Research Article

Association between vitamin D receptor *BsmI*, *FokI*, and *Cdx2* polymorphisms and osteoporosis risk: an updated meta-analysis

Bin Chen¹, Wang-fa Zhu¹, Yi-yang Mu¹, Biao Liu¹, Hong-zhuo Li² and Xiao-feng He³

¹Changzhi Medical College, No. 161, Jiefangdong Street, Shanxi Province, Changzhi 046000, China; ²Department of Orthopaedics, Heping Hospital Affiliated to Changzhi Medical College, Shanxi, Changzhi 046000, China; ³Department of Science and Education, Heping Hospital Affiliated to Changzhi Medical College, Shanxi, Changzhi 046000, China

Correspondence: Hong-Zhuo Li (ljhz0999@sina.com) or Xiao-Feng He (393120823@qq.com)

Background: Many studies have reported the association between vitamin D receptor (*VDR*) polymorphism and osteoporosis risk. However, their results were conflicting. Six previous meta-analyses have been published to analyze *VDR* BsmI, FokI, and Cdx2 polymorphisms on osteoporosis risk. However, they did not evaluate the reliability of statistically significant associations. Furthermore, a lot of new articles have been published on these themes, and therefore an updated meta-analysis was performed to further explore these issues.

Objectives: To explore the association between *VDR BsmI*, FokI, and Cdx2 polymorphisms polymorphisms and osteoporosis risk.

Methods: The odds ratios (ORs) and 95% confidence intervals (95% CIs) were pooled to evaluate the association between *VDR BsmI*, FokI, and Cdx2 polymorphisms and osteoporosis risk. To evaluate the credibility of statistically significant associations, we applied the false-positive report probabilities (FPPRs) test and the Venice criteria.

Results: Overall, statistically significantly increased osteoporosis risk was found in Indians and women for *VDR FokI* polymorphism. Statistically significantly decreased osteoporosis risk was found in West Asians for *VDR BsmI* polymorphism. However, when we performed a sensitivity analysis after excluding low quality and Hardy–Weinberg Disequilibrium (HWD) studies, significantly decreased osteoporosis risk was only found in overall population for *VDR BsmI* polymorphism. Further, less-credible positive results were identified when we evaluated the credibility of positive results.

Conclusion: These positive findings should be interpreted with caution and indicate that significant association may most likely result from less-credible, rather than from true associations or biological factors on the *VDR BsmI* and *FokI* polymorphisms with osteoporosis risk.

Introduction

Osteoporosis is a systemic skeletal disease characterized by a systemic impairment of bone mass and microarchitecture that results in a high risk of fractures [1]. According to WHO, osteoporosis is the reduction in bone density below 2.5 standard deviation from the average for healthy and mature adults with similar ethnicity and age. It is one of the most common metabolic bone diseases in the world, affecting women over the age of 59 and men over the age of 74 [2]. It was reported that there were approximately 200 million osteoporosis patients in the world [3]. Therefore, it is very important to explore the potential pathogenic factors.

Multiple factors were reported to affect osteoporosis, including environmental factors such as exercise, smoking and alcohol consumption, metabolic syndrome, and genetic factors [4–6]. Among them, genes were a very important factor. The heritability of osteoporosis-related traits (such as bone mineral density)
was reported to be up to 60–80% [7]. Up till now, tens of hundreds of risk genes have been identified for osteoporosis, including collagen type I α1 gene (COL1A1), calcitonin receptor (CTR), estrogen receptor (ESR), vitamin D receptor (VDR), and so on [8–10]. Most of these genes are known to influence the reabsorption of bone by osteoclasts and the formation of bone by osteoblasts.

VDR was the most extensively reported, located on chromosome 12q13 [11], through mediating 1,25-dihydroxycholecalciferol (1,25(OH)2D3) to play a variety of biological effects [12]. In human monocytes, 1,25(OH)2D3 modulates chromatin accessibility at 8979 loci [13]. Therefore, VDR polymorphisms were associated with a variety of diseases, including bone mineral density and osteoporosis [14,15]. Morrison et al. [16] first investigated that variability in osteocalcin levels reflect allelic variation in the VDR gene. Since then, a large number of studies have reported that VDR gene mutations (such as FokI (rs10735810), BsmI (rs1544410) and Cdx2 (rs11568820) were related to osteoporosis risk. However, these results were inconsistent or even conflicting. For example, Ling et al. [15] found that VDR Cdx-2 A allele was associated with decreased bone mineral density (BMD) risk and increased fracture risk. On the contrary, A allele was found to have protective effect on osteoporotic fractures in some studies [14,17]. Similarly, they were also conflicting in different studies [18–23] on the associations between the VDR FokI and BsmI polymorphisms and osteoporosis risk. These different results may be caused by small sample size, different races, regions, and sampling methods. Although several related meta-analyses have reported the associations between VDR BsmI, FokI, and Cdx2 polymorphisms and osteoporosis risk [24–29]. However, their studies have some disadvantages. First, the results of these meta-analyses were inconsistent. For example, Jia et al. [27] found that the VDR BsmI polymorphism may have a protective effect on the development of osteoporosis. However, Gang et al. [28] concluded that there was no association between VDR BsmI polymorphism and osteoporosis risk. Second, literature quality assessments had not been performed in some studies [24,25,27–29]. In addition, they did not evaluate the credibility of statistically significant associations [24–29]. Furthermore, some new studies have been published on the VDR polymorphisms and osteoporosis risk. Therefore, we performed an updated meta-analysis to provide more reliable results on these issues.

**Materials and methods**

**Search strategy**

We performed the meta-analysis according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) group [30]. Databases including PubMed, Embase, and Chinese Wanfang Data Knowledge Service Platform were searched to investigate the association between VDR polymorphisms and osteoporosis risk. The following search strategy were used: (VDR OR vitamin D receptor OR BsmI OR FokI OR Cdx2) AND (polymorphism OR mutaion OR variant) AND (osteoporosis OR osteoporoses). The search deadline was November 2019.

**Selection criteria**

The inclusion criteria were as follows: (1) case–control or cohort studies; (2) describe the association among VDR BsmI, FokI, and Cdx2 polymorphisms and osteoporosis risk; (3) the case and control groups have sufficient genotype data in the selected literature.

The exclusion criteria were: (1) duplicated studies; (2) studies without available data; (3) case reports, reviews, letters, and meta-analyses.

**Data extraction**

The data extraction tables in the present study were prepared in advance. According to the established inclusion and exclusion criteria, the data were independently extracted and cross-checked; if there was any objection, the consensus can not be reached after discussion and negotiation. The third author was invited to extract the data again, and finally check and confirm. If the data are not detailed or in doubt, try to contact the original author, supplement and confirm the accuracy and integrity of the data. The extracted information was as follows: first author’s surname, publication year, country, ethnicity, age of cases and controls, the number of cases and controls, diagnostic criteria for osteoporosis, menopausal status, matching variables, site of BMD measurement, and number of genotype distributions in cases and controls.

**Quality assessment**

The quality of all eligible studies was independently assessed by the two authors. We designed quality assessment criteria on the basis of two previous meta-analyses [31,32]. Supplementary Table S1 lists the scale for quality assessment
of molecular association studies of osteoporosis risk. The total score was 20 points, studies scoring above 12 were excellent, those scoring less than 9 were poor, and those scoring between 9 and 12 were moderate.

