Vitamin D receptor Bsm I polymorphism and osteoporosis risk in postmenopausal women: a meta-analysis from 42 studies

Jun Long Liao 1†, Qiang Qin 2†, Yong Sheng Zhou 1, Ru Ping Ma 1, He Chao Zhou 1, Mao Rong Gu 1, Yun Ping Feng 1, Bo Yuan Wang 3* and Ling Yang 1*

Abstract

Objective: This study aimed to quantitatively summarize the evidence for VDR BsmI gene polymorphism and osteoporosis risk in postmenopausal women.

Materials and methods: The PubMed, EMBASE, Weipu, CNKI, and Wanfang databases were searched for eligible studies. Case-control studies containing available genotype frequencies of B/b were chosen, and odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of this association.

Results: 4485 osteoporosis and 5490 controls were identified in our meta-analysis. In the stratified analysis, a significant association was observed between VDR BsmI gene polymorphism and osteoporosis susceptibility in Caucasians (additive model: OR = 0.809, 95% CI 0.678~0.965, \( p = 0.019 \); recessive model: OR = 0.736, 95% CI 0.568~0.955, \( p = 0.021 \); and co-dominant model: bb vs. BB OR = 0.701, 95% CI 0.511~0.962 \( p = 0.028 \), and we failed to find any significant relationship in Asians.

Conclusion: The present meta-analysis suggests that VDR BsmI genotype is associated with increased risk of postmenopausal osteoporosis in Caucasians but not in Asians. To draw comprehensive and true conclusions, further prospective studies with larger numbers of participants worldwide are needed to examine associations between VDR BsmI polymorphism and osteoporosis in postmenopausal women.

Keywords: Vitamin D receptor, BsmI polymorphism, Osteoporosis, Postmenopausal, Meta-analysis

Introduction

Osteoporosis, as a systemic bone disease characterized by decreased bone mineral density, micro-structure deterioration of bone tissue, and increased risk of bone fracture [1, 2], is commonly seen in postmenopausal females and aged males; about 30% of postmenopausal females suffer from osteoporosis [3]. Bone fractures caused by osteoporosis are extremely harmful and are one of the main causes of disability and death in elderly patients. Research on early identification of high-risk groups has been carried out, which is of substantial clinical significance. The pathogenesis of osteoporosis is currently unclear. It is widely accredited that osteoporosis is related to individual genetic differences, estrogen levels, nutritional status, and lifestyle. In addition, osteoporosis can also be induced by bone formation and bone resorption disorder caused by physical injury, diseases affecting bone metabolism, or long-term use of hormone drugs [4].

The interaction between vitamin D and its receptor exerts an important role in calcium homeostasis and bone metabolism by regulating osteocyte growth and differentiation, intestinal calcium absorption, and parathyroid hormone secretion [5]. The vitamin D receptor (VDR) gene is...
located on chromosome 12 (12q13.1), with a length of more than 100 kb, and more than 100 polymorphic sites are predicted [6, 7]. VDR, therefore, is seen as one of the significant candidate genes to explore the genetic factors leading to osteoporosis. In 1992, Morrison et al. reported that bone mineral density and circulating osteocalcin levels may be affected by VDR BsmI polymorphism (rs1544410) [8, 9].

Postmenopausal osteoporosis, resulting from estrogen deficiency, is the most common type of osteoporosis, and estrogen deficiency results in an increase in bone turnover owing to effects on all types of bone cells [10]. In 1996, Berg et al. reported for the first time that VDR BsmI polymorphism was associated with bone mineral density in postmenopausal females [11]. Since then, epidemiological investigations regarding the assessment of BsmI polymorphism and the susceptibility of postmenopausal osteoporosis have been widely reported. However, the relevant research results have been controversial. For example, in a survey of the Thai population, VDR BsmI polymorphism did not seem to be associated with the risk of postmenopausal osteoporosis [12]. However, significant correlation was observed between VDR genotype and BMD in Chinese postmenopausal females, with bb genotype having the lowest bone density [13]. In recent years, meta-analysis, as a powerful statistical analysis tool, has been adopted to integrate and analyze the data of several published articles; a more accurate and objective assessment is expected to be made on the research results and to explain the heterogeneity between these results [14]. Therefore, the meta-analysis was performed on the currently published eligible case-control studies combined with the previous research results, and the relationship between Bsm I polymorphism and the risk of osteoporosis in postmenopausal females was also explored.

