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ORIGINAL ARTICLE

Association of *MTHFR* C667T polymorphism with bone mineral density and fracture risk: an updated meta-analysis

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Abstract
Summary This meta-analysis investigated the association of C677T polymorphism in *MTHFR* gene with bone mineral density (BMD) and fracture risk. The results suggested that C677T polymorphism was marginally associated with fracture risk. In addition, this polymorphism was modestly associated with BMD of lumbar spine, femoral neck, total hip, and total body, respectively.
Introduction The methylenetetrahydrofolate reductase (*MTHFR*) gene has been implicated in the regulation of BMD and, thus, may serve as a potential risk factor for the development of fracture. However, results have been inconsistent. In this study, a meta-analysis was performed to clarify the association of C677T polymorphism in *MTHFR* gene with BMD and fracture risk.
Methods Published literature from PubMed and EMBASE were searched for eligible publications. Pooled odds ratio (OR) or weighted mean difference (WMD) and 95% confidence interval (CI) were calculated using a fixed- or random-effects model.
Results Twenty studies (3,525 cases and 17,909 controls) were included in this meta-analysis. The TT genotype of C677T polymorphism was marginally associated with an increased risk of fracture under recessive model (TT vs. TC+CC: OR=1.23, 95% CI 1.04–1.47). Using this model, similar results were found among East Asians (OR=1.40, 95% CI 1.07–1.83), female subpopulation (1.27, 95% CI 1.04–1.55), cohort studies (OR=1.24, 95% CI 1.08–1.44), and subjects younger than aged 60 years (OR=1.51, 95% CI 1.10–2.07). In addition, under homogeneous co-dominant model, there was a modest association of C677T polymorphism with BMD of lumbar spine (WMD=−0.017 g/cm^2; 95%CI, −0.030–(−0.005) g/cm^2), femoral neck (WMD=−0.010 g/cm^2; 95% CI −0.017–(−0.003) g/cm^2), total hip (WMD=−0.013 g/cm^2, 95% CI −0.022–(−0.004) g/cm^2), and total body (WMD=−0.020 g/cm^2; 95% CI −0.027–(−0.013) g/cm^2), respectively.
Conclusions This meta-analysis suggested that C677T polymorphism was marginally associated with fracture risk. In addition, this polymorphism was modestly associated with BMD of lumbar spine, femoral neck, total hip, and total body, respectively.

Keywords Bone mineral density · Fracture · Meta-analysis · *MTHFR* · Polymorphism

H. Wang and C. Liu contributed equally to this work.

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Introduction

Osteoporosis is a common complex disease, which is characterized by decrease in bone mineral density (BMD) and deterioration of skeletal microarchitecture, leading to increased bone fragility and fracture [1]. Although osteoporosis and fracture are influenced by many environmental factors, such as exercise and calcium intake [2], genetic factors also play important roles in the pathogenesis of fracture [3]. Evidence has suggested that about 30% of

heritability for fracture can be attributed to the genetics [4]. In recent years, several candidate genes, including *vitamin D receptor* (*VDR*) [5], *estrogen receptor* [6], and *collagen type 1α1* (*COL1A1*) [7], have been demonstrated to be involved in bone mineral homeostasis, bone remodeling, and bone matrix composition. The genome-wide association studies also identified many susceptibility loci, including *GPR177*, *SPTBN1*, *LRP5*, *TNFRSF11B*, *RANKL*, and *OPG*, which have been associated with BMD or fracture risk [8–11]. Although polymorphisms of those genes alone have limited capability to predict risk of individual, they provide insight into the genetic pathways underling osteoporosis and fracture [11].

The enzyme methylenetetrahydrofolate reductase (MTHFR) plays an important role in the removal of circulating homocysteine via the methionine cycle. The *MTHFR* gene is located on chromosome 1p36 within a linkage region for regulation of BMD [12]. Two functional polymorphisms (C677T and A1298C) have been identified, which both result in amino acid substitutions in the MTHFR protein. Two variants are both associated with higher plasma homocysteine levels, which could affect collagen maturation [13]. To date, C677T polymorphism has been the most studied one; therefore, in this meta-analysis, we only focus on this polymorphism. Jørgensen et al. [14] first reported that C677T polymorphism in *MTHFR* gene was associated with fracture risk in European postmenopausal women. Since then, a great number of studies regarding the association between C677T polymorphism and fracture have been published. However, the results have been inconsistent [15–26]. In addition, the association between C677T polymorphism and BMD has also been conflicting.

