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Association between the *ESR1* and *ESR2* polymorphisms and osteoporosis risk

An updated meta-analysis

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Abstract

Background: Gene polymorphisms of estrogen receptor (ESR) 1 *PvuII* (rs2234693), *XbaI* (rs9340799), *G2014A* (rs2228480), ESR2 *AluI* (rs4986938), and *RsaI* (rs1256049) had been reported to be associated with the risk of osteoporosis. However, these conclusions were inconsistent, therefore, an updated meta-analysis was conducted to further explore these issues.

Objective: To evaluate the association between gene polymorphisms of ESR1 *PvuII* (rs2234693), *XbaI* (rs9340799), *G2014A* (rs2228480), ESR2 *AluI* (rs4986938), *RsaI* (rs1256049), and osteoporosis risk.

Materials and methods: PubMed, Medline, Ovid, Embase, CNKI, and China Wanfang databases were searched. Association was assessed using odds ratio with 95% confidence interval. Moreover, the false-positive reporting probability, Bayesian false-finding probability, and Venetian criteria were used to assess the credibility of statistically significant associations.

Results: Overall, ESR1 *PvuII* (rs2234693) and *XbaI* (rs9340799) were associated with the risk of osteoporosis in Indians. Moreover, ESR1 *G2014A* (rs2228480) was associated with the decreased risk of osteoporosis in East Asians. Moreover, ESR2 *AluI* (rs4986938) was associated with the increased risk of osteoporosis in East Asians and Caucasians. There was a significant association between ESR2 *RsaI* (rs1256049) and osteoporosis risk in overall population. When only high-quality and Hardy–Weinberg equilibrium studies were included in the sensitivity analysis, all results did not change in the present study. When the credibility was evaluated applying false-positive reporting probability, Bayesian false-finding probability, and Venetian criteria, all significant associations were considered as false positive results.

Conclusions: In summary, this study shows that all substantial associations between gene polymorphisms of ESR1 (*PvuII*, *XbaI*, and *G2014A*) and ESR 2 (*AluI* and *RsaI*) and osteoporosis risk are possibly false positive results instead of real associations or biological variables.

Abbreviations: BFDP = Bayesian false discovery probability, CI = confidence interval, ER = estrogen, ESR = estrogen receptor, FPRP = false-positive report probabilities, OR = odds ratio.

Keywords: ESR, meta-analysis, osteoporosis, polymorphism

1. Introduction

Osteoporosis is a common metabolic bone disease characterized by low bone density and increased bone fragility, resulting in increased susceptibility to fractures. With the extension of human life expectancy, more and more elderly people suffer from osteoporosis.[1] As a result, osteoporosis is becoming a huge economic burden for society and families.[2] Epidemiological studies have indicated that fracture is laid low with numerous risk factors, like age, fracture history, gender, lifestyle, etc.[3] In addition, genetic factors as well as genes and genetic polymorphisms may play a very important role within the development of osteoporosis.

Estrogen plays a crucial role in control bone equilibrium and preventing biological time bone loss.[4] Estrogen activity is modulated through estrogen receptor α (ER-α) and β (ER-β) which are encoded by ESR1 on chromosome 6q25.1 and ESR2 on chromosome 14q23.2 respectively.[5] ESR1 and ESR2 isoforms are expressed in osteoblasts, osteoclast and bone marrow stromal cells, which means that these receptors have functional roles in bone metabolism.[6]

XB and JS contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

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Many studies reported ESR1 *PvuII* (rs2234693), *XbaI* (rs9340799), *G2014A* (rs2228480), ESR2 *AluI* (rs4986938), *RsaI* (rs1256049), and osteoporosis risk.[7–49] However, this specific association remains controversial. Two meta-analyses assessed the association of osteoporosis risk with ESR1 and ESR2 gene polymorphisms with conflicting results.[50,51] Moreover, the previously published meta-analyses did not conduct a credibility analysis. Therefore, an updated meta-analysis was conducted to further investigate the association between ESR1 [*PvuII*(rs2234693), *XbaI*(rs9340799), *G2014A*(rs2228480)] and ESR2 (*Alul*(rs4986938), *Rsal*(rs1256049)) polymorphisms and the risk of osteoporosis. The present analysis enclosed 71 additional studies which may reflect better results in the analysis of ESR 1 and 2 in the osteoporosis installation.

2. Materials and Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[52]

2.1. Search strategy

PubMed, Medline, Ovid, Embase, China National Knowledge Network (CNKI), and China Wanfang Databases were used for literature retrieval. The search strategies are as follows ("estrogen receptor" OR "ESR" OR "Estrogen receptor alpha" OR "Estrogen receptor β" OR "ERα" OR "ERβ" OR "Estrogen receptor 1" OR "Estrogen receptor 2" OR "ESR1" OR "ESR2") and ("polymorphism" OR "variability" OR "mutation" OR "gene") and ("Osteoporosis" OR "Osteoporoses") literature searches were conducted until May 30, 2023. In addition, a careful review of the reference list of antecedently printed meta-analyses was conducted to spot all eligible studies.[50,51]

2.2. Selection criteria

Inclusion criteria were as follows: (1) case-control or cohort studies; (2) associations were described between ESR1 *PvuII* (rs2234693), *XbaI* (rs9340799), *G2014A* (rs2228480) and ESR2 *AluI* (rs4986938) and *RsaI* (rs1256049) polymorphisms and risk of osteoporosis; (3) detailed genotype data or odds ratios (OR) and their corresponding 95% confidence intervals (CI). Exclusion criteria were as follows: (1) animal experiments or overlapping studies; (2) case reports, abstracts, reviews, letters, and meta-analysis; (3) insufficient genotype data or unavailable for study.

2.3. Data extraction and quality assessment

We predesigned a knowledge extraction table. Two researchers screened all the literatures by the inclusion and exclusion criteria. Conflicts were discussed between the 2 authors to reach an agreement. Data extraction from each study included year of publication, first author, country, sex, geographic region, ethnicity, menopausal status, number of samples of cases and controls, and genotypes frequency (Table S2, Supplemental Digital Content, http://links.lww.com/MD/K139). The evaluation criteria of studies quality were shown in Table S1, Supplemental Digital Content, http://links.lww.com/MD/K138 according to previous studies.[53–55] Two authors assessed the studies quality, respectively. The total score was 21 points, studies scoring > 13 were high quality.

2.4. Statistical analysis

STATA code version12.0 (STATA Corp, College Station, TX) calculated all applied math analyses for this meta-analysis. In 5 genetic models (dominant model; recessive model; additive model; overdominant model; allele model). Hardy–Weinberg equilibrium was calculated using Chi-square test for the genotype frequency of the control population (P < .05 was considered as Hardy–Weinberg disequilibrium [HWD]).[56]

Heterogeneity among studies used Q test and I^2 value. Obvious heterogeneity was observed among studies if P < .10 and/or I^2 > 50%[57] and the ORs were pooled applying a random-effects model. Otherwise, a fixed-effects model was applied. Moreover, if I^2 > 75%, the results will not be combined. Meanwhile, the sources of heterogeneity were evaluated applied meta-regression analysis.[58] Subgroups were conducted by ethnicity, sex, and menopausal status. Sensitivity analyses were assessed by eliminating each study individually or by eliminating studies with both low quality and HWD. Egger[59] and Begg test[60] were performed for potential publication bias. If publication bias exists, a nonparametric "trim and fill" approach[61] was used to estimate and supplement the number of missing studies. False positive reporting probability (FPRP),[62] Bayesian error detection probability (BFDP),[63] and Venetian criteria[64] were used to assess the credibility of statistically significant associations. associations were regarded as positive results if they met the following criteria: (1) significant associations were found in a minimum of 2 of the genetic models; (2) I^2 < 50%; (3) FPRP < 0.2 and BFDP < 0.8; (4) statistical power > 80%.

3. Results

According to the pre-search strategy, 2712 articles were retrieved (Fig. 1). After deleting the duplicate items, 1513 records were remained. After careful selection of titles and abstracts, we eliminated 1415 articles. After we filtered by full text availability and article type, 15 articles were eliminated due to data duplication or lack of access to detailed data, and 9 articles were eliminated due to poor control. Finally, our study included 44 articles and 195 studies (Tables S2–S4, Supplemental Digital Content, http://links.lww.com/MD/K139, http://links.lww.com/MD/K140, http://links.lww.com/MD/K141, Fig. 1), 54,360 controls were included. As shown in Tables S2–S4, Supplemental Digital Content, http://links.lww.com/MD/K139, http://links.lww.com/MD/K140, http://links.lww.com/MD/K141 *ESR1 Pvull* (rs2234693) was reported in 28 studies (4562 cases and 5711 controls), ESR1 *Xbal* (rs9340799) in 23 studies (4000 cases and 4657 controls), and ESR1 *G2014A* (rs2228480) in 5 studies (294 cases and 1350 controls); as shown in Tables S5 and S6, Supplemental Digital Content, http://links.lww.com/MD/K142, http://links.lww.com/MD/K143 ESR2 *Alul* (rs4986938) had 8 studies (1880 cases and 3385 controls) and *Rsal* (rs1256049) had 7 studies (1701 cases and 2648 controls). In addition, ESR1 *Pvull* (rs2234693) had 7 low quality articles and 22 high quality articles, ESR1 *Xbal* (rs9340799) had 5 low quality articles and 19 high quality articles, ESR1 *G2014A* (rs2228480) had one low quality article and 4 high quality articles, ESR2 *Alul* (rs4986938) and *Rsal* (rs1256049) are full of high-quality articles and no low-quality articles (Table S7, Supplemental Digital Content, http://links.lww.com/MD/K144). In addition, the complete features and genotype frequencies of the literatures finally included by us are shown in Tables S2–S6, Supplemental Digital Content, http://links.lww.com/MD/K139, http://links.lww.com/MD/K140, http://links.lww.com/MD/K141, http://links.lww.com/MD/K142, http://links.lww.com/MD/K143.

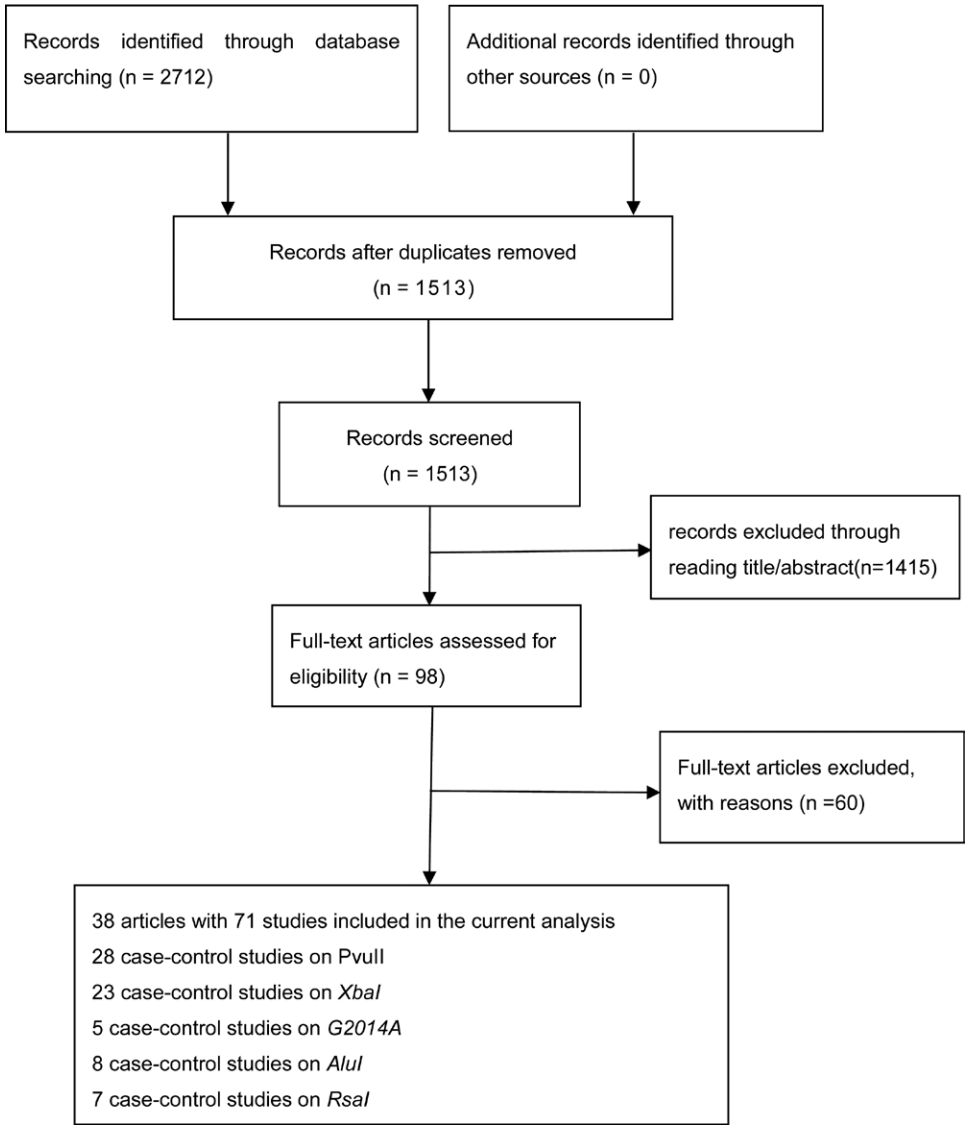

Figure 1. Flow diagram of the literature search.

