CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2017: 92: 243–258
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CLINICAL GENETICS
doi: 10.1111/cge.12929

Review

Geographical and ethnic distribution of *MTHFR* gene polymorphisms and their associations with diseases among Chinese population

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Yang B., Fan S., Zhi X., Xia R., Wang Y., Zheng Q., Sun G. Geographical and ethnic distribution of *MTHFR* gene polymorphisms and their associations with diseases among Chinese population.
Clin Genet 2017: 92: 243–258. © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd, 2016

Numerous studies have investigated the distribution of methylenetetrahydrofolate reductase (*MTHFR*) C677T and A1298C polymorphisms and their associations with diseases in China. In this study we conducted a systematic review and meta-analysis of these studies (715 eligible studies in total).Results revealed that the frequencies of the *MTHFR* C677T and A1298C polymorphisms varied markedly in different areas and ethnicities, and even showed geographical gradients. The *MTHFR* C677T polymorphism was significantly associated with 42 clinical disorders ($p < 0.05$), mostly relating to the diseases of circulatory system, birth defects and cancers. The association of the A1298C polymorphism with three diseases (coronary heart disease, breast cancer and neural tube defects fathers) was statistically significant ($p < 0.05$). However, according to the Venice criteria, only the associations of the C677T polymorphism with breast and ovarian cancers were assessed as having strong epidemiological credibility. This is the first study to provide a comprehensive assessment of the current status and gaps in genetic epidemiological study of the two polymorphisms in China, and its findings may be useful for medical and public health practices. Future studies are warranted to focus on the interactions of *MTHFR* genes with environmental exposure and with other genes, and to improve their methodological quality and reporting of findings.

Conflict of interest

The authors declare that they have no conflict of interest.

Key words: A1298C – C677T – Chinese – methylenetetrahydrofolate reductase – polymorphism – systematic review

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Received 17 September 2016, revised and accepted for publication 22 November 2016

Methylenetetrahydrofolate reductase (MTHFR) catalyzes the irreversible conversion of 5,10-methylene tetrahydrofolate to 5-methyltetrahydrofolate, which resides at a key metabolic branch point directing the distribution of folate derivatives to homocysteine remethylation and DNA methylation or to DNA and

RNA biosynthesis (1, 2). C677T and A1298C are the two most common polymorphisms in *MTHFR* gene that are associated with reduced MTHFR activity, elevated homocysteine concentrations, and aberrant DNA methylation patterns (2–5).

In terms of the *MTHFR* C677T and A1298C polymorphisms, prior research has demonstrated that their frequencies vary markedly across different regions and ethnic groups worldwide, and even show geographical gradients in some regions like Europe, North America and India (6–11).There were also numerous studies in China investigating its geographical and ethnic distribution of the two polymorphisms (12–14), yet the results were irreproducible and inconclusive. Accurate information on the distribution of the two polymorphisms may be beneficial for studies of gene-disease associations and population genetics as well as for differential diseases prevention and health impact assessment (6). Furthermore, in the past decades, a large number of human studies have explored the associations of the *MTHFR* C677T and A1298C polymorphisms with various clinical conditions (e.g. vascular diseases, birth defects, diabetes mellitus and cancers) (15), which, however, often yield controversial results.

Meta-analysis is a widely utilized statistical method that can quantitatively synthesize information across studies endeavoring to increase statistical power and settle uncertainty from single studies. Up to now, over 300 meta-analyses have been done to evaluate associations of the C677T and A1298C polymorphisms with various diseases. Results from these meta-analyses showed that the associations often depended on ethnicity and geographical location of the population studied (15–18). This indicates a necessity of constructing a database of gene-disease associations for a specific area and/or ethnicity. Given the above considerations, this study thus aimed to investigate the distribution of the *MTHFR* C677T and A1298C polymorphisms and their associations with diseases among Chinese population. We comprehensively retrieved all relevant literature to date and conducted a systematic review and meta-analysis of them, in order to achieve the purpose of this study.

Methods

Search strategy

All relevant publications reporting genotype distribution of the *MTHFR* C677T and A1298C polymorphisms or investigating the relationships of the two polymorphisms with any diseases among the Chinese population were identified by computerized searches in seven databases. The search strategy for each database is detailed in Table S1 (Supporting information). All databases were searched from their inception to February 2015. Reference lists from identified articles were manually scrutinized.

Study selection and eligibility criteria

Duplicates were removed from the initially retrieved records of literature, and the remaining articles were screened for eligibility in two phases. First, titles and abstracts of articles were assessed for potential eligibility. Second, for articles rated as potentially eligible, their full text was thoroughly gone through to decide whether the studies should be included for final analysis (Fig. S1). Two reviewers worked independently to screen eligible articles for inclusion. Any discrepancies were reconciled through consensus and discussion with a third reviewer.

Studies were included if they met the following criteria: (i) the study design was cross-sectional, cohort or case–control; (ii) the study subjects in cross-sectional and cohort studies should be apparently healthy; (iii) the number of individual genotypes was provided or could be calculated; (iv) Hardy–Weinberg equilibrium (HWE) can be evaluated; (v) case–control or case-cohort studies must provide sufficient data for calculating odds ratio (OR) and 95% confidence interval (CI); (vi) the published language was English or Chinese; (vii) if the same study population was reported more than once, only the one that provided the most detailed information was included.

Quality assessment

Two reviewers independently assessed the quality of the included studies. Case–control studies were assessed using Newcastle Ottawa Scale (NOS). Each study was evaluated on a score from 0 to 9, and a score of 6 or more was regarded as 'high quality'. For cross-sectional studies, we adopted the Joanna Briggs Institute (JBI) meta-analysis of statistics assessment and review instrument. The study was categorized as 'high quality' if its quality score was greater than 13 out of a maximum score 20.