One previous meta-analysis suggested null association between C677T polymorphism and fracture [20], and another meta-analysis indicated modest association of C677T polymorphism with BMD of both lumbar spine and total hip [27]. However, limited studies were included in both meta-analyses. Recently, several new papers are further available. Therefore, in this study, we performed an updated meta-analysis to clarify the association of C677T polymorphism in *MTHFR* gene with BMD and fracture risk across different populations.

Materials and methods

Literature and search strategy

PubMed and EMBASE were searched for eligible articles. The search strategy to identify all potential studies involved use of combinations of the following key words: "methylenetetrahydrofolate reductase" or "MTHFR"; and "variant" or "variation" or "polymorphism;" and "bone mineral density" or "BMD" or "fracture." The reference lists of retrieved reviews and articles were hand-searched. The publication language was restricted to English. If more than one article was published using the same case series, only the study with largest sample size was selected. The literature search was updated on December 5, 2011.

Inclusion criteria and data extraction

Studies were included if they met the following three inclusion criteria: (1) using case–control or cohort design, (2) evaluating the association of C677T polymorphism with fracture risk or BMD, and (3) providing sufficient data for calculation of odds ratio (OR) or weighted mean difference (WMD) with 95% confidence interval (CI). For fracture phenotype, the following information was extracted from each study: (1) name of the first author, (2) year of publication, (3) country of origin, (4) ethnicity of the studied population, (5) study design, (6) sample size in cases and controls, (7) genotype distributions in cases and controls, (8) minor allele frequency in controls, and (9) p value for the test of Hardy–Weinberg equilibrium in controls. For BMD phenotype, the following information was extracted: (1) name of the first author, (2) year of publication, (3) country of origin, (4) ethnicity of the studied population, (5) study design, (6) type of BMD phenotype, (7) mean and standard deviation of BMD across three genotypes, and (8) sample size across three genotypes. Two authors independently assessed the articles for compliance with the inclusion criteria, and disagreement was followed by discussion until consensus was reached.

Statistical analysis

The association between C677T polymorphism and fracture risk was estimated by calculating a pooled OR and 95% CI under co-dominant model, dominant model, and recessive model, respectively. The association between C677T polymorphism and BMD was estimated by a pooled WMD under three genetic models above, respectively. The significance of the pooled OR or WMD was determined by a Z test ($p<0.05$ was considered statistically significant). A Q test was performed to evaluate whether the variation was due to heterogeneity or due to chance. A random (DerSimonian–Laird method [28]) or fixed (Mantel–Haenszel method) effects model [29] was used to calculate the pooled OR or WMD in the presence ($p<=0.10$) or absence ($p>0.10$) of heterogeneity, respectively. Begg's funnel plot, a scatter plot of effect against a measure of study size, was generated as a visual aid to detect bias or systematic heterogeneity [30]. Publication bias was assessed by Egger's test [31] ($p<0.05$ was considered statistically significant). Subgroup analyses based on ethnicity (European vs. East Asian),

type of fracture (hip fracture vs. vertebral fracture), sex (male vs. female), study design (case–control design vs. cohort design), and mean age of subjects (<60 years vs. ≥60 years) were performed. Sensitivity analysis was performed by removing one study at a time to evaluate the stability of the results. Data analyses were performed using STATA version 11 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of the studies

The literature search identified a total of 41 potentially relevant papers. Of these, 25 papers were excluded after reading the title or abstract because of obvious irrelevance to our study aim. In addition, one duplicated paper [32] and one paper [33], which did not provide sufficient data for the calculation of an OR and 95%CI, were further excluded. If more than one study was included in one paper or data were presented by sex, they were considered as separate study in our meta-analysis. Therefore, 20 studies for fracture risk [14–27] and 16 studies for BMD [15, 17–19, 22, 25, 26, 34–38] met the inclusion criteria and were included in the final meta-analysis. A flow chart summarizing the process of study inclusion is depicted in Fig. 1. For fracture, 15 studies were performed in Europeans, and five studies were performed in East Asians; ten studies were on vertebral fracture, and five studies were on hip fracture; 14 studies were performed in female, five studies were performed in male, and one study did not present the sex-specific data; ten studies used case–control design, and ten studies used cohort design (Supplementary Table 1). For BMD phenotypes, 14 studies were on BMD of lumbar spine, 13 studies were on BMD of femoral neck, six studies were on BMD of total hip, and seven studies were on BMD of total body (Supplementary Table 2).

