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Association of the insulin-like growth factor-1 single nucleotide polymorphisms rs35767, rs2288377, and rs5742612 with osteoporosis risk

A meta-analysis

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Abstract

Background: Insulin-like growth factor-1 (IGF-1) plays an important role in the regulation of bone formation and mineralization. We aimed to perform a meta-analysis to assess the association of three *IGF-1* single nucleotide polymorphisms (SNPs) rs35767, rs2288377, and rs5742612 with osteoporosis risk.

Methods: A systematic search of PubMed, Web of Science, Embase, Medline, Scopus, CNKI, and Wanfang databases was conducted. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using a fixed effects model.

Results: Four Chinese case-control studies with a total of 2807 participants were included in this meta-analysis. The results revealed an association between rs35767 and osteoporosis risk in all study subjects (women and men) in dominant (OR 1.32, 95% CI 1.13–1.53, $P < .001$), recessive (OR 1.73, 95% CI 1.35–2.21, $P < .001$), homozygote (OR 1.89, 95% CI 1.46–2.45, $P < .001$), and allelic (OR 1.31, 95% CI 1.18–1.47, $P < .001$) models. Subgroup analysis according to gender showed that rs35767 was associated with osteoporosis risk in women under dominant (OR 1.29, 95% CI 1.08–1.54, $P = .005$), recessive (OR 1.59, 95% CI 1.19–2.12, $P = .002$), homozygote (OR 1.73, 95% CI 1.28–2.34, $P < .001$), and allelic (OR 1.28, 95% CI 1.12–1.47, $P < .001$) models. Meta-analysis did not find associations of rs2288377 and rs5742612 with osteoporosis risk. There was no evidence of between-study heterogeneity and publication bias.

Conclusion: Our results suggest that rs35767 is associated with osteoporosis risk in Chinese, whereas there is no association of rs2288377 and rs5742612 with osteoporosis risk.

Abbreviations: BMD = bone mineral density, BTB40 = BTB domain-containing protein 40, BUA = broadband ultrasound attenuation, CI = confidence interval, CNKI = China national knowledge infrastructure, CYP19A1 = cytochrome P450 family 19 subfamily A member 1, GH = growth hormone, IGF-1 = insulin-like growth factor-1, IGF1R = insulin-like growth factor-1 receptor, LRP5 = low-density lipoprotein-related receptors 5, MPP7 = membrane palmitoylated protein 7, NOS = Newcastle–Ottawa scale, OR = odds ratio, PI3K = phosphoinositide 3-kinase, PRISMA = preferred reporting items for systematic reviews and meta-analyses, SNP = single nucleotide polymorphism, WHO = World Health Organization.

Keywords: meta-analysis, osteoporosis, polymorphism

1. Introduction

Osteoporosis is defined by the World Health Organization (WHO) as a value for bone mineral density (BMD) 2.5 standard deviations below the population average in young healthy individuals (BMD T-score of -2.5 or less).[1] It is the commonest metabolic bone disease worldwide and often remains asymptomatic and undetected until bone fracture occurs. Osteoporosis is a major public health problem and the economic burden of the disease is increasing dramatically as populations age.[2] The pathogenesis of osteoporosis is complex and multifactorial. Familial and linkage studies have suggested that genetic factors play an important role in both osteoporosis and its associated phenotypes, including BMD, bone mass, and broadband ultrasound attenuation (BUA).[3,4] Over the past 2 decades, candidate gene association studies and genome-wide association studies have identified many susceptibility genes for osteoporosis, including cytochrome P450 family 19 subfamily A member 1 (*CYP19*A1), low-density lipoprotein-related receptors 5 (*LRP5*), membrane palmitoylated protein 7 (*MPP7*), and Zinc finger and BTB domain-containing protein 40 (*BTB40*).[5] Identifying disease susceptibility genes is one of the key challenges in osteoporosis research and has attracted considerable attention from researchers, which will help to increase our understanding of the pathogenesis and pathophysiology of osteoporosis.