### Statistical analysis

The odds ratios (ORs) and 95% confidence intervals (95% CIs) were pooled to evaluate the association strength, \( P < 0.05 \) was considered as statistically significant. Five genetic model comparisons were used: (1) allele model; (2) additive model; (3) dominant model; (4) recessive model; (5) overdominant model. Heterogeneity test used Chi-square-based \( Q \)-test and \( I^2 \) test. There was no obvious heterogeneity among studies when \( P > 0.10 \) and/or \( I^2 \leq 50 \% \) [33] and the ORs were pooled to apply a fixed-effects model [34]. Otherwise, a random-effects model was selected [35]. Furthermore, a meta-regression analysis was applied to explore sources of heterogeneity. Subgroup analyses were performed according to ethnicity or gender. Sensitivity analysis was estimated by the following three methods: (1) a single study was removed each time; (2) exclude low quality and Hardy–Weinberg Disequilibrium (HWD) studies; (3) the studies met the following conditions: high-quality studies, Hardy–Weinberg Equilibrium (HWE), and matching studies. Chi-square goodness-of-fit test was applied to examine HWE, and it was considered as HWE in control groups if \( P > 0.05 \). In addition, the false-positive report probabilities (FPRP) test [36] and the Venice criteria [37] were applied to assess the credibility of statistically significant associations. Begg’s funnel plot [38] and Egger’s test were used to evaluate the publication bias [39]. All statistical analyses were conducted using Stata 12.0 software.

### Results

#### Description of included studies

We got 506 articles by searching, according to the inclusion and exclusion criteria, 43 studies met our requirements (involving 4680 osteoporosis cases and 5373 controls) [21,22,40–80], of which 34 studies explored the association between \( VDR \) BsmI and osteoporosis risk (involving 2973 osteoporosis cases and 3724 controls), 19 studies reported \( VDR \) FokI (involving 3694 osteoporosis cases and 2943 controls), and 4 studies explored \( VDR \) Cdx2 (involving 378 osteoporosis cases and 743 controls). In addition, 23, 11, 4, 3, 1, and 1 case–control studies were conducted to analyze Caucasians, East Asians, West Asians, Indians, Southeast Asians, and Africans, respectively. Among them, seven studies were performed to examine the association between men and osteoporosis risk, and 38 studies explored the association between women and osteoporosis risk. Thirty studies on postmenopausal women, two studies on premenopausal women, and nine studies did not describe menopause status. Finally, there were 9 high-quality studies, 20 medium-quality studies, and 5 low-quality studies on \( VDR \) BsmI; 7 high-quality studies, 10 medium-quality studies, and 2 low-quality studies on \( VDR \) FokI; and 3 medium-quality studies and 1 low-quality study on \( VDR \) Cdx2.

The detailed characteristics and scoring of each study are displayed in Table 1. The literature selection and inclusion processes are shown in Figure 1. The genotype frequencies of \( VDR \) BsmI, FokI, and Cdx2 polymorphisms with osteoporosis risk and HWE test results were shown in Tables 2-4.

#### Meta-analysis results

Table 5 summarizes the assessment of the association between \( VDR \) BsmI polymorphism and osteoporosis risk. Overall, significantly increased the risk of osteoporosis was not found for \( VDR \) BsmI polymorphism (\( P > 0.05 \) in all genetic models). However, subgroup analysis by ethnicity, we observed that the \( VDR \) b allele genotype increased the osteoporosis risk (OR = 1.36, 95% CI: 1.06–1.74) and bb genotype (additive model: OR = 0.55, 95% CI: 0.33–0.92; recessive model: OR = 0.65, 95% CI: 0.45–0.96) reduced the risk of osteoporosis in the West Asians, as shown in Figure 2.

At the overall analysis, significantly increased osteoporosis risk was found in \( VDR \) FokI ff genotype (additive model: OR = 1.49, 95% CI: 1.07–2.07; recessive model: OR = 1.47, 95% CI: 1.13–1.93). In addition, when stratified by ethnicity, the results showed that f allele and ff genotypes were significantly associated with risk of osteoporosis in Indians. We further performed subgroup analysis according to gender, significantly elevated osteoporosis risk was also observed in ff genotype. All the data are shown in Table 6, Figures 3 and 4.

No significant association was observed between \( VDR \) Cdx2 polymorphism and osteoporosis risk, as shown in Table 7.

#### Heterogeneity and sensitivity analyses

Heterogeneity was observed in overall and several subgroup analyses. Some potential factors were considered as sources of heterogeneity, such as ethnicity, gender, HWE, and menopausal status. Then, we applied meta-regression
Table 1 Main characteristics and quality score of studies included