**Methods**

**Literature search**

PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com), Weipu (http://www.cqvip.com/), CNKI (http://www.cnki.net/), and Wanfang (http://g.wanfangdata.com.cn/) databases were thoroughly searched by the authors (last search update, July 10, 2020). The keywords were “vitamin D receptor” or “VDR” and “osteoporosis” or “fracture” and “BsmI” or “rs1544410” in combination with “genetic” or “polymorphism” or “variant”.

**Inclusion criteria**

Selection criteria of this meta-analysis are listed as follows: ① case-control or cohort studies, ② participants included postmenopausal women, ③ assessment of the relationship of BsmI and osteoporosis or fracture, ④ containing available genotype frequencies of BsmI, ⑤ provided BMD values (mean and standard deviation) of lumbar spine and femoral neck, osteoporosis was defined as BMD ≤ −2.5 SDs (T-score).

**Exclusion criteria**

Exclusion criteria of this meta-analysis are listed as follows: ① reviews, case reports, comments, and letters; ② incomplete data; ③ without full text. In addition, all relevant references were also reviewed. If there were duplicate data in papers published by the same author, only the most recent or complete study was included in this analysis.

**Data extraction**

Two independent investigators extracted data from eligible studies; the characteristics included the following: ① the 1st author, ② publication year, ③ region, ④ ethnicity, ⑤ age range, ⑥ sample size, ⑦ allele frequency of cases and controls, and ⑧ genotyping method. Any different evaluation results need to be revisited until a consensus is reached.

**Quality assessment**

The quality of eligible publications was assessed by the Newcastle-Ottawa quality assessment scales (NOS) [15]. The scale contains three parts: the selection of groups (4 questions, 1 score each), the comparability of groups (1 question, 2 scores), the ascertainment of exposure (3 questions, 1 score each). The scores ≥ 5 were regarded as a high-quality study.

**Statistics analysis**

The observed genotype frequencies of the VDR BsmI polymorphism in control groups were assessed for Hardy-Weinberg equilibrium using the X² test. The gene frequencies of the control group must conform to the Hardy-Weinberg equilibrium (p > 0.05). The relationship between VDR BsmI gene and osteoporosis was accessed by calculating odds ratios (ORs) and 95% confidence intervals (CIs). The pooled ORs were performed for additive genetic model (b vs. B), dominant model (bb + Bb vs. BB), recessive model (bb vs. Bb + BB), and codominant model (Bb vs. BB, bb vs. BB) respectively. The subgroup analyses by ethnic groups were also performed. The statistically significant p value was set at 0.05. Heterogeneity assumption was evaluated by a chi-square-based Q test (p < 0.05 indicated heterogeneity across studies). The summary OR estimate of each study was calculated by the fixed-effects model if there was no significant heterogeneity. Otherwise, the random-effects model was used [16, 17]. The potential for publication bias was examined by a Begg’s test (funnel plot method, p < 0.05 considered representative of statistical significance) [18]. All analyses were performed by the Stata software (version 11.0).
Results

Eligible studies

Literature screening process is shown in Fig. 1. Based on the pre-established search strategy, 42 studies were finally enrolled for integrated analyses, including 4485 osteoporosis and 5490 controls. Twenty-three studies [19–46] were performed in Caucasians, and 9 studies [12, 13, 47–53] were subsumed into Asians. In addition, 2 interracial studies [32, 54] were conducted in mixed race. The main characteristics of the selected studies are listed in Table 1. According to the NOS for assessing the quality of case-control studies, all the selected articles meet the requirements (the scores ≥ 5, Table 2). The observed genotype frequencies of the VDR BsmI polymorphism in each control group were assessed by Hardy-Weinberg equilibrium (Table 3), and 11 unequal studies were excluded [20, 25, 27, 33, 36–39, 46, 47, 53].

