

Vitamin D Receptor Bsm I Polymorphism and Osteoporosis Risk in postmenopausal women: A Meta-Analysis from 42 Studies

JunLong Liao

Sixth Affiliated Hospital of Kunming Medical University: Peoples Hospital of Yuxi City

Qiang Qin

Zhejiang University of Science and Technology

YongSheng Zhou

Peoples Hospital of Yuxi City

RuPing Ma

Peoples Hospital of Yuxi City

HeChao Zhou

Sixth Affiliated Hospital of Kunming Medical University: Peoples Hospital of Yuxi City

MaoRong Gu

Sixth Affiliated Hospital of Kunming Medical University: Peoples Hospital of Yuxi City

Yunping Feng

Sixth Affiliated Hospital of Kunming Medical University: Peoples Hospital of Yuxi City

BoYuan Wang

Yuxi Normal University


Ling Yang (✉ yangling6th@163.com)

Sixth Affiliated Hospital of Kunming Medical University: Peoples Hospital of Yuxi City <https://orcid.org/0000-0003-3240-9751>

Research

Keywords: Vitamin D Receptor, BsmI Polymorphism, Osteoporosis, postmenopausal, Meta-analysis

DOI: <https://doi.org/10.21203/rs.3.rs-70193/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

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 database 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 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.

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 osteoporosis³. 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 drugs⁴. 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 secretion⁵. 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}. In 1996, Berg et al. reported for the first time that VDR BsmI polymorphism was associated with bone mineral density in postmenopausal females¹⁰. 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 osteoporosis¹¹. However, significant correlation was observed between VDR genotype and BMD in Chinese postmenopausal females, with bb genotype having the lowest bone density¹². 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 results¹³. Therefore, the meta-analysis was performed on the currently published eligible case-control studies combined with the previous research results, and the relationship between BsmI 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 key words 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 were listed below: □case-control or cohort studies. □participants included postmenopausal women. □assessment of the relationship of BsmI and osteoporosis or fracture. □containing available genotype frequencies of BsmI. □provided BMD values (mean and standard deviation) of lumbar spine and femoral neck, osteoporosis was defined as BMD \leq -2.5 SDs (T-score).

Exclusion criteria

Exclusion criteria of this meta-analysis were listed below: □reviews, case reports, comments and letters. □incomplete data. □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 1st author. □publication year. □region. □ethnicity. □age range. □sample size. □allele frequency of cases and controls. and □genotyping method. Any different evaluation results needs 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)¹⁴. 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 was regarded as a high quality study.

Statistic analysis

The observed genotype frequencies of the VDR BsmI polymorphism in control groups were assessed for Hardy-Weinberg equilibrium using the χ^2 test. 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 co-dominant model (Bb vs. BB, bb vs. BB) respectively. The subgroup analyses by ethnic groups also be 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 not significant heterogeneity. Otherwise, the random-effects model was used^{15,16}. The potential for publication bias was examined by a Begg's test (funnel plot method, $p < 0.05$ considered representative of statistical significance)¹⁷. All analysis were performed by Stata software (version 11.0).

Results

Eligible studies

Literature screening process is shown in Figure 1. Based on the pre-established search strategy, 42 studies were finally enrolled for integrated analyses, including 4485 osteoporosis and 5490 controls. 23 studies¹⁸⁻⁴⁵ were performed in Caucasians and 9 studies^{11,12,46-52} were subsumed into Asians. In addition, 2 interracial studies^{31,53} were conducted in Mix-race. The main characteristics of the selected studies are listed in Table 1. 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^{19,24,26,32,35-38,45,46,52}.

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 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 $p=0.028$). 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, suggest 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 BsmI 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 BsmI polymorphism and susceptibility to osteoporosis are various, but the results are not consistent. A recent meta-analysis⁵⁴ 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 tow previously published studies^{55,56}. 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 population⁵⁷. 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, 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 role⁵⁸. 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 involved. Therefore, referring to the analysis methods of other researchers⁵⁹, 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, exercise, etc. should be considered more comprehensively when cases are included in the group.

Conclusion

In conclusion, our study believes that VDR BsmI polymorphism and 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.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by Yuxi Social Science Foundation (YXSK226).

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 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.

