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ORIGINAL ARTICLE

A single nucleotide polymorphism in the *TGF-β1* gene (rs1982073 C>T) may contribute to increased risks of bone fracture, osteoporosis, and osteoarthritis: a meta-analysis

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Abstract Genetic factors have been shown to be of great importance for the pathogenesis of bone diseases, such as fracture, osteoporosis (OP), and osteoarthritis (OA). However, published studies on the correlations of transforming growth factor-β1 (*TGF-β1*) gene polymorphisms with bone diseases have been hampered by small sample sizes or inconclusive findings. We hence aimed at examining the relationships between a single nucleotide polymorphism in the *TGF-β1* gene (rs1982073 C>T) with bone fracture, OP, and OA risks in this meta-analysis. A systematic electronic search of literature was conducted to identify all published studies in English or Chinese on the association between the *TGF-β1* gene and fracture, OP, or OA risks. Data were abstracted independently by two reviewers. To investigate the strength of this relationship, crude odds ratios with 95 % confidence intervals were used. An updated meta-analysis based on nine independent case–control studies were chosen (patients with fracture, OP, or OA=1569; healthy controls=1638). Results identified a higher frequency of rs1982073 C>T in patients with fracture, OP, or OA than in healthy controls. Ethnicity and genotyping method-stratified analysis under both models implied that the rs1982073 C>T polymorphism was positively correlated with the risk of fracture, OP, and OA among Asians under detection via the non-PCR-RFLP method. Disease-stratified results yielded that rs1982073 C>T may increase the risk of fracture, OP, and OA under the allele model, but was only significantly related to OP under the dominant model. According to the sample size-stratified analysis, subjects with the rs1982073 C>T polymorphism in the allele model were more likely to develop the three bone diseases in both the small and large sample size groups, and only in the large sample size under the dominant model. Our findings show that *TGF-β1* rs1982073 C>T has a modest effect in increasing susceptibility to bone fracture, OP, and OA.

Keywords Bone fracture · Meta-analysis · Osteoarthritis · Osteoporosis · Single nucleotide polymorphism · Transforming growth factor-β1

Introduction

Bone fracture is one of the major public health problems in the world and can be classified into various types, such as foot and ankle fractures [1]. Of note, the morbidity and mortality of bone fracture are very high, resulting in financial burdens worldwide [2]. According to statistics, out of 10,000 people, approximately 78 to 94 might suffer from bone fracture [3]. It is reported that many factors, including age, physiology, body habitus, and traumatic injury, might be significantly related to the risk of bone fracture [4, 5]. Acting as another risk factor for bone fracture, osteoporosis (OP) is well known as a systemic skeletal disease, which negatively influences susceptibility to fractures and the fragility of bones [6]. Investigations have revealed the incidence of OP varies greatly across race, with a prevalence rate of 7 % among white men but 3 % among black men [7]. Compared with women, men with OP have higher morbidity and mortality rates [8]. Apart from bone fracture and OP, osteoarthritis (OA) is another common musculoskeletal disease and is one of the leading causes of disability among the elderly [9]. Historically, patients who are

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diagnosed with OA have chronic nociceptive pain, which results in disabilities and increased health care costs [10]. According to studies published on the prevalence of OA, out of 100 people aged 60 years or older, approximately 10 people have clinical problems that might be attributable to OA [11]. As for the etiology of OP and OA, they are deemed to be complex multifactorial diseases, both of which are caused by the interaction and correlation between environmental and genetic factors [12, 13]. Recently, numerous studies have shown that transforming growth factor-β, impacting cartilage maintenance and formation, might be protective against bone fracture, OP, and OA [14–16].

Transforming growth factor-β1 (TGF-β1), a potent cytokine and bone-derived factor, is the main member of the TGF-β super family, which also includes activins, inhibins, and bone morphogenetic proteins [17]. TGF-β family encodes large protein precursors with a N-terminal signal peptide of 20–30 amino acids and mature TGF-β molecule from pre-region released by proteolytic cleavage [18]. TGF-β1 is localized on chromosome 19q13.1–q13.3, consisting of seven exons and six large introns [19]. Secreted by platelets, macrophages, and other cell types, TGF-β1 exerts lots of physiological and pathological effects involving cell cycle, proliferation, differentiation, maturation, and apoptosis or immune activity [20]. Specifically speaking, TGF-β1 has a crucial role in osteoblast differentiation, assisting tissue regeneration and bone remodeling, while it also reversely acts on osteoclast growth, affecting bone resorption and recovery [21]. Up to now, large experimental studies have shown that genetic polymorphisms of *TGF-β1* are found to be a predictive marker during the bone healing process [22]. Among these *TGF-β1* genetic variations, it was found that *TGF-β1* gene, single nucleotide polymorphism (SNPs), rs2278422, along with being overweight, may increase the risk of knee OA [23]. Additionally, previous studies among Japanese community-dwelling adolescents and postmenopausal women discovered that the *TGF-β1* rs1982073 C>T polymorphism, a substitution of leucine (Leu) to proline (Pro), was associated with lower bone mineral density (BMD), suggesting higher risk of osteoporotic fracture [24, 25]. Moreover, observational studies verified that the *TGF-β1* polymorphism rs1982073 is found to be located in the signal peptides, consequently leading to dysfunction of the signal peptide and blockage of intracellular signal traffic, indicating that the variation has an impact on the prevalence of vertebral fractures by affecting the signaling pathway and mediating cell apoptosis [26]. The existing findings support the possibility that the *TGF-β1* polymorphism rs1982073 may be implicated in susceptibility to bone fracture, OP, and OA [27, 28]. Nevertheless, other results suggest that there is no relationship between the genetic polymorphisms of *TGF-β1* and bone diseases [29, 30]. Accordingly, this meta-analysis synthesized data from available previous studies to explore the correlation between *TGF-β1* gene polymorphism at rs1982073 with susceptibility to bone fracture, OP, and OA.

Materials and methods

Data sources and keywords

To identify all pertinent papers that assessed the correlations of *TGF-β1* rs1982073 C>T polymorphism with the susceptibility of fracture, OP, and OA, we comprehensively searched PubMed, Embase, Web of Science, Cochrane Library, CISCOM, CINAHL, Google Scholar, China BioMedicine (CBM), and China National Knowledge Infrastructure (CNKI) databases (last updated search in May 30, 2014). We utilized the following common keywords regarding the *TGF-β1* gene, fracture, OP, and OA: ("Transforming Growth Factor beta1" or "Transforming Growth Factor beta-1" or "Transforming Growth Factor beta 1" or "TGF beta 1" or "TGF-beta-1" or "TGF-beta1" or "Transforming Growth Factor beta 1 Latency Associated Peptide" or "TGF-beta1 Latency-Associated Protein" or "TGF beta1 Latency Associated Protein") for the exposure factors, and ("Fractures, Bone" or "Broken Bones" or "Fractures" or "Fracture" or "Broken Bone" or "Bone Fractures" or "Bone Fracture"), ("Osteoporosis, Postmenopausal" or "Osteoporosis" or "Juvenile OP" or "Osteoporoses" or "Age-Related Bone Loss" or "Age-Related Osteoporosis"), and ("Osteoarthritis, Spine" or "Osteoarthritis, Knee" or "Osteoarthritis, Hip" or "osteoarthritis" or "knee OA" or "spine OA" or "hip OA" or "spinal OA" or "lumbar OA" or "coxarthrosis") for the outcome factors. No restriction was set on the language of the article. We also further scanned the bibliographies of relevant articles manually to identify additional relevant papers. When the enrolled papers supplied unclear data in their original publications, the first authors would be contacted and asked for clarifications.