Data extraction

Information extracted from each eligible study included: authors' names, title, year of publication, source of controls, year of data collection, ethnicity, study location, percentage of males, mean age, endpoints (diseases), counts of alleles and genotypes and sample size. If an article reported results separately for more than one ethnicity or disease, each was considered as an independent data set. The total number of included studies was counted as equivalent to that of data sets.

Statistical analysis

All statistical analyses were performed using Stata S.E. version 12.1 (StataCorporation, Colloege station, TX). Two-tailed p value < 0.05 was taken as statistically significant unless otherwise stated. The HWE was recalculated using χ^2 goodness of fit. Genotypic and allelic frequencies with corresponding 95% CIs were pooled using the inverse variance method (19). Subgroup analyses by study region (Table S2) and ethnicity were further performed. For diseases with available genotype data in ≥ 2 independent samples, the pooled ORs and 95% CIs were calculated under homozygous co-dominant,

heterozygous co-dominant, dominant, recessive, and allelic models, to estimate the strength of gene-disease association. The significance of the pooled ORs was determined by the *Z* test. The most appropriate genetic model was selected according to the method suggested by Thakkinstian et al. (20), and further secondary analyses were based on the selected genetic model.

Between-study heterogeneity was investigated using the *Q* test and I^2 statistics (21, 22). If the heterogeneity was statistically significant ($p < 0.10$ from Q test or $I^2 > 50\%$), the random effects model was used; otherwise, the fixed effects model was applied (23). Sensitivity analyses were performed to examine the influence of excluding some specific studies (small study or genotype distribution not in HWE) on the overall estimates (24). Potential publication bias was evaluated using funnel plot and Egger's test (25).

For each significant association identified by meta-analysis, we applied the Venice criteria to appraise its epidemiological credibility. Details of the criteria were published elsewhere (26, 27). Briefly, each meta-analyzed association was graded according to the amount of evidence, consistency of replication, and protection from bias. Based on these assessments, the overall epidemiological credibility was graded as strong (grade A), moderate (grade B), or weak (grade C).

Results

Literature search and study characteristics

A total of 5518 articles were retrieved in the initial searches. After exclusion of duplicates and those that did not meet our inclusion criteria, 566 articles comprising 715 studies were finally included for analysis (Fig. S1). Table S3 shows the baseline characteristics of the included studies, and Tables S4 and S5 summarize the genotype and allele distribution of the two polymorphisms in each study. The average NOS and JBI scores of included studies were 6.11 and 10.08, respectively, and 502 studies were regarded as 'high quality' (Tables S4 and S5).

Concerning the C677T polymorphism, there were 408 studies (including 117,661 participants) providing genotype data, which covered investigations on all Chinese provinces except the Tibet autonomous region (Table 1 and Fig. 1), and were mainly conducted in the south-eastern coast of China (Fig. S2). There were 209 studies reporting the ethnicity of its participants, leading to a total inclusion of 23 ethnicities and the Han nationality as the most studied one (Table S6). With regards to the 1298C polymorphism, a total of 142 studies (including 69,439 participants) were identified to have contributed the genotype data on it (Table 2); and these studies covered 27 provinces and were also mostly conducted in the south-eastern coast of China (Fig. S3). Eighty-four studies provided information on ethnicity, where 16 ethnicities were included and the Han was still the most studied ethnic group (Table S7).

The relationships of the *MTHFR* C677T polymorphism with 103 diseases were examined in 617 studies (including 137,013 participants). The number of studies per disease ranged from 1 to 88, and the sample size from 57 to 27,628 (Table 3). One hundred and fifty-four studies (including 72,248 participants) explored the associations of the *MTHFR* A1298C polymorphism with 55 diseases. The number of studies and the sample size per disease varied from 1 to 10 and from 110 to 11,310, respectively (Table 4).

Pooled population frequency by geographical area and ethnicity

The C677T polymorphism

The overall pooled frequencies of the 677TT genotype and the 677T allele were 15.0% and 36.9%, respectively, in Chinese population (Table 1). The distribution of the polymorphism varied among different provinces and presented apparent geographical trends: (i) initially increasing and subsequently decreasing, along with the increase in latitude (e.g. the TT frequency was 6.6% in south region, 14.2% in central region, 21.3% in north region and 15.0% in northernmost region); (ii) initially increasing and subsequently decreasing, along with the increase in longitude (e.g. the TT frequency was 11.1% in west region, 20.5% in central region, and 14.0% in east region) (Table 1, Figs 1 and S4–S33). Also, the 677TT genotype and 677T allele frequencies differed among ethnic groups (Table S6, Fig. S34–S39). After excluding the studies where genotype distribution violated HWE, the above estimations did not change substantially (Tables S8 and S9).

The A1298C polymorphism

The overall pooled frequencies of the 1298C allele and the 1298CC genotype were 22.4% and 4.4%, respectively, in Chinese population (Table 2). The distribution of the polymorphism also differed among various provinces. However, in contrast to the C677T polymorphism, it presented reverse geographical trends: (i) initially decreasing and subsequently increasing, along with the increase in the latitude (e.g. the CC frequency was 7.6% in south region, 3.7% in central region, 3.0% in north region and 4.5% in northernmost region); (ii) initially decreasing and subsequently increasing, along with the increase in the longitude (e.g. the CC frequency was 6.5% in west region, 3.2% in central region and 4.2% in east region) (Table 2, Figs 2 and S40–S59). Regarding the distribution of the polymorphism among ethnic groups, it differed considerably as well (Table S7, Figs S60–S62). These pooled frequencies did not change materially after excluding the studies where genotype distribution departed from HWE (Tables S10 and S11).

