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Review Article

The *COL1A1* rs1800012 polymorphism is associated with osteoporosis or fracture risk: a meta-analysis of 30 studies

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Abstract: Objectives: Osteoporosis is a complex disease that is influenced by several genetic markers. Many studies have examined the link between the *COL1A1* gene rs1800012 polymorphism and osteoporosis risk. However, the findings of these studies are contradictory. Therefore, we performed a meta-analysis to aggregate additional information and obtain increased statistical power to more efficiently examine this correlation. Methods: A meta-analysis was conducted to evaluate the association between the *COL1A1* rs1800012 (G > T) polymorphism and the risk of osteoporosis or fracture. A total of 30 case-control studies were included that contained 2,943 patients and 4,724 control subjects. The Stata 11.0 statistical software package was used to evaluate the odds ratio (OR) and 95% confidence interval. Results: Overall, the recessive and homozygote models showed no heterogeneity, with a significant fixed effect pooled OR ($P < 0.001$). Moreover, the allelic ($P < 0.001$), dominant ($P < 0.001$), and heterozygote ($P = 0.002$) models were associated with a significantly increased risk of osteoporosis or fracture by random effect analysis. Sub-group analyses revealed that all the hereditary models showed an increased risk of osteoporosis or fracture in a European population. Additionally, we found a significant association in the dominant ($P = 0.035$) and heterozygote ($P = 0.030$) models in North Americans. In addition, we observed an association between *COL1A1* and osteoporosis and fracture risk. Conclusions: Combined with data from previous studies, this meta-analysis suggested that *COL1A1* is associated with osteoporosis or fracture risk.

Keywords: Osteoporosis, bone mineral density, fracture, *COL1A1* rs1800012, polymorphism, meta-analysis

Introduction

Osteoporosis is a systemic skeletal disease that is characterized by low bone mineral density (BMD), microarchitectural deterioration of bone tissue, and enhanced bone fragility that leads to an increased fracture risk [1, 2]. In its early stages, osteoporosis is often asymptomatic and lasts for years, with pain being the most common first manifestation of symptoms. With disease progression, osteoporotic fracture becomes the most frequent and serious complication [3, 4]. Osteoporotic fractures are associated with a substantial financial burden to the individual, as well as to society, and are a leading cause of disability and increasing mortality [5-7]. Because osteoporosis is an age-related disease, the prevalence of osteoporosis and osteoporotic fractures is expected to rise, as the overall population is growing older. With this disease affecting 1.2 million Australians, osteoporosis and osteopenia-related fractures in Australians over 50 years of age cost $2.75 billion in 2012 [8]. Moreover, Peyman Hadji suggested that there are approximately 885,000 new osteoporosis cases in Germany each year [1].

As a complex disease, osteoporosis is influenced by several risk factors, including age, sex, race, geographical region, diet, lifestyle, hormonal status, bone density, bone quality, body mass index, and medical comorbidities [4, 9, 10]. These factors can be broadly catego-

rized into modifiable and non-modifiable risk factors. Non-modifiable risk factors include age, sex, and race. For example, osteoporosis is more common in postmenopausal women from their estrogen level decline, which plays a crucial role in bone metabolism [9, 11-13]. Additionally, advancing age is a major risk factor [14], as bone density naturally decreases with age, particularly after the third decade of life [15]. Modifiable risk factors, which include lifestyle choices, medical conditions, and dietary factors, can impair bone metabolism and increase the risk of osteoporosis [16]. However, many of these modifiable risk factors can fortunately be prevented or mitigated through targeted interventions. Dietary supplementation with calcium and vitamin D, regular physical activity, smoking cessation, and moderation of alcohol intake can significantly reduce the risk of osteoporosis [17, 18]. Physical activity is an important modifiable factor, as regular weight-bearing and resistance exercises have been shown to improve bone density and reduce the risk of osteoporosis [19]. Understanding these factors and their interplay is essential for developing effective strategies to reduce the burden of osteoporosis on individuals and society.

Osteoporosis is a multifactorial and polygenic disease that results from the interactions of several genes and environmental factors [20, 21]. There is a clear need to identify reliable biomarkers of poor bone quality. Although researchers have performed considerable studies to find specific genes that underlie osteoporosis [22-25], most of its heritability remains unexplained. Nevertheless, researchers have been intrigued by the collagen gene, which has been most frequently studied for its association with low BMD or fracture [26].

The *major alpha chain of the collagen type I* (*COL1A1*) gene is a member of the collagen gene family. Many single nucleotide polymorphisms (SNPs) have been identified in this gene, which was associated with osteoporosis or fracture risk. The rs1800012 (G > T) SNP is located in the 5' untranslated region (5' UTR) of the *COL1A1* gene. Of the *COL1A1* SNPs examined, rs1800012 showed one of the strongest associations with the risk of osteoporosis or fracture. To date, various articles related to the *COL1A1* rs1800012 SNP and osteoporosis or fracture risk have been published [27-29]. However, inconsistencies in the *COL1A1* rs1800012 variant effect sizes have rendered it unclear if *COL1A1* is truly associated with osteoporosis or fractures.

To confirm if *COL1A1* rs1800012 impacts osteoporosis or fracture, as well as to determine the heterogeneity across rs1800012 SNP-related studies, we performed a meta-analysis of the existing data. This involved performing a gene-based test of the association between *COL1A1* and osteoporosis or fracture risk.