Selection criteria

We searched for all human case–control studies providing genotypic data for *TGF-β1* genetic polymorphisms, including subjects with fracture, OP, or OA, and reporting the adjusted odd ratios (ORs) and 95 % confidence intervals (CIs). We only included studies that supplied the sample number and sufficient information about *TGF-β1* genetic variants, and excluded articles with incomplete, unavailable, or inappropriate clinicopathologic data or those regarding fracture, OP, or OA not confirmed by histopathologic examinations. OP is defined by the World Health Organization as a T score <−2.5 SD, and OA is diagnosed based on clinical and radiographic evaluation, or ascertained by total joint replacement [31, 32]. In addition, only studies involving more than 25 cases were enrolled. Furthermore, only those studies that conformed to Hardy–

Weinberg equilibrium (HWE) in the control group were enrolled. However, when the extracted studies had more than 50 % of subjects overlapping, we merely enrolled the one whose population was the most comprehensive. At the same time, only the newest or most complete study was included when multiple studies were published by the same authors on the same study population.

Data extraction

In order to reduce bias and enhance credibility, two investigators independently extracted information from all included papers and arrived at a consensus on all the items through discussion and reexamination. The following relevant data were extracted from eligible studies: surname of first author, year of publication, source of publication, source of controls, study type, study design, sample size, age, sex, ethnicity and country of origin, disease type, genotyping method, source of controls, disease type, available genotype, genotype and mutation frequencies, and HWE evidence in controls. All authors approved the final determinant of the studies to be enrolled.

Quality assessment

To decide whether the study in question is of high quality, the two investigators used the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) quality score systems to assess the studies independently [33]. The STROBE is comprised of 40 assessment items associated with quality appraisal, with scores ranging from 0 to 40. According to the STROBE scores, the included studies were classified into three levels: low quality (0–19), moderate quality (20–29), and high quality (30–40), respectively. Any discrepancies in assigned STROBE scores were resolved through discussion with a third reviewer.

Statistical analysis

To calculate the effect size for each study, the summary ORs with 95 % CIs were used under the allele model [mutant (M) allele versus wild (W) allele] and dominant model (WM+MM versus WW) with the utilization of the Z test. In order to supply quantitative evidence of all selected studies and minimize the variance of the summary ORs with 95 % CIs, we conducted the current statistical meta-analyses by utilizing a random-effects model (DerSimonian and Laird method) or a fixed-effects model (Mantel–Haenszel method) of individual study results under the situation where data from independent studies could be combined. The random-effect model was applied when heterogeneity exists among studies, while the fixed-effect model was applied when there was no statistical heterogeneity. The subgroup meta-analyses were also conducted by ethnicity, disease type, genotyping method, and sample size to explore potential effect modification, and heterogeneity across the enrolled studies was evaluated by the Cochran's Q-statistic ($P<0.05$ was regarded as statistically significant) [34]. As a result of the low statistical power of the Cochran's Q-statistic, the I^2 test (0 %, no heterogeneity; 100 %, maximal heterogeneity) was also conducted to reflect the possibility of heterogeneity between studies [35]. The one-way sensitivity analysis was performed to evaluate whether the results could have been affected significantly by excluding each study in our meta-analysis one by one to reflect the influence of the individual data set on the pooled ORs. The funnel plot was constructed to assess publication bias, which might affect the validity of the estimates. The symmetry of the funnel plot was further evaluated by Egger's linear regression test [36]. All tests were two-sided and a P value of <0.05 was regarded as statistically significant. To make sure that the results are credible and accurate, two investigators inputted all information in the STATA software, version 12.0 (Stata Corp, College Station, TX, USA) separately and arrived at an agreement.

Results

Included studies

Our present meta-analysis hit a total of nine case–control papers that provided information on the correlation between *TGF-β1* genetic variants and susceptibility to fracture, OP, or OA (two, four, and three articles, respectively) [26–30, 37–40]. Six studies were conducted in populations of Asian descent and three in populations of Caucasian descent, including 3207 subjects altogether (1569 patients with fracture, OP, or OA and 1638 healthy controls), which were published between 2000 and 2013. The characteristics and methodological quality of the extracted studies are presented in Table 1. The countries where the studies were performed include Turkey, Thailand, Croatia, Czech, China, Denmark, and Japan. The sources of controls in our present meta-analysis were all from population-based (PB) subjects. The genotyping methods detecting *TGF-β1* genetic polymorphisms in this current meta-analysis include TaqMan assay ($n=1$), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) ($n=5$), and allele-specific PCR ($n=3$). The available SNP involved in our meta-analysis was rs1982073 C>T in the *TGF-β1* gene. All included studies showed evidence of HWE (all $P>0.05$). Additionally, as for the step of screening, a flow chart of the study selection process is displayed in Fig. 1. Initially, a total of 101 papers were selected from the nine databases through screening the title and key words. We then excluded duplicates ($n=1$), letters, reviews or meta-analyses ($n=11$), non-human studies ($n=15$),

Table 1 Baseline characteristics and methodological quality of all included studies

First author	Year	Country	Ethnicity	Total	Sample size		Gender (M/F)		Age (years)		Genotyping methods	Gene	STROBE scores
					Case	Control	Case	Control	Case	Control			
Tural S [30]	2013	Turkey	Asians	255	152	103	–	–	63.7±8.6	60.8±7.0	PCR-RFLP	TGFβ1	37
Utennam D [27]	2012	Thailand	Asians	373	95	278	–	–	53 (36–72)	59 (41–75)	PCR-RFLP	TGFβ1	37
Kolundzic R [37]	2011	Croatia	Caucasians	48	28	20	5/23	9/11	44 (34–57)	21 (20–35)	PCR-RFLP	TGFβ1	35
Hubacek JA [29]	2006	Czech	Caucasians	369	218	151	0/218	0/151	58.7±5.7	48.8±10.6	PCR-RFLP	TGFβ1	36
Lau EM [39]	2004	China	Asians	439	266	173	124/142	108/65	70–79	70–79	TaqMan assay	TGFβ1	37
Langdahl BL [38]	2003	Denmark	Caucasians	583	279	304	–	–	6105±10.3	59.0±13.2	PCR-RFLP	TGFβ1	24
Yamada Y [28]	2001	Japan	Asians	456	286	170	–	–	–	–	Allele-specific PCR	TGFβ1	23
Yamada Y [26]	2000	Japan	Asians	227	127	100	–	–	68.9±10.5	61.6±10.0	Allele-specific PCR	TGFβ1	22
Yamada Y [30]	2000	Japan	Asians	457	118	339	–	–	73.2±9.2	65.3±9.0	Allele-specific PCR	TGFβ1	23

M male, *F* female, *SNP* single nucleotide polymorphism, *BMP4* bone morphogenetic protein 4, *PCR-RFLP* polymerase chain reaction-restriction fragment length polymorphism, *HWE* Hardy–Weinberg Equilibrium, *NOS* Newcastle–Ottawa Scale

and studies not related to our research topics (n=21). The remaining studies (n=53) were reviewed and an additional 41 studies were excluded for not being case–control or cohort studies (n=12), not relevant to the *TGF-β1* gene (n=14), or not relevant to fracture, OP, or OA (n=15). After the remaining 12 trials were further reviewed, nine papers were enrolled in the final analysis. During the final selection process, the major reason for exclusion was not supplying enough information (n=3). All quality scores of the included studies were higher than 20 (moderate to high quality). From 2001 to 2014, the number of articles selected from those electronic databases is shown in Fig. 2.