3.1. Quantitative synthesis

3.1.1. ESR1 PvuII (rs2234693) polymorphism. The summary of results and ethnic distributions is presented in Table 1 and Figure 2. Overall analysis indicated that the ESR1 *PvuII* (rs2234693) polymorphism was not associated with osteoporosis risk. However, there was a significantly increased osteoporosis risk in Indians (pp vs Pp + PP: OR = 1.69, 95% CI = 1.35–2.11; pp versus PP: OR = 1.65, 95% CI = 1.23–2.2; PP + pp vs Pp: OR = 1.68, 95% CI = 1.21–2.67; p vs P: OR 1.38, 95% CI = 1.18–1.6). Similarly, an elevated risk of osteoporosis was also observed in Mexican-American population and premenopausal female. Moreover, these significant associations did not be changed by the results of sensitivity analysis (Table 1). However, after FPRP, BFDP, and Venetian standard tests of the above significant results, we believed that they were not credible (Table 6).

3.1.2. ESR1 XbaI (rs9340799) polymorphism. We found a significantly increased risk of osteoporosis in Indians (xx + Xx vs XX: OR = 1.59, 95% CI = 1.23–2.07; xx vs Xx + XX: OR = 1.99, 95% CI = 1.15–3.44; xx vs XX: OR = 2.63, 95% CI = 1.32–5.27; x vs X: OR = 1.53, 95% CI = 1.12–2.08), as well as mixed population, premenopausal status, and hospital-based controls population (Table 2 and Fig. 3). Moreover, these significant associations did not be changed by the results of sensitivity analysis. However, these associations were not credible when we used FPRP, BFDP to correct for the significant results (Table 6).

3.1.3. ESR1 G2014A (rs2228480) polymorphism. We found no significant association between ESR1 *G2014A* (rs2228480) polymorphism and the risk of osteoporosis in overall population. The ESR1 *G2014A* (rs2228480) polymorphism was related to a reduced risk of osteoporosis in East Asians (AA + GG vs GA: OR = 0.71, 95% CI = 0.51–0.99, Table 3 and Fig. 4), and so on. The source of heterogeneity was found in the source of controls of ESR1 *G2014A* (rs2228480) polymorphism (AA + GA vs GG: P = .046; AA vs AG + GG: P = .03; AA vs GG: P = .02; A vs G: P = .01). Moreover, In the sensitivity analysis, we found association with reduced risk of osteoporosis in the overall analysis (AA + AG vs GG: OR = 0.38, 95% CI = 0.22–0.66; AA vs GA + GG: OR = 0.5, 95% CI = 0.36–0.7; AA vs GG: OR = 0.26, 95% CI = 0.14–0.5; A vs G: OR = 0.55, 95% CI =

Table 1

Meta-analysis of the association of *ESR1 Pvull* polymorphism with risk of osteoporosis.

Variable	n (cases/controls)	pp + Pp versus PP		pp versus Pp + PP		pp versus PP		pp + PP versus Pp		p versus P	
		OR (95% CI)	P_h/I^2 (%)	OR (95% CI)	P_h/I^2 (%)	OR (95% CI)	P_h/I^2 (%)	OR (95% CI)	P_h/I^2 (%)	OR (95% CI)	P_h/I^2 (%)
Overall	28 (4562/5711)	*	<0.001/83.6	*	<0.001/86.1	*	<0.001/87.8	**1.07 (0.93–1.24)**	**<0.001/60.1**	*	<0.001/88.7
Ethnicity											
Caucasian	9 (1036/1487)	*	<0.001/89	1.06 (0.88–2.17)	0.435/0	1.19 (0.69–2.05)	<0.001/74.4	0.97 (0.83–1.15)	0.43/70	1.09 (0.87–1.37)	0.0.1/69.4
East Asian	15 (2791/3439)	*	<0.001/87	*	0.001/93.8	*	<0.001/93.4	0.98 (0.88–1.09)	0.019/48.3	*	<0.001/92.6
Indian	3 (647/748)	1.25 (0.96–1.62)	0.739/0	**1.69 (1.35–2.11)**	0.65/0	**1.65 (1.23–2.20)**	0.67/0.0	**1.68 (1.06–2.67)**	0.033/70.7	**1.38 (1.18–1.60)**	0.507/0
Mixed	1 (88/37)	**0.43 (0.24–0.76)**	*	0.55 (0.16–1.87)	*	**0.28 (0.07–1.03)**	*	**3.31 (1.49–7.35)**	*	**0.40 (0.22–0.71)**	*
Sex											
Male	3 (459/725)	1.02 (0.71–1.46)	0.659/0	1.15 (0.88–1.50)	0.46/0.0	1.09 (0.74–1.62)	0.862/0	1.13 (0.87–1.46)	0.07/32.2	1.10 (0.92–1.32)	0.525/0
Female	27 (4044/4841)	*	<0.001/84.5	*	<0.001/82.8	*	<0.001/87.6	1.05 (0.95–1.13)	0.004/47.6	*	<0.001/89.2
Menopause											
Postmenopausal	23 (2946/3774)	*	<0.001/90.3	*	<0.001/84.7	*	<0.001/88.1	1.00 (0.91–1.11)	0.04/35.7	*	<0.001/92
Non-postmenopausal	4 (1882/2216)	*	<0.001/87.9	1.04 (0.70–1.55)	0.011/73.3	*	<0.001/88	**1.37 (1.15–1.62)**	0.428/0.0	1.13 (0.88–1.45)	0.019/69.9
Source of controls											
HB	16 (2049/1731)	*	<0.001/87.5	*	<0.001/89.1	*	<0.001/90.8	1.03 (0.81–1.31)	<0.001/65.9	*	<0.001/92.5
PB	12 (2710/3468)	1.08 (0.81–1.46)	<0.001/69.8	1.1 (0.99–1.23)	0.447/0	1.15 (0.84–1.59)	0.001/66.6	1.04 (0.94–1.16)	0.584/0	1.09 (0.94–1.25)	0.003/61
Sensitivity analysis											
HWE and quality score > 12											
Overall	19 (3586/4970)	*	<0.001/82.5	*	<0.001/88.8	*	<0.001/88.6	0.99 (0.83–1.17)	<0.001/64.2	*	<0.001/89.7
Ethnicity											
Caucasian	6 (664/1180)	**2.01 (1.15–3.51)**	0.001/74.9	1.17 (0.95–1.44)	**0.665/0.0**	**1.61 (1.21–2.14)**	0.338/12.1	0.84 (0.7–1.03)	0.989/0	**1.24 (1.08–1.42)**	0.342/11.4
East Asian	11 (2401/3124)	*	<0.001/89.9	*	<0.001/95.6	*	<0.001/95.3	0.89 (0.72–1.09)	0.017/55.4	*	<0.001/93.8
Indian	3 (647/748)	1.25 (0.96–1.62)	0.739/0	**1.69 (1.35–2.11)**	0.65/0	**1.65 (1.23–2.20)**	0.67/0	**1.68 (1.06–2.67)**	0.033/70.7	**1.38 (1.18–1.60)**	0.507/0
Sex											
Male	3 (459/725)	1.02 (0.71–1.16)	0.659/0	1.15 (0.88–1.50)	0.46/0	1.09 (0.74–1.62)	0.862/0	1.13 (0.87–1.46)	0.24/29.8	1.10 (0.92–1.32)	0.525/0
Female	18 (3090/4021)	*	<0.001/85.3	*	<0.001/85.6	*	<0.001/88.7	1.08 (0.90–1.30)	0.001/58.7	*	<0.001/90.3
Menopause											
Postmenopausal	16 (2278/3250)	*	<0.001/92	*	<0.001/87.2	*	<0.001/89.5	0.95 (0.84–1.07)	0.026/45.2	*	<0.001/92.0
Non-postmenopausal	4 (1882/2216)	*	<0.001/87.9	1.04 (0.70–1.55)	0.011/73.3	*	<0.001/88	**1.37 (1.15–1.62)**	0.428/0	1.13 (0.88–1.45)	0.019/69.9
Source of controls											
HB	10 (1268/1809)	*	<0.001/89.5	*	<0.001/92	*	<0.001/92.9	0.89 (0.66–1.20)	0.001/69.4	*	<0.001/94.4
PB	9 (2318/3161)	1.22 (1.05–1.41)	0.13/36	1.14 (1.01–1.28)	0.738/0	1.27 (1.08–1.50)	0.179/30	1.00 (0.90–1.12)	0.721/0	1.13 (1.04–1.22)	0.234/23.6
Egger test											
P_E		0.400		0.802		0.520		0.503		0.488	

ESR1 Pvull: allele model: p versus P, additive model: pp versus PP, dominant model: pp + Pp versus PP, recessive model: pp versus PP + Pp overdominant model: PP + pp versus Pp.

HB = hospital-based; HWE = Hardy–Weinberg equilibrium; PB = population-based.

*Results I^2 > 75% and were not pooled.

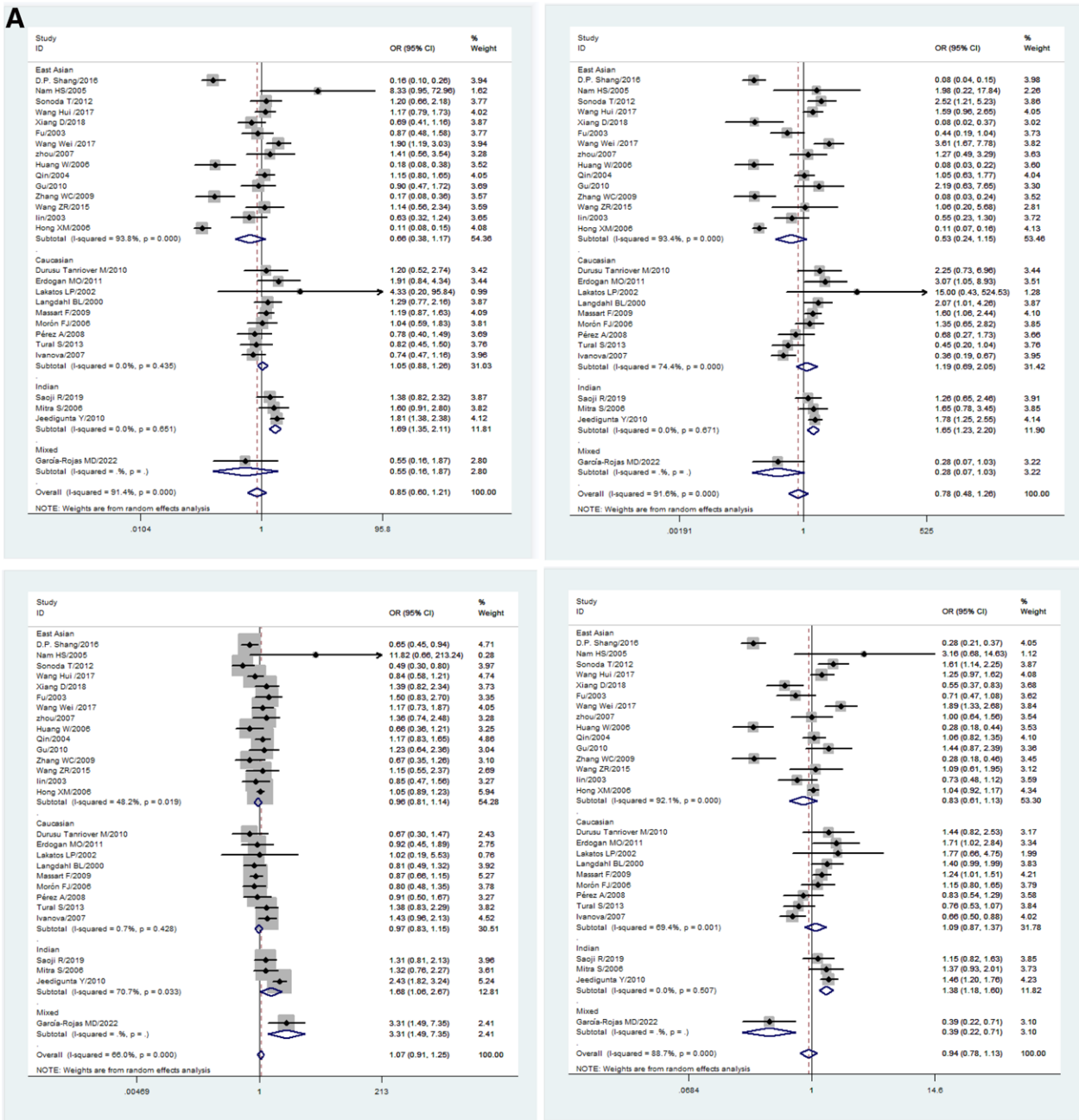

Figure 2. (A) *PvuII* polymorphism and osteoporosis risk in ethnic subgroup analysis. (B) Sensitivity analysis of the correlation between *PvuII* polymorphism and the risk of osteoporosis in the control group source analysis forest map.