Materials and methods

Literature search

A systematic search of the association between *COL1A1* and BMD and/or fracture susceptibility was conducted by collecting articles in PubMed and Google Scholar that were published between 1996 and 2016. The following search terms were used: "*COL1A1* or *major alpha chains of the collagen type I*", "genetic polymorphism or variation", "Sp1 or rs1800012 or *COL1A1* + 1245G/T", "low bone mineral density", "osteoporosis", and "fracture". We reviewed the abstracts to identify any studies that described an association between *COL1A1* gene polymorphisms and osteoporosis and/or fractures. The results were collated, then duplicate data were eliminated. All references cited in these studies were also investigated to find additional publications that were missed in the original search. Finally, we applied specific criteria to the identified studies to determine their inclusion or exclusion in the present meta-analysis, as described below.

Inclusion and exclusion criteria

The following criteria were applied to select articles for inclusion in the meta-analysis: (1) independent case-control studies that were designed to examine the association between *COL1A1* rs1800012 and low BMD or fracture; (2) the rs1800012 genotype frequencies met Hardy-Weinberg equilibrium (HWE) in healthy controls ($P > 0.05$); (3) the studies presented original data on genotype or allele distribution to calculate odds ratios (ORs); (4) the studies must have included BMD or fracture diagnoses made by either World Health Organization (WHO) criteria or using standard diagnostic

instruments; and (5) the studies did not restrict the language.

The following criteria were applied to exclude studies from the meta-analysis: (1) studies that included non-original data; (2) studies with insufficient information on genotype frequency; (3) studies that did not use a case-control design; and (4) studies that used non-human subjects or specimens.

Data extraction

We collected certain data from each available study, which included the following: (1) author's first name; (2) year of publication; (3) country of origin; (4) ethnicity of the study population; (5) number of cases and controls; (6) study design; and (7) *COL1A1* rs1800012 polymorphism genotype counts. If HWE in the controls was not reported, an online program (https://ihg.gsf.de/cgi-bin/hw/hwa1.pl) was used to test the HWE by chi-squared tests for goodness of fit. The articles were assessed by two reviewers using the inclusion criteria, then the disagreement terms were addressed by a third investigator. After this process was completed, 30 studies with 32 independent samples were included in this meta-analysis.

Meta-analysis methods

The Stata11.0 statistical software package (http://www.stata.com/) was used to measure and analyze the rs1800012 genotypes. The intensity of the association between rs1800012 and the osteoporosis or fracture risk was calculated from the ORs with 95% confidence intervals (CIs). We calculated the pooled ORs for the allelic model (T versus G), homozygote model (TT versus GG), heterozygote model (TG versus GG), dominant model (TT + TG versus GG), and recessive model (TT versus TG + GG). Cochran's Q statistic and I^2 tests were used to test the heterogeneity between studies. If the Q test showed a *P*-value < 0.05 or I^2 was > 50%, which indicates significant heterogeneity, the random effect model was used to combine the effect sizes of the included studies. Additionally, the fixed effect model and random effect *P*-values were identical when no heterogeneity was present. Potential publication bias was estimated using the Begg test. Funnel plot asymmetry was used to analyze and display Egger's results.

Results

Eligible studies selected for the COL1A1 and BMD/fracture meta-analysis

After applying the inclusion and exclusion criteria, a total of 26 European populations [27, 30-50], two North American populations [28, 42], one Asian population [29], and one Oceania population [51] were identified in 30 case-control studies that contained 2,943 osteoporosis or fracture patients and 4,724 control subjects. The basic information of each included study is listed in **Table 1**. As shown in **Figure 1**, the detailed literature screening process resulted in 797 articles that were retrieved using different combinations of key term searches. After reviewing the titles and abstracts, 596 of these studies were excluded. Of the 201 remaining studies that potentially showed an association between *COL1A1* and osteoporosis or fracture risk, 175 were further excluded for either not being candidate locus studies or containing insufficient data.

In the included studies, osteoporosis or fracture diagnosis in all patients followed the WHO criteria or used standard diagnostic instruments [3]. Blood samples were collected, while DNA was dissolved from whole blood leukocyte samples in all studies. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays were used for genotyping in 20 studies and TaqMan genotyping assays were performed in six studies. HWE testing was conducted to evaluate the control sample genotype distributions in all studies. The results indicated that no studies deviated from HWE ($P > 0.05$).

Meta-analysis results

The pooled ORs for *COL1A1* rs1800012 and osteoporosis or fracture risk are listed in **Table 2**. The homozygote model (TT vs. GG) showed a significant fixed effects pooled OR (OR = 1.968, 95% CI = 1.546-2.505, $P < 0.001$, **Figure 2**). We also observed a significantly increased risk of osteoporosis or fracture in the dominant model (TT + TG vs. GG: OR = 1.482, 95% CI = 1.220-1.802, $P < 0.001$, Supplementary Figure 1A). Additionally, significant associations were found in the allelic model (T vs. G: OR = 1.416, 95% CI = 1.226-1.635, $P < 0.001$, Supplementary Figure 1B), recessive

Table 1. Characteristics of relevant studies included in meta-analysis and genotypic frequencies of *COL1A1* rs1800012

