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Original Article

MTHFR C677T polymorphism and coronary artery disease risk in the Chinese population: a meta-analysis based on 33 studies

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Abstract: Background: Although many epidemiologic studies have investigated the MTHFR C677T polymorphism and its associations with coronary artery disease (CAD), definite conclusions cannot be drawn. To clarify the impact of methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism on the risk of CAD, a meta-analysis was performed in the Chinese population. Methods: Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) till March 2015. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of the associations. Results: A total of 33 studies including 6130 CAD cases and 6163 controls were involved in this meta-analysis. Overall, significant association was found between MTHFR C677T polymorphism and CAD risk when all studies in the Chinese population pooled into this meta-analysis (T vs. C: OR = 1.44, 95% CI = 1.29-1.61; TT vs. CC: OR = 1.88, 95% CI = 1.54-2.30; TT vs. CC+CT: OR = 1.41, 95% CI = 1.22-1.62; TT + CT vs. CC: OR = 1.71, 95% CI = 1.45-2.02). When we performed stratified analyses by geographical locations and source of controls, significantly increased risks were found in all the subgroups. Conclusions: This meta-analysis provides the evidence that MTHFR C677T polymorphism may contribute to the CAD development in the Chinese population.

Keywords: Meta-analysis, MTHFR C677T, polymorphism, coronary artery disease, Chinese

Background

Coronary artery disease (CAD), one of the major causes of morbidity and mortality worldwide [1], had become a public health problem in China during the past few decades. Recently, age-standardized CAD mortality increased in China, in contrast to the declining trends in various developed countries [2]. The overall CAD mortality rate (per 100000 individuals per year) in China was projected to rise from 95.3 in 1999 to 103.4 in 2008 [3]. In 2008, crude morbidity rate of ischemic heart disease was 12.7% among Chinese urban residents [4]. Numerous epidemiological studies have identified several risk factors for CAD, including dyslipidaemia, diabetes, obesity, birth weight, smoking, dietary, gender, and genetic variance [5]. In recent years the role of genetic variability on the development of CAD has been extensively been studied [6], which is impacting upon our understanding of phenotypic outcomes and clinical complications. An important one is Methylenetetrahydrofolate reductase (MTHFR), which plays a critical role in folate metabolism and is involved in DNA synthesis, DNA repair and DNA methylation. A common polymorphism in MTHFR gene at nucleotide 677C/T (amino acid 222Ala/Val, rs1801133) has drawn special attention as its mutation can impair the enzyme activity and hyperhomocysteinemia [7]. An association between MTHFR C677T polymorphism and CAD was first reported by Kang and co-workers in 1988 in Chicago [8]. As a consequence, many studies analyzed the influence of MTHFR C677T polymorphism on CAD risk, however, no clear consensus was reached. Meta-analyses of studies on the gene in other ethnic groups have been reported elsewhere and produced conflicting results [9-14]. Mo-

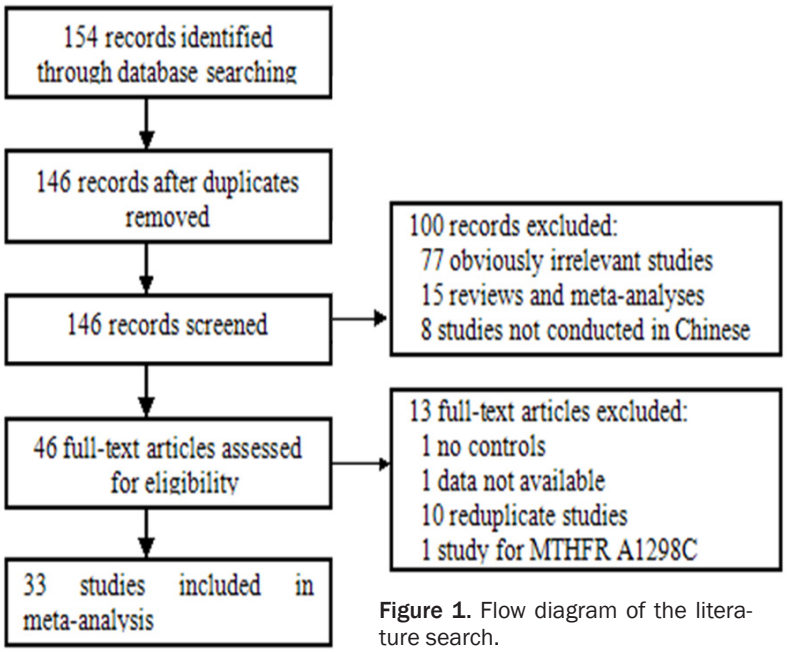

Figure 1. Flow diagram of the literature search.

reover, two appraisals [15, 16] also conclude that more accurate evaluation of MTHFR C677T polymorphism with CAD in specific population needs to be presented. In order to clarify the effects of MTHFR C677T on the risk of CAD in Chinese, an updated meta-analysis was performed.