Insulin-like growth factor-1 (IGF-1) is the primary ligand for the cell surface tyrosine kinase signaling molecule, IGF receptor 1 (IGF1R).[6] It plays an important role in cell proliferation,

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differentiation, and apoptosis and is the major mediator of the effect of growth hormone (GH) on both bone growth and mineralization.[7,8] IGF-1 decreased osteoblast apoptosis and promoted osteoblastogenesis through the phosphoinositide 3-kinase (PI3K) pathway.[9] Animal studies showed that IGF-1-deficient mice developed smaller skeletons with a significant delay in mineralization at 14.5 dpc and onward.[10] In addition, conditional *igf1* receptor null mice demonstrated reduced bone formation and reduced trabecular bone volume.[11] In agreement with the findings from animal studies, clinical studies showed a positive association between serum IGF-1 levels and BMD in different ethnic groups.[12–14] Low serum levels of IGF-1 were found to be associated with osteoporotic fractures.[15,16] These lines of evidence suggest an important role of IGF-1 in bone formation and mineralization. Thus, the *IGF-1* gene may be a candidate gene for osteoporosis risk. Located on chromosome 12, the *IGF-1* gene consists of 6 exons, including 2 leader exons, and has 2 promoters.[17] Previous case-control association studies have evaluated the association of several common single nucleotide polymorhisms (SNPs) in the *IGF-1* gene with osteoporosis risk, but the evidence has not been reviewed and analyzed systematically.

In the present study, we aimed to conduct a meta-analysis of publically available data to clarify if 3 SNPs (rs35767, rs 2288377, and rs5742612) in the *IGF-1* gene are associated with osteoporosis risk.

2. Materials and methods

2.1. Study identification

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. An electronic search of the literature was performed to identify case-control association studies investigating the relationship of the *IGF-1* SNPs (rs35767, rs 2288377, and rs5742612) with osteoporosis risk. We searched PubMed, Web of Science, Embase, Medline, Scopus, China National Knowledge Infrastructure (CNKI), and Wanfang databases for articles published in peer-review journals. No date restrictions were placed on the search. The search strategy included using the keywords "case-control studies, polymorphism, osteoporosis, insulin-like growth factor-1, rs35767, rs2288377, rs5742612, risk." Titles and abstracts of relevant papers identified through the search were screened by one of us and were rejected if the paper clearly did not meet the inclusion criteria. Full-text papers were then assessed for eligibility. We screened the reference lists of review articles to find relevant papers that were potentially missed by the initial search. We did not contact authors for additional data. Since we only dealt with published data in this meta-analysis, we did not obtain ethics approval from the local ethics committee.

2.2. Study inclusion/exclusion criteria

Studies were selected for review if they met the following criteria: a case-control association study, examined the association of the *IGF-1* SNPs with osteoporosis risk, there were at least 2 comparison groups, and provided sufficient data for genotypic distribution in both cases and controls. We excluded studies that were published only as abstracts or conference reports. Familial-based studies were also excluded.

2.3. Data extraction and quality assessment

Data were extracted by 2 reviewers using a customized database for data extraction. The following information was collected for each study: first author, year of publication, country, number of cases and controls, gender and mean age of subjects, genotype distributions by case/control status, and genotyping method. The quality of individual studies was assessed using the Newcastle–Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Each study was judged on 8 items, categorized into 3 key areas including selection of subjects, comparability, and exposure. A score of ≤ 5 (out of 9) indicated a high risk of bias.[18] Disagreements were resolved by consensus.

