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Original Article

Association between Hip Fracture and BsmI Vitamin D Receptor (VDR) Polymorphism: A Meta-Analysis

Sangyeob Lee [a,b], Jun-Il Yoo [c *]

[a] *Department of Biomedical Research Institute, Gyeongsang National University Hospital, Jinju, South Korea,* [b] *Department of Theriogenology and Biotechnology, College of Veterinary Medicine, Gyeongsang National University, Jinju, South Korea,* [c] *Department of Orthopaedic Surgery, Gyeongsang National University Hospital, Jinju, South Korea*

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SUMMARY

Background: The purpose of this study was to perform a systematic review and meta-analysis evaluating the potential relationship between BsmI vitamin D receptor (VDR) polymorphism and hip fractures as a practical, useful disease prediction method.
Methods: The assessment of eligibility of the selected studies was performed based on the following criteria: a) studies showing an analysis of the association between a genetic variant in BsmI and hip fractures; b) case-control design study or cohort study; c) data enabling the counting of genotypes/alleles to calculate risk estimates; d) studies providing definite information on the source of controls and patients with hip fractures, diagnostic methods and protocols, genotyping and statistical analysis, and e) studies written in English.
Results: The genetic variant BsmI was not associated with overall hip fractures except in one model. In age-based subgroup meta-analysis (age over 75 or under 75 years), statistically significant associations were observed in the age over 75 years subgroup for the same genetic models as in the overall data synthesis. However, the over-dominant model did not show any significant difference.
Conclusions: BsmI VDR polymorphism conferred an increased risk of hip fracture in people over 75 years old. It was supposed that people, specifically very old aged people, with functional defects in VDR experience more rapid decreases in bone mineral density than those with normally functional VDR. These results indicate that BsmI VDR polymorphisms might be a predictor of hip fractures in older people.

1. Background

Hip fractures are serious osteoporotic fractures that have high mortality and societal financial burden.[1] Hip fracture refers to femoral neck fracture and intertrochanteric hip fracture, which occurs near the hip joint, and these fractures are related to a large number of deaths with higher medical costs than other osteoporotic fractures.[2–4] The causes of hip fractures are usually osteoporosis, low bone mineral density (BMD), a fall caused by sarcopenia, and various chronic diseases. Although diverse studies are ongoing for hip fracture prediction, there are still no effective prevention methods.

Many previous studies reported that vitamin D prevented fractures by enhancing BMD.[5–7] Vitamin D is important for skeletal health by promoting calcium absorption and the mineralization of bone. In addition, it has an impact on the wide mineralization of the skeletal bone, bone turnover, and the frequency of fractures. Vitamin D deficiency is also related to the severity of sarcopenia associated with various types of fractures. However, it is still not clear if vitamin D treatment is essential for the prevention of fractures in specific condition groups such as post-menopausal or aged people.

The vitamin D effects on skeletal components are mediated through the vitamin D receptor (VDR), a nuclear transcription factor regulating gene expressions. The VDR is a nuclear receptor superfamily member whose gene is 75 kb long and whose location is mapped on chromosome 12q13.[8,9] The VDR has gained increasing attention recently as having an important role in maintaining skeletal health by regulating phosphate and calcium metabolism.[10] Therefore, VDR polymorphisms produce various bone diseases including arthritis, osteoporosis, and fractures.[11] In recent years, a large number of studies have demonstrated that VDR gene mutations were related to BMD which is associated with osteoporotic fractures.[12–14] Furthermore, VDR alleles have a high predictive value in the bone health of an individual.[15]

One of the most commonly studied VDR polymorphisms in joint research today is BsmI, a single nucleotide polymorphism (SNP) at the 3′ end of the VDR gene. The 3′-untranslated region (UTR) is considered a potentially functional region, including stability of the VDR.[16] A study by Morrison et al. showed that individuals homozygous for the B allele of BsmI had a significantly lower BMD than subjects homozygous for the b allele.[15] Similarly, Viitanen A et al. also represented that a femoral neck BMD in hip fracture patients with BB genotype was lower than in those with the bb genotype in young Finns (20–29 years).[17] As a result, VDR disequilibrium affected by BsmI polymorphism resulted in frequent fractures due to lowered BMD.