0.44–0.69, Table 3 and Fig. 4). At the same time, it was found again that East Asians, Mexican mixed race premenopausal status, postmenopausal status, and population control sources were significantly associated with reduced risk of osteoporosis. After the above significant results was corrected by FPRP and BFDP, only in East Asians (AA + GG vs AG FPRP = 0.124, BFDP = 0.124), menopausal status (AA + GG vs AG FPRP = 0.124, BFDP = 0.124, Table 6).

3.1.4. ESR2 AluI(rs4986938) polymorphism. Significantly increased risk of osteoporosis was observed in East Asians (aa vs AA: OR = 1.35, 95% CI = 1.02–1.79) and hospital-based controls (aa + Aa vs AA: OR = 1.93, 95% CI = 1.25–2.99; a vs A: OR = 1.64, 95% CI = 1.05–2.56, Table 4 and Fig. 5). However, contrasting findings were observed in Caucasians (aa + AA vs Aa: OR = 0.71, 95% CI = 0.51–0.99), Indians, premenopausal status (aa + AA vs Aa: OR = 0.49, 95% CI = 0.38–0.64; a vs A: OR = 0.79, 95% CI = 0.65–0.96), and population control sources (aa + AA vs Aa: OR = 0.84, 95% CI = 0.71–0.99, Table 4) yielded. Meta-regression analysis showed that ethnicity (aa + Aa vs AA: P = .006) and source of control (aa + Aa vs AA = 0.008; a vs A: P = .04) were the source of heterogeneity between the ESR2 *AluI*(rs4986938) polymorphism and the risk of osteoporosis. Moreover, these significant associations did not be changed by the results of sensitivity analyses. However, when we perform FPRP and BFDP tests on the above significant results, they cannot be considered credible (Table 6).

3.1.5. ESR2 RsaI(rs1256049) polymorphism. The results showed that ESR2 *RsaI*(rs1256049) polymorphism increased

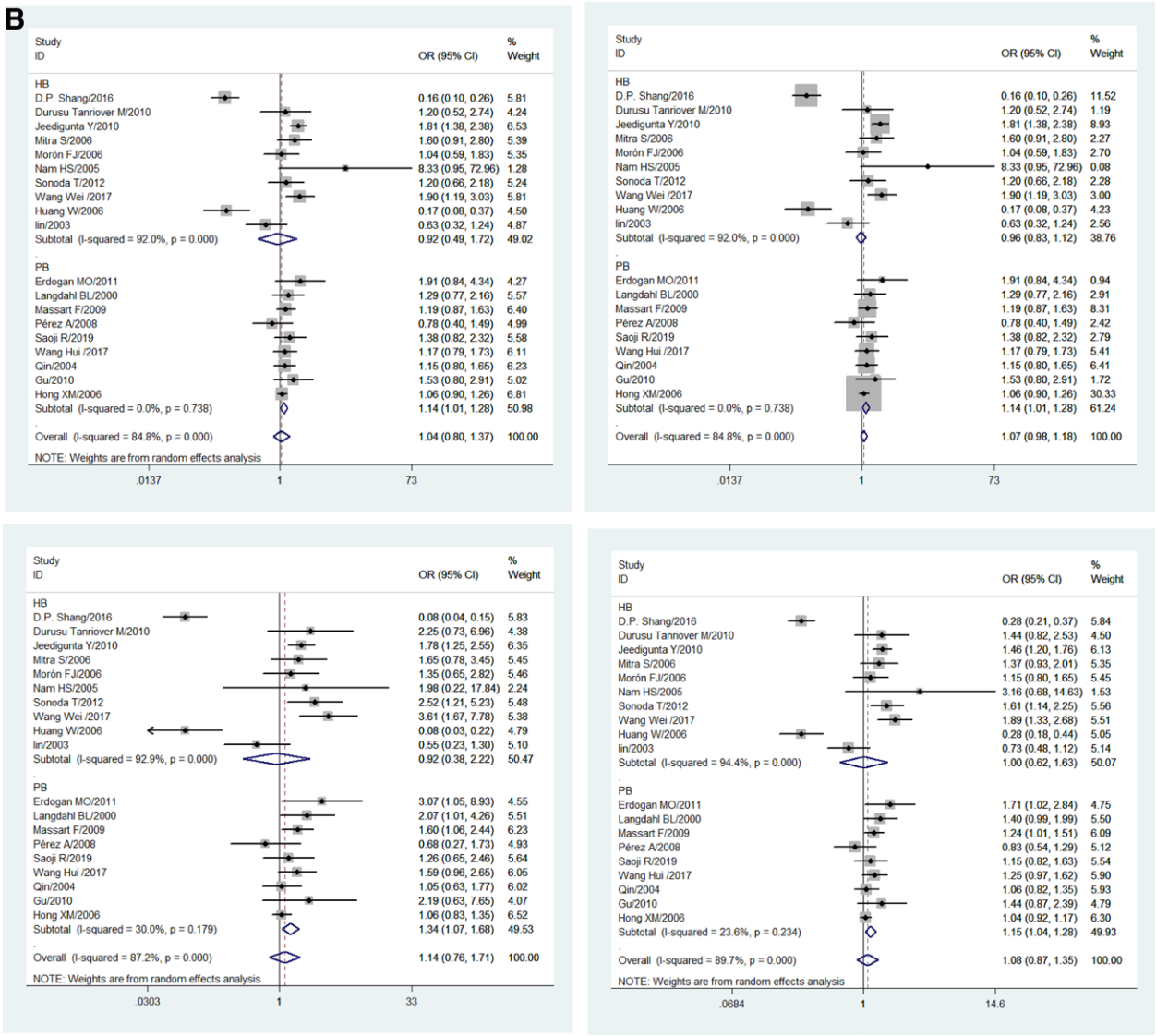

Figure 2. Continued

the risk of osteoporosis in the whole population (rr vs RR: OR = 1.68, 95% CI = 1.14–2.48; r vs R: OR = 1.44, 95% CI = 1.32–1.57, Table 5 and Fig. 6) and several subgroup analyses (Table 5). Meta regression analysis showed that menopausal status (rr + Rr vs RR: P = .003; rr vs Rr + RR: P = .001; rr vs RR: P = 001; rr + RR vs Rr: P = .003, r vs R: P = .001), source of control (rr + Rr vs RR: P < .01; rr vs Rr + RR: P = .02; rr vs RR: P = .02) were the source of heterogeneity. However, when we use FPRP, BFDP to correct the above significant results, it is shown that these results are not very credible (Table 6).

3.2. Publication bias

Begg funnel plot and Egger test showed publication bias only between ESR2 *Rsal*(rs1256049) polymorphism and osteoporosis risk (rr + Rr vs RR: P = .07; rr vs RR: P = .003; rr + RR vs Rr: P = .02, credibility). Then, publication bias was adjusted using a nonparametric "trim and fill" method. We need to add 3 articles for the rr + RR vs Rr model in the future (Fig. 7), rr + Rr vs RR, and rr vs RR without additional studies. In the overall analysis, the results for the rr + RR vs Rr, rr + Rr vs RR, and rr vs RR models did not change (data not shown), suggesting that more studies could not change the pooled results.

4. Discussion

This meta-analysis enclosed 38 articles and 71 studies. ESR1 *Pvull*(rs2234693) was reportable in 28 studies, ESR1 *Xbal*(rs9340799) in 23 studies, ESR1 *G2014A*(rs2228480) in 5 studies, ESR2 *Alul*(rs4986938) had 8 studies, ESR2 *Rsal*(rs1256049) had 7 studies. Overall, once ESR1 *Pvull*(rs2234693) was analyzed, the analysis indicated that polymorphisms in *Pvull*(rs2234693) did not influence the danger of osteoporosis. In the Indians race, Mexican mixed-race, premenopausal status subgroup study, we found that the ESR1 *Pvull*(rs2234693) polymorphism significantly increased the risk of osteoporosis. Whereas no significant results were found in other subgroup analyses and in the final sensitivity analysis. Quantitative synthesis and low-quality information mixing may affect the confidence of the final results, and although 28 studies in this study assessed the association between *Pvull*(rs2234693) polymorphism and

Table 2

Meta-analysis of the association of *ESR1 XbaI* polymorphism with risk of osteoporosis.

Variable	n (cases/controls)	xx + Xx versus XX		xx versus Xx + XX		xx versus XX		xx + XX versus Xx		x versus X	
		OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)
Overall	23 (4000/4657)	*	<0.001/92.7	*	<0.001/83.4	*	<0.001/90.5	1.08 (0.92–1.28)	<0.001/55	*	<0.001/94.3
Ethnicity											
Caucasian	6 (508/600)	*	<0.001/79.1	0.89 (0.68–1.17)	0.697/0	*	0.003/75.2	1.00 (0.67–1.50)	0.058/53.5	*	<0.001/93.5
East Asian	13 (2632/3139)	*	<0.001/92.9	*	<0.001/91.3	*	<0.001/91.1	*	<0.001/79	*	<0.001/96.4
Indian	3 (647/748)	**1.59 (1.23–2.07)**	0.163/44.9	**1.99 (1.15–3.44)**	0.026/72.7	**2.63 (1.32–5.27)**	0.057/65.2	1.15 (0.93–1.43)	0.989/0	**1.53 (1.12–2.08)**	0.054/65.8
Mixed	1 (88/37)	0.78 (0.45–1.34)	NA	0.45 (0.13–1.54)	NA	**0.13 (0.03–0.54)**	NA	**5.29 (2.18–12.81)**	NA	**0.40 (0.22–0.71)**	NA
Sex											
Male	3 (540/809)	0.98 (0.54–1.78)	0.652/0	0.95 (0.50–1.79)	0.132/50.6	0.97 (0.53–1.80)	0.601/0	0.97 (0.49–1.90)	0.107/55.2	1.13 (0.90–1.42)	0.3235/31
Female	22 (3344/3904)	*	<0.001/89.6	*	<0.001/85.7	*	<0.001/89.9	1.10 (0.96–1.26)	0.056/34.8	*	<0.001/94.9
Menopause											
Postmenopausal	20 (3495/4235)	*	<0.001/89.8	*	<0.001/88.7	*	<0.001/91	1.07 (0.95–1.20)	0.11/29	*	<0.001/95.2
Non-postmenopausal	4 (1802/1949)	0.97 (0.69–1.36)	0.739/0	1.15 (0.70–1.91)	0.031/66.1	1.27 (0.84–1.93)	0.195/36.2	**1.29 (1.03–1.61)**	0.133/46.4	1.16 (0.94–1.33)	0.23/30.4
Source of controls											
HB	13 (1714/1892)	*	<0.001/92.9	*	<0.001/90.7	*	<0.001/93	**1.17 (1.02–1.34)**	0.027/48	*	<0.001/96.8
PB	10 (2286/2765)	0.79 (0.50–1.25)	<0.001/72.3	*	<0.001/95.7	*	<0.001/89.8	*	<0.001/94.6	0.97 (0.88–1.06)	0.085/40.9
Sensitivity analysis											
HWE and quality score > 12											
Overall	16 (3176/3983)	*	<0.001/95.8	*	<0.001/86.1	*	<0.001/91.3	1.01 (0.84–1.23)	0.005/54.7	*	<0.001/95.8
Ethnicity											
Caucasian	4 (274/401)	1.55 (0.97–2.48)	0.194/36.3	1.02 (0.73–1.40)	0.973/0	1.40 (0.80–2.36)	0.40/0	0.83 (0.61–1.13)	0.44/0	1.12 (0.89–1.10)	0.689/0
East Asian	9 (2255/2834)	*	<0.001/95	*	<0.001/93.1	*	<0.001/93.6	*	<0.001/79	*	<0.001/97.4
Indian	3 (647/748)	**1.59 (1.23–2.07)**	0.163/44.9	**1.99 (1.15–3.44)**	0.026/72.7	**2.63 (1.32–5.74)**	0.057/65.2	**1.15 (0.93–1.43)**	0.989/0	**1.53 (1.12–2.08)**	0.054/65.8
Sex											
Male	3 (540/809)	0.98 (0.54–1.78)	0.652/0	0.95 (0.50–1.79)	0.132/50.6	0.97 (0.53–1.80)	0.601/0	0.97 (0.49–1.90)	0.107/55.2	1.13 (0.90–1.42)	0.235/31
Female	17 (2805/3472)	*	<0.001/91	*	<0.001/87	*	<0.001/91	1.01 (0.91–1.12)	0.451/0.2	*	<0.001/95.8
Menopause											
Postmenopausal	16 (3176/3983)	*	<0.001/91.3	*	<0.001/87.9	*	<0.001/91.4	1.05 (0.93–1.19)	0.439/1.2	*	<0.001/95.8
Non-postmenopausal	4 (1802/1949)	0.97 (0.69–1.36)	0.739/0	1.15 (0.70–1.91)	0.031/66.1	1.27 (0.84–1.93)	0.195/36.2	**1.29 (1.03–1.61)**	0.133/46.4	1.12 (0.94–1.33)	0.23/30.4
Source of controls											
HB	8 (1124/1417)	*	<0.001/95.7	*	<0.001/94.2	*	<0.001/95.8	1.18 (0.99–1.40)	0.142/36	*	<0.001/98.0
PB	8 (2052/2566)	0.93 (0.57–1.52)	<0.001/70.3	*	<0.001/96.2	*	<0.001/90.8	*	<0.001/94.8	1.03 (0.93–1.14)	0957/0
Egger test											
P_E		0.549		0.938		0.788		0.422		0.859	