Pooled association between the C677T polymorphism and disease

Table 3 and Figs S63–S109 present the pooled ORs and 95% CIs for the relationships of the C677T polymorphism with diseases. Table S12 and Figs S110–S117 display the results for heterogeneity test, publication bias

Table 1. Pooled frequencies of the *MTHFR* 677T allele and the 677TT genotype by geographical area

Area	No. of studies	No. of total participants	*MTHFR* 677TT genotype				*MTHFR* 677T allele			
			Frequency (%)	95% CI	Heterogeneity test I^2 (%)	Heterogeneity test p value	Frequency (%)	95% CI	Heterogeneity test I^2 (%)	Heterogeneity test p value
Total	408	117,661	15.0	14.1, 16.0	95.7	<0.01	36.9	35.7, 38.2	97.6	<0.01
Province/municipality										
Heilongjiang	16	1510	14.6	9.9, 19.3	88.0	<0.01	37.5	30.2, 44.9	94.5	<0.01
Jilin	11	879	16.4	13.4, 19.4	30.0	0.16	39.1	36.5, 41.7	21.1	0.24
Inner Mongolia	10	1269	10.6	7.1, 14.1	72.6	<0.01	32.6	26.9, 38.2	87.6	<0.01
Liaoning	16	4396	19.8	16.8, 22.9	82.0	<0.01	45.1	41.5, 48.7	89.8	<0.01
Xinjiang	23	2422	13.1	9.8, 16.4	86.2	<0.01	36.7	32.5, 41.0	89.9	<0.01
Beijing	31	7284	23.4	21.0, 25.8	81.7	<0.01	46.3	43.7, 48.9	89.2	<0.01
Tianjin	11	3771	21.8	15.0, 28.5	95.4	<0.01	44.6	38.5, 50.7	95.6	<0.01
Hebei	17	4754	24.6	20.6, 28.6	86.8	<0.01	46.3	42.2, 50.5	93.0	<0.01
Shanxi	14	1541	19.3	13.0, 25.6	94.5	<0.01	40.0	30.7, 49.2	96.7	<0.01
Ningxia	8	1293	15.4	8.8, 22.1	92.4	<0.01	40.0	32.8, 47.3	92.9	<0.01
Shandong	22	7944	18.9	14.2, 23.7	94.7	<0.01	43.0	38.2, 47.8	96.5	<0.01
Qinghai	1	40	20.0	7.6, 32.4			43.8	32.9, 54.6		
Gansu	2	155	11.6	3.0, 20.1	66.3	0.09	33.0	13.1, 52.8	93.1	<0.01
Henan	16	6190	22.5	16.0, 29.1	97.1	<0.01	43.4	35.6, 51.2	98.6	<0.01
Shaanxi	8	6045	21.8	16.3, 27.3	94.4	<0.01	43.3	34.1, 52.5	98.8	<0.01
Jiangsu	31	11,111	16.0	14.3, 17.7	79.2	<0.01	39.4	37.4, 41.5	88.1	<0.01
Anhui	10	2467	17.3	14.9, 19.6	47.6	0.05	39.5	36.5, 42.5	73.2	<0.01
Shanghai	22	5462	14.6	12.8, 16.3	63.9	<0.01	38.7	36.7, 40.6	73.5	<0.01
Hubei	9	4396	14.4	11.7, 17.1	65.2	<0.01	36.4	33.4, 39.3	72.5	<0.01
Sichuan	10	4991	10.6	7.4, 13.7	91.3	<0.01	33.0	29.3, 36.7	92.0	<0.01
Chongqing	4	1060	10.2	4.0, 16.4	85.4	<0.01	29.7	22.8, 36.6	83.7	<0.01
Zhejiang	16	5231	13.4	10.9, 16.0	85.1	<0.01	33.5	29.7, 37.4	93.8	<0.01
Jiangxi	3	899	14.0	11.8, 16.3	0.0	0.54	36.7	34.5, 38.9	0.0	0.38
Hunan	7	2371	11.6	7.1, 16.0	86.7	<0.01	34.4	28.7, 40.1	89.6	<0.01
Guizhou	7	659	2.1	1.0, 3.2	0.0	0.48	21.2	16.1, 26.3	82.0	<0.01
Fujian	7	1085	7.5	4.5, 10.6	73.8	<0.01	27.1	20.3, 33.8	92.4	<0.01
Guangxi	13	4687	5.5	3.9, 7.0	82.8	<0.01	23.2	19.1, 27.2	95.4	<0.01
Yunnan	8	757	7.2	2.9, 11.5	86.7	<0.01	31.3	24.3, 38.3	87.8	<0.01
Guangdong	32	5945	8.0	6.3, 9.7	85.7	<0.01	26.8	24.0, 29.5	91.0	<0.01
Taiwan	13	4274	6.9	5.6, 8.3	64.5	<0.01	26.1	24.3, 28.0	69.6	<0.01
Hongkong	3	934	6.6	3.1, 10.1	79.3	0.01	26.0	16.7, 35.3	95.3	<0.01
Hainan	3	11,520	5.7	0.9, 10.4	97.5	<0.01	21.3	12.0, 30.6	98.9	<0.01
North-central-south geographical divide										
Northernmost	76	10,477	15.0	13.3, 16.7	84.8	<0.01	38.6	36.4, 40.9	91.2	<0.01
North	130	39,017	21.3	19.3, 23.3	95.5	<0.01	43.7	41.7, 45.7	96.9	<0.01
Central	112	37,988	14.2	13.2, 15.2	85.1	<0.01	36.7	35.5, 37.9	91.0	<0.01
South	86	29,862	6.6	5.7, 7.4	87.0	<0.01	25.7	24.2, 27.1	92.8	<0.01
East-central-west geographical divide										
East	203	64,062	14.0	12.9, 15.2	95.0	<0.01	35.9	34.2, 37.6	97.6	<0.01
Central	107	29,902	20.5	18.5, 22.6	95.1	<0.01	42.3	40.1, 44.5	96.7	<0.01
West	94	23,379	11.1	9.4, 12.7	95.1	<0.01	32.9	30.4, 35.4	97.0	<0.01
Coastal-inland geographical divide										
Coastal	206	71,114	14.1	12.9, 15.3	96.1	<0.01	35.6	33.8, 37.4	98.1	<0.01
Inland	198	46,229	16.0	14.6, 17.4	94.9	<0.01	38.3	36.6, 39.9	96.2	<0.01

CI, confidence interval; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase.

assessment and p value from association test. The results of sensitivity analyses are displayed in Table S13. The Venice grading of the epidemiological credibility for significant associations is shown in Table S14.

