

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

A meta-analysis

Yuqin Peng, MD^a, Xiaowen Sheng, MD^a, Feng Xue, MD^a, Yufeng Qian, MD^{a,b,*}

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 GC 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, <math>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

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^a Department of Orthopedics, The First Affiliated Hospital of Suzhou University, Suzhou, ^b Department of Orthopedics, Changshu First People's Hospital, Changshu, People's Republic of China.

^{*} Correspondence: Yufeng Qian, Department of Orthopedics, Changshu First People's Hospital, Changshu 215500, People's Republic of China (e-mail: yarbj@163.com).

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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

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 metaanalysis. 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-squarebased Cochran Q test and Higgins I-squared statistic (I² = $100\% \times (Q-df)/Q$). If significant heterogeneity was observed across studies (P < .05 or I² > 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 < .05indicated 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

| The characteres of i | ncluded | studies. | | | | | | |
|--------------------------------------|---------|-----------------|--------|---------------------|---------------------|---------------|-------------------------------|------------|
| First author | Year | Ethnicity | Number | Age | BMI (kg/m²) | 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 | 7 |
| o i o i ^[45] | 0010 | | 500 | 00.0.05 | 00.0 4.0 | | (0.49), 1245G (0.09) | - |
| | 2013 | Maya-Mestizo | 580 | 60.0 ± 8.5 | 29.9 ± 4.8 | LS,FH,TH | G1181C (0.34) | / |
| Garcia-Unzueta ^[20] | 2008 | Spain | 332 | 61 ± 7.86 | NA | LS,FH, IH | A163G (0.13), G1181C | 6 |
| Kim ^[29] | 2007 | Korean | 297 | 57.7±0.4 | 24.2±0.2 | LS,FH,TH | G1181C (0.29), T245G | 7 |
| | | | | | | | (0.09) | |
| Langdahl ^[32] | 2002 | Finland | 216 | 64.2 ± 9.2 | NA | LS,FH,TH | A163G (0.20), G1181C | 6 |
| | | | | | | | (0.56), 1245G (0.07), 1950C | |
| Mancai Radrac ^[28] | 2011 | Slovonia | 1/2 | 644 92 | 262.28 | | (U.31) C1181C (0.51) T245C | 7 |
| Mericej-Deurac | 2011 | Siuverila | 145 | 04.4 <u>±</u> 0.2 | 20.2±3.0 | L0,I 11, I 11 | (0.07) | 1 |
| 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 | 8 |
| | | | | | | | (0.54), T245G (0.12), T950C | |
| | | | | | | | (0.48) | |
| Shang ^[38] | 2013 | Chinese | 235 | 52.8±3.2 | 23.9±3.0 | LS,FH,TH | A163G (0.14), G1181C | 7 |
| | | | | | | | (0.30) | |
| Ueland ^[33] | 2007 | Australian | 980 | 75.0±3.0 | NA | FH,TH | A163G (0.13), G1181C | 6 |
| | | | | | | | (0.52), T950C (0.52) | |
| Wynne ^[34] | 2002 | Irish | 130 | 61.26±11.75 | NA | LS,FH,TH | G1181C (0.20), T950C | 6 |
| [01] | | | | | | | (0.46) | |
| Zhao | 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 | 7 |
| . [41] | | | | | | | (0.55), T950C (0.15) | |
| Cheng ^[+1] | 2011 | Chinese | 99 | 78.2 ± 7.6 | 24.2 ± 3.7 | LS | T245G (0.17) | 8 |
| Yamada ^[33] | 2003 | Japanese | 818 | 64.0 ± 0.3 | NA | LS,FH,TH | 1245G (0.12), 1950C (0.40) | 6 |
| Wu ^[+0,00] | 2007 | Chinese | 73 | 64.59 ± 5.9 | 22.534 ± 3.015 | LS,FH,TH | 1245G (0.69), 1950C (0.35) | 7 |
| | 2004 | Chinese | 141 | $5/.0 \pm 4.0$ | NA | LS,FH,TH | 1950C (0.27) | 6 |
| | 2004 | Chinese | 118 | 70.0 ± 4.0 | NA | LS,FH,TH | 1950C (0.27) | 6 |
| LIU | 2010 | Chinese | 100 | //.55 <u>+</u> 8.01 | 23.41 <u>+</u> 3.43 | LS,FH,TH | 1950C (0.48) | 1 |

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 metaanalysis (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).

