RESEARCH

A meta-analysis of *VDR* polymorphisms and postmenopausal osteoporosis

Lijuan Fu[1], Jinhuan Ma[2], Sumei Yan[3] and **Qijun Si[4]**

[1]Department of Laboratory, Changyi People's Hospital of Shandong Province, Changyi, Shandong, China
[2]Department of Laboratory, Changyi Maternal and Child Health Hospital of Shandong Province, Changyi, Shandong, China
[3]Department of Obstetrics, Changyi Maternal and Child Health Hospital of Shandong Province, Changyi, Shandong, China
[4]Department 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.

Key Words

- postmenopausal osteoporosis (PMOP)
- vitamin D receptor (VDR)
- gene polymorphisms
- meta-analysis

Endocrine Connections (2020) **9**, 882–889

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

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0296

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 I^2 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 I^2 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

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0296

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).

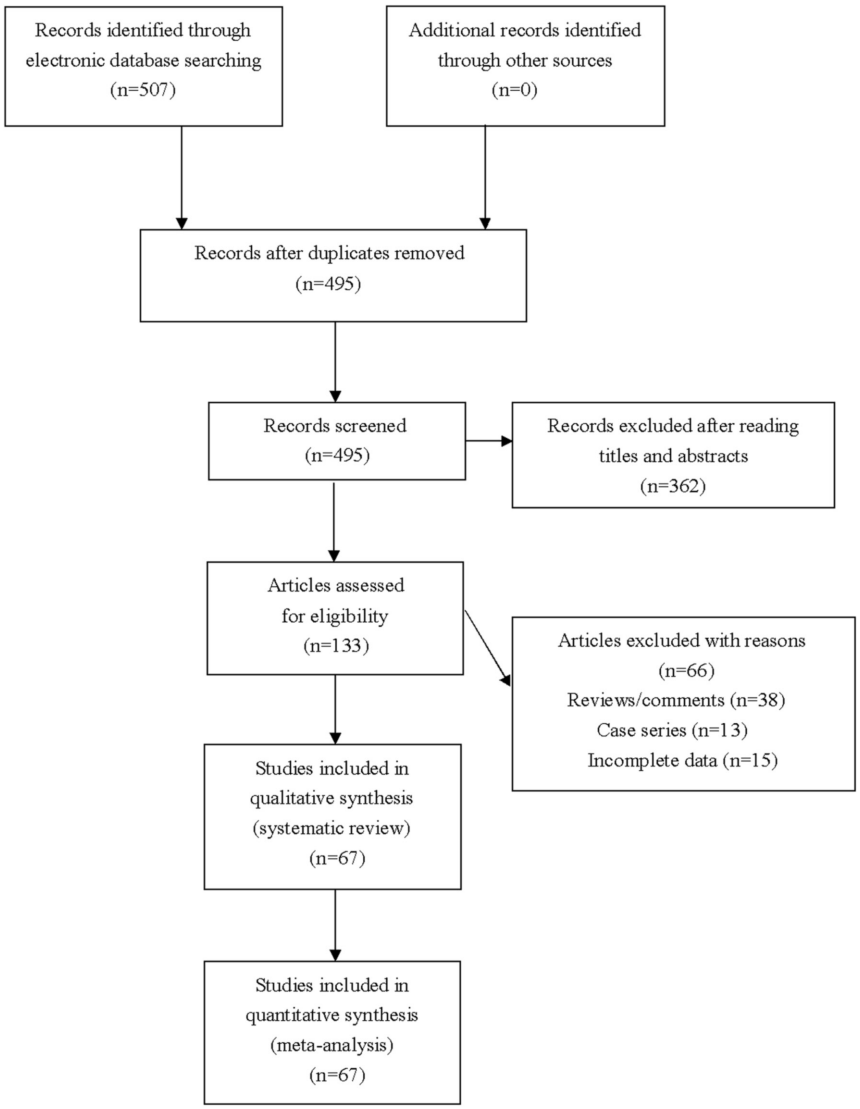

Figure 1
Flowchart of study selection for this meta-analysis.

Table 1 The characteristics of included studies in current meta-analysis.