Association of TGFβ1 genetic polymorphisms with fracture, OP, or OA

As shown in Fig. 3 and Table 2, the major findings of the present meta-analysis revealed a higher frequency of the rs1982073 C>T genetic mutation in the *TGF-β1* gene in patients with fracture, OP, or OA than in healthy controls (allele model—OR=1.26, 95 % CI=1.13–1.41, P<0.001; dominant model—OR=1.41, 95 % CI=1.13–1.75, P=0.002). Subgroup analysis based on ethnicity implies that the rs1982073 C>T genetic polymorphism in the *TGF-β1* gene was positively correlated with the risk of fracture, OP, and OA in Asians (allele model—OR=1.33, 95 % CI=1.18–1.49, P<0.001; dominant model—OR=1.51, 95 % CI=1.19–1.93, P=0.001), but a similar correlation was not found in Caucasians (both P>0.05) (as shown in Fig. 4). In addition, subgroup analyses by disease type revealed that the frequencies of the *TGF-β1* rs1982073 C>T genetic polymorphism in the case groups were higher than those in the control groups in all fracture, OP, and OA subgroups under the allele model (all P<0.05) (as seen in Fig. 4). However, the association of the *TGF-β1* rs1982073 C>T genetic polymorphism with the occurrence of fracture, OP, and OA was observed by subgroup analyses based on disease type (Fig. 4) to be positive in OP patients under the dominant model (OR=1.34, 95 % CI=1.04–1.72, P=0.026), but not in OA or fracture patients under the dominant model (both P>0.05). Further subgroup analysis based on genotyping method implied that the rs1982073 C>T genetic polymorphism in the *TGF-β1* gene was positively related to fracture, OP, and OA occurrence for both PCR-RFLP and non-PCR-RFLP methods under the allele model (PCR-RFLP, OR=1.25, 95 % CI=1.00–1.57, P=0.048; non-PCR-RFLP, OR=1.31, 95 % CI=1.15–1.49, P<0.001), as shown in Fig. 4. However, in Fig. 4, subgroup analysis by genotyping method revealed that the positive relationship between the *TGF-β1* rs1982073 C>T genetic variant and fracture, OP, and OA susceptibility was only observed in the non-PCR-RFLP subgroup under the dominant model (OR=1.53, 95 % CI=1.21–1.93, P<0.001) and not in the PCR-RFLP subgroup under the dominant model (P=0.156). In

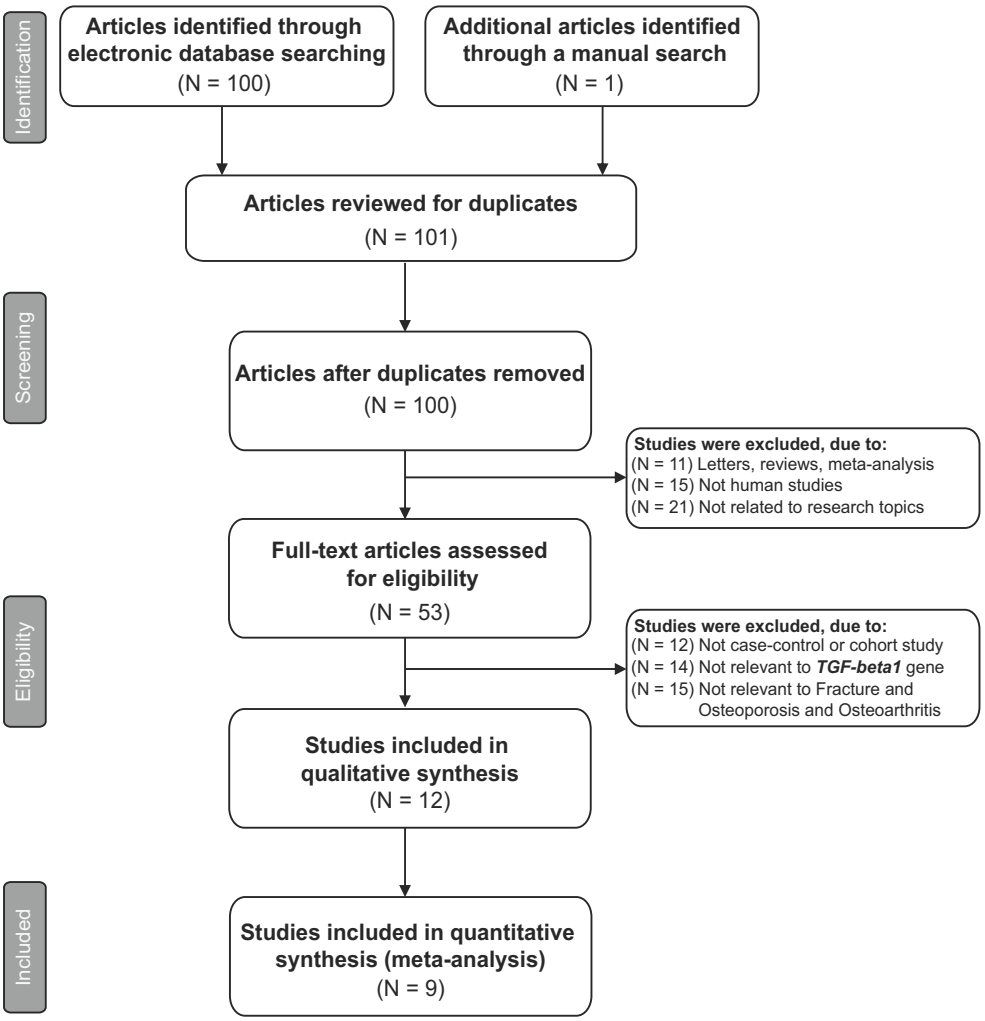


Fig. 1 Flow chart of literature search and study selection. Nine clinical case–control studies were included in this meta-analysis

addition, subgroup analysis by sample size under the allele model (Fig. 4) suggested that the *TGF-β1* rs1982073 C>T mutation in fracture, OP, or OA patients occurred more frequently than in normal controls in both the small size subgroup (OR=1.38, 95 % CI=1.03–1.83, P=0.028) and the large size subgroup (OR=1.24, 95 % CI=1.10–1.41, P=

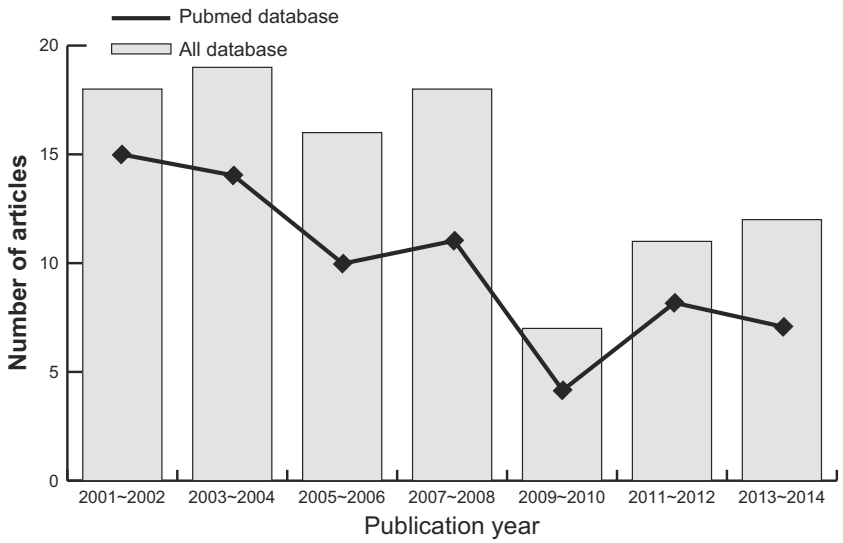


Fig. 2 Distribution of topic-related literature in electronic database over the last decade

