RESEARCH

A meta-analysis of VDR polymorphisms and postmenopausal osteoporosis

Lijuan Fu¹, Jinhuan Ma², Sumei Yan³ and Qijun Si⁴

¹Department of Laboratory, Changyi People’s Hospital of Shandong Province, Changyi, Shandong, China
²Department of Laboratory, Changyi Maternal and Child Health Hospital of Shandong Province, Changyi, Shandong, China
³Department of Obstetrics, Changyi Maternal and Child Health Hospital of Shandong Province, Changyi, Shandong, China
⁴Department of Laboratory, Zhuji Affiliated Hospital of Shaoxing University, Zhuji, Zhejiang, China

Correspondence should be addressed to Q Si: sldc06@163.com

Abstract

Background: Whether polymorphisms in VDR gene affect the risk of postmenopausal osteoporosis or not remain unclear. Thus, the authors performed a meta-analysis to more robustly assess associations between polymorphisms in VDR gene and the risk of postmenopausal osteoporosis by integrating the results of previous literature.

Methods: Medline, Embase, Wanfang, VIP and CNKI were searched comprehensively for eligible literature, and 67 genetic association studies were finally selected to be included in this meta-analysis.

Results: We found that ApaI rs7975232 (dominant comparison: OR = 0.77, P = 0.007; allele comparison: OR = 0.81, P = 0.04), BsmI rs1544410 (dominant comparison: OR = 0.69, P = 0.002; allele comparison: OR = 0.78, P = 0.008) and TaqI rs731236 (recessive comparison: OR = 1.32, P = 0.01) polymorphisms were significantly associated with the risk of postmenopausal osteoporosis in Caucasians, whereas FokI rs10735810 polymorphism was significantly associated with the risk of postmenopausal osteoporosis in Asians (dominant comparison: OR = 0.61, P = 0.0001; recessive comparison: OR = 2.02, P = 0.001; allele comparison: OR = 0.68, P = 0.002).

Conclusions: This meta-analysis shows that ApaI rs7975232, BsmI rs1544410 and TaqI rs731236 polymorphisms may affect the risk of postmenopausal osteoporosis in Caucasians, while BsmI rs1544410 polymorphism may affect the risk of postmenopausal osteoporosis in Asians.

Introduction

Postmenopausal osteoporosis (PMOP) is featured by a decreased bone mineral density and an increased risk of bone fractures in postmenopausal women (1, 2). According to a recent epidemiological research, postmenopausal osteoporosis currently affects nearly 50% of elderly women over 60 years old, and with more and more countries entering the aging society, the incidence of osteoporosis in postmenopausal women is still rapidly increasing, making it the most common disorder of bone metabolism for elderly women across the world (3, 4, 5).

The pathogenesis mechanisms of postmenopausal osteoporosis are still unclear despite previous investigations, but substantial evidence supports that vitamin D deficiency is definitely an important contributing factor to the development of postmenopausal osteoporosis (6, 7). Considering that the action of vitamin D, one of the most crucial modulating factor of bone metabolism, is mediated by the vitamin D receptor (VDR), it is thought that polymorphisms of VDR gene may also affect the risk of postmenopausal osteoporosis (8, 9, 10). Over the last decade, investigators across the world have repeatedly attempted...
to assess the associations between polymorphisms in VDR gene and the risk of postmenopausal osteoporosis, yet the relationships between these polymorphisms and the risk of postmenopausal osteoporosis are still inconclusive. So a meta-analysis was performed to robustly assess the associations between polymorphisms in VDR gene and the risk of postmenopausal osteoporosis by integrating the results of previous literature.

Materials and methods

This meta-analysis was conducted in accordance with the PRISMA guideline (11).

Literature search and inclusion criteria

Medline, Embase, Wanfang, VIP and CNKI were comprehensively searched by the authors using the below keywords: (vitamin D receptor OR VDR) AND (polymorphism OR polymorphic OR variation OR variant OR mutant OR mutation OR SNP OR genotypic OR genotype OR allelic OR allele) AND (postmenopausal OR postmenopause) AND (osteoporosis OR bone loss). Moreover, we also manually screened the references of retrieved literature to make up for the potential incompleteness of literature searching from databases.