Meta-analysis

Differences in allelic distribution by ethnicity could be partially responsible for the observed differences in the association between VDR BsmI and osteoporosis. The evaluations of the association between VDR BsmI polymorphism and osteoporosis risk in postmenopausal women are summarized in Table 4. The overall results suggested that there was no association between BsmI polymorphism and the risk of osteoporosis in all genetic models. In the subgroup analysis based on ethnicity, the included studies were divided into Asian, Caucasian, and mix populations. The results showed that VDR BsmI polymorphism was significantly associated with the risk of postmenopausal osteoporosis in Caucasian populations (additive model: OR 0.809, 95% CI 0.678–0.965, p = 0.019; recessive model: OR 0.736, 95% CI 0.568–0.955, p = 0.021; and co-dominant model: bb vs. BB OR 0.701, 95% CI 0.511–0.962, p = 0.028, Fig. 2). However, no significant association was found in any genetic models in both Asian and mix populations.

Publication bias

Begg’s test was performed to quantitatively evaluate the publication bias of literatures on osteoporosis. The results provided statistical evidence in overall results, suggesting the absence of publication bias. All graphical funnel plots of the included studies appeared to be symmetrical. There was no visual evidence of publication bias visually from the funnel plot, which implied that the publication bias was low in the present overall meta-analysis (b vs. BB: p = 0.856; b/b vs. Bb/BB: p = 0.851; Bb/bb vs. BB: p = 0.813; Bb vs. BB: p = 0.510; bb vs. BB p = 0.937).

Discussion

Genetic difference is one important factor affecting the susceptibility to osteoporosis. VDR gene has been widely studied because of its important role in regulating bone metabolism and bone homeostasis. The VDR Bsml polymorphism is located in the 3’ untranslated region (UTR). It is involved in regulating the stability of VDR mRNA and is one of the most important subtypes of VDR gene polymorphism. Studies on VDR Bsml polymorphism and
Table 1: Main characteristics of studies included in the meta-analysis

