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The genetic association between osteoprotegerin (*OPG*) gene polymorphisms and bone mineral density (BMD) in postmenopausal women

A meta-analysis

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Abstract

Background: Osteoporosis is a common skeletal disorder in eldest people, especially in postmenopausal women. The osteoprotegerin (*OPG*) gene has been reported to be associated with the BMD and pathogenesis of osteoporosis. However, the results were inconsistent and inconclusive in previous studies.

Methods: A meta-analysis was performed to investigate the effect of four common *OPG* gene polymorphisms (A163G, G1181C, T245G, and T950C) on BMD in postmenopausal women.

Results: A total of 23 eligible studies with 12,973 postmenopausal women were enrolled in present study. Individuals who with AA genotype of A163G were found to have slightly higher femoral hip ($P = .03$, SMD = 0.49, [95% CI] = [0.06, 0.91]) and total hip BMD ($P = .002$, SMD = −0.25, [95% CI] = [−0.42, −0.09]) than those with AG genotype. Subjects with GG genotype of G1181C was found to have lower BMD than those with CC or GC genotypes in lumbar spine (GG vs GC: $P = .0002$, SMD = −0.85, [95% CI] = [−1.29, −0.41]; GG vs CC: $P = .02$, SMD = −0.21, [−0.39, −0.03]) and total hip BMD (GG vs GC: $P = .002$, SMD = −0.25, [95% CI] = [−0.42, −0.09]; GG vs CC: $P = .01$, SMD = −0.15, [95% CI] = [−0.26, −0.03]). In addition, the subjects with GC genotype of G1181C was detected to have lower BMD than those with CC genotype in lumbar spine BMD ($P < .05$). Furthermore, individuals with TT genotype of T950C were shown to have significant lower lumbar spine BMD compared with those with genotype CC in Caucasian ($P < .05$). The lumbar spine BMD was lower for subjects with TC genotype of T950C than those with CC genotype in both Caucasian and Asian populations ($P < .05$). In contrast to A163G, G1181C, and T950G, no association was detected between T245G polymorphism and BMD ($P > .05$).

Conclusion: The present meta-analysis demonstrated the *OPG* A163G, G1181C, and T950G, but not T245G, might influence the BMD in postmenopausal women.

Abbreviations: BMD = bone mineral density, BMI = Body Mass Index, CNKI = Chinese National Knowledge Infrastructure, CTR = calcitonin receptor, LD = linkage disequilibrium, NOS = Newcastle-Ottawa Scale, *OPG* = osteoprotegerin, *RANK* = receptor activator of nuclear factor-B, *RANKL* = receptor activator of nuclear factor-B ligand, SD = standard deviation, TGFB1 = transforming growth factor b1, TNFRS11B = tumor necrosis factor receptor superfamily member 11b, VDR = vitamin D receptor.

Keywords: bone mineral density (BMD), meta-analysis, Osteoprotegerin (*OPG*) gene, postmenopausal women

1. Introduction

Osteoporosis, characterized by low bone mineral density (BMD), microarchitectural deterioration, and increased bone fragility and fracture risk, is a systemic skeletal disease, especially in the postmenopausal women.[1–4] Multiple factors including metabolic factors, environmental factors such as exercise, smoking and diet, and genetic factors were reported to have affected on BMD.[5–7] Studies from twins and families have shown that BMD in key skeletal sites such as spine and hip was genetically determined.[8,9] A number of susceptible genes such as vitamin D receptor (VDR),[10] transforming growth factor b1 (TGFB1),[11] calcitonin receptor (CTR),[12] and osteoprotegerin gene (*OPG*), also known as tumor necrosis factor receptor superfamily member 11b (TNFRS11B)[13,14] have been identified to be involved in the pathologenesis of osteoporosis. Osteoprotegerin, a member of the tumor necrosis factor receptor superfamily, is one of the most important candidate genes in the control of bone resorption.[15,16] Growing evidence has indicated that *OPG* gene plays an important role in influencing the etiology of osteoporosis.[17,18] Several polymorphisms including A163G, G1181C, T245G, T950C, A19163G, and G27563A in *OPG* gene have

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been shown to influence the BMD and development of osteoporosis.[19–21] The A163G polymorphism, located at the *OPG* promoter region, was shown to regulate *OPG* gene expression and may contribute to the genetic regulation of bone mass.[22] However, the association between the A163G polymorphism and BMD is very contradictory. Although Geng et al[23] has reported a significant association of A163G polymorphism with lumbar spine and femoral neck BMD, most other studies have shown no association between A163G polymorphism and lumbar spine, femoral hip, and top hip BMD.[24–26] For G1181C, the first single nucleotide polymorphism (SNP) described in the *OPG* gene, was shown involved in cellular secretion of *OPG*.[27] In previous association studies, genotype of G1181C was related to peripheral BMD in Slovak,[28] Spain,[26] Korean,[29] American,[30] and Chinese populations.[31] However, these positive results cannot be replicated in several other populations such as in Finland,[32] Australian,[33] and Irish.[34] For another 2 common polymorphisms (T245G and T950C), significant associations were observed between genotypes of T245G and T950C and BMD in Japanese [35] and Finland populations,[32] but not in Chinese,[36] Korean,[29] and Slovak [24] populations. These inconsistent in different populations may due to the different ethnic backgrounds, as well as the relatively small number of subjects included in previous studies. Meta-analysis is an effective tool to compensate the limitations by combined all publications and improves statistical power to obtain potential effects of individual studies with small or moderate sizes of subjects. In order to obtain a more precise effect of *OPG* gene polymorphisms in postmenopausal women, a meta-analysis was performed to assess the association between *OPG* polymorphisms and BMD.

2. Materials and methods

2.1. Patient and public involvement

There was no patient and public involvement in present meta-analysis. Ethical approval is not necessary for a meta-analysis.

2.2. Literature search

An exhaustive literature search for studies on the association of *OPG* polymorphisms and BMD in postmenopausal women was conducted in the following databases: Pubmed, Embase, Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) using the keywords "osteoprotegerin" or "*OPG*" or "tumor necrosis factor receptor superfamily member 11b" or "TNFRS11B" and "polymorphism" or "variation" or "single nucleotide polymorphisms" or "SNP" and "bone mineral density" or "bone density" or "BMD" and "postmenopausal women". No language was restricted. The last search date was June 1, 2018. All available publications from the database have screened the title firstly. Then the abstracts were checked in case of the titles fulfilled our criteria. Meanwhile, other potentially relevant literatures were identified by searching cross-references within available studies.