Acknowledgements

Not applicable

References

1. Melhus H, Kindmark A, Amer S, et al. Vitamin D receptor genotypes in osteoporosis. . *Lancet (London, England)* 1994;344:2.
2. Kanis JA, Melton LJ, 3rd, Christiansen C, et al. The diagnosis of osteoporosis. *J Bone Miner Res* 1994;9(8):1137-41. doi: 10.1002/jbmr.5650090802 [published Online First: 1994/08/01]
3. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol* 2006;194(2 Suppl):S3-11. doi: 10.1016/j.ajog.2005.08.047 [published Online First: 2006/02/02]
4. Lamichhane AP. Osteoporosis-an update. *JNMA J Nepal Med Assoc* 2005;44(158):60-6. [published Online First: 2006/03/30]
5. Williams FM, Spector TD. The genetics of osteoporosis. *Acta Reumatol Port* 2007;32(3):231-40. [published Online First: 2007/10/18]
6. Horst-Sikorska W, Dytfeld J, Wawrzyniak A, et al. Vitamin D receptor gene polymorphisms, bone mineral density and fractures in postmenopausal women with osteoporosis. *Mol Biol Rep* 2013;40(1):383-90. doi: 10.1007/s11033-012-2072-3 [published Online First: 2012/10/17]
7. Dennison EM, Arden NK, Keen RW, et al. Birthweight, vitamin D receptor genotype and the programming of osteoporosis. *Paediatr Perinat Epidemiol* 2001;15(3):211-9. [published Online First: 2001/08/08]
8. Morrison NA, Yeoman R, Kelly PJ, et al. Contribution of trans-acting factor alleles to normal physiological variability: vitamin D receptor gene polymorphism and circulating osteocalcin. *Proc Natl Acad Sci U S A* 1992;89(15):6665-9. doi: 10.1073/pnas.89.15.6665 [published Online First: 1992/08/01]
9. Morrison NA, Qi JC, Tokita A, et al. Prediction of bone density from vitamin D receptor alleles. *Nature* 1994;367(6460):284-7. doi: 10.1038/367284a0 [published Online First: 1994/01/20]