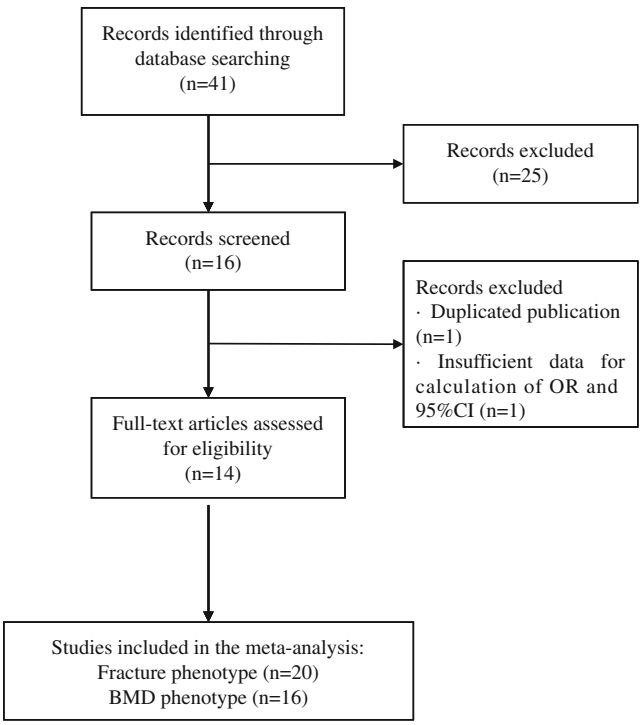


Fig. 1 Flow chart of meta-analysis for exclusion/inclusion of studies

Fractures

A total of 3,525 cases and 17,909 controls were identified for the analysis on C677T polymorphism and fracture. The overall result showed that there was a marginally significant association between this polymorphism and fracture risk under homogeneous co-dominant model (TT vs. CC: OR=1.23; 95% CI 1.00–1.51) and under recessive model (TT vs. TC+CC: OR=1.23, 95% CI 1.04–1.47; Fig. 2). Subgroup analyses showed that the effect size was statistically significant among East Asians (TT vs. TC+CC: OR=1.40, 95% CI 1.07–1.83), studies with vertebral fracture (TT vs. CC: OR=1.46, 95% CI 1.07–1.98), female subpopulation (TT vs. TC+CC: 1.27, 95% CI 1.04–1.55), cohort studies (TT vs. CC: OR=1.21, 95% CI 1.02–1.42; TT vs. TC+CC: OR=1.24, 95% CI 1.08–1.44), and subjects younger than aged 60 years (TT vs. CC: OR=1.68, 95% CI 1.17–2.40; TT vs. TC+CC: OR=1.51, 95% CI 1.10–2.07), but not among Europeans, studies with hip fracture, male subpopulation, case–control studies, and subjects younger than 60 years under all genetic models (Table 1).

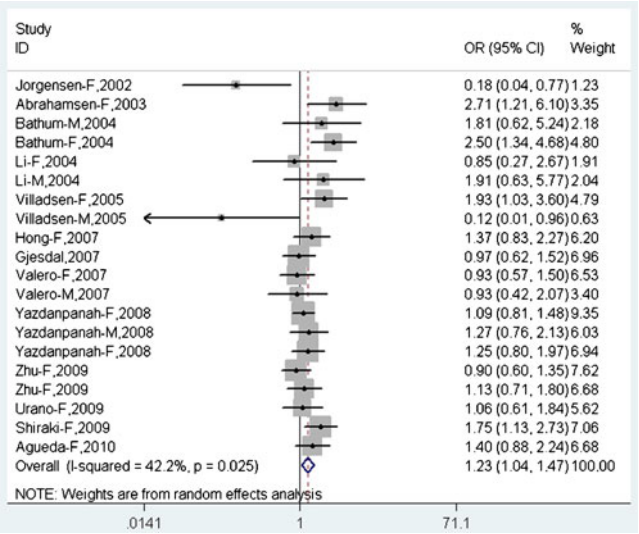


Fig. 2 Meta-analysis of the association between C667T polymorphism in the *MTHFR* gene and fracture risk under recessive model (TT vs. TC+CC). *Square sizes* are proportional to the weight of each study in the meta-analysis

Table 1 Pooled ORs and 95% CIs of the association between C667T polymorphism in the *MTHFR* gene and fracture