Methods

Literature search

A comprehensive literature search was performed using the PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) for relevant articles published with the following Mesh terms: (coronary artery disease or coronary heart disease) and (methylenetetrahydrofolate reductase or MTHFR) and (Chinese or China or Taiwan). An upper date limit of 13 March 2015 was applied and no lower date limit was used. The search was performed without any restrictions on language and focused on studies conducted in humans. Concurrently, the reference lists of reviews and retrieved articles were searched manually.

Inclusion/exclusion criteria

For inclusion, the studies must have met the following criteria: (1) case-control study or cohort study studying on association between the MTHFR C677T polymorphisms and CAD susceptibility; (2) all patients diagnosis based on angiographic features, clinical or laboratory findings; (3) sufficient published data about sample size, odds ratio (OR), and their 95% confidence interval (CI); (4) all participants were Chinese; (5) containing complete information about all genotype frequencies. Studies were excluded when they were: (1) not case-control study or cohort study; (2) duplicate of previous publication; (3) based on incomplete data; (4) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Information was extracted carefully from all eligible studies independently by two investigators according to the inclusion criteria listed above. Disagreements were resolved by discussion. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following data was collected from each study: first author's surname, year of publication, geographical locations, source of controls, total numbers of cases and controls, and the numbers of cases and controls who harbored the MTHFR C677T genotypes.

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 10, STATA, College Station, TX). The χ^2-test was used for Hardy-Weinberg equilibrium (HWE) of genotypes in the control group of each reviewed study and the heterogeneity of rare allele frequencies in control groups among all studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association between the MTHFR C677T poly-

Table 1. Characteristics of studies included in the meta-analysis

References	Source of controls	Geographical location	Case number	Control number	Case			Control			HWE	
					CC	CT	TT	CC	CT	TT	χ^2	*P*
Chen 1998	PB	Heilongjiang	69	79	10	36	23	26	43	10	1.44	0.230
Xu 1999	PB	Beijing	209	101	56	95	58	43	35	23	7.84	0.005
Dai 2001	HB	Hunan	73	100	32	33	8	37	47	16	0.03	0.868
Hus 2001	PB	Taiwan	218	218	120	85	13	125	78	15	0.35	0.555
Fang 2002	PB+HB	Beijing	161	125	34	80	47	44	60	21	0.01	0.943
Mao 2002	HB	Tianjin	136	298	27	61	48	53	142	103	0.11	0.738
Chen 2002	HB	Tianjin	107	96	36	41	30	36	40	20	1.96	0.162
Zhang 2002	HB	Beijing	81	72	27	40	14	29	33	10	0.02	0.901
Ma 2003	PB	Tianjin	50	50	13	22	15	26	14	10	7.07	0.008
Gao 2004	HB	Zhejiang	96	82	22	48	26	40	32	10	0.80	0.370
Gu 2005	HB	Fujian	122	56	30	55	37	24	18	14	6.32	0.012
Li 2005	HB	Hunan	161	74	62	83	16	37	32	5	0.30	0.583
Xu 2005	PB	Guangdong	47	143	34	11	2	90	50	3	1.74	0.187
Li 2005a	HB	Shandong	105	33	18	60	27	15	12	6	1.52	0.218
Lian 2006	PB	Shanxi	80	70	19	39	22	24	34	12	0.00	0.994
Chen 2007	HB	Xinjiang	189	131	44	108	37	61	47	23	6.14	0.013
Luo 2007	PB	Beijing	105	91	27	61	17	42	35	14	2.06	0.152
Jiao 2007	PB	Henan	208	500	32	95	81	178	220	102	4.92	0.027
Zhu 2007	PB	Tianjin	50	50	13	22	15	26	14	10	7.07	0.008
Xiao 2007	PB	Guizhou	87	73	29	54	4	47	25	1	1.35	0.245
Lin 2008	PB	Taiwan	121	155	66	47	8	88	57	10	0.04	0.851
Wu 2009	PB	Hubei	942	942	339	424	179	346	408	188	11.13	0.001
Gu 2009	HB	Ningxia	186	175	48	110	28	63	78	34	1.22	0.270
Li 2010	HB	Yunnan	114	31	36	51	27	10	15	6	0.01	0.930
Jin 2010	PB	Inner Mongolia	62	120	26	22	14	70	39	11	2.45	0.118
Sun 2010	PB	Hubei	126	114	43	52	31	63	31	20	15.26	0.000
Yang 2011	HB	Jiangsu	120	58	19	52	49	19	20	19	5.59	0.018
Hu 2011	PB	Ningxia	202	199	47	106	49	41	109	49	1.88	0.170
Jin 2011	HB	Chongqing	98	59	31	56	11	39	18	2	0.00	0.965
Jiang 2012	HB	Anhui+Jiangsu	131	131	32	58	41	58	52	21	2.47	0.116
Yan 2013	HB	Inner Mongolia	117	155	40	55	22	61	69	25	0.54	0.463
Yu 2014	HB	Liaoning	1133	1106	401	523	209	422	542	142	2.47	0.116
Chen 2014	HB	Tianjin	424	476	98	209	117	141	221	114	2.23	0.135