First author, year	Country	Ethnicity	Sample size	Genotypes (wtwt/wtmt/mtmt)		*P*-value for HWE	NOS score
				Cases	Controls		
ApaI rs7975232							
Ahmad 2018	India	Mixed	254/254	62/140/52	75/134/45	0.264	7
Castelán-Martínez 2015	Mexico	Mixed	387/147	141/160/86	46/75/26	0.631	7
Chen 2007	China	Asian	155/113	108/40/7	60/41/12	0.223	7
Dabirnia 2016	Iran	Mixed	50/50	24/25/1	30/18/2	0.729	7
Douroudis 2003	Hellenic Republic	Caucasian	35/44	11/14/10	17/26/1	0.016	7
Duman 2004	Turkey	Caucasian	75/66	13/56/6	15/45/6	0.002	7
Dundar 2009	Turkey	Caucasian	112/24	26/61/25	8/14/2	0.231	7
Ge 2009	China	Asian	353/208	160/157/36	102/84/22	0.453	8
González-Mercado 2013	Mexico	Mixed	232/87	79/118/35	29/41/17	0.715	7
Gu 2010	China	Asian	186/148	79/86/21	74/61/13	0.932	7
Iván 2008	Chile	Caucasian	67/59	25/31/11	18/27/14	0.536	7
Kim 2015	Korea	Asian	153/47	97/53/3	24/19/4	0.931	7
Langdahl 2000	Denmark	Caucasian	78/74	22/44/12	25/32/17	0.283	7
Liang 2002	China	Asian	30/30	20/6/4	27/2/1	0.011	7
Luan 2011	China	Asian	140/88	71/56/13	44/34/10	0.390	7
Marozik 2013	Belarus	Caucasian	54/77	7/24/23	29/34/14	0.472	7
Marozik 2018	Lithuania	Caucasian	149/172	27/67/55	60/74/38	0.105	7
Meng 2018	China	Asian	90/246	60/25/5	161/69/16	0.028	8
Mitra 2006	India	Mixed	119/97	50/44/25	34/33/30	0.002	7
Mosaad 2014	Egypt	Mixed	30/150	13/15/2	69/71/10	0.142	7
Riggs 1995	USA	Mixed	30/128	12/19/9	38/59/31	0.394	7
Sassi 2015	Tunisia	Mixed	335/231	130/143/62	90/115/26	0.233	7
Seremak-Mrozikiewicz 2009	Poland	Caucasian	163/63	35/82/46	12/32/19	0.821	7
Tanriover 2010	Turkey	Caucasian	50/50	15/23/12	22/15/13	0.007	8
Uysal 2008	Turkey	Caucasian	100/146	35/50/15	46/79/21	0.165	7
Vandevyver 1997	Belgium	Caucasian	87/699	20/45/22	197/375/127	0.027	8
Wu 2016	China	Asian	79/234	43/27/9	105/111/18	0.123	7
Wu 2019	China	Asian	610/616	331/218/61	366/207/43	0.070	8
Xie 2005	China	Asian	295/56	240/43/12	34/16/6	0.075	7
Yoldemir 2011	Turkey	Caucasian	130/130	34/60/36	31/73/26	0.155	7
Zajickova 2002	Czech Republic	Caucasian	65/33	23/33/9	10/17/6	0.793	7
BsmI rs1544410							
Ahmad 2018	India	Mixed	254/254	54/137/63	54/152/48	0.002	7
Berg 1996	Norway	Caucasian	19/30	4/8/7	8/11/11	0.156	7
Boroń 2015	Poland	Caucasian	278/292	101/121/56	128/113/51	0.004	7
Cheishvili 2017	Israel	Mixed	37/37	13/11/13	15/12/10	0.039	7
Chen 2003	China	Asian	78/81	65/13/0	69/12/0	0.472	7
Douroudis 2003	Hellenic Republic	Caucasian	35/44	20/12/3	29/10/5	0.019	7
Duman 2004	Kuwait	Mixed	75/66	54/18/3	42/17/7	0.021	7
Efesoy 2011	Turkey	Caucasian	40/30	12/23/5	10/15/5	0.876	7
Ge 2009	China	Asian	353/208	314/33/6	192/12/4	<0.001	8
Gennari 1998	Italy	Caucasian	155/136	23/92/40	49/76/11	0.013	7
González-Mercado 2013	Mexico	Mixed	232/88	143/76/13	46/38/4	0.267	7
Houston 1996	UK	Caucasian	44/44	17/19/8	16/19/9	0.450	7
Huang 2000	China	Asian	14/27	13/1/0	26/1/0	0.922	7
Hussien 2013	Egypt	Mixed	150/50	50/57/43	19/21/10	0.351	7
Iván 2008	Chile	Caucasian	67/59	10/46/11	13/37/9	0.046	7
Kim 2015	Korea	Asian	153/47	142/11/0	42/5/0	0.700	7
Langdahl 2000	Denmark	Caucasian	80/80	23/38/19	25/34/21	0.186	7
Li 2000	China	Asian	96/42	54/36/6	20/21/1	0.095	7
Liang 2002	China	Asian	30/30	28/1/1	30/0/0	NA	7
Lim 1995	Korea	Asian	72/70	61/9/2	60/9/1	0.349	7
Liu 2005	China	Asian	56/89	50/6/0	76/11/2	0.060	7
Marozik 2013	Belarus	Caucasian	54/77	11/31/12	40/26/11	0.062	7
Marozik 2018	Lithuania	Caucasian	149/172	32/64/53	64/73/35	0.098	7