The diseases of circulatory system

The 4 most widely studied diseases were stroke, coronary heart disease, essential hypertension and venous thrombosis. Each of them was investigated in ≥20 studies. Type II diabetes mellitus with cardiovascular complications, myocardial infarction, hypertension with vascular complications and cerebral vascular stenosis were explored in 11, 9, 4 and 3 studies, respectively. Meta-analyses showed that all the aforementioned 8 diseases were significantly associated with the C677T polymorphism. The co-dominant model was appropriate for all these diseases (ORs ranged from 1.87 to 2.76 and from 1.31 to 1.71 in homozygous and heterozygous co-dominant models, respectively) except type

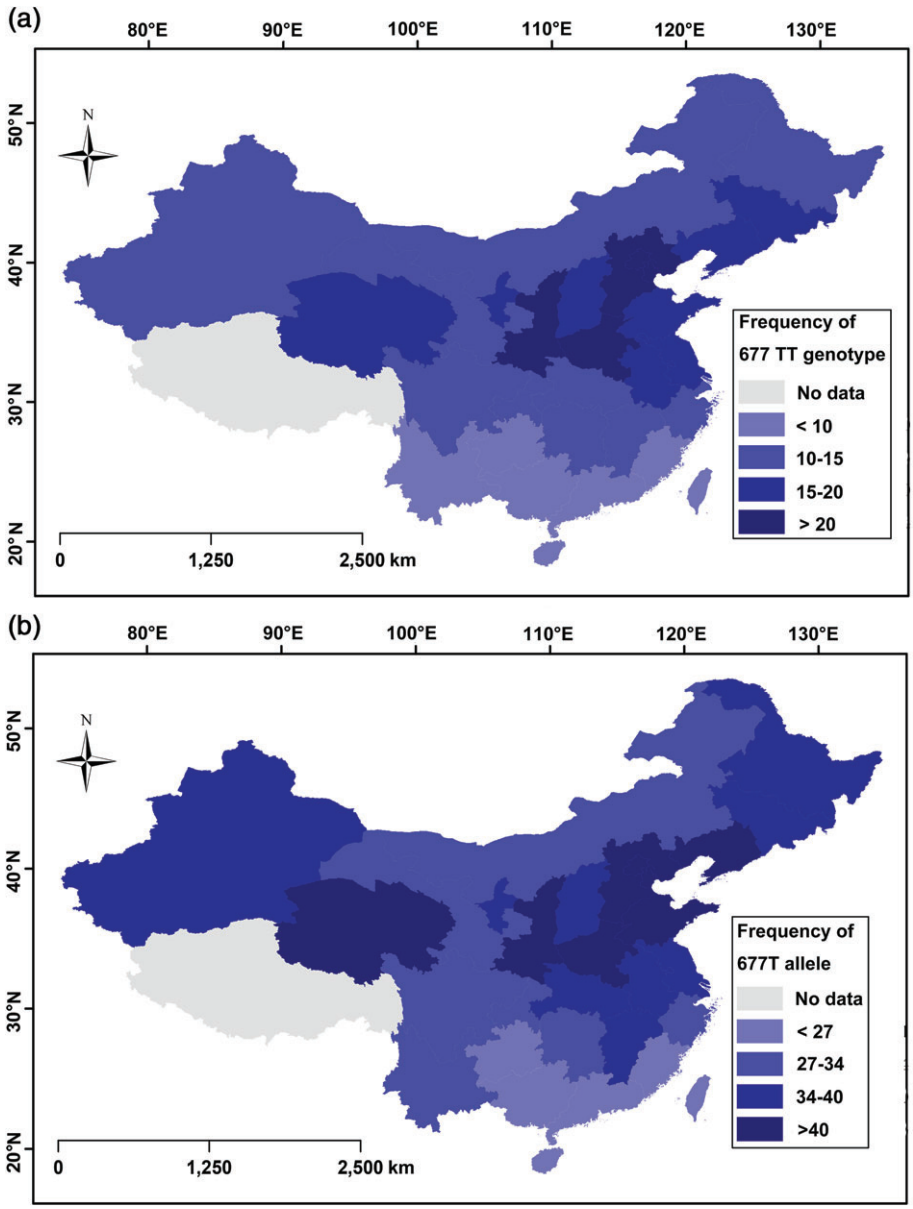

Fig. 1. The pooled frequencies of the methylenetetrahydrofolate reductase (*MTHFR*) 677TT genotype (a) and 677T allele (b) in China.

II diabetes mellitus with cardiovascular complications (OR: 2.07; 95% CI: 1.64–2.61; dominant) and cerebral vascular stenosis (OR: 2.13; 95% CI: 1.30–3.49; recessive). Based on the Venice criteria, the cumulative evidence was moderate for venous thrombosis, essential hypertension, type II diabetes mellitus with cardiovascular disease, and myocardial infarction, and was weak for the remaining four diseases. There were three studies investigating aneurysm and aortic dissection and two studies examining pulmonary thromboembolism, but no significant association was observed.