First Authors	Year	Country	Ethnic group	Bone quality	Genotyping method	Sample Size	Case			Control		
						Case/control	GG	GT	TT	GG	GT	TT
Huili Jin	2008	Royal	Europe	Fracture	PCR-RFLP	98/143	66	28	4	95	44	4
Joanna	2016	Poland	Europe	Fracture	PCR-RFLP	82/229	54	23	5	150	74	5
Selezneva	2008	Russian	Europe	Fracture	PCR-RFLP	124/150	89	34	1	128	22	0
Edith	2015	Mexico	North America	Fracture	TaqMan	100/100	80	19	1	88	12	0
Urreizti	2011	Barcelona	Europe	Fracture	TaqMan	101/397	61	35	5	243	133	21
Urreizti	2011	Cantabria	Europe	Fracture	TaqMan	102/397	61	36	5	243	133	21
Blades	2010	Sheffield	Europe	Fracture	PCR-RFLP	195/183	121	72	2	124	54	5
Stergioti	2013	Helsinki	Europe	BMD	PCR-RFLP	40/10	31	7	2	9	1	0
Mikhail	2013	Caucasians	Europe	BMD	PCR-RFLP	43/153	30	13	0	107	44	2
Korvala	2010	Finnish	Europe	Fracture	PCR-RFLP	72/120	53	17	2	85	34	1
Morteza	2015	Iran	Asian	BMD	PCR-RFLP	130/70	12	98	20	40	22	8
Український	2015	Київ	Europe	BMD	PCR-RFLP	44/30	10	16	18	18	8	4
Aerssens	2000	European	Europe	Fracture	PCR-RFLP	135/239	93	35	7	151	73	15
DANIEL	2003	European	Europe	Fracture	PCR-RFLP	17/116	10	2	5	75	35	6
BERNAD	2002	Spanish	Europe	Fracture	TaqMan	82/98	41	20	21	48	44	6
BERNAD	2002	Spanish	Europe	BMD	TaqMan	139/98	68	62	9	48	44	6
Husted	2008	Denmark	Europe	Fracture	TaqMan	228/224	155	64	9	156	62	6
Husted	2008	Denmark	Europe	Fracture	TaqMan	62/57	41	18	3	35	21	1
Hustmyer	1999	USA	North America	Fracture	PCR-RFLP	56/78	35	19	2	58	16	4
Hustmyer	1999	U.K.	Europe	Fracture	PCR-RFLP	55/205	26	26	3	124	72	9
Lidén	1998	Sweden	Europe	BMD	PCR-RFLP	64/72	45	18	1	48	22	2
McGuigan	2000	U.K.	Europe	Fracture	TaqMan	93/88	54	33	6	70	17	1
McGuigan	2001	U.K.	Europe	Fracture	PCR-RFLP	30/155	16	11	3	113	41	1
McGuigan	2001	U.K.	Europe	Fracture	PCR-RFLP	9/147	6	2	1	92	45	10
Mezquita	2002	Spain	Europe	Fracture	PCR-RFLP	43/101	13	26	4	54	43	4
Tuan	2005	Australia	Australia	Fracture	TaqMan	69/608	38	24	7	395	186	27
Peris	2000	Spain	Europe	Fracture	PCR-RFLP	35/60	17	16	2	48	11	1
Christian Roux	1998	French	Europe	BMD	PCR-RFLP	110/107	68	40	2	81	24	2
Stiina	2001	Finland	Europe	BMD	PCR-RFLP	402/111	271	120	11	81	27	3
Weichetova	2004	Czech Republic	Europe	Fracture	PCR-RFLP	183/178	108	65	10	127	44	7

COL1A1: major alpha chain of the collagen type I.

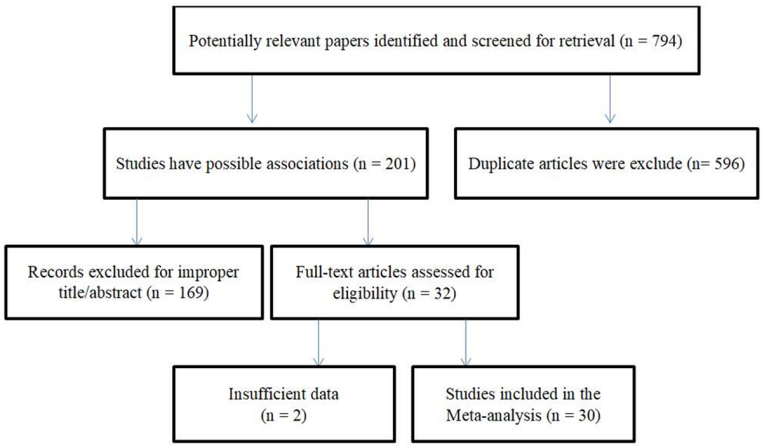

Figure 1. Flow chart of literature search and relevant study selection.

model (TT vs. GG + TG: OR = 1.691, 95% CI = 1.334-2.143, *P* < 0.001, Supplementary Figure 1C), and heterozygote model (TG vs. GG: OR = 1.393, 95% CI = 1.132-1.713, *P* = 0.002, Supplementary Figure 1D).

We then performed sub-group analyses to investigate the effects of bone quality and ethnicity on the risk. For bone quality, an increased osteoporosis risk was found in the homozygote model (TT vs. GG: OR = 2.454, 95% CI = 1.479-4.071, *P* = 0.001, **Figure 3**), dominant model (TT + TG vs. GG: OR = 1.985, 95% CI = 1.058-3.724, *P* = 0.033, Supplementary Figure 2A), and allelic model (T vs. G: OR = 1.553, 95% CI = 1.042-2.317, *P* = 0.031, Supplementary Figure 2B). However, no significant association between *COL1A1* rs1800012 and osteoporosis risk was observed in the recessive model (TT vs. GG + TG: OR = 1.456, 95% CI = 0.899-2.358, *P* = 0.127, Supplementary Figure 2C) or heterozygote model (TG vs. GG: OR = 2.070, 95% CI = 0.888-4.828, *P* = 0.092, Supplementary Figure 2D). Furthermore, the results showed that there was a statistically significant increased fracture risk in the allelic model (T vs. G: OR = 1.365, 95% CI = 1.180-1.578, *P* < 0.001, Supplementary Figure 2B), dominant model (TT + TG vs. GG: OR = 1.352, 95% CI = 1.137-1.607, *P* = 0.001, Supplementary Figure 2A), recessive model (TT vs. GG + TG: OR = 1.781, 95% CI = 1.359-2.334, *P* < 0.001, Supplementary Figure 2C), homozygote model (TT vs. GG: OR = 1.829, 95% CI = 1.388-2.411, *P* < 0.001, **Figure 3**), and heterozygote model (TG vs. GG: OR = 1.926, 95% CI = 1.373-2.702, *P* < 0.001, Supplementary Figure 2D).