(Continued)

Table 1 (Continued).

First author, year	Country	Ethnicity	Sample size	Genotypes (wtwt/wtmt/mtmt)		*P*-value for HWE	NOS score
				Cases	Controls		
Melhus 1994	Sweden	Caucasian	70/76	14/29/27	34/35/7	0.637	8
Mencej-Bedrac 2009	Slovenia	Caucasian	240/228	103/110/27	88/100/40	0.215	8
Meng 2017	China	Asian	90/246	74/12/4	216/24/6	<0.001	7
Mitra 2006	India	Mixed	119/97	51/46/22	40/38/19	0.080	7
Mosaad 2014	Egypt	Mixed	30/150	2/19/9	36/74/40	0.877	7
Musumeci 2009	Iran	Mixed	50/20	27/15/8	17/2/1	0.047	7
Perez 2008	Argentina	Mixed	64/68	17/35/12	20/32/16	0.649	7
Pollak 2001	Israel	Mixed	75/143	24/38/13	60/67/16	0.675	7
Pouresmaeili 2013	Iran	Mixed	64/82	17/33/14	36/33/13	0.252	7
Riggs 1995	USA	Mixed	40/129	9/20/11	20/61/48	0.932	7
Seremak-Mrozikiewicz 2009	Poland	Caucasian	163/63	70/66/27	26/27/10	0.506	7
Tanriover 2010	Turkey	Caucasian	50/50	16/19/15	24/19/7	0.320	8
Techapatiphandee 2018	Thailand	Asian	105/132	85/19/1	103/25/4	0.123	7
Uysal 2008	Turkey	Caucasian	100/146	18/48/34	24/78/44	0.283	7
Vandevyver 1997	Belgium	Caucasian	86/698	24/50/12	203/368/127	0.076	8
Wang 2007	China	Asian	50/48	43/7/0	39/9/0	0.474	7
Yanagi 1996	Japan	Asian	66/66	22/12/12	57/7/2	0.013	7
Yoldemir 2011	Turkey	Caucasian	130/130	35/73/22	43/65/22	0.760	7
Zajickova 2002	Czech Republic	Caucasian	65/33	20/24/21	10/13/10	0.223	7
Zhang 1998	China	Asian	17/164	14/3/0	148/16/0	0.511	8
Zhang 2000	China	Asian	77/35	38/33/6	14/18/3	0.403	7
Zhu 2004	China	Asian	40/158	26/8/6	105/46/7	0.500	7
FokI rs10735810							
Ahmad 2018	India	Mixed	254/254	148/92/14	169/80/5	0.20	7
Castelán-Martínez 2015	Mexico	Mixed	232/88	61/118/53	24/45/19	0.807	7
Choi 2000	Korea	Asian	48/65	12/23/13	26/33/6	0.327	7
González-Mercado 2013	Mexico	Mixed	88/88	25/48/15	24/45/19	0.807	7
Gu 2010	China	Asian	186/148	46/100/40	40/84/24	0.071	7
Iván 2008	Chile	Caucasian	67/59	29/27/11	27/25/7	0.744	7
Kanan 2013	Jordan	Mixed	120/90	40/62/18	29/48/13	0.336	7
Kim 2015	Korea	Asian	153/47	50/83/20	14/25/8	0.577	7
Langdahl 2000	Denmark	Caucasian	30/128	12/19/9	38/59/31	0.394	7
Li 2019	China	Asian	224/155	66/103/55	58/68/29	0.259	7
Lisker 2003	Mexico	Mixed	65/57	27/29/9	20/29/8	0.625	7
Lucotte 1999	France	Caucasian	124/105	45/69/10	40/52/13	0.535	7
Mamolini 2017	Italy	Caucasian	170/73	97/60/13	40/25/8	0.194	7
Mansour 2010	Iran	Mixed	50/20	34/9/7	20/0/0	NA	7
Mencej-Bedrac 2009	Slovenia	Caucasian	240/228	88/108/44	105/97/26	0.618	8