Contrasts	Number of studies (cases/controls)	TT vs. CC[a]			TC vs. CC[a]			TT+TC vs. CC[a]			TT vs. TC+CC		
		OR	95% CI	P_H	OR	95% CI	P_H	OR	95% CI	P_H	OR	95% CI	P_H
All	20 (3,525/17,909)	1.23	1.00–1.51	0.008	1.02	0.93–1.11	0.118	1.05	0.93–1.17	0.028	1.23	1.04–1.47	0.025
Ethnicity													
European	15 (2,864/14,963)	1.20	0.95–1.53	0.005	1.01	0.92–1.11	0.170	1.04	0.92–1.18	0.043	1.20	0.97–1.48	0.012
East Asian	5 (661/2,946)	1.32	0.91–1.91	0.295	1.02	0.71–1.47	0.095	1.06	0.74–1.52	0.076	1.40	1.07–1.83	0.557
Type of fracture													
Vertebral	10 (973/4,199)	1.46	1.07–1.98	0.120	1.03	0.84–1.27	0.967	1.11	0.92–1.35	0.796	1.44	0.95–2.18	0.081
Hip	5 (645/6,695)	0.95	0.68–1.31	0.142	0.98	0.60–1.61	0.007	0.94	0.58–1.53	0.005	0.92	0.68–1.25	0.521
Sex [b]													
Female	14 (2,590/11,028)	1.22	0.95–1.56	0.006	0.97	0.88–1.07	0.296	1.00	0.88–1.14	0.046	1.27	1.04–1.55	0.021
Male	5 (426/2,392)	1.22	0.83–1.79	0.117	1.11	0.87–1.42	0.159	1.13	0.90–1.43	0.152	1.12	0.78–1.62	0.163
Study design													
Case-control	10 (1,611/2,448)	1.12	0.69–1.81	0.001	0.99	0.85–1.14	0.110	1.03	0.82–1.30	0.010	1.10	0.73–1.65	0.005
Cohort	10 (1,914/15,461)	1.21	1.02–1.42	0.589	1.04	0.93–1.15	0.225	1.07	0.96–1.18	0.340	1.24	1.08–1.44	0.469
Age (years)													
<60	3 (295/3,244)	1.68	1.17–2.40	0.417	1.15	0.87–1.52	0.101	1.27	0.98–1.64	0.181	1.51	1.10–2.07	0.326
≥60	17 (3,230/14,665)	1.14	0.91–1.43	0.015	1.00	0.92–1.10	0.175	1.02	0.90–1.15	0.042	1.17	0.97–1.42	0.031

OR odds ratio, *CI* confidence interval, P_H *P* value based on *Q* test for between-study heterogeneity

[a] The study by Shiraki et al. was not included in the meta-analysis since it just presented the data on TT and TC+CC genotypes in cases and controls

[b] The study by Gjesdal et al. did not present the sex-specific data

Sensitivity analysis was conducted by excluding each study at a time. The results confirmed the marginally significant association under recessive model, with OR with 95% CI ranging from 1.20 (1.01–1.43) to 1.27(1.06–1.51). However, the results were not robust under homogeneous co-dominant model, with OR with 95% CI ranging from 1.17 (0.96–1.43) to 1.26 (1.02–1.57).

BMD phenotypes

For BMD of lumbar spine, a total of 13,454 subjects were identified for the data analysis. C677T polymorphism was modestly associated with BMD of the lumbar spine from the L2 to L4 vertebrae (TT vs. CC: WMD=−0.017 g/cm^2, 95% CI −0.030–(−0.005)g/cm^2, Fig. 3a; TC vs. CC: WMD=−0.009 g/cm^2, 95% CI −0.015–(−0.004)g/cm^2; dominant model: WMD=−0.011 g/cm^2, 95% CI −0.016–(−0.005)g/cm^2). Similar results were found among each group by ethnicity, sex, and study design (Table 2).

For BMD of femoral neck, a total of 13,567 subjects were identified for the data analysis. There was a modest association between C677T polymorphism and BMD of femoral neck (TT vs. CC: WMD=−0.010 g/cm^2, 95% CI −0.017–(−0.003)g/cm^2, Fig. 3b). The results were similar when different sexes, ethnicities, and study designs were considered separately (Table 2).

For BMD of total hip and total body, a total of 6,356 and 5,652 individuals were identified for the data analysis, separately. There was a modest association between C677T polymorphism and BMD of total hip (TT vs. CC: WMD=−0.013 g/cm^2, 95% CI −0.022–(−0.004)g/cm^2, Fig. 3c; TT vs. TC+CC: WMD=−0.012 g/cm^2, 95% CI −0.020–(−0.004)g/cm^2) and BMD of total body (TT vs. CC: WMD=−0.020 g/cm^2, 95% CI −0.027–(−0.013)g/cm^2, Fig. 3d; TC vs. CC: WMD=−0.007 g/cm^2, 95% CI −0.012–(−0.002)g/cm^2; TT+TC vs. CC: WMD=−0.011 g/cm^2, 95% CI −0.017–(−0.004)g/m^2; TT vs. TC+CC: WMD=−0.015 g/m^2, 95% CI −0.022–(−0.008)g/m^2) (Table 2).