Selection criteria of this meta-analysis were listed below: (1) studies of case–control or cohort design; (2) give genotypic frequencies of VDR polymorphisms in cases with postmenopausal osteoporosis and population-based controls; (3) the full manuscript with detailed genotypic frequencies of VDR polymorphisms is retrievable or buyable. Articles would be excluded if one of the following three criteria is satisfied: (1) studies without complete genotypic data of VDR polymorphisms in cases with postmenopausal osteoporosis and population-based controls; (2) narrative or systematic reviews, meta-analysis or comments; (3) case series of subjects with postmenopausal osteoporosis only. If duplicate reports are retrieved, we would only include the most complete one for integrated analyses.

Data extraction and quality assessment

The authors extracted the following data items from eligible studies: (1) last name of the leading author; (2) year of publication; (3) country and ethnicity of study population; (4) the number of cases with postmenopausal osteoporosis and population-based controls; (5) genotypic frequencies of VDR polymorphisms in cases with postmenopausal osteoporosis and population-based controls. We also examined Hardy–Weinberg equilibrium (HWE) by comparing the actual genotypic frequencies of investigated VDR polymorphisms to their expected distributions using the chi-square test. The significance threshold of HWE was set at 0.05, if P value > 0.05, then we considered that the genotypic distribution of the investigated polymorphism was in agreement with HWE. The quality of eligible literature was assessed by the Newcastle–Ottawa scale (NOS) (12), and these with a score of 7–9 were considered to be literature of good quality. Two authors extracted data and assessed quality of eligible literature in parallel. A thorough discussion until a consensus is reached would be endorsed in case of any discrepancy between two authors.

Statistical analyses

All statistical analyses in this meta-analysis were performed with the Cochrane Review Manager software version 5.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom). Associations between VDR gene polymorphisms and the risk of postmenopausal osteoporosis were explored by using odds ratio and its 95% CI. The statistically significant P value was set at 0.05. All investigated VDR polymorphisms have a major allele (M) and a minor allele (m), the dominant comparison was defined as MM vs Mm + mm, the recessive comparison was defined as mm vs MM + Mm, the over-dominant comparison was defined as Mm vs MM + mm, and the allele comparison was defined as M vs m. The authors used F statistics to estimate heterogeneities among included studies. The authors would use DerSimonian–Laird method, which is also known as the random effect model, to integrate the results of eligible studies if F is larger than 50%. Otherwise, the authors would use Mantel–Haenszel method, which is also known as the fixed effect model, to integrate the results of eligible studies. Meanwhile, the authors also conduct subgroup analyses by ethnic groups. Stabilities of integrated results were tested by deleting studies that violated HWE, and then integrating the results of the rest of eligible studies. Publication biases were evaluated by assessing symmetry of funnel plots.

Results

Characteristics of included studies

Five hundred and seven papers were retrieved by the authors by using our searching strategy. One hundred and thirty-three papers were then selected to screen for eligibility after
omitting unrelated and repeated items. Thirty-eight reviews and 13 case series were further excluded, and another 15 papers without complete genotypic data were further excluded by the authors. Totally 67 studies met the inclusion criteria, and were finally enrolled for integrated analyses (Fig. 1). Data extracted from eligible studies were summarized in Table 1.

**ApaI rs7975232 polymorphism and the risk of postmenopausal osteoporosis**

Thirty papers assessed relationship between ApaI rs7975232 polymorphism and the risk of postmenopausal osteoporosis. The integrated analyses demonstrated that ApaI rs7975232 polymorphism was significantly associated with the risk of postmenopausal osteoporosis in overall population (recessive comparison: OR = 1.20, \( P = 0.004 \)) and Caucasians (dominant comparison: OR = 0.77, \( P = 0.007 \); allele comparison: OR = 0.81, \( P = 0.04 \)), but not in Asians (Table 2).