2.3. Inclusion and exclusion criteria

Inclusion criteria:

1) number of subjects and genotypes, means, and standard deviation (SD) of BMD were available;
2) all subjects must be postmenopausal women;

Exclusion criteria:

1) repeated studies, letters, dissertations, abstracts or reviews;
2) the outcome was not BMD;
3) only haplotype data;
4) publications that violating the inclusion criteria.

2.4. Data extraction and quality assessment

Two independent authors (YPP and XWS) extracted the information and assessed the quality of each study. The following terms were extracted: the first author, year of published, ethnicity, age in cases, minor allele frequency of *OPG* polymorphisms, Body Mass Index (BMI) in postmenopausal women, number of subjects in each genotype, and the BMD data for each genotype. All discrepancies were resolved by a consensus achieved by discussion. The study quality was evaluated by the Newcastle-Ottawa Scale (NOS).[37] Total score ranged from 0 (lowest quality) to 8 (highest quality). A study with a score of 6 or higher was considered to be of high quality.

2.5. Statistical analysis

The standard deviation (SD) of BMD difference between genotypes of A163G, G1181C, T950C, and T245G (A163G: AA vs GG, AA vs AG, AG vs GG; G1181C: GG vs CC, GG vs GC, GC vs CC; T950C: TT vs CC, TT vs TC, TC vs CC; and, T245G: TT vs GG, TT vs TG, TG vs GG) were calculated. Variation and heterogeneity were evaluated using a chi-square-based Cochran Q test and Higgins I-squared statistic ($I^2 = 100\% \times (Q - df)/Q$). If significant heterogeneity was observed across studies ($P < .05$ or $I^2 > 50$), the random effect model was used for meta-analysis. Otherwise, the fixed effect model was used. Egger test was used to access publication bias. $P < .05$ indicated a statistical difference. Statistical analyses were performed with the STATA 12.0 software (StataCorp, College Station, TX, USA) and Revman 5 (Cochrane Collaboration, London, UK).

3. Results

3.1. Characteristics of the eligible studies

A total of 2183 publications were originally retrieved from databases. After screened the titles, abstracts and contexts, 1957 were excluded for duplicated studies, 147 were excluded for not related to the association between *OPG* gene polymorphisms and BMD, 10 were excluded for not related to the association between *OPG* gene polymorphisms and BMD in postmenopausal women, 47 were excluded for being review, letters, and short communications. Finally, 22 eligible records were selected for data extraction and assessment[23–26,28–36,38–46](Fig. 1). Among these publications, 1 paper by Chen et al[40] contained 2 independent studies. Therefore, there were 23 papers that encompassed 12,973 cases in the present meta-analysis. Two studies referred to the same subjects in Chinese population.[36,43] 12 groups were conducted in Asian,[23,29,31,34–36,38,40–44] and 10 groups were in Caucasian.[24–26,28,30,32,33,39,45,46] For A163G, we enrolled 9 studies consisted of 2933 cases. For G1181C, 14 publications met the inclusion criteria, comprising 11,235 cases. For T245G, 9 articles with 2388 cases were identified. For T950C, 10 publications including 3028 cases were enrolled. The

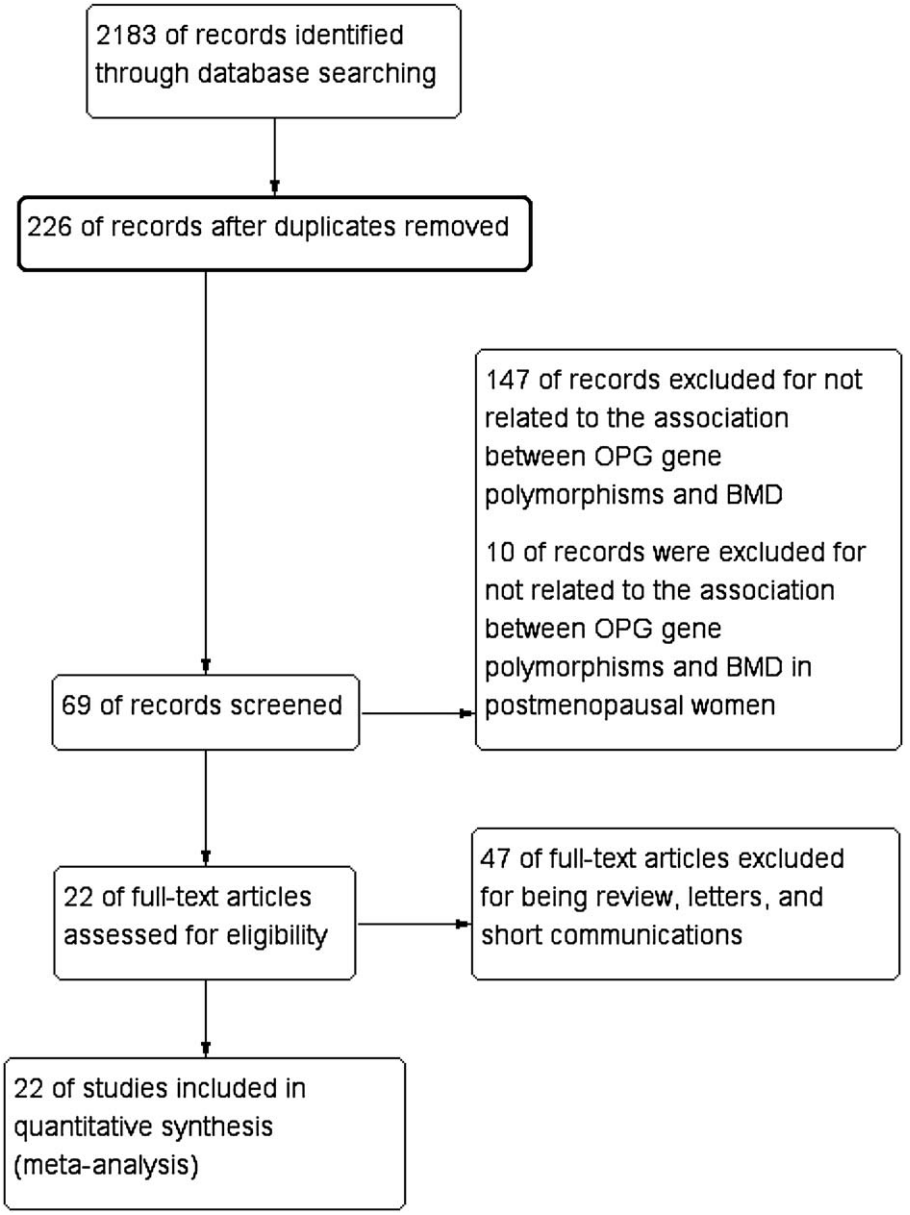

Figure 1. PRISMA flow chart of studies inclusion and exclusion.

demographic characteristics of these selected studies enrolled in present meta-analysis were listed in Table 1.