10. Berg JP, Falch JA, Haug E. Fracture rate, pre- and postmenopausal bone mass and early and late postmenopausal bone loss are not associated with vitamin D receptor genotype in a high-endemic area of osteoporosis. *Eur J Endocrinol* 1996;135(1):96-100. [published Online First: 1996/07/01]
11. Techapatiphandee M, Tammachote N, Tammachote R, et al. VDR and TNFSF11 polymorphisms are associated with osteoporosis in Thai patients. *Biomed Rep* 2018;9(4):350-56. doi: 10.3892/br.2018.1137 [published Online First: 2018/09/21]
12. Zhang H, Su PJ, Chen GF, et al. Relationship between vitamin D receptor gene polymorphism and bone mineral density and traditional Chinese medicine differentiation type in postmenopausal women in Zhongshan area of Guangdong. *Chin J Tradit Med Traumatol Orthop* 2011;19(2):3. [published Online First: 21]
13. Nakagawa S, Noble DW, Senior AM, et al. Meta-evaluation of meta-analysis: ten appraisal questions for biologists. *BMC Biol* 2017;15(1):18. doi: 10.1186/s12915-017-0357-7 [published Online First: 2017/03/05]
14. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25(9):603-5. doi: 10.1007/s10654-010-9491-z [published Online First: 2010/07/24]
15. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22(4):719-48. [published Online First: 1959/04/01]
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7(3):177-88. [published Online First: 1986/09/01]
17. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629 [published Online First: 1997/10/06]
18. Marozik PM, Tamulaitiene M, Rudenka E, et al. Association of Vitamin D Receptor Gene Variation With Osteoporosis Risk in Belarusian and Lithuanian Postmenopausal Women. *Front Endocrinol (Lausanne)* 2018;9:305. doi: 10.3389/fendo.2018.00305 [published Online First: 2018/06/21]
19. Ahmad I, Jafar T, Mahdi F, et al. Association of Vitamin D Receptor (FokI and BsmI) Gene Polymorphism with Bone Mineral Density and Their Effect on 25-Hydroxyvitamin D Level in North Indian Postmenopausal Women with Osteoporosis. *Indian J Clin Biochem* 2018;33(4):429-37. doi: 10.1007/s12291-017-0706-x [published Online First: 2018/10/16]
20. Moran JM, Pedrera-Canal M, Rodriguez-Velasco FJ, et al. Lack of association of vitamin D receptor BsmI gene polymorphism with bone mineral density in Spanish postmenopausal women. *PeerJ* 2015;3:e953. doi: 10.7717/peerj.953 [published Online First: 2015/07/15]
21. Marozik P, Mosse I, Alekna V, et al. Association Between Polymorphisms of VDR, COL1A1, and LCT genes and bone mineral density in Belarusian women with severe postmenopausal osteoporosis. *Medicina (Kaunas)* 2013;49(4):177-84. [published Online First: 2013/08/30]
22. Gonzalez-Mercado A, Sanchez-Lopez JY, Regla-Nava JA, et al. Association analysis of vitamin D receptor gene polymorphisms and bone mineral density in postmenopausal Mexican-Mestizo women. *Genet Mol Res* 2013;12(3):2755-63. doi: 10.4238/2013.July.30.13 [published Online First: 2013/08/28]
23. Efesoy A. Relationship of the Vitamin D Receptor and Collagen Ia1 Gene Polymorphisms with Low Bone Mineral Density and Vertebral Fractures in Postmenopausal Turkish Women. *Turkish Journal of Rheumatology* 2011;26(4):295-302. doi: 10.5606/tjr.2011.047
24. Durusu Tanriover M, Bora Tatar G, Uluturk TD, et al. Evaluation of the effects of vitamin D receptor and estrogen receptor 1 gene polymorphisms on bone mineral density in postmenopausal women. *Clin Rheumatol* 2010;29(11):1285-93. doi: 10.1007/s10067-010-1548-6 [published Online First: 2010/08/11]
25. Mansour L, Sedky M, AbdelKhader M, et al. The role of vitamin D receptor genes (FOKI and BSMI) polymorphism in osteoporosis. *Middle East Fertility Society Journal* 2010;15(2):79-83. doi: 10.1016/j.mefs.2010.05.002
26. Musumeci M, Vadala G, Tringali G, et al. Genetic and environmental factors in human osteoporosis from Sub-Saharan to Mediterranean areas. *J Bone Miner Metab* 2009;27(4):424-34. doi: 10.1007/s00774-009-0041-2 [published Online First: 2009/03/04]
27. Mencej-Bedrac S, Prezelj J, Kocjan T, et al. The combinations of polymorphisms in vitamin D receptor, osteoprotegerin and tumour necrosis factor superfamily member 11 genes are associated with bone mineral density. *J Mol Endocrinol* 2009;42(3):239-47. doi: 10.1677/JME-08-0108 [published Online First: 2009/01/10]
28. Seremak-Mrozikiewicz A, Drews K, Mrozikiewicz PM, et al. Correlation of vitamin D receptor gene (VDR) polymorphism with osteoporotic changes in Polish postmenopausal women. *Neuro Endocrinol Lett* 2009;30(4):540-6. [published Online First: 2009/12/17]
29. Perez A, Ulla M, Garcia B, et al. Genotypes and clinical aspects associated with bone mineral density in Argentine postmenopausal women. *J Bone Miner Metab* 2008;26(4):358-65. doi: 10.1007/s00774-007-0840-2 [published Online First: 2008/07/05]
30. Uysal AR, Sahin M, Gursoy A, et al. Vitamin D receptor gene polymorphism and osteoporosis in the Turkish population. *Genet Test* 2008;12(4):591-4. doi: 10.1089/gte.2008.0052 [published Online First: 2008/11/04]
31. Quevedo LI, Martinez BM, Castillo NM, et al. [Vitamin D receptor gene polymorphisms and risk of hip fracture in Chilean elderly women]. *Rev Med Chil* 2008;136(4):475-81. doi: /S0034-98872008000400008 [published Online First: 2008/09/05]
32. Wengreen H, Cutler DR, Munger R, et al. Vitamin D receptor genotype and risk of osteoporotic hip fracture in elderly women of Utah: an effect modified by parity. *Osteoporos Int* 2006;17(8):1146-53. doi: 10.1007/s00198-006-0100-7 [published Online First: 2006/06/08]
33. Garnero P, Munoz F, Borel O, et al. Vitamin D receptor gene polymorphisms are associated with the risk of fractures in postmenopausal women, independently of bone mineral density. *J Clin Endocrinol Metab* 2005;90(8):4829-35. doi: 10.1210/jc.2005-0364 [published Online First: 2005/05/12]
34. Mitra S, Desai M, Ikram Khatkhatay M. Vitamin D receptor gene polymorphisms and bone mineral density in postmenopausal Indian women. *Maturitas* 2006;55(1):27-35. doi: 10.1016/j.maturitas.2006.01.003 [published Online First: 2006/02/09]
35. Duman BS, Tanakol R, Erensoy N, et al. Vitamin D receptor alleles, bone mineral density and turnover in postmenopausal osteoporotic and healthy women. *Med Princ Pract* 2004;13(5):260-6. doi: 10.1159/000079524 [published Online First: 2004/08/19]