PB, Population-based, HB, hospital-based.

morphism and CAD risk. The significance of the pooled OR was determined by the Z test. Dependent on the results of heterogeneity test among individual studies, the fixed-effect model (Mantel-Haenszel) or random-effect model (DerSimonian and Laird) was selected to summarize the combined ORs and their 95% CIs. Sensitivity analysis was conducted to verify stability of the meta-analysis using both models (the fixed effect model and random effect model). Begg's funnel plots and Egger's linear regression test were used to assess publication bias. In addition to the comparison among all subjects, we also performed stratification analyses by geographical locations and source of controls. All the *P*-values were two-sided, a *P*-value <0.05 was considered statistically significant.

Results

Eligible studies

Figure 1 graphically illustrates the trial flow chart. A total of 154 articles regarding MTHFR

Table 2. Main results in the total and subgroup analysis

Analysis model	Study groups	n	Random-effect model	Fixed-effect model	Heterogeneity	
			OR (95% CI)	OR (95% CI)	χ^2	P
T vs. C	Total analysis	33	1.44 (1.29-1.61)	1.31 (1.24-1.38)	115.59	0.000
	PB	15	1.50 (1.22-1.83)	1.30 (1.20-1.41)	70.94	0.000
	HB	17	1.38 (1.21-1.58)	1.30 (1.21-1.39)	42.09	0.000
	South China	13	1.39 (1.12-1.72)	1.20 (1.09-1.31)	50.09	0.000
	North China	19	1.45 (1.27-1.65)	1.35 (1.26-1.44)	54.23	0.000
TT vs. CC	Total analysis	33	1.88 (1.54-2.30)	1.63 (1.47-1.82)	86.73	0.000
	PB	15	2.03 (1.39-2.97)	1.58 (1.34-1.85)	54.50	0.000
	HB	17	1.72 (1.37-2.16)	1.64 (1.42-1.89)	29.23	0.022
	South China	13	1.69 (1.15-2.49)	1.31 (1.09-1.58)	30.16	0.003
	North China	19	1.92 (1.52-2.42)	1.78 (1.55-2.03)	44.22	0.001
TT vs. CC+CT	Total analysis	33	1.41 (1.22-1.62)	1.35 (1.23-1.48)	56.13	0.005
	PB	15	1.50 (1.14-1.96)	1.32 (1.14-1.52)	35.04	0.001
	HB	17	1.33 (1.14-1.55)	1.35 (1.19-1.53)	19.03	0.267
	South China	13	1.21 (0.97-1.52)	1.213 (0.99-1.33)	14.38	0.277
	North China	19	1.44 (1.21-1.70)	1.43 (1.28-1.61)	32.17	0.021
TT + CT vs. CC	Total analysis	33	1.71 (1.45-2.02)	1.45 (1.34-1.56)	119.35	0.000
	PB	15	1.75 (1.33-2.31)	1.44 (1.28-1.61)	63.06	0.000
	HB	17	1.68 (1.34-2.10)	1.43 (1.29-1.59)	54.63	0.000
	South China	13	1.62 (1.19-2.20)	1.32 (1.17-1.50)	53.91	0.000
	North China	19	1.75 (1.42-2.15)	1.50 (1.36-1.66)	59.15	0.000