| BsmI rs1544410 (G > A) | Publication year | Region | Genotyping methods | Osteoporosis n | Age (year) mean ± SD | Control n | Age (year) mean ± SD |
|------------------------|-----------------|--------|--------------------|----------------|---------------------|-----------|---------------------|
| Marozik et al. [19]    | 2018            | Belarus, Lithuania | PCR-RFLP   | 149            | 61.40 ± 6.50        | 172       | 57.50 ± 7.30        |
| Ahmad et al. [20]      | 2018            | India | PCR-RFLP           | 254            | 55.82 ± 6.91        | 254       | 54.76 ± 6.26        |
| Techapatiphandee et al. [12] | 2018            | Thailand | PCR-RFLP   | 105            | 73.10 ± 8.90        | 132       | 63.40 ± 8.70        |
| Moran et al. [21]      | 2015            | Spain | TaqMan            | 150            | 60.24 ± 7.74        | 30        | 59.73 ± 9.28        |
| Marozik et al. [22]    | 2013            | Belarus | PCR-RFLP   | 54             | 58.30 ± 6.20        | 77        | 56.70 ± 7.40        |
| Gonzalez et al. [23]   | 2013            | Mexico | TaqMan            | 88             | 57.65 ± 5.58        | 88        | 56.34 ± 4.98        |
| Efesoy et al. [24]     | 2011            | Turkey | PCR-RDB          | 40             | 65.75 ± 9.80        | 30        | 62.40 ± 8.70        |
| Zhang et al. [13]      | 2011            | China | PCR-RFLP         | 120            | 60.12 ± 3.26        | 60        | 58.69 ± 2.48        |
| Tanriöver et al. [25]  | 2010            | Turkey | PCR-RFLP         | 50             | 58.30 ± 6.50        | 50        | 57.30 ± 6.60        |
| Mansour et al. [26]    | 2010            | Egypt  | PCR-RFLP         | 50             | 54.40 ± 5.10        | 20        | 53.50 ± 5.40        |
| Musumeci et al. [27]   | 2009            | Italy  | PCR-RFLP         | 100            | 49.91 ± 3.08        | 100       | 52.39 ± 4.38        |
| Mencej et al. [28]     | 2009            | Slovenia | PCR-RFLP   | 240            | 64.50 ± 8.20        | 228       | 61.50 ± 8.30        |
| Seremak et al. [29]    | 2009            | Poland | PCR-RFLP         | 163            | 64.27 ± 8.72        | 63        | 63.08 ± 7.24        |
| Perez et al. [30]      | 2008            | Argentina | PCR-RFLP   | 64             | 62.70 ± 0.86        | 68        | 59.40 ± 0.85        |
| Uysal et al. [31]      | 2008            | Turkey | PCR-RFLP         | 100            | —                   | 146       | —                   |
| Quevedo et al. [32]    | 2008            | Chile  | PCR-RFLP         | 67             | 77.00 ± 4.00        | 59        | 78.00 ± 9.00        |
| Wengreen et al. [33]   | 2006            | USA    | PCR-RFLP         | 819            | 76.70 ± 9.10        | 854       | 76.00 ± 9.40        |
| Garnero et al. [34]    | 2005            | France | PCR-RFLP         | 120            | 61.77 ± 8.40        | 469       | 61.77 ± 8.40        |
| Mitra et al. [35]      | 2006            | India  | PCR-RFLP         | 119            | 54.10 ± 3.50        | 97        | 54.10 ± 3.50        |
| Duman et al. [36]      | 2004            | Turkey | PCR-RFLP         | 75             | 53.16 ± 1.31        | 66        | 52.62 ± 1.69        |
| Zhu et al. [47]        | 2004            | China  | PCR-RFLP         | 40             | 57.55 ± 5.18        | 158       | 57.55 ± 5.18        |
| Douroudis et al. [37]  | 2003            | Greece | PCR-RFLP         | 35             | 61.37 ± 0.96        | 44        | 58.68 ± 1.01        |
| Chen et al. [48]       | 2003            | China  | PCR-RFLP         | 40             | 54.72 ± 2.60        | 21        | 54.72 ± 2.60        |
| Lisker et al. [38]     | 2003            | Mexico | PCR-RFLP         | 66             | 65.20 ± 6.80        | 57        | 56.50 ± 6.00        |
| Borjas et al. [39]     | 2003            | Venezuela | PCR-RFLP   | 54             | —                   | 55        | —                   |
| Leng et al. [49]       | 2002            | China  | PCR-RFLP         | 22             | 51.67 ± 4.93        | 46        | 51.67 ± 4.93        |
| A et al. [50]          | 2002            | China  | PCR-RFLP         | 10             | 53.70 ± 7.11        | 13        | 53.70 ± 7.11        |
| Zajickova et al. [40]  | 2002            | Czech  | PCR-RFLP         | 65             | 63.60 ± 7.80        | 33        | 60.10 ± 10.30       |
| Pollak et al. [41]     | 2001            | Israel | PCR-RFLP         | 75             | 49.57 ± 2.97        | 143       | 49.57 ± 2.97        |
| Valimaki et al. [42]   | 2001            | Finland | PCR-RFLP   | 372            | —                   | 111       | —                   |
| Aerssens et al. [43]   | 2000            | Belgium | PCR-RFLP   | 135            | 78.00 ± 9.00        | 239       | 76.00 ± 4.00        |
| Garrofe et al. [44]    | 2000            | Spain  | PCR-RFLP         | 75             | 58.30 ± 5.00        | 51        | 57.20 ± 4.50        |
Table 1: Main characteristics of studies included in the meta-analysis (Continued)