ESR1 XbaI: allele model: x versus X, additive model: xx versus XX, dominant model: xx + Xx versus XX, recessive model: xx versus XX + Xx, overdominant model: xx + XX versus Xx.

HB = hospital-based; HWE = Hardy–Weinberg equilibrium; PB = population-based.

*Results I^2 > 75% and were not pooled.

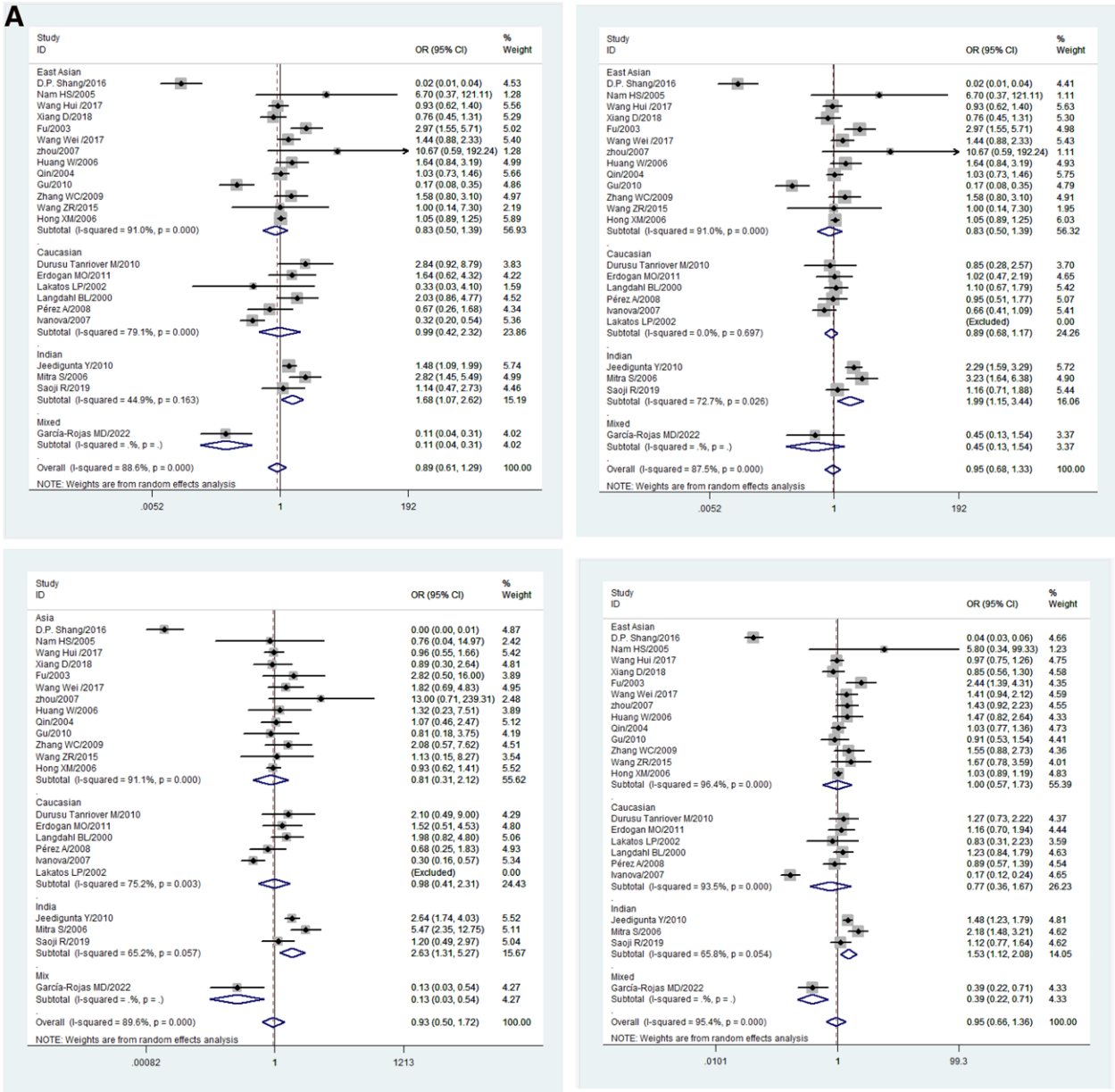

Figure 3. (A) Forest map of the correlation between *Xbal* polymorphism and osteoporosis risk in ethnic subgroup analysis (xx + Xx vs XX; xx vs Xx + XX; xx vs XX; x vs X). (B) Forest map of the correlation between *Xbal* polymorphism and the risk of osteoporosis in postmenopausal status analysis (xx + XX vs Xx). (C) Forest map of the correlation between *Xbal* polymorphism and the risk of osteoporosis in the source analysis of the control group (xx vs XX).

osteoporosis risk, more high-quality studies are needed to draw a large number of robust conclusions. In the overall analysis, the ESR1 *Xbal*(rs9340799) polymorphism similarly found no association with osteoporosis. In the stratified analysis of subgroups, the quantitative composite analysis found that this polymorphism significantly increased the risk of osteoporosis in the Indians race, and mixed race, premenopausal status, hospital control source in Mexico. The association between ESR1 *G2014A*(rs2228480) polymorphism and the risk of osteoporosis showed opposite results in subgroup analysis between population-based and hospital-based controls. East Asians, Mexican mixed race, premenopausal status, postmenopausal status, *G2014A*(rs2228480) significantly reduced the risk of osteoporosis. For the overall study, we did not find a significant association between ESR1 *G2014A*(rs2228480) polymorphism and the incidence of osteoporosis. However, further in the sensitivity analysis, a significant association with osteoporosis risk was found in the overall analysis, indicating that pooled data from relatively high-quality studies often indicate that *G2014A* (rs2228480) polymorphism increases osteoporosis risk. Overall, no association was found between the ESR2 *AluI* (rs4986938) polymorphism and also the risk of osteoporosis. In subgroup analysis, the East Asians subgroup and hospital management cluster had opposite results compared with the Caucasian race subgroup, Indians race subgroup, biological time standing, and population-based management cluster. Within the sensitivity analysis, *AluI*(rs4986938) was found to be related to the danger of osteoporosis within the overall analysis. Within the overall analysis, the ESR2

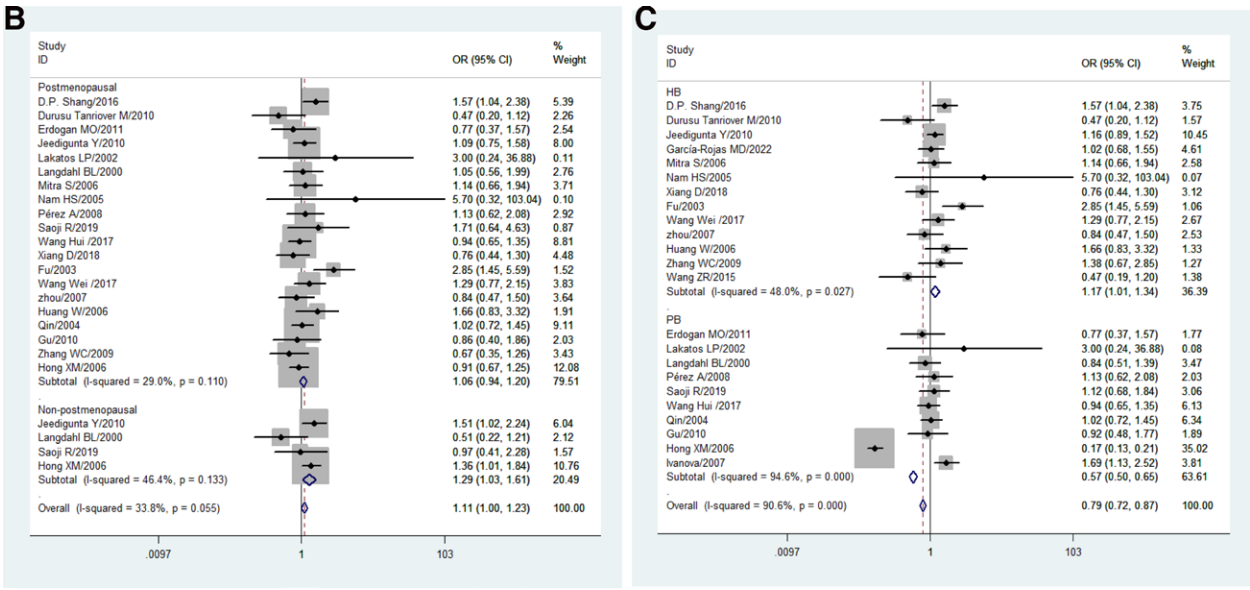

Figure 3. Continued

Rsal(rs1256049) polymorphism considerably redoubled the danger of osteoporosis. Particularly among Esat Asian, Caucasian, and Indians race subgroup. In addition, the association between population control source and hospital control source again demonstrated that the *Rsal*(rs1256049) polymorphism significantly increased the risk of osteoporosis. The current study used many subgroups and different genetic models, which resulted in multiple comparisons, making it necessary to correct the pooled *P* values. Venice criteria, statistical power, and I^2 values are very important criteria.[65] Given the large amount of genomic data currently being generated, we therefore investigated false positive results based on FPRP, BFDP, and Venice criteria. FPRP is a recognized method for investigating multiple hypothesis tests in molecular epidemiology to assess the confidence of important results.[66] Wakefield proposed an exact Bayesian Approach to the test that has been reported as false positive in genetic epidemiological investigations. Using FPRP, BFDP, and Venice criteria, we considered the results of the association between gene polymorphisms of ESR1 *Pvull*(rs2234693), ESR1 *Xbal*(rs9340799), ESR1 *G2014A*(rs2228480), ESR2 *Alul*(rs4986938), ESR2 *Rsal*(rs1256049) and the risk of osteoporosis to be less credible.

Until then, 2 connected meta-analyses[50,51] have published the results of the association between gene polymorphisms of ESR1 *Pvull*(rs2234693), ESR1 *Xbal*(rs9340799), ESR1 *G2014A*(rs2228480), ESR2 *Alul*(rs4986938), ESR2 *Rsal*(rs1256049) and the risk of osteoporosis (Table S8, Supplemental Digital Content, http://links.lww.com/MD/K145). The results[50] suggest that the ESR2 *RsaI*(rs1256049) polymorphism may play a significant protective role. Gene polymorphisms in ESR1 *PvuII*(rs2234693), ESR1 *XbaI*(rs9340799), ESR1 *G2014A*(rs2228480), and ESR2 *AluI*(rs4986938) are unlikely to be associated with the risk of osteoporosis. ESRα/β gene polymorphisms are significantly associated with osteoporosis risk and decreased BMD in postmenopausal women, but there are differences in gene expression and regulation between East Asians and Caucasian populations.[51] The determined association among these studies has been inconsistent. Additionally, revealed meta-analyses concerned studies with some information overlap and lots of uncalled-for information, and a close quality assessment of eligible studies wasn't performed. moreover, none of the studies used correction tools (e.g., FPRP, BFDP) to regulate for multiple comparisons of positive results.