| First author/year | Country | Ethnicity | Gender | Cases | BMD | Diagnosis | Matching | Controls | Score |
|-------------------|---------|-----------|--------|-------|-----|-----------|----------|----------|-------|
| Kow, 2019         | British | Caucasian | Men    | 69    | 58.96 ± 12.78 | Ne | LS-fn | WHO | Age and Sex | 121 | Yes | 64.98 ± 10.06 | Ne | LS-hip | 15 |
| Techapattiphandee, 2018 | Thai | Southeast Asian | Female | 105 | 73.10 ± 8.90 | PSM | LS-hip | WHO | Sex | 132 | Yes | 63.40 ± 8.70 | PSM | LS-hip | 13 |
| Ahmad, 2018       | India   | Indian    | Female | 254   | 56.12 ± 7.00 | PSM | LS-hip-fr | WHO | Age and Sex | 254 | Yes | 55.11 ± 5.66 | PSM | LS-hip | 14 |
| Meng, 2017        | China   | East Asian | Female | 90    | 67.20 ± 8.60 | Ne | LS-hip | WHO | Age and Sex | 246 | Yes | 55.90 ± 9.60 | Female | LS-hip | 8 |
| Dehghan, 2016     | Iran    | West Asian | Men    | 130   | 46.10 ± 6.00 | Ne | LS-fn | WHO | Age and Sex | 70 | Yes | 46.10 ± 6.00 | Men | LS-hip | 10 |
| Ziaibitsev, 2015  | Ukraine | Caucasian | Female | 30    | Ne | Ne | Ne | Ne | Sex | 44 | Yes | Ne | PSM | Ne | 8 |
| Mohammad, 2015    | Iran    | West Asian | Female | 101   | 35.40 ± 9.00 | Pre | LS-hip-fr | WHO | Age and Sex | 374 | Yes | 35.40 ± 9.00 | Pre | LS-hip | 15 |
| Mohammad, 2015    | Iran    | West Asian | Men < 50 | 75   | 32.90 ± 8.60 | Ne | LS-hip-fr | WHO | Age and Sex | 195 | Yes | 32.90 ± 8.60 | Ne | LS-hip | 15 |
| Mohammad, 2015    | Iran    | West Asian | Men ≥ 50 | 112  | 61.20 ± 8.90 | Ne | LS-hip-fr | WHO | Age and Sex | 24 | Yes | 61.20 ± 8.90 | Ne | LS-hip | 14 |
| Moran, 2015       | Spanish | Caucasian | Female | 150   | 60.24 ± 7.74 | PSM | LS-fn | WHO | Age and Sex | 30 | Yes | 59.73 ± 9.28 | PSM | LS-hip | 16 |
| Boroń, 2015       | Poland  | Caucasian | Female | 278   | Ne | Ne | Ne | Ne | Age and Sex | 292 | Yes | Ne | PSM | LS-13 |
| Marozik, 2013     | Belarus | Caucasian | Female | 54    | 58.30 ± 6.20 | PSM | LS-fn | WHO | Age and Sex | 77 | Yes | 56.70 ± 7.40 | PSM | LS-hip | 11 |
| González, 2013    | Mexico  | Caucasian | Female | 88    | 57.65 ± 5.58 | PSM | LS-fn | WHO | Age and Sex | 88 | Yes | 56.34 ± 4.98 | PSM | LS-hip | 11 |
| Pounesi, 2013     | Iran    | West Asian | Female | 64    | 53.53 ± 9.80 | Ne | LS-fn | WHO | Age and Sex | 82 | Yes | 53.53 ± 9.80 | Ne | LS-hip | 12 |
| Efesoy, 2011      | Turkey  | Caucasian | Female | 40    | 65.75 ± 9.80 | PSM | LS-fn | WHO | Age and Sex | 30 | Yes | 62.40 ± 8.70 | PSM | LS-hip | 11 |
| Yasovanthi, 2011  | India   | Indian    | Female | 247   | 57.70 ± 4.60 | PSM | LS-fn | WHO | Age and Sex | 254 | Yes | 57.70 ± 4.60 | PSM | LS-hip | 16 |
| Yasovanthi, 2011  | India   | Indian    | Female | 180   | 39.50 ± 4.40 | Pre | LS-hip-fr | WHO | Age and Sex | 206 | Yes | 39.50 ± 4.40 | Pre | LS | 15 |
| Xing, 2011        | China   | East Asian | Female | 32    | 72.50 ± 6.40 | Ne | LS | WHO | T-score < 2.0 | 70 | Yes | 70.50 ± 5.20 | Female | LS | 9 |
| Mansour, 2010     | Egypt   | African   | Female | 50    | 54.40 ± 5.10 | PSM | LS-fn | WHO | Age and Sex | 20 | Yes | 53.50 ± 5.40 | PSM | LS-hip | 8 |
| Durusu, 2010      | Turkey  | Caucasian | Female | 50    | 58.30 ± 6.50 | PSM | LS-hip-fr | WHO | Age and Sex | 50 | Yes | 57.30 ± 6.60 | PSM | LS-hip-fr | 11 |
| Gu, 2010          | China   | East Asian | Female | 33    | 58.40 ± 6.30 | PSM | LS-fn | WHO | Age and Sex | 148 | Yes | 58.40 ± 6.30 | PSM | Fn | 11 |
| Gu, 2010          | China   | East Asian | Men    | 8     | 61.60 ± 7.00 | Ne | LS-fn | WHO | Age and Sex | 260 | Yes | 61.60 ± 7.00 | PSM | Fn | 12 |
| Mencej, 2009      | Slovenia | Caucasian | Female | 239   | 64.50 ± 8.20 | PSM | LS-fn | WHO | Age and Sex | 228 | Yes | 61.50 ± 8.30 | PSM | LS-hip-fr | 12 |
| Seremak, 2009     | Poland  | Caucasian | Female | 163   | 64.27 ± 8.72 | PSM | LS-fn | WHO | Age and Sex | 83 | Yes | 63.08 ± 7.24 | PSM | LS-hip-fr | 10 |
| Uysal, 2008       | Turkey  | Caucasian | Female | 100   | Ne | Ne | Ne | Ne | Age and Sex | 146 | Yes | Ne | PSM | LS-hip-fr | 12 |
| Pérez, 2008       | Argentina | Caucasian | Female | 64    | 62.70 ± 0.86 | PSM | LS-fn | WHO | Age and Sex | 68 | Yes | 59.40 ± 0.85 | PSM | LS-hip-fr | 14 |
| Mitra, 2006       | India   | Indian    | Female | 119   | 54.2 ± 3.40 | PSM | LS-fn | WHO | Age and Sex | 97 | Yes | 54.20 ± 3.40 | PSM | LS-hip-fr | 11 |
| Zhang, 2006       | China   | East Asian | Men    | 26    | 70.5 ± 5.30 | Ne | LS | T-score < 2.0 | 66 | Yes | 73.40 ± 4.30 | Men | LS | 7 |

Continued over
| First author/year | Country | Ethnicity | Gender | Cases | Controls | Score |
|-------------------|---------|-----------|--------|-------|----------|-------|
| n | Age\(^1\) | BMD site | Diagnosis | Matching | n | Healthy Age\(^1\) | BMD site |
| Liu, 2005 | China | East Asian | Men | 89 | Ne | Ne | LS-hip | T-score < 2.0 | Sex | 56 | Yes | Ne | Men | LS-hip | 10 |
| Zhu, 2004 | China | East Asian | Female | 40 | Ne | PSM | LS-fn | WHO | Sex | 158 | Yes | Ne | PSM | LS-fn | 10 |
| Duman, 2004 | Turkey | Caucasian | Female | 75 | 53.16 ± 1.31 | PSM | LS-hip | WHO | Sex and Menopause | 66 | Yes | 52.62 ± 1.69 | PSM | LS-hip | 10 |
| Lisker, 2003 | Mexico | Caucasian | Female | 65 | 65.20 ± 6.80 | PSM | LS-fn | WHO | Sex | 57 | Yes | 56.60 ± 6.00 | PSM | LS-fn | 11 |
| Douroudis, 2003 | Greece | Caucasian | Female | 35 | 61.37 ± 0.96 | PSM | Forearm | WHO | Sex | 44 | Yes | 58.60 ± 1.01 | PSM | Forearm | 12 |
| Chen, 2003 | China | East Asian | Female | 78 | 54.72 ± 2.60 | PSM | Forearm | T-score < 2.0 | Sex | 81 | Yes | 53.60 ± 2.90 | PSM | Forearm | 9 |
| Zajickova, 2002 | Czech | Caucasian | Female | 65 | 60.10 ± 10.30 | PSM | LS-hip | WHO | Sex | 33 | Yes | 63.60 ± 7.80 | PSM | LS-hip | 10 |
| Pollak, 2001 | Israel | West Asian | Female | 75 | Ne | Ne | LS-fn | WHO | Sex | 143 | Yes | Ne | Ne | LS-fn | 13 |
| Langdahl, 2000 | Aarhus, Denmark | Caucasian | Men | 30 | 55.70 ± 11.00 | Ne | LS-hip | WHO | Age and Menopause | 73 | Yes | 51.10 ± 15.70 | Ne | LS-fn | 13 |
| Langdahl, 2000 | Aarhus, Denmark | Caucasian | Female | 80 | 58.20 ± 6.40 | Ne | LS-hip | WHO | Age and Sex | 80 | Yes | 56.20 ± 7.70 | Ne | LS-fn | 13 |
| Fontova Garrofe, 2000 | Spanish | Caucasian | Female | 75 | 58.30 ± 5.00 | PSM | LS-hip | WHO | Sex | 51 | Yes | 57.20 ± 4.50 | PSM | LS-hip | 9 |
| Choi, 2000 | Korea | East Asian | Female | 48 | 55.10 ± 6.00 | PSM | LS-fn | WHO | Sex | 65 | Yes | 55.10 ± 6.00 | PSM | LS-fn | 11 |
| Zhang, 1998 | China | East Asian | Female | 17 | 56.76 | Ne | LS | Ne | Sex | 52 | Yes | 54.38 | Female | LS | 6 |
| Lucotte, 1999 | French | Caucasian | Female | 124 | 63.00 ± 12.30 | PSM | LS-fn | WHO | Age and Sex | 105 | Yes | 63.00 ± 12.30 | PSM | LS-fn | 15 |
| Gennari, 1999 | Italian | Caucasian | Female | 164 | 57.70 ± 0.60 | PSM | LS | WHO | Sex | 119 | Yes | 56.90 ± 0.60 | PSM | LS | 12 |
| Gennari, 1998 | Italian | Caucasian | Female | 155 | 58.20 ± 0.60 | PSM | LS | WHO | Sex | 136 | Yes | 57.10 ± 0.70 | PSM | LS | 12 |
| Vandervyver, 1997 | Belgium | Caucasian | Female | 698 | 75.20 ± 4.70 | PSM | LS-fn | WHO | Sex | 86 | Yes | 63.30 ± 8.40 | PSM | LS-fn | 9 |
| Tamai, 1997 | Japan | East Asian | Female | 90 | 71.00 ± 10.00 | Ne | LS | Ne | Sex | 92 | Yes | 43.00 ± 17.00 | Female | LS | 7 |
| Yanagi, 1996 | Japan | East Asian | Female | 23 | Ne | Ne | LS | Ne | Sex | 66 | Yes | Ne | Female | LS | 7 |
| Houston, 1996 | U.K. | Caucasian | Female | 44 | 66.00 ± 0.85 | Ne | LS-hip | WHO | Sex | 44 | Yes | 65.30 ± 0.95 | Female | LS-hip | 13 |