Congenital malformations, deformations and chromosomal abnormalities

Eighteen studies examined the risk for congenital heart disease affected infants, yielding pooled ORs of 2.38 (95% CI: 1.64–3.45) and 1.38 (95% CI: 1.09–1.74) in homozygous and heterozygous co-dominant models, respectively. Five studies explored the risk for having a congenital heart disease affected child in parents, and the pooled OR was 1.43 (95% CI: 1.09–1.87; dominant). Nonsyndromic cleft lip with or without cleft palate in infants and parents were explored in 12 and 5 studies, respectively. An increased risk was found in infants (OR: 1.92; 95% CI: 1.23–3.00; dominant), but the association in parents was in the opposite direction (OR: 0.60; 95% CI: 0.40–0.91; homozygous; OR: 0.62; 95% CI: 0.46–0.84; heterozygous). Neural tube defects in infants and parents were investigated in 11 studies each. A significantly increased risk was found in both infants (OR: 1.83; 95% CI: 1.08–3.12; recessive) and parents (OR: 3.49; 95% CI: 1.82–6.69; homozygous;

Table 2. Pooled frequencies of the *MTHFR* 1298C allele and the 1298CC genotype by geographical area

Area	No. of studies	No. of total participants	*MTHFR* 1298CC genotype				*MTHFR* 1298C Allele			
			Frequency (%)	95% CI	Heterogeneity test		Frequency (%)	95% CI	Heterogeneity test	
					I^2 (%)	p value			I^2 (%)	p value
Total	142	69,439	4.4	3.9, 4.9	92.4	<0.01	22.4	21.2, 23.5	96.4	<0.01
Province/municipality										
Heilongjiang	3	620	6.2	4.3, 8.1	0.0	0.82	17.2	10.4, 24.0	89.8	<0.01
Jilin	2	79	7.7	0.0, 22.8	82.9	0.02	23.5	0.0, 50.1	94.1	<0.01
Liaoning	5	1157	3.3	1.3, 5.2	75.6	<0.01	19.0	15.7, 22.2	74.3	<0.01
Xinjiang	13	1258	5.1	3.0, 7.2	74.0	<0.01	24.7	20.2, 29.2	86.7	<0.01
Beijing	9	2457	4.9	2.5, 7.3	94.7	<0.01	22.6	15.3, 29.8	97.9	<0.01
Hebei	6	2723	2.6	1.7, 3.5	38.1	0.15	18.7	15.0, 22.5	90.3	<0.01
Shanxi	5	532	2.4	0.1, 4.2	36.2	0.18	17.8	13.7, 21.9	57.3	0.05
Ningxia	2	567	12.2	0.0, 30.2	95.7	<0.01	32.7	2.2, 63.2	98.8	<0.01
Shandong	5	6128	2.0	0.2, 3.7	92.3	<0.01	18.2	12.3, 24.2	98.2	<0.01
Henan	6	4882	3.6	1.9, 5.4	93.7	<0.01	20.2	14.5, 25.9	97.9	<0.01
Shaanxi	4	5692	2.6	1.8, 3.3	62.6	0.05	20.8	11.4, 30.3	99.3	<0.01
Jiangsu	19	9719	2.8	1.8, 3.8	90.8	<0.01	18.2	17.3, 19.2	58.3	<0.01
Anhui	3	528	1.5	0.5, 2.5	0.0	0.55	17.9	15.5, 20.2	3.3	0.36
Shanghai	9	3162	3.1	2.5, 3.8	11.8	0.34	18.7	17.2, 20.2	49.8	0.04
Hubei	2	2949	9.1	0.0, 20.1	79.4	0.03	32.3	6.3, 58.2	96.4	<0.01
Sichuan	4	3028	15.0	7.1, 23.0	97.3	<0.01	35.6	20.7, 50.5	99.0	<0.01
Chongqing	2	936	4.9	3.5, 6.3	0.0	0.99	22.0	20.1, 23.9	0.0	0.53
Zhejiang	5	2449	4.7	1.9, 7.5	92.2	<0.01	21.6	16.2, 27.1	95.2	<0.01
Jiangxi	1	224	1.3	0.3, 3.9			16.3	13.0, 20.0		
Hunan	3	1955	2.7	0.0, 5.8	92.5	<0.01	14.9	6.3, 23.6	96.0	<0.01
Guizhou	4	374	11.5	4.7, 18.3	80.1	<0.01	39.6	31.1, 48.0	82.7	<0.01
Fujian	2	248	49.6	43.4, 55.8	0.0	0.37	69.4	65.3, 73.4	0.0	0.81
Guangxi	4	1675	7.4	5.7, 9.1	46.3	0.13	26.3	24.8, 27.7	0.0	0.40
Yunnan	5	575	10.2	4.0, 16.3	84.7	<0.01	30.6	20.8, 40.4	91.9	<0.01
Guangdong	10	2213	6.1	3.0, 9.3	90.4	<0.01	24.3	18.9, 29.7	93.5	<0.01
Taiwan	4	1554	3.6	2.5, 4.7	17.7	0.30	21.9	19.2, 24.7	65.4	0.03
Hainan	2	11,437	8.2	5.3, 11.1	88.3	<0.01	26.9	22.6, 31.2	93.6	<0.01
North-central-south geographical divide										
Northern most	23	3114	4.5	3.2, 5.8	72.8	<0.01	21.8	19.1, 24.5	85.8	<0.01
North	38	23,065	3.0	2.4, 3.7	89.3	<0.01	20.4	18.2, 22.7	97.5	<0.01
Central	48	24,951	3.7	2.9, 4.4	92.9	<0.01	20.4	19.0, 21.9	93.3	<0.01
South	31	18,149	7.6	6.2, 9.0	89.8	<0.01	28.3	25.9, 30.8	94.6	<0.01
East-central-south geographical divide										
East	67	38,923	4.2	3.4, 4.9	94.1	<0.01	20.8	19.3, 22.3	95.9	<0.01
Central	35	16,250	3.2	2.4, 4.0	89.8	<0.01	19.9	17.8, 22.1	95.9	<0.01
West	38	14,105	6.5	5.3, 7.7	89.6	<0.01	28.1	25.2, 31.1	97.0	<0.01
Coastal-inland geographical divide										
Coastal	72	42,622	4.2	3.5, 4.9	94.0	<0.01	21.1	19.7, 22.6	96.0	<0.01
Inland	68	26,656	4.7	3.9, 5.4	90.3	<0.01	24.1	22.1, 26.0	96.8	<0.01

CI, confidence interval; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase.