3.2. Meta-analyses for OPG SNPs and lumbar spine BMD

The 13 publications have shown the association between G1181C and lumbar spine BMD. The pooled results revealed that subjects with the GG genotype were found to have significant lower BMD values than that with the GC and CC genotypes (GG vs GC: $P=.0002$, SMD = −0.85, [95% CI] = [−1.29, −0.41]; GG vs CC: $P=.02$, SMD = −0.21, [−0.39, −0.03])(Fig. 2A and B). And individuals with GC genotype have significant lower BMD values than that with the CC genotype (=$P=.0002$, SMD = −0.64, [95% CI] = [−0.98, −0.31]) (Fig. 2C). Whereas, the significant difference of lower BMD values disappeared between subjects with GG genotype compared with GC genotype in Caucasian and Asian ($P>.05$). In addition, the BMD values were significant lower in individuals with GG genotype than those with CC genotype in Caucasian ($P=.03$, SMD = −0.22, [95% CI] = [−0.42, −0.02]). And the BMD values were significant lower in individuals with GC genotype than that with CC genotype in Asian ($P=.03$, SMD = −2.69, [95%CI] = [−5.08,–0.31]) (Table 3).

As for T950C polymorphism, 9 publications have shown the association between T950C and lumbar spine BMD. Significant lower BMD values were found in subjects with TC genotype compared with those with CC genotype ($P=.0004$, SMD = −0.25, [95% CI] = [−0.38, −0.11]) (Fig. 2D). Subgroup analysis stratified by ethnicity, shown that the mean BMD in subjects with TT and TC genotypes were significantly lower than those with CC genotype in Caucasian (TC vs CC: $P=.002$, SMD = −0.39, [95% CI] = [−0.63, −0.14]; TT vs CC: $P=.002$, SMD = −0.39, [95% CI] = [−0.63, −0.14]). Furthermore, we noticed that subjects with the TC genotype had a slightly lower BMD than

Table 1

The characteres of included studies.

First author	Year	Ethnicity	Number	Age	BMI (kg/m^2)	BMD type	SNPs (MAF)	NOS scores
Geng[23]	2007	Chinese	200	51.82±6.15	NA	LS,FH,TH	A163G (0.66)	6
Yu[44]	2006	Chinese	189	24.53±7.27	24.64±3.25	LS,FH,TH	A163G (0.13), T245G (0.10)	7
Boroňová[24]	2015	Slovak	327	65.01±9.26	25.45±4.53	LS,FH,TH	A163G (0.17), G1181C (0.49), T245G (0.09)	7
Canto-Cetina[45]	2013	Maya-Mestizo	580	60.0±8.5	29.9±4.8	LS,FH,TH	G1181C (0.34)	7
García-Unzueta[26]	2008	Spain	332	61±7.86	NA	LS,FH,TH	A163G (0.13), G1181C (0.48)	6
Kim[29]	2007	Korean	297	57.7±0.4	24.2±0.2	LS,FH,TH	G1181C (0.29), T245G (0.09)	7
Langdahl[32]	2002	Finland	216	64.2±9.2	NA	LS,FH,TH	A163G (0.20), G1181C (0.56), T245G (0.07), T950C (0.51)	6
Mencej-Bedrac[28]	2011	Slovenia	143	64.4±8.2	26.2±3.8	LS,FH,TH	G1181C (0.51), T245G (0.07)	7
Moffett[30]	2008	American	6658	71.4±5.3	26.6±4.7	LS,FH,TH	G1181C (0.55)	8
Rojano-Mejía[39]	2012	Mexican-Mestizo	750	60.0±7.55	29.25±4.8	LS,FH,TH	G1181C (0.42)	8
Seremak-Mrozikiewicz[46]	2011	Polish	139	54.5±8.5	23.69±3.14	LS	A163G (0.13), G1181C (0.54), T245G (0.12), T950C (0.48)	8
Shang[38]	2013	Chinese	235	52.8±3.2	23.9±3.0	LS,FH,TH	A163G (0.14), G1181C (0.30)	7
Ueland[33]	2007	Australian	980	75.0±3.0	NA	FH,TH	A163G (0.13), G1181C (0.52), T950C (0.52)	6
Wynne[34]	2002	Irish	130	61.26±11.75	NA	LS,FH,TH	G1181C (0.20), T950C (0.46)	6
Zhao[31]	2005	Chinese	134	62.4±0.43	23.3±0.23	LS,FH	G1181C (0.22)	7
Boron[25]	2015	Polish	314	56.26±6.03	24.25±4.12	LS	A163G (0.15), G1181C (0.55), T950C (0.15)	7
Cheng[41]	2011	Chinese	99	78.2±7.6	24.2±3.7	LS	T245G (0.17)	8
Yamada[35]	2003	Japanese	818	64.0±0.3	NA	LS,FH,TH	T245G (0.12), T950C (0.40)	6
Wu[43,36]	2007	Chinese	73	64.59±5.9	22.534±3.015	LS,FH,TH	T245G (0.69), T950C (0.35)	7
Chen-1[40]	2004	Chinese	141	57.0±4.0	NA	LS,FH,TH	T950C (0.27)	6
Chen-2[40]	2004	Chinese	118	70.0±4.0	NA	LS,FH,TH	T950C (0.27)	6
Liu[42]	2010	Chinese	100	77.55±8.01	23.41±3.43	LS,FH,TH	T950C (0.48)	7

NOS = Newcastle-Ottawa Scale, BMI = Body Mass Index, lumbar spine = LS, Femoral hip = FH, Total hip = TH, SNPs = SNPs = single nucleotide polymorphism, MAF = minor allele frequency, NA = not available.

those with CC genotype in Asian ($P=.01$, SMD = −0.37, [95% CI] = [−0.65, −0.09]) (Table 4). In contrast to G1181C and T950C results, no association was observed between the A163G and T245G polymorphisms and lumbar spine BMD ($P>.05$) (Tables 2 and 5).

3.3. Meta-analyses for OPG, SNPs, and femoral hip BMD

The 7 publications have shown the association between A163G and Femoral hip BMD. A slightly higher femoral hip BMD was found in subjects with AA genotype compared to AG genotype ($P=.03$, SMD = 0.49, [95% CI] = [0.06, 0.91])(Fig. 3). However, this significant difference didn't exist in ethnicity-specific meta-analysis ($P>.05$) (Table 2). In addition, 12 publications have reported the association between G1181C and femoral hip BMD (Table 3). the individuals with G1181C GG genotype had significantly lower femoral hip BMD compared to those with CC genotype in Caucasian ($P=.001$, SMD = −0.10, [95%CI] = [−0.15,–0.04]). No association was found between T950C, T245G and femoral hip BMD ($P>.05$) (Tables 4 and 5).