Mitra 2006	India	Mixed	119/97	38/42/39	46/33/18	0.011	7
Mohammadi 2015	Iran	Mixed	96/356	52/36/8	198/128/30	0.158	7
Mosaad 2014	Egypt	Mixed	30/150	23/6/1	93/55/2	0.049	7
Pérez 2008	Argentina	Mixed	64/68	22/32/10	22/36/10	0.444	7
Tanriover 2010	Turkey	Caucasian	50/50	27/22/1	29/18/3	0.926	8
Techapatiphandee 2018	Thailand	Asian	105/132	31/46/28	41/73/18	0.106	7
Wu 2019	China	Asian	610/616	296/235/79	404/186/26	0.436	8
Xing 2011	China	Asian	32/70	7/14/11	27/35/8	0.506	7
Yasovanthi 2011	India	Mixed	247/254	104/119/24	122/124/8	<0.001	8
Yoldemir 2011	Turkey	Caucasian	130/130	66/55/9	62/55/13	0.876	7
Zajickova 2002	Czech Republic	Caucasian	78/74	22/44/12	25/32/17	0.283	7
TaqI rs731236							
Ahmad 2018	India	Mixed	254/254	124/96/34	89/123/42	0.964	7
Dabirnia 2016	Iran	Mixed	50/50	20/24/6	16/29/5	0.121	7
Duman 2004	Kuwait	Mixed	75/66	10/42/23	15/28/23	0.259	7
Gennari 1998	Italy	Caucasian	160/144	33/87/40	62/71/11	0.126	7
González-Mercado 2013	Mexico	Mixed	232/88	142/77/13	46/36/6	0.769	7
Iván 2008	Chile	Caucasian	67/59	26/31/10	17/34/8	0.167	7

(Continued)

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0296

Table 1 (Continued).

First author, year	Country	Ethnicity	Sample size	Genotypes (wtwt/wtmt/mtmt)		*P*-value for HWE	NOS score
				Cases	Controls		
Kim 2015	Korea	Asian	153/47	140/12/1	42/5/0	0.700	7
Langdahl 2000	Denmark	Caucasian	46/284	11/30/5	91/159/34	0.005	7
Larin 2015	Ukraine	Caucasian	44/30	20/18/6	14/12/4	0.584	7
Marozik 2013	Belarus	Caucasian	54/77	17/26/11	39/24/14	0.008	7
Marozik 2018	Lithuania	Caucasian	149/172	38/62/49	58/74/40	0.088	7
Masi 1998	Italy	Caucasian	90/111	41/36/13	38/64/9	0.013	7
Mitra 2006	India	Mixed	119/97	34/42/43	44/31/22	0.001	7
Mosaad 2014	Egypt	Mixed	30/150	9/19/2	39/74/37	0.872	7
Riggs 1995	USA	Mixed	31/130	11/23/7	53/57/20	0.475	7
Sassi 2015	Tunisia	Mixed	335/231	165/128/42	103/95/33	0.152	7
Seremak-Mrozikiewicz 2009	Poland	Caucasian	163/63	78/59/26	22/29/12	0.659	7
Tanriover 2010	Turkey	Caucasian	50/50	15/29/6	25/17/8	0.102	8
Techapatiphandee 2018	Thailand	Asian	105/132	97/6/2	116/15/1	0.513	7
Uysal 2008	Turkey	Caucasian	100/146	40/46/14	54/75/17	0.237	7
Vandevyver 1997	Belgium	Caucasian	46/284	11/30/5	91/159/34	0.005	8
Wang 2013	China	Asian	92/98	47/48/7	48/40/10	0.698	7
Yoldemir 2011	Turkey	Caucasian	130/130	51/59/20	49/59/22	0.558	7
Zajickova 2002	Czech Republic	Caucasian	65/33	11/31/23	8/14/11	0.407	7
Ziablitsev 1994	Ukraine	Caucasian	44/30	20/18/6	14/12/4	0.584	7