| | | GG | | | CC | | | Std. Mean Difference | | Sto | . Mean Differ | ence | |
|--|--|---|---|---|--|---|--|---|--------------|--------------------------------------|---|--|-----|
| Study or Subaroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random, 95% C | | IV | Random, 95 | % CI | |
| Boroň 2015 | 0.806 | 0.08 | 80 | 0.792 | 0.08 | 72 | 8.0% | 0.17 [-0.14, 0.49] | | 1013 | | 0.000 | |
| Boroňová 2015 | 0.78 | 0.07 | 57 | 0.85 | 0.07 | 86 | 8.0% | -0.99 [-1.35, -0.64] | | | 1 | | |
| Canto-Cetina 2013 | 0.989 | 0.164 | 261 | 0.984 | 0.166 | 78 | 8.2% | 0.03 [-0.22, 0.28] | | | 1 | | |
| García-Unzueta 2008 | 0.832 | 0.127 | 83 | 0.904 | 0.136 | 72 | 8.0% | -0.55 [-0.87, -0.22] | | | 1 | | |
| Kim 2007 | 0.992 | 0.012 | 156 | 1.081 | 0.035 | 36 | 7.3% | -4.79 [-5.39, -4.18] | | | • | | |
| Langdahl 2002 | 0.746 | 0.143 | 37 | 0.768 | 0.146 | 61 | 7.8% | -0.15 [-0.56, 0.26] | | | 1 | | |
| Mencej-Bedrac 2011 | 0.714 | 0.095 | 61 | 0.747 | 0.08 | 64 | 8.0% | -0.37 [-0.73, -0.02] | | | 1 | | |
| Moffett 2008 | 0.84 | 0.17 | 1358 | 0.87 | 0.17 | 1984 | 8.4% | -0.18 [-0.25, -0.11] | | | 1 | | |
| Rojano-Mejía 2012 | 0.861 | 0.131 | 243 | 0.836 | 0.155 | 124 | 8.2% | 0.18 [-0.04, 0.40] | | | t - | | |
| Seremak-Mrozikiewicz 2011 | 0.81 | 0.08 | 27 | 0.83 | 0.06 | 39 | 7.6% | -0.29 [-0.78, 0.21] | | | 1 | | |
| Shang 2013 | 0.975 | 0.137 | 107 | 1.037 | 0.144 | 15 | 7.5% | -0.45 [-0.99, 0.10] | | | 1 | | |
| wynne 2002 | 1.01 | 0.18 | 60 | 0.98 | 0.19 | 15 | 7.4% | 0.16 [-0.40, 0.73] | | | 1 | | |
| Zhao 2005 | 0.92 | 0.02 | 85 | 1.028 | 0.01 | 9 | 5.6% | -5.54 [-6.60, -4.48] | | | | | |
| Total (95% CI) | | | 2615 | | | 2655 | 100.0% | -0.85 [-1.29, -0.41] | | | | | |
| Heterogeneity: $Tau^2 = 0.60$ | $Chi^2 = 36!$ | 5 48 df | = 12 (P | < 0.00 | 001)- 12 | = 97% | | | 1 | - 1- | | + | |
| . Test for overall effect: Z = 3 | .79 (P = 0. | .0002) | | 0.00 | | 01 /0 | | | -100 | -50 | 0 | 50 | 100 |
| A | | · · · · · | | | | | | | | | GG CC | | |
| | | GG | | | GC | | | Std. Mean Difference | | Std | . Mean Differe | ence | |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random, 95% CI | | IV. | Random, 95 | % CI | |
| Boroň 2015 | 0.806 | 0.08 | 80 | 0.797 | 0.1 | 175 | 8.5% | 0.10 [-0.17, 0.36] | | | | | |
| Boroňová 2015 | 0.78 | 0.07 | 57 | 0.8 | 0.06 | 171 | 8.1% | -0.32 [-0.62, -0.02] | | | 1 | | |
| Canto-Cetina 2013 | 0.989 | 0.164 | 261 | 0.99 | 0.146 | 241 | 9.5% | -0.01 [-0.18, 0.17] | | | 1 | | |
| García-Unzueta 2008 | 0.832 | 0.127 | 83 | 0.848 | 0.133 | 177 | 8.6% | -0.12 [-0.38, 0.14] | | | - t | | |
| Kim 2007 | 0.992 | 0.012 | 156 | 0.998 | 0.014 | 105 | 8.7% | -0.47 [-0.72, -0.22] | | | 1 | | |
| Langdahl 2002 | 0.746 | 0.143 | 37 | 0.738 | 0.126 | 118 | 7.3% | 0.06 [-0.31, 0.43] | | | t | | |
| Mencej-Bedrac 2011 | 0.714 | 0.095 | 61 | 0.753 | 0.086 | 118 | 8.0% | -0.44 [-0.75, -0.12] | | | 1 | | |
| Moffett 2008 | 0.84 | 0.17 | 1358 | 0.86 | 0.17 | 3316 | 10.4% | -0.12 [-0.18, -0.05] | | | t (| | |
| Rojano-Mejía 2012 | 0.861 | 0.131 | 243 | 0.847 | 0.139 | 383 | 9.7% | 0.10 [-0.06, 0.26] | | | t (| | |
| Seremak-Mrozikiewicz 2011 | 0.81 | 0.08 | 27 | 0.81 | 0.07 | 73 | 6.4% | 0.00 [-0.44, 0.44] | | | t | | |
| Shang 2013 | 0.975 | 0.137 | 107 | 0.953 | 0.146 | 113 | 8.5% | 0.15 [-0.11, 0.42] | | | 1 | | |
| Zhao 2005 | 0.92 | 0.02 | 85 | 0.958 | 0.02 | 40 | 6.4% | -1.89 [-2.33, -1.44] | | | 1 | | |
| Total (95% CI) | | | 2555 | | | 5030 | 100.0% | -0.21 [-0.39, -0.03] | | | | | |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. | Chi² = 90.4 29 (P = 0.0 | 48, df = 02) | 2555 11 (P < | 0.0000 | 1); 2 = | 5030 88% | 100.0% | -0.21 [-0.39, -0.03] | -100 | -50 | GG GC | 50 | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. | Chi² = 90.4 29 (P = 0.0 | 48, df = 02) GC | 2555 11 (P < | 0.0000 | 1); l ² = | 5030 88% | 100.0% | -0.21 [-0.39, -0.03] Std. Mean Difference | -100 | -50 Std | 0 GG GC | 50 ence | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> | Chi ² = 90.4 29 (P = 0.0 Mean | 48, df = 02) GC SD | 2555 11 (P < Total | 0.0000 | 1); l ² = CC SD | 5030 88% Total | 100.0% Weight | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random. 95% Cl | -100 | -50 Std | 0 GG GC . Mean Differ . Random. 95 | f 50 ence % CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 | Chi ² = 90.4 29 (P = 0.0 <u>Mean</u> 0.797 | 48, df = 02) GC SD 0.1 | 2555 11 (P < <u>Total</u> 175 | 0.0000 Mean 0.792 | 1); I ² = CC SD 0.08 | 5030 88% <u>Total</u> 72 | 100.0% Weight 8.9% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] | -100 | -50 Std | 0 GG GC I. Mean Differ Random, 95 | 50 ence % CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 | Chi ² = 90.4 29 (P = 0.6 <u>Mean</u> 0.797 0.8 | 48, df = 02) GC SD 0.1 0.06 | 2555 11 (P < <u>Total</u> 175 171 | 0.0000 Mean 0.792 0.85 | CC SD 0.08 0.07 | 5030 88% Total 72 86 | 100.0% Weight 8.9% 8.9% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random. 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] | -100 | -50 Std | 0 GG GC I. Mean Differ Random. 95 | 50 ence % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 | Chi ² = 90.4 29 (P = 0.0 <u>Mean</u> 0.797 0.8 0.99 | 48, df = 02) GC SD 0.1 0.06 0.146 | 2555 11 (P < Total 175 171 241 | 0.0000 Mean 0.792 0.85 0.984 | CC SD 0.08 0.07 0.166 | 5030 88% Total 72 86 78 | 100.0% Weight 8.9% 8.9% 9.0% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] | -100 | -50 Std | 0 GG GC . Mean Differ . Random. 