| BsmI rs1544410 (G > A) | Publication year | Region | Genotyping methods | Osteoporosis n | Age (year) mean ± SD | Control n | Age (year) mean ± SD |
|------------------------|------------------|--------|--------------------|----------------|----------------------|-----------|---------------------|
| Zhang et al. [51]      | 2000             | China  | PCR-RFLP           | 34             | 66.70 ± 8.50         | 78        | 66.70 ± 8.50        |
| Gomez et al. [45]      | 1999             | Spain  | PCR-RFLP           | 37             | 66.30 ± 8.67         | 122       | 63.00 ± 8.67        |
| Ramalho et al. [54]    | 1998             | Brazil | PCR-RFLP           | 56             | 78.50 ± 7.20         | 36        | 72.90 ± 5.20        |
| Gennari et al. [46]    | 1998             | Italy  | Southern Blotting  | 160            | 58.20 ± 0.60         | 144       | 57.10 ± 0.70        |
| Zhang et al. [52]      | 1998             | China  | PCR-RFLP           | 17             | 56.76 ± 2.80         | 162       | 58.78 ± 3.00        |
| Vandevyver et al. [55] | 1997             | Belgium| PCR-RFLP           | 75.50 ± 5.00   | 698                  | 66.60 ± 8.40 |
| Houston et al. [56]    | 1996             | UK     | PCR-RFLP           | 44             | 66.00 ± 0.85         | 44        | 65.30 ± 0.95        |
| Berg et al. [11]       | 1996             | Norway | PCR-RFLP           | 19             | 63-65                | 30        | 63-65               |
| Yanagi et al. [53]     | 1996             | Japanese| PCR-RFLP           | 46             | 65.00 ± 8.80         | 66        | 64.90 ± 6.30        |
| Melhus et al. [1]      | 1994             | Sweden | PCR-RFLP           | 70             | 70.00 ± 8.00         | 76        | 69.00 ± 8.00        |

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism. TaqMan Taqman probe-based real-time fluorescent quantitative polymerase chain reaction assay in polymorphism. PCR-RDB: polymerase chain reaction-reverse dot blot. SD: standard deviation.

---: The original text only showed “postmenopausal” and did not provide a specific age range.
| Study | Selection | Comparability | Exposure | Non-response rate | Total score |
|-------|-----------|---------------|-----------|-------------------|-------------|
| Adequate definition of the cases | Representativeness of the cases | Selection of controls | Definition of controls | Control for important factors | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate |
| Marozik et al. [19] | √ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Techapatiphandee et al. [12] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Ahmad et al. [20] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 8 |
| Moran et al. [21] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |
| Marozik et al. [22] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Gonzalez et al. [23] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Efesoy et al. [24] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |
| Zhang et al. [13] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |
| Mansour et al. [26] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |
| Tanriover et al. [25] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 8 |
| Musumeci et al. [27] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |
| Mencej et al. [28] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Seremak et al. [29] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 5 |
| Perez et al. [30] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 8 |
| Uysal et al. [31] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 5 |
| Quevedo et al. [32] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 5 |
| Wengreen et al. [33] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 9 |
| Mitra et al. [35] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Garnero et al. [34] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 5 |
| Duman et al. [36] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Zhu et al. [47] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Douroudis et al. [37] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |
| Borjys-Fajardo et al. [39] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 5 |
| Chen et al. [48] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |
| Lisker et al. [38] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Zajickova et al. [40] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Leng et al. [49] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |
| Ly et al. [50] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 5 |
| Pollak et al. [41] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 5 |
| Study                      | Selection                | Comparability                  | Exposure                        | Total score |
|----------------------------|--------------------------|--------------------------------|---------------------------------|-------------|
|                            | Adequate definition of the cases | Representativeness of the cases | Selection of controls | Definition of controls | Control for important factors | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate |
| Valimaki et al. [42]       | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 5            |
| Aerssens et al. [43]       | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 8            |
| Garrofe et al. [44]        | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 7            |
| Zhang et al. [51]          | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 6            |
| Gennari et al. (1999)      | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 7            |
| Gomez et al. [45]          | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 6            |
| Ramalho et al. [54]        | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 7            |
| Gennari et al. [46]        | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 8            |
| Zhang et al. [52]          | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 6            |
| Vandevyver et al. [55]     | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 7            |
| Houston et al. [56]        | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 6            |
| Berg et al. [11]           | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 5            |
| Yanagi et al. [53]         | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 5            |
| Melhus et al. [1]          | ✓                        | ✓                              | ✓                               | ✓           | ✓                           | ✓                           | ✓                           | ✓                       | 5            |