Abbreviations: Fn, femoral neck; LS, lumbar spine; N, not available; Pre, premenopause; PSM, postmenopausal.
\(^1\)Mean ± SD years.
Figure 1. Flow diagram of the literature search

analysis to explore sources of heterogeneity. The results suggested that the studies of HWD were source of heterogeneity in overall population (additive model: \( P = 0.024 \)). In addition, the studies of HWD was also the source of heterogeneity on the association between women and osteoporosis risk (additive model: \( P = 0.029 \) and recessive model: \( P = 0.025 \)).

Sensitivity analysis was estimated by applying three methods in this meta-analysis. First, results did not change when removing a single study each time to appraise the robustness. However, when we excluded studies of low quality and HWD, significantly decreased osteoporosis risk was found in overall analysis for \( VDR \) BsmI bb genotype (additive model: \( OR = 0.74, 95\% \text{ CI: 0.56–0.99} \); recessive model: \( OR = 0.79, 95\% \text{ CI: 0.63–0.98} \)). Further, when we
Figure 2. VDR BsmI polymorphism and osteoporosis risk in different races
The forest plots of all selected studies on the association between VDR BsmI polymorphism and osteoporosis risk in different races (A) allele model; (B) additive model; (C) recessive model.
Table 2 Genotype frequencies of VDR BsmI polymorphism in studies included in this meta-analysis

| First author/year | Ethnicity | Gender | Case | Control | HWE | Chi-square | P  |
|-------------------|-----------|--------|------|---------|-----|------------|----|
| Kow, 2019         | Caucasian | Male   | 31   | 66      | 21  | 11         | 34 | 13  | 1.752 | 0.1856 |
| Techapatiphandee, 2018 | Southeast Asian | Female | 85   | 19      | 1   | 103        | 25 | 4   | 2.377 | 0.1231 |
| Ahmad, 2018       | Indian    | Female | 54   | 137     | 63  | 54         | 152| 48  | 9.909 | 0.0016 |
| Meng, 2017        | East Asian| Female | 4    | 12      | 74  | 6          | 24 | 216 | 19.383 | 0     |
| Dehghan, 2016     | West Asian| Male   | 31   | 70      | 29  | 14         | 39 | 17  | 0.947 | 0.3304 |
| Moran, 2015       | Caucasian | Female | 18   | 65      | 67  | 3          | 19 | 8   | 2.752 | 0.0972 |
| Boron, 2015       | Caucasian | Female | 101  | 121     | 56  | 54         | 152| 48  | 9.909 | 0.0016 |
| Marozić, 2013     | Caucasian | Female | 12   | 31      | 11  | 11         | 26 | 40  | 3.495 | 0.0616 |
| González-Mercado, 2013 | Caucasian | Female | 6    | 28      | 54  | 4          | 38 | 46  | 1.234 | 0.2667 |
| Pouremsaeli, 2013 | West Asian| Female | 14   | 33      | 17  | 13         | 33 | 36  | 1.31  | 0.2524 |
| Efeso, 2011       | Caucasian | Female | 5    | 23      | 12  | 5          | 15 | 10  | 0.024 | 0.8756 |
| Mansour, 2010     | African   | Female | 27   | 15      | 8   | 1          | 2  | 17  | 3.961 | 0.0469 |
| Mencej-Bedrac, 2009 | Caucasian | Female | 27   | 110     | 103 | 40         | 100| 88  | 1.538 | 0.2149 |
| Seremak, 2009     | Caucasian | Female | 27   | 66      | 70  | 10         | 27 | 26  | 0.442 | 0.5062 |
| Deras, 2010       | Caucasian | Female | 15   | 19      | 16  | 19         | 7  | 24  | 25.717 | 0     |
| Uysal, 2008       | Caucasian | Female | 18   | 48      | 34  | 24         | 78 | 44  | 9.909 | 0.0016 |
| Pérez, 2008       | Caucasian | Female | 17   | 35      | 12  | 20         | 32 | 16  | 0.21  | 0.6469 |
| Mitra, 2006       | Indian    | Female | 51   | 46      | 22  | 19         | 38 | 40  | 3.072 | 0.0796 |
| Liu, 2005         | East Asian| Male   | 2    | 11      | 78  | 0          | 8  | 50  | 0.179 | 0.6719 |
| Zhu, 2004         | East Asian| Female | 6    | 28      | 8   | 7          | 105| 46  | 27.257 | 0     |
| Duman, 2004       | Caucasian | Female | 18   | 54      | 13  | 24         | 72 | 4   | 25    | 0     |
| Lisker, 2003      | Caucasian | Female | 15   | 17      | 34  | 13         | 38 | 6   | 7.133 | 0.0076 |
| Douroudis, 2003   | Caucasian | Female | 3    | 12      | 20  | 10         | 29 | 5   | 4.95  | 0.0261 |
| Chen, 2003        | East Asian| Female | 0    | 13      | 65  | 0          | 12 | 69  | 0.518 | 0.4715 |
| Zajickova, 2002   | Caucasian | Female | 21   | 24      | 20  | 10         | 13 | 10  | 1.485 | 0.223 |
| Pollak, 2001      | West Asian| Female | 18   | 50      | 32  | 11         | 47 | 42  | 0.16  | 0.6896 |
| Langdahl, 2000    | Caucasian | Male   | 8    | 16      | 6   | 15         | 28 | 30  | 2.893 | 0.089 |
| Douroudis, 2000   | Caucasian | Female | 23   | 38      | 19  | 25         | 34 | 21  | 1.749 | 0.186 |
| Fontova, 2000     | Caucasian | Female | 9    | 49      | 17  | 10         | 22 | 19  | 0.612 | 0.4341 |
| Zhang, 1998       | East Asian| Female | 0    | 3       | 14  | 0          | 3  | 49  | 0.046 | 0.8304 |
| Gennari, 1998     | Caucasian | Female | 40   | 92      | 23  | 11         | 76 | 49  | 6.129 | 0.0133 |
| Vandevyver, 1997  | Caucasian | Female | 12   | 50      | 24  | 127        | 388| 203 | 3.142 | 0.0763 |
| Tamai, 1997       | East Asian| Female | 5    | 11      | 74  | 3          | 16 | 73  | 2.784 | 0.0952 |
| Yanagi, 1996      | East Asian| Female | 2    | 7       | 57  | 5          | 7  | 11  | 2.767 | 0.0962 |
| Houston, 1996     | Caucasian | Female | 8    | 19      | 17  | 9          | 19 | 16  | 0.571 | 0.4498 |

restrained only including high-quality HWE, and matching studies, the corresponding pooled OR do not appear to be significantly affected. Therefore, the results of the sensitivity analysis are shown in Tables 8 and 9.

