CI −0.01, 0.02; $P=0.73$) were not significant. However, the estimated D1 (0.02, 95% CI 0.00, 0.03; $P=0.02$), D2 (0.01, 95% CI 0.00, 0.03; $P=0.02$), and D3 (0.00, 95% CI −0.01, 0.02; $P=0.68$) suggested that a dominant model should be used to test the association between *BsmI* and lumbar spine BMD. Under the dominant model, data for group BB and Bb were combined and compared to group bb. The estimated MD was 0.01 (95% CI −0.01, 0.03; $P=0.23$), suggesting AIS patients with BB or Bb genotypes had equivalent lumbar spine BMD as patients who had bb genotype (Fig. 3).

Sensitivity analysis and subgroup analysis

Sensitivity analysis was performed by removing each included study at one time, and the results suggested that the overall effect of the association between *BsmI* and AIS was stable. Furthermore, when removing the study conducted by Wang et al. [23], the between-study heterogeneity was not significant ($I^2=23\%$ after its removal). Thus, the study performed by Wang and coworkers was deemed as one potential source of heterogeneity across studies and consequently removed from the meta-analysis (Fig. 4).

The subgroup analysis by ethnicity showed that *BsmI* was associated with an increased risk of AIS in Asians (OR 2.06, 95% CI 1.56, 2.73) but not in Caucasians (OR 0.70, 95% CI 0.23, 2.19) (Fig. 5). The Egger's test ($t=-1.72$, $P=0.228$) and Begg's test ($z=0.34$, $P=0.734$) suggested no significant publication bias in the association between *BsmI* and AIS. The publication bias was not detected in other comparisons due to limited number of included studies.

Discussion

The present study was performed to validate the relationship of VDR gene polymorphisms (*ApaI* and *BsmI*) and AIS susceptibility. Five reports were eligible for this study based on the inclusion criteria. Data from the five published reports were merged to estimate genetic associations between the two commonly detected polymorphisms and the risk of AIS as well as BMD. Through no evidence of association with BMD was observed, the *BsmI* polymorphism in VDR gene suggested a positive association with increased risk of AIS.

VDR has been found in most tissues and plays a critical role in cellular proliferation and differentiation in a variety of cell types [31]. Previous findings indicated that polymorphisms in VDR gene are of great importance to various diseases including musculoskeletal disorders like osteoporosis, osteoarthritis, and disc degenerative disease [11]. It was proved by researchers that the variation at different polymorphic locus was essential to VDR functional activity. However, separating effects of each locus also should be considered [32]. For the purpose of identifying functional sequence variations, current studies focused on 3′ regulatory region of the VDR gene [11]. The *BsmI*, which is

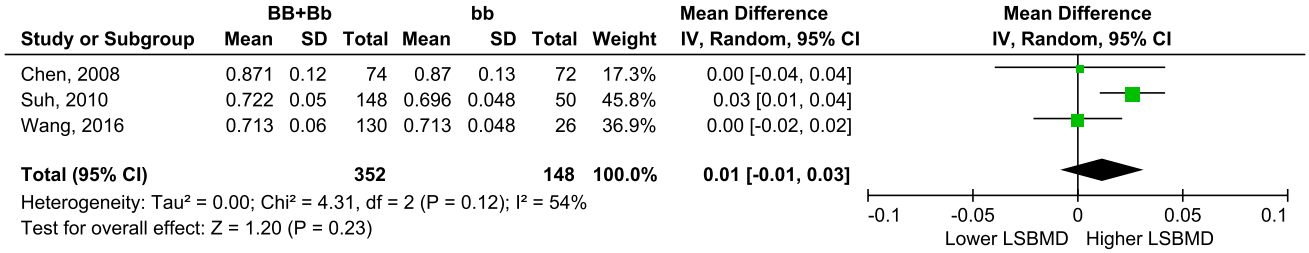

Fig. 3 Forest plot of association between *BsmI* polymorphism in VDR and lumbar spine BMD: dominant model