To help clarify the sooner inconclusive findings and therefore the results of many recently revealed studies, we have a tendency to conducted this meta-analysis. Compared with previous meta-analyses, the current meta-analysis has the following blessings: (1) assess the standard of the enclosed studies; (2) Hardy–Weinberg equilibrium check was performed within the management group; (3) we have a tendency to applied FPRP, BFDP, and Venezia criteria to assess the many associations within the current meta-analysis; (4) Stricter inclusion criteria and bigger sample size; (5) subgroup analysis was additional comprehensive. We not only grouped women by sex, but also separately grouped women according to whether they were menopausal or not. Despite the utilization of multiple methods to ameliorate the issues of previous studies, there square measure many limitations of this study. First, we included only published articles, so it is inevitable that some studies may have been missed. Second, there was no management for contradictory factors like smoking, alcohol consumption, and variable study style that square measure closely associated with influencing the results. Third, the rating scale for study characteristics employed in this meta-analysis still has some limitations. though such assessment criteria are used before, this rating scale might not be elaborate enough, and conventional scores square measure merely calculated while not coefficient every item in line with its importance. Fourth, in our study, some low-quality studies were included in this meta-analysis, and small samples accounted for a certain proportion, which may affect the results of the overall analysis. Therefore, a more accurate analysis should be performed when sufficient data are available in the future.

5. Conclusion

In conclusion, there were no credible results demonstrating a robust association between ESR1 *Pvull*(rs2234693), ESR1 *Xbal*(rs9340799), ESR1 *G2014A*(rs2228480), ESR2 *Alul*(rs4986938), ESR2 *Rsal*(rs1256049) polymorphisms and

Table 3

Meta-analysis of the association of ESR1 *G2014A* polymorphism with risk of osteoporosis.

Variable	n (cases/controls)	AA + GA versus GG		AA versus GA + GG		AA versus GG		AA + GG versus GA		A versus G	
		OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)
Overall	5 (294/1350)	0.50 (0.22–1.14)	0.006/72.4	0.66 (0.37–1.16)	0.028/63.3	*	0.001/77.6	0.88 (0.67–1.16)	0.197/33.6	*	<0.001/99
Ethnicity											
East Asian	4 (224/780)	*	0.03/79	0.70 (0.36–1.37)	0.013/72.4	*	<0.001/83.2	**0.76 (0.51–0.99)**	0.851/0	*	<0.001/84.2
Mixed	1 (70/570)	**0.60 (0.36–0.99)**	NA	0.51 (0.15–1.69)	NA	0.42 (0.13–1.41)	NA	1.45 (0.86–2.42)	NA	**0.65 (0.43–0.99)**	NA
Menopause											
Postmenopausal	4 (224/780)	*	0.03/79	0.70 (0.36–1.37)	0.013/72.4	*	<0.001/83.2	**0.76 (0.51–0.99)**	0.851/0	*	<0.001/84.2
Non-postmenopausal	1 (70/570)	**0.60 (0.36–0.99)**	NA	0.51 (0.15–1.69)	NA	0.42 (0.13–1.41)	NA	1.45 (0.86–2.42)	NA	**0.65 (0.43–0.99)**	NA
Source of controls											
HB	1 (25/41)	2.75 (0.96–7.70)	NA	**3.89 (1.20–12.64)**	NA	**4.79 (1.32–17.46)**	NA	1.06 (0.35–3.20)	NA	**2.84 (1.37–5.90)**	NA
PB	4 (269/1309)	**0.45 (0.30–0.68)**	0.234/29.8	**0.50 (0.36–0.70)**	0.99/0	**0.26 (0.14–0.50)**	0.745/0	0.87 (0.65–1.16)	0.117/49.1	**0.55 (0.44–0.69)**	0.749/0
Sensitivity analysis											
HWE and quality score > 12											
Overall	4 (269/1309)	**0.45 (0.30–0.68)**	0.234/29.8	**0.50 (0.36–0.70)**	0.99/0	**0.26 (0.14–0.50)**	0.745/0	0.87 (0.65–1.16)	0.001/49.1	**0.55 (0.44–0.69)**	0.749/0
Ethnicity											
East Asian	3 (199/739)	**0.25 (0.13–0.49)**	0.909/0	**0.50 (0.35–0.70)**	0.904/0	**0.20 (0.10–0.41)**	0.893/0	**0.68 (0.48–0.96)**	0.9/0	**0.50 (0.38–0.66)**	0.912/0
Mixed	1 (70/570)	**0.60 (0.36–0.99)**	NA	0.51 (0.15–1.69)	NA	0.42 (0.13–1.41)	NA	1.45 (0.86–2.42)	NA	**0.65 (0.43–0.99)**	NA
Menopause											
Postmenopausal	3 (199/739)	**0.25 (0.13–0.49)**	0.909/0	**0.50 (0.35–0.70)**	0.904/0	**0.20 (0.10–0.41)**	0.893/0	**0.68 (0.48–0.96)**	0.9/0	**0.50 (0.38–0.66)**	0.912/0
Non-postmenopausal	1 (70/570)	**0.60 (0.36–0.99)**	NA	0.51 (0.15–1.69)	NA	0.42 (0.13–1.41)	NA	1.45 (0.86–2.42)	NA	**0.65 (0.43–0.99)**	NA
Source of controls											
HB	–	–	–	**–**	–	**–**	–	–	–	**–**	–
PB	4 (269/1309)	**0.45 (0.30–0.68)**	0.234/29.8	**0.50 (0.36–0.70)**	0.99/0	**0.26 (0.14–0.50)**	0.745/0	0.87 (0.65–1.16)	0.117/49.1	**0.55 (0.44–0.69)**	0.749/0
Egger test											
P_E		0.709		0.257		0.792		0.864		0.137	

ESR1 *G2014A*: allele model: A versus G, additive model: AA versus GG, dominant model: AA + GA versus GG, recessive model: AA versus GG + GA, overdominant model: AA + GG versus GA.

HB = hospital-based; HWE = Hardy–Weinberg equilibrium; PB = population-based.

*Results $I^2 > 75\%$ and were not pooled.

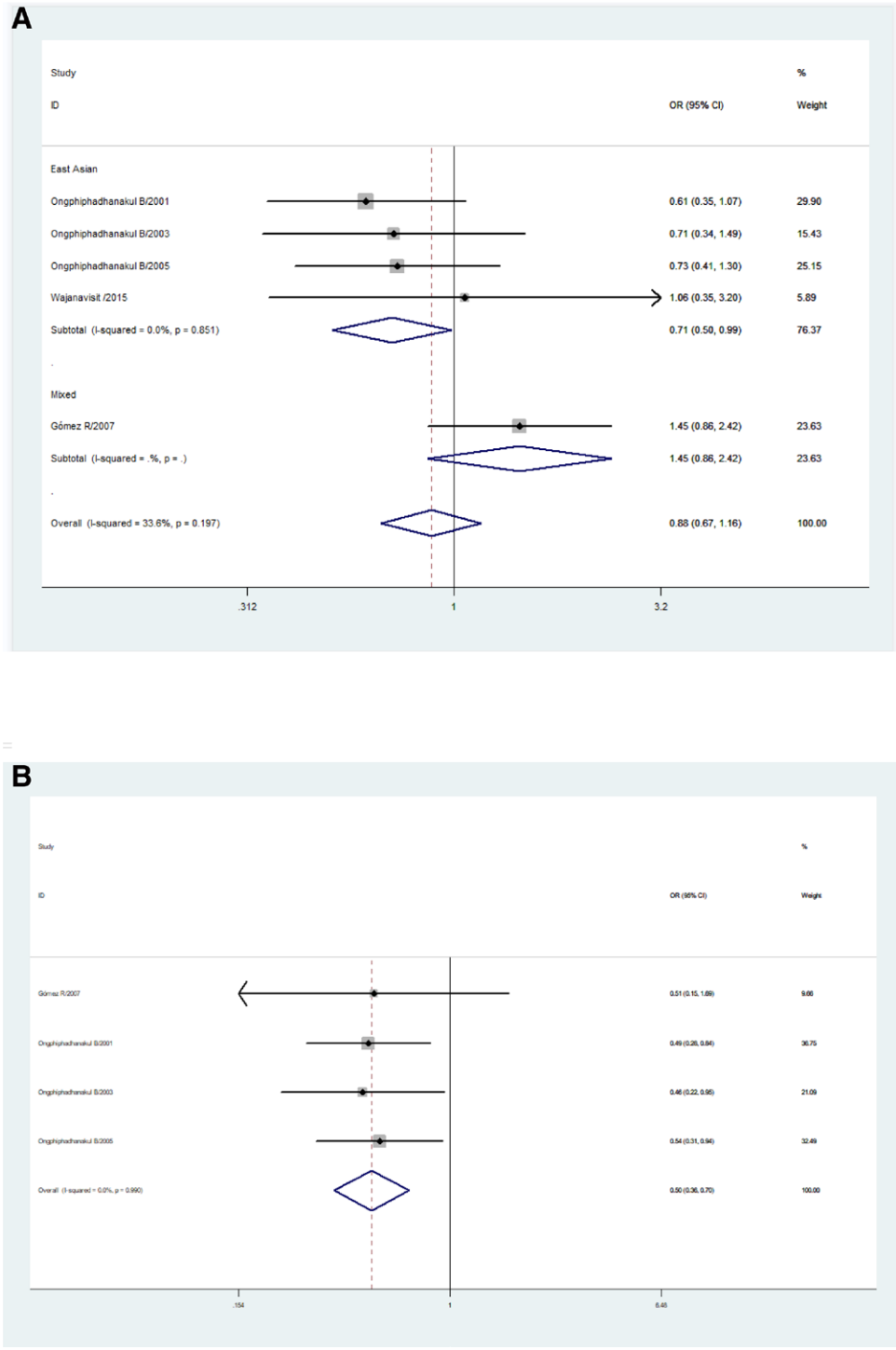

Figure 4. (A) Forest map of the correlation between *G2014A* polymorphism and osteoporosis risk in ethnic subgroup analysis (AA + GG vs GA). (B) Overall sensitivity analysis (AA vs GA + GG).

the risk of osteoporosis. Other evidence of an increased risk of osteoporosis associated with these 5 polymorphisms is most likely due to false positive results. Significant associations should be interpreted with caution, and it is critical that future analyses be based on study quality to effectively identify the effects of genetic variants on osteoporosis risk, especially for combined effects such as gene-body status and gene-environment. In the future, larger epidemiological studies on this topic should be conducted to confirm or refute our findings.

Author contributions

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Formal analysis: Xiao-Hui Bai, Xi-Qin Zhang.
Methodology: Xiao-Hui Bai.
Writing – original draft: Xiao-Hui Bai.
Writing – review & editing: Hong-Zhuo Li, Xiao-Feng He, Xiao-Feng He.

Table 4

Meta-analysis of the association of *ESR2 AluI* polymorphism with risk of osteoporosis.