However, ethnicity greatly affected osteoporosis or fracture susceptibility. In Europeans, there was a statistically significant increased low BMD or fracture risk in the allelic model (T vs. G: OR = 1.345, 95% CI = 1.162-1.557, *P* < 0.001, Supplementary Figure 3A), dominant model (TT + TG vs. GG: OR = 1.332, 95% CI = 1.125-1.577, *P* = 0.001, Supplementary Figure 3B), recessive model (TT vs. GG + TG: OR = 1.708, 95% CI = 1.317-2.213, *P* < 0.001, Supplementary Figure 3C), homozygote model (TT vs. GG: OR = 1.771, 95% CI = 1.360-2.307, *P* < 0.001, Supplementary Figure 3D), and heterozygote model (TG vs. GG: OR = 1.223, 95% CI = 1.086-1.376, *P* = 0.001, Supplementary Figure 3E). In North Americans, we also found a statistically significant increased low BMD or fracture risk in the dominant model (TT + TG vs. GG: OR = 1.784, 95% CI = 1.043-3.051, *P* = 0.035, Supplementary Figure 3B) and heterozygote model (TG vs. GG: OR = 1.849, 95% CI = 1.061-3.223, *P* = 0.030, Supplementary Figure 3E). However, no significant associations were observed between *COL1A1* rs1800012 and osteoporosis or fracture risk in the allelic model, recessive model, or homozygote model in the North American population (Supplementary Figure 3).

Heterogeneity and sensitivity tests

Between-study heterogeneity was observed in our meta-analysis of the *COL1A1* rs1800012 polymorphism and osteoporosis or fracture risk (**Table 2**). Thus, the random effects model was used in the allelic, dominant, and heterozygote models. The source of heterogeneity was investigated by bone quality (low BMD or fracture) and ethnicity (studies with European participants were categorized as "Europe" and studies with participants of other ethnicities were categorized as "No Europe") with meta-regression in the allelic, dominant, and heterozygote models. The meta-regression results revealed that ethnicity significantly contributed to the source of heterogeneity in the dominant model (*P* = 0.034) and heterozygote model (*P* = 0.025), but not in the allelic model (*P* = 0.116). However,

Table 2. Main result of pooled ORs of *COL1A1* rs1800012 (G > T) polymorphism

	T versus G			GT versus GG			TT versus GG			TT + GT versus GG			TT versus TG + GG		
	OR	95% CI	I^2 (%)	OR	95% CI	I^2 (%)	OR	95% CI	I^2 (%)	OR	95% CI	I^2 (%)	OR	95% CI	I^2 (%)
Overall	1.416	1.226-1.635*	57.1	1.393	1.132-1.713*	66.8	1.968	1.546-2.505*	30.8	1.48	1.220-1.802*	66.1	1.691	1.334-2.143*	14.1
Ethnicity															
Europe	1.345	1.162-1.557*	52.4	1.223	1.086-1.376*	48.5	1.771	1.360-2.307*	23.1	1.33	1.125-1.577*	49.0	1.708	1.317-2.213*	21.3
North American	1.580	0.980-2.560	0.0	1.849	1.061-3.223*	0.0	1.180	0.280-5.070	0.0	1.78	1.043-3.051*	0.0	1.000	0.240-4.200	0.0
Bone Quality															
Fracture	1.365	1.180-1.578*	46.4	1.926	1.373-2.702*	20.2	1.829	1.388-2.411*	20.2	1.35	1.137-1.607*	46.1	1.781	1.359-2.334*	22.5
BMD	1.553	1.042-2.317*	74.0	2.070	0.888-4.828	52.9	2.454	1.479-4.071*	52.9	1.99	1.058-3.724*	83.9	1.456	0.899-2.358	0.0

OR: odds ratio; 95% CI: 95% confidence intervals; I^2: Heterogeneity test; *COL1A1: major alpha chain of the collagen type I.* *indicates statistical significance.