3.4. Meta-analyses for OPG SNPs and total hip BMD

The 7 publications have shown the association between A163G and Total hip BMD. A slightly higher total hip BMD was found in subjects with AA genotype compared to those with AG genotype ($P=.002$, SMD = −0.25, [95% CI] = [−0.42, −0.09]) (Fig. 4 A). However, this significant difference didn't exist in ethnicity-specific meta-analysis ($P>.05$) (Table 2). As for G1181C, GG genotype were found to have significantly lower BMD values than that with the GC and CC genotypes (GG vs GC: $P=.002$, SMD = −0.25, [95% CI] = [−0.42, −0.09]; GG vs CC: $P=.01$, SMD = −0.15, [95% CI] = [−0.26, −0.03])(Fig. 4B and C). The results of subgroup meta-analysis were more complicated. The GG genotype were found to have significantly lower BMD values than that with the CC genotypes in both Caucasian ($P=.0006$, SMD = −0.10, [95% CI] = [−0.16, −0.04]) and Asian ($P=.03$, SMD = −0.85, [95% CI] = [−1.64, −0.06]), and that with the GC genotypes in Caucasian ($P=.002$, SMD = −0.08, [95% CI] = [−0.13, −0.03]). In addition, The GC genotype were found to have significantly lower BMD values than that with the CC genotypes in Asian ($P=.008$, SMD = −0.43, [95% CI] = [−0.75, −0.12]) (Table 3). Furthermore, a slightly lower total hip BMD was detected in subjects with T950C TT genotype compared to those with TC genotype in Caucasian ($P=.04$, SMD = −0.16, [95% CI] = ($P=.008$, SMD = −0.43, [95% CI] = [−0.75, −0.12]) (Table 4). No association was found between T245G and total hip BMD ($P>.05$) (Table 5).

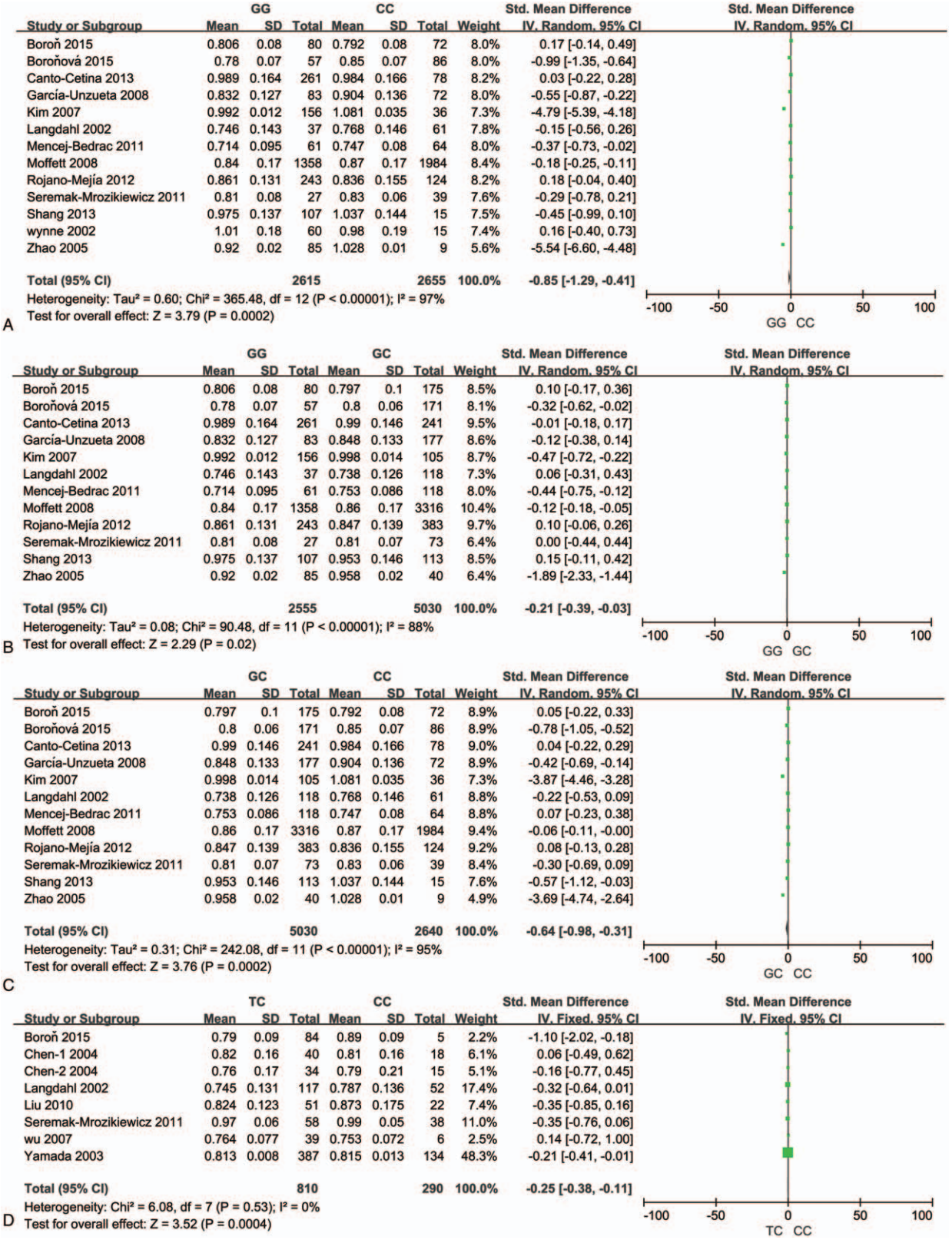

Figure 2. Association between genotypes of G1181C and T950C and lumbar spine BMD. A: G1181C, GG vs CC; B: G1181C, GG vs GC; C: G1181C, GC vs CC; D: T950C, TC vs CC.

Table 2

The association between osteoprotegerin gene (*OPG*) A163G and BMD in postmenopausal women.