36. Douroudis K, Tarassi K, Ioannidis G, et al. Association of vitamin D receptor gene polymorphisms with bone mineral density in postmenopausal women of Hellenic origin. *Maturitas* 2003;45(3):191-7. [published Online First: 2003/06/24]
37. Lisker R, Lopez MA, Jasqui S, et al. Association of vitamin D receptor polymorphisms with osteoporosis in Mexican postmenopausal women. *Hum Biol* 2003;75(3):399-403. [published Online First: 2003/10/07]
38. Borjas-Fajardo L, Zambrano M, Fernandez E, et al. [Analysis of Bsm I polymorphism of the vitamin D receptor (VDR) gene in Venezuelan female patients living in the state of Zulia with osteoporosis]. *Invest Clin* 2003;44(4):275-82. [published Online First: 2004/01/20]
39. Zajickova K, Zofkova I, Bahbouh R, et al. Vitamin D receptor gene polymorphisms, bone mineral density and bone turnover: FokI genotype is related to postmenopausal bone mass. *Physiol Res* 2002;51(5):501-9. [published Online First: 2002/12/10]
40. Pollak RD, Blumenfeld A, Bejarano-Achache I, et al. The BsmI vitamin D receptor gene polymorphism in Israeli populations and in perimenopausal and osteoporotic Ashkenazi women. *Am J Nephrol* 2001;21(3):185-8. doi: 10.1159/000046245 [published Online First: 2001/06/26]
41. Valimaki S, Tahtela R, Kainulainen K, et al. Relation of collagen type I alpha 1 (COLIA1) and vitamin D receptor genotypes to bone mass, turnover, and fractures in early postmenopausal women and to hip fractures in elderly people. *Eur J Intern Med* 2001;12(1):48-56. doi: 10.1016/s0953-6205(00)00137-0 [published Online First: 2001/02/15]
42. Aerssens J, Dequeker J, Peeters J, et al. Polymorphisms of the VDR, ER and COLIA1 genes and osteoporotic hip fracture in elderly postmenopausal women. *Osteoporos Int* 2000;11(7):583-91. doi: 10.1007/s001980070079 [published Online First: 2000/11/09]
43. Fontova Garrofe R, Gutierrez Fornes C, Broch Montane M, et al. [Polymorphism of the gene for vitamin D receptor, bone mass, and bone turnover in women with postmenopausal osteoporosis]. *Rev Clin Esp* 2000;200(4):198-202. [published Online First: 2000/06/17]
44. Gomez C, Naves ML, Barrios Y, et al. Vitamin D receptor gene polymorphisms, bone mass, bone loss and prevalence of vertebral fracture: differences in postmenopausal women and men. *Osteoporos Int* 1999;10(3):175-82. doi: 10.1007/s001980050213 [published Online First: 1999/10/20]
45. Gennari L, Becherini L, Masi L, et al. Vitamin D and estrogen receptor allelic variants in Italian postmenopausal women: evidence of multiple gene contribution to bone mineral density. *J Clin Endocrinol Metab* 1998;83(3):939-44. doi: 10.1210/jcem.83.3.4649 [published Online First: 1998/03/20]
46. Zhu MJ, D. YX, F. W. Relationship between vitamin D receptor genotypes and bone mineral density in Guangxi Zhuang and Han nationality postmenopausal women. *Chinese Journal of Osteoporosis* 2004;2004-02
47. Chen J, Zhang LP, Qiu JF, et al. The relationship between VDR gene polymorphism and PMOP in Chongqing Area. *Chinese Journal of Medical Genetics* 2003(20):2.
48. Leng XW, Chen RY, LY A, et al. Relationship between vitamin D receptor gene alleles and bone mineral density in women from Urumqi. *Chin J Endocrinol Metab* 2002;18(2):1. [published Online First: 213]