**BsmI rs1544410 polymorphism and the risk of postmenopausal osteoporosis**

Forty-five papers assessed relationship between BsmI rs1544410 polymorphism and the risk of postmenopausal osteoporosis. The integrated analyses demonstrated that BsmI rs1544410 polymorphism was significantly associated with the risk of postmenopausal osteoporosis in overall population (dominant comparison: OR = 0.77, \( P = 0.002 \); recessive comparison: OR = 1.28, \( P = 0.0001 \); allele comparison: OR = 0.80, \( P = 0.002 \)) and Caucasians (dominant comparison: OR = 0.69, \( P = 0.002 \); allele comparison: OR = 0.78, \( P = 0.008 \)), but not in Asians (Table 2).
| First author, year | Country | Ethnicity | Sample size | Genotypes (wt/wt/wtmt/wmtmt) | P-value for HWE | NOS score |
|-------------------|---------|-----------|-------------|-----------------------------|----------------|-----------|
| Apal rs7975232    | India   | Mixed     | 254/254     | 62/140/52                   | 0.264          | 7         |
| Ahmad 2018        | Mexico  | Mixed     | 387/147     | 141/160/86                  | 0.631          | 7         |
| Castelán-Martínez 2015 | China | Asian     | 155/113     | 108/40/7                   | 0.223          | 7         |
| Chen 2007         | Iran     | Mixed     | 50/50       | 24/25/1                     | 0.729          | 7         |
| Dabirnia 2016     | Hellenic Republic | Caucasian | 35/44       | 11/14/10                   | 0.016          | 7         |
| Douroudis 2003    | Turkey   | Caucasian | 75/66       | 13/56/6                    | 0.002          | 7         |
| Duan 2004         | Turkey   | Caucasian | 112/24      | 26/61/25                   | 0.231          | 7         |
| Dundar 2009       | Turkey   | Caucasian | 254/254     | 60/25/5                    | 0.208          | 8         |
| Ge 2009           | China    | Asian     | 353/208     | 160/157/36                 | 0.453          | 8         |
| González-Mercado 2013 | Mexico | Mixed     | 232/87      | 79/118/35                 | 0.715          | 7         |
| Gu 2010           | China    | Asian     | 186/148     | 79/86/21                  | 0.932          | 7         |
| Iván 2008         | Chile    | Caucasian | 67/59       | 25/31/11                  | 0.536          | 7         |
| Kim 2015          | Korea    | Asian     | 153/47      | 97/53/3                    | 0.931          | 7         |
| Langdahl 2000     | Denmark  | Caucasian | 78/74       | 22/44/12                   | 0.283          | 7         |
| Liang 2002        | China    | Asian     | 30/30       | 20/6/4                     | 0.011          | 7         |
| Luan 2011         | China    | Asian     | 140/88      | 71/56/13                   | 0.390          | 7         |
| Marozik 2013      | Belarus  | Caucasian | 54/77       | 7/24/3                     | 0.472          | 7         |
| Marozik 2018      | Lithuania | Caucasian | 149/172     | 27/67/55                  | 0.105          | 7         |
| Meng 2018         | China    | Asian     | 90/246      | 60/25/5                    | 0.028          | 8         |
| Mitra 2006        | India    | Mixed     | 119/87      | 50/44/25                  | 0.002          | 7         |
| Mosaad 2014       | Egypt    | Mixed     | 30/150      | 13/15/2                    | 0.142          | 7         |
| Riggs 1995        | USA      | Mixed     | 30/128      | 12/19/9                   | 0.394          | 7         |
| Sassi 2015        | Tunisia  | Mixed     | 335/231     | 130/143/62                 | 0.233          | 7         |
| Seremak-Mrozikiewicz 2009 | Poland | Caucasian | 163/63 | 35/82/46                  | 0.821          | 7         |
| Tanriover 2010    | Turkey   | Caucasian | 50/50       | 15/23/12                  | 0.007          | 8         |
| Uysal 2008        | Turkey   | Caucasian | 100/146     | 35/50/15                  | 0.165          | 7         |
| Vandeweyer 1997   | Belgium  | Caucasian | 87/699      | 20/45/22                  | 0.027          | 8         |
| Wu 2016           | China    | Asian     | 79/234      | 43/27/9                   | 0.123          | 7         |
| Wu 2019           | China    | Asian     | 610/616     | 331/218/61                | 0.070          | 8         |
| Xie 2005          | China    | Asian     | 295/56      | 240/43/12                 | 0.075          | 7         |
| Yoldemir 2011     | Turkey   | Caucasian | 130/130     | 34/60/36                  | 0.155          | 7         |
| Zajickova 2002    | Czech Republic | Caucasian | 65/33 | 23/33/9                   | 0.793          | 7         |
| BsmI rs1544410    | India    | Mixed     | 254/254     | 54/137/63                 | 0.002          | 7         |
| Ahmad 2018        | Norway   | Caucasian | 19/30       | 4/8/7                     | 0.156          | 7         |
| Berg 1996         | Norway   | Caucasian | 278/292     | 101/121/56                | 0.004          | 7         |
| Boroí 2015        | Poland   | Caucasian | 147/152     | 117/131/51               | 0.007          | 8         |
| Cheishvili 2017   | Israel   | Mixed     | 37/37       | 13/11/13                  | 0.039          | 7         |
| Chen 2003         | China    | Asian     | 78/81       | 65/13/0                   | 0.472          | 7         |
| Douroudis 2003    | Hellenic Republic | Caucasian | 35/44 | 20/12/3                    | 0.019          | 7         |
| Duan 2004         | Kuwait   | Mixed     | 75/66       | 54/18/3                   | 0.021          | 7         |
| Efesoy 2011       | Turkey   | Caucasian | 40/30       | 12/23/5                   | 0.876          | 7         |
| Ge 2009           | China    | Asian     | 353/208     | 314/33/6                   | <0.001          | 8         |
| Gennari 1998      | Italy    | Caucasian | 155/136     | 23/92/40                  | 0.013          | 7         |
| González-Mercado 2013 | Mexico | Mixed | 232/88 | 143/76/13                 | 0.267          | 7         |
| Houston 1996      | UK       | Caucasian | 44/44       | 17/19/8                  | 0.450          | 7         |
| Huang 2000        | China    | Asian     | 14/27       | 13/1/0                    | 0.922          | 7         |
| Hussien 2013      | Egypt    | Mixed     | 150/50      | 50/52/43                   | 0.351          | 7         |
| Iván 2008         | Chile    | Caucasian | 67/59       | 10/46/11                  | 0.046          | 7         |
| Kim 2015          | Korea    | Asian     | 153/47      | 142/11/0                  | 0.700          | 7         |
| Langdahl 2000     | Denmark  | Caucasian | 80/80       | 23/38/19                  | 0.186          | 7         |
| Li 2000           | China    | Asian     | 96/42       | 54/36/6                   | 0.201          | 7         |
| Liang 2002        | China    | Asian     | 30/30       | 28/1/1                    | NA             | 7         |
| Lim 1995          | Korea    | Asian     | 72/70       | 61/9/2                    | 0.349          | 7         |
| Liu 2005          | China    | Asian     | 56/89       | 50/6/0                    | 0.060          | 7         |
| Marozik 2013      | Belarus  | Caucasian | 54/77       | 11/31/12                  | 0.062          | 7         |
| Marozik 2018      | Lithuania | Caucasian | 149/172     | 32/64/53                  | 0.098          | 7         |
Table 1 (Continued).