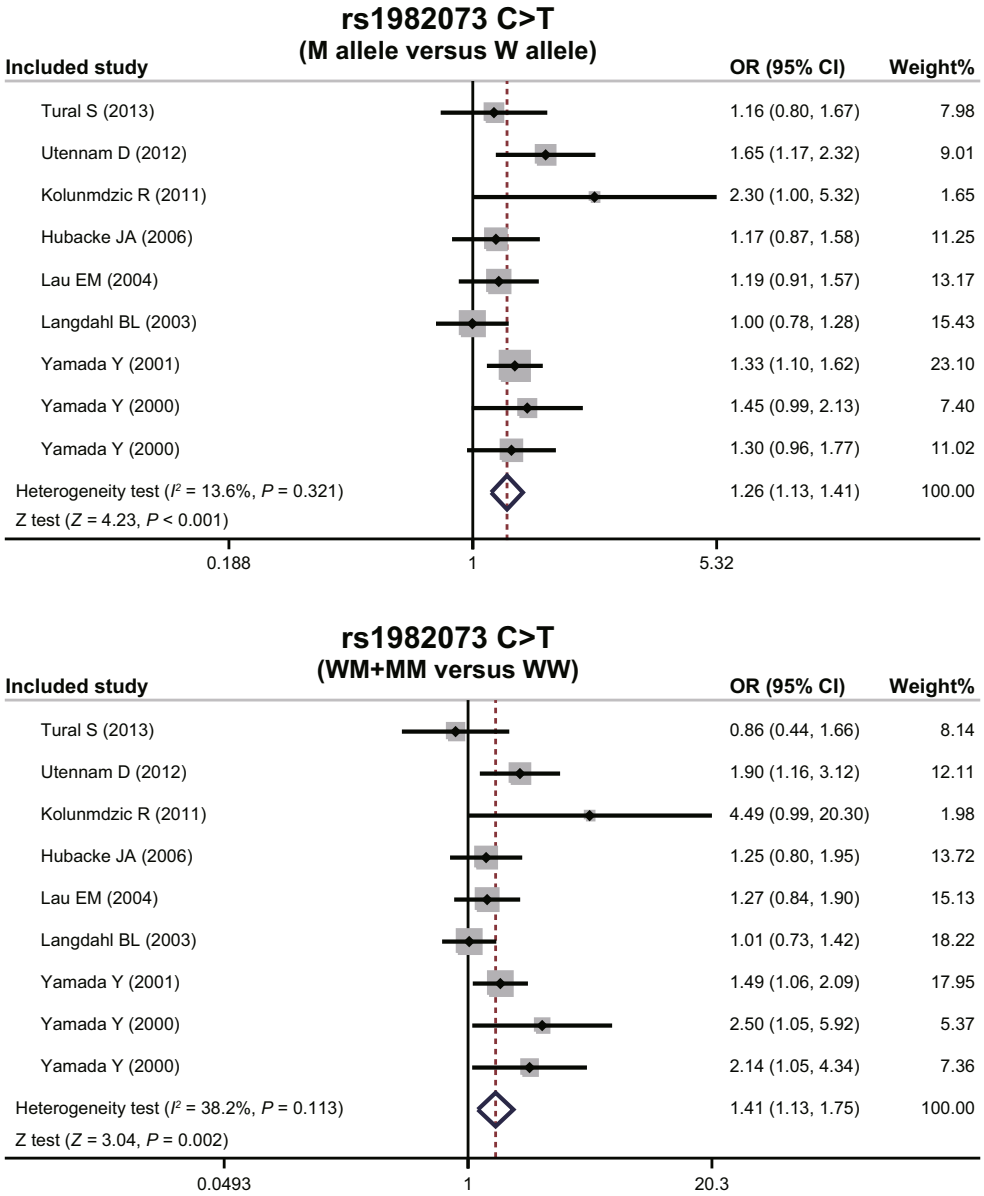


Fig. 3 Forest plots for the correlations of a single nucleotide polymorphism of *TGF-β1* (rs1982073 C>T) between the risks of bone fracture, osteoporosis, and osteoarthritis

0.001). However, the positive relationship between the *TGF-β1* rs1982073 C>T variant and susceptibility of fracture, OP, and OA, in subgroup analysis by sample size under the dominant model (Fig. 4), was only detected in the large sample subgroup (OR=1.36, 95 % CI=1.11–1.67, P=0.003) and not in the small sample subgroup (P=0.214).

Sensitivity analysis and publication bias

A leave-one-out sensitivity analysis was carried out to evaluate whether the present meta-analysis is stable. Each study enrolled in our meta-analysis was evaluated one by one to reflect its effect on the significance of pooled SMDs (Table 3). The overall statistical significance did not change when any single study was omitted. Therefore, the current meta-analysis data is relatively stable and credible (Fig. 5). The graphical funnel plots of those nine studies for *TGF-β1* rs1982073 C>T genetic variant are symmetrical for both the allele and dominant models, and Egger's test showed no publication bias (all P>0.05) (Fig. 6).

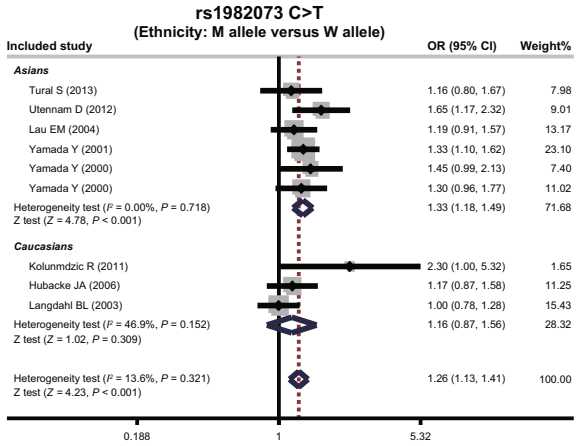
Discussion

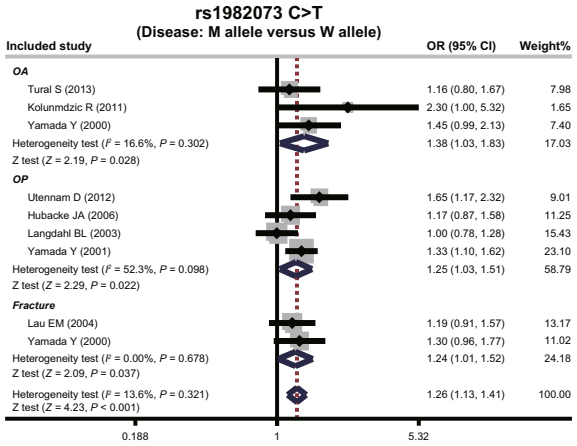
A meta-analysis of the connection between the rs1982073 C>T polymorphism in the *TGF-β1* gene and the susceptibility to bone diseases (fracture, OP, and OA) was established with the main results of our meta-analysis demonstrating an obvious connection. TGF-β1, belonging to the TGF-β super

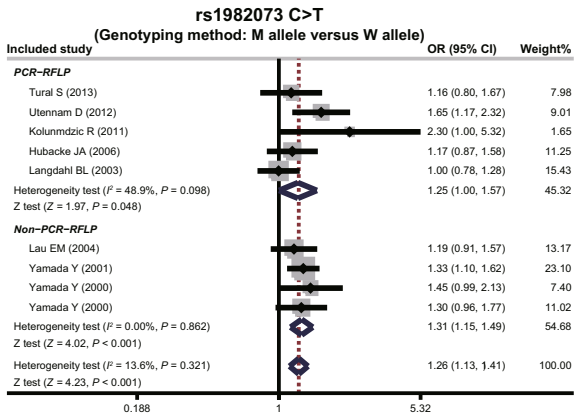
Table 2 Meta-analysis of the relationships of *IFN-γ* genetic polymorphisms with breast cancer