49. Ly A, Leng XJ, Chen RY, et al. Association of vitamin D receptor gene polymorphisms with bone mineral density in Uighurs in China. *Health Care Med Chin PLA* 2002;1:2. [published Online First: 42]
50. Zhang QX, Wang WJ, Kuang JQ, et al. Relationship between the polymorphism of vitamin D receptor gene and bone mineral density in pre- and postmenopausal women. *Acad J SUMS* 2000(5):4. doi: 10.13471/j.cnki [published Online First: 379]
51. Zhang HH, Tao GQ, Wu Q, et al. Preliminary Studies on the Relationship between Vitamin D Receptor Gene Polymorphism and Osteoporosis in Chinese Women. *Chinese Journal of Epidemiology* 1998(19):3.
52. Yanagi H, Tomura S, Kawanami K, et al. Vitamin D receptor gene polymorphisms are associated with osteoporosis in Japanese women. *J Clin Endocrinol Metab* 1996;81(11):4179-81. doi: 10.1210/jcem.81.11.8923886 [published Online First: 1996/11/01]
53. Ramalho AC, Lazaretti-Castro M, Hauache O, et al. Fractures of the proximal femur: correlation with vitamin D receptor gene polymorphism. *Braz J Med Biol Res* 1998;31(7):921-7. doi: 10.1590/s0100-879x1998000700006 [published Online First: 1998/08/12]
54. Zhang L, Yin X, Wang J, et al. Associations between VDR Gene Polymorphisms and Osteoporosis Risk and Bone Mineral Density in Postmenopausal Women: A systematic review and Meta-Analysis. *Sci Rep* 2018;8(1):981. doi: 10.1038/s41598-017-18670-7 [published Online First: 2018/01/19]
55. Shen H, Xie J, Lu H. Vitamin D receptor gene and risk of fracture in postmenopausal women: a meta-analysis. *Climacteric* 2014;17(4):319-24. doi: 10.3109/13697137.2013.856401 [published Online First: 2013/10/26]
56. Wang D, Liu R, Zhu H, et al. Vitamin D receptor FokI polymorphism is associated with low bone mineral density in postmenopausal women: a meta-analysis focused on populations in Asian countries. *Eur J Obstet Gynecol Reprod Biol* 2013;169(2):380-6. doi: 10.1016/j.ejogrb.2013.03.031 [published Online First: 2013/05/08]
57. Conti V, Russomanno G, Corbi G, et al. A polymorphism at the translation start site of the vitamin D receptor gene is associated with the response to anti-osteoporotic therapy in postmenopausal women from southern Italy. *Int J Mol Sci* 2015;16(3):5452-66. doi: 10.3390/ijms16035452 [published Online First: 2015/03/13]
58. Mezquita-Raya P, Munoz-Torres M, Alonso G, et al. Susceptibility for postmenopausal osteoporosis: interaction between genetic, hormonal and lifestyle factors. *Calcif Tissue Int* 2004;75(5):373-9. doi: 10.1007/s00223-004-0187-9 [published Online First: 2004/12/14]
59. Wang S, Ai Z, Song M, et al. The association between vitamin D receptor FokI gene polymorphism and osteoporosis in postmenopausal women: a meta-analysis. *Climacteric* 2020;1-6. doi: 10.1080/13697137.2020.1775806 [published Online First: 2020/06/20]
60. Vandevyver C, Wylin T, Cassiman JJ, et al. Influence of the vitamin D receptor gene alleles on bone mineral density in postmenopausal and osteoporotic women. *J Bone Miner Res* 1997;12(2):241-7. doi: 10.1359/jbmr.1997.12.2.241 [published Online First: 1997/02/01]
61. Houston LA, Grant SF, Reid DM, et al. Vitamin D receptor polymorphism, bone mineral density, and osteoporotic vertebral fracture: studies in a UK population. *Bone* 1996;18(3):249-52. [published Online First: 1996/03/01]