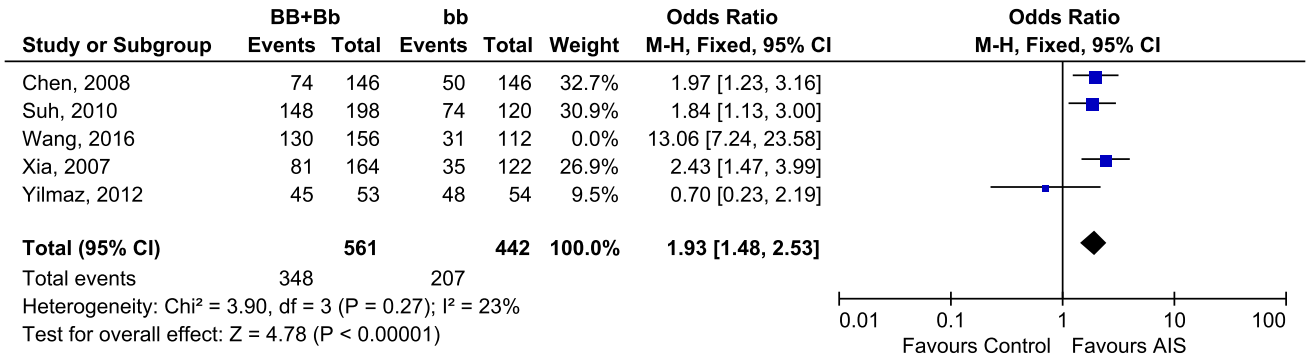

Fig. 4 Forest plot of association between *BsmI* polymorphism in VDR and AIS: sensitivity analysis

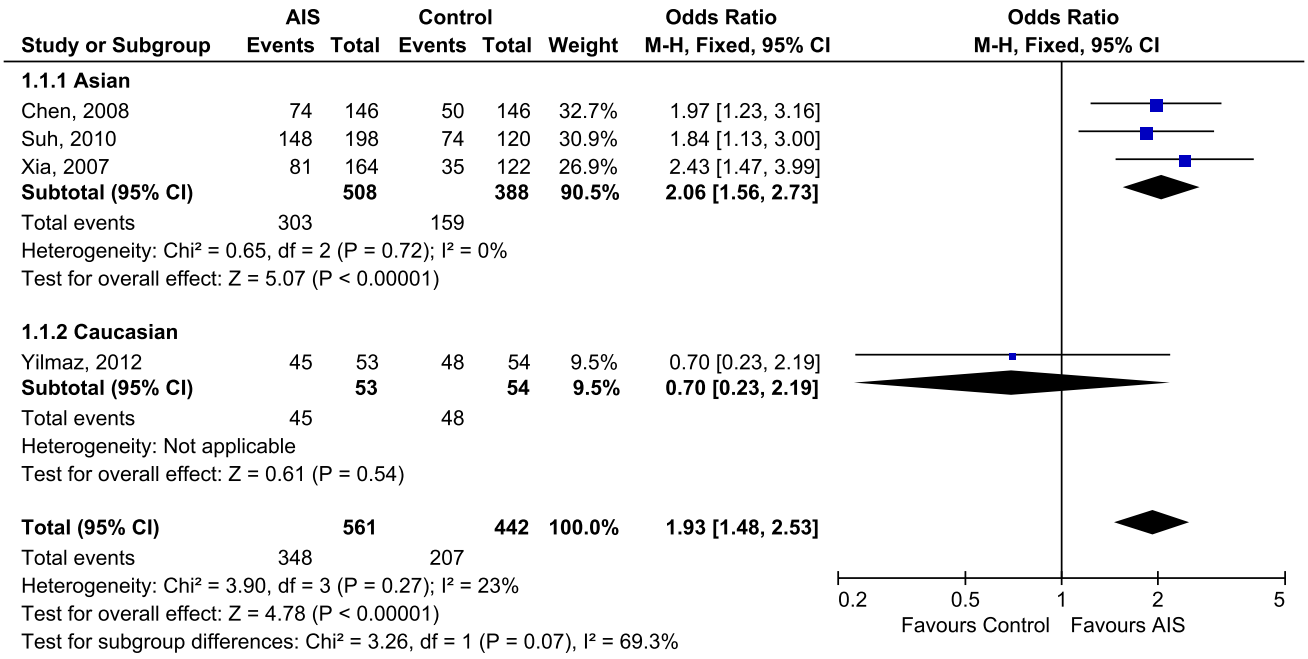

Fig. 5 Subgroup analysis of *BsmI* polymorphism in VDR and AIS: by ethnicity

located at the 3′ untranslated region (3′UTR) of VDR gene, shows strong linkage disequilibrium (LD) with other polymorphisms. This variant could affect the transcription and stability of VDR mRNA [33].