* Corresponding author. Department of Orthopaedic Surgery, Gyeongsang National University Hospital, 90 Chilamdong, Jinju, Gyeongnamdo 660-702, Republic of Korea.
E-mail address: furim@hanmail.net (J.-I. Yoo)

For these reasons, BsmI polymorphism may affect BMD and hip fracture risk on a population level. Several meta-analyses on BsmI and hip fractures have been conducted, but the age-related results were not represented. Therefore, the purpose of this study was to perform a systematic review and meta-analysis evaluating the potential relationship between BsmI VDR polymorphism and hip fractures as a practical, useful disease prediction method.

2. Materials and methods

Our systematic review and meta-analysis were done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO).

2.1. Publication search

The eligible studies were selected from the PubMed database by searching for correlations between hip fracture and BsmI, which is a SNP of the VDR gene. The search terms were as follows: ("fracture") AND ("VDR" OR "vitamin D receptor" OR "BsmI" OR "rs154410") AND ("polymorphism" OR "mutation" OR "variant" OR "SNP" OR "single nucleotide polymorphism"). We checked the references of the retrieved studies including relevant reviews and meta-analyses. All selected studies were published before March 2021.

2.2. Inclusion/exclusion criteria and data extraction

The assessment of eligibility of the selected studies was performed based on the following criteria: a) studies showing an analysis of the association between a genetic variant in BsmI and hip fractures; b) case-control design study or cohort study; c) data enabling the counting of genotypes/alleles to calculate risk estimates; d) studies providing definite information on the source of the controls and patients with hip fractures, diagnostic methods and protocols, genotyping and statistical analyses, and e) studies written in English. The exclusion criteria were poor quality study design or having obvious major errors, retraction of articles, and discordance between the data presented in the tables or figures and the related findings described within. The selected studies were evaluated using Newcastle-Ottawa scale (NOS)[18] for quality assessment.

The extracted data included the first author's name, the year of publication, study type and period, country and ethnicity of the participants, genotyping method, age, gender, diagnostic methods, and genotypes/alleles counts. The data were independently extracted and cross-checked by two authors and if there were discrepancies, the third author performed a final check and confirmation.

2.3. Statistical analysis

Pearson's chi-squared test was performed to check for the presence of Hardy-Weinberg equilibrium (HWE) in the controls. A p-value of < 0.05 suggested a significant departure from HWE. Statistical software MetaGenyo (Pfizer-University of Granada-Junta de Andalucía Centre for Genomics and Oncological Research, (GENYO), Granada, Spain), was used for conducting the heterogeneity tests and meta-analyses.

Heterogeneity was assessed by Cochran's Q test and the inconsistency index (I^2). Heterogeneity was regarded as significant at $p < 0.1$, while an I^2 of 0–25% showed no heterogeneity, an I^2 of 25–50% was moderate heterogeneity, an I^2 of 50–75% was substantial heterogeneity, and an I^2 of > 75% indicated considerable heterogeneity. Significant results in the heterogeneity tests of $p < 0.1$ or $I^2 > 50\%$ were analyzed by the random-effects model, while in other cases, the fixed-effect model was chosen for data synthesis. The DerSimonian-Laird Random effect estimated method was used, while inverse variance was applied for pooling results under the fixed-effect model. Genetic models including the allele contrast model, recessive model, dominant model, and over-dominant model were assessed. Also, the potential contribution of heterozygotes and minor allele homozygotes to hip fractures was estimated.

Association value was calculated using the odds ratio. Fixed effect model or random effect model was selected based on heterogeneity test. Additionally, meta-regression was performed using Comprehensive Meta-Analysis (Version 3; Biostat, Englewood, NJ) software package.

Publication bias was assessed by funnel plots for visual inspection and by Egger's test for statistical calculation with a p-value of 0.05 as a threshold for significance. Sensitivity analysis applying the leave-one-out method was also performed to estimate the stability of the data results by repeating the meta-analysis after removing one study at a time.

3. Results

3.1. Study identification and HWE assessment

The flow chart shown in Figure 1 displayed the study selection process for the meta-analysis. The initial database search yielded a total of 103 potentially related publications from literature retrieval (n = 101) and reference searches (n = 2). After the duplicate records were removed, 88 articles were enrolled. In addition, 74 articles were not relevant to the subject of this meta-analysis. After excluding 74 articles, 14 articles were reviewed. Among the 14 articles, eight articles did not satisfy the inclusion criteria, four studies were meta-analyses, two articles were not in English, and another two did not show detailed data.