BMD/Polymorphism	Genotype	Population	Number of studies	Test of association				Test of heterogeneity	
				SMD	95% CI	*P*value	Model	*P* value	I^2 (%)
Lumbar spine L1–L4	AA vs GG	Overall	6	0.93	[−0.44,2.29]	.18	R	<.00001	95
		European	4	0.28	[−0.07, 0.63]	.12	F	.44	0
		Asian	2	2.18	[−2.13, 6.49]	.32	R	<.00001	99
	AA vs AG	Overall	8	0.34	[−0.04, 0.73]	.08	R	<.00001	92
		European	5	−0.04	[−0.16, 0.08]	.53	F	.57	0
		Asian	3	1.05	[−0.15, 2.24]	.09	R	<.00001	97
	AG vs GG	Overall	6	0.55	[−0.39, 1.48]	.25	R	<.00001	92
		European	4	0.30	[−0.06, 0.67]	.10	F	.49	0
		Asian	2	0.94	[−1.44,3.32]	.44	R	<.00001	97
Femoral hip	AA vs GG	Overall	6	0.81	[−0.66, 2.28]	.28	R	<.00001	97
		European	4	−0.09	[−0.45, 0.27]	.62	F	.25	27
		Asian	2	2.75	[−2.15, 7.66]	.27	R	<.00001	99
	AA vs AG	Overall	7	0.49	[0.06, 0.91]	.03	R	<.00001	94
		European	4	0.03	[−0.07, 0.14]	.53	F	.89	0
		Asian	3	1.23	[−0.17, 2.64]	.09	R	<.00001	97
	AG vs GG	Overall	6	0.32	[−0.74, 1.39]	.55	R	<.00001	95
		European	4	−0.10	[−0.41, 0.22]	.55	F	.48	0
		Asian	2	1.26	[−0.91, 3.42]	.25	R	<.00001	96
Total hip	AA vs GG	Overall	6	0.87	[−0.57, 2.32]	.24	R	<.00001	97
		European	4	−0.02	[−0.35, 0.31]	.90	F	.32	14
		Asian	2	2.76	[−2.14, 7.65]	.27	R	<.00001	99
	AA vs AG	Overall	7	0.65	[0.12, 1.19]	.02	R	<.00001	96
		European	4	−0.00	[−0.11, 0.11]	.98	F	.68	0
		Asian	3	1.69	[0.14, 3.25]	.03	R	<.00001	98
	AG vs GG	Overall	6	0.37	[−0.59, 1.34]	.45	R	<.00001	94
		European	4	0.02	[−0.30, 0.34]	.90	F	.41	0
		Asian	2	1.12	[−0.97, 3.20]	.29	R	<.00001	96

R = random model, F = fixed model, SMD = standard mean difference, CIs = confidence intervals, BMD = bone mineral density.
P value: chi-square-based Cochran *Q* test; I^2: Higgins I-squared statistic.

Table 3

The association between osteoprotegerin gene (*OPG*) G1181C and BMD in postmenopausal women.

BMD/Polymorphism	Genotype	Population	Number of studies	Test of association				Test of heterogeneity	
				SMD	95% CI]	*P* value	Model	*P* value	I^2 (%)
Lumbar spine L1–L4	GG vs CC	Overall	13	−0.85	[−1.29, −0.41]	.0002	R	<.00001	97
		European	9	−0.22	[−0.42, −0.02]	.03	R	<.00001	82
		Asian	4	−2.63	[−5.34, 0.08]	.06	R	<.00001	99
	GG vs GC	Overall	12	−0.21	[−0.39, −0.03]	.02	R	<.00001	88
		European	9	−0.07	[−0.17, 0.03]	.18	R	.03	52
		Asian	3	−0.72	[−1.68, 0.25]	.15	R	<.00001	97
	GC vs CC	Overall	12	−0.64	[−0.98, −0.31]	.0002	R	<.00001	95
		European	9	−0.16	[−0.32, 0.00]	.06	R	<.00001	80
		Asian	3	−2.69	[−5.08, −0.31]	.03	R	<.00001	97
Femoral hip	GG vs CC	Overall	12	−0.30	[−0.59, −0.00]	.05	R	<.00001	93
		European	8	−0.10	[−0.15, −0.04]	.001	F	.93	0
		Asian	4	−0.75	[−2.57, 1.07]	.42	R	<.00001	98
	GG vs GC	Overall	11	−0.20	[−0.41, 0.01]	.07	R	<.00001	92
		European	8	−0.06	[−0.12, −0.00]	.05	F	.36	9
		Asian	3	−0.86	[−2.28, 0.56]	.24	R	<.00001	98
	GC vs CC	Overall	11	−0.19	[−0.45, 0.07]	.15	R	<.00001	93
		European	8	−0.03	[−0.09, 0.03]	.34	F	.35	11
		Asian	3	−0.54	[−3.07, 1.99]	.67	R	<.00001	98
Total hip	GG vs CC	Overall	10	−0.25	[−0.42, −0.09]	.002	R	<.00001	78
		European	8	−0.10	[−0.16, −0.04]	.0006	F	.49	0
		Asian	2	−0.85	[−1.64, −0.06]	.03	R	.02	82
	GG vs GC	Overall	10	−0.15	[−0.26, −0.03]	.01	R	.0004	70
		European	8	−0.08	[−0.13, −0.03]	.002	F	.61	0
		Asian	2	−0.38	[−1.07, 0.31]	.28	R	.0002	93
	GC vs CC	Overall	10	−0.08	[−0.18, 0.02]	.13	R	.02	53
		European	10	−0.04	[−0.13, 0.05]	.38	F	.09	43
		Asian	2	−0.43	[−0.75, −0.12]	.008	F	.60	0

R = random model, F = fixed model, SMD = standard mean difference, CIs = confidence intervals, BMD = bone mineral density.
P value: chi-square-based Cochran *Q* test; I^2: Higgins I-squared statistic.

Table 4

The association between osteoprotegerin gene (*OPG*) T950C and BMD in postmenopausal women.