2.4. Statistical analyses

Meta-analyses were performed using Stata version 11.0. Between-study heterogeneity was assessed using the Q-test and I^2 statistic, with significance set at $P < .10$.[19] I^2 values of 25%, 50%, and 75% were considered low, medium, and high heterogeneity, respectively. Odds ratio (OR) and 95% interval confidence (CI) were calculated from the dominant, recessive, homozygote, and allelic model for each SNP having the minor allele frequency as the reference category. In case of substantial heterogeneity, random effects summary ORs were calculated using the DerSimonian method.[20] When heterogeneity was absent, the Mantel–Haenszel method was used to calculate fixed effects summary ORs.[21] The significance of the summary ORs was determined by the Z-test and a P value of less than .05 was assumed to be statistically significant. Forest plots were produced to visually assess the individual study ORs and overall ORs with corresponding 95% CIs. Summary minor allele frequency of each *IGF-1* SNP in control subjects was calculated using Meta-analyst 3.13. Sensitivity analysis was performed to evaluate whether the omission of 1 study would have a disproportionate impact on the results of the meta-analyses. For the assessment of publication bias, we utilized Egger test and Begg test. Since there were fewer than 10 studies qualified for each SNP, funnel plots were not produced for evaluating publication bias.[22]

3. Results

3.1. Characteristics of published studies

Our initial literature searches yielded 127 reports in total. Of these, 121 duplicated or nonrelevant studies were excluded after screening of the titles/abstracts. Six full-text studies were assessed for eligibility. Among these, 4 case-control studies met the inclusion criteria and were included in the final analyses.[23–26]Figure 1

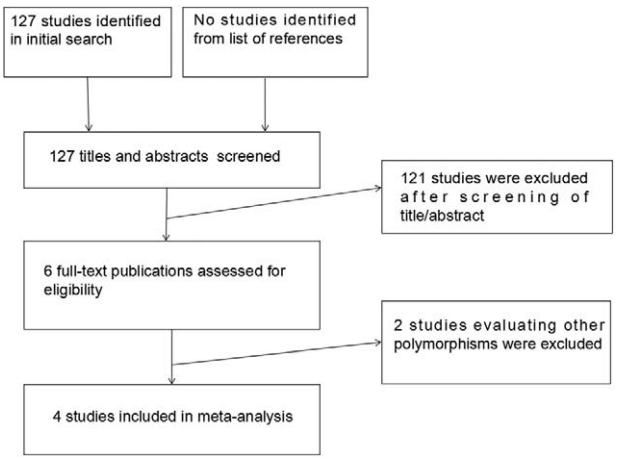

Figure 1. Flow diagram of the screening process of retrieved studies.

Table 1

Summary of included studies.

First author	Year	Country	Number		Age (years)		Gender (female %)		Genotyping method	Evaluated SNPs	NOS score
			Cases	Controls	Cases	Controls	Cases	Controls			
Yun-Kai	2014	Chinese	216	220	57.4±6.2	56.3±6.7	100.0%	100.0%	Direct genome sequencing and PCR-based assay	rs35767, rs2288377 and rs5742612	7
Li	2015	Chinese	486	485	66.7±7.2	67.2±6.8	100.0%	100.0%	PCR-RFLP	rs35767, rs2288377 and rs5742612	8
Zhang	2015	Chinese	428	428	60.5±7.1	61.1±7.3	44.4%	44.4%	PCR-RFLP	rs35767, rs2288377 and rs5742612	7
Wei	2015	Chinese	272	272	65.7±8.10	66.4±7.9	100.0%	100.0%	PCR-RFLP	rs35767 and rs972936	8

NOS = Newcastle–Ottawa Scale, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SNP = single nucleotide polymorphism.

summarizes the process of identifying eligible studies. All of the studies were published in English. A total of 2807 participants took part in the studies, with 1 recruiting men and women,[25] and 3 women only.[23,24,26] Four studies investigated rs35767,[23–26] 3 studies assessed rs2288377,[23–25] and 3 studies evaluated rs5742612.[23–25] The pooled minor allele frequency for rs35767, rs2288377, rs5742612 was 0.291 (95% CI: 0.275–0.308), 0.100 (95% CI: 0.088–0.113), and 0.131 (95% CI: 0.118–0.146), respectively. The main characteristics of the eligible studies are presented in Table 1. The genotype and allele frequencies for each SNP in the eligible studies are summarized in Table 2.