| First author, year | Country       | Ethnicity      | Sample size | Genotypes (wtt/wtmt/mmtt) | P-value for HWE | NOS score |
|---------------------|---------------|----------------|-------------|---------------------------|----------------|-----------|
| Melhus 1994         | Sweden        | Caucasian      | 70/76       | 14/29/27                  | 0.637           | 8         |
| Mencej-Bedarc 2009  | Slovenia      | Caucasian      | 240/228     | 103/110/27                | 0.215           | 7         |
| Meng 2017           | China         | Asian          | 90/246      | 74/12/4                   | <0.001          | 7         |
| Mitra 2006          | India         | Mixed          | 119/97      | 51/46/22                  | 0.080           | 7         |
| Mosaad 2014         | Egypt         | Mixed          | 30/150      | 2/19/9                    | 0.877           | 7         |
| Musumeci 2009       | Iran          | Mixed          | 50/20       | 27/15/8                   | 0.047           | 7         |
| Perez 2008          | Argentina     | Mixed          | 64/68       | 17/35/12                  | 0.649           | 7         |
| Pollak 2001         | Israel        | Mixed          | 75/143      | 24/38/13                  | 0.675           | 7         |
| Pouremsaeili 2013   | Iran          | Mixed          | 64/82       | 17/33/14                  | 0.252           | 7         |
| Riggs 1995          | USA           | Mixed          | 40/129      | 9/20/11                   | 0.932           | 7         |
| Seremak-Mrozikiewicz 2009 | Poland       | Caucasian      | 163/63      | 70/66/27                  | 0.506           | 7         |
| Tanrıover 2010      | Turkey        | Caucasian      | 50/50       | 16/19/15                  | 0.320           | 8         |
| Techapatiphandee 2018 | Thailand      | Asian          | 105/132     | 85/19/1                   | 0.123           | 7         |
| Uysal 2008          | Turkey        | Caucasian      | 100/146     | 18/48/34                  | 0.283           | 7         |
| Vandezeyer 1997     | Belgium       | Caucasian      | 86/698      | 24/50/12                  | 0.076           | 7         |
| Wang 2007           | China         | Asian          | 50/48       | 43/7/0                    | 0.474           | 7         |
| Yanagi 1996         | Japan         | Asian          | 66/66       | 22/12/12                  | 0.013           | 7         |
| Yoldemir 2011       | Turkey        | Caucasian      | 130/130     | 35/73/22                  | 0.760           | 7         |
| Zajickova 2002      | Czech Republic| Caucasian      | 65/33       | 20/24/21                  | 0.223           | 7         |
| Zhang 1998          | China         | Asian          | 17/164      | 14/3/0                    | 0.511           | 8         |
| Zhang 2000          | China         | Asian          | 77/25       | 38/33/6                   | 0.403           | 7         |
| Zhu 2004            | China         | Asian          | 40/158      | 26/8/6                    | 0.500           | 7         |