95 | 50 ence % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 | Chi ² = 90.4 29 (P = 0.0 <u>Mean</u> 0.797 0.8 0.99 0.848 | 48, df = 02) GC 0.1 0.06 0.146 0.133 | 2555 11 (P < Total 175 171 241 177 | 0.0000 Mean 0.792 0.85 0.984 0.904 | CC SD 0.08 0.07 0.166 0.136 | 5030 88% Total 72 86 78 72 | Weight 8.9% 8.9% 9.0% 8.9% | -0.21 [-0.39, -0.03] Std. Mean Difference <u>IV. Random, 95% CI</u> 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] | -100 | -50 Std | 0 GG GC I. Mean Differ Random, 95 | i 50 ence % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 | Chi ² = 90.4 29 (P = 0.4 0.797 0.8 0.99 0.848 0.998 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 | 2555 11 (P < Total 175 171 241 177 105 | Mean 0.792 0.85 0.984 0.904 1.081 | 1); l ² = CC SD 0.08 0.07 0.166 0.136 0.035 | 5030 88% Total 72 86 78 72 36 | Weight 8.9% 8.9% 9.0% 8.9% 7.3% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random. 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] | -100 | -50 Std | 0 GG GC I. Mean Differ Random, 95 | i 50 ence % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 | Chi ² = 90.4 29 (P = 0.0 0.797 0.8 0.99 0.848 0.998 0.738 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 0.126 | 2555 11 (P < Total 175 171 241 177 105 118 | Mean 0.792 0.85 0.984 0.904 1.081 0.768 | 1); l ² = CC SD 0.08 0.07 0.166 0.035 0.146 | 5030 88% Total 72 86 78 72 36 61 | Weight 8.9% 8.9% 9.0% 8.9% 7.3% 8.8% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random. 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] | -100 | -50 Std | 0 GG GC I. Mean Differ Random. 95 | i 50 ence % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 | Chi ² = 90.4 29 (P = 0.0 <u>Mean</u> 0.797 0.8 0.99 0.848 0.998 0.738 0.753 | 48, df = 02) GC 0.1 0.06 0.146 0.133 0.014 0.126 0.086 | 2555 11 (P < Total 175 171 241 177 105 118 118 | 0.0000 Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.747 | 1); I ² = CC SD 0.08 0.07 0.166 0.035 0.146 0.08 | 5030 88% Total 72 86 78 72 36 61 64 | Weight 8.9% 8.9% 9.0% 8.9% 7.3% 8.8% 8.8% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random. 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] | -100 | + -50 Std | 0 GG GC I. Mean Differ Random, 95 | i 50 ence % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 | Chi ² = 90.4 29 (P = 0.0 0.797 0.8 0.99 0.848 0.998 0.738 0.753 0.86 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 0.126 0.086 0.17 | 2555 11 (P < Total 175 171 241 177 105 118 118 3316 | 0.0000 Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.747 0.87 | CC SD 0.08 0.07 0.166 0.035 0.146 0.08 0.17 | 5030 88% 72 86 78 72 36 61 64 1984 | Weight 8.9% 8.9% 9.0% 7.3% 8.8% 8.8% 9.4% | -0.21 [-0.39, -0.03] Std. Mean Difference <u>IV. Random, 95% CI</u> 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] | -100 | + -50 Std | GG GC I. Mean Differ Random, 95 | Fo 50 % CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 | Chi ² = 90.4 29 (P = 0.0 0.797 0.8 0.99 0.848 0.798 0.738 0.753 0.86 0.860 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 0.126 0.086 0.17 0.139 | 2555 11 (P < Total 175 171 241 177 105 118 118 3316 383 | Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.747 0.87 0.836 | CC SD 0.08 0.07 0.166 0.035 0.146 0.035 0.146 0.08 0.17 0.155 | 5030 88% 72 86 78 72 36 61 64 1984 124 | Weight 8.9% 8.9% 9.0% 8.9% 7.3% 8.8% 8.8% 8.8% 9.4% 9.2% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] | -100 | + -50 Std | GG GC I. Mean Differ Random, 95 | i 50 % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 | Chi ² = 90.2 29 (P = 0.0 0.797 0.8 0.99 0.848 0.798 0.738 0.753 0.86 0.847 0.81 | 48, df = 02) GC SD 0.14 0.133 0.014 0.126 0.086 0.17 0.139 0.07 | 2555 11 (P < Total 175 171 241 177 105 118 118 3316 383 73 | Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.747 0.87 0.836 0.836 | CC SD 0.08 0.07 0.166 0.136 0.035 0.146 0.08 0.17 0.155 0.06 | 5030 88% 72 86 78 72 36 61 64 1984 124 39 | 100.0% Weight 8.9% 9.0% 8.9% 7.3% 8.8% 8.8% 9.4% 9.2% 8.4% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] | -100 | + -50 Std IV. | GG GC I. Mean Differ Random. 95 | i 50 ence % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 | Chi ² = 90. 29 (P = 0.1 0.797 0.8 0.99 0.848 0.998 0.738 0.753 0.86 0.847 0.81 0.953 | 48, df = 02) GC SD 0.14 0.133 0.014 0.126 0.086 0.17 0.139 0.07 0.146 | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 | Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.747 0.836 0.836 0.833 1.037 | 1); I ² = CC SD 0.08 0.166 0.136 0.035 0.146 0.08 0.17 0.155 0.06 0.144 | 5030 88% 72 86 78 72 36 61 64 1984 124 39 15 | 100.0% Weight 8.9% 9.0% 8.9% 7.3% 8.8% 9.4% 9.2% 8.4% 7.6% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random. 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] | -100 | + -50 Std | 0 GG GC I. Mean Differ Random. 95 | i 50 ence % Ci | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 | Chi ² = 90. 29 (P = 0.1 0.797 0.8 0.99 0.848 0.998 0.738 0.753 0.866 0.847 0.847 0.847 0.953 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 0.086 0.17 0.139 0.07 0.146 0.02 | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 40 | Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.747 0.836 0.836 0.833 1.037 1.028 | CC SD 0.08 0.07 0.166 0.136 0.035 0.146 0.035 0.146 0.08 0.17 0.155 0.06 0.144 0.01 | 5030 88% 72 86 61 64 1984 124 39 15 9 | Weight 8.9% 9.0% 8.9% 7.3% 8.8% 9.4% 9.2% 8.4% 7.6% 4.9% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random. 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] | -100 | + -50 Std | 0 GG GC I. Mean Differ Random. 95 | i 50 % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 | Chi ² = 90. 29 (P = 0.0 0.797 0.8 0.99 0.848 0.998 0.738 0.753 0.86 0.847 0.847 0.81 0.953 0.958 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 0.086 0.17 0.139 0.07 0.146 0.02 | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 40 | Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.767 0.836 0.833 1.037 1.028 | CC SD 0.08 0.07 0.166 0.136 0.136 0.136 0.035 0.146 0.046 0.17 0.155 0.06 0.144 0.01 | 5030 88% 72 36 61 64 1984 124 39 15 9 | Weight 8.9% 9.0% 8.9% 7.3% 8.8% 9.4% 9.2% 8.4% 7.6% 4.9% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random. 