PB, Population-based, HB, hospital-based, South China includes Hunan, Taiwan, Zhejiang, Fujian, Guangdong, Guizhou, Hubei, Yunnan, Jiangsu and Chongqing; North China includes Heilongjiang, Beijing, Tianjin, Shaxi, Xinjiang, Liaoning, Inner Mongolia, Anhui, Ningxia, Shandong and Henan.

polymorphisms with respect to CAD were identified. After screening the titles and abstracts, 108 articles were excluded because they were review articles, duplicates, not Chinese population, or irrelevant to the current study. In addition, of these published articles, 13 articles were excluded for full-text articles assessing due to no controls, unavailable data, reduplicate studies, or other polymorphisms of MTHFR. Finally, 33 studies [17-49] including 6130 CAD cases and 6163 controls were involved in this meta-analysis according to the inclusion criteria. The publication year of studies ranged from 1998 to 2014. Twenty-nine of these studies were written in Chinese, four studies in English. The characteristics of the included studies are summarized in **Table 1**.

Meta-analysis results

Table 2 lists the primary results. Overall, a significantly elevated risk of CAD was associated with all variants of MTHFR C677T (TT vs. CC: OR = 1.88, 95% CI = 1.54-2.30; TT vs. CC+CT: OR = 1.41, 95% CI = 1.22-1.62; TT + CT vs. CC: OR = 1.71, 95% CI = 1.45-2.02). For the allele T versus allele C, the pooled OR was 1.44 (95% CI = 1.29-1.61) (**Figure 2**). However, there was significant heterogeneity between studies. Hence, we then performed subgroup analysis by geographical locations and source of control. In the stratified analysis by geographical locations, significantly increased risks were found both in the North China (T vs. C: OR = 1.45, 95% CI = 1.27-1.65; TT vs. CC: OR = 1.92, 95% CI = 1.52-2.42; TT vs. CC+CT: OR = 1.44, 95% CI = 1.21-1.70; TT + CT vs. CC: OR = 1.75, 95% CI = 1.42-2.15) and in the South China (T vs. C: OR = 1.39, 95% CI = 1.12-1.72; TT vs. CC: OR = 1.69, 95% CI = 1.15-2.49; TT + CT vs. CC: OR = 1.62, 95% CI = 1.19-2.20). In the stratified analysis by source of controls, significantly increased risks were found in the population-based studies (T vs. C: OR = 1.50, 95% CI = 1.22-1.83; TT vs. CC: OR = 2.03, 95% CI = 1.39-2.97; TT vs. CC+CT: OR = 1.50, 95% CI = 1.14-1.96; TT + CT vs. CC: OR = 1.75, 95% CI = 1.33-2.31) and in the hospital-based studies (T vs. C: OR = 1.38, 95% CI = 1.21-1.58; TT vs. CC: OR =