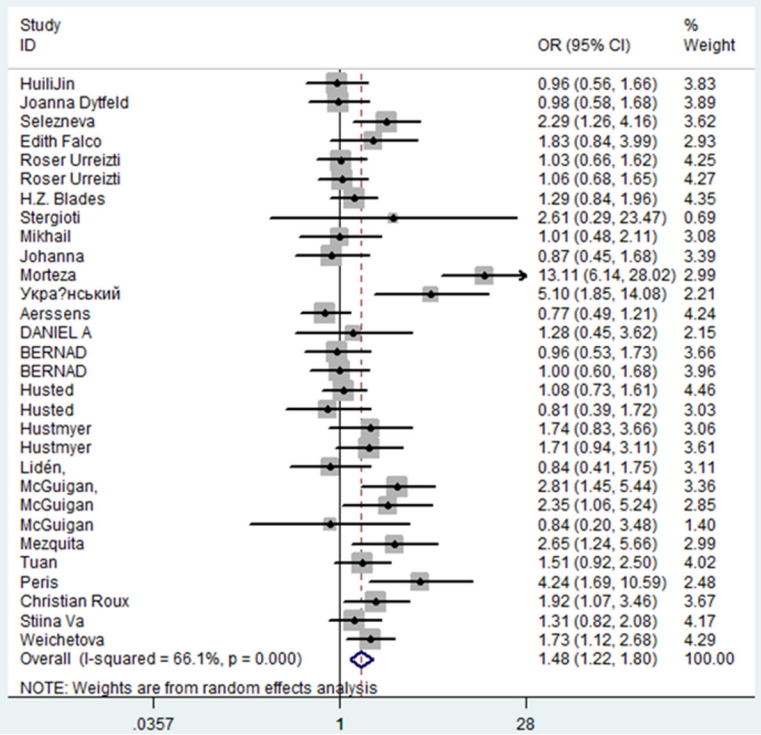

Figure 2. The image showing forest plots of *COL1A1* rs1800012 polymorphism was associated with low BMD or fracture: homozygote model (TT versus GG).

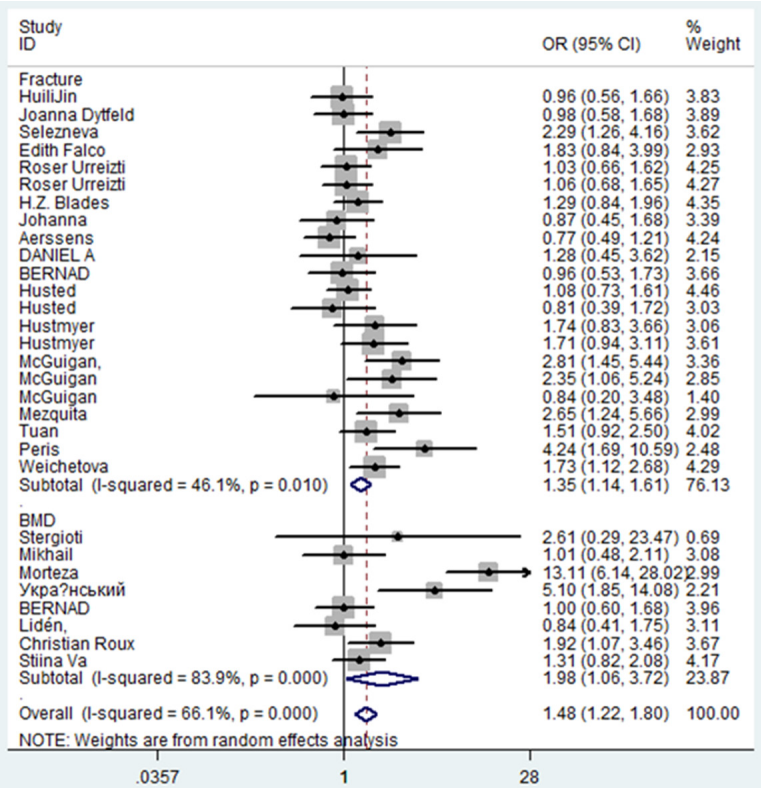

Figure 3. The image showing forest plots of *COL1A1* rs1800012 polymorphism in bone quality subgroup: homozygote model (TT versus GG).

bone quality was not significantly associated with the source of heterogeneity in the allelic model (P = 0.571), dominant model (P = 0.232), or heterozygote model (P = 0.176). Additionally, ethnicity could explain 22.46% of the between-study variance (τ^2) in the dominant model and 23.33% of the variance (τ^2) in the heterozygote model.

A sensitivity test was performed to examine the stability of each study on the overall pooled ORs. The results demonstrated that no individual study significantly affected the pooled ORs (data not shown).

Publication bias test

Publication bias was assessed using Begg's funnel plot (**Figure 4**) and Egger's test. The results showed that Begg's funnel plot was roughly symmetrical in the allelic model, dominant model, recessive model, homozygote model, and heterozygote model in this meta-analysis. However, Egger's test showed statistical evidence for publication bias in the allelic model and dominant model (P = 0.034 and P = 0.033, respectively). Further investigation revealed that the study reported by J. Aerssens et al. [38] was responsible for the Egger's test results. After removing this study, there was no evidence of publication bias in the allelic model (P = 0.055) or dominant model (P = 0.053). Furthermore, the pooled ORs were still significant in all hereditary models and the heterogeneity between studies also decreased.

Discussion

In this study, the association between the *COL1A1*

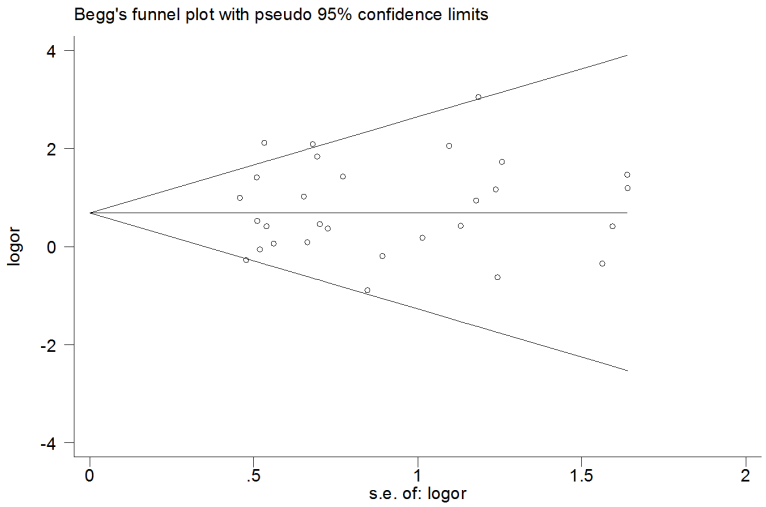

Figure 4. Begg's funnel plot for the publications bias under homozygote model (TT versus GG).