Publication bias
Publication bias was assessed in the overall publication by Begg’s funnel plot and Egger’s test, the shape of the funnel plots revealed no significant funnel asymmetry (Figure 5) in overall population. The Egger tests also indicated that there was no obvious evidence of publication bias ($P > 0.05$ in all genetic models), as shown in Tables 5-7.

Credibility of the identified genetic associations
We classified statistically significant associations that met the following criteria as ’positive results’ [81]: (1) the $P$-value of Z-test is less than $0.05$ in at least two gene models; (2) at the $P$-value level of 0.05, the FPRP is less than 0.2; (3) statistical power $> 0.8$; (4) $I^2 < 50%$. Considered as ‘less credible affirmation’ with lower threshold when the following conditions were met: (1) $P$-value $< 0.05$ in at least one of the genetic models; (2) the statistical power was between 50 and 79% or FPRP $> 0.2$ or $I^2 > 50%$. Otherwise, the association was classified as ’null’ or ’negative’. After credibility assessment, we identified 'less-credible positive results’ for the statistically significant associations in the current meta-analysis. The detailed credibility assessment results are listed in Table 10.
Table 3 Genotype frequencies of VDR FokI polymorphism in studies included in this meta-analysis

| First author/year | Ethnicity          | Gender | Case | Control | HWE | Chi-square test | P     |
|-------------------|--------------------|--------|------|---------|-----|----------------|-------|
|                   |                    |        | FF   | Ff      | ff  | FF             | Ff    |       |
| Techapatiphandee, 2018 | Southeast Asian | Female | 31 | 46      | 28 | 41             | 73    | 18    | 2.613 | 0.106 |
| Ahmad, 2018       | Indian             | Female | 148 | 56      | 3  | 11             | 17    | 3     | 0.95  | 0.3298|
| Mohammadi, 2015   | West Asian        | Female | 80  | 36      | 8  | 198            | 128   | 30    | 1.996 | 0.1577|
| Mohammadi, 2015   | West Asian        | Male   | 40  | 26      | 3  | 111            | 73    | 9     | 0.476 | 0.4903|
| Mohammadi, 2015   | West Asian        | Female | 64  | 41      | 4  | 12             | 9     | 1     | 0.182 | 0.6698|
| González, 2013    | Caucasian         | Female | 24  | 45      | 19 | 25             | 48    | 15    | 0.974 | 0.3238|
| Yasovanthi, 2011  | Indian            | Female | 104 | 119     | 24 | 122            | 124   | 8     | 12.594| 0.0004|
| Yasovanthi, 2011  | Indian            | Female | 73  | 82      | 25 | 97             | 101   | 8     | 8.71  | 0.0032|
| Xing, 2011        | East Asian        | Female | 11  | 14      | 7  | 8              | 35    | 27    | 0.443 | 0.5058|
| Mansour, 2010     | African           | Female | 34  | 9       | 7  | 20             | 0     | 0     | 0     | 0     |
| Durusu, 2010      | Caucasian         | Female | 27  | 22      | 1  | 29             | 18    | 3     | 0.009 | 0.9259|
| Gu, 2010          | East Asian        | Female | 6   | 18      | 9  | 40             | 84    | 24    | 3.266 | 0.0707|
| Gu, 2010          | East Asian        | Male   | 2   | 5       | 1  | 76             | 137   | 47    | 1.711 | 0.2791|
| Mencej-Bedrac, 2009 | Caucasian    | Female | 88  | 108     | 44 | 105            | 97    | 26    | 0.249 | 0.6179|
| Pérez, 2008       | Caucasian         | Female | 22  | 32      | 10 | 22             | 36    | 10    | 0.586 | 0.4438|
| Mitra, 2006       | Indian            | Female | 38  | 42      | 39 | 46             | 33    | 18    | 6.444 | 0.0111|
| Zhang, 2006       | East Asian        | Male   | 4   | 13      | 9  | 28             | 28    | 10    | 0.458 | 0.4964|
| Lisker, 2003      | Caucasian         | Female | 27  | 29      | 9  | 20             | 29    | 8     | 0.239 | 0.625 |
| Zajikova, 2002    | Caucasian         | Female | 26  | 28      | 11 | 7              | 21    | 5     | 2.54  | 0.111 |
| Langdahl, 2000    | Caucasian         | Male   | 12  | 13      | 5  | 30             | 34    | 9     | 0.018 | 0.8943|
| Langdahl, 2000    | Caucasian         | Female | 28  | 42      | 10 | 34             | 31    | 15    | 2.554 | 0.11 |
| Choi, 2000        | East Asian        | Female | 12  | 23      | 13 | 26             | 33    | 6     | 0.961 | 0.327 |
| Lucotte, 1999     | Caucasian         | Female | 45  | 69      | 10 | 40             | 52    | 13    | 0.386 | 0.5348|
| Gennari, 1999     | Caucasian         | Female | 60  | 73      | 31 | 53             | 55    | 11    | 0.372 | 0.542 |

Table 4 Genotype frequencies of VDR Cdx2 polymorphism in studies included in this meta-analysis

| First author/year | Ethnicity | Gender | Case | Control | HWE | Chi-square test | P     |
|-------------------|-----------|--------|------|---------|-----|----------------|-------|
|                   | GG        | GA     | AA   | GG      | GA  | AA             |       |
| Ziablitsev, 2015  | Caucasian | Female | 16  | 20      | 8  | 2              | 12    | 16    | 0.015 | 0.9009|
| Marozik, 2013     | Caucasian | Female | 41  | 13      | 0  | 53             | 24    | 0     | 2.624 | 0.1052|
| Gu, 2010          | East Asian| Female | 12  | 16      | 5  | 38             | 72    | 38    | 0.108 | 0.7423|
| Gu, 2010          | East Asian| Male   | 4   | 3       | 1  | 81             | 116   | 63    | 2.78  | 0.0955|
| Mencej-Bedrac, 2009 | Caucasian| Female | 155 | 75      | 9  | 172            | 48    | 8     | 3.709 | 0.0541|