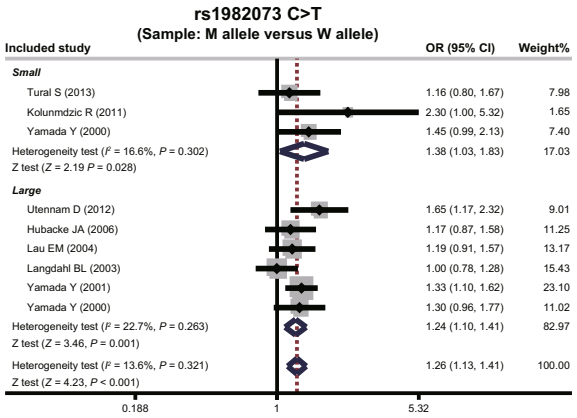
Subgroup analysis	M allele vs. W			WM+MM vs. WW			MM vs. WW+WM			MM vs. WW			MM vs. WM		
	(Allele model)			(Dominant model)			(Recessive model)			(Homozygous model)			(Heterozygous model)		
	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*
rs1982073 C>T	1.26	1.13–1.41	<0.001	1.41	1.31–1.75	0.002	1.37	1.16–1.62	<0.001	1.66	1.27–2.19	<0.001	1.27	1.06–1.51	0.008
Ethnicity															
Asians	1.33	1.18–1.49	<0.001	1.51	1.19–1.93	0.001	1.44	1.20–1.73	<0.001	1.83	1.43–2.34	<0.001	1.32	1.09–1.60	0.005
Caucasians	1.16	0.87–1.56	0.309	1.23	0.80–1.90	0.34	1.14	0.74–1.75	0.559	1.38	0.67–2.87	0.385	1.07	0.72–1.59	0.74
Disease															
OA	1.38	1.03–1.83	0.028	1.83	0.70–4.78	0.214	1.6	1.07–2.37	0.02	2.39	0.88–6.54	0.089	1.54	1.02–2.33	0.038
OP	1.25	1.03–1.51	0.022	1.34	1.04–1.72	0.026	1.35	1.06–1.72	0.015	1.56	1.06–2.28	0.024	1.25	1.00–1.58	0.055
Fracture	2.14	1.01–1.52	0.037	1.51	0.93–2.46	0.095	1.25	0.90–1.75	0.185	1.67	1.06–2.63	0.026	1.13	0.80–1.59	0.502
Genotyping method															
PCR-RFLP	1.25	1.00–1.57	0.048	1.29	0.91–1.82	0.156	1.38	1.00–1.91	0.051	1.54	0.93–2.54	0.092	1.3	0.97–1.76	0.082
Non-PCR-RFLP	1.31	1.15–1.49	<0.001	1.53	1.21–1.93	<0.001	1.38	1.12–1.69	0.002	1.82	1.37–2.41	<0.001	1.25	1.01–1.55	0.043
Sample															
Non-TaqMan assay	1.38	1.03–1.83	0.028	1.83	0.70–4.78	0.214	1.6	1.07–2.37	0.02	2.39	0.88–6.54	0.089	1.54	1.02–2.33	0.038
TaqMan assay	1.24	1.10–1.41	0.001	1.36	1.11–1.67	0.003	1.33	1.10–1.59	0.002	1.59	1.21–2.09	0.001	1.21	1.00–1.47	0.049

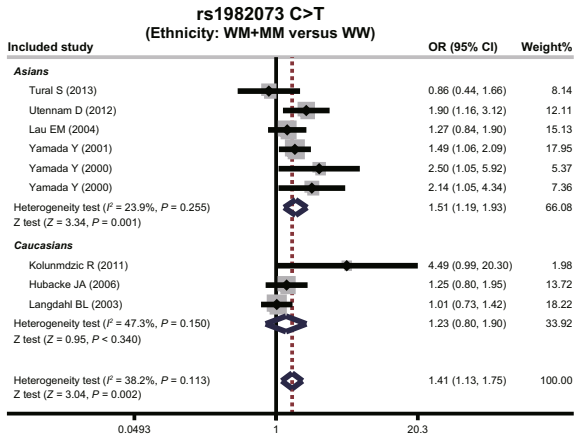
W wild allele, *M* mutant allele, *WW* wild homozygote, *WM* heterozygote, *MM* mutant homozygote, *OR* odds ratio, *95% CI* 95 % confidence interval, *PCR-RFLP* polymerase chain reaction-restriction fragment length polymorphism

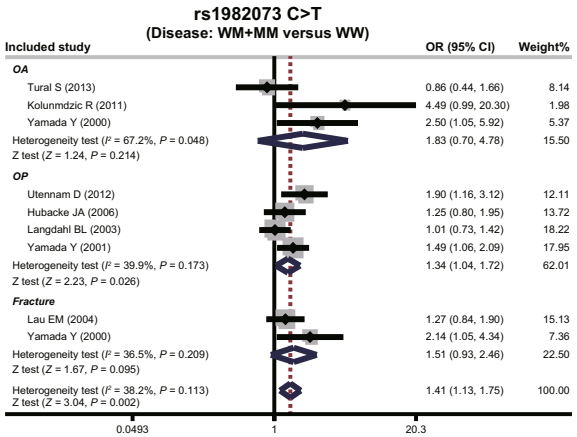

rs1982073 C>T
(Ethnicity: M allele versus W allele)
Included study
OR (95% CI)
Weight%
Asians
Tural S (2013) 1.16 (0.80, 1.67) 7.98
Utennam D (2012) 1.65 (1.17, 2.32) 9.01
Lau EM (2004) 1.19 (0.91, 1.57) 13.17
Yamada Y (2001) 1.33 (1.10, 1.62) 23.10
Yamada Y (2000) 1.45 (0.99, 2.13) 7.40
Yamada Y (2000) 1.30 (0.96, 1.77) 11.02
Heterogeneity test (I² = 0.00%, P = 0.718) 1.33 (1.18, 1.49) 71.68
Z test (Z = 4.78, P < 0.001)
Caucasians
Kolunmdzic R (2011) 2.30 (1.00, 5.32) 1.65
Hubacke JA (2006) 1.17 (0.87, 1.58) 11.25
Langdahl BL (2003) 1.00 (0.78, 1.28) 15.43
Heterogeneity test (I² = 46.9%, P = 0.152) 1.16 (0.87, 1.56) 28.32
Z test (Z = 1.02, P = 0.309)
Heterogeneity test (I² = 13.6%, P = 0.321) 1.26 (1.13, 1.41) 100.00
Z test (Z = 4.23, P < 0.001)
0.188
1
5.32

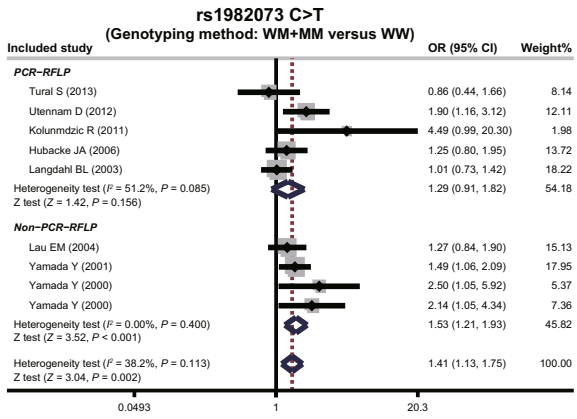

rs1982073 C>T
(Disease: M allele versus W allele)
Included study
OR (95% CI)
Weight%
OA
Tural S (2013) 1.16 (0.80, 1.67) 7.98
Kolunmdzic R (2011) 2.30 (1.00, 5.32) 1.65
Yamada Y (2000) 1.45 (0.99, 2.13) 7.40
Heterogeneity test (I² = 16.6%, P = 0.302) 1.38 (1.03, 1.83) 17.03
Z test (Z = 2.19, P = 0.028)
OP
Utennam D (2012) 1.65 (1.17, 2.32) 9.01
Hubacke JA (2006) 1.17 (0.87, 1.58) 11.25
Langdahl BL (2003) 1.00 (0.78, 1.28) 15.43
Yamada Y (2001) 1.33 (1.10, 1.62) 23.10
Heterogeneity test (I² = 52.3%, P = 0.098) 1.25 (1.03, 1.51) 58.79
Z test (Z = 2.29, P = 0.022)
Fracture
Lau EM (2004) 1.19 (0.91, 1.57) 13.17
Yamada Y (2000) 1.30 (0.96, 1.77) 11.02
Heterogeneity test (I² = 0.00%, P = 0.678) 1.24 (1.01, 1.52) 24.18
Z test (Z = 2.09, P = 0.037)
Heterogeneity test (I² = 13.6%, P = 0.321) 1.26 (1.13, 1.41) 100.00
Z test (Z = 4.23, P < 0.001)
0.188
1
5.32