rs1800012 polymorphism and fracture or osteoporosis risk was investigated in a cohort of 2,943 patients and 4,724 controls from 30 case-control studies. Our study confirms and extends the observations made in three previously reported meta-analyses in which the *COL1A1* rs1800012 polymorphism was found to be significantly associated with osteoporotic fractures and osteoporosis [52-54]. Combining the data from these published articles showed that the rs1800012 SNP might be related to fracture or osteoporosis risk.

The overall results suggested that all the genetic models demonstrated the relevance of the "T" allele of *COL1A1* rs1800012 in the fracture or osteoporosis risk. However, the between-study heterogeneity in the meta-analysis could not be ignored. The reasons underlying this heterogeneity were unclear, but could possibly reflect that the osteoporosis values in the subjects were not equal to osteoporosis. In addition, ethnicity-related genetic differences also likely contributed to the substantial heterogeneity in the effect strength across different studies. Thus, we performed subgroup analyses by fracture or osteoporosis and ethnicity to reduce the heterogeneity with the allelic, homozygote, heterozygote, dominant, and recessive models.

With the homozygote model of *COL1A1* rs1800012, the effect size was a 1.829-fold increased fracture risk, which was very similar to the previously reported results that the fracture risk was 1.31-fold [53], 1.68-fold [54] and 1.78-fold [52] higher, respectively, in "TT" homozygotes. In addition, we found that "GT" heterozygotes were associated with a 1.926-fold increased risk of any fracture. This was consistent with the findings reported in the Zoe et al. (1.25-fold) [54] and Mann et al. (1.26-fold) [52] meta-analyses, but not with the results of a previous meta-analysis by Jin et al. [53]. The modest increase in the risk of any fracture found in this study was also driven mainly by the allelic, dominant, and recessive models, which were not included in the results of the previous meta-analysis.

We also observed a significant association between the *COL1A1* rs1800012 polymorphism and osteoporosis risk with the allelic, homozygote, and dominant models. The genotype-specific differences reported here were slightly similar to those reported in a previous meta-analysis, which included 32 studies [53]. However, the differences were not significant with the heterozygote and recessive models, likely because different body sites have varied susceptibilities to reduced BMD.

After stratifying by ethnicity, the rs1800012 polymorphism was found to be related to increased fracture or osteoporosis risk. Additionally, in this study, we found a difference in fracture or osteoporosis risk for the European population with all genetic models, which was not included in the results of the previous meta-analysis.

Although we made a meticulous effort to identify all relevant data, there are some limitations of our meta-analysis that should be noted. First, the heterogeneity was not reduced in the further stratified analysis. Moreover, publication bias was found in the allelic and dominant models in this study. Further sensitivity analysis found the main source of publication bias to be the study conducted by Aerssens [38]. After removing this study, no significant publication

bias was observed. This is likely because the Aerssens study enrolled hip fracture cases of female patients ranging in age from 70 to 90 years old, while the other studies enrolled cases without such rigorous and specific inclusion criteria. Finally, different gender distributions, fracture or osteoporosis in a different body region, average case group age, and the study year all contributed to the heterogeneity. However, we did not analyze this heterogeneity using the above subgroups because of insufficient data.

Conclusion

This meta-analysis confirmed that the *COL1A1* rs1800012 polymorphism was associated with fracture susceptibility. Additionally, we found a significant association between the *COL1A1* rs1800012 polymorphism and osteoporosis risk. Importantly, the fractures could be predicted by the *COL1A1* rs1800012 genotype, as well as by the mechanisms of the effect on osteoporosis. However, even if the results of this study were stable, the rs1800012 SNP accounts for only a small proportion of the genetic risk of osteoporosis. Because of the subtle nature and increasing complexity of genetic effects, a larger patient sample size is required to achieve a reasonable statistical power to test these results.

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Disclosure of conflict of interest

None.