BMD/Polymorphism	Genotype	Population	Number of studies	Test of association			Model	Test of heterogeneity	
				SMD	[95% CI]	*P* value		*P* value	I^2 (%)
Lumbar spine L1–L4	TT vs CC	Overall	9	−0.35	[−0.78, 0.07]	.10	R	<.00001	88
		European	3	−0.37	[−0.65, −0.09]	.01	F	.60	0
		Asian	6	−0.33	[−0.94, 0.29]	.30	R	<.00001	92
	TT vs TC	Overall	8	−0.16	[−0.75, 0.44]	.60	R	<.00001	96
		European	3	0.20	[−0.25, 0.65]	.39	R	.003	83
		Asian	5	−0.37	[−1.07, 0.34]	.30	R	<.00001	95
	TC vs CC	Overall	8	−0.25	[−0.38, −0.11]	.0004	F	.53	0
		European	3	−0.39	[−0.63, −0.14]	.002	F	.28	21
		Asian	5	−0.18	[−0.35, −0.02]	.03	F	.78	0
Femoral hip	TT vs CC	Overall	8	−0.21	[−0.65, 0.23]	.36	R	<.00001	92
		European	2	−0.15	[−0.32, 0.02]	.08	F	.33	0
		Asian	6	−0.18	[−0.82, 0.47]	.59	R	<.00001	93
	TT vs TC	Overall	7	−0.16	[−0.39, 0.08]	.19	R	.0001	78
		European	2	−0.12	[−0.27, 0.02]	.10	F	.70	0
		Asian	5	−0.15	[−0.51, 0.22]	.43	R	.0002	82
	TC vs CC	Overall	7	−0.14	[−0.57, 0.29]	.52	R	<.00001	91
		European	2	−0.02	[−0.16, 0.12]	.78	F	.38	0
		Asian	5	−0.15	[−0.79, 0.50]	.66	R	<.00001	89
Total hip	TT vs CC	Overall	7	−0.35	[−1.08, 0.38]	.35	R	<.00001	96
		European	2	−0.18	[−0.48, 0.11]	.22	R	.16	50
		Asian	5	−0.39	[−1.43, 0.66]	.47	R	<.00001	96
	TT vs TC	Overall	7	−0.37	[−1.04, 0.29]	.27	R	<.00001	97
		European	2	−0.16	[−0.30, −0.01]	.04	F	.49	0
		Asian	5	−0.44	[−1.37, 0.49]	.36	R	<.00001	97
	TC vs CC	Overall	7	−0.10	[−0.38, 0.17]	.46	R	.0002	77
		European	2	0.03	[−0.12, 0.18]	.73	F	.30	6
		Asian	5	−0.14	[−0.52, 0.24]	.47	R	.02	66

R = random model, F = fixed model, SMD = standard mean difference, CIs = confidence intervals, BMD = bone mineral density.
P value: chi-square-based Cochran *Q* test; I^2: Higgins I-squared statistic.

3.5. Test of heterogeneity

Significant between-study heterogeneity were detected in all the meta-analysis of A163G, G1181C, T950C, and T245G polymorphisms (Table 2–5). Therefore, subgroup analysis stratified by ethnicity was conducted. Notable, most of the between-study heterogeneity in Caucasian disappeared (except for G1181C, T950C (TT vs TC) and T245G in lumbar spine BMD, T950C (TT vs CC) in total hip BMD). The significant heterogeneity in A163G were contributed mainly by Gen et al[23] Removal of this study from meta-analysis gave 0% to 32% ($P > .05$) heterogeneities. The significant heterogeneity in T245G were contributed mainly by Yamada et al[35] and Kim et al[29]. Removal of these studies from meta-analysis gave 0% to 36% ($P > .05$) heterogeneity. In addition, the significant heterogeneity in T950C were contributed mainly by Yamada et al[35] and Boron et al[25]. Removal of these studies from meta-analysis gave 0% to 27% ($P > .05$) heterogeneity. In addition, Hardy-Weinberg equilibrium fitness by using the Chi-square goodness-of-fit test for all the genotypes of A163G, G1181C, T245G, and T950C were performed out. The data in Kim et al for G1181C, and Chen et al for T950C were not in Hardy-Weinberg equilibrium (Table S1, http://links.lww.com/MD/C703). After excluding the study conducted by Kim et al the pooled SMDs of G1181C have no significant change. After excluded the study conducted by Chen et al The combined SMDs changed slightly, which may indicate the state of Hardy-Weinberg equilibrium fitness has no effect on the association between *OPG* polymorphisms (A163G, G1181C, T245G, and T950C) SNPs and BMD in postmenopausal women.

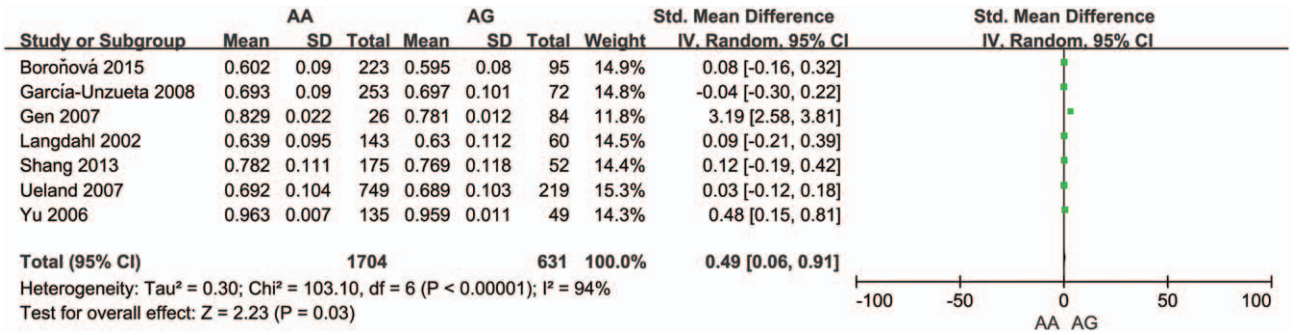

Figure 3. Association between AA genotype of A163G and femoral hip BMD compared with AG genotype.