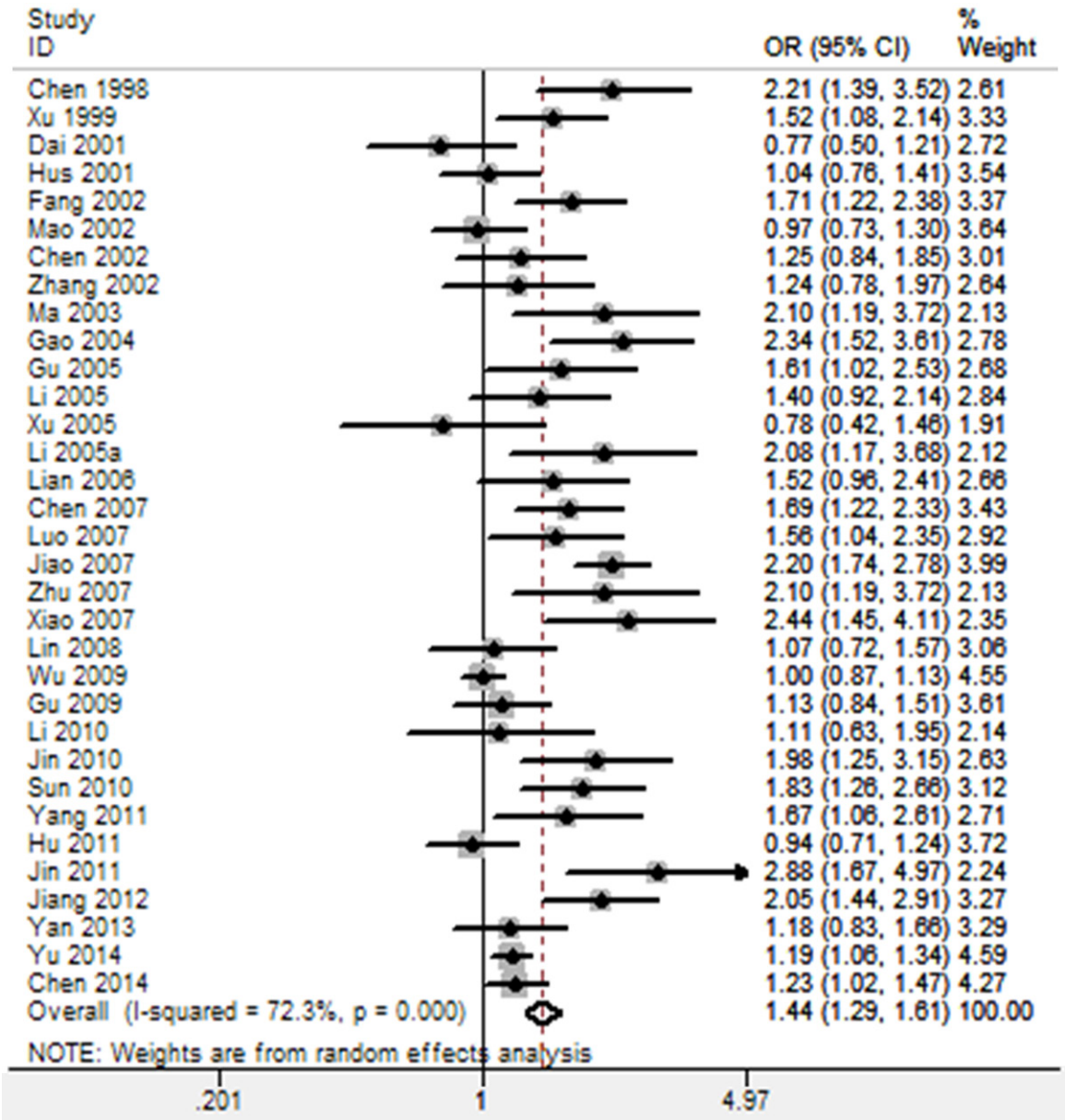

Figure 2. Forest plot (random-effects model) of CAD risk associated with MTHFR C677T polymorphism using the allele genetic model.

1.72, 95% CI = 1.37-2.16; TT vs. CC+CT: OR = 1.33, 95% CI = 1.14-1.55; TT + CT vs. CC: OR = 1.68, 95% CI = 1.34-2.10).

Sensitive analysis and bias diagnosis

In order to compare the difference and evaluate the sensitivity of the meta-analyses, we used both models (the fixed effect model and random effect model) to evaluate the stability of the meta-analysis. None of the results were materially altered (**Table 2**). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible. The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plots did not reveal obvious asymmetry (**Figure 3A**). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. However, the Egger's test indicated that there were obvious publication bias under the allele model in overall analyses (t = 3.06, *P* = 0.005, **Figure 3B**).