Discussion

Osteoporosis is a multifactorial disease and is strongly related to heredity [7]. Genes are very important factors for the risk of osteoporosis. Osteoporosis is characterized by low BMD and microarchitectural deterioration of bone leading to increased bone fragility and a high risk of fracture. The VDR gene is considered as a candidate gene and has been widely studied due to it plays a key role in regulating bone resorption and metabolism [10]. And the VDR gene has also been implicated as a factor affecting bone mass [84]. Hence, it will be very important to investigate the association between VDR gene polymorphism and osteoporosis. Moreover, the VDR polymorphisms play an important role in the pathogenesis, prevention, diagnosis and treatment of osteoporosis and other disease such as acute ischemic stroke [85]. In addition, single nucleotide polymorphism (SNP) may affect the function of VDR and may be related with osteoporosis risk [82]. Although many studies attempted to explore the association between VDR polymorphisms and the risk of osteoporosis. However, it is regrettable that no solid evidence has been obtained, which may be due to different reasons, including small sample size, ethnic, and regional differences. In order to overcome these shortcomings, meta-analysis is effective alternative.
A total of six previous meta-analyses explored the association between VDR polymorphisms and osteoporosis risk. Wang et al. [24] and Yu et al. [26] explored the association between osteoporosis risk and VDR BsmI polymorphism in Chinese and Han Chinese population, respectively. Their results suggested that there was no significant association between VDR BsmI polymorphism and osteoporosis risk. In 2013, Jia et al. [27] examined 26 studies including 2274 cases and 3150 controls to show that the VDR BsmI polymorphism was associated with increased osteoporosis risk. However, the examination of 41 studies on VDR BsmI polymorphism (including 3080 cases and 4157 controls) by Gang et al. [28] indicated that the VDR BsmI polymorphism was not significantly associated with osteoporosis risk. In addition, the examination of 36 studies on VDR BsmI, 15 studies on VDR FokI, and three studies on VDR Cdx2 by Zhang et al. [25] indicated that the VDR BsmI and VDR FokI polymorphisms were associated with an increased risk of developing osteoporosis in overall and Asians, while the VDR Cdx2 polymorphism may not be associated with osteoporosis risk. However, VDR BsmI and VDR FokI polymorphisms had not been found to increase the risk of osteoporosis by Zintzaras et al. [29]. Further, when we examined these meta-analyses carefully, we found some disadvantages. First, quality assessments of the eligible studies had not been performed in some studies [24,25,27–29], and low-quality literature may be included in these meta-analyses, resulting in deviation of the results. Second, HWE

### Table 5: Pooled estimates of association of VDR BsmI polymorphism and osteoporosis risk

| Genetic model | Variable | Test of association | Tests for heterogeneity | Egger's test |
|---------------|----------|---------------------|-------------------------|--------------|
|               |          | OR (95% CI)        | P            | $P_h$  | $I^2$ | PE |
| B vs b        | Overall  | 1.11 (0.94–1.31)   | 0.22         | <0.001 | 77.40% | 0.34 |
|               | Caucasian| 0.99 (0.83–1.18)   | 0.87         | <0.001 | 70.70% |     |
|               | East Asian| 1.06 (0.59–1.91)  | 0.85         | <0.001 | 76.40% |     |
|               | West Asian| 1.36 (1.06–1.74) | 0.02         | 0.49   | 0.00%  |     |
|               | Indian   | 1.49 (0.53–4.19)   | 0.45         | <0.001 | 95%    |     |
|               | Female   | 1.09 (0.90–1.31)   | 0.39         | <0.001 | 79.60% |     |
|               | Male     | 1.29 (0.99–1.67)   | 0.06         | 0.75   | 0.00%  |     |
| bb vs BB      | Overall  | 0.79 (0.57–1.09)   | 0.15         | <0.001 | 70.70% | 0.28 |
|               | Caucasian| 0.97 (0.68–1.39)   | 0.88         | <0.001 | 65.20% |     |
|               | East Asian| 0.77 (0.19–3.08)  | 0.71         | 0.01   | 72.40% |     |
|               | West Asian| 0.56 (0.33–0.92)  | 0.02         | 0.63   | 0.00%  |     |
|               | Indian   | 0.53 (0.09–3.26)   | 0.49         | <0.001 | 93.70% |     |
|               | Female   | 0.82 (0.58–1.17)   | 0.28         | <0.001 | 73.60% |     |
|               | Male     | 0.58 (0.33–1.02)   | 0.06         | 0.79   | 0.00%  |     |
| Bb+bb vs BB   | Overall  | 0.87 (0.70–1.07)   | 0.19         | <0.001 | 53.00% | 0.15 |
|               | Caucasian| 1.02 (0.83–1.27)   | 0.83         | 0.06   | 34.20% |     |
|               | East Asian| 0.74 (0.22–2.46)  | 0.63         | 0.02   | 65.80% |     |
|               | West Asian| 0.68 (0.44–1.07)  | 0.09         | 0.82   | 0.00%  |     |
|               | Indian   | 0.58 (0.19–1.76)   | 0.34         | <0.001 | 88.40% |     |
|               | Female   | 0.89 (0.70–1.12)   | 0.32         | <0.001 | 57.90% |     |
|               | Male     | 0.71 (0.45–1.13)   | 0.15         | 0.94   | 0.00%  |     |
| bb vs BB+Bb   | Overall  | 0.86 (0.67–1.11)   | 0.24         | <0.001 | 76.10% | 0.44 |
|               | Caucasian| 0.99 (0.72–1.35)   | 0.94         | <0.001 | 75.70% |     |
|               | East Asian| 0.98 (0.53–1.75)  | 0.89         | 0.01   | 66.80% |     |
|               | West Asian| 0.65 (0.45–0.96)  | 0.02         | 0.42   | 0.00%  |     |
|               | Indian   | 0.68 (0.16–2.93)   | 0.61         | <0.001 | 93.40% |     |
|               | Female   | 0.89 (0.87–1.17)   | 0.40         | <0.001 | 78.30% |     |
|               | Male     | 0.70 (0.46–1.06)   | 0.09         | 0.53   | 0.00%  |     |
| BB+bb vs Bb   | Overall  | 0.98 (0.82–1.15)   | 0.76         | <0.001 | 55.20% | 0.84 |
|               | Caucasian| 0.98 (0.77–1.24)   | 0.85         | <0.001 | 66.60% |     |
|               | East Asian| 1.04 (0.68–1.59)  | 0.87         | 0.19   | 31.50% |     |
|               | West Asian| 0.87 (0.61–1.22)  | 0.41         | 0.49   | 0.00%  |     |
|               | Indian   | 1.19 (0.89–1.61)   | 0.24         | 0.51   | 0.00%  |     |
|               | Female   | 0.98 (0.82–1.18)   | 0.86         | <0.001 | 59.30% |     |
|               | Male     | 0.94 (0.65–1.35)   | 0.74         | 0.56   | 0.00%  |     |

VDR BsmI: allele model: B vs b, additive model: bb vs BB, dominant model: Bb + bb vs BB, recessive model: bb vs BB + Bb, overdominance model: BB + bb vs Bb.
### Table 6 Pooled estimates of association of VDR *FokI* polymorphism and osteoporosis risk