Sensitivity analysis was conducted by excluding each study at a time. The results confirmed the modest association of C677T polymorphism with BMD of lumbar spine, femoral neck, total hip, and total body, respectively (data not shown).

Potential publication bias

Using the Egger's test, no publication bias could be detected for the association of C677T polymorphism with fracture risk (TT vs. CC, p=0.949; TC vs. CC, p=0.631; TT+TC vs. CC, p=0.541; TT vs. TC+CC, p=0.666) and BMD phenotypes (BMD of lumbar spine: TT vs. CC, p=0.896; TC vs. CC, p=0.276; TT+TC vs. CC, p=0.427; TT vs. TC+CC,

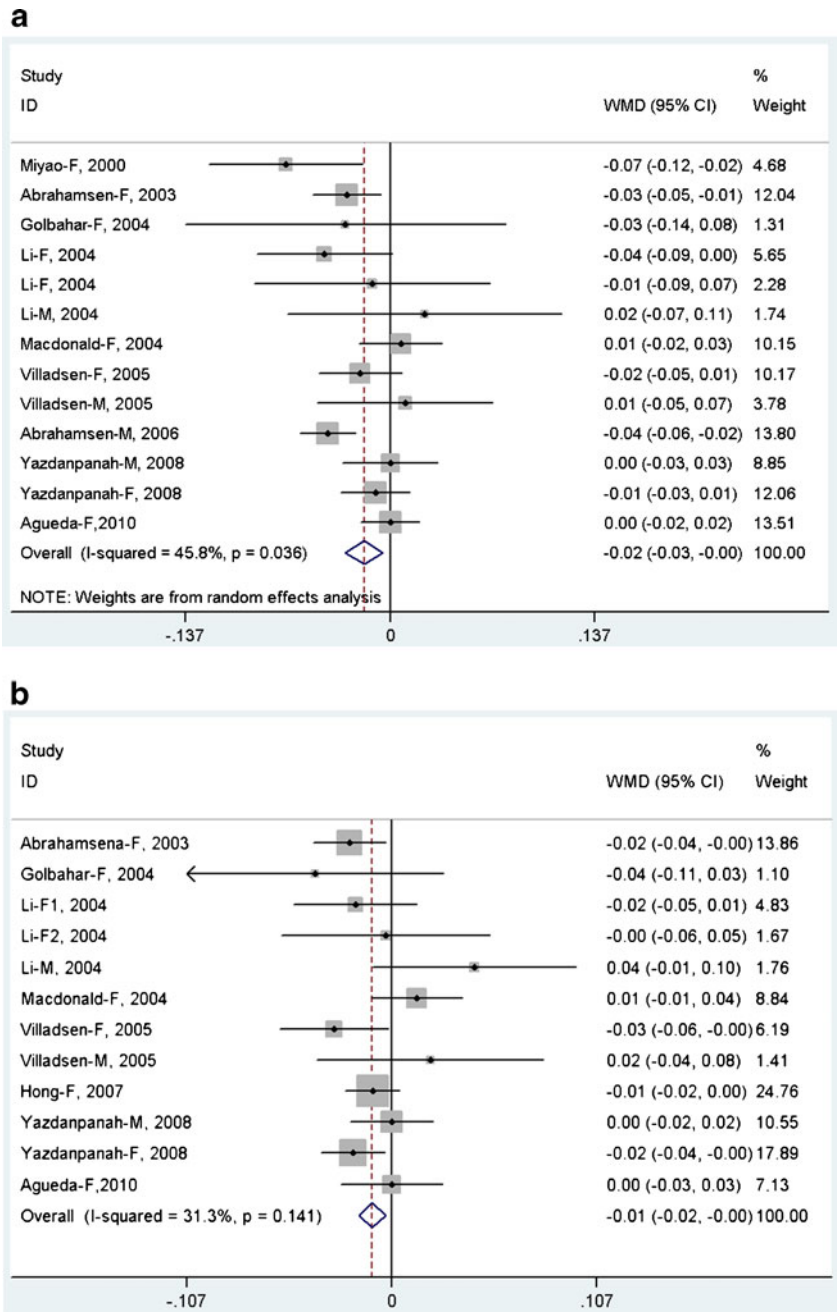


Fig. 3 Meta-analysis of the association between C667T polymorphism in the *MTHFR* gene and BMD of lumbar spine (**a**), femoral neck (**b**), total hip (**c**), and total body (**d**) under a homogeneous co-dominant model (TT vs. CC). *Square sizes* are proportional to the weight of each study in the meta-analysis