(Continued)
FokI rs10735810 polymorphism and the risk of postmenopausal osteoporosis

Twenty-six papers assessed relationship between FokI rs10735810 polymorphism and the risk of postmenopausal osteoporosis. The integrated analyses demonstrated that FokI rs10735810 polymorphism was significantly associated with the risk of osteoporosis in overall population (dominant comparison: OR = 0.76, \( P < 0.0001 \); recessive comparison: OR = 1.40, \( P = 0.005 \); allele comparison: OR = 0.86, \( P = 0.04 \) and Asians (dominant comparison: OR = 0.61, \( P = 0.0001 \); recessive comparison: OR = 2.02, \( P = 0.001 \); allele comparison: OR = 0.68, \( P = 0.002 \)), but not in Caucasians (Table 2).

Taql rs731236 polymorphism and the risk of postmenopausal osteoporosis

Twenty-five papers assessed relationship between Taql rs731236 polymorphism and the risk of postmenopausal osteoporosis. The integrated analyses demonstrated that Taql rs731236 polymorphism was significantly associated with the risk of postmenopausal osteoporosis in Caucasians (recessive comparison: OR = 1.32, \( P = 0.01 \)), but not in Asians (Table 2).

Sensitivity analyses

The authors examined stabilities of integrated analyses results by deleting studies that violated HEW, and then integrating the results of the rest of studies. The trends of associations were not significantly altered in sensitivity analyses, which indicated that from statistical perspective, our integrated analyses results were reliable and stable.

Publication biases

The authors examined potential publication biases in this meta-analysis by assessing symmetry of funnel plots. Funnel plots were found to be generally symmetrical, which indicated that our integrated analyses results were not likely to be severely deteriorated by publication biases (Supplementary Fig. 1, see section on supplementary materials given at the end of this article).

Discussion

This meta-analysis, robustly assessed associations between gene polymorphisms in VDR and the risk of postmenopausal osteoporosis. The integrated analyses results showed that Apal rs7975232, BsmI rs1544410 and Taql rs731236 polymorphisms were significantly associated with the risk of postmenopausal osteoporosis in Caucasians, whereas FokI rs10735810 polymorphism was significantly associated with the risk of postmenopausal osteoporosis in Asians.

The following points should be considered when interpreting our integrated findings. First, based on the findings of previous observational studies,
Table 2  Integrated analyses results of the current meta-analysis.