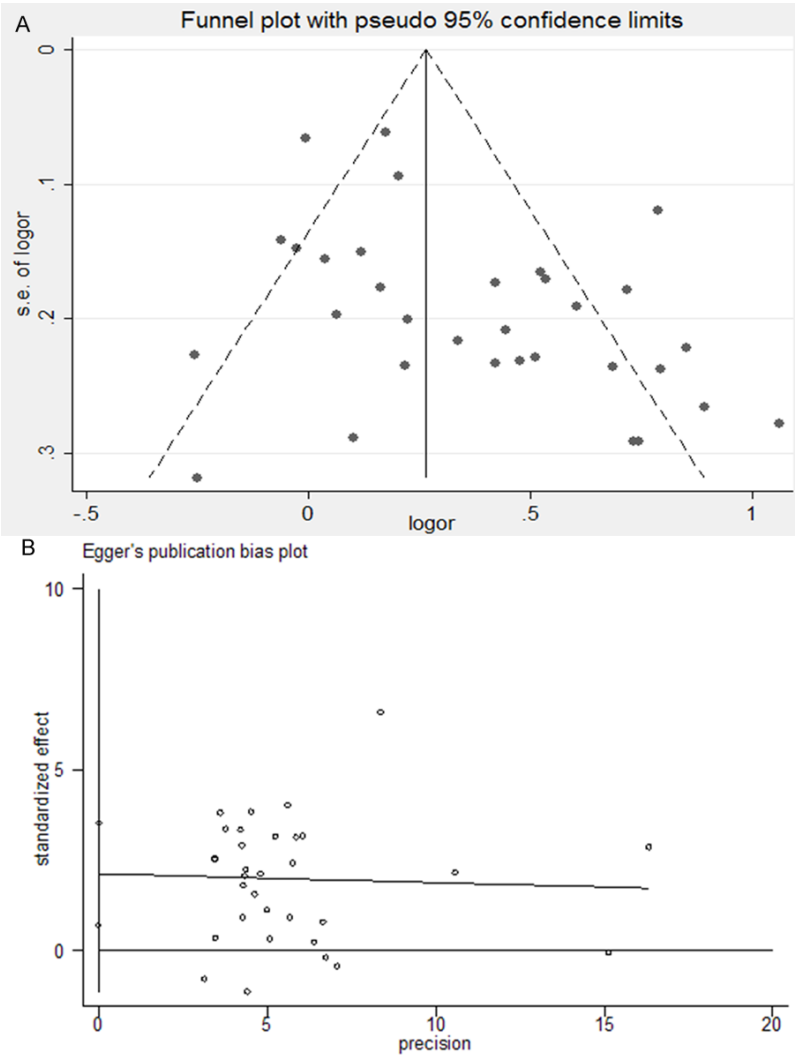

Figure 3. Publication bias evaluation for allele contrast (T vs. C) of MTHFR C677T polymorphism in overall analysis (A: Funnel plot, B: Egger's test).

Discussion

Up to this time, a series of meta-analyses have been carried out to investigate the role of MTHFR C677T polymorphism in the development of CAD in some ethnic groups, but these have produced conflicting or inconclusive results [9-14]. One of major problems with these meta-analyses [9-14] is that there are limited studies in the Chinese population contained. A recent meta-analysis was done to clarify the relationship in the Chinese population, however, there is some space needed to improve in the article [50] due to the relevant small sample size. Therefore, we conducted this meta-analysis to derive a more precise estimation of MTHFR C677T and susceptibility to CAD in the Chinese population. Our meta-analysis involved 33 case-control studies with 6130 patients and 6163 controls. The results showed that a significantly elevated risk of CAD was associated with all variants of MTHFR C677T in the Chinese population. The results were consistent with Li's meta-analysis [50] which based on fourteen studies and the sensitivity analysis confirmed the reliability and stability. Therefore, the findings from our meta-analysis provide a strong evidence for the association between MTHFR C677T polymorphism and risk of CAD in the Chinese population.

To further explain environmental risk factors can modulate the risk, subgroup analyses stratified by geographical locations and source of controls were performed. We found that the variants of MTHFR C677T significantly increase the risk of CAD in population-based studies, in hospital-based studies, in North and South China. However, the risk conferred by MTHFR C677T polymorphism is higher in North China than in South China (**Table 2**). So, genetic backgrounds and the environment they lived in play an important role in susceptibility to CAD. There are different living habits in South and North China. Moreover, according to the previous studies, there exist seasonal and gender differences in folate status among the Chinese people [51, 52]. People living in North China have a higher prevalence folate concentration deficiency [51]. These results support the hypothesis, suggesting that concomitant inadequate folate intake and impaired MTHFR activity might be important susceptibility factors for CAD.

Some limitations of this meta-analysis should be addressed. The key limitation of this study is the lack of an assessment of folate status.

However, considering stratification by geographical locations, the folate status may have limited influence on the association between MTHFR C677T polymorphism and CAD susceptibility. Another potential limitation was that our results were based on unadjusted estimates. More precise analyses can be conducted if individual data were available, which would allow for the adjustment by other covariates including age, sex, race and other factors. Third, publication bias has occurred due to that only published articles were included in this study. Finally, heterogeneity can interfere with the interpretation of the results of a meta-analysis. Although we minimized this likelihood by performing a careful search of published studies and subgroup analyses, significant inter-study heterogeneity nevertheless existed in most of the comparisons.

In conclusion, this meta-analysis suggests that MTHFR C677T polymorphism is associated with CAD in the Chinese population. The variants of MTHFR C677T increased susceptibility to CAD both in North and South China. And the risk conferred by MTHFR C677T polymorphism is higher among people from North China than South China. Further studies analyzing gene-gene and gene-environment interactions are required. Such studies may eventually lead to have a better, comprehensive understanding of the association between the MTHFR C677T polymorphism and CAD risk.

Disclosure of conflict of interest

None.

Authors' contribution

JS and SX participated in the design of this study, they both performed the data collection and statistical analysis. JS drafted the manuscript. All authors read and approved the final manuscript.

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