The findings of our study did not support the hypothesis that *BsmI* contributed to lower BMD. Low BMD as well as osteopenia has been found in patients with AIS, while the underlying mechanism is still indeterminate [34, 35]. Osteoporosis, mainly caused by low BMD, is a disorder with a strong genetic component [36]. Several loci polymorphisms in VDR gene including *ApaI* and *BsmI* have been reported to correlate with osteoporosis. Suh et al. [22] initially linked the VDR gene polymorphisms and bone mass in AIS, with subsequent researchers trying to replicate the initial findings. Among the included studies of our meta-analysis, only Suh et al. [22] reported a positive relationship between the variant *BsmI* and lower LSBMD. To minimize the confounding effect of baseline, Suh et al. enrolled an age- and sex-matched healthy control group. However, it should be noted that osteoporosis is a systemic disease resulting from the interaction of multiple genetic factors, gender, age, race, nutrients, endocrine factors, and environmental factors [37, 38]. Besides, the other two studies performed in China failed to replicate the initial finding. How the *BsmI* polymorphism works to affect the LSBMD still needs further investigation.

Prior to accepting the estimate, it is essential to investigate the sources of heterogeneity of included studies. In this meta-analysis, significant heterogeneity was observed in dominant model ($I^2 = 89\%$, $P < 0.00001$) for *BsmI*. We conducted sensitivity analysis by removing each individual study at a time, and then we found that the study by Wang et al. [23] might be the source of heterogeneity. After its removal, the between-study heterogeneity sharply decreased ($I^2 = 23\%$, $P = 0.27$). The possible reason for the discrepancy between Wang et al.'s study and the remaining studies might be the inclusion criteria of Wang's study. Unlike other studies, patients with Risser sign 0–3 were enrolled in Wang et al.'s research, while it was reported that the Risser stages was closely related to the incidence of curve progression, especially in stage 0 or 1 [39]. Another possible explanation is that the relatively small sample size of corresponding study will lead to sampling error. Therefore, more studies based on larger sample size and rigorous design are encouraged in future research.

It is well known that differences in ethnic groups might affect genetic predisposition to human diseases. Hence we conducted subgroup analysis in the present study, and we found that the study from Turkey did not detect the association between the VDR *BsmI* polymorphism and the risk of AIS, which might be due to the diverse ethnicity of the included study participants. However, only one study of Caucasian ethnicity with a small sample size was included in this meta-analysis. In the future, more studies based on lager sample size and case–control design are still needed to confirm whether there is an ethnicity-specific effect on the association between VDR polymorphisms and risk of AIS.

Several limitations of the present meta-analysis should be acknowledged. First, studies included in our analysis did not cover all ethnicities, which might reduce the generalizability of the outcome. Second, the included studies did not

contain sufficient information to perform subgroup analysis by gender and geographical location [40, 41], both of which are considered to be associated with AIS. Third, sample size of each included study is quite limited, thus lacking adequately statistic power to guarantee the association. Fourth, this meta-analysis actually included very few papers, and more studies are encouraged to ensure the outcome. Lastly, only articles in English and Chinese from five databases were retrieved for the meta-analysis, potential relevant articles published in other languages might have been skipped, which could lead to a potential of publication bias.

Conclusion

In summary, the present meta-analysis suggested that *BsmI* but not *ApaI* polymorphism in VDR gene was significantly associated with increased risk of AIS susceptibility in Asian population. While, *BsmI* and *ApaI* polymorphisms were not associated with lower BMD in AIS patients. The presence of *BsmI*–AIS association suggests the possibility of a personalized clinical evaluation aimed to early detect the risk of AIS and even prevent the rapid progression of the curve. Concerning limitations of our meta-analysis, further studies with larger sample size among more ethnicities are encouraged to validate the associations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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