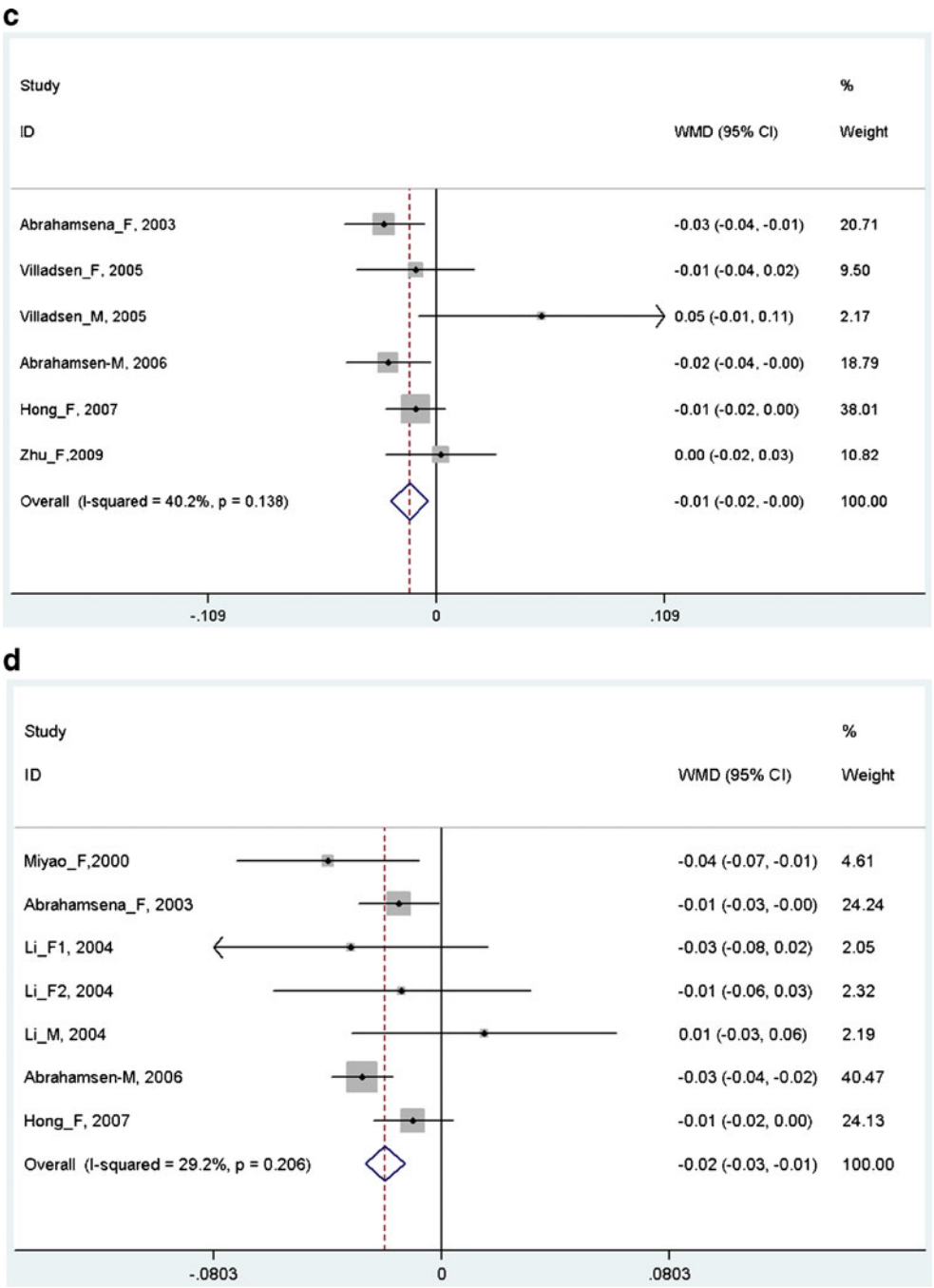
p=0.686; BMD of femoral neck: TT vs. CC, p=0.366; TC vs. CC, p=0.237; TT+TC vs. CC, p=0.175; TT vs. TC+CC, p=0.911; BMD of total hip, TT vs. CC: p=0.175; TC vs. CC, p=0.403; TT+TC vs. CC, p=0.796; TT vs. TC+CC, p=0.132; BMD of total body: TT vs. CC, p=0.747; TC vs. CC, p=0.841; TT+TC vs. CC, p=0.770; TT vs. TC+CC, p=0.977).