✓: matched the condition, scored one point
Table 3 The distribution of VDR BsmI genotypes for postmenopausal osteoporosis and controls

| BsmI rs1544410 (G > A) | Publication year | Ethnicity | Osteoporosis BB | Bb | bb | Control BB | Bb | bb | p value |
|------------------------|------------------|-----------|-----------------|----|----|-------------|----|----|---------|
| Marozik et al. [19]    | 2018             | Caucasian | 53              | 64 | 32 | 35          | 73 | 64 | 0.098   |
| Ahmad et al. [20]      | 2018             | Caucasian | 54              | 137| 63 | 54          | 152| 48 | 0.002   |
| Moran et al. [21]      | 2015             | Caucasian | 18              | 65 | 67 | 3           | 19 | 8  | 0.097   |
| Marozik et al. [22]    | 2013             | Caucasian | 12              | 31 | 11 | 11          | 26 | 40 | 0.061   |
| Gonzalez et al. [23]   | 2013             | Caucasian | 54              | 28 | 6  | 46          | 38 | 4  | 0.267   |
| Efesoy et al. [24]     | 2011             | Caucasian | 5               | 23 | 12 | 5           | 15 | 10 | 0.876   |
| Tanriover et al. [25]  | 2010             | Caucasian | 15              | 19 | 16 | 19          | 7  | 24 | < 0.001 |
| Mansour et al. [26]    | 2010             | Caucasian | 27              | 15 | 8  | 1           | 2  | 17 | 0.050   |
| Musumeci et al. [27]   | 2009             | Caucasian | 30              | 55 | 15 | 13          | 60 | 27 | 0.025   |
| Mencej et al. [28]     | 2009             | Caucasian | 103             | 110| 27 | 88          | 100| 40 | 0.215   |
| Seremak et al. [29]    | 2009             | Caucasian | 27              | 66 | 70 | 10          | 27 | 26 | 0.506   |
| Perez et al. [30]      | 2008             | Caucasian | 17              | 35 | 12 | 20          | 32 | 16 | 0.647   |
| Uysal et al. [31]      | 2008             | Caucasian | 18              | 48 | 34 | 24          | 78 | 44 | 0.283   |
| Quevedo et al. [32]    | 2008             | Caucasian | 11              | 46 | 10 | 9           | 37 | 13 | 0.050   |
| Wengreen et al. [33]   | 2006             | Caucasian | 154             | 393| 272| 140         | 376| 338| 0.043   |
| Garnero et al. [34]    | 2005             | Caucasian | 25              | 62 | 33 | 65          | 224| 180| 0.724   |
| Mitra et al. [35]      | 2006             | Caucasian | 51              | 46 | 22 | 19          | 38 | 40 | 0.080   |
| Durman et al. [36]     | 2004             | Caucasian | 18              | 54 | 3  | 17          | 42 | 7  | 0.014   |
| Douroudis et al. [37]  | 2003             | Caucasian | 3               | 12 | 20 | 10          | 29 | 5  | 0.026   |
| Lisker et al. [38]     | 2003             | Caucasian | 15              | 17 | 34 | 13          | 38 | 6  | 0.008   |
| Borjas et al. [39]     | 2003             | Caucasian | 28              | 20 | 6  | 11          | 36 | 8  | 0.020   |
| Zajickova et al. [40]  | 2002             | Caucasian | 21              | 24 | 20 | 10          | 13 | 10 | 0.223   |
| Pollak et al. [41]     | 2001             | Caucasian | 13              | 38 | 24 | 16          | 67 | 60 | 0.675   |
| Valimaki et al. [42]   | 2001             | Caucasian | 44              | 175| 153| 20          | 55 | 36 | 0.899   |
| Aerssens et al. [43]   | 2000             | Caucasian | 26              | 60 | 49 | 52          | 125| 62 | 0.459   |
| Garrofe et al. [44]    | 2000             | Caucasian | 9               | 49 | 17 | 10          | 22 | 19 | 0.434   |