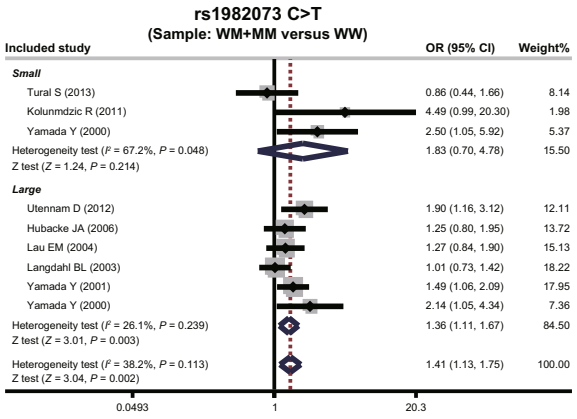

rs1982073 C>T
(Genotyping method: M allele versus W allele)
Included study
OR (95% CI)
Weight%
PCR–RFLP
Tural S (2013) 1.16 (0.80, 1.67) 7.98
Utennam D (2012) 1.65 (1.17, 2.32) 9.01
Kolunmdzic R (2011) 2.30 (1.00, 5.32) 1.65
Hubacke JA (2006) 1.17 (0.87, 1.58) 11.25
Langdahl BL (2003) 1.00 (0.78, 1.28) 15.43
Heterogeneity test (I² = 48.9%, P = 0.098) 1.25 (1.00, 1.57) 45.32
Z test (Z = 1.97, P = 0.048)
Non–PCR–RFLP
Lau EM (2004) 1.19 (0.91, 1.57) 13.17
Yamada Y (2001) 1.33 (1.10, 1.62) 23.10
Yamada Y (2000) 1.45 (0.99, 2.13) 7.40
Yamada Y (2000) 1.30 (0.96, 1.77) 11.02
Heterogeneity test (I² = 0.00%, P = 0.862) 1.31 (1.15, 1.49) 54.68
Z test (Z = 4.02, P < 0.001)
Heterogeneity test (I² = 13.6%, P = 0.321) 1.26 (1.13, 1.41) 100.00
Z test (Z = 4.23, P < 0.001)
0.188
1
5.32


rs1982073 C>T
(Sample: M allele versus W allele)
Included study
OR (95% CI)
Weight%
Small
Tural S (2013) 1.16 (0.80, 1.67) 7.98
Kolunmdzic R (2011) 2.30 (1.00, 5.32) 1.65
Yamada Y (2000) 1.45 (0.99, 2.13) 7.40
Heterogeneity test (I² = 16.6%, P = 0.302) 1.38 (1.03, 1.83) 17.03
Z test (Z = 2.19 P = 0.028)
Large
Utennam D (2012) 1.65 (1.17, 2.32) 9.01
Hubacke JA (2006) 1.17 (0.87, 1.58) 11.25
Lau EM (2004) 1.19 (0.91, 1.57) 13.17
Langdahl BL (2003) 1.00 (0.78, 1.28) 15.43
Yamada Y (2001) 1.33 (1.10, 1.62) 23.10
Yamada Y (2000) 1.30 (0.96, 1.77) 11.02
Heterogeneity test (I² = 22.7%, P = 0.263) 1.24 (1.10, 1.41) 82.97
Z test (Z = 3.46, P = 0.001)
Heterogeneity test (I² = 13.6%, P = 0.321) 1.26 (1.13, 1.41) 100.00
Z test (Z = 4.23, P < 0.001)
0.188
1
5.32


rs1982073 C>T
(Ethnicity: WM+MM versus WW)
Included study
OR (95% CI)
Weight%
Asians
Tural S (2013) 0.86 (0.44, 1.66) 8.14
Utennam D (2012) 1.90 (1.16, 3.12) 12.11
Lau EM (2004) 1.27 (0.84, 1.90) 15.13
Yamada Y (2001) 1.49 (1.06, 2.09) 17.95
Yamada Y (2000) 2.50 (1.05, 5.92) 5.37
Yamada Y (2000) 2.14 (1.05, 4.34) 7.36
Heterogeneity test (I² = 23.9%, P = 0.255) 1.51 (1.19, 1.93) 66.08
Z test (Z = 3.34, P = 0.001)
Caucasians
Kolunmdzic R (2011) 4.49 (0.99, 20.30) 1.98
Hubacke JA (2006) 1.25 (0.80, 1.95) 13.72
Langdahl BL (2003) 1.01 (0.73, 1.42) 18.22
Heterogeneity test (I² = 47.3%, P = 0.150) 1.23 (0.80, 1.90) 33.92
Z test (Z = 0.95, P < 0.340)
Heterogeneity test (I² = 38.2%, P = 0.113) 1.41 (1.13, 1.75) 100.00
Z test (Z = 3.04, P = 0.002)
0.0493
1
20.3


rs1982073 C>T
(Disease: WM+MM versus WW)
Included study
OR (95% CI)
Weight%
OA
Tural S (2013) 0.86 (0.44, 1.66) 8.14
Kolunmdzic R (2011) 4.49 (0.99, 20.30) 1.98
Yamada Y (2000) 2.50 (1.05, 5.92) 5.37
Heterogeneity test (I² = 67.2%, P = 0.048) 1.83 (0.70, 4.78) 15.50
Z test (Z = 1.24, P = 0.214)
OP
Utennam D (2012) 1.90 (1.16, 3.12) 12.11
Hubacke JA (2006) 1.25 (0.80, 1.95) 13.72
Langdahl BL (2003) 1.01 (0.73, 1.42) 18.22
Yamada Y (2001) 1.49 (1.06, 2.09) 17.95
Heterogeneity test (I² = 39.9%, P = 0.173) 1.34 (1.04, 1.72) 62.01
Z test (Z = 2.23, P = 0.026)
Fracture
Lau EM (2004) 1.27 (0.84, 1.90) 15.13
Yamada Y (2000) 2.14 (1.05, 4.34) 7.36
Heterogeneity test (I² = 36.5%, P = 0.209) 1.51 (0.93, 2.46) 22.50
Z test (Z = 1.67, P = 0.095)
Heterogeneity test (I² = 38.2%, P = 0.113) 1.41 (1.13, 1.75) 100.00
Z test (Z = 3.04, P = 0.002)
0.0493
1
20.3


rs1982073 C>T
(Genotyping method: WM+MM versus WW)
Included study
OR (95% CI)
Weight%
PCR–RFLP
Tural S (2013) 0.86 (0.44, 1.66) 8.14
Utennam D (2012) 1.90 (1.16, 3.12) 12.11
Kolunmdzic R (2011) 4.49 (0.99, 20.30) 1.98
Hubacke JA (2006) 1.25 (0.80, 1.95) 13.72
Langdahl BL (2003) 1.01 (0.73, 1.42) 18.22
Heterogeneity test (I² = 51.2%, P = 0.085) 1.29 (0.91, 1.82) 54.18
Z test (Z = 1.42, P = 0.156)
Non–PCR–RFLP
Lau EM (2004) 1.27 (0.84, 1.90) 15.13
Yamada Y (2001) 1.49 (1.06, 2.09) 17.95
Yamada Y (2000) 2.50 (1.05, 5.92) 5.37
Yamada Y (2000) 2.14 (1.05, 4.34) 7.36
Heterogeneity test (I² = 0.00%, P = 0.400) 1.53 (1.21, 1.93) 45.82
Z test (Z = 3.52, P < 0.001)
Heterogeneity test (I² = 38.2%, P = 0.113) 1.41 (1.13, 1.75) 100.00
Z test (Z = 3.04, P = 0.002)
0.0493
1
20.3


rs1982073 C>T
(Sample: WM+MM versus WW)
Included study
OR (95% CI)
Weight%
Small
Tural S (2013) 0.86 (0.44, 1.66) 8.14
Kolunmdzic R (2011) 4.49 (0.99, 20.30) 1.98
Yamada Y (2000) 2.50 (1.05, 5.92) 5.37
Heterogeneity test (I² = 67.2%, P = 0.048) 1.83 (0.70, 4.78) 15.50
Z test (Z = 1.24, P = 0.214)
Large
Utennam D (2012) 1.90 (1.16, 3.12) 12.11
Hubacke JA (2006) 1.25 (0.80, 1.95) 13.72
Lau EM (2004) 1.27 (0.84, 1.90) 15.13
Langdahl BL (2003) 1.01 (0.73, 1.42) 18.22
Yamada Y (2001) 1.49 (1.06, 2.09) 17.95
Yamada Y (2000) 2.14 (1.05, 4.34) 7.36
Heterogeneity test (I² = 26.1%, P = 0.239) 1.36 (1.11, 1.67) 84.50
Z test (Z = 3.01, P = 0.003)
Heterogeneity test (I² = 38.2%, P = 0.113) 1.41 (1.13, 1.75) 100.00
Z test (Z = 3.04, P = 0.002)
0.0493
1
20.3