OR: 1.76; 95% CI: 1.23–2.51; heterozygous). Five studies explored the risk for Down syndrome in infants and no significant association was found. In contrast, the synthesis of 6 studies evaluating maternal genotype showed a significant increased risk of Down syndrome affected infant (OR: 1.94; 95% CI: 1.12–3.37; homozygous; OR: 1.58; 95% CI: 1.17–2.13; heterozygous). Five studies explored cerebral palsy, but no significant association was observed. Based on the Venice criteria, the cumulative evidence was moderate for congenital heart disease, neural tube defects and Down syndrome, and was weak for the remaining diseases.

Cancers

Acute lymphoblastic leukemia, esophageal, gastric, breast, lung, colorectal and liver cancers were explored in ≥8 studies. An elevated risk was found for esophageal (OR: 1.60; 95% CI: 1.15–2.22; homozygous; OR: 1.29; 95% CI: 1.03–1.61; heterozygous), gastric (OR: 1.27; 95% CI: 1.10–1.46; dominant), breast (OR: 1.68; 95% CI: 1.35–2.09; homozygous; OR: 1.12; 95% CI: 1.02–1.24; heterozygous) and lung cancers (OR: 1.32; 95% CI: 1.02–1.71; dominant) cancers but no association for colorectal and liver cancers and acute lymphoblastic leukemia. Risks for ovarian and intestinal

Table 3. Summarized OR and 95% CI for the association of the *MTHFR* C677T polymorphism with disease

Diseases	No. of studies (cases/controls)	Homozygous		Heterozygous		Dominant		Recessive		Allelic	
		OR	95% CI	OR	95% CI	OR		OR	95% CI	OR	95% CI
The diseases of circulatory system											
Stroke	88 (12,490/15,138)	2.07	1.81, 2.38	1.67	1.50, 1.84	1.79	1.61, 2.00	1.50	1.37, 1.64	1.50	1.40, 1.62
Coronary heart disease	41 (7146/6564)	1.87	1.55, 2.25	1.59	1.38, 1.85	1.69	1.45, 1.96	1.41	1.22, 1.62	1.41	1.28, 1.56
Venous thrombosis	20 (1612/3213)	2.39	1.95, 2.94	1.36	1.18, 1.58	1.59	1.30, 1.93	1.97	1.64, 2.35	1.53	1.39, 1.69
Essential hypertension	21 (5602/4738)	1.92	1.49, 2.48	1.31	1.13, 1.51	1.47	1.26, 1.72	1.68	1.34, 2.10	1.41	1.23, 1.61
Type II diabetes mellitus with vascular complication	11 (928/953)	2.30	1.64, 3.22	1.93	1.55, 2.39	2.07	1.64, 2.61	1.69	1.25, 2.27	1.74	1.42, 2.13
Myocardial infarction	9 (975/1423)	2.58	1.55, 4.28	1.71	1.28, 2.29	1.93	1.37, 2.72	1.82	1.34, 2.47	1.62	1.28, 2.06
Hypertension with vascular complications	4 (537/730)	2.76	2.00, 3.83	1.31	1.01, 1.70	1.67	1.32, 2.12	2.45	1.82, 3.29	1.75	1.48, 2.07
Aneurysm and aortic dissection	3 (692/762)	1.76	0.96, 3.21	1.51	0.93, 2.44	1.52	1.07, 2.15	1.50	0.87, 2.60	1.35	1.16, 1.56
Cerebral vascular stenosis	3 (212/747)	2.79	1.14, 6.85	1.71	0.85, 3.44	1.93	0.88, 4.20	2.13	1.30, 3.49	1.67	1.01, 2.79
Pulmonary thromboembolism	2 (182/235)	1.07	0.85, 1.35	1.21	0.74, 1.97	1.19	0.76, 1.87	1.05	0.69, 1.60	1.10	0.83, 1.45
Angina	1 (90/90)	3.75	0.97, 14.47	2.19	0.97, 4.80	2.50	1.23, 5.07	3.22	0.84, 12.32	2.49	1.36, 4.55
Atherosclerosis	1 (143/91)	3.22	1.42, 7.28	1.27	0.71, 2.27	1.65	0.96, 2.85	2.83	1.33, 6.02	1.75	1.19, 2.57