| Variables    | Sample size | Dominant comparison | Recessive comparison | Over-dominant comparison | Allele comparison |
|--------------|-------------|----------------------|----------------------|--------------------------|------------------|
|              |             | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) |
| Apal rs7975232 |             |         |            |         |            |         |            |         |            |
| Overall      | 4693/4567   | 0.64    | 0.96 (0.83–1.12) | 0.004    | 1.20 (1.06–1.37) | 0.59    | 0.98 (0.89–1.07) | 0.53    | 0.96 (0.85–1.09) |
| Caucasian    | 1165/1637   | 0.007   | 0.77 (0.64–0.93) | 0.11     | 1.31 (0.94–1.82) | 0.85    | 0.98 (0.83–1.16) | 0.04    | 0.81 (0.67–0.99) |
| Asian        | 2091/1786   | 0.39    | 1.14 (0.85–1.52) | 0.59    | 0.90 (0.61–1.32) | 0.40    | 0.91 (0.72–1.14) | 0.38    | 1.12 (0.87–1.45) |
| BsmI rs154410 |             |         |            |         |            |         |            |         |            |
| Overall      | 4312/5015   | 0.002   | 0.77 (0.65–0.91) | 0.0001   | 1.28 (1.13–1.45) | 0.17    | 1.07 (0.97–1.18) | 0.002   | 0.80 (0.70–0.92) |
| Caucasian    | 1825/2388   | 0.002   | 0.69 (0.55–0.87) | 0.08    | 1.29 (0.97–1.71) | 0.05    | 1.14 (1.00–1.30) | 0.008   | 0.78 (0.65–0.94) |
| Asian        | 1297/1443   | 0.30    | 0.81 (0.54–1.21) | 0.06    | 1.76 (0.98–3.17) | 0.99    | 1.00 (0.79–1.27) | 0.17    | 0.74 (0.48–1.14) |
| FokI rs10735810 |            |         |            |         |            |         |            |         |            |
| Overall      | 3612/3602   | <0.0001 | 0.76 (0.69–0.84) | 0.005    | 1.40 (1.11–1.78) | 0.07    | 1.10 (0.99–1.21) | 0.04    | 0.86 (0.75–0.99) |
| Caucasian    | 889/847     | 0.30    | 0.90 (0.74–1.10) | 0.08    | 1.02 (0.76–1.37) | 0.08    | 1.19 (0.98–1.45) | 0.71    | 1.04 (0.83–1.31) |
| Asian        | 1358/1233   | 0.0001  | 0.61 (0.52–0.72) | 0.001    | 2.02 (1.32–3.08) | 0.18    | 1.12 (0.95–1.31) | 0.002   | 0.68 (0.54–0.87) |
| TaqI rs731236 |             |         |            |         |            |         |            |         |            |
| Overall      | 2684/2956   | 0.57    | 0.94 (0.76–1.16) | 0.13     | 1.13 (0.96–1.32) | 0.67    | 1.04 (0.87–1.24) | 0.93    | 0.99 (0.86–1.15) |
| Caucasian    | 1208/1613   | 0.20    | 0.83 (0.62–1.10) | 0.01     | 1.32 (1.06–1.63) | 0.81    | 1.02 (0.87–1.20) | 0.16    | 0.87 (0.73–1.05) |
| Asian        | 350/277     | 0.33    | 1.24 (0.80–1.93) | 0.79    | 0.89 (0.37–2.14) | 0.77    | 0.89 (0.40–1.96) | 0.06    | 1.42 (0.98–2.06) |

The values in bold represent there is statistically significant differences between cases and controls. NA, not available; OR, odds ratio.
in their publications, so it is impossible for us to explore genetic-environmental interactions in a meta-analysis based on these previous literature (17). Thirdly, we did not select gray literature for integrated analyses because this literature is generally considered to be incomplete and it is almost impossible for us to extract all necessary data items, or assess their quality through the NOS scale. Nevertheless, since we did not select gray literature for integrated analyses, despite that funnel plots were found to be overall symmetrical, it should be acknowledged that publication biases still may influence reliability of our integrated analyses results (18).

In conclusion, this meta-analysis shows that Apal rs7975232, BsmI rs1544410 and TaqI rs731236 polymorphisms may affect the risk of postmenopausal osteoporosis in Caucasians, while FokI rs10735810 polymorphism may affect the risk of postmenopausal osteoporosis in Asians. Further studies with larger sample sizes are still needed to confirm our findings. In addition, scholars should also try to reveal the exact underlying mechanisms of the positive associations observed between aforementioned VDR polymorphisms and the risk of postmenopausal osteoporosis in the future.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EC-20-0296.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author contribution statement
Lijuan Fu and Qijun Si conceived and designed this meta-analysis. Lijuan Fu and Jinhuan Ma searched literature. Sumei Yan analyzed data. Lijuan Fu and Qijun Si wrote the manuscript. All authors have approved the final manuscript as submitted.