Tables

Table 1. Main characteristics of studies included in the meta-analysis.

BsmI rs1544410 (G>A)	Publication year	Region	Genotyping methods	Osteoporosis		Control	
				n	Age (y) mean \pm SD	n	Age (y) mean \pm SD
Marozik PM et al. ¹⁸	2018	Belarus, Lithuania	PCR-RFLP	149	61.40 \pm 6.50	172	57.50 \pm 7.30
Ahmad et al. ¹⁹	2018	India	PCR-RFLP	254	55.82 \pm 6.91	254	54.76 \pm 6.26
Techapatiphandee et al. ¹¹	2018	Thailand	PCR-RFLP	105	73.10 \pm 8.90	132	63.40 \pm 8.70
Moran et al. ²⁰	2015	Spain	TaqMan	150	60.24 \pm 7.74	30	59.73 \pm 9.28
Marozik et al. ²¹	2013	Belarus	PCR-RFLP	54	58.30 \pm 6.20	77	56.70 \pm 7.40
Gonzalez et al. ²²	2013	Mexico	TaqMan	88	57.65 \pm 5.58	88	56.34 \pm 4.98
Efesoy et al. ²³	2011	Turkey	PCR-RDB	40	65.75 \pm 9.80	30	62.40 \pm 8.70
Zhang et al. ¹²	2011	China	PCR-RFLP	120	60.12 \pm 3.26	60	58.69 \pm 2.48
Tanriover et al. ²⁴	2010	Turkey	PCR-RFLP	50	58.30 \pm 6.50	50	57.30 \pm 6.60
Mansour et al. ²⁵	2010	Egypt	PCR-RFLP	50	54.40 \pm 5.10	20	53.50 \pm 5.40
Musumeci et al. ²⁶	2009	Italy	PCR-RFLP	100	49.91 \pm 3.08	100	52.39 \pm 4.38
Mencej et al. ²⁷	2009	Slovenia	PCR-RFLP	240	64.50 \pm 8.20	228	61.50 \pm 8.30
Seremak et al. ²⁸	2009	Poland	PCR-RFLP	163	64.27 \pm 8.72	63	63.08 \pm 7.24
Perez et al. ²⁹	2008	Argentina	PCR-RFLP	64	62.70 \pm 0.86	68	59.40 \pm 0.85
Uysal et al. ³⁰	2008	Turkey	PCR-RFLP	100	—	146	—
Quevedo et al. ³¹	2008	Chile	PCR-RFLP	67	77.00 \pm 4.00	59	78.00 \pm 9.00
Wengreen et al. ³²	2006	USA	PCR-RFLP	819	76.70 \pm 9.10	854	76.00 \pm 9.40
Garnero et al. ³³	2005	France	PCR-RFLP	120	61.77 \pm 8.40	469	61.77 \pm 8.40
Mitra et al. ³⁴	2006	India	PCR-RFLP	119	54.10 \pm 3.50	97	54.10 \pm 3.50
Duman et al. ³⁵	2004	Turkey	PCR-RFLP	75	53.16 \pm 1.31	66	52.62 \pm 1.69
Zhu et al. ⁴⁶	2004	China	PCR-RFLP	40	57.55 \pm 5.18	158	57.55 \pm 5.18
Douroudis et al. ³⁶	2003	Greece	PCR-RFLP	35	61.37 \pm 0.96	44	58.68 \pm 1.01
Chen et al. ⁴⁷	2003	China	PCR-RFLP	40	54.72 \pm 2.60	21	54.72 \pm 2.60
Lisker et al. ³⁷	2003	Mexico	PCR-RFLP	66	65.20 \pm 6.80	57	56.50 \pm 6.00
Borjas et al. ³⁸	2003	Venezuela	PCR-RFLP	54	—	55	—
Leng et al. ⁴⁸	2002	China	PCR-RFLP	22	51.67 \pm 4.93	46	51.67 \pm 4.93
A et al. ⁴⁹	2002	China	PCR-RFLP	10	53.70 \pm 7.11	13	53.70 \pm 7.11
Zajickova et al. ³⁹	2002	Czech	PCR-RFLP	65	63.60 \pm 7.80	33	60.10 \pm 10.30
Pollak et al. ⁴⁰	2001	Israel	PCR-RFLP	75	49.57 \pm 2.97	143	49.57 \pm 2.97
Valimaki et al. ⁴¹	2001	Finland	PCR-RFLP	372	—	111	—
Aerssens et al. ⁴²	2000	Belgium	PCR-RFLP	135	78.00 \pm 9.00	239	76.00 \pm 4.00
Garrofe et al. ⁴³	2000	Spain	PCR-RFLP	75	58.30 \pm 5.00	51	57.20 \pm 4.50
Zhang et al. ⁵⁰	2000	China	PCR-RFLP	34	66.70 \pm 8.50	78	66.70 \pm 8.50
Gomez et al. ⁴⁴	1999	Spain	PCR-RFLP	37	66.30 \pm 8.67	122	63.00 \pm 8.67
Ramalho et al. ⁵³	1998	Brazil	PCR-RFLP	56	78.50 \pm 7.20	36	72.90 \pm 5.20
Gennari et al. ⁴⁵	1998	Italy	Southern Blotting	160	58.20 \pm 0.60	144	57.10 \pm 0.70

Zhang et al. ⁵¹	1998	China	PCR-RFLP	17	56.76 ± 2.80	162	58.78 ± 3.00
Vandevyver et al. ⁶⁰	1997	Belgium	PCR-RFLP		75.50 ± 5.00	698	66.60 ± 8.40
Houston et al. ⁶¹	1996	UK	PCR-RFLP	44	66.00 ± 0.85	44	65.30 ± 0.95
Berg et al. ¹⁰	1996	Norway	PCR-RFLP	19	63-65	30	63-65
Yanagi et al. ⁵²	1996	Japanes	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.

—: The original text only shown "postmenopausal" and did not provide a specific age range.

SD: standard deviation.

Table 2. Results of quality assessment by the Newcastle-Ottawa Scale for case-control studies.