3.2. Association between the IGF-1 SNPs and osteoporosis risk

Four case-control association studies with a total of 1402 cases and 1405 controls assessed the relation of rs35767 with osteoporosis risk. The fixed-effect meta-analyses revealed that rs35767 was associated with osteoporosis risk in all study subjects (women and men) under dominant (TT + CT vs CC, OR 1.32, 95% CI 1.13–1.53, $P < .001$), recessive (TT vs CT + CC, OR 1.73, 95% CI 1.35–2.21, $P < .001$), homozygote (TT vs CC, OR 1.89, 95% CI 1.46–2.45, $P < .001$), and allelic (T allele vs C allele, OR 1.31, 95% CI 1.18–1.47, $P < .001$) models (Fig. 2 and Table 3). We further performed stratified analyses according to gender. The results showed that there was an association between rs35767 and osteoporosis risk in women under dominant (TT + CT vs CC, OR 1.29, 95% CI 1.08–1.54, $P = .005$), recessive (TT vs CT + CC, OR 1.59, 95% CI 1.19–2.12, $P = .002$), homozygote (TT vs CC, OR 1.73, 95% CI 1.28–2.34, $P < .001$), and allelic (T allele vs C allele, OR 1.28, 95% CI 1.12–1.47, $P < .001$) models (Fig. 2 and Table 3). We did not identify any between-study heterogeneity in the analyses for rs35767 ($I^2 = 0.0\%$, $P > .10$) (Fig. 2 and Table 3). Sensitivity analyses by excluding each study in turn ensured that no single study was solely responsible for the significance of the results.

Three studies including 1128 cases and 1133 controls to date assessed the relationship of rs2288377 with osteoporosis risk. Pooling data from these showed that rs2288377 was associated with osteoporosis risk in all study subjects (women and men) under dominant (TT + AT vs AA, OR 1.26, 95% CI 1.01–1.58, $P = .042$), recessive (TT vs AT + AA, OR 1.44, 95% CI 1.02–2.03, $P = .037$), homozygote (TT vs AA, OR 1.46, 95% CI 1.04–2.06, $P = .031$), and allelic (T allele vs A allele, OR 1.31, 95% CI 1.08–1.57, $P = .005$) models (Table 4). However, in subgroup analysis according to gender, the results did not suggest an association between rs2288377 and osteoporosis risk in women under dominant (TT + AT vs AA, OR 1.23, 95% CI 0.93–1.64, $P = .151$), recessive (TT vs AT + AA, OR 1.36, 95% CI 0.87–2.11, $P = .173$), homozygote (TT vs AA, OR 1.38, 95% CI 0.89–2.15, $P = .154$), and allelic (T allele vs A allele, OR 1.26, 95% CI 1.00–1.60, $P = .054$) models (Table 4). The single study containing women and men subjects did not find an association between rs2288377 and osteoporosis risk (not shown).[25] Sensitivity

Table 2

Genotypic and allelic distribution of each SNP.