Discussion

Our study suggested that C677T polymorphism in *MTHFR* gene was marginally associated with fracture risk. In the subgroup analyses, significant associations were observed among East Asians, female subpopulation, cohort studies, and subjects younger than aged 60 years. The result was somewhat different from a previous meta-analysis, which suggested non-significant association between C677T polymorphism and fracture risk [20]. In addition, the present meta-analysis suggested the modest association of C677T polymorphism with BMD of lumbar spine, femoral neck, total hip, and total body, respectively, which was in agreement with the previous meta-analysis [27].

It is possible that the effect sizes of genetic factors predisposing to human diseases are different across

Fig. 3 (continued)



various ethnic populations [39]. The frequency of C677T polymorphism TT genotype is much lower in Europeans than East Asians, according to the HapMap data. For example, the frequencies of CC, CT, and TT were about 59.3%, 33.9%, and 6.8%, respectively, in European population, while the frequencies of CC, CT, and TT were about 26.7%, 44.4%, and 28.9%, respectively in the Chinese population. Indeed, we observed a significant association between C677T polymorphism and fracture risk among East Asians but not Europeans. In addition, we also found a significant association in women rather than in men. It should be noted that nearly all women included in the present meta-analysis were postmenopausal. As is known, menopause is a critical period that presents a high bone turnover state. Moreover, some evidences have indicated that the plasma homocysteine level of a woman could increase even more when she reaches menopause, causing further worsening of bone quality and eventually increasing her risk of osteoporotic fractures [40]. A significant association was also observed among subjects younger than 60 years. However, the result should be interpreted with caution because of the limited sample size within this subgroup.

Table 2 WMDs and 95% CIs of the association between C667T polymorphism in the *MTHFR* gene and bone mineral density

Contrasts	Number of studies (sample size)	TT vs. CC[a]			TC vs. CC[a]			TT+TC vs. CC[a]			TT vs. TC+CC		
		WMD	95% CI	P_H	WMD	95% CI	P_H	WMD	95% CI	P_H	WMD	95% CI	P_H
Lumbar spine													
All	14 (13,454)	−0.017	−0.030–(−0.005)	0.036	−0.009	−0.015–(−0.004)	0.695	−0.011	−0.016–(−0.005)	0.234	−0.010	−0.021–0.000	0.015
Ethnicity													
European	10 (12,490)	−0.014	−0.027–(−0.001)	0.044	−0.008	−0.014–(−0.002)	0.658	−0.010	−0.016–(−0.005)	0.187	−0.007	−0.018–0.004	0.022
East Asian	4 (964)	−0.039	−0.073–(−0.006)	0.305	−0.022	−0.042–(−0.001)	0.660	−0.023	−0.042–(−0.004)	0.542	−0.034	−0.062–(−0.006)	0.368
Sex [b]													
Female	9 (8,172)	−0.017	−0.030–(−0.003)	0.132	−0.008	−0.014–(−0.001)	0.529	−0.009	−0.015–(−0.003)	0.407	−0.013	−0.025–(−0.000)	0.140
Male	4 (3,386)	−0.013	−0.045–0.020	0.049	−0.014	−0.026−(–0.002)	0.765	−0.018	−0.029−(–0.006)	0.171	−0.007	−0.036–0.021	0.077
Study design													
Cross-sectional	8 (3,834)	−0.026	−0.046–(−0.006)	0.393	−0.014	−0.026–(−0.002)	0.874	−0.015	−0.026–(−0.004)	0.776	−0.004	−0.015–0.006	0.131
Cohort	6 (9,620)	−0.014	−0.030–0.003	0.010	−0.008	−0.014–(−0.001)	0.323	−0.010	−0.019–(−0.000)	0.048	−0.010	−0.024–0.005	0.016
Femoral neck													
All	13 (13,567)	−0.010	−0.017−(–0.003)	0.141	−0.004	−0.010–0.002	0.077	−0.005	−0.011–0.001	0.072	−0.006	−0.012–0.000	0.206
Ethnicity													
European	9 (11,011)	−0.011	−0.020–(−0.003)	0.112	−0.002	−0.007–0.004	0.455	−0.003	−0.009–0.002	0.243	−0.008	−0.015–(−0.001)	0.236
East Asian	4 (2,556)	−0.008	−0.020–(0.004)	0.244	−0.015	−0.023−(–0.006)	0.185	−0.013	−0.021−(–0.005)	0.132	0.001	−0.011–0.012	0.302
Sex[b]													
Female	9 (9,328)	−0.013	−0.021–(−0.005)	0.288	−0.005	−0.012–0.003	0.040	−0.006	−0.013–0.001	0.064	−0.009	−0.016–(−0.002)	0.239
Male	3 (2,343)	0.008	−0.011–0.026	0.304	0.000	−0.011–0.012	0.655	0.002	−0.009–0.012	0.540	0.007	−0.011–0.025	0.316
Study design													
Cross-sectional	7 (3,525)	−0.013	−0.030–(−0.002)	0.165	−0.005	−0.016–0.006	0.905	−0.006	−0.016–0.005	0.663	−0.006	−0.016–0.005	0.179
Cohort	6 (10,042)	−0.010	−0.017–(−0.002)	0.155	−0.003	−0.013–0.006	0.005	−0.004	−0.013–0.004	0.010	−0.006	−0.013–0.001	0.233
Total hip	6 (6,356)	−0.013	−0.022–(−0.004)	0.138	−0.001	−0.007–0.005	0.492	−0.004	−0.009–0.002	0.345	−0.012	−0.020–(−0.004)	0.138
Total body	7 (5,652)	−0.020	−0.027–(−0.013)	0.206	−0.007	−0.012–(−0.002)	0.638	−0.011	−0.017–(−0.004)	0.097	−0.015	−0.022–(−0.008)	0.243