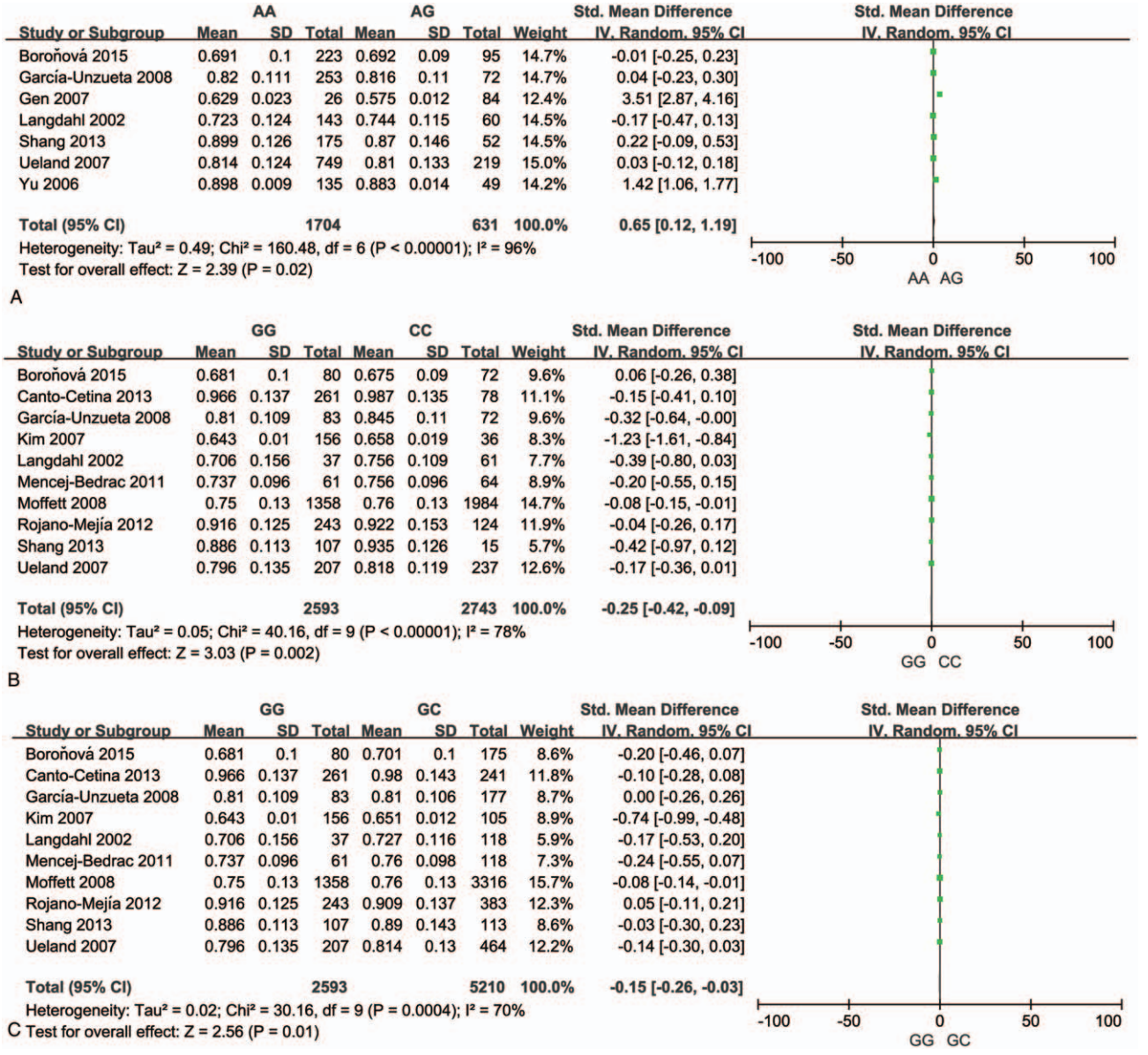

Figure 4. Association between genotypes of G1181C and A163G and total hip BMD.A: A163G, AA vs AG; B: G1181C, GG vs CC; C: G1181C, GG vs GC.

3.6. Publication bias

The results of Egger regression test for A163G have shown slight publication bias of individuals with AG genotype of A163G compared to those with GG genotype at lumbar spine, femoral hip and total hip BMD ($P < .05$)(Table 6). And the funnel plots of A163G, T950C, and T245G showed no apparent evidence of publication bias was found for another comparison of A163G, G1181C, T950C, and T245G (Table 6).

4. Discussion

In present study, we investigated the effect of *OPG* polymorphisms (A163G, G1181C, T245G, and T950C) on the BMD in postmenopausal women and detected the A163G may be associated with the femoral hip and total hip BMD, G1181C and T950C may be associated with the lumbar spine and total hip BMD. In addition, T245G has no effect on BMD in postmenopausal women.

Osteoprotegerin (*OPG*) has been discovered in regulating osteoclastogenesis in 1997.[47,48] Together with receptor activator of nuclear factor-B ligand (*RANKL*),[49] receptor activator of nuclear factor-B (*RANK*),[50]*OPG* plays a key role in osteoclastogenesis. Transgenic mice (*OPG* (−/−)) exhibited a decreased total bone density and developed severe osteoporosis,[51] whereas mice over-expressing *OPG* develop an osteopetrotic phenotype.[52]*OPG* is 1 member of the TNF and TNF receptor superfamily, encoded in humans by the *TNFRSF11B* gene that is located at 8q24.12.[53] Many genetic polymorphisms, such as A163G, T245G, T950C and G1181C, A27450T, and G19074A, have been investigated to be associated with BMD and osteoporosis.[54,55]

The A163G polymorphism located in the promoter region of *OPG* gene and was identified by Kusk.[56] Although no recognition sites of the known transcription factors have been found, there is a possibility that the *OPG* polymorphism is in linkage disequilibrium (LD) with nearby genetic variations that are associated with BMD.[57] In previous studies, the G allele of A163G polymorphism

Table 5

The association between osteoprotegerin gene (*OPG*) T245G and BMD in postmenopausal women.

BMD/Polymorphism	Genotype	Population	Number of studies	Test of association			Model	Test of heterogeneity	
				SMD	95% CI]	*P* value		*P* value	I^2 (%)
Lumbar spine L1–L4	TT vs GG	Overall	5	2.01	[−3.13, 7.16]	.44	R	<.00001	99
		European	2	0.07	[−1.16, 1.30]	.91	R	.14	53
		Asian	3	3.36	[−4.74, 11.46]	.42	R	<.00001	99
	TT vs TG	Overall	9	0.01	[−0.42, 0.44]	.97	R	<.00001	92
		European	4	0.06	[−0.27, 0.39]	.72	R	.04	64
		Asian	5	−0.05	[−0.78, 0.69]	.90	R	<.00001	95
	TG vs GG	Overall	5	1.22	[−1.37, 3.81]	.36	R	<.00001	98
		European	2	0.32	[−0.96, 1.60]	.63	R	.14	53
		Asian	3	1.87	[−2.22, 5.95]	.37	R	<.00001	99
Femoral hip	TT vs GG	Overall	4	3.52	[−4.19, 11.22]	.37	R	<.00001	98
		European	2	0.23	[−0.58, 1.03]	.58	F	.38	0
		Asian	2	6.92	[−8.33, 22.17]	.37	R	<.00001	99
	TT vs TG	Overall	6	−0.04	[−0.61, 0.53]	.89	R	<.00001	94
		European	3	−0.06	[−0.46, 0.34]	.78	R	.03	73
		Asian	3	−0.06	[−1.32, 1.21]	.93	R	<.00001	98
	TG vs GG	Overall	4	2.07	[−1.70, 5.84]	.28	R	<.00001	98
		European	2	0.42	[−0.42, 1.25]	.33	F	.54	0
		Asian	2	3.80	[-4.17, 11.77]	.35	R	<.00001	98
Total hip	TT vs GG	Overall	3	5.03	[−4.93, 14.99]	.32	R	<.00001	99
		European	1	0.35	[−0.64, 1.34]	.49	-	-	-
		Asian	2	7.37	[−8.20, 22.94]	.35	R	<.00001	99
	TT vs TG	Overall	7	0.12	[−0.17, 0.42]	.42	R	<.00001	81
		European	3	−0.05	[−0.33, 0.23]	.71	F	.16	46
		Asian	4	0.24	[−0.23, 0.72]	.32	R	<.0001	87
	TG vs GG	Overall	3	2.93	[−1.84, 7.71]	.23	R	<.00001	99
		European	1	0.56	[−0.46, 1.59]	.28	-	-	-
		Asian	2	4.12	[−3.88, 12.13]	.31	R	<.00001	99