SNP	Cases						Controls					
rs35767	Total	CC (%)	CT (%)	TT (%)	C allele (%)	T allele (%)	Total	CC (%)	CT (%)	TT (%)	C allele (%)	T allele (%)
Yun-Kai et al.	216	95 (44.0)	94 (43.5)	27 (12.5)	284 (65.7)	148 (34.3)	220	114 (51.8)	89 (40.5)	17 (7.7)	317 (72.0)	123 (28.0)
Li et al.	486	202 (41.6)	210 (43.2)	74 (15.2)	614 (63.2)	358 (36.8)	485	238 (49.1)	201 (41.5)	46 (9.4)	677 (69.8)	293 (30.2)
Zhang et al.	428	182 (42.6)	193 (45.1)	53 (12.3)	557 (65.1)	299 (34.9)	428	216 (50.4)	186 (43.5)	26 (6.1)	618 (72.2)	238 (27.8)
Wei et al.	272	124 (45.6)	118 (43.4)	30 (11.0)	366 (67.3)	178 (32.7)	272	132 (48.4)	116 (42.7)	24 (8.9)	380 (69.9)	164 (30.1)
rs2288377	Total	AA (%)	AT (%)	TT (%)	A allele (%)	T allele (%)	Total	AA (%)	AT (%)	TT (%)	A allele (%)	T allele (%)
Yun-Kai et al.	216	182 (84.3)	21 (9.7)	13 (6.0)	385 (89.1)	47 (10.9)	220	189 (85.9)	21 (9.5)	10 (4.5)	399 (90.7)	41 (9.3)
Li et al.	484	396 (81.7)	52 (10.8)	36 (7.5)	844 (87.2)	124 (12.8)	485	413 (85.2)	45 (9.3)	27 (5.5)	871 (89.8)	99 (10.2)
Zhang et al.	428	349 (81.6)	44 (10.3)	35 (8.1)	742 (86.7)	114 (13.3)	428	365 (85.2)	40 (9.4)	23 (5.4)	770 (90.0)	86 (10.0)
rs5742612	Total	CC (%)	CT (%)	TT (%)	C allele (%)	T allele (%)	Total	CC (%)	CT (%)	TT (%)	C allele (%)	T allele (%)
Yun-Kai et al.	216	178 (82.4)	21 (9.7)	17 (7.9)	377 (87.3)	55 (12.7)	220	183 (83.2)	21 (9.5)	16 (7.3)	387 (88.0)	53 (12.0)
Li et al.	485	389 (80.2)	55 (11.3)	41 (8.5)	833 (85.9)	137 (14.1)	485	400 (82.5)	50 (10.3)	35 (7.2)	850 (87.6)	120 (12.4)
Zhang et al.	428	336 (78.4)	48 (11.3)	44 (10.3)	720 (84.1)	136 (15.9)	429	346 (80.8)	42 (9.7)	41 (9.5)	734 (85.5)	124 (14.5)

SNP = single nucleotide polymorphism.