HWE, Hardy–Weinberg equilibrium; mt, Mutant type; NA, not available; NOS, Newcastle-Ottawa scale; wt, Wild type;.

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).

TaqI rs731236 polymorphism and the risk of postmenopausal osteoporosis

Twenty-five papers assessed relationship between TaqI rs731236 polymorphism and the risk of postmenopausal osteoporosis. The integrated analyses demonstrated that TaqI 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 ApaI rs7975232, BsmI rs1544410 and TaqI 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)
ApaI 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 rs1544410									
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)	0.89	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.

we speculated that these investigated *VDR* polymorphisms may alter mRNA expression level or protein function of VDR, impact vitamin D metabolism, and then affect the risk of postmenopausal osteoporosis (13, 14). Nevertheless, further experimental studies are still warranted to figure out the exact mechanisms underlying the observed positive associations between *VDR* gene polymorphisms and the risk of postmenopausal osteoporosis in the current meta-analysis. Second, we want to study all polymorphic loci of *VDR* gene initially. Nevertheless, our comprehensive literature searching did not reveal sufficient eligible literature to support integrated analyses for other polymorphic loci of *VDR* gene, so we only explored associations with the risk of postmenopausal osteoporosis for four most commonly investigated polymorphisms of *VDR* gene in this meta-analysis. Third, it is worth noting that previously, Zhang et al. (15) also tried to investigate associations between *VDR* gene polymorphisms and postmenopausal osteoporosis through a meta-analysis. Nevertheless, this previous meta-analysis only covered relevant genetic association studies that were published before 2015. Since our literature searching revealed that many related studies were published after 2015, an updated meta-analysis like ours is of course warranted to get more reliable findings. Consistent with the previous meta-analysis, similar significant findings for ApaI rs7975232, FokI rs10735810 and TaqI rs731236 polymorphisms were observed in our integrated analyses. Additionally, we also found that BsmI rs1544410 polymorphism was significantly associated with the risk of postmenopausal osteoporosis in overall population and Caucasians, which was failed to be detected by the previous meta-analysis. Considering that our integrated analyses were derived from more eligible studies, our observations should be considered as a valuable supplement to pre-existing literature.

The major limitations of our integrated analyses were listed below. First, our integrated analyses results were derived from unadjusted pooling of previous literature. Without access to raw data of eligible studies, we can only assess associations between *VDR* gene polymorphisms and the risk of postmenopausal osteoporosis based on recalculations of raw genotypic frequencies provided by eligible literature, and we need to admit that lack of further adjustment for baseline characteristics may possibly influence reliability of our findings (16). Secondly, environmental factors such as food intake, sunshine exposure or exercise levels may also influence associations between polymorphisms in *VDR* gene and the risk of postmenopausal osteoporosis. However, most of the authors only paid attention to genetic associations

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-20-0296

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 ApaI 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.2005.08.047)

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.S51940)

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 Sassi 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 Moher 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/MD.0000000000011506)

18 Mashhadiabbas F, Neamatzadeh H, Nasiri R, Foroughi E, Farahnak S, Piroozmand P, Mazaheri M & Zare-Shehneh M. Association of vitamin D receptor BsmI, TaqI, FokI, and ApaI 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