References

1 Aspray TJ & Hill TR. Osteoporosis and the ageing skeleton. Sub-Cellular Biochemistry 2019 91 453–476. (https://doi.org/10.1007/978-981-13-3681-2_16)

2 Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. American Journal of Obstetrics and Gynecology 2006 194 (Supplement) S3-S11. (https://doi.org/10.1016/j.ajog.2005.06.047)

3 Thambiah SC & Yeap SS. Osteoporosis in South-East Asian countries. Clinical Biochemist: Reviews 2020 41 29–40. (https://doi.org/10.33176/AACB-19-00034)

4 Sidlauskas KM, Sutton EE & Biddle MA. Osteoporosis in men: epidemiology and treatment with denosumab. Clinical Interventions in Aging 2014 9 593–601. (https://doi.org/10.2147/CIA.S19140)

5 Harvey N, Dennison E & Cooper C. Osteoporosis: impact on health and economics. Nature Reviews: Rheumatology 2010 6 99–105. (https://doi.org/10.1038/nrrheum.2009.260)

6 Armas LA & Recker RR. Pathophysiology of osteoporosis: new mechanistic insights. Endocrinology and Metabolism Clinics of North America 2012 41 475–486. (https://doi.org/10.1016/j.ecl.2012.04.006)

7 Wimalawansa SJ. Vitamin D deficiency: effects on oxidative stress, epigenetics, gene regulation, and aging. Biology 2019 8 E30. (https://doi.org/10.3390/biology8020030)

8 Saxi F, Tamone C & D’Amelio P. Vitamin D: nutrient, hormone, and immunomodulator. Nutrients 2018 10 E1656. (https://doi.org/10.3390/nu10111656)

9 Haussler MR, Whitfield GK, Kaneko I, Haussler CA, Hsieh D, Hsieh JC & Jurutka PW. Molecular mechanisms of vitamin D action. Calcified Tissue International 2013 92 77–98. (https://doi.org/10.1007/s00223-012-9619-0)

10 Goltzman D. Functions of vitamin D in bone. Histochemistry and Cell Biology 2018 149 305–312. (https://doi.org/10.1007/s00418-018-1648-y)

11 Mohler D, Liberati A, Tetzlaff J, Altman DG & PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine 2009 151 264–269. (https://doi.org/10.7326/0003-4819-151-4-200908180-00135)

12 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology 2010 25 603–605. (https://doi.org/10.1007/s10654-010-9491-z)

13 Uitterlinden AG, Fang Y, Van Meurs JB, Pols HA & Van Leeuwen JP. Genetics and biology of vitamin D receptor polymorphisms. Gene 2004 338 143–156. (https://doi.org/10.1016/j.gene.2004.05.014)

14 Valdivielso JM & Fernandez E. Vitamin D receptor polymorphisms and diseases. Clinica Chimica Acta: International Journal of Clinical Chemistry 2006 371 1–12. (https://doi.org/10.1016/j.cca.2006.02.016)

15 Zhang L, Yin X, Wang J, Xu D, Wang Y, Yang J, Tao Y, Zhang S, Feng X & Yan C. Associations between VDR gene polymorphisms and osteoporosis risk and bone mineral density in postmenopausal women: a systematic review and meta-analysis. Scientific Reports 2018 8 981. (https://doi.org/10.1038/s41598-017-18670-7)

16 Zhang YJ, Zhang L, Chen SY, Yang GJ, Huang XL, Duan Y, Yang LJ, Ye DQ & Wang J. Association between VDR polymorphisms and multiple sclerosis: systematic review and updated meta-analysis of case-control studies. Neurological Sciences 2018 39 225–234. (https://doi.org/10.1007/s10072-017-3175-3)

17 Zhang JZ, Wang M, Ding Y, Gao F, Feng YY, Yakeya B, Wang P, Wu XJ, Hu FX, Xian J, et al. Vitamin D receptor gene polymorphism, serum 25-hydroxyvitamin D levels, and risk of vitiligo: a meta-analysis. Medicine 2018 97 e11506. (https://doi.org/10.1097/MDC.0000000000011506)

18 Mashhadiabas F, Neamatzadeh H, Nastri R, Foroughi E, Farahnak S, Phiozzo Zand M, Mazaheri M & Zare-Shenbeh M. Association of vitamin D receptor BsmI, TaqI, FokI, and Apal polymorphisms with susceptibility of chronic periodontitis: a systematic review and meta-analysis based on 38 case-control studies. Dental Research Journal 2018 15 155–165.

Received in final form 17 July 2020
Accepted 28 July 2020
Accepted Manuscript published online 28 July 2020