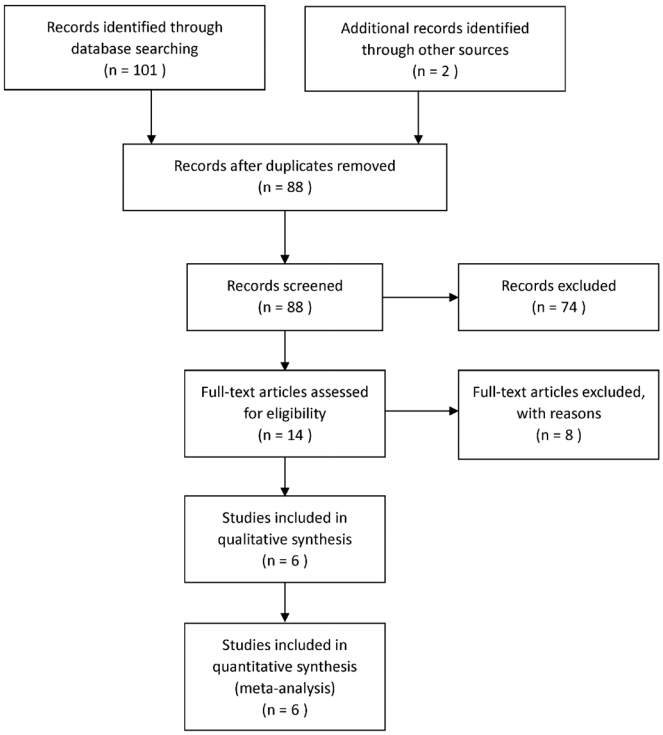

Figure 1. Flowchart of study selection process.

The remaining six full-text articles (H. Wengreen et al., 2006; Aerssens et al., 2000; Dincel et al., 2008; Valimakia et al., 2001; Feskanich et al., 1998; and Ramalho et al., 1998)[17,19–23] of case-control studies were selected in the eligibility assessment (Table 1). All studies showed a p-value of > 0.05 in Pearson's chi-squared test for HWE deviations in the control group of each article. A total of 2513 subjects, including 1147 hip fracture cases and 1366 controls, were registered in our meta-analysis. The detailed article selection process is described in Figure 1. In addition, quality assessment results were conducted in Supplementary Table 1.

3.2. Meta-analysis results

Table 2 summarizes the assessment of the association between VDR BsmI polymorphism and hip fractures.

Genetic BsmI variants were not associated with overall hip fractures except in one model. Specifically 1) Figure 2A showed $P_{allelic}$ = 0.164, $OR_{allelic}$ = 1.165, 95% CI: 0.940–1.445; 2) Figure 2B showed P_{dom} = 0.400, OR_{dom} = 1.155, 95% CI: 0.826–1.615; 3) Figure 2C showed $P_{overdom}$ = 0.443, $OR_{overdom}$ = 1.065, 95% CI: 0.908–1.249; 4) Figure 2D showed $P_{BB\ vs.\ bb}$ = 0.024, $OR_{BB\ vs.\ bb}$ = 1.306, 95% CI: 1.037–1.647. The pooled OR indicated that subjects with the BB genotype had a higher risk of hip fracture compared to those with bb genotype. However, the other genotype models did not show any significant difference in the prevalence of hip fractures (Table 3).

In this stage, just one study (Aerssens et al.) consistently showed results contradictory to those of the other studies. Therefore, we decided to proceed with subgroup analysis excluding it. When the age-based subgroup meta-analysis (age over 75 or under 75 years) was conducted, statistically significant associations were observed in the age over 75 years subgroup for the same genetic models as in the overall data synthesis ($P_{BB\ vs.\ bb}$ = 0.009, $OR_{BB\ vs.\ bb}$ = 1.415, 95% CI: 1.089–1.839; P_{allele} = 0.002, OR_{allele} = 1.223, 95% CI: 1.075–1.391; P_{dom} = 0.002, OR_{dom} = 1.352, 95% CI: 1.122–1.630). However, the over-dominant model did not show any significant difference ($P_{overdom}$ = 0.058, OR_{overdo} = 1.190, 95% CI: 0.9942–1.4250) (Table 4). In Supplementary Table 2, we used meta-regression to assess the effect of age (age 75 and up or age 75 and down), but no significant findings were observed.