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] 0.64 [-0.98, -0.31] | -100 | + -50 Std | 0 GG GC I. Mean Differ Random, 95 | i 50 % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; | Chi ² = 90.4 29 (P = 0.1 0.797 0.8 0.797 0.8 0.999 0.738 0.753 0.753 0.753 0.86 0.847 0.811 0.953 0.958 | 48, df = 02) GC SD 0.1 0.06 0.146 0.086 0.17 0.139 0.07 0.146 0.02 0.08 df = | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 40 5030 | Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.747 0.836 0.833 1.037 1.028 | CC SD 0.08 0.07 0.166 0.136 0.136 0.136 0.146 0.146 0.17 0.155 0.06 0.144 0.01 | 5030 88% 72 36 61 64 1984 124 39 15 9 2640 | Weight 8.9% 9.0% 8.9% 7.3% 8.8% 9.4% 9.2% 8.4% 7.6% 4.9% 100.0% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random. 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] | -100 | + -50 IV. | 0 GG GC I. Mean Differ Random, 95 | i 50 % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3 | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.788 0.753 0.86 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. | 48, df = 02) GC SD 0.1 0.06 0.133 0.014 0.126 0.086 0.17 0.139 0.07 0.146 0.02 2.08, df = | 2555 11 (P < Total 175 171 241 177 105 118 3316 3383 73 113 40 5030 5030 | Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.747 0.87 0.836 0.833 1.037 1.028 | CC SD 0.08 0.07 0.166 0.035 0.146 0.035 0.146 0.035 0.146 0.035 0.146 0.035 0.146 0.035 0.146 0.035 0.146 0.017 0.155 0.06 0.144 0.01 0.014 0.017 0.165 0.08 0.07 0.166 0.035 0.017 0.166 0.035 0.017 0.166 0.035 0.017 0.166 0.035 0.017 0.166 0.035 0.017 0.166 0.035 0.017 0.166 0.035 0.017 0.166 0.035 0.017 0.166 0.035 0.017 0.166 0.035 0.017 0.016 0.035 0.017 0.016 0.035 0.017 0.016 0.017 0.016 0.017 0.016 0.017 0.016 0.017 0.017 0.016 0.017 0.017 0.016 0.017 0.017 0.017 0.001 0.017 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 0.017 0.001 | 5030 88% 72 366 61 1984 1984 1984 124 39 15 9 2640 = 95% | Weight 8.9% 8.9% 9.0% 8.8% 8.8% 8.8% 9.4% 9.2% 8.4% 7.6% 4.9% 100.0% | -0.21 [-0.39, -0.03] Std. Mean Difference <u>IV. Random, 95% CI</u> 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] | -100 -100 | + -50 IV. -50 | GG GC . Mean Differ . Random, 95 | 1 50 % CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.788 0.783 0.868 0.783 0.868 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. | 48, df = 02) GC SD 0.11 0.06 0.146 0.133 0.014 0.0866 0.17 0.139 0.07 0.146 0.02 2.08, df = 002) | 2555 11 (P < Total 175 171 241 177 105 118 3316 333 113 3316 383 73 113 40 5030 = 11 (P | Mean 0.792 0.85 0.984 0.904 1.081 0.768 0.747 0.836 0.833 1.037 1.028 < 0.0000 | 1); I ² = CC <u>SD</u> 0.08 0.07 0.166 0.035 0.146 0.035 0.045 0.06 0.044 0.011); I ² = | 5030 88% 72 86 78 72 36 61 64 1984 124 39 15 9 9 2640 = 95% | Weight 8.9% 8.9% 7.3% 8.8% 8.8% 9.4% 9.2% 8.4% 7.6% 4.9% 100.0% | -0.21 [-0.39, -0.03] Std. Mean Difference <u>IV. Random, 95% CI</u> 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] | -100 -100 | + -50 IV. -50 | GG GC . Mean Differ . Random, 95 | + 50 % CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.999 0.848 0.738 0.738 0.753 0.86 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. | 48, df = 02) GC SD 0.11 0.06 0.146 0.133 0.014 0.086 0.07 0.139 0.07 0.139 0.07 0.146 0.02 2.08, df = 0002) TC | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 40 5030 = 11 (P | 0.0000 Mean 0.792 0.85 0.984 0.904 1.081 0.767 0.836 0.83 1.037 1.028 < 0.000 | 1); l ² = CC SD 0.08 0.07 0.166 0.035 0.046 0.035 0.046 0.035 0.06 0.144 0.01 0.01; l ² = CC | 5030 88% 72 86 78 72 36 61 64 1984 124 39 15 9 9 2640 = 95% | Weight 8.9% 9.0% 8.9% 7.3% 8.8% 9.4% 9.4% 9.2% 8.4% 7.6% 4.9% 100.0% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference | -100 -100 | + -50 Std IV | GG GC . Mean Differ . Random, 95 | + 50 % CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. Study or Subgroup Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C Study or Subgroup | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.999 0.848 0.738 0.738 0.738 0.866 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. | 48, df = 02) GC SD 0.11 0.06 0.146 0.133 0.014 0.126 0.07 0.139 0.07 0.139 0.07 0.146 0.02 2.08, df = 0002) TC SD | 2555 11 (P < Total 175 171 241 277 105 118 118 3316 383 73 113 40 5030 = 11 (P | 0.0000 Mean 0.792 0.85 0.984 0.904 1.081 0.767 0.836 0.83 1.037 1.028 < 0.000 Mean | 1); l ² = CC SD 0.08 0.07 0.166 0.035 0.146 0.08 0.17 0.155 0.06 0.144 0.01); l ² = CC SD | 5030 88% Total 72 86 61 72 36 61 1984 124 39 15 9 2640 9 2640 5% | Weight 8.9% 8.9% 9.0% 8.8% 9.4% 9.4% 9.4% 100.0% Weight | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV, Fixed, 95% CI | -100 -100 | + -50 IV. -50 | GG GC . Mean Differ . Random, 95 GC CC . Mean Differ V, Fixed, 95% | + 50 % CI 50 | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. Study or Subgroup Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C Study or Subgroup Boroň 2015 | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.738 0.738 0.738 0.738 0.738 0.847 0.847 0.847 0.847 0.853 0.958 Chi ² = 242 76 (P = 0. Mean 0.79 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 0.126 0.07 0.139 0.07 0.146 0.02 2.08, df = 0002) TC SD 0.09 | 2555 11 (P < Total 175 171 241 177 105 118 118 3316 3383 73 113 40 5030 = 11 (P | Mean 0.792 0.85 0.984 0.904 1.081 0.747 0.836 0.831 1.037 1.028 < 0.000 | 1); I ² = CC SD 0.08 0.07 0.166 0.035 0.146 0.08 0.17 0.155 0.06 0.144 0.01); I ² = CC SD 0.09 | 5030 88% 72 86 61 64 1984 1984 124 39 15 9 2640 € 95% Total | Weight 8.9% 8.9% 9.0% 8.8% 9.3% 8.8% 9.4% 7.3% 8.8% 9.4% 7.6% 4.9% 100.0% Weight 2.2% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] | -100 -100 | + -50 IV. -50 Std | GG GC . Mean Differ . Random, 95 GC CC . Mean Differ V. Fixed, 95% | For the second s | 100 |