Study	Selection				Comparability	Exposure			Total score
	adequate definition of the cases	representativeness of the cases	selection of controls	definition of controls		ascertainment of exposure	same method of ascertainment for cases and controls	non-response rate	
Marozik et al.2018	√		√	√	√	√	√	√	7
Techapatiphandee et al.2018	√	√		√	√	√	√	√	7
Ahmad et al.2018	√	√		√	√√	√	√	√	8
Moran et al.2015	√				√√	√	√	√	6
Mohammadi et al.2015	√	√	√	√	√	√	√	√	8
Marozik et al.2013	√			√	√√	√	√	√	7
Gonzalez et al.2013	√	√		√	√	√	√	√	7
Efesoy et al.2011	√		√	√	√	√	√		6
Zhang et al.2011	√			√	√	√	√	√	6
Mansour et al.2010	√			√	√	√	√	√	6
Tanriover et al.2010	√	√		√	√√	√	√	√	8
Musumeci et al.2009	√			√	√	√	√	√	6
Mencej et al.2009	√	√		√	√	√	√	√	7
Seremak et al.2009	√			√		√	√	√	5
Perez et al.2008	√	√	√	√	√	√	√	√	8
Uysal et al.2008	√			√		√	√	√	5
Quevedo et al.2008	√		√	√		√	√		5
Wengreen et al.2006	√	√	√	√	√√	√	√	√	9
Mitra et al.2006	√	√		√	√	√	√	√	7
Garnero2005	√			√	√	√	√		5
Duman et al. 2004	√			√	√√	√	√	√	7
Zhu et al.2004	√		√	√	√	√	√	√	7
Douroudis et al.2003	√			√	√	√	√	√	6
Borjas-Fajardo et al.2003	√			√		√	√	√	5
Chen et al.2003	√		√	√		√	√	√	6
Lisker et al.2003	√	√		√	√	√	√	√	7
Zajickova et al.2002	√	√		√	√	√	√	√	7
Zhang et al.2002	√	√	√	√	√	√	√	√	8
Leng et al.2002	√		√	√		√	√	√	6
A et al.2002	√		√			√	√	√	5
Pollak et al.2001	√			√		√	√	√	5
Valimaki et al.2001	√		√	√		√	√		5
Aerssens et	√	√	√	√	√	√	√	√	8

al.2000									
Garrofe et al.2000	√		√	√	√	√	√	√	7
Zhang et al.2000	√			√	√	√	√	√	6
Choi et al.2000	√	√		√	√√	√	√	√	8
Gennari et al.1999	√	√		√	√	√	√	√	7
Lucotte et al.1999	√	√	√		√	√	√	√	7
Gomez et al.1999	√			√	√√	√	√		6
Ramalho et al.1998	√			√	√√	√	√	√	7
Gennari et al.1998	√		√	√	√√	√	√	√	8
Zhang et al.1998	√		√	√		√	√	√	6
Vandevyver et al.1997	√			√	√√	√	√	√	7
Houston et al.1996	√				√√	√	√	√	6
Berg et al.1996	√			√	√	√	√		5
Yanagi et al.1996	√		√	√		√	√		5
Melhus et al.1994	√		√			√	√	√	5

√: matched the condition, scored one point;

Table 3. The distribution of VDR BsmI genotypes for osteoporosis and controls.

Bsm1 rs1544410 (G>A)	Publication year	Ethnicity	Osteoporosis			Control			p ^a
			BB	Bb	bb	BB	Bb	bb	
Marozik et al. ¹⁸	2018	Caucasian	53	64	32	35	73	64	0.098
Ahmad et al. ¹⁹	2018	Caucasian	54	137	63	54	152	48	0.002
Moran et al. ²⁰	2015	Caucasian	18	65	67	3	19	8	0.097
Marozik et al. ²¹	2013	Caucasian	12	31	11	11	26	40	0.061
Gonzalez et al. ²²	2013	Caucasian	54	28	6	46	38	4	0.267
Efesoy et al. ²³	2011	Caucasian	5	23	12	5	15	10	0.876
Tanriover et al. ²⁴	2010	Caucasian	15	19	16	19	7	24	<0.001
Mansour et al. ²⁵	2010	Caucasian	27	15	8	1	2	17	0.050
Musumeci et al. ²⁶	2009	Caucasian	30	55	15	13	60	27	0.025
Mencej et al. ²⁷	2009	Caucasian	103	110	27	88	100	40	0.215
Seremak et al. ²⁸	2009	Caucasian	27	66	70	10	27	26	0.506
Perez et al. ²⁹	2008	Caucasian	17	35	12	20	32	16	0.647
Uysal et al. ³⁰	2008	Caucasian	18	48	34	24	78	44	0.283
Quevedo et al. ³¹	2008	Caucasian	11	46	10	9	37	13	0.050
Wengreen et al. ³²	2006	Caucasian	154	393	272	140	376	338	0.043
Garnero et al. ³³	2005	Caucasian	25	62	33	65	224	180	0.724
Mitra et al. ³⁴	2006	Caucasian	51	46	22	19	38	40	0.080
Duman et al. ³⁵	2004	Caucasian	18	54	3	17	42	7	0.014
Douroudis et al. ³⁶	2003	Caucasian	3	12	20	10	29	5	0.026
Lisker et al. ³⁷	2003	Caucasian	15	17	34	13	38	6	0.008
Borjas et al. ³⁸	2003	Caucasian	28	20	6	11	36	8	0.020
Zajickova et al. ³⁹	2002	Caucasian	21	24	20	10	13	10	0.223
Pollak et al. ⁴⁰	2001	Caucasian	13	38	24	16	67	60	0.675
Valimaki et al. ⁴¹	2001	Caucasian	44	175	153	20	55	36	0.899
Aerssens et al. ⁴²	2000	Caucasian	26	60	49	52	125	62	0.459
Garrofe et al. ⁴³	2000	Caucasian	9	49	17	10	22	19	0.434
Gomez et al. ⁴⁴	1999	Caucasian	7	20	10	20	51	51	0.241
Gennari et al. ⁴⁵	1998	Caucasian	40	92	28	11	76	57	0.035
Vandevyver et al. ⁶⁰	1997	Caucasian	12	50	24	127	368	203	0.076
Houston et al. ⁶¹	1996	Caucasian	8	19	17	9	19	16	0.450
Berg et al. ¹⁰	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. ¹¹	2018	Asian	85	19	1	103	25	4	0.123
Zhang et al. ¹²	2011	Asian	9	25	86	16	36	8	0.086
Zhu et al. ⁴⁶	2004	Asian	6	26	8	7	105	46	<0.001