The funnel plot was represented in Figure 3. In BB vs. bb, allelic, and dominant genetic model of funnel plot, Aerssens et al. was outside the funnel pyramid (Figure 3A, 3B, 3C). On the other hand, the overdominant genetic model of the funnel plot didn't show such a significance (Figure 3D).

The pooled ORs from the data synthesis in the sensitivity tests showed that in BB vs. bb, allelic, and dominant genetic models showed higher OR (Figure 4A, 4B, 4C). Overdominant model of sensitivity analysis showed contradictory results when omitting the study of H. Wengreen et al. (Figure 4D).

4. Discussion

The main finding of this meta-analyses was that BsmI polymorphism of VDR increased risk of hip fracture in people over 75 years old.

In present meta-analysis, the study of Aerssens et al. showed the opposite result in almost all genotype models compared to the other studies. This discrepancy remained in other analyses including race, sex, age, or environmental interactions. Especially, because the countries where the studies performed varied, differences could have come from the geographical diversity of the patients. However, the publications on the association between BsmI and hip fractures were in distinct countries. One was in Belgium (Aerssens et al.),[20] one in Turkey (Dincel et al.),[21] one in Finland (Valimakia et al.),[17] one in Brazil (Ramalho et al.),[23] and two in the United States (Wengreen et al. and Feskanich et al.).[19,22] It seems that further studies evaluating the importance of research performed in different regions are required for more concrete results. In the sensitivity analyses,

Table 1
Characteristics of the included studies.

Study	Year of publication	Study type	Study period	Country/ Ethnicity	Genotyping method	Age mean (range)	Gender (M/F)	Diagnosis	Polymorphism	No. of cases	No. of controls*
H. Wengreen	2006	Case-control	1997-2001	USA/NA	PCR-RFLP	76.3 (50–89)	F	ICD-9	BsmI	819	854
J. Aerssens	2000	Case-control	NA	Belgium/ Caucasian	PCR-RFLP	76.7 (60–95)	F	Radiography	BsmI	135	239
Ercan Dincel	2008	Case-control	NA	Turkey/ Caucasian	Non-RFLP	74.5 (±8.9)	M, F	Radiography	BsmI	19	21
Stiina Valimakia	2001	Case-control	1991	Finland/ Caucasian	PCR-RFLP	89 (85–98)	M, F	NA	BsmI	402	111
Diane Feskanich	1998	Cohort	1976-1990	USA/ Caucasian	PCR-RFLP	62.2 (±0.6)	F	NA	BsmI	54	108
A.C. Ramalho	1998	Case-control	NA	Brazil/NA	PCR-RFLP	76.3 (±0.9)	F	NA	BsmI	56	36

NO, number; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

Table 2
Characteristics of the studies included in the meta-analysis.

Study	Year	Cases/controls	Genotype distribution in cases			Genotype distribution in controls			B allele frequency in controls	P_{HWE} in controls
			BB	Bb	Bb	BB	Bb	Bb		
H. Wengreen	2006	819/854	154	393	272	140	376	338	0.384	0.101
J. Aerssens	2000	135/239	26	60	49	52	125	62	0.479	0.551
Ercan Dincel	2008	19/21	2	11	6	0	14	7	0.333	0.101
Stiina Valimakia	2001	64/108	9	35	20	10	54	44	0.343	0.379
Diane Feskanich	1998	54/108	16	21	17	16	53	39	0.394	0.770
A.C. Ramalho	1998	56/36	13	23	20	7	11	18	0.347	0.101

HWE, Hardy-Weinberg Equilibrium.