| Gomez et al. [45]      | 1999             | Caucasian | 7               | 20 | 10 | 20          | 51 | 51 | 0.241   |
| Gennari et al. [46]    | 1998             | Caucasian | 40              | 92 | 28 | 11          | 76 | 57 | 0.035   |
| Vandevyver et al. [55] | 1997             | Caucasian | 12              | 50 | 24 | 127         | 368| 203| 0.076   |
| Houston et al. [56]    | 1996             | Caucasian | 8               | 19 | 17 | 9           | 19 | 16 | 0.450   |
| Berg et al. [11]       | 1996             | Caucasian | 4               | 8  | 7  | 8           | 11 | 11 | 0.156   |
| Melhus et al. [1]      | 1994             | Caucasian | 14              | 29 | 27 | 7           | 35 | 34 | 0.637   |
| Techapatiphandee et al. [12] | 2018 | Asian | 85              | 19 | 1  | 103         | 25 | 4  | 0.123   |
| Zhang et al. [13]      | 2011             | Asian     | 9               | 25 | 86 | 16          | 36 | 8  | 0.086   |
| Zhu et al. [47]        | 2004             | Asian     | 6               | 26 | 8  | 7           | 105| 46 | < 0.001 |
| Chen et al. [48]       | 2003             | Asian     | 0               | 7  | 33 | 0           | 3  | 18 | 0.724   |
| Leng et al. [49]       | 2002             | Asian     | 0               | 11 | 11 | 7           | 19 | 20 | 0.488   |
| Ly et al. [50]         | 2002             | Asian     | 0               | 4  | 6  | 1           | 5  | 7  | 0.935   |
| Zhang et al. [51]      | 2000             | Asian     | 2               | 15 | 17 | 7           | 36 | 35 | 0.598   |
| Zhang et al. [52]      | 1998             | Asian     | 0               | 3  | 14 | 0           | 14 | 148| 0.565   |
susceptibility to osteoporosis are various, but the results are not consistent. A recent meta-analysis [57] shows that VDR BsmI is associated with an increased risk of postmenopausal osteoporosis in Asians, while in Caucasians seem to be unrelated, which is contrary to the results of two previously published studies [58, 59]. Since the previous meta-analysis only involved genetic association studies published before 2015, the combination of different original data in each study might have a great impact on the mixed distribution of genotypes. So introducing new data to update meta-analysis is necessary. Through our meta-analysis, it has been found that the VDR BsmI gene polymorphism generally seems not to be a susceptibility gene for postmenopausal osteoporosis. However, in the subgroup analysis, BsmI polymorphism was found to be associated with the risk of postmenopausal osteoporosis in Caucasians, which was not found in the previous meta-analysis. In Asian postmenopausal women, there was no obvious relationship between BsmI polymorphism and osteoporosis susceptibility, which was consistent with the results of a previous meta-analysis of the Chinese population [60]. Through sensitivity analysis and publication bias detection, the results of this meta-analysis were true and credible. The original data of all published eligible studies were almost covered by this meta-analysis. However, according to a recently published meta-analysis of Yadav et al. [61], in the absence of a subgroup analysis based on the sex and age of patients or the type of osteoporosis, BsmI polymorphism seemed not to be associated with the pathogenesis of osteoporosis. It indicated that possible relationship between VDR gene polymorphisms and osteoporosis may be related to gender, race, and age difference of subjects. There may be different