WMD weighted mean difference, *CI* confidence interval, P_H *P* value based on Q test for between-study heterogeneity

[a] The study by McLean et al was not included in the meta-analysis since it just presented the data on TT and TC+CC genotypes in cases and controls

[b] The study by McLean et al did not present the sex-specific data

Recent meta-analyses have indicated that C677T polymorphism was associated with several chronic diseases, including hypertension [41], coronary heart disease [42], Alzheimer's disease [43], migraine [44], stroke [45], and some cancers [46]. The mechanisms by which *MTHFR* gene affects these diseases, as well as BMD and fracture, remain unknown. Besides folate intake, homocysteine levels are also affected by the activity of the MTHFR, which converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary circulatory form of folate, and directs the homeostasis between DNA synthesis and methylation [45]. Evidences have suggested that TT genotype of C677T polymorphism was associated with elevated levels of circulating homocysteine [47, 48], which could interfere with collagen synthesis, resulting in lower bone quality and increased fracture risk [13]. In addition, homocysteine may have a direct effect on bone by stimulating osteoclast formation and osteoclast activity [49]. Further function studies are required to investigate the effect of *MTHFR* gene on BMD and fracture.

The current meta-analysis has some limitations. First, the present meta-analysis was based primarily on unadjusted effect estimates and 95% CIs, so the confounding factors might influence the effect estimates. Second, the effects of gene–gene/gene–environment (e.g., riboflavin and folate) interactions were not addressed in this meta-analysis. Besides C677T polymorphism, other genes, such as *VDR*, *estrogen receptor*, and *COL1A1*, may affect BMD and fracture and modulate the effect of C677T polymorphism on BMD and fracture [50]. In addition, environmental factors, such as diet, physical activity, smoking, and alcohol consumption, have been shown to influence BMD, osteoporosis, and fracture [51]. Therefore, these gene–environmental factors may act as modifiers that affect the association between C677T polymorphism and fracture. However, most included studies did not provided the related data, which impeded us for further analysis.

In summary, our meta-analysis suggested that C677T polymorphism was marginally associated with fracture risk. In addition, there was modest association between C677T polymorphism and BMD. We believe that our conclusions were credible since our meta-analyses had sufficient statistical power (using Quanto software http://hydra.usc.edu/gxe/, we calculated the power for the overall cohort (dominant model, 99%; recessive model, 98%), the European cohort (dominant model, 99%; recessive model, 75%), and the East Asian cohort (dominant model, 85%; recessive model, 63%). However, further studies with the consideration of gene–gene/gene–environment interactions are needed to investigate the role of the *MTHFR* gene polymorphisms in the regulation of BMD and the pathogenesis of fracture in the future.

Conflicts of interest None.

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