Variable	n (Cases/ Controls)	aa + Aa versus AA		aa versus Aa + AA		aa versus AA		aa + AA versus Aa		a versus A	
		OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)	OR (95% CI)	P_h/*I2* (%)
Overall	8 (1880/3385)	1.37 (0.98–1.91)	0.001/72.9	*	<0.001/85.9	*	<0.001/82.3	0.84 (0.66–1.08)	0.001/72.4	*	<0.001/89.3
Ethnicity											
Caucasian	3 (570/953)	*	0.002/83.7	*	<0.001/93.4	*	<0.001/92.1	**0.71 (0.51–0.99)**	0.125/51.9	*	<0.001/95.7
Asian	4 (1209/2241)	1.45 (0.99–2.14)	0.077/56.2	1.22 (0.91–1.64)	0.04/63.9	**1.35 (1.02–1.79)**	0.14/45.1	*	0.0049/77.5	*	0.001/81.2
Indian	1 (101/191)	**0.21 (0.13–0.36)**	NA	**0.17 (0.08–0.37)**	NA	**0.08 (0.03–0.19)**	NA	0.84 (0.52–1.37)	NA	**0.66 (0.46–0.95)**	NA
Sex	–	–	–	–	–	–	–	–	–	–	–
Menopause											
Postmenopausal	7 (1598/2789)	1.45 (0.97–2.15)	0.002/70.5	*	<0.001/82.4	*	<0.001/79.8	0.89 (0.67–1.20)	0.002/71.2	*	<0.001/88.5
Non-postmenopausal	2 (383/787)	1.25 (0.29–5.40)	0.003/89	0.47 (0.07–3.00)	0.062/71.4	*	0.01/85	**0.49 (0.38–0.64)**	0.352/0	**0.79 (0.65–0.96)**	0.837/0
Source of controls											
HB	4 (808/1235)	**1.93 (1.25–2.99)**	0.061/59.3	*	<0.001/85.4	*	0.002/79.2	*	<0.001/85.2	**1.64 (1.06–2.56)**	<0.001/87.4
PB	4 (2710/3468)	0.79 (0.56–1.12)	0.009/74.1	0.89 (0.65–1.20)	0.032/70.8	0.85 (0.53–1.36)	0.21/69.1	**0.84 (0.71–0.99)**	0.241/29.7	0.91 (0.80–1.03)	0.149/47.5
Sensitivity analysis											
HWE and quality score > 12											
Overall	5 (1297/2418)	**1.45 (1.14–1.84)**	0.14/43	1. 11 (0.81–1.52)	0.01/69.9	**1.32 (1.02–1.73)**	0.228/29.1	*	<0.001/80.6	*	0.002/76.9
Ethnicity											
Caucasian	1 (88/177)	1.66 (0.80–3.47)	NA	0.61 (0.35–1.07)	NA	1.09 (0.48–2.51)	NA	0.50 (0.29–0.84)	NA	0.92 (0.64–1.33)	NA
Asian	4 (1209/2241)	1.45 (0.99–2.14)	0.077/56.2	1.22 (0.91–1.64)	0.04/63.9	**1.35 (1.02–1.79)**	0.14/45.1	*	0.049/77.5	*	0.001/81.2
Indian	–	–	–	–	–	–	–	–	–	–	–
Menopause											
Postmenopausal	5 (1297/2418)	**1.45 (1.14–1.84)**	0.135/43	1.11 (0.81–1.52)	0.01/69.9	**1.32 (1.02–1.73)**	0.228/39.1	*	<0.001/80.6	*	0.002/76.9
Non-postmenopausal	–	–	–	–	–	–	–	–	–	–	–
Source of controls											
HB	3 (608/1055)	1.71 (0.96–3.05)	0.061/62.5	*	0.04/81.9	1.70 (0.73–3.96)	0.067/62.9	*	<0.001/90.1	*	0.005/81.3
PB	2 (689/1363)	*	0.004/88.2	1.03 (0.85–1.26)	0.743/0	1.24 (0.89–1.73)	0.836/0	0.94 (0.76–1.17)	0.856/0	0.99 (0.84–1.16)	0.383/0
Egger test P_E		0.511		0.902		0.619		0.125		0.470	

ESR2 AluI: allele model: a versus A, additive model: aa versus AA, dominant model: aa + Aa versus AA, recessive model: aa versus AA + TA, overdominant model: aa + AA versus TA.

HB = hospital-based; HWE = Hardy–Weinberg equilibrium; PB: population-based.

*Results $I^2 > 75\%$ and were not pooled.

Figure 5. (A) Forest map of the correlation between *AluI* polymorphism and osteoporosis risk in ethnic subgroup analysis (aa vs AA). (B) Sensitivity analysis of the correlation between *AluI* polymorphism and the risk of osteoporosis in the overall analysis forest map (aa + Aa vs AA; aa vs AA).

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Table 5

Meta-analysis of the association of *ESR2 RasI* polymorphism with risk of osteoporosis.

Variable	n (cases/controls)	rr + Rr versus RR		rr versus Rr + RR		rr versus RR		rr + RR versus Rr		r versus R	
		OR (95% CI)	P_h/I2 (%)	OR (95% CI)	P_h/I2 (%)	OR (95% CI)	P_h/I2 (%)	OR (95% CI)	P_h/I2 (%)	OR (95% CI)	P_h/I2 (%)
Overall	7 (1701/2839)	*	<0.001/85.3	1.02 (0.89–1.16)	0.611/0	**1.68 (1.14–2.48)**	0.003/70.3	*	<0.001/80.5	**1.44 (1.32–1.57)**	0.509/0
Ethnicity											
Caucasian	1 (200/180)	1.33 (0.82–2.17)	NA	1.81 (0.16–20.11)	NA	1.92 (0.17–20.41)	NA	0.76 (0.47–1.25)	NA	**1.79 (1.10–2.92)**	NA
East Asian	5 (1400/2468)	**1.30 (1.09–1.55)**	0.522/0	**1.67 (1.45–1.93)**	0.512/0	**2.04 (1.67–2.48)**	0.14/45.1	**1.20 (1.09–1.42)**	0.926/0	**1.43 (1.30–1.57)**	0.347/10.3
Indian	1 (101/191)	1.27 (0.77–2.10)	NA	**1.86 (1.03–3.36)**	NA	1.91 (0.99–3.69)	NA	1.20 (0.73–1.96)	NA	1.38 (0.98–1.95)	NA
Sex	–	–	–	–	–	–	–	–	–	–	–
Menopause											
Postmenopausal	7 (1676/2819)	**1.51 (1.28–1.77)**	0.448/0	*	0.525/80	**2.09 (1.72–2.54)**	0.415/1.2	**1.20 (1.06–1.37)**	0.595/0	**1.46 (1.33–1.60)**	0.182/32.3
Non-postmenopausal	1 (25/20)	**3.14 (1.39–7.09)**	NA	2.00 (0.84–4.79)	NA	2.24 (0.81–6.23)	NA	1.13 (0.52–2.46)	NA	0.94 (0.51–1.73)	NA
Source of controls											
HB	4 (911/1285)	1.10 (0.96–1.25)	0.41/30	**1.55 (1.27–1.90)**	0.566/0	**1.80 (1.38–2.43)**	0.475/0	**1.21 (1.01–1.44)**	0.22/32.3	*	<0.001/99
PB	3 (7900/1554)	**1.56 (1.26–1.94)**	0.642/0	**1.81 (1.50–2.18)**	0.901/0	**2.19 (1.70–2.82)**	0.819/0	**1.34 (1.01–1.77)**	0.106/55.5	**1.48 (1.31–1.67)**	0.786/0
Sensitivity analysis											
HWE and quality score > 12											
Overall	6 (1288/2062)	*	<0.001/85.3	1.02 (0.87–1.19)	0.561/0	1.49 (0.91–2.45)	0.002/73.8	*	<0.001/83.3	**1.44 (1.29–1.60)**	0.38/5.3
Ethnicity											
Caucasian	1 (200/180)	1.33 (0.82–2.17)	NA	1.81 (0.16–20.11)	NA	1.92 (0.17–20.41)	NA	0.76 (0.47–1.25)	NA	**1.79 (1.10–2.92)**	NA
East Asian	4 (987/1691)	**1.45 (1.29–1.63)**	0.335/11.6	**1.64 (1.39–1.90)**	0.37/4.6	**2.01 (1.59–2.54)**	0.298/18.6	**1.26 (1.07–1.48)**	0.837/0	1.43 (1.27–1.60)	0.217/32.6
Indian	1 (101/191)	1.27 (0.77–2.10)	NA	1.86 (1.03–3.36)	NA	1.91 (0.99–3.69)	NA	1.20 (0.73–1.96)	NA	1.38 (0.98–1.95)	NA
Menopause											
Postmenopausal	6 (1263/2042)	**1.50 (1.24–1.81)**	0.332/13	**1.67 (1.41–1.97)**	0.425/0	**2.08 (1.65–2.62)**	0.3/17.5	**1.19 (1.03–1.39)**	0.116/43.4	**1.47 (1.32–1.64)**	0.116/43.4
Non-postmenopausal	1 (25/20)	**3.14 (1.39–7.09)**	NA	2.00 (0.84–4.79)	NA	2.24 (0.81–6.23)	NA	1.13 (0.52–2.46)	NA	0.94 (0.51–1.73)	NA
Source of controls											
HB	3 (498/508)	1.20 (0.87–1.64)	0.443/30	1.31 (0.95–1.80)	0.935/0	1.46 (0.92–2.30)	0.621/0	1.17 (0.78–1.75)	0.01/54.6	*	0.001/96.4
PB	3 (790/1554)	**1.56 (1.26–1.94)**	0.642/0	**1.81 (1.50–2.18)**	0.901/0	**2.19 (1.70–2.82)**	0.819/0	**1.34 (1.01–1.77)**	0.106/55.5	**1.48 (1.31–1.67)**	0.786/0
Egger test											
P_E		**0.007**		0.986		**0.003**		**0.02**		0.599	

ESR2 RasI: allele model:r versus R, additive model: rr versus RR, dominant model: rr + Rr versus RR, recessive model: rr versus RR + Rr, overdominant model: rr + RR versus Rr.

HB = hospital-based; HWE = Hardy–Weinberg equilibrium; PB: population-based.

*Results I^2 > 75% and were not pooled.

Table 6

Credibility of the current meta-analysis.