◀ **Fig. 4** Subgroup analyses for the correlations of a single nucleotide polymorphism of *TGF-β1* (rs1982073 C>T) between the risks of bone fracture, osteoporosis, and osteoarthritis

family, which includes TGF-β, inhibits activins, MIS, and BMPs, and plays an essential role in the regulation of tissue morphogenesis and repair through its function on the proliferation, differentiation, and apoptosis of cells and production of extracellular matrix [41]. The participation of TGF-β1 in gene transcription regulation starts with a cell surface heteromeric receptor complex and combines with the intracellular signal-transducing Smad, which could be activated and transferred to the nucleus sites [42]. The role of TGF-β1 in the progression of cancer could be double sided: on the one hand, TGF-β1 could induce cell growth arrest, which might induce the dormancy of cancer cells, beneficial at the cancer early stages; on the other hand, TGF-β1 could activate extracellular matrix components expression to affect the cancer cell microenvironment, thus promoting the metastasis and invasion of tumors [43, 44]. Besides, TGF-β1, also known as a major factor in the immune system, could influence the proliferation and immunomodulation of cells responsible for chronic inflammatory diseases due to their role in regenerative processes and immune response [45]. TGF-β1 is an abundant cytokine in the bone matrix that could influence the biology and physiology of bones by increasing the formation of bone through osteoprogenitor proliferation stimulation and osteoblast precursor expansion [21]. Functioning on the osteoclast–osteoblast coupling, TGF-β1 could remodel the bones by facilitating recruit osteoblast progenitors to bone resorption sites and by stimulating RANKL production, a critical factor for osteoclast differentiation [46]. The expression of TGF-β1 could be regulated by the *TGF-β1* gene and thus the polymorphism of the TGF-β1 gene might have a close connection with bone diseases, such as fracture, OP, and OA. It has been reported the rs1982073 (T869C) polymorphism with the TC genotype had a higher fracture possibility and bone turnover rate in postmenopausal women because of the role of TGF-β1 in mediating formation and resorption of bones [47]. Additionally, the T869C polymorphism in the *TGF-b1* gene, resulting in a protein substitution at the tenth amino acid from Leu to Pro, is connected with the bone mineral density in both postmenopausal women and adolescents, and susceptibility to OP, which may also be due to the role of TGF-β1 in controlling bone formation and resorption [48]. Furthermore, *TGF-β1* gene polymorphism at rs1982073 might also be involved in OA due to the function of TGF-β1 in the integrity of cartilage which is found to be decreased in the cartilage of OA patients [23]. Thus, we could know that the rs1982073 polymorphism in the *TGF-β1* gene could regulate the expression of TGF-β1, causing many kinds of bone diseases, including fracture, OP, and OA, due to the role of TGF-β1 in the formation and resorption of bone and the integrity of cartilage. This conclusion is also supported by other studies. Utennam et al. demonstrated that the CT and CC genotype of the rs1982073 polymorphism in the *TGF-β1* gene was linked with lower expression of TGF-β1 in OP of Thai women [27]. Kolundzic et al. found that the *TGF-β1* gene polymorphism in the rs1982073 and the C allele carriage phenomenon were associated with higher TGF-β1 circulation levels in adult OA [37].

Many other factors which might affect the connection between rs1982073 in *TGF-β1* gene polymorphisms and susceptibility to bone diseases were taken into consideration via stratified analyses based on ethnicity, different kind of

Table 3 Univariate and multivariate meta-regression analyses of potential source of heterogeneity

Heterogeneity factors	Coefficient	SE	*z*	*P*	95 % CI	
					LL	UL
Publication year						
Univariate	0.007	0.013	0.52	0.603	−0.019	0.032
Multivariate	0.005	0.016	0.29	*0.768*	−0.027	0.036
Ethnicity						
Univariate	−0.182	0.112	−1.62	0.106	−0.402	0.038
Multivariate	−0.23	0.165	−1.39	0.164	−0.553	0.094
Disease						
Univariate	−0.043	0.088	−0.48	0.628	−0.215	0.13
Multivariate	−0.07	0.176	−0.4	0.692	−0.414	0.275
Genotyping method						
Univariate	0.024	0.079	0.3	0.761	−0.131	0.178
Multivariate	−0.022	0.157	−0.14	0.891	−0.329	0.286
Sample						
Univariate	0.093	0.148	0.63	0.532	−0.198	0.384
Multivariate	−0.076	0.256	−0.3	0.767	−0.578	0.426

SE standard error, *95% CI* 95 % confidence interval, *UL* upper limit, *LL* lower limit