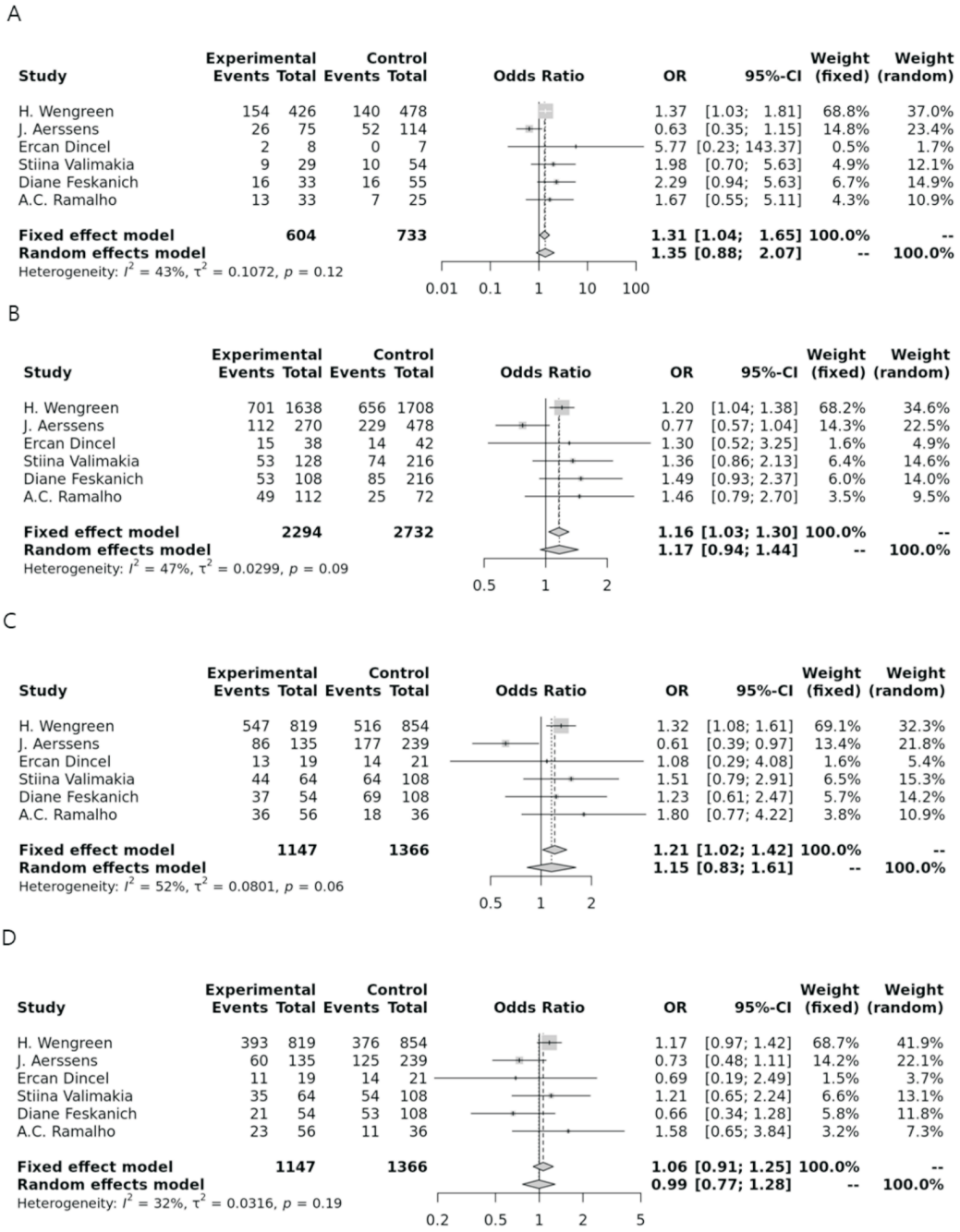

Figure 2. Meta-analysis of the association between BsmI and hip fracture risk. (A) BB vs. bb, (B) allelic model, (C) dominant model, and (D) over-dominant model. The results of the included studies are presented as ORs with 95% CI, and the overall effect with 95% CI is shown in the forest plot. The p-values presented are derived from heterogeneity tests.

Table 3

Meta-analysis of association between genetic variants BsmI in VDR and hip fracture.