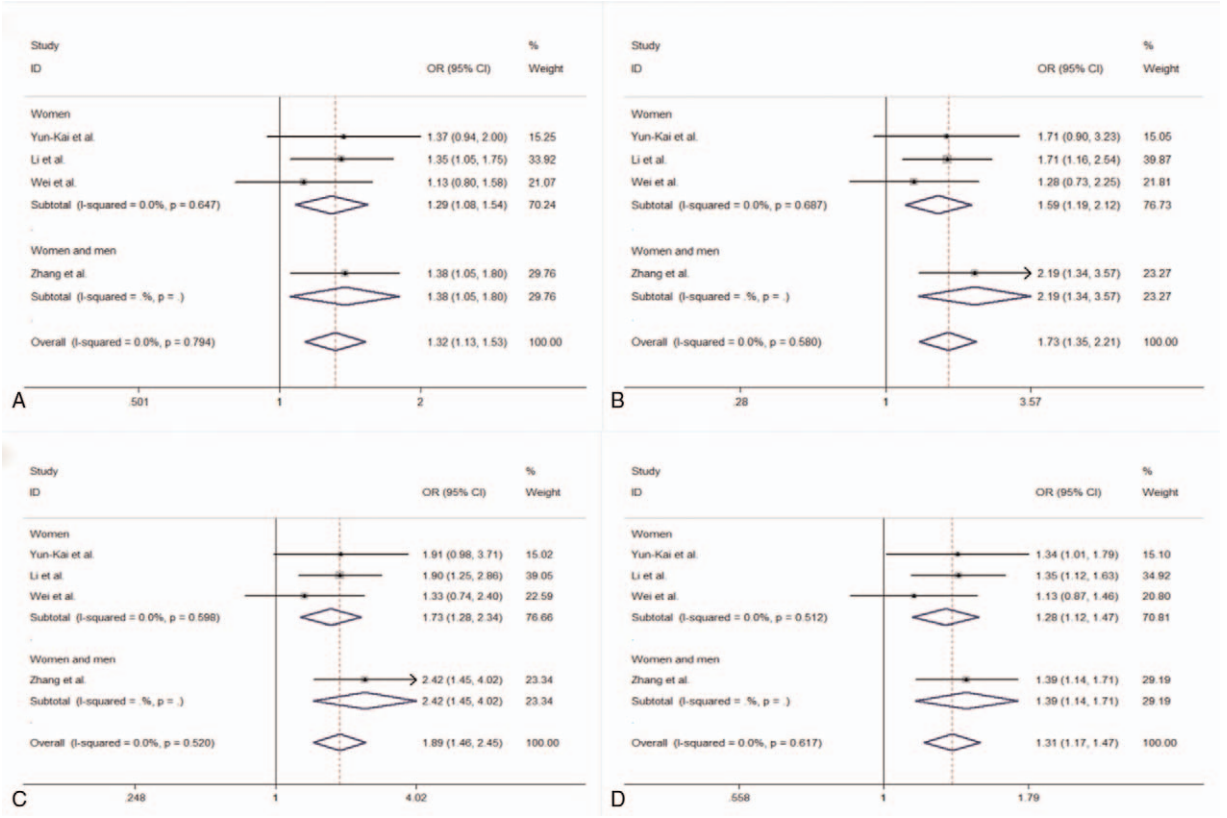

Figure 2. Forest plots showing meta-analysis of the association between rs35767 and osteoporosis risk. A, Meta-analysis of the association between rs35767 and osteoporosis risk under dominant model (TT + CT vs CC). B, Meta-analysis of the association between rs35767 and osteoporosis risk under recessive model (TT vs CT + CC). C, Meta-analysis of the association between rs35767 and osteoporosis risk under homozygote model (TT vs CC). D, Meta-analysis of the association between rs35767 and osteoporosis risk under allelic model (T allele vs C allele).

Table 3

The results of the meta-analysis for the association of rs35767 with osteoporosis.

Genetic model	Subjects	No. of studies	Test of association			Test of heterogeneity		Test of publication bias	
			OR	95% CI	*P*	I^2	*P*	P_E	P_B
Dominant	All	4	1.32	1.13–1.53	< .001	0.0%	.794	.574	.734
(TT + CT vs CC)	Women	3	1.29	1.08–1.54	.005	0.0%	.647	NA	NA
Recessive	All	4	1.73	1.35–2.21	< .001	0.0%	.580	.732	1.000
(TT vs CT + CC)	Women	3	1.59	1.19–2.12	.002	0.0%	.687	NA	NA
Homozygote	All	4	1.89	1.46–2.45	< .001	0.0%	.520	.708	1.000
(TT vs CC)	Women	3	1.73	1.28–2.34	< .001	0.0%	.598	NA	NA
Allelic	All	4	1.31	1.18–1.47	< .001	0.0%	.617	.511	.734
(T allele vs C allele)	Women	3	1.28	1.12–1.47	< .001	0.0%	.512	NA	NA

CI = confidence interval, NA = not applicable, OR = odds ratio, P_B = *P* value of Begg test, P_E = *P* value of Egger test.

Table 4

The results of the meta-analysis for the association of rs2288377 with osteoporosis.

Genetic model	Subjects	No. of studies	Test of association			Test of heterogeneity		Test of publication bias	
			OR	95% CI	*P*	I^2	*P*	P_E	P_B
Dominant	All	3	1.26	1.01–1.58	.042	0.0%	.909	.255	1.000
(TT + AT vs AA)	Women	2	1.23	0.93–1.64	.151	0.0%	.725	NA	NA
Recessive	All	3	1.44	1.02–2.03	.037	0.0%	.922	.795	1.000
(TT vs AT + AA)	Women	2	1.36	0.87–2.11	.173	0.0%	.979	NA	NA
Homozygote	All	3	1.46	1.04–2.06	.031	0.0%	.922	.745	1.000
(TT vs AA)	Women	2	1.38	0.89–2.15	.154	0.0%	.953	NA	NA
Allelic	All	3	1.31	1.08–1.57	.005	0.0%	.861	.451	1.000
(T allele vs A allele)	Women	2	1.26	1.00–1.60	.054	0.0%	.752	NA	NA

CI = confidence interval, NA = not applicable, OR = odds ratio, P_B = *P* value of Begg test, P_E = *P* value of Egger test.