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| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. Study or Subgroup Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C <u>Study or Subgroup</u> Boroň 2015 Chen-1 2004 Chen-2 2004 | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.788 0.753 0.86 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. <u>Mean</u> 0.79 0.82 0.79 | 48, df = 02) GC SD 0.11 0.066 0.133 0.014 0.126 0.0866 0.17 0.139 0.07 0.146 0.086 0.07 0.146 0.086 0.07 0.146 0.086 0.07 0.146 0.086 0.07 0.146 0.086 0.07 0.146 0.086 0.07 0.146 0.086 0.07 0.146 0.086 0.014 0.086 0.014 0.086 0.014 0.086 0.014 0.086 0.014 0.086 0.014 0.086 0.014 0.086 0.014 0.086 0.017 0.139 0.07 0.146 0.02 0.02 TC SD 0.09 0.17 0.09 0.17 0.09 0.17 0.09 0.17 0.19 0.09 0.17 0.17 0.09 0.17 0.09 0.17 0.17 0.09 0.17 0.17 0.09 0.17 0.17 0.09 0.17 0.09 0.17 0.17 0.09 0.17 0.09 0.17 0.17 0.09 0.17 0.09 0.17 0.09 0.17 0.09 0.17 0.17 0.17 0.19 0.09 0.17 0.17 0.19 0.09 0.17 0.17 0.19 0.09 0.17 0.17 0.19 0.09 0.17 0.17 0.19 0.09 0.17 0.17 0.19 0.09 0.17 0.17 0.17 0.19 0.09 0.17 0.17 0.17 0.19 0.09 0.17 0.17 0.17 0.17 0.19 0.09 0.17 0.17 0.17 0.17 0.17 0.17 0.17 0.17 0.17 0.09 0.17 0.17 0.17 0.17 0.09 0.17 0.17 0.17 0.17 0.17 0.09 0.17 | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 40 5030 = 11 (P 5030 = 11 (P | 0.0000 Mean 0.792 0.85 0.984 0.904 1.081 0.762 0.87 0.836 0.836 0.837 1.037 1.028 < 0.000 | 1); l ² = CC SD 0.08 0.07 0.166 0.035 0.146 0.035 0.146 0.015 0.06 0.144 0.01); l ² = CC SD 0.09 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.166 0.08 0.07 0.146 0.017 0.0146 0.0144 0.01 0.144 0.0146 0.016 0.016 0.016 0.016 0.00 0.016 0.00 | 5030 88% 72 866 78 72 36 61 1984 1984 1984 1984 1984 1984 2640 9 9 2640 5 710tal 5 18 5 18 5 | Weight 8.9% 8.9% 9.0% 8.9% 7.3% 8.8% 8.8% 9.4% 9.2% 8.4% 7.6% 4.9% 100.0% Weight 2.2% 6.1% 5.1% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] 0.06 [-0.49, 0.62] -0.16 [-0.77, 0.45] | -100 -100 | + -50 Std IV. -50 Std | GG GC . Mean Differ . Random, 95 . GC CC . Mean Differ V. Fixed, 95% | 1 50 % CI 50 ence . CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C <u>Study or Subgroup</u> Boroň 2015 Chen-1 2004 Chen-2 2004 Langdahl 2002 | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.738 0.753 0.86 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. Mean 0.79 0.82 0.76 0.74 | 48, df = 02) GC SD 0.11 0.06 0.146 0.133 0.014 0.086 0.17 0.139 0.07 0.146 0.02 2.08, df = 0002) TC SD 0.09 0.16 0.131 | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 40 5030 = 11 (P Total 84 40 34 | Mean 0.792 0.85 0.984 0.904 1.081 0.762 0.87 0.836 0.831 0.836 0.836 0.837 1.028 < 0.000 | 1); l ² = CC SD 0.08 0.07 0.166 0.035 0.046 0.035 0.06 0.144 0.01 0.155 0.06 0.144 0.01 CC SD 0.09 0.16 0.09 0.136 0.21 0.136 | 5030 88% 72 86 78 72 36 61 1984 124 39 15 9 2640 = 95% Total 5 18 15 5 2 | 100.0% Weight 8.9% 8.9% 9.0% 8.8% 9.4% 9.2% 8.8% 9.2% 8.4% 7.6% 4.9% 100.0% Weight 2.2% 6.1% 5.1% 17.4% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] 0.06 [-0.47, 0.45] -0.32 [-0.64, 0.01] | -100 -100 | + -50 Std -50 Std | GG GC . Mean Differ . Random, 95 | + 50 % CI 50 ence . CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C <u>Study or Subgroup</u> Boroň 2015 Chen-1 2004 Chen-2 2004 Langdahl 2002 Liu 2010 | Chi ² = 90. 29 (P = 0. 29 (P = 0. 0.797 0.8 0.998 0.738 0.738 0.738 0.868 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. Mean 0.79 0.82 0.745 0.824 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 0.126 0.07 0.139 0.07 0.139 0.07 0.146 0.02 2.08, df = 0.002) TC SD 0.09 0.16 0.17 0.131 0.02 | 2555 11 (P < Total 175 171 241 177 105 118 118 318 383 73 113 40 5030 = 11 (P Total 84 40 34 117 51 | 0.0000 Mean 0.792 0.85 0.984 0.904 1.081 0.762 0.873 0.836 0.831 0.900 Mean 0.89 0.800 0.89 0.81 0.787 0.873 | 1); I ² = CC SD 0.08 0.07 0.166 0.035 0.046 0.035 0.046 0.035 0.06 0.144 0.011; I ² = CC SD 0.09 0.166 0.09 0.166 0.09 0.166 0.0175 0.09 0.166 0.017 0.016 0.0175 0.06 0.0175 0.0144 0.0175 0.0166 0.0175 0.0175 0.0146 0.0175 0.0146 0.0175 0.0146 0.0175 0.0146 0.0175 0.0146 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 0.0166 0.0175 | 5030 88% 72 86 67 72 36 61 14 4 1984 124 39 15 9 2640 = 95% Total 5 18 15 5 22 | 100.0% Weight 8.9% 9.0% 8.9% 7.3% 8.8% 9.4% 9.4% 9.2% 8.4% 7.6% 4.9% 100.0% Weight 2.2% 6.1% 5.1% 17.4% 7.4% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] 0.06 [-0.49, 0.62] -0.32 [-0.64, 0.01] -0.32 [-0.64, 0.01] | -100 -100 | + -50 Std -50 Std | GG GC Mean Differ Random, 95 GC CC Mean Differ V. Fixed, 95% | + 50 % CI 50 ence . CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C <u>Study or Subgroup</u> Boroň 2015 Chen-1 2004 Chen-2 2004 Langdahl 2002 Liu 2010 Seremak-Mrozikiewicz 2011 | Chi ² = 90. 29 (P = 0. 29 (P = 0. 0.797 0.8 0.999 0.848 0.738 0.738 0.753 0.866 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. Mean 0.79 0.82 0.76 0.745 0.824 0.97 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 0.126 0.037 0.139 0.07 0.139 0.07 0.146 0.02 2.08, df = 0.09 0.16 0.17 0.131 0.123 0.09 0.16 0.17 0.133 0.06 0.17 0.133 0.06 0.146 0.146 0.133 0.014 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.146 0.133 0.014 0.02 0.17 0.139 0.07 0.139 0.07 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.146 0.02 0.167 0.133 0.016 0.02 0.16 0.166 0.177 0.139 0.07 0.146 0.02 0.16 0.09 0.16 0.177 0.131 0.09 0.166 0.177 0.131 0.126 0.09 0.166 0.177 0.126 0.09 0.166 0.177 0.126 0.09 0.166 0.177 0.126 0.09 0.166 0.177 0.126 0.09 0.166 0.177 0.123 0.09 0.166 0.177 0.123 0.09 0.166 0.177 0.123 0.09 0.166 0.123 0.066 0.166 0.166 0.177 0.126 0.066 0.166 0 | 2555 11 (P < Total 175 171 175 171 241 241 177 105 118 118 3316 3316 333 113 3316 383 73 113 40 5030 = 11 (P \$ | 0.0000 Mean 0.792 0.85 0.85 0.86 0.87 0.87 0.83 0.84 0.787 0.873 0.99 | 1); l ² = CC SD 0.08 0.07 0.166 0.035 0.146 0.08 0.17 0.155 0.06 0.144 0.01); l ² = CC SD 0.09 0.16 0.09 