Model	Age	Number of studies	Test of association			Test of heterogeneity			Publication bias
			OR	95% CI	*p*-val	Model	*p*-val	I^2	*p*-val (Egger's test)
BB vs. bb	Overall	6	1.306	[1.0365; 1.6467]	0.024	Fixed	0.117	0.433	0.560
	75 down	2	2.452	[1.0336; 5.8183]	0.042	Fixed	0.588	0.000	NA
	75 over	4	1.194	[0.7385; 1.9315]	0.469	Random	0.097	0.525	0.941
Allele contrast (B vs. b)	Overall	6	1.165	[0.9396; 1.4450]	0.164	Random	0.092	0.471	0.804
	75 down	2	1.446	[0.9549; 2.1894]	0.082	Fixed	0.804	0.000	NA
	75 over	4	1.115	[0.8492; 1.4634]	0.434	Random	0.042	0.635	0.925
Dominant model (BB + Bb vs. bb)	Overall	6	1.155	[0.8258; 1.6146]	0.400	Random	0.062	0.525	0.820
	75 down	2	1.197	[0.6464; 2.2162]	0.567	Fixed	0.868	0.000	NA
	75 over	4	1.158	[0.7376; 1.8167]	0.525	Random	0.015	0.714	0.864
Overdominant model (Bb vs. BB + bb)	Overall	6	1.065	[0.9075; 1.2486]	0.443	Fixed	0.194	0.323	0.422
	75 down	2	0.666	[0.3691; 1.2019]	0.177	Fixed	0.957	0.000	NA
	75 over	4	1.105	[0.9359; 1.3036]	0.240	Fixed	0.190	0.370	0.899

Table 4
Meta-analysis of association between genetic variants BsmI in VDR and hip fracture excepting J.Aerssens study.

Model	Age	Number of studies	Test of association			Test of heterogeneity			Publication bias
			OR	95% CI	*p*-val	Model	*p*-val	I^2	*p*-val (Egger's test)
BB vs. bb	Overall	5	1.482	[1.1532; 1.9043]	0.002	Fixed	0.688	NA	0.028
	75 down	2	2.452	[1.0336; 5.8183]	0.042	Fixed	0.588	NA	NA
	75 over	3	1.415	[1.0886; 1.8386]	0.009	Fixed	0.763	NA	0.222
Allele contrast (B vs. b)	Overall	5	1.241	[1.0969; 1.4036]	0.001	Fixed	0.872	NA	0.067
	75 down	2	1.446	[0.9549; 2.1894]	0.082	Fixed	0.804	NA	NA
	75 over	3	1.223	[1.0745; 1.3911]	0.002	Fixed	0.740	NA	0.021
Dominant model (BB + Bb vs. bb)	Overall	5	1.339	[1.1197; 1.6001]	0.001	Fixed	0.941	NA	0.645
	75 down	2	1.197	[0.6464; 2.2162]	0.567	Fixed	0.868	NA	NA
	75 over	3	1.352	[1.1222; 1.6296]	0.002	Fixed	0.736	NA	0.144
Overdominant model (Bb vs. BB + bb)	Overall	5	1.133	[0.9537; 1.3458]	0.155	Fixed	0.430	NA	0.513
	75 down	2	0.666	[0.3691; 1.2019]	0.177	Fixed	0.957	NA	NA
	75 over	3	1.190	[0.9942; 1.4250]	0.058	Fixed	0.809	NA	0.385