Table 5

The results of the meta-analysis for the association of rs5742612 with osteoporosis.

Genetic model	Subjects	No. of studies	Test of association			Test of heterogeneity		Test of publication bias	
			OR	95% CI	*P*	I^2	*P*	P_E	P_B
Dominant	All	3	1.13	0.92–1.40	.241	0.0%	.951	.108	.296
(TT + CT vs CC)	Women	2	1.13	0.86–1.48	.381	0.0%	.753	NA	NA
Recessive	All	3	1.13	0.84–1.51	.435	0.0%	.959	.848	1.000
(TT vs CT + CC)	Women	2	1.16	0.78–1.71	.467	0.0%	.843	NA	NA
Homozygote	All	3	1.14	0.85–1.54	.383	0.0%	.959	.763	1.000
(TT vs CC)	Women	2	1.17	0.79–1.73	.436	0.0%	.823	NA	NA
Allelic	All	3	1.13	0.95–1.34	.164	0.0%	.933	.386	.296
(T allele vs C allele)	Women	2	1.13	0.91–1.41	.262	0.0%	.716	NA	NA

CI = confidence interval, NA = not applicable, OR = odds ratio, P_B = *P* value of Begg test, P_E = *P* value of Egger test.

analyses demonstrated that after the exclusion of the study by Li et al or the study by Zhang et al, the association between rs2288377 and osteoporosis risk in all study subjects was not statistically significant ($P > .05$), suggesting that the results of meta-analysis in all study subjects were not stable. There was no between-study heterogeneity among the studies ($I^2 = 0.0\%$, $P > .10$) (Table 4).

For rs5742612, 3 studies with 1129 cases and 1134 controls were included in the meta-analysis. The pooled effect estimates from all studies did not suggest an association between this SNP and osteoporosis risk in all study subjects (women and men) under dominant (TT + CT vs CC, OR 1.13, 95% CI 0.92–1.40, $P = .241$), recessive (TT vs CT + CC, OR 1.13, 95% CI 0.84–1.51, $P = .435$), homozygote (TT vs CC, OR 1.14, 95% CI 0.85–1.54, $P = .383$), and allelic (T allele vs C allele, OR 1.13, 95% CI 0.95–1.34, $P = .164$) models (Table 5). In stratified analysis by gender, rs5742612 was not associated with osteoporosis risk in women under any of the genetic models (Table 5). There was no evidence of significant between-study heterogeneity ($I^2 = 0.0\%$, $P > .10$). Sensitivity analysis for the association between rs5742612 and osteoporosis risk did not change our results.

3.3. Publication bias

Begg test and Egger test did not indicate any evidence of publication bias (Tables 3–5). As there were less than 10 studies for each *IGF-1* polymorphism, we did not produce funnel plots to assess publication bias.[22]

4. Discussion

IGF-1 is a 70 amino acid single chain polypeptide synthesized by many tissues, particularly by the liver in response to GH stimulation. It is one of the most important growth factors for the development and growth of the skeleton and maintenance of bone mass. In vitro studies demonstrated that IGF-1 treatment effectively inhibited apoptosis and increased proliferation and differentiation of primary osteoblasts.[27,28] In animal models of osteoporosis, treatment with IGF-1 enhanced the recruitment of osteoblastic cells, increased trabecular bone formation, and prevented trabecular bone loss.[29] Compared to control littermate mice at 8 weeks of age, *IGF-1*-deficient mice had significantly reduced femoral areal and volumetric BMD.[30] Consistent with the animal data, clinical studies found that serum levels of IGF-1 were remarkably downregulated in osteoporosis patients and associated with increased risk of fractures.[16,31] In addition, bone marrow IGF-1 concentrations were 40% lower in individuals with osteoporosis than control subjects.[32] Furthermore, recombinant IGF-1 treatment increased osteoblastic function and stimulated both bone resorption and formation in healthy older women.[33] Given the pivotal role of IGF-1 in bone health, the *IGF-1* gene has become a candidate to study in osteoporosis.