						Credibility		
						Prior probability of 0.001		
Gene	Variable	Model	n (Cases/Controls)	OR	Ph/I2 (%)	Power	FPRP	BFDP
Pvull	Indian	pp versus Pp + PP	3 (647/748)	1.69 (1.35–2.11)	0.65/0	0.001	0.742	0.014
Pvull	Indian	pp versus PP	3 (647/748)	1.65 (1.23–2.20)	0.67/0	0.015	0.977	0.944
Pvull	Indian	pp + PP versus Pp	3 (647/748)	1.68 (1.06–2.67)	0.033/70.7	0.077	0.997	0.997
Pvull	Indian	p versus P	3 (647/748)	1.38 (1.18–1.60)	0.507/0	0.032	0381	0.494
Pvull	Mixed	pp + Pp versus PP	2 (188/237)	0.35 (0.22–0.56)	0.266/19.1	0	0.988	0.435
Pvull	Mixed	pp versus Pp + PP	2 (188/237)	0.42 (0.22–0.78)	0.61/0	0.099	0.998	0.991
Pvull	Mixed	pp versus PP	2 (188/237)	0.24 (0.12–0.49)	0.821/0	0	0.996	0.892
Pvull	Mixed	p versus P	2 (188/237)	0.53 (0.39–0.71)	0.267/18.9.	0.001	0.945	0.454
Pvull	Non-postmenopausal	pp + PP versus Pp	4 (1882/2216)	1.37 (1.15–1.62)	0.428/0	0.061	0.739	0.898
Xbal	Indian	Xx + Xx versus XX	3 (647/748)	1.59 (1.23–2.07)	0.163/44.9	0.018	0.969	0.94
Xbal	Indian	xx versus XX + Xx	3 (647/748)	1.99 (1.15–3.44)	0.026/72.7	0.035	0.997	0.995
Xbal	Indian	xx versus XX	3 (647/748)	2.63 (1.32–5.27)	0.057/65.2	0.013	0.998	0.992
Xbal	Indian	x versus X	3 (647/748)	1.53 (1.12–2.08)	0.054/65.8	0.992	0.991	0.992
Xbal	Mixed	xx versus XX + Xx	2 (188/237)	0.42 (0.22–0.80)	0.919/0	0.019	0.998	0.993
Xbal	Mixed	xx versus XX	2 (188/237)	0.28 (0.13–0.58)	0.25/24.4	0.002	0.997	0.968
Xbal	Mixed	x versus X	2 (188/237)	0.53 (0.39–0.71)	0.267/18.9	0.001	0.945	0.452
Xbal	Non-postmenopausal	Xx + XX versus Xx	4 (1802/1949)	1.29 (1.03–1.61)	0.133/46.4	0.261	0.989	0.998
G2014A	East Asian	AA + GG versus GA	4 (224/780)	0.76 (0.51–0.99)	0.851/0	0.173	0.996	0.998
G2014A	Mixed	AA + AG versus GG	1 (70/570)	0.60 (0.36–0.99)	NA	0.102	0.998	0.998
G2014A	Mixed	A versus G	1 (70/570)	0.65 (0.43–0.99)	NA	0.124	0.997	0.998
G2014A	Postmenopausal	AA + GG versus GA	4 (224/780)	0.76 (0.51–0.99)	0.851/0	0.173	0.996	0.998
G2014A	Non-postmenopausal	AA + AG versus GG	1 (70/570)	0.60 (0.36–0.99)	NA	0.102	0.998	0.998
G2014A	Non-postmenopausal	A versus G	1 (70/570)	0.65 (0.43–0.99)	NA	0.124	0.997	0.998
G2014A	HP	AA versus GA + GG	1 (25/41)	3.89 (1.20 to 12.64)	NA	0.025	0.999	0.998
G2014A	HP	AA versus GG	1 (25/41)	4.79 (1.32–17.46)	NA	0.018	0.999	0.998
G2014A	HP	A versus G	1 (25/41)	2.84 (1.37–5.90)	NA	0.01	0.998	0.992
G2014A	PB	AA + AG versus GG	4 (269/1309)	0.45 (0.30–0.68)	0.234/29.8	0.002	0.989	0.84
G2014A	PB	AA versus GA + GG	4 (269/1309)	0.50 (0.36–0.70)	0.99/0	0.001	0.974	0.664
G2014A	PB	AA versus GG	4 (269/1309)	0.26 (0.14–0.50)	0.745/0	0	0.996	0.826
G2014A	PB	A versus G	4 (269/1309)	0.55 (0.44–0.69)	0.749/0	0	0.591	0.013
AluI	Caucasian	aa + AA versus Aa	3 (570/953)	0.71 (0.51–0.99)	0.125/51.9	0.98	0.966	0.998
AluI	East Asian	aa versus AA	4 (1209/2241)	1.35 (1.02–1.79)	0.14/45.1	0.207	0.994	0.998
AluI	Indian	aa + Aa versus AA	1 (101/191)	0.21 (0.13–0.36)	NA	0	0.981	0.005
AluI	Indian	aa versus Aa + AA	1 (101/191)	0.17 (0.08–0.37)	NA	0	0.996	0.797
AluI	Indian	aa versus AA	1 (101/191)	0.08 (0.03–0.19)	NA	0	0.995	0.006
AluI	Indian	a versus A	1 (101/191)	0.66 (0.46–0.95)	NA	0.105	0.996	0.997
AluI	Non-postmenopausal	aa + AA versus Aa	2 (383/787)	0.49 (0.38–0.64)	0.352/0	0	0.772	0.01
AluI	Non-postmenopausal	a versus A	2 (383/787)	0.79 (0.65–0.96)	0.837/0	0.296	0.984	0.997
AluI	HB	aa + Aa versus AA	4 (808/1235)	1.93 (1.25–2.99)	0.061/59.3	0.017	0.994	0.985
AluI	HB	a versus A	4 (808/1235)	1.64 (1.06–2.56)	<0.001/87.4	0.085	0.997	0.997
AluI	PB	aa + AA versus Aa	4 (2710/3468)	0.84 (0.71–0.99)	0.241/29.7	0.032	0381	0.494
RasI	Overall	rr versus RR	7 (1701/2839)	1.68 (1.14–2.48)	0.003/70.3	0.046	0.995	0. 993
RasI	Overall	rr + RR versus Rr	7 (1701/2839)	1.55 (1.12–2.14)	<0.001/80.5	0.06	0.992	0.993
RasI	Overall	r versus R	7 (1701/2839)	1.44 (1.32–1.57)	0.509/0	0	0	0
RasI	Caucasian	r versus R	1 (200/180)	1.79 (1.10–2.92)	NA	0.055	0.997	0.996
RasI	East Asian	rr + Rr versus RR	5 (1400/2468)	1.30 (1.09–1.55)	0.522/0	0.186	0.949	0.99
RasI	East Asian	rr versus Rr + RR	5 (1400/2468)	1.67 (1.45–1.93)	0.512/0	0	0.001	0
RasI	East Asian	rr versus RR	5 (1400/2468)	2.04 (1.67–2.48)	0.14/45.1	0	0.016	0
RasI	East Asian	rr + RR versus Rr	5 (1400/2468)	1.20 (1.09–1.42)	0.926/0	0.5	0.985	0.99
RasI	East Asian	r versus R	5 (1400/2468)	1.43 (1.30–1.57)	0.347/10.3	0	0	0
RasI	Indian	rr versus Rr + RR	1 (101/191)	1.86 (1.03–3.36)	NA	0.073	0.998	0.998
RasI	Postmenopausal	rr + Rr versus RR	7 (1676/2819)	1.51 (1.28–1.77)	0.448/0	0.002	0.139	0.002
RasI	Postmenopausal	rr versus Rr + RR	7 (1676/2819)	1.70 (1.48–1.96)	0.525/80	0.002	0.002	0.002
RasI	Postmenopausal	rr versus RR	7 (1676/2819)	2.09 (1.72–2.54)	0.415/1.2	0	0.01	0
RasI	Postmenopausal	rr + RR versus Rr	7 (1676/2819)	1.20 (1.06–1.37)	0.595/0	0.5	0.933	0.996
RasI	Non-postmenopausal	rr + Rr versus RR	1 (25/20)	3.14 (1.39–7.09)	NA	0.001	0.998	0.993
RasI	HB	rr versus Rr + RR	4 (911/1285)	1.55 (1.27–1.90)	0.566/0	0.007	0.781	0.781
RasI	HB	rr versus RR	4 (911/1285)	1.80 (1.38–2.43)	0.475/0	0.004	0.968	0.8
RasI	HB	rr versus RR	4 (911/1285)	1.21 (1.01–1.44)	0.22/32.3	0.463	0.986	0.999
RasI	PB	rr + Rr versus RR	3 (7900/1554)	1.56 (1.26–1.94)	0.642/0	0.009	0.874	0.701
RasI	PB	rr versus Rr + RR	3 (7900/1554)	1.81 (1.50–2.18)	0.901/0	0	0.052	0
RasI	PB	rr versus RR	3 (7900/1554)	2.19 (1.70–2.82)	0.819/0	0	0.492	0
RasI	PB	rr + RR versus Rr	3 (7900/1554)	1.34 (1.01–1.77)	0.106/55.5	0.219	0.994	0.998
RasI	PB	r versus R	3 (7900/1554)	1.48 (1.31–1.67)	0.786/0	0.998	0.001	0.998

(*Continued*)

Table 6

(***Continued***)

Gene	Variable	Model	n (Cases/Controls)	OR	Ph/I2 (%)	Credibility: Prior probability of 0.001 Power	FPRP	BFDP
Sensitivity analysis								
HWE and quality score > 12								
Pvull	Caucasian	pp + Pp versus PP	6 (664/1180)	2.01 (1.15–3.51)	0.001/74.9	0.03	0.998	0.995
Pvull	Caucasian	pp versus PP	6 (664/1180)	1.61 (1.21–2.14)	0.338/12.1	0.021	0.98	0.963
Pvull	Caucasian	p versus P	6 (664/1180)	1.24 (1.08–1.42)	0.342/11.4	0.318	0.854	0.986
Pvull	Indian	pp versus Pp + PP	3 (647/748)	1.69 (1.35–2.11)	0.65/0	0.001	0.742	0.014
Pvull	Indian	pp versus PP	3 (647/748)	1.65 (1.23–2.20)	0.67/0	0.015	0.977	0.944
Pvull	Indian	pp + PP versus Pp	3 (647/748)	1.68 (1.06–2.67)	0.033/70.7	0.077	0.997	0.997
Pvull	Indian	p versus P	3 (647/748)	1.38 (1.18–1.60)	0.507/0	0.032	0381	0.494
Pvull	Mixed	pp + PP versus Pp	1 (200/300)	0.51 (0.40–0.64)	NA	0	0.354	0
Pvull	Mixed	pp versus Pp + PP	1 (200/300)	0.38 (0.18–0.80)	NA	0.019	0.998	0.997
Pvull	Mixed	pp versus PP	1 (200/300)	0.23 (0.10–0.54)	NA	0.015	0.977	0.944
Pvull	Mixed	p versus P	1 (200/300)	0.58 (0.41–0.82)	NA	0.032	0.381	0.494
Pvull	PB	pp + PP versus Pp	9 (2318/3161)	1.22 (1.05–1.41)	0.13/36	0.411	0.945	0.995
Pvull	PB	pp versus Pp + PP	9 (2318/3161)	1.14 (1.01–1.28)	0.738/0	0.807	0.971	0.999
Pvull	PB	pp versus PP	9 (2318/3161)	1.27 (1.08–1.50)	0.179/30	0.252	0.951	0.993
Pvull	PB	p versus P	9 (2318/3161)	1.13 (1.04–1.22)	0.234/23.6	0.938	0.654	0.991
XbaI	Indian	xx + Xx versus XX	3 (647/748)	1.59 (1.23–2.07)	0.163/44.9	0.018	0.969	0.94
XbaI	Indian	xx versus Xx + XX	3 (647/748)	1.99 (1.15–3.44)	0.026/72.7	0.035	0.997	0.995
XbaI	Indian	xx versus XX	3 (647/748)	2.63 (1.32–5.27)	0.057/65.2	0.013	0.998	0.992
XbaI	Indian	x versus X	3 (647/748)	1.53 (1.12–2.08)	0.054/65.8	0.992	0.991	0.992
XbaI	Mixed	xx versus Xx + XX	1 (100/200)	0.42 (0.20–0.87)	NA	0.033	0.998	0.996
XbaI	Mixed	xx versus XX	1 (100/200)	0.33 (0.15–0.76)	NA	0.015	0.998	0.995
XbaI	Non-postmenopausal	xx + XX versus Xx	4 (1802/1949)	1.29 (1.03–1.61)	0.133/46.4	0.261	0.989	0.998
XbaI	HB	xx + XX versus Xx	9 (1224/1617)	1.18 (1.01–1.39)	0.205/26.9	0.58	0.988	0.999
G2014A	Overall	AA + GA versus GG	4 (269/1309)	0.38 (0.22–0.66)	0.236/29.3	0.003	0.996	0.952
G2014A	Overall	AA versus GA + GG	4 (269/1309)	0.50 (0.36–0.70)	0.99/0	0.001	0.974	0.974
G2014A	Overall	AA versus GG	4 (269/1309)	0.26 (0.14–0.50)	0.745/0	0	0.996	0.826
G2014A	Overall	A versus G	4 (269/1309)	0.55 (0.44–0.69)	0.749/0	0	0.591	0.013
G2014A	East Asian	AA + GA versus GG	3 (199/739)	0.25 (0.13–0.49)	0.909/0	0	0.996	0.836
G2014A	East Asian	AA versus GA + GG	3 (199/739)	0.50 (0.35–0.70)	0.904/0	0.001	0.974	0.664
G2014A	East Asian	AA versus GG	3 (199/739)	0.20 (0.10–0.41)	0.893/0	0	0.996	0.678
G2014A	East Asian	AA + GG versus GA	3 (199/739)	0.68 (0.48–0.96)	0.9/0	0.124	0.124	0.124
G2014A	East Asian	A versus G	3 (199/739)	0.50 (0.38–0.66)	0.912/0	0	0	0.005
G2014A	Mixed	AA + GA versus GG	1 (70/570)	0.60 (0.36–0.99)	NA	0.102	0.998	0.998
G2014A	Mixed	A versus G	1 (70/570)	0.65 (0.43–0.99)	NA	0.124	0.997	0.998
G2014A	Postmenopausal	AA + GA versus GG	3 (199/739)	0.25 (0.13–0.49)	0.909/0	0	0.996	0.836
G2014A	Postmenopausal	AA versus GA + GG	3 (199/739)	0.50 (0.35–0.70)	0.904/0	0.001	0.974	0.664
G2014A	Postmenopausal	AA + GG versus GA	4 (224/780)	0.76 (0.51–0.99)	0.851/0	0.173	0.996	0.998
G2014A	Non-postmenopausal	AA + GA versus GG	1 (70/570)	0.60 (0.36–0.99)	NA	0.102	0.998	0.998
G2014A	Non-postmenopausal	A versus G	1 (70/570)	0.65 (0.43–0.99)	NA	0.124	0.997	0.998
G2014A	HP	AA versus GA + GG	1 (25/41)	3.89 (1.20–12.64)	NA	0.025	0.999	0.998
G2014A	HP	AA versus GG	1 (25/41)	4.79 (1.32–17.46)	NA	0.018	0.999	0.998
G2014A	HP	A versus G	1 (25/41)	2.84 (1.37–5.90)	NA	0.01	0.998	0.992
G2014A	PB	AA + GA versus GG	4 (269/1309)	0.45 (0.30–0.68)	0.234/29.8	0.002	0.989	0.84
G2014A	PB	AA versus GA + GG	4 (269/1309)	0.50 (0.36–0.70)	0.99/0	0.001	0.974	0.664
G2014A	PB	AA versus GG	4 (269/1309)	0.26 (0.14–0.50)	0.745/0	0	0.996	0.826
G2014A	PB	A versus G	4 (269/1309)	0.55 (0.44–0.69)	0.749/0	0	0.591	0.013
G2014A	Postmenopausal	AA versus GG	3 (199/739)	0.20 (0.10–0.41)	0.893/0	0	0.996	0.678
G2014A	Postmenopausal	AA + GG versus GA	3 (199/739)	0.68 (0.48–0.96)	0.9/0	0.124	0.124	0.124
G2014A	Postmenopausal	A versus G	3 (199/739)	0.50 (0.38–0.66)	0.912/0	0	0	0.005
G2014A	Non-postmenopausal	AA + GA versus GG	1 (70/570)	0.60 (0.36–0.99)	NA	0.102	0.998	0.998
G2014A	Non-postmenopausal	A versus G	1 (70/570)	0.65 (0.43–0.99)	NA	0.124	0.997	0.998
G2014A	PB	AA + GA versus GG	4 (269/1309)	0.45 (0.30–0.68)	0.234/29.8	0.002	0.989	0.84
G2014A	PB	AA versus GA + GG	4 (269/1309)	0.50 (0.36–0.70)	0.99/0	0.001	0.974	0.664
G2014A	PB	AA versus GG	4 (269/1309)	0.26 (0.14–0.50)	0.745/0	0	0.996	0.826
G2014A	PB	A versus G	4 (269/1309)	0.55 (0.44–0.69)	0.749/0	0	0.591	0.013
AluI	Overall	aa + Aa versus AA	5 (1297/2418)	1.45 (1.14–1.84)	0.14/43	0.06	0.974	0.982
AluI	Overall	aa versus Aa + AA	5 (1297/2418)	1.32 (1.02–1.73)	0.228/29.1	0.245	0.994	0.998
AluI	East Asian	aa versus AA	4 (1209/2241)	1.35 (1.02–1.79)	0.14/45.1	0.7	0.994	0.998
AluI	Postmenopausal	aa + Aa versus AA	5 (1297/2418)	1.45 (1.14–1.84)	0.14/43	0.06	0.974	0.982
AluI	Postmenopausal	aa versus Aa + AA	5 (1297/2418)	1.32 (1.02–1.73)	0.228/29.1	0.245	0.994	0.998
AluI	PB	a versus A	9 (2318/3161)	1.13 (1.04–1.22)	0.234/23.6	0.938	0.654	0.991
RasI	Overall	rr + RR versus Rr	6 (1288/2062)	1.73 (1.14–2.63)	<0.001/83.3	0.059	0.997	0.996
RasI	Overall	r versus R	6 (1288/2062	1.44 (1.29–1.60)	0.38/5.3	0	0	0
RasI	Caucasian	r versus R	1 (200/180)	1.79 (1.10–2.92)	NA	0.055	0.997	0.996