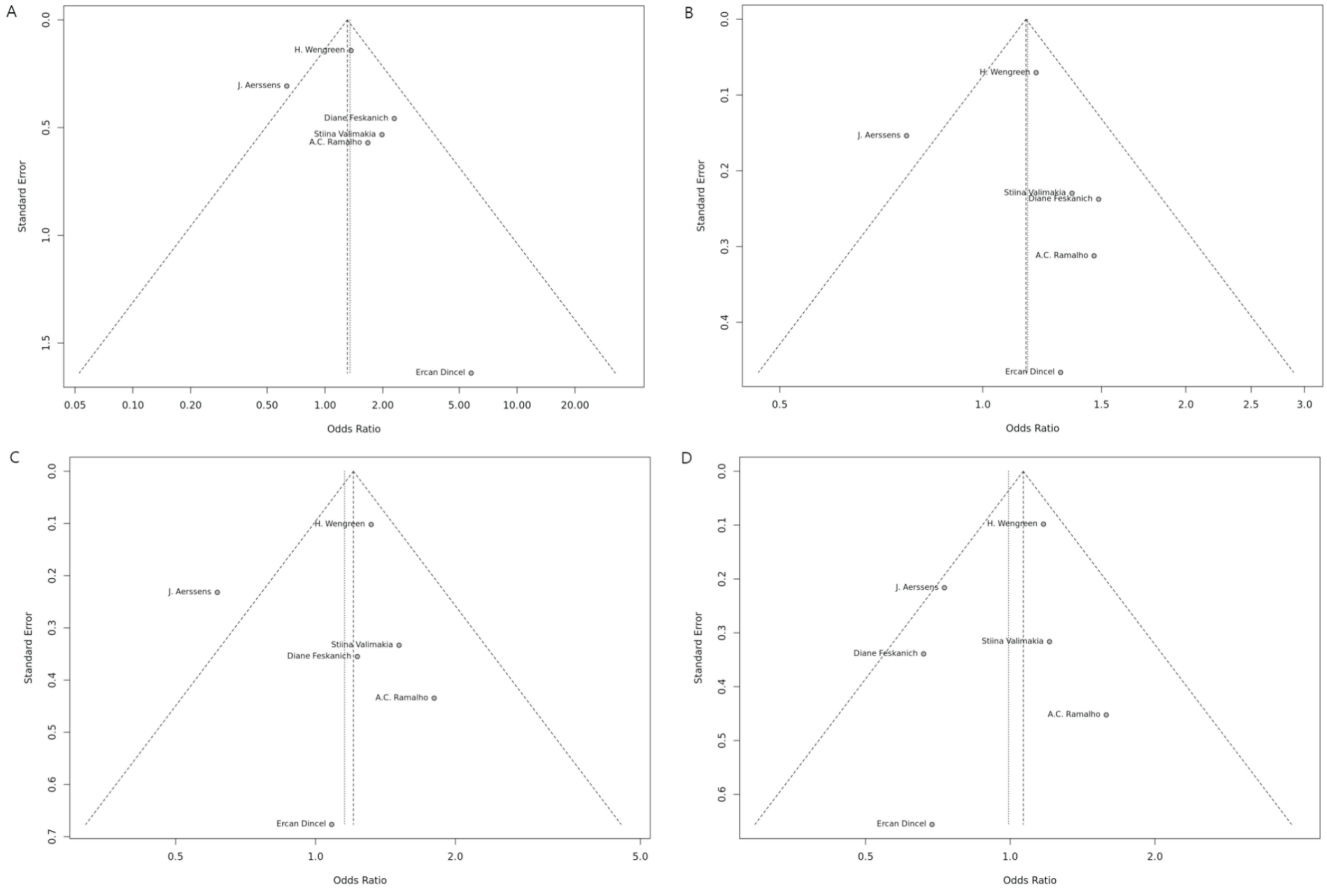

Figure 3. Funnel plots for publication bias evaluation. (A) BB vs. bb, (B) allelic model, (C) dominant model, and (D) over-dominant model.

omitting study of H. Wengreen et al. in the overdominant model showed low OR compared with other results. It could mean that heterozygote of BsmI decreases the risk of hip fracture.[24]

In the subgroup analysis, we decided to exclude the study of Aerssens et al. for its opposite result tendencies as described. The other studies were divided into groups with a mean age of over 75 years and under 75 years. The analysis of the over-75-year-old group showed that almost all genotype models had significant differences except the over-dominant model. The findings suggest that the b allele increased the risk of hip fracture. Despite not examining hip fractures, other studies also demonstrated similar data. In a study by Langdahl et al., VDR BsmI polymorphism was associated with an increased risk of all fractures in a dominant model.[25] The study by Yanagi et al. also reported the same results in Japanese women.[26] These results may be caused by VDR disequilibrium, arising from the BsmI B allele.[27]

Vitamin D is acquired by food intake and the effect of sunlight on the skin. When vitamin D is metabolized by the liver and kidneys, the active form of vitamin D called 1α,25-dihydroxyvitamin D [1,25-$(OH)_2D$] is produced. This bioactive form of vitamin D requires the VDR for a high-affinity receptor and upregulates VDR mRNA in practically all cell types.[28,29] If VDR expression is decreased, the associated functions are also downregulated. Because genetic alterations in the VDR gene change gene activation, causing several diseases. For example, when VDR did not function well, BMD decreases, resistance to vitamin D stimulation, and susceptibility to autoimmune diseases, infections, and cancer occurred.[13,30,31] In addition, polymorphisms like BsmI has an effect on the level of VDR gene tran-