rs35767, rs2288377, and rs5742612 are 3 common SNPs in the IGF-1 gene. In the past 5 years, several case-control association studies have investigated their relationship with osteoporosis risk. However, overall evidence is mixed, and no systematic reviews or meta-analyses are available. In the present study, we conducted a meta-analysis of 4 case-control studies with a total of 2807 participants to evaluate the association of these SNPs with osteoporosis risk. The results showed that rs35767 was associated with the risk of osteoporosis in the Chinese population, whereas current evidence was not sufficient to support an association of rs2288377 and rs5742612 with osteoporosis risk. To the best of our knowledge, this is the first meta-analysis on the topic.

It was noteworthy that although meta-analysis found an association between rs2288377 and osteoporosis risk in all subjects (women and men), in subgroup analysis by gender, the results showed no association between this SNP and osteoporosis risk in women, and the single study containing women and men found rs2288377 was not associated with osteoporosis under dominant, recessive, and homozygote models.[25] In addition, sensitivity analysis demonstrated that the association between rs2288377 and osteoporosis risk was not statistically significant after the exclusion of the study by Li et al or the study by Zhang et al.[24,25] Subgroup analysis and sensitivity analysis suggested that the results of rs2288377 were not stable, and future studies were needed to derive a more definitive conclusion. Our meta-analysis did not identify any between-study heterogeneity among the eligible studies ($P > .10$, $I^2 = 0.0\%$), and there was no evidence of publication bias. Based on strict selection of studies and careful evaluation, the results of our meta-analysis could be reliable.

BMD has been utilized as the phenotype of choice for defining heritable markers for osteoporosis. Previous genetic studies have shown that regulation of BMD is determined by the effects of genetic variations.[4] Among the included studies, the study by Yun-kai demonstrated that carriers of the rs35767 T allele had lower values of BMD at L1-L4 vertebrae, femoral neck, total hip, and trochanter than those carrying the C allele.[23] Similar findings were obtained from the study by Zhang et al, which showed that BMD levels at L1-L4 vertebrae, femoral neck, total hip, and trochanter were significantly decreased in the CT + TT genotypes of rs35767 in comparison with the CC genotypes in osteoporosis patients.[25] It was of interest to evaluate the association between rs35767 and BMD. However, there was

discrepancy between the 2 studies in the selection of cases and controls for evaluating BMD. Yun-kai et al divided subjects according to allele status,[23] whereas the study by Zhang et al utilized genotypes.[25] Due to discrepancy in study design and limited data availability ($n < 3$), we did not perform subgroup analysis for BMD. No included studies assessed the relation of rs35767, rs2288377, and rs5742612 with osteoporotic fractures.

This meta-analysis has potential limitations. First, all of the included studies were performed in the Chinese population. We did not find relevant studies from other regions. The association between these *IGF-1* SNPs and osteoporosis risk needed to be evaluated in other ethnic groups, including Koreans, Japanese, and Europeans. Second, although we included all published case-control association studies on the topic through extensive literature search, the sample size of eligible studies in this meta-analysis was still relatively small. In addition, among the 4 eligible studies, 3 were performed on postmenopausal female subjects. Future research containing both male and female subjects with a larger sample size is required to validate our findings. Third, we only evaluated the relation of SNPs with osteoporosis risk. Other variants in the *IGF-1* gene including the promoter CA-repeat polymorphism were not included in this meta-analysis.

In summary, we found that the *IGF-1* SNP rs35767 was associated with osteoporosis risk in the Chinese population, whereas there was no association of rs2288377 and rs5742612 with osteoporosis risk.

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