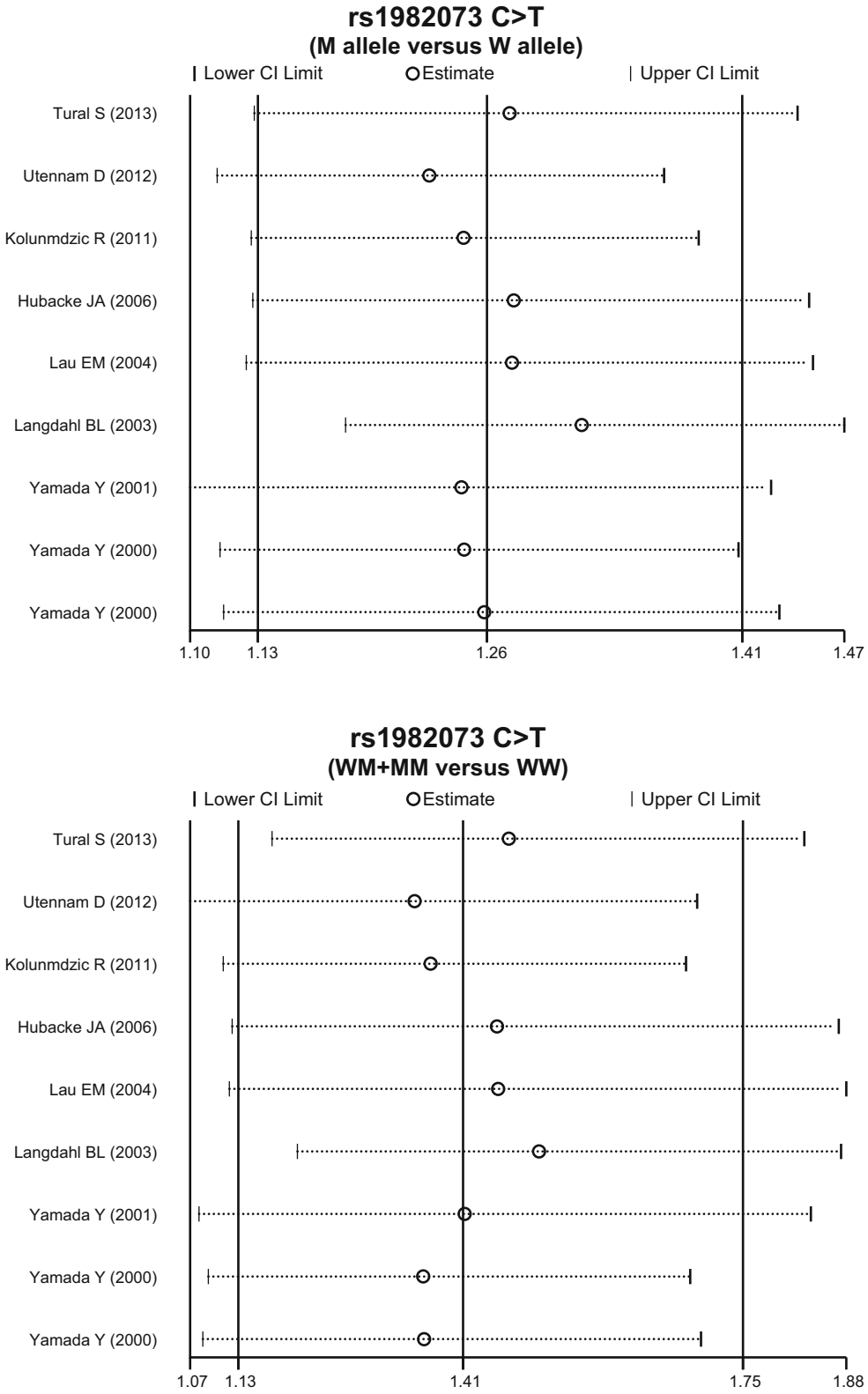


Fig. 5 Sensitivity analysis of the summary odds ratio coefficients for the correlations of a single nucleotide polymorphism of *TGF-β1* (rs1982073 C>T) between the risks of bone fracture, osteoporosis, and osteoarthritis

diseases, genotyping method, and the size of samples. Subgroup analysis on ethnicity showed effects in Caucasians but not in Asians, perhaps due to living environment and genetic background differences. As for different kinds of diseases, fracture and OA had an effect on the relationship in the dominant model but not in the allele model. In addition, the PCR-RFLP method influenced the relationship in the dominant model, while the non-PCR-RFLP showed no influence,

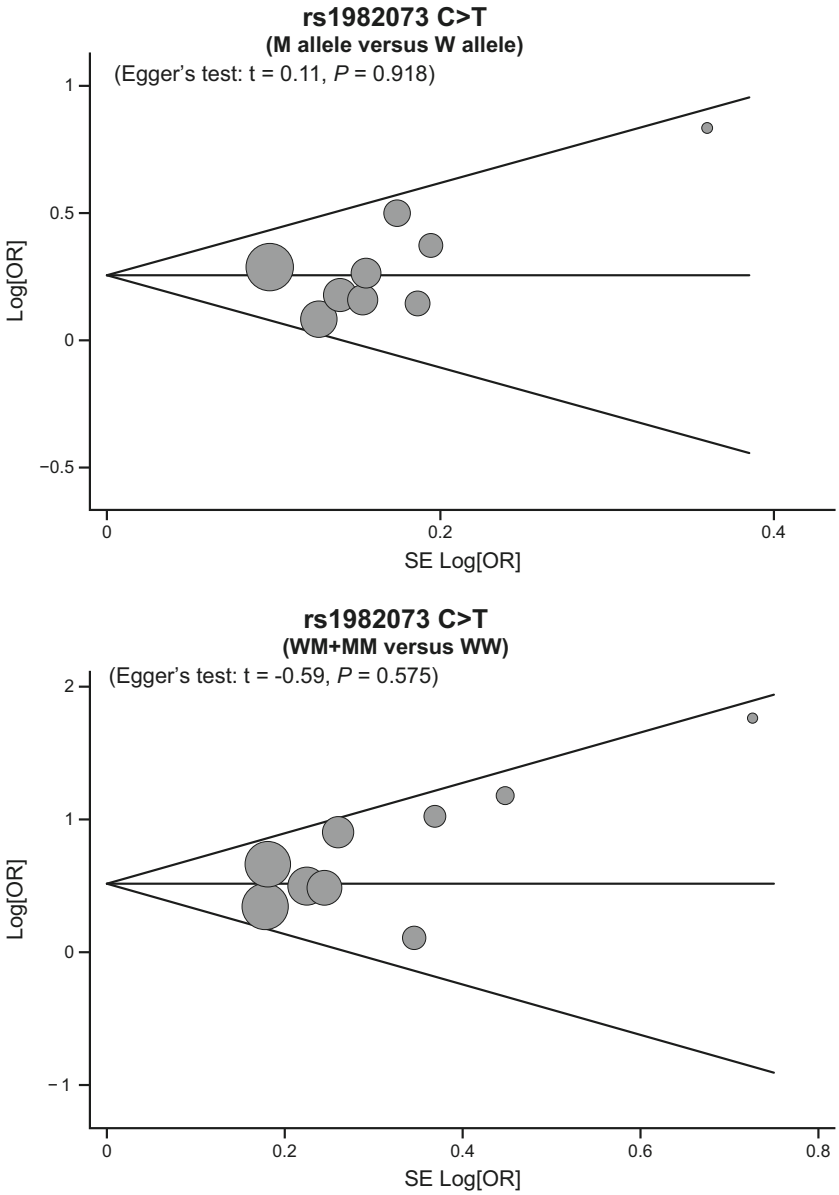


Fig. 6 Funnel plot of publication biases for the correlations of a single nucleotide polymorphism of *TGF-β1* (rs1982073 C>T) between the risks of bone fracture, osteoporosis, and osteoarthritis

which may be explained by detection deviation. At the time the small size of samples affected the relationship in the dominant model, the large size of samples did not affect the relationship, suggesting that a large sample size could be more objective. In brief, polymorphism of rs1982073 in the *TGF-β1* gene was significantly associated with fracture, OP, and OA. This significant relationship suggests a role for rs1982073 polymorphisms as a potent marker for bone disease diagnosis.

Finally, our meta-analysis has several potential advantages. First, our research sheds light on the relation of the rs1982073 C>T polymorphism in the *TGFβ1* gene with susceptibility to bone fracture, OP, and OA. Additionally, our exhaustive search for unpublished articles via additional electronic databases and manual searches enhances the power and persuasion of our conclusion. Moreover, all included literatures had acceptable moderate to high quality scores (quality scores were higher than 20). However, some limitations of this meta-analysis should also be acknowledged when interpreting the results. Firstly, only one single SNP (rs1982073 C>T) was included, though the relation of other SNPs to bone fracture, OP, and OA risk has also been studied. More importantly, the existence of selection bias was due to the lack of a screening process for papers published in languages other than English or Chinese. In addition, the crude division criteria of ethnic groups into "Caucasian", "Asian", or "African" may also lead to bias. Nearly all of the studies were performed in Asians and Caucasians, but to capture the full range of possible ethnic differences in *TGFβ1* rs1982073 C>T polymorphisms, deeper investigations of different populations are warranted to clarify the present results. Another important concern should also be taken into consideration: different diseases have different risk

factors and diverse sensitivities to them. In particular, we did not evaluate family history or the clinical implications of bone fracture, OP, or OA in our study since such data was not available for collection. Finally, the present sample size (only nine articles included in interpreting three different bone diseases) limits the power to identify the small influence of the *TGFβ1* rs1982073 C>T polymorphism on bone fracture, OP, and OA.

In summary, we have identified that the *TGFβ1* rs1982073 C>T variant may increase the susceptibility to bone fracture, OP, and OA among all our studied populations. SNP in *TGFβ1* genes may act as a potential candidate biomarker for the screening, diagnosis, and treatment of bone fracture, OP, and OA. The results needed replication in other populations for confirmation and further well-designed research studies with larger sample sizes are needed to better understand the underlying mechanisms responsible for bone fracture, OP, and OA.

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Conflicts of interest We declare that we have no conflicts of interest.

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