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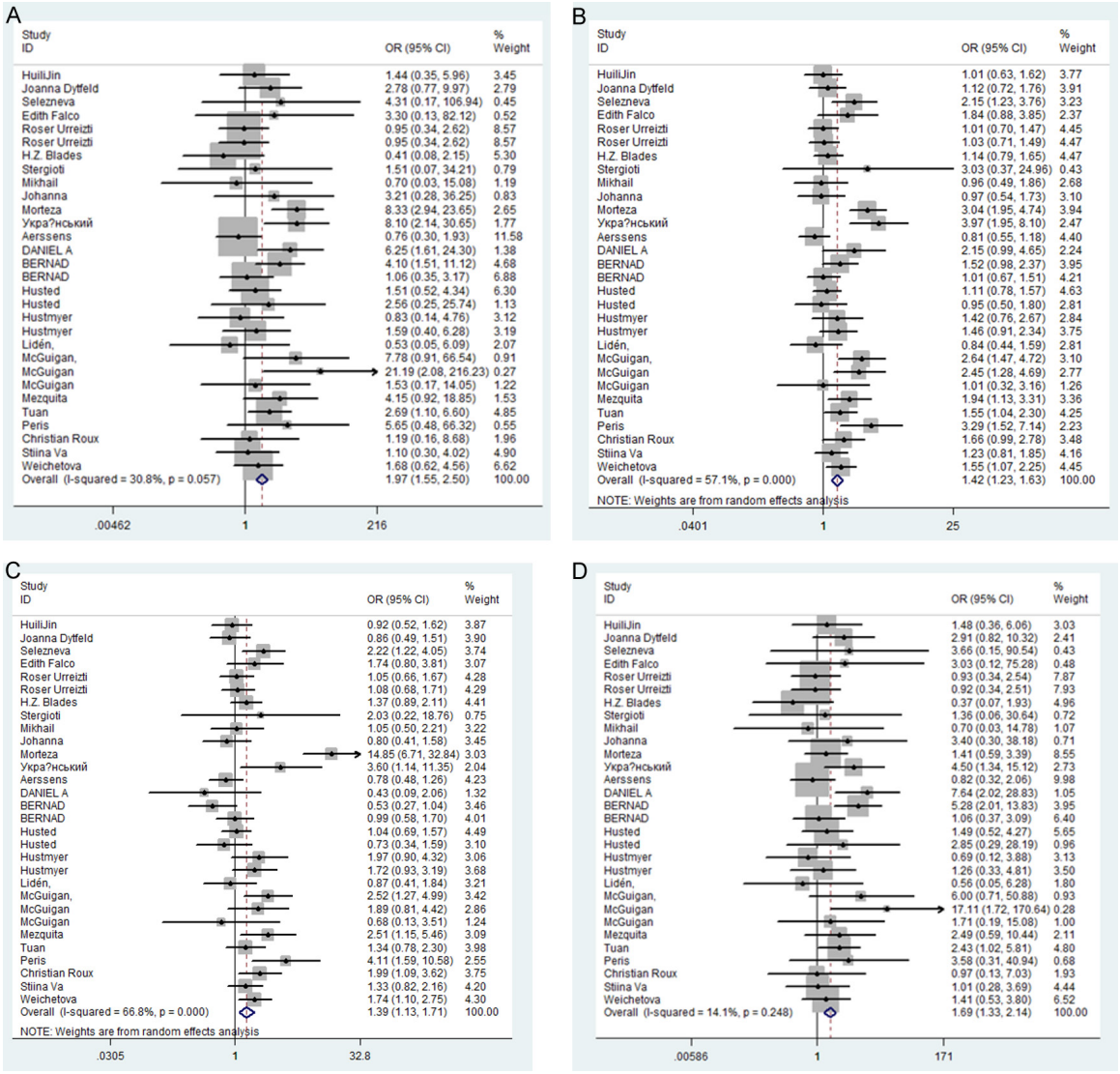
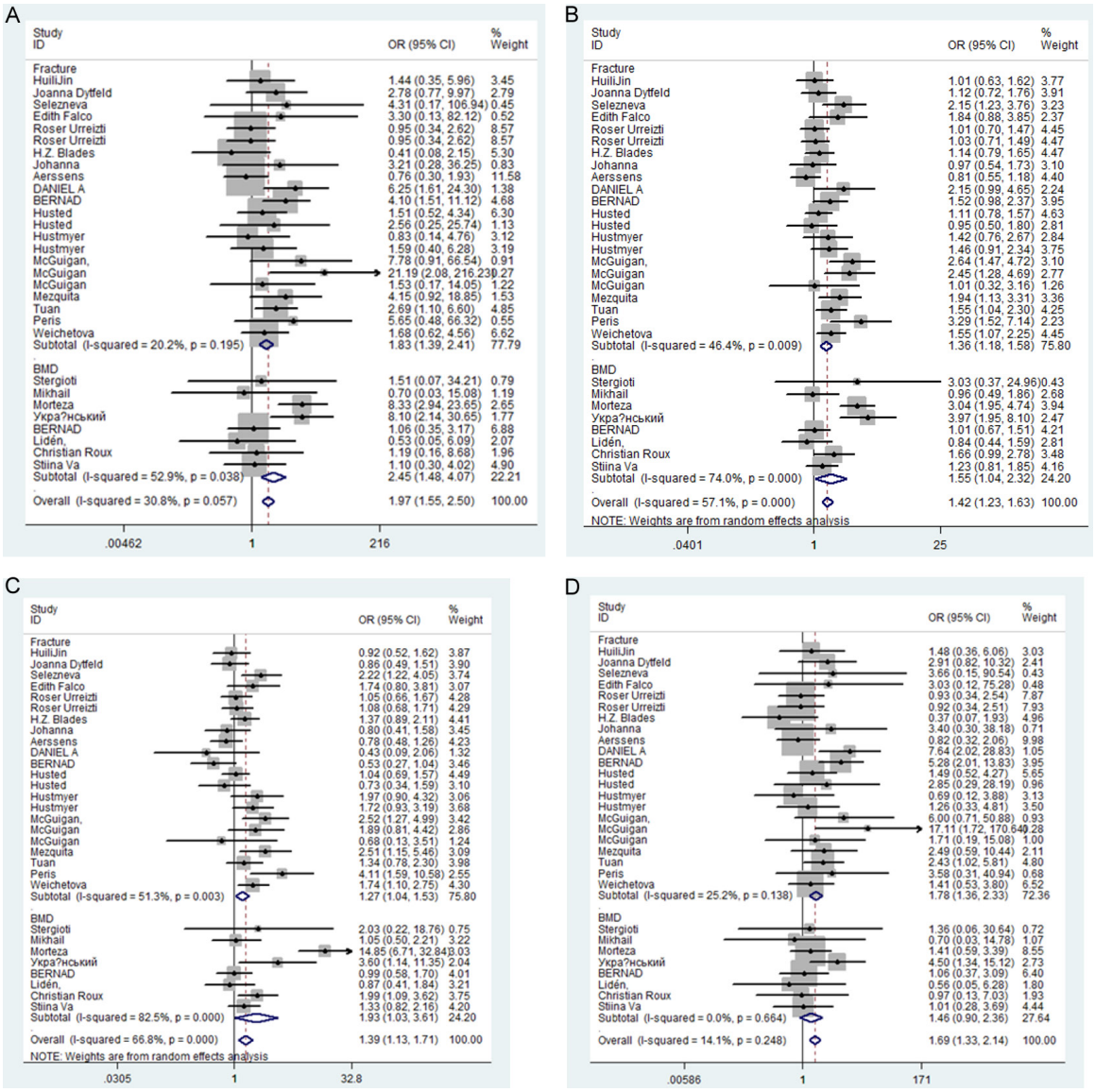
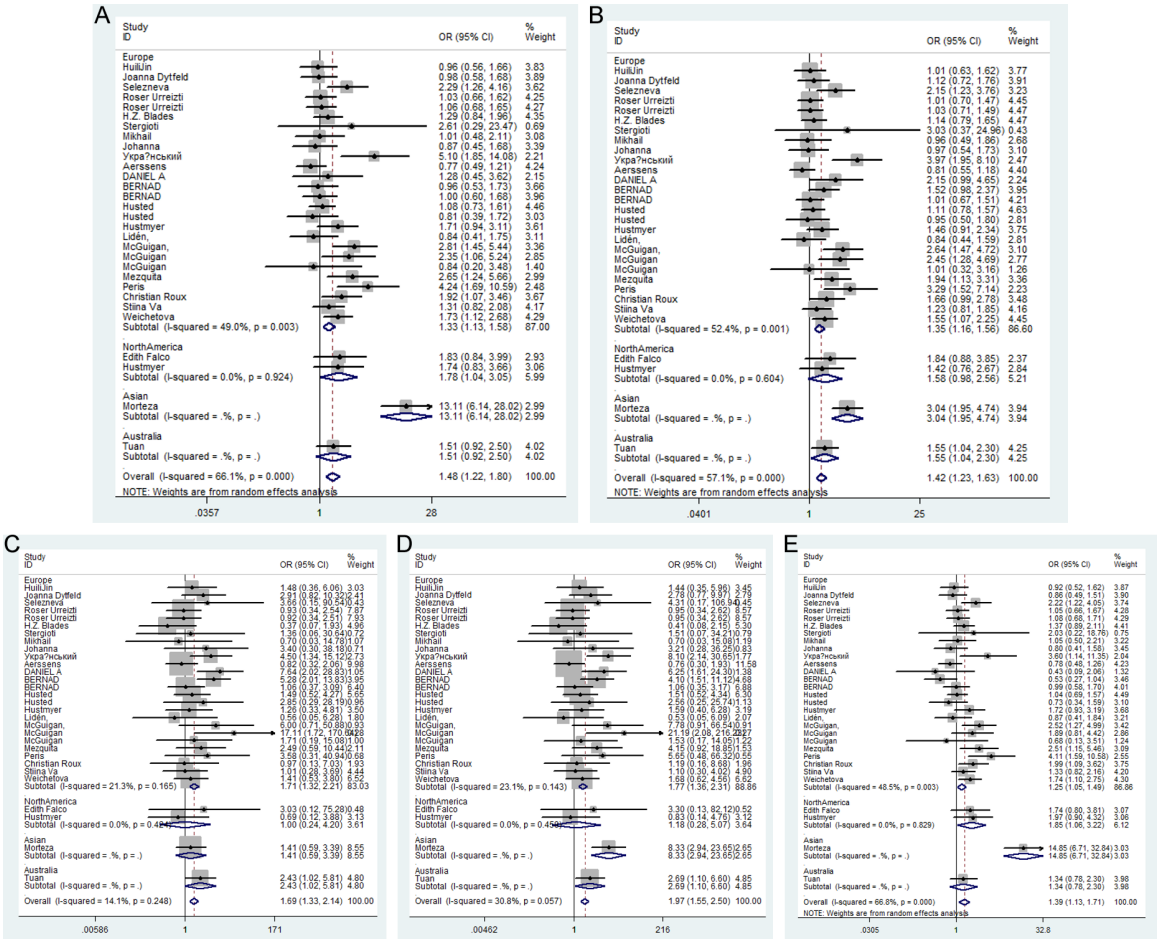


Supplementary Figure 1. Figure showing forest plots of *COL1A1* rs1800012 polymorphism was associated with low BMD or fracture: (A) dominant model (TT + TG versus GG), (B) allelic model (T versus G) homozygote model (TT versus GG), (C) recessive model (TT versus TG + GG) and (D) heterozygote model (TG versus GG).



Supplementary Figure 2. Figure showing forest plots of *COL1A1* rs1800012 polymorphism in bone quality subgroup: (A) dominant model (TT + TG versus GG), (B) allelic model (T versus G) homozygote model (TT versus GG), (C) recessive model (TT versus TG + GG) and (D) heterozygote model (TG versus GG).



Supplementary Figure 3. Figure showing forest plots of *COL1A1* rs1800012 polymorphism in ethnicity subgroup: (A) allelic model (T versus G), (B) homozygote model (TT versus GG), (C) heterozygote model (TG versus GG), (D) dominant model (TT + TG versus GG) and (E) recessive model (TT versus TG + GG).