Atrial fibrillation	1 (76/101)	1.07	0.50, 2.27	0.96	0.47, 1.96	1.01	0.53, 1.91	1.09	0.57, 2.08	1.04	0.68, 1.59
Peripheral arterial occlusive disease	1 (83/100)	4.30	1.75, 10.57	2.42	1.09, 5.39	2.94	1.37, 6.31	2.29	1.17, 4.49	1.98	1.30, 3.01
Brain white matter ischemia	1 (50/50)	6.64	2.40, 18.41	2.42	0.86, 6.79	4.20	1.81, 9.73	4.85	1.90, 12.38	4.06	2.24, 7.36
Secondary hypertension	1 (27/30)	2.10	0.31, 14.15	1.80	0.55, 5.91	1.87	0.63, 5.55	1.75	0.27, 11.36	1.71	0.71, 4.15
Congenital malformations, deformations and chromosomal abnormalities											
Congenital heart disease infants	18 (2380/2831)	2.38	1.64, 3.45	1.38	1.09, 1.74	1.65	1.27, 2.13	1.95	1.49, 2.55	1.56	1.29, 1.90
Congenital heart disease parents	5 (465/597)	2.01	1.29, 3.12	1.33	1.00, 1.77	1.43	1.09, 1.87	1.64	1.14, 2.37	1.37	1.13, 1.65
Nonsyndromic cleft lip with or without cleft palate infants	12 (1791/1739)	1.79	1.08, 2.94	1.98	1.28, 3.08	1.92	1.23, 3.00	1.12	0.86, 1.47	1.37	1.04, 1.79
Nonsyndromic cleft lip with or without cleft palate parents	5 (477/436)	0.60	0.40, 0.91	0.62	0.46, 0.84	0.62	0.46, 0.83	0.86	0.61, 1.21	0.78	0.65, 0.94
Neural tube defects infants	11 (730/1541)	2.06	1.03, 4.11	1.04	0.80, 1.35	1.34	0.90, 2.00	1.83	1.08, 3.12	1.46	1.04, 2.05
Neural tube defects parents	11 (446/574)	3.49	1.82, 6.69	1.76	1.23, 2.51	2.13	1.53, 2.96	2.05	1.33, 3.16	1.71	1.30, 2.24
Down syndrome infants	5 (289/375)	2.43	0.75, 7.90	1.93	0.84, 4.41	2.05	0.91, 4.65	1.53	0.61, 3.85	1.55	0.92, 2.60
Down syndrome mothers	6 (463/523)	1.94	1.12, 3.37	1.58	1.17, 2.13	1.66	1.27, 2.18	1.57	0.99, 2.50	1.54	1.13, 2.10
Cerebral palsy	5 (848/952)	1.26	0.74, 2.16	1.07	0.85, 1.34	1.13	0.78, 1.65	1.18	0.83, 1.69	1.12	0.85, 1.47
Embryos stop growing	1 (76/50)	0.35	0.11, 1.16	0.29	0.12, 0.67	0.30	0.14, 0.65	0.53	0.17, 1.67	0.40	0.22, 0.72
Low birth weight mothers	2 (155/303)	3.23	1.10, 9.47	1.04	0.61, 1.78	1.73	0.61, 4.85	1.26	0.74, 2.15	1.39	0.92, 2.11
Congenital malformation of respiratory system	1 (106/402)	0.47	0.24, 0.93	0.83	0.52, 1.33	0.72	0.46, 1.12	0.52	0.28, 0.98	0.71	0.52, 0.98
Hypospadias	1(100/100)	0.95	0.42, 2.16	1.39	0.62, 3.12	1.16	0.54, 2.48	0.75	0.42, 1.32	0.90	0.60, 1.35
Klippel–Feil syndrome	1(49/402)	0.30	0.10, 0.92	0.86	0.45, 1.61	0.69	0.37, 1.27	0.33	0.12, 0.95	0.64	0.41, 0.99
Cancer											
Esophageal cancer	18 (3642/4527)	1.60	1.15, 2.22	1.29	1.03, 1.61	1.38	1.09, 1.76	1.37	1.10, 1.70	1.29	1.09, 1.52
Gastric cancer	17 (4795/6323)	1.32	1.06, 1.65	1.21	1.07, 1.36	1.27	1.10, 1.46	1.22	1.02, 1.46	1.16	1.03, 1.30
Breast cancer	16 (6164/6803)	1.68	1.35, 2.09	1.12	1.02, 1.24	1.24	1.09, 1.40	1.55	1.28, 1.88	1.27	1.14, 1.42
Acute lymphoblastic leukemia	12 (1275/1693)	1.01	0.62, 1.63	0.81	0.68, 0.95	0.82	0.65, 1.03	1.16	0.75, 1.79	0.94	0.76, 1.16
Lung cancer	12 (2665/3396)	1.49	1.06, 2.10	1.25	0.97, 1.61	1.32	1.02, 1.71	1.33	1.02, 1.75	1.20	1.02, 1.42
Colorectal cancer	9 (2076/3253)	0.83	0.58, 1.17	0.89	0.78, 1.00	0.85	0.76, 0.96	0.87	0.63, 1.19	0.90	0.78, 1.03