Chen et al. ⁴⁷	2003	Asian	0	7	33	0	3	18	0.724
Leng et al. ⁴⁸	2002	Asian	0	11	11	7	19	20	0.488
A et al. ⁴⁹	2002	Asian	0	4	6	1	5	7	0.935
Zhang et al. ⁵⁰	2000	Asian	2	15	17	7	36	35	0.598
Zhang et al. ⁵¹	1998	Asian	0	3	14	0	14	148	0.565
Yanagi et al. ⁵²	1996	Asian	12	12	22	2	7	57	0.013
Ramvalho et al. ⁵³	1998	mix	13	23	20	7	11	18	0.050
Quevedo et al. ³¹	2008	mix	11	46	10	9	37	13	0.050

a: p value for Hardy–Weinberg equilibrium in control group.

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

Table 4. ORs and 95% CI for osteoporosis and the VDR BsmI polymorphism under different genetic models.

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.

Figures

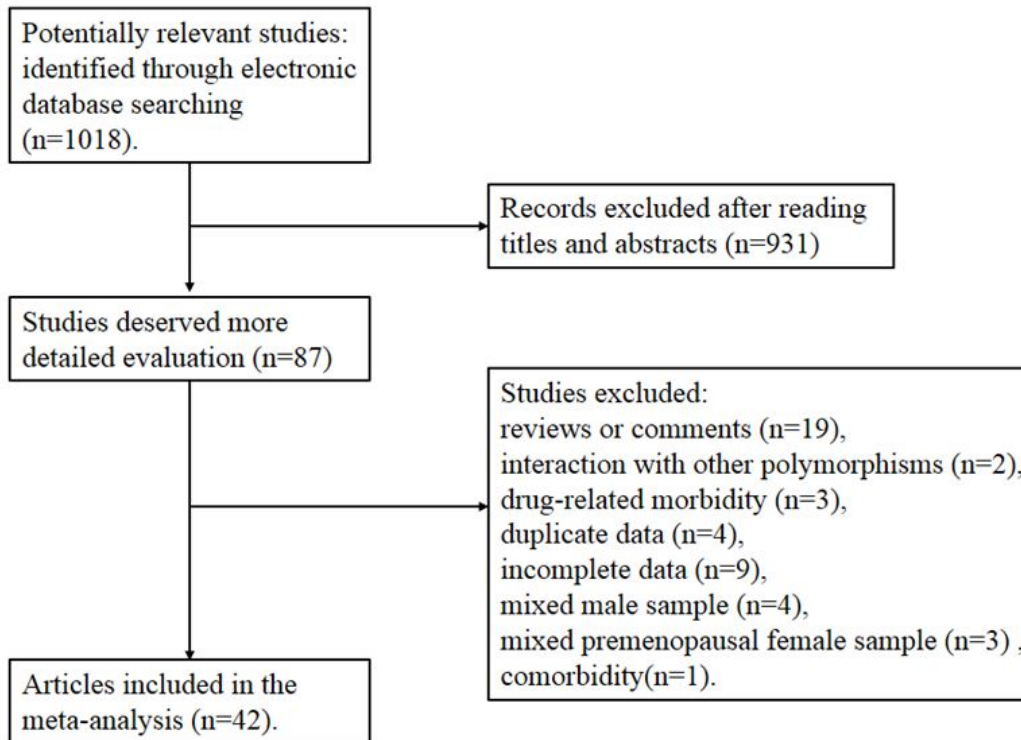


Figure 1

Flow chart indicating search results