(*Continued*)

Table 6

(*Continued*)

Gene	Variable	Model	n (Cases/Controls)	OR	Ph/I2 (%)	Credibility		
						Prior probability of 0.001		
						Power	FPRP	BFDP
Rasl	East Asian	rr + Rr versus RR	4 (987/1691)	1.45 (1.29–1.63)	0.335/11.6	0.001	0.001	0
Rasl	East Asian	rr versus Rr + RR	4 (987/1691)	1.64 (1.39–1.90)	0.37/4.6	0	0.003	0
Rasl	East Asian	rr versus RR	4 (987/1691)	2.01 (1.59–2.54)	0.298/18.6	0	0.319	0
Rasl	East Asian	rr + RR versus Rr	4 (987/1691)	1.26 (1.07–1.48)	0.837/0	0.276	0.946	0.993
Rasl	East Asian	r versus R	4 (987/1691)	1.43 (1.27–1.60)	0.217/32.6	0.001	0	0
Rasl	Postmenopausal	rr + Rr versus RR	6 (1263/2042)	1.50 (1.24–1.81)	0.332/13	0.01	0.701	0.498
Rasl	Postmenopausal	rr versus Rr + RR	6 (1263/2042)	1.67 (1.41–1.97)	0.425/0	0	0.026	0
Rasl	Postmenopausal	rr versus RR	6 (1263/2042)	2.08 (1.65–2.62)	0.3/17.5	0	0.25	0
Rasl	Postmenopausal	rr + RR versus Rr	6 (1263/2042)	1.19 (1.03–1.39)	0.116/43.4	0.542	0.981	0.999
Rasl	Postmenopausal	r versus R	6 (1263/2042)	1.47 (1.32–1.64)	0.116/43.4	0	0	0
Rasl	Non-postmenopausal	rr + Rr versus RR	1 (25/20)	3.14 (1.39–7.09)	NA	0.001	0.998	0.993
Rasl	PB	rr + Rr versus RR	3 (790/1554))	1.56 (1.26–1.94)	0.642/0	0.009	0.874	0.701
Rasl	PB	rr versus Rr + RR	3 (790/1554))	1.81 (1.50–2.18)	0.901/0	0	0.052	0
Rasl	PB	rr versus RR	3 (790/1554))	2.19 (1.70–2.82)	0.819/0	0	0.492	0
Rasl	PB	rr + RR versus Rr	3 (790/1554))	1.34 (1.01–1.77)	0.106/55.5	0.219	0.994	0.998
Rasl	PB	r versus R	3 (790/1554))	**1.48 (1.31–1.67)**	0.786/0	0	0.998	0

HB = hospital-based, PB = population-based.

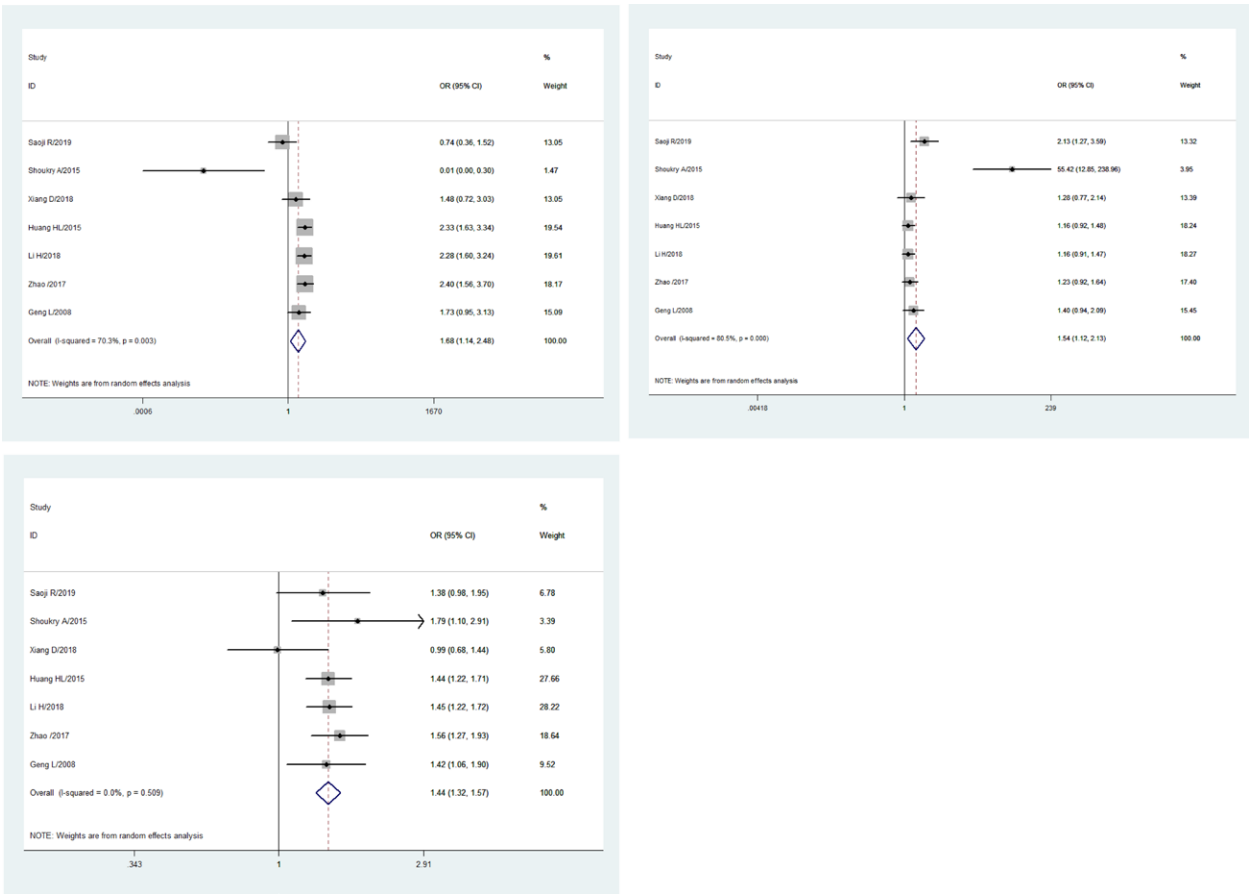

Figure 6. Forest map of the correlation between *Rsal* polymorphism and the risk of osteoporosis in overall analysis (rr vsRR; rr + RR vs Rr; r vs R).

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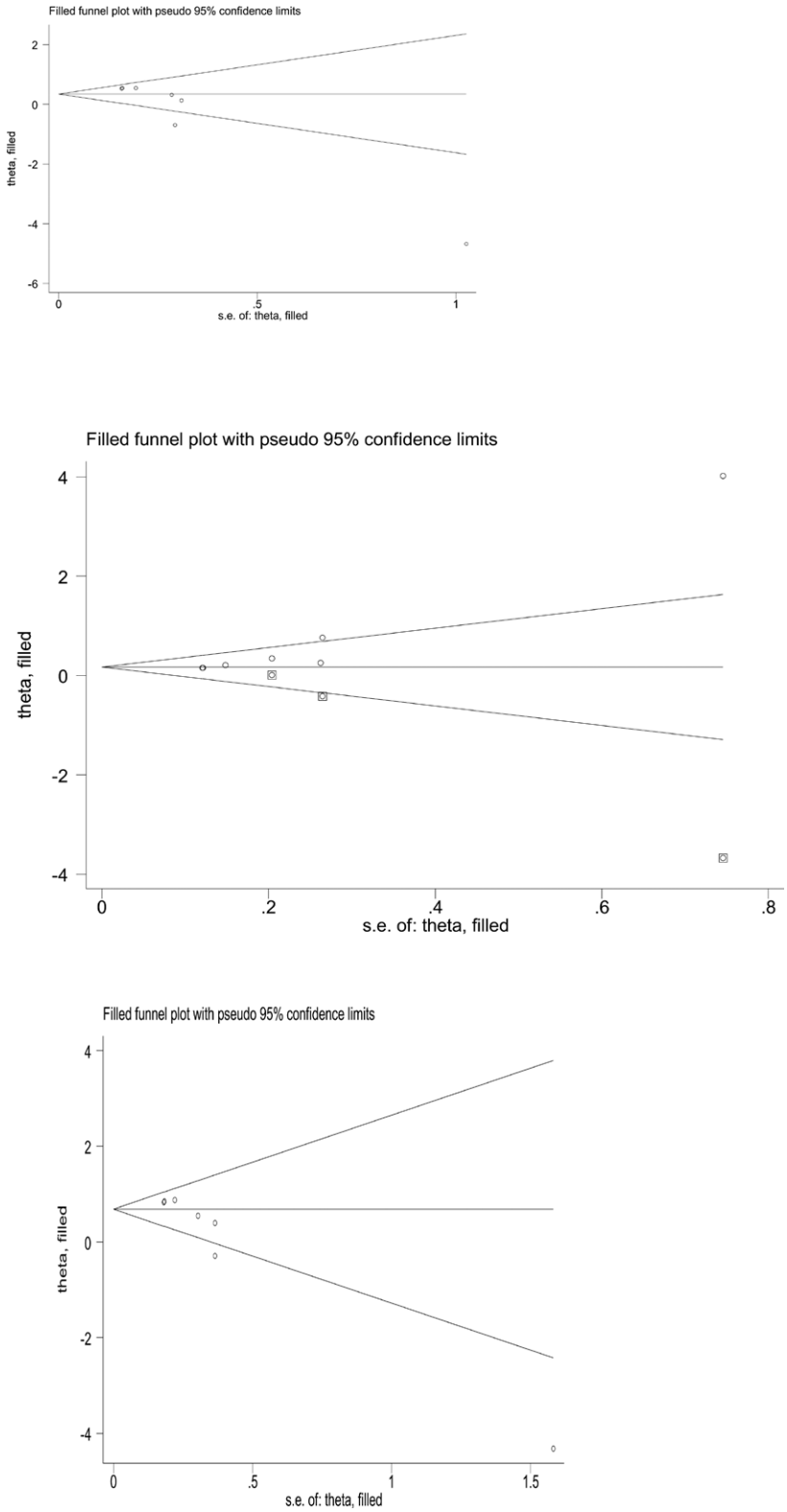

Figure 7. Publication bias of the combined effect of Begg funnel plot assessment of *Rsal* polymorphism and overall population risk of osteoporosis: (A) rr + Rr vs RR; (B) rr vs RR; (C) rr + RR vs Rr.

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