0.16 0.09 0.16 0.09 0.16 0.09 0.16 0.09 0.16 0.09 0.16 0.09 0.16 0.09 0.01 0.09 0.01 0.09 0.01 0.09 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.01 0.02 0.01 0.05 0. | 5030 88% 72 36 61 1984 124 39 15 9 2640 5 5 8 5 18 15 5 2 238 | 100.0% Weight 8.9% 9.0% 8.8% 9.4% 7.3% 8.8% 9.4% 7.6% 4.9% 100.0% Weight 2.2% 6.1% 5.1% 5.1% 11.0% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] 0.06 [-0.49, 0.62] -0.35 [-0.85, 0.16] -0.35 [-0.85, 0.16] -0.35 [-0.76, 0.061] | -100 -100 | + -50 Std -50 Std | GG GC . Mean Differ . Random, 95 GC CC . Mean Differ V. Fixed, 95% | For the second s | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C <u>Study or Subgroup</u> Boroň 2015 Chen-1 2004 Chen-2 2004 Langdahl 2002 Liu 2010 Seremak-Mrozikiewicz 2011 wu 2007 | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.738 0.738 0.738 0.738 0.753 0.847 0.811 0.953 0.958 Chi ² = 242 76 (P = 0. Mean 0.79 0.822 0.76 0.745 0.824 0.97 0.764 | 48, df = 02) GC SD 0.1 0.06 0.143 0.014 0.126 0.037 0.146 0.07 0.139 0.07 0.146 0.02 2.08, df = 0.09 0.16 0.17 0.131 0.06 0.077 | 2555 11 (P < Total 175 171 241 177 105 118 118 3316 3316 3383 73 113 40 5030 = 11 (P Total 18 118 40 5030 = 11 (P 5030 5030 5030 5030 5030 5030 5030 50 | Mean 0.792 0.85 0.984 0.984 0.702 0.836 0.836 0.833 1.037 1.028 < 0.000 | 1); I ² = CC SD 0.08 0.07 0.166 0.035 0.146 0.08 0.155 0.06 0.144 0.01 0.155 0.06 0.144 0.01 0.155 0.06 0.144 0.01 0.155 0.06 0.146 0.136 0.136 0.146 0.01 0.155 0.06 0.146 0.136 0.136 0.146 0.136 0.146 0.136 0.146 0.155 0.06 0.146 0.155 0.06 0.146 0.155 0.06 0.146 0.155 0.06 0.146 0.155 0.06 0.146 0.155 0.06 0.146 0.155 0.06 0.146 0.155 0.06 0.146 0.013 0.155 0.06 0.146 0.013 0.155 0.06 0.146 0.013 0.155 0.06 0.146 0.013 0.155 0.06 0.146 0.013 0.155 0.06 0.144 0.013 0.155 0.06 0.144 0.013 0.09 0.09 0.166 0.136 0.09 0.166 0.09 0.165 0.09 0.165 0.00 0.00 0.165 0.09 0.00 0.165 0.00 0.00 0.165 0.09 0.00 0.165 0.09 0.052 0.055 0.00 0.00 0.165 0.09 0.052 0.055 0.055 0.09 0.052 0.055 0.057 0.09 0.052 0.055 0.09 0.055 0.057 0.057 0.09 0.055 0.057 | 5030 88% 72 36 61 64 1984 124 39 15 9 2640 = 95% 5 18 15 52 222 38 6 6 | 100.0% Weight 8.9% 9.0% 8.8% 9.0% 8.8% 9.4% 8.8% 9.2% 8.4% 7.6% 4.9% 100.0% Weight 2.2% 6.1% 5.1% 17.4% 7.4% 11.0% 2.5% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] 0.06 [-0.49, 0.62] -0.35 [-0.85, 0.16] -0.35 [-0.76, 0.06] 0.14 [-0.72, 1.00] | -100 -100 | + -50 Std IV. -50 | GG GC I. Mean Differ GC CC I. Mean Differ V. Fixed, 95% | I 50 % CI 50 ence . CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C <u>Study or Subgroup</u> Boroň 2015 Chen-1 2004 Langdahl 2002 Liu 2010 Seremak-Mrozikiewicz 2011 wu 2007 Yamada 2003 | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.738 0.738 0.753 0.846 0.953 0.847 0.811 0.953 0.958 Chi ² = 242 76 (P = 0. Mean 0.797 0.822 0.766 0.745 0.824 0.745 0.824 0.745 | 48, df = 02) GC SD 0.1 0.06 0.146 0.133 0.014 0.126 0.07 0.139 0.07 0.146 0.02 2.08, df = 0.09 0.16 0.17 0.131 0.123 0.09 0.16 0.077 0.131 0.008 | 2555 11 (P < Total 175 171 241 177 105 118 118 3316 3316 383 73 113 40 5030 = 11 (P Total 118 40 5030 = 11 (P 5030 5030 5030 5030 5030 5030 5030 50 | 0.0000 Mean 0.792 0.85 0.984 0.984 1.081 0.747 0.876 0.833 1.028 < 0.000 Mean 0.89 0.819 0.787 0.873 0.879 0.873 0.879 0.875 0.875 0.815 | 1); I ² = CC SD 0.08 0.07 0.166 0.035 0.146 0.08 0.17 0.155 0.06 0.144 0.01 0.155 0.06 0.144 0.01 0.155 0.06 0.136 0.136 0.136 0.136 0.136 0.136 0.136 0.136 0.137 0.166 0.136 0.136 0.136 0.136 0.136 0.136 0.136 0.136 0.137 0.166 0.136 0.136 0.136 0.136 0.136 0.137 0.166 0.136 0.136 0.137 0.155 0.06 0.142 0.155 0.06 0.142 0.155 0.06 0.136 0.136 0.136 0.136 0.136 0.146 0.137 0.155 0.06 0.136 0.136 0.136 0.136 0.136 0.136 0.136 0.142 0.013 0.155 0.06 0.144 0.01 0.155 0.09 0.09 0.166 0.136 0.09 0.166 0.136 0.09 0.166 0.09 0.166 0.09 0.166 0.136 0.09 0.166 0.136 0.09 0.165 0.00 0.165 0.09 0.166 0.176 0.09 0.165 0.009 0.165 0.007 0.166 0.09 0.057 0.057 0.009 0.165 0.057 0.057 0.09 0.057 0.057 0.057 0.09 0.057 0.057 0.057 0.057 0.09 0.057 0.05 | 5030 88% 72 36 61 64 1984 124 39 15 9 2640 = 95% 5 5 8 5 5 8 8 6 134 | 100.0% Weight 8.9% 9.0% 8.8% 9.3% 8.8% 9.4% 9.2% 8.4% 7.6% 4.9% 100.0% Weight 2.2% 6.1% 5.1% 17.4% 7.4% 11.0% 2.5% 48.3% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] 0.06 [-0.49, 0.62] -0.35 [-0.64, 0.01] -0.35 [-0.65, 0.16] -0.35 [-0.76, 0.06] 0.14 [-0.72, 1.00] -0.21 [-0.41, -0.01] | -100 | + -50 Std IV. -50 | GG GC I. Mean Differ GC CC I. Mean Differ V. Fixed, 95% | i 50 % Cl | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. <u>Study or Subgroup</u> Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C <u>Study or Subgroup</u> Boroň 2015 Chen-1 2004 Chen-2 2004 Langdahl 2002 Líu 2010 Seremak-Mrozikiewicz 2011 wu 2007 Yamada 2003 | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.738 0.738 0.753 0.86 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. Mean 0.79 0.82 0.76 0.745 0.824 0.97 0.764 0.813 | 48, df = 02) GC SD 0.14 0.066 0.133 0.014 0.126 0.086 0.17 0.139 0.07 0.146 0.086 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.09 0.17 0.131 0.09 0.17 0.131 0.09 0.17 0.133 0.09 0.17 0.133 0.09 0.17 0.131 0.09 0.17 0.131 0.066 0.077 0.088 0.077 0.09 0.177 0.131 0.068 0.077 0.088 0.077 0.131 0.09 0.177 0.131 0.088 0.077 0.131 0.09 0.077 0.131 0.088 0.077 0.131 0.123 0.09 0.077 0.131 0.088 0.077 0.131 0.173 0.088 0.077 0.131 0.173 0.088 0.077 0.131 0.173 0.088 0.077 0.131 0.088 0.077 0.131 0.088 0.077 0.131 0.068 0.077 0.088 0.077 0.088 0.077 0.088 0.077 0.098 0.077 0.098 0.077 0.098 0.077 0.088 0.077 0.078 0.0778 0.0778 0.0778 0.0778 0.0778 0.0778 0.0778 0.0778 | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 40 5030 = 11 (P 5030 = 11 (P 7 7 7 84 40 40 40 5030 = 11 (P 84 40 34 117 51 53 83 387 387 51 51 51 51 51 51 51 51 51 51 51 51 51 | 0.0000 Mean 0.792 0.85 0.984 