### Table 3  The distribution of VDR BsmI genotypes for postmenopausal osteoporosis and controls (Continued)

| BsmI rs1544410 (G > A) | Publication year | Ethnicity | Osteoporosis | Control | p* |
|------------------------|-----------------|-----------|--------------|---------|----|
|                        |                 |           | BB | Bb | bb | BB | Bb | bb |
| Yanagi et al. [53]     | 1996            | Asian     | 12 | 12 | 22 | 2  | 7  | 57 | 0.013 |
| Ramalho et al. [54]    | 1998            | mix       | 13 | 23 | 20 | 7  | 11 | 18 | 0.050 |
| Quevedo et al. [32]    | 2008            | mix       | 11 | 46 | 10 | 9  | 37 | 13 | 0.050 |

The bold values emphasize that the data does not conform to the Hardy–Weinberg equilibrium, to facilitate the readers to scan the content

* p value for Hardy–Weinberg equilibrium in the control group

| Genetic model | Population | Pooled OR [95% CI] p | Heterogeneity p value* | Publication bias Begg's test p value |
|---------------|------------|----------------------|------------------------|-------------------------------------|
| Additive (b vs. B) | Caucasian | 0.809 [0.678–0.965] 0.019 | < 0.001 | 0.893 |
|                | Asian      | 1.353 [0.628–2.915] 0.440 | < 0.001 | 0.881 |
|                | Mix        | 0.778 [0.530–1.144] 0.202 | 0.594 | 0.317 |
|                | overall    | 0.880 [0.729–1.063] 0.185 | < 0.001 | 0.856 |
| Recessive (bb vs. Bb/BB) | Caucasian | 0.736 [0.568–0.955] 0.021 | < 0.001 | 0.853 |
|                | Asian      | 1.340 [0.442–4.061] 0.605 | < 0.001 | 0.652 |
|                | Mix        | 0.585 [0.314–1.090] 0.091 | 0.862 | 0.317 |
|                | overall    | 0.813 [0.619–1.066] 0.134 | < 0.001 | 0.815 |
| Dominant (Bb/bb vs. BB) | Caucasian | 0.810 [0.654–1.004] 0.055 | 0.009 | 0.833 |
|                | Asian      | 2.107 [0.768–5.784] 0.148 | 0.033 | 0.806 |
|                | Mix        | 0.860 [0.426–1.736] 0.673 | 0.848 | 1 |
|                | overall    | 0.884 [0.715–1.092] 0.253 | 0.001 | 0.813 |
| Bb vs. BB      | Caucasian | 0.880 [0.754–1.027] 0.105 | 0.427 | 0.579 |
|                | Asian      | 1.206 [0.738–1.969] 0.455 | 0.627 | 0.117 |
|                | Mix        | 1.061 [0.501–2.248] 0.878 | 0.896 | 0.317 |
|                | overall    | 0.911 [0.788–1.053] 0.206 | 0.615 | 0.510 |
| bb vs. BB      | Caucasian | 0.701 [0.511–0.962] 0.028 | < 0.001 | 0.895 |
|                | Asian      | 3.146 [0.566–17.50] 0.190 | 0.007 | 0.117 |
|                | Mix        | 0.612 [0.270–1.391] 0.241 | 0.952 | 0.317 |
|                | overall    | 0.811 [0.576–1.141] 0.228 | < 0.001 | 0.937 |

CI confidence interval
* p value for heterogeneity test; random-effects model was used when p value for heterogeneity test < 0.05
mechanisms of VDR gene polymorphisms on different types of osteoporosis [62]. Our research also verified this point, and it should be regarded as a valuable supplement to the published related studies. The causes of osteoporosis are complex; in addition to the joint effects of multi-gene regulation, environmental factors and lifestyles also play an important role [63]. This meta-analysis only discussed genetic factors in the original literature, and the interaction of other factors such as dietary calcium and light exposure and VDR gene polymorphisms on osteoporosis was uninvolved. Therefore, referring to the analysis methods of other researchers [64], we focused on checking the details of the dietary habits of the participants in each study and determined that there was no difference in calcium intake between the case-control group. We believe that for more accurate evaluation of the relationship between vitamin D receptor gene polymorphism and postmenopausal osteoporosis, researches having large samples are required, and the synergy of other factors such as diet, environment, and exercise should be considered more comprehensively when cases are included in the group.

Conclusions

In conclusion, our study believes that VDR BsmI polymorphism and postmenopausal osteoporosis are genetically linked in Caucasians, but not in Asians. It is necessary to conduct large-scale studies to verify the correlation of different populations and environmental factors in the susceptibility to osteoporosis.

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Authors' contributions

Ling Yang and Boyuan Wang conceived and designed this meta-analysis. Qiang Qin, Yongsheng Zhou, and Hechao Zhou searched literatures. Maorong Gu and Yunping Feng typed data entry in the tables. Junlong Liao and Ruping Ma performed analysis. Ling Yang and Boyuan Wang wrote the manuscript. All authors have approved the final manuscript as submitted.

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Competing interests

The authors declare that they have no competing interests.

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**Fig. 2** Association of VDR BsmI polymorphism under different genetic models with osteoporosis risk in postmenopausal women. a Additive model. b Recessive model. c Co-dominant model (bb vs. BB)