| Genetic model | Variable | Test of association | Tests for heterogeneity | Egger’s test |
|---------------|----------|---------------------|-------------------------|--------------|
|               |          | OR (95% CI)         | P           | $P_h$ | $I^2$ | PE |
| F vs f        | Overall  | 0.86 (0.74–0.98)    | 0.03        | <0.001 | 55.80% | 0.30 |
|               | Caucasian | 0.89 (0.77–1.03)    | 0.12        | 0.35  | 9.70%  |    |
|               | East Asian | 0.78 (0.42–1.45)   | 0.43        | 0.001 | 79.10% |    |
|               | West Asian | 1.18 (0.85–1.63)   | 0.32        | 0.002 | 73.90% |    |
|               | Indian    | 0.68 (0.38–0.80)   | 0.05        | <0.001 | 59.90% |    |
|               | Female    | 0.86 (0.74–1.00)   | 0.05        | <0.001 | 41.90% |    |
|               | Male      | 0.83 (0.56–1.23)   | 0.03        | 0.14  | 49.00% |    |
| ff vs FF      | Overall   | 1.49 (1.07–2.07)   | 0.02        | <0.001 | 57.10% | 0.11 |
|               | Caucasian | 1.23 (0.87–1.73)   | 0.24        | 0.26  | 19.50% |    |
|               | East Asian | 1.69 (0.44–6.58)  | 0.45        | 0.001 | 79.30% |    |
|               | West Asian | 0.66 (0.29–1.54)  | 0.34        | 0.23  | 31.10% |    |
|               | Indian    | 3.25 (0.14–4.94)   | 0.04        | <0.001 | 62.60% |    |
|               | Female    | 1.46 (0.21–2.91)   | 0.04        | <0.001 | 22.70% |    |
|               | Male      | 1.61 (0.71–3.66)   | 0.04        | 0.27  | 40.00% | 0.42 |
| Ff+ff vs FF   | Overall   | 1.16 (0.98–1.37)   | 0.08        | 0.02  | 40.00% | 0.13 |
|               | Caucasian | 1.16 (0.96–1.40)   | 0.12        | 0.45  | 0.00%  |    |
|               | East Asian | 1.33 (0.55–3.35)  | 0.55        | 0.01  | 73.00% |    |
|               | West Asian | 0.85 (0.58–1.24)  | 0.40        | 0.23  | 30.70% |    |
|               | Indian    | 1.40 (0.14–7.11)   | 0.001       | 0.64  | 0.00%  |    |
|               | Female    | 1.15 (0.96–1.38)   | 0.12        | 0.02  | 45.20% |    |
|               | Male      | 1.19 (0.74–1.70)   | 0.04        | 0.26  | 24.10% |    |
| ff vs FF+Ff   | Overall   | 1.47 (1.13–1.93)   | 0.01        | 0.01  | 47.50% | 0.13 |
|               | Caucasian | 1.21 (0.89–1.64)   | 0.24        | 0.28  | 17.70% |    |
|               | East Asian | 1.55 (0.67–3.60)  | 0.31        | 0.02  | 64.70% |    |
|               | West Asian | 0.77 (0.42–1.43)  | 0.41        | 0.41  | 0.00%  |    |
|               | Indian    | 2.87 (0.19–4.26)   | 0.01        | 0.67  | 0.00%  |    |
|               | Female    | 1.48 (0.10–2.00)   | 0.01        | 0.001 | 54.40% |    |
|               | Male      | 1.50 (0.81–2.79)   | 0.20        | 0.55  | 0.00%  |    |
| FF+ff vs Ff   | Overall   | 1.01 (0.90–1.13)   | 0.87        | 0.69  | 0.00%  | 0.96 |
|               | Caucasian | 0.97 (0.81–1.18)   | 0.78        | 0.41  | 3.60%  |    |
|               | East Asian | 1.02 (0.69–1.51)  | 0.91        | 0.88  | 0.00%  |    |
|               | West Asian | 1.06 (0.78–1.45)  | 0.71        | 0.53  | 0.00%  |    |
|               | Indian    | 0.97 (0.80–1.19)   | 0.80        | 0.63  | 0.00%  |    |
|               | Female    | 1.03 (0.90–1.15)   | 0.78        | 0.45  | 0.80%  |    |
|               | Male      | 0.94 (0.65–1.37)   | 0.76        | 0.93  | 0.00%  |    |

**VDR FokI**: allele model: F vs f, additive model: ff vs FF, dominant model: Ff+ff vs FF, recessive model: ff vs FF+Ff, overdominance model: FF+ff vs Ff.

### Table 7 Pooled estimates of association of VDR *Cdx2* polymorphism and osteoporosis risk

| Genetic model | Test of association | Tests for heterogeneity | Egger’s test |
|---------------|---------------------|-------------------------|--------------|
|               | OR (95% CI)         | P           | $P_h$ | $I^2$ | PE |
| G vs A        | 1.54 (0.80–2.97)    | 0.20        | <0.001 | 82.40% | 0.12 |
| AA VS GG      | 0.37 (0.11–1.28)    | 0.11        | 0.02  | 68.30% | 0.29 |
| GA+AA VS GG   | 0.64 (0.29–0.93)    | 0.27        | 0.002 | 75.70% | 0.01 |
| AA VS GG+GA   | 0.48 (0.22–1.07)    | 0.07        | 0.14  | 45.70% | 0.85 |
| GG+AA VS GA   | 0.84 (0.58–1.22)    | 0.36        | 0.28  | 21.30% | 0.12 |

**VDR Cdx2**: allele model: G vs A, additive model: AA VS GG, dominant model: GA+AA VS GG, recessive model: AA VS GG+GA, overdominance model: GG+AA VS GA.
Figure 3. VDR FokI polymorphism and osteoporosis risk in different races

The forest plots of all selected studies on the association between VDR FokI polymorphism and osteoporosis risk in different races (A) allele model; (B) additive model; (C) dominant model; (D) recessive model.

is absolutely necessary for a sound genetic association study. There may be selection bias or genotyping errors if the control group did not meet HWE. It can lead to misleading results. The distribution of genotypes in the control group was not tested by HWE [24,25]. Then, the statistical power was not calculated in some previous meta-analyses [24,26-29]. Finally, the FPRPs of statistically significant association was not evaluated in all previous meta-analyses [24–29]. Therefore, results of their meta-analyses may be not credible.

A total of 43 studies were included in the current meta-analysis, of which 34 studies explored the association between VDR BsmI and osteoporosis risk, 19 studies reported VDR FokI polymorphism, and four studies related to VDR Cdx2 polymorphism. Furthermore, five genetic models are compared separately. Overall, compared with the FF and Ff genotypes, statistically significant increased osteoporosis risk was found in the VDR FokI ff genotype. In
Figure 4. VDR FokI polymorphism and osteoporosis risk between different gender

The forest plots of all selected studies on the association between VDR FokI polymorphism and osteoporosis risk between different gender (A) additive model; (B) recessive model.

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Figure 5. Begg's funnel plot to assess publication bias.
Table 8 Pooled estimates of association of VDR BsmI, FokI, Cdx2 polymorphism and osteoporosis risk, excluding low quality and HWD studies

| Genetic model | Test of association | Tests for heterogeneity |
|---------------|---------------------|-------------------------|
|               | OR (95% CI) | P | $P_h$ | $I^2$ |
| VDR BsmI      |             |     |      |       |
| B vs b        | 1.16 (1.00–1.35) | 0.05 | 0.002 | 53.00% |
| bb vs BB      | 0.74 (0.56–0.99) | 0.04 | 0.021 | 42.50% |
| Bb vs BB+BB   | 0.88 (0.72–1.08) | 0.22 | 0.194 | 20.60% |
| bb vs BB+Bb   | 0.79 (0.63–0.98) | 0.04 | 0.004 | 50.70% |
| BB+bb vs Bb   | 0.91 (0.79–1.06) | 0.23 | 0.224 | 17.80% |
| VDR FokI      |             |     |      |       |
| F vs f        | 0.93 (0.81–1.08) | 0.33 | 0.009 | 48.00% |
| ff VS FF      | 1.17 (0.83–1.66) | 0.37 | 0.006 | 50.20% |
| Ff+ff VS FF   | 1.07 (0.89–1.27) | 0.47 | 0.080 | 32.60% |
| ff VS FF+Ff   | 1.23 (0.93–1.63) | 0.16 | 0.036 | 39.60% |
| FF+ff VS Ff   | 1.01 (0.88–1.15) | 0.90 | 0.596 | 0.00% |
| VDR Cdx2      |             |     |      |       |
| G vs A        | 1.17 (0.68–2.00) | 0.57 | 0.026 | 67.50% |
| AA VS GG      | 0.68 (0.29–1.58) | 0.37 | 0.269 | 23.80% |
| GA+AA VS GG   | 0.86 (0.44–1.66) | 0.65 | 0.030 | 66.40% |
| AA VS GG+GA   | 0.72 (0.37–1.40) | 0.34 | 0.531 | 0.00% |
| GG+AA VS GA   | 0.89 (0.55–1.45) | 0.64 | 0.166 | 41.00% |