0.904 1.081 0.762 0.873 0.836 0.836 0.8373 0.792 0.873 0.873 0.815 | 1); l ² = CC SD 0.08 0.07 0.166 0.035 0.146 0.035 0.046 0.146 0.018 0.016 0.015 0.06 0.144 0.01 0.144 0.01 0.155 0.06 0.046 0.072 0.013 0.072 0.013 | 5030 88% 72 866 78 72 36 61 1984 1984 1984 1984 1984 1984 1984 198 | Weight 8.9% 8.9% 9.0% 8.9% 7.3% 8.8% 9.4% 9.2% 8.4% 7.6% 4.9% 100.0% Weight 2.2% 6.1% 5.1% 7.4% 11.0% 2.5% 48.3% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] 0.06 [-0.49, 0.62] -0.35 [-0.76, 0.45] -0.35 [-0.76, 0.06] 0.14 [-0.72, 1.00] -0.21 [-0.41, -0.01] | -100 -100 | + -50 Std -50 Std | GG GC . Mean Differ . Random, 95 GC CC . Mean Differ V. Fixed, 95% | 1 50 % CI 50 ence . CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C <u>Study or Subgroup</u> Boroň 2015 Chen-1 2004 Chen-2 2004 Langdahl 2002 Liu 2010 Seremak-Mrozikiewicz 2011 wu 2007 Yamada 2003 Total (95% CI) | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.738 0.738 0.753 0.86 0.847 0.81 0.953 0.958 Chi ² = 242 76 (P = 0. Mean 0.79 0.82 0.76 0.745 0.824 0.97 0.764 0.813 | 48, df = 02) GC SD 0.11 0.066 0.133 0.014 0.133 0.014 0.0866 0.17 0.139 0.07 0.146 0.086 0.07 0.146 0.086 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.139 0.07 0.146 0.086 0.07 0.126 0.09 0.17 0.131 0.09 0.17 0.133 0.09 0.17 0.133 0.09 0.17 0.133 0.09 0.17 0.133 0.09 0.17 0.133 0.09 0.17 0.131 0.09 0.17 0.131 0.09 0.17 0.131 0.09 0.17 0.09 0.17 0.09 0.17 0.09 0.17 0.088 0.077 0.09 0.177 0.131 0.09 0.177 0.131 0.09 0.177 0.131 0.09 0.077 0.131 0.066 0.077 0.008 0.077 0.131 0.09 0.077 0.131 0.066 0.077 0.008 0.077 0.131 0.066 0.077 0.008 0.077 0.131 0.066 0.077 0.008 0.077 0.008 0.077 0.131 0.068 0.077 0.008 0.077 0.098 0.077 0.098 0.077 0.098 0.077 0.098 0.098 0.098 0.098 0.098 0.077 0.0088 0.077 0.0088 0.077 0.0088 0.077 0.0088 0.077 0.0088 0.077 0.0088 0.077 0.0088 0.0077 0.0088 0.0088 0.0077 0.0088 0.0088 0.0077 0.0088 0.0077 0.0088 0.0088 0.0088 0.0077 0.0088 0.0088 0.0088 0.0088 0.0088 0.0077 0.00888 0.00888 0.00888 0.0088 0.00888 0 | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 40 5030 = 11 (P 5030 = 11 (P 5030 = 11 (P 5030 40 5030 34 113 40 5030 81 84 40 84 84 84 84 85 83 9 387 810 | 0.0000 Mean 0.792 0.85 0.984 0.904 1.081 0.762 0.87 0.836 0.837 0.836 0.8373 0.792 0.787 0.793 0.753 0.815 | 1); l ² = CC SD 0.08 0.07 0.166 0.035 0.146 0.035 0.046 0.136 0.035 0.06 0.144 0.01 0.155 0.06 0.144 0.01 0.155 0.06 0.015 0.072 0.06 0.21 0.136 0.21 0.136 0.21 0.136 0.21 0.146 0.015 0.015 0.015 0.015 0.016 0.02 0.0146 0.035 0.046 0.035 0.046 0.035 0.046 0.035 0.046 0.035 0.046 0.035 0.046 0.046 0.035 0.046 0.017 0.0146 0.035 0.0146 0.017 0.0146 0.017 0.0146 0.0146 0.017 0.0146 0.017 0.016 0.017 0.016 0.017 0.016 0.017 | 5030 88% 72 866 78 72 36 61 1984 1984 1984 1984 124 39 15 9 9 2640 9 2640 5 5 18 15 5 2 22 38 6 134 290 | 100.0% Weight 8.9% 8.9% 8.9% 7.3% 8.8% 8.8% 8.8% 8.8% 8.4% 7.6% 4.9% 100.0% Weight 2.2% 6.1% 5.1% 17.4% 7.4% 11.0% 2.5% 48.3% 100.0% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] 0.06 [-0.49, 0.62] -0.35 [-0.76, 0.06] 0.14 [-0.72, 1.00] -0.25 [-0.38, -0.11] -0.25 [-0.38, -0.11] | -100 -100 | + -50 Std -50 Std | GG GC . Mean Differ . Random, 95 GC CC I. Mean Differ V. Fixed, 95% | 1 50 % CI 50 ence . CI | 100 |
| Total (95% CI) Heterogeneity: Tau ² = 0.08; B Test for overall effect: Z = 2. Study or Subgroup Boroň 2015 Boroňová 2015 Canto-Cetina 2013 García-Unzueta 2008 Kim 2007 Langdahl 2002 Mencej-Bedrac 2011 Moffett 2008 Rojano-Mejía 2012 Seremak-Mrozikiewicz 2011 Shang 2013 Zhao 2005 Total (95% CI) Heterogeneity: Tau ² = 0.31; Test for overall effect: Z = 3. C <u>Study or Subgroup</u> Boroň 2015 Chen-1 2004 Chen-2 2004 Langdahl 2002 Liu 2010 Seremak-Mrozikiewicz 2011 wu 2007 Yamada 2003 Total (95% CI) Heterogeneity: Chi ² = 6.08, | Chi ² = 90. 29 (P = 0. 0.797 0.8 0.998 0.738 0.738 0.753 0.866 0.847 0.813 0.958 Chi ² = 242 76 (P = 0. Mean 0.799 0.82 0.766 0.744 0.813 df = 7 (P = | 48, df = 02) GC SD 0.11 0.066 0.146 0.133 0.014 0.0866 0.177 0.139 0.07 0.146 0.02 2.08, df = 0.09 0.16 0.17 0.131 0.123 0.06 0.077 0.008 0.077 0.008 | 2555 11 (P < Total 175 171 241 177 105 118 3316 383 73 113 40 5030 = 11 (P 5030 = 11 (P 5030 = 11 (P 5030 5030 = 11 (P 5030 2 = 0% | 0.0000 Mean 0.792 0.85 0.85 0.87 0.87 0.87 0.83 0.87 0.83 1.037 1.028 < 0.000 | 1); I ² = CC SD 0.08 0.07 0.166 0.035 0.046 0.035 0.06 0.144 0.01 0.155 0.06 0.144 0.01 0.155 0.06 0.144 0.01 0.155 0.06 0.146 0.07 0.07 0.06 0.07 0.155 0.06 0.146 0.07 0.155 0.06 0.146 0.07 0.155 0.06 0.146 0.07 0.155 0.06 0.146 0.07 0.155 0.06 0.146 0.07 0.155 0.06 0.146 0.07 0.155 0.06 0.146 0.017 0.155 0.06 0.146 0.017 0.05 0.07 0.07 0.07 0.06 0.07 0.155 0.06 0.146 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.155 0.06 0.144 0.01 0.175 0.09 0.175 0.09 0.175 0.09 0.116 0.117 0.03 0.017 0.03 0.017 0.03 0.017 0.03 0.017 0.03 0.017 0.03 0.017 0.03 0.017 0.013 0.017 0.013 0.017 0.013 0.017 0.013 0.017 0.013 0.017 0.013 0.017 0.013 0.0 | 5030 88% 72 866 61 64 64 1984 124 39 15 9 2640 = 95% Total 5 5 18 15 5 5 18 15 22 23 8 6 134 290 | 100.0% Weight 8.9% 8.9% 7.3% 8.8% 8.8% 9.4% 9.2% 8.4% 7.6% 4.9% 100.0% <u>Weight</u> 2.2% 6.1% 5.1% 17.4% 11.0% 2.5% 48.3% | -0.21 [-0.39, -0.03] Std. Mean Difference IV. Random, 95% CI 0.05 [-0.22, 0.33] -0.78 [-1.05, -0.52] 0.04 [-0.22, 0.29] -0.42 [-0.69, -0.14] -3.87 [-4.46, -3.28] -0.22 [-0.53, 0.09] 0.07 [-0.23, 0.38] -0.06 [-0.11, -0.00] 0.08 [-0.13, 0.28] -0.30 [-0.69, 0.09] -0.57 [-1.12, -0.03] -3.69 [-4.74, -2.64] -0.64 [-0.98, -0.31] Std. Mean Difference IV. Fixed, 95% CI -1.10 [-2.02, -0.18] 0.06 [-0.49, 0.62] -0.16 [-0.77, 0.45] -0.35 [-0.64, 0.01] -0.35 [-0.64, 0.01] -0.35 [-0.76, 0.06] 0.14 [-0.72, 1.00] -0.21 [-0.41, -0.01] -0.25 [-0.38, -0.11] | -100 | + -50 -50 -50 | GG GC . Mean Differ . Random, 95 GC CC J. Mean Differ V. Fixed, 95% | + 50 ence % CI 50 ence .CI | 100 |