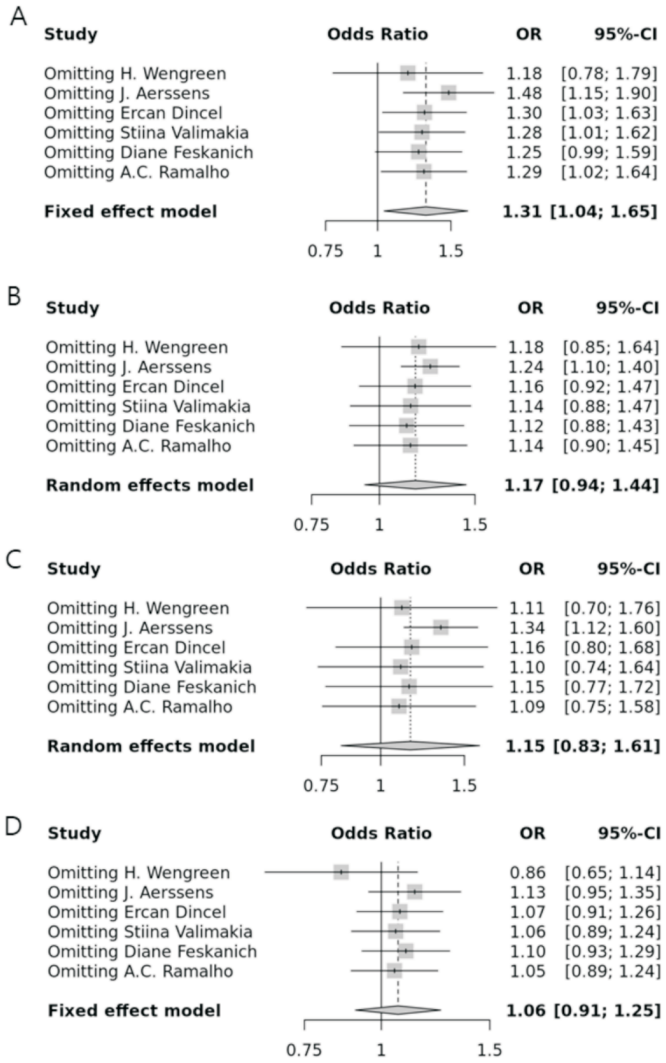

Figure 4. Sensitivity analysis applied using the leave-one-out method. (A) BB vs. bb, (B) allelic model, (C) dominant model, and (D) over-dominant model.

scription, transcript stability, and posttranscriptional modification.[32] Thus, BsmI VDR polymorphism could make many functional disorders by disturbing VDR function.[33]

Our data suggest that elderly people with BsmI polymorphism are at relatively higher risk for hip fracture. Age is an important factor in bone health. Vitamin D and calcium metabolism are affected by age as decreased dietary vitamin D, decreased renal production of the metabolite, and decreased calcium absorption were shown to decrease the level of the VDR.[34] Some studies indicated that a reduction in the VDR with age could contribute to the age-related resistance to vitamin D.[35] In one study, 321 subjects showed VDR concentration decreases at an older age but no serum concentration change in $1,25(OH)_2D_3$ which is inactive precursor of vitamin D.[36] These results suggest that although osteoporotic fracture patients get sufficient vitamin D and maintain adequate serum $1,25(OH)_2D_3$, VDR dysfunction could bring about an unhealthy bone status and cause fractures in old people. The relationship between hip fracture and VDR can be interpreted as the meaning of VDR in osteoporosis and sarcopenia in other words.[37] Based on these results, current researchers' interest in genetic variation of VDR may expand to research into the growing sarcopenia area, and it is also worth using as a biomarker for vitamin D treatment effects in patients with sarcopenia.

There were several limitations to the study. First, the number of included studies was low. Second, included studies have slight heterogeneity. However, there was no statistical significance. Third, various ethnicities including East Asian were not evaluated. Fourth, this study only included articles showing detailed data including specific alleles of BsmI in hip fracture patients. Therefore other hip fracture studies associated with BsmI could be excluded in the analysis.

5. Conclusion

BsmI VDR polymorphism conferred an increased risk of hip fracture in people over 75 years old. It was supposed that people, specifically very old aged people, with functional defects in VDR experience more rapid decreases in BMD than those with normally functional VDR. These results indicate that BsmI VDR polymorphisms might be a predictor of hip fractures in older people.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

None declared by all authors.

Author's contributions

Concept – YJI, LSY; Design – YJI, LSY; Supervision – YJI, LSY; Materials – YJI, LSY; Data collection and/or processing – YJI, LSY; Analysis and/or interpretation – YJI, LSY; Literature search – YJI, LSY; Writing manuscript – YJI, LSY; Critical review – YJI, LSY.

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Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=20.

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