Table 9 Pooled estimates of association of VDR BsmI, FokI polymorphism and osteoporosis risk, only studies with high-quality matching, and studies conforming to HWE

| Genetic model | Test of association | Test for heterogeneity |
|---------------|---------------------|------------------------|
|               | OR (95% CI) | P | $P_h$ | $I^2$ |
| VDR BsmI      |             |     |      |       |
| B vs b        | 1.14 (0.96–1.36) | 0.14 | 0.469 | 0.00% |
| bb VS BB      | 0.71 (0.48–1.03) | 0.07 | 0.652 | 0.00% |
| Bb vs BB+BB   | 0.86 (0.64–1.14) | 0.28 | 0.870 | 0.00% |
| bb VS BB+Bb   | 0.81 (0.61–1.08) | 0.15 | 0.215 | 26.80% |
| BB+bb vs Bb   | 0.96 (0.76–1.22) | 0.74 | 0.410 | 2.60% |
| VDR FokI      |             |     |      |       |
| F vs f        | 0.96 (0.81–1.14) | 0.63 | 0.157 | 31.50% |
| ff VS FF      | 1.17 (0.84–1.61) | 0.36 | 0.120 | 36.00% |
| Ff+ff VS FF   | 1.08 (0.91–1.30) | 0.39 | 0.434 | 0.40% |
| ff VS FF+Ff   | 1.16 (0.86–1.57) | 0.35 | 0.069 | 43.30% |
| FF+ff VS Ff   | 0.97 (0.81–1.15) | 0.70 | 0.301 | 15.50% |

the subgroup analysis, the VDR FokI ff genotype was significantly associated with increased osteoporosis risk in Indians and women population. However, significantly decreased the risk of osteoporosis were observed in the West Asians for VDR BsmI b allele and bb genotype. In addition, when we excluded studies of low quality and HWD, a significantly decreased the risk of osteoporosis was found in the overall analysis for the VDR BsmI bb genotype. Further, significant association did not observed when the pooled analysis was limited only involving high quality, HWE, and matching studies. Furthermore, the current meta-analysis was performed by applying multiple subgroups and different genetic models, at the cost of multiple comparisons, in which case the pooled $P$-value must be adjusted [83]. The Venice criteria, statistical power, and $I^2$ value were very important criteria [37]. Hence, the FPRP test and Venice criteria were used to assess positive results. After credibility assessment, we identified 'less-credible positive results' for the statistically significant associations in the current meta-analysis. Heterogeneity has also been observed in the current meta-analysis. Results of meta-regression analysis suggested that studies of HWD were the source of heterogeneity. In addition, no obvious asymmetry was found in the study of VDR BsmI and FokI by the Begg's funnel.
Table 10 FPRP values for the statistically significant associations in current meta-analysis

| Variables | OR (95% CI) | \(I^2\) (%) | Statistical power | Prior probability of 0.001 |
|-----------|-------------|-------------|------------------|--------------------------|
|           |             |             | OR = 1.2         | OR = 1.5                 | OR = 1.2         | OR = 1.5                 |
| Overall   |             |             |                  |                          |                |
| ff vs FF  | 1.49 (1.07–2.07) | 57.10%     | 0.098            | 0.516                    | 0.994           | 0.971                    |
| ff vs FF+Ff | 1.47 (1.13–1.93)     | 47.50%     | 0.072            | 0.558                    | 0.987           | 0.909                    |
| West Asian |             |             |                  |                          |                |
| B vs b    | 1.36 (1.06–1.74)     | 0%         | 0.160            | 0.782                    | 0.989           | 0.949                    |
| bb vs BB  | 0.55 (0.33–0.92)      | 0%         | 0.057            | 0.232                    | 0.998           | 0.990                    |
| bb vs BB+Bb | 0.65 (0.45–0.96)     | 0%         | 0.106            | 0.449                    | 0.997           | 0.985                    |
| Indian    |             |             |                  |                          |                |
| F vs f    | 0.68 (0.58–0.80)      | 0%         | 0.007            | 0.594                    | 0.317           | 0.006                    |
| ff vs FF  | 3.25 (2.14–4.94)     | 0%         | 0               | 0                        | 0.957           | 0.189                    |
| Ff+ff vs FF | 1.40 (1.14–1.71)    | 0%         | 0.065            | 0.75                     | 0.937           | 0.565                    |
| ff vs FF+Ff | 2.87 (1.93–4.26)     | 0%         | 0               | 0.001                    | 0.967           | 0.207                    |
| Female    |             |             |                  |                          |                |
| ff vs FF  | 1.46 (1.02–2.11)     | 62.80%     | 0.148            | 0.557                    | 0.997           | 0.987                    |
| ff vs FF+Ff | 1.48 (1.09–2.03)    | 55.40%     | 0.086            | 0.535                    | 0.992           | 0.952                    |
| Exclude low quality and HWD studies |             |             |                  |                          |                |
| Overall   |             |             |                  |                          |                |
| bb VS BB | 0.74 (0.56–0.99)      | 42.50%     | 0.212            | 0.759                    | 0.995           | 0.982                    |
| bb VS BB+Bb | 0.79 (0.63–0.98)     | 50.70%     | 0.314            | 0.939                    | 0.99            | 0.972                    |

plots and Egger tests. Due to the limited number of studies, the Begg's funnel plot was not performed to explored publication bias in the VDR Cdx2 study. Meantime, the Egger tests revealed that there was no clear statistical evidence of publication bias.

The current meta-analysis has the following advantages: (1) the quality of included studies was assessed; (2) the HWE test was performed in the control group; (3) we applied FPRP and Venice criteria to evaluate the significant association in current meta-analysis; (4) the sample size was much larger than the previous meta-analyses; (5) we explored sources of heterogeneity based on meta-regression analysis. However, there are still some limitations in the present study. First, we did not control confounding factors such as smoking, drinking, and variable study designs, were closely related to affect the results. Second, in the subgroup analyses, the number of studies were relatively small in Indians, and there was not enough statistical power to explore the real association. Moreover, due to the limited number of studies, we did not perform subgroup analyses in the pooled analysis of VDR Cdx2 polymorphism and osteoporosis risk. Therefore, the study with large sample size and large enough subgroup will help to verify our findings.

In conclusion, these positive findings should be interpreted with caution and indicate that significant association may most likely result from less-credible, rather than from true associations or biological factors on the VDR BsmI and FokI polymorphisms with osteoporosis risk.

Competing Interests
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Author Contribution
Bin Chen: designed and performed the research, collected and analyzed the data, wrote the paper. Wang-fa Zhu: collected data. Yi-yang Mu and Biao Liu: checked the data. Hong-zhuo Li and Xiao-feng He: designed the research and revised the article.

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Abbreviations
BMD, bone mineral density; FPRP, false-positive report probability; HWD, Hardy–Weinberg disequilibrium; HWE, Hardy–Weinberg equilibrium; LS, lumbar spine; OR, odds ratio; SNP, single nucleotide polymorphism; VDR, vitamin D receptor; 95% CI, 95% confidence interval.

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