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.

| | | | | | Test of association | ı | | Test of hete | erogeneity |
|--------------------|----------|------------|-------------------|-------|---------------------|----------------|-------|--------------|--------------------|
| BMD/Polymorphism | Genotype | Population | Number of studies | SMD | 95% CI | P value | Model | P value | l 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; I²: Higgins I-squared statistic.

Table 3

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

| | | | | | Test of association | ı | | Test of hete | erogeneity |
|--------------------|----------|------------|-------------------|-------|---------------------|---------|-------|--------------|--------------------|
| BMD/Polymorphism | Genotype | Population | Number of studies | SMD | 95% CI] | P value | Model | P value | l 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

| | | | | | Test of association | 1 | | Test of hete | erogeneity |
|--------------------|----------|------------|-------------------|-------|---------------------|---------|-------|--------------|------------|
| BMD/Polymorphism | Genotype | Population | Number of studies | SMD | [95% CI] | P value | Model | P value | l² (%) |
| 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; I²: 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.

| 2000 032250 | 0227 | AA | | 11 | AG | 2000 | 122022 | Std. Mean Difference | | Sto | I. Mean Differe | nce | |
|-------------------------------------|-----------------------|----------------------|-----------|----------|---------|----------------------|--------|--|--|------|----------------------|------|------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random. 95% CI | | IV | <u>. Random, 95%</u> | | |
| Boronová 2015 | 0.691 | 0.1 | 223 | 0.692 | 0.09 | 95 | 14.7% | -0.01 [-0.25, 0.23] | | | I | | |
| Garcia-Unzueta 2008 | 0.82 | 0.111 | 253 | 0.816 | 0.11 | 72 | 14.7% | 0.04 [-0.23, 0.30] | | | I. | | |
| Gen 2007 | 0.629 | 0.023 | 26 | 0.575 | 0.012 | 84 | 12.4% | 3.51 [2.87, 4.16] | | | r - | | |
| Langdahl 2002 | 0.723 | 0.124 | 143 | 0.744 | 0.115 | 60 | 14.5% | -0.17 [-0.47, 0.13] | | | I | | |
| Shang 2013 | 0.899 | 0.126 | 175 | 0.87 | 0.146 | 52 | 14.5% | 0.22 [-0.09, 0.53] | | | I | | |
| Ueland 2007 | 0.814 | 0.124 | 749 | 0.81 | 0.133 | 219 | 15.0% | 0.03 [-0.12, 0.18] | | | L | | |
| Yu 2006 | 0.898 | 0.009 | 135 | 0.883 | 0.014 | 49 | 14.2% | 1.42 [1.06, 1.77] | | | | | |
| Total (95% CI) | | | 1704 | | | 631 | 100.0% | 0.65 [0.12, 1.19] | | | | | |
| Heterogeneity: Tau ² = 0 | .49; Chi | ² = 160. | 48, df = | = 6 (P < | 0.0000 | 1); 2 = | 96% | | 100 | 50 | | 50 | 100 |
| Test for overall effect: Z | = 2.39 (| (P = 0.0) | 2) | | | | | | -100 | -50 | AA AG | 50 | 100 |
| ١ | | | | | | | | | | | | | |
| | | GG | | | CC | | | Std. Mean Difference | | Std | . Mean Differe | nce | |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random. 95% CI | | IV | Random. 95% | CI | |
| Boroňová 2015 | 0.681 | 0.1 | 80 | 0.675 | 0.09 | 72 | 9.6% | 0.06 [-0.26, 0.38] | | | 1 | | |
| Canto-Cetina 2013 | 0.966 | 0.137 | 261 | 0.987 | 0.135 | 78 | 11.1% | -0.15 [-0.41, 0.10] | | | 1 T | | |
| García-Unzueta 2008 | 0.81 | 0.109 | 83 | 0.845 | 0.11 | 72 | 9.6% | -0.32 [-0.64, -0.00] | | | 1 | | |
| Kim 2007 | 0.643 | 0.01 | 156 | 0.658 | 0.019 | 36 | 8.3% | -1.23 [-1.61, -0.84] | | | 1 | | |
| Langdahl 2002 | 0.706 | 0.156 | 37 | 0.756 | 0.109 | 61 | 7.7% | -0.39 [-0.80, 0.03] | | | 1 | | |
| Mencej-Bedrac 2011 | 0.737 | 0.096 | 61 | 0.756 | 0.096 | 64 | 8.9% | -0.20 [-0.55, 0.15] | | | + | | |
| Moffett 2008 | 0.75 | 0.13 | 1358 | 0.76 | 0.13 | 1984 | 14.7% | -0.08 [-0.15, -0.01] | | | + | | |
| Rojano-Mejía 2012 | 0.916 | 0.125 | 243 | 0.922 | 0.153 | 124 | 11.9% | -0.04 [-0.26, 0.17] | | | + | | |
| Shang 2013 | 0.886 | 0.113 | 107 | 0.935 | 0.126 | 15 | 5.7% | -0.42 [-0.97, 0.12] | | | + | | |
| Ueland 2007 | 0.796 | 0.135 | 207 | 0.818 | 0.119 | 237 | 12.6% | -0.17 [-0.36, 0.01] | | | - t | | |
| Total (95% CI) | | | 2593 | | | 2743 | 100.0% | -0.25 [-0.42, -0.09] | | | | | |
| Heterogeneity: Tau ² = 0 | .05: Chi ² | 2 = 40.1 | 6. df = 9 | 9 (P < 0 | .00001) | : 1 ² = 7 | 8% | Setter: Top: Webbara | - | - | | 1 | |
| Test for overall effect: Z | = 3.03 (| P = 0.0 | 02) | | | | | | -100 | -50 | GG CC | 50 | 100 |
| 1 | | | | | | | | | | | 122 22 | | |
| | | GG | | | GC | | | Std. Mean Difference | | St | d. Mean Differ | ence | |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Tota | Weight | IV. Random. 95% C | 1 | I | /. Random. 95 | % CI | |
| Boroňová 2015 | 0.681 | 0.1 | 80 | 0.701 | 0.1 | 175 | 8.6% | -0.20 [-0.46, 0.07] | | | 1 | | |
| Canto-Cetina 2013 | 0.966 | 0.137 | 261 | 0.98 | 0.143 | 241 | 11.8% | -0.10 [-0.28, 0.08] | | | 1 | | |
| García-Unzueta 2008 | 0.81 | 0.109 | 83 | 0.81 | 0.106 | 177 | 8.7% | 0.00 [-0.26, 0.26] | | | | | |
| Kim 2007 | 0.643 | 0.01 | 156 | 0.651 | 0.012 | 105 | 8.9% | -0.74 [-0.99, -0.48] | | | 1 | | |
| Langdahl 2002 | 0.706 | 0.156 | 37 | 0.727 | 0.116 | 118 | 5.9% | -0.17 [-0.53, 0.20] | | | 1 | | |
| Mencej-Bedrac 2011 | 0.737 | 0.096 | 61 | 0.76 | 0.098 | 118 | 7.3% | -0.24 [-0.55, 0.07] | | | 1 | | |
| Moffett 2008 | 0.75 | 0.13 | 1358 | 0.76 | 0.13 | 3316 | 15.7% | -0.08 [-0.14, -0.01] | | | + | | |
| Rojano-Mejía 2012 | 0.916 | 0.125 | 243 | 0.909 | 0.137 | 383 | 12.3% | 0.05 [-0.11, 0.21] | | | + | | |
| Shang 2013 | 0.886 | 0.113 | 107 | 0.89 | 0.143 | 113 | 8.6% | -0.03 [-0.30, 0.23] | | | t - | | |
| Ueland 2007 | 0.796 | 0.135 | 207 | 0.814 | 0.13 | 464 | 12.2% | -0.14 [-0.30, 0.03] | | | 1 | | |
| Total (95% CI) | | | 2593 | | | 5210 | 100.0% | -0.15 [-0.26, -0.03] | | | | | |
| Heterogeneity: Tau ² = | 0.02; Ch | i ² = 30. | 16, df = | 9 (P = | 0.0004) | ; 2 = 70 | 0% | an a | -100 | -50 | 0 | 50 | 10 |
| | | n = 0 | 17) | | | | | | and the second sec | 1000 | | | 1.11 |

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

| | | | | | Test of association | n | | Test of hete | erogeneity |
|--------------------|----------|------------|-------------------|-------|---------------------|---------|-------|--------------|------------|
| BMD/Polymorphism | Genotype | Population | Number of studies | SMD | 95% CI] | P value | Model | P value | l² (%) |
| 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; I²: 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.

| Langer 1 | | t ior iuniei piot asy | | GII010, 12400, all | | | | i | |
|-----------|-----------------------------|------------------------------|---------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|--------------------|
| BMD | | LS | | | L | | | H | |
| 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 | -7.3675940780236 | -5.37502 - 2.479699 | -5.899282 - 2.996339 | -5.455485 - 2.529411 | -4.0131594135829 | -3.526946 - 1.306131 | -2.576484354744 |
| T245G | TT vs GG | TT vs TG | TG vs GG | TT vs GG | TT vs TG | TG vs GG | Π 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 = bon | e mineral density, LS=Lumbs | ar spine, FH=Femoral hip, TH | I=Total hip, Cls = confidence i | ntervals. | | | | | |

Medicine

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.

Author contributions

- Conceptualization: Feng Xue.
- Data curation: Yuqin Peng and Xiaowen Sheng.
- Formal analysis: Xiaowen Sheng.
- Methodology: Yuqin Peng and Xiaowen Sheng.
- Project administration: Yufeng Qian.
- Software: Yugin Peng and Feng Xue.
- Writing original draft: Yufeng Qian.
- Writing review & editing: Feng Xueand Yufeng Qian.

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