R = random model, F = fixed model;SMD = standard mean difference, CIs = confidence intervals; BMD = bone mineral density;.
P value: chi-square-based Cochran *Q* test; I^2: Higgins I-squared statistic.

was shown to be a risk factor for low BMD.[31,32] Among the included studies, only Geng et al have reported that the AA genotype of A163G was associated with the lumbar spine, femoral hip and total hip BMD in Chinese.[23] However, our combined results showed that the subjects with AA genotype of A163G have significant higher femoral hip and total hip BMD in postmenopausal women. It seemed the AA genotype of A163G has more effect on the femoral hip and total hip BMD, but not lumbar spine BMD in postmenopausal women. The results were slightly different from the previous meta-analysis conducted by Lee et al[57], which may mainly due to the 6 more included publications in our study. Notable, the difference of femoral hip and total hip BMD in postmenopausal women disappeared in Caucasian and Asian populations, which may due to the limited number of studies in ethnic subgroup analysis.

The G1181C polymorphism has been firstly discovered in Irish postmenopausal women in 2002.[34] Most subsequent researches have indicated the G1181C was associated with BMD. Zhao et al reported that the individuals with 1181G allele have lower lumbar spine BMD and 2.7 fold risk of osteoporosis than those with 1181C.[31] Similar results were observed in 6640 American postmenopausal women. However, no association was also reported between G1181C and BMD in Maltese and Australian postmenopausal women.[33,45] Lee et al have investigated the association between G1181C and BMD using a meta-analysis with 5 studies and found the GG genotype of G1181C might have a significantly lower lumbar, femoral neck, and total hip BMD than subjects with the CC genotype.[57] However, the results changed in subgroup analysis stratified by ethnicity. Notable, subjects such as premenopausal women, postmenopausal women, and males with osteoporosis were all included in study conducted by Lee et al[57], while, no subgroup analysis were performed. In addition, most studies conducted in Chinese population were not included in Lee et al[57] for the language limited and earlier publication years, which might partly influence the final results. Subsequently, Zhang et al[58] performed a meta-analysis on the association between G1181C and BMD with 9 studies and found that GG and GC genotypes of G1181C seems to have significantly lower mean lumbar BMD than subjects with the CC genotype in Asian population, GG and GC genotypes of G1181C may have significantly lower mean femoral neck BMD than subjects with the CC genotype in Caucasian population. In present study, we included 13 studies in analyzing the association between G1181C and BMD. More complicated results were detected. GG genotype of G1181C seems to have significantly lower lumbar, femoral neck and total hip BMD than subjects with the CC genotype in Caucasian population. In addition, GC genotype of G1181C seems to have significantly lower lumbar and total hip BMD than subjects with the CC genotype in Asian population. The inconsistent in these 3 meta-analyses might mainly due to the limited number of included studies and subjects. To identify the results, more studies larger number of individuals was needed in the future.

For T950C, we observed that subjects with TT genotype of T950C seem to have significantly lower lumbar BMD than those with the CC genotype in Caucasian population, TC genotype of T950C seems to have significantly lower lumbar BMD than subjects with the CC genotype both in Caucasian and Asian populations, which were significantly different from the results reported by Lee et al[57] these difference may mainly due to the larger number of subjects in present study.

Table 6

Egger linear regression test for funnel plot asymmetries of A163G, G1181C, T245G, and T950C.

BMD	LS			FN			TH		
A163G	AA vs GG	AA vs AG	AG vs GG	AA vs GG	AA vs AG	AG vs GG	AA vs GG	AA vs AG	AG vs GG
P value	.807	.124	.019	.309	.056	.020	.257	.054	.020
95%CI	−44.63346–53.89685	−6.157081–20.58129	−16.11719–2.502204	−22.07811–53.97884	−.2969318–16.34106	−24.47038–3.630999	−19.10018–53.71961	−.2392931–19.72671	−21.24944–3.188107
G1181C	GG vs CC	GG vs GC	GC vs CC	GG vs CC	GG vs GC	GC vs CC	GG vs CC	GG vs GC	GC vs CC
P value	.118	.413	.054	.431	.479	.429	.098	.320	.140
95%CI	−8.13918–1.061031	−4.344705–1.936748	−7.367594–.0780236	−5.37502–2.479699	−5.899282–2.996339	−5.455485–2.529411	−4.013159–.4135829	−3.526946–1.306131	−2.57648–.4354744
T245G	TT vs GG	TT vs TG	TG vs GG	TT vs GG	TT vs TG	TG vs GG	TT vs GG	TT vs TG	TG vs GG
P value	.388	.144	.647	.778	.503	.528	.378	.691	.512
95%CI	−140.6921−73.09238	−1.980656–10.99011	−23.90263–32.94745	−290.8523–250.2636	−8.846914–15.20916	−38.9868–55.62452	−3465.067–4379.378	−6.965782–5.001745	−188.0465–218.9036
T950C	TT vs CC	TT vs TC	TC vs CC	TT vs CC	TT vs TC	TC vs CC	TT vs CC	TT vs TC	TC vs CC
P value	.224	.088	.692	.432	.243	.675	.649	.380	.750
95%CI	−2.294554−8.241903	−1.67783–18.35816	−2.154473–1.527969	−4.632248–9.487634	−2.135322–6.663011	−5.613889–7.959536	−9.329704–13.65233	−8.913715–19.58063	−3.687176–4.797347

BMD = bone mineral density, LS = Lumbar spine, FH = Femoral hip, TH = Total hip, CIs = confidence intervals.

Several limitations should be considered in present study. First, although more number of studies has been enrolled in present study, the number of studies included in this meta-analysis was relatively small and insufficient to detect associations with small effects, especially in terms of subgroup analysis stratified by ethnicity. Second, the interaction between gene polymorphisms and metabolic factors and environmental factors, as well as other genes and the *OPG* gene may also be risk factors for low BMD in postmenopausal women. Thirdly, several polymorphisms in *OPG* gene has been shown to be in linkage disequilibrium, which may indicate not only polymorphisms in *OPG* gene, but also the haplotypes containing *OPG* polymorphisms were associated with the risk of BMD in postmenopausal women. However, the polymorphisms contained in haplotypes in each study were not consistent. We failed to performed a linkage analyse of *OPG* haplotypes and BMD risk.

5. Conclusions

The present study demonstrates that A163G might be associated with the femoral hip and total hip BMD, G1181C and T950C might be associated with the lumbar spine and total hip BMD. And, T245G has no effect on BMD in postmenopausal women.

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