Table 3. Continued

Diseases	No. of studies (cases/controls)	Homozygous		Heterozygous		Dominant		Recessive		Allelic	
		OR	95% CI	OR	95% CI	OR		OR	95% CI	OR	95% CI
Liver cancer	8 (4429/5503)	1.13	0.94, 1.36	1.14	0.99, 1.31	1.14	0.99, 1.31	1.04	0.91, 1.19	1.07	0.97, 1.17
Ovarian cancer	3 (520/730)	2.69	1.76, 4.12	1.34	1.04, 1.72	1.52	1.12, 2.07	2.22	1.49, 3.31	1.48	1.20, 1.82
Intestinal cancer	3 (509/835)	0.98	0.47, 2.04	0.97	0.75, 1.24	0.97	0.66, 1.42	1.02	0.55, 1.89	0.99	0.68, 1.45
Meningioma	2 (917/920)	1.29	0.20, 8.50	1.32	0.75, 2.34	1.35	0.57, 3.20	1.11	0.23, 5.43	1.22	0.53, 2.85
Bladder cancer	2 (551/575)	2.00	1.39, 2.89	1.34	1.02, 1.74	1.46	1.13, 1.89	1.66	1.20, 2.30	1.36	1.15, 1.60
Prostate cancer	2 (435/656)	0.48	0.31, 0.75	0.68	0.51, 0.89	0.63	0.48, 0.82	0.57	0.39, 0.84	0.68	0.56, 0.83
Cervical cancer	2 (257/299)	1.05	0.09, 11.92	1.06	0.74, 1.53	1.22	0.53, 2.83	0.95	0.11, 7.96	1.17	0.50, 2.76
Pancreatic cancer	2 (284/674)	3.88	2.58, 5.86	2.47	1.74, 3.52	2.85	2.04, 3.98	2.20	1.58, 3.05	2.01	1.65, 2.45
Nasopharyngeal cancer	2 (1084/1031)	1.09	0.72, 1.64	1.12	0.84, 1.51	1.12	0.88, 1.42	1.07	0.71, 1.59	1.09	0.94, 1.27
Endometrial cancer	1 (1029/1016)	1.00	0.77, 1.30	0.92	0.76, 1.16	0.94	0.78, 1.13	1.05	0.83, 1.33	0.99	0.87, 1.12
Oral cancer	1 (620/620)	0.57	0.38, 0.87	0.65	0.51, 0.83	0.63	0.50, 0.79	0.67	0.45, 1.01	0.69	0.57, 0.82
Cancer[a]	1 (247/100)	2.13	0.92, 4.62	1.49	0.91, 2.46	1.62	1.01, 2.59	1.74	0.83, 3.63	1.49	1.05, 2.11
Laryngeal cancer	1 (207/400)	3.32	2.06, 5.36	1.61	1.07, 2.42	2.03	1.39, 2.97	2.49	1.67, 3.72	1.86	1.46, 2.36
Malignant lymphoma	1 (116/191)	0.87	0.44, 1.72	0.87	0.53, 1.45	0.87	0.54, 1.41	0.94	0.51, 1.74	0.92	0.66, 1.28
Multiple myeloma	1 (30/157)	4.21	1.50, 11.83	1.33	0.52, 3.42	1.98	0.85, 4.59	3.63	1.48, 8.91	2.16	1.24, 3.77
Endocrine, nutritional and metabolic diseases											
Type II diabetes mellitus	30 (3843/3501)	1.26	1.05, 1.51	1.23	1.06, 1.42	1.25	1.08, 1.45	1.11	0.97, 1.28	1.17	1.05, 1.30
Hyperuricemia	5 (521/320)	4.19	2.74, 6.42	2.80	2.01, 3.92	3.45	2.13, 5.57	2.49	1.70, 3.65	2.66	1.69, 4.19
Metabolic syndrome	2 (373/175)	3.05	0.92, 10.09	2.38	1.19, 4.74	2.54	1.14, 5.68	1.98	0.87, 4.52	2.00	1.08, 3.71
Hyperlipidemia	3 (913/1137)	2.10	1.09, 4.03	1.64	0.97, 2.76	1.79	0.99, 3.24	1.47	1.06, 2.05	1.50	1.04, 2.15
Hyperhomocysteinemia	2 (141/116)	2.67	1.34, 5.31	1.83	1.01, 3.32	2.10	1.21, 3.65	1.87	1.04, 3.35	1.74	1.22, 2.48
Overweight/obesity	1 (751/978)	1.13	0.77, 1.65	1.03	0.84, 1.25	1.04	0.86, 1.26	1.11	0.77, 1.61	1.04	0.90, 1.21
Graves' disease	1 (199/235)	0.62	0.36, 1.08	0.47	0.29, 0.79	0.53	0.33, 0.85	1.06	0.70, 1.60	0.83	0.64, 1.09
Type I diabetes mellitus	1 (114/159)	1.65	0.70, 3.87	1.24	0.67, 2.30	1.28	0.72, 2.29	1.22	0.63, 2.36	1.20	0.81, 1.76
Hypothyroidism	1 (32/50)	1.75	0.52, 5.90	1.05	0.38, 2.94	1.27	0.52, 3.10	1.72	0.54, 5.48	1.37	0.70, 2.68
Hyperthyroidism	1 (48/50)	0.92	0.27, 3.11	1.15	0.48, 2.78	1.08	0.49, 2.39	0.88	0.27, 2.83	1.01	0.54, 1.87
Pregnancy, stillbirth and the puerperium											
Unexplained recurrent pregnancy loss	21 (1798/1893)	3.29	2.43, 4.44	1.80	1.38, 2.35	2.08	1.68, 2.58	2.29	1.77, 2.98	1.79	1.57, 2.03
Hypertension in pregnancy	16 (1118/1076)	2.23	1.69, 2.92	1.80	1.23, 2.65	1.91	1.38, 2.64	1.79	1.41, 2.26	1.64	1.38, 1.95
Premature birth	2 (321/391)	2.76	1.84, 4.15	1.48	1.04, 2.10	1.85	1.34, 2.56	2.22	1.55, 3.16	1.77	1.43, 2.19
Premature rupture of membranes	1 (206/287)	1.75	0.97, 3.17	1.80	1.00, 3.24	1.78	1.02, 3.10	1.11	0.77, 1.59	1.21	0.93, 1.58
Adverse pregnancy outcomes	1 (84/87)	5.72	2.38, 13.76	2.45	1.11, 4.54	3.12	1.65, 5.90	3.85	1.73, 8.57	2.79	1.79, 4.37
Fetal growth restriction	1 (62/65)	2.65	0.79, 8.87	3.45	1.51, 7.90	3.21	1.53, 6.77	1.78	0.55, 5.76	2.43	1.34, 4.38
Adverse obstetric history	1 (53/57)	6.60	1.23, 35.44	2.00	0.64, 6.26	2.30	0.74, 7.12	3.68	0.94, 14.43	1.54	0.91, 2.63
Mental and behavioral disease											
Autism	2 (386/386)	3.15	1.42, 6.97	1.55	0.67, 3.58	1.91	0.75, 4.86	2.75	1.58, 4.77	1.96	0.88, 4.37
Dementia	23 (2217/2455)	1.44	1.21, 1.72	1.34	1.16, 1.53	1.39	1.22, 1.57	1.20	1.02, 1.41	1.24	1.11, 1.38
Depression	8 (1890/1843)	1.62	1.09, 2.43	1.25	0.78, 2.02	1.39	0.89, 2.18	1.43	1.05, 1.97	1.30	1.03, 1.65
Schizophrenia	7 (1768/1758)	1.43	0.82, 2.48	1.15	0.81, 1.62	1.25	0.84, 1.84	1.31	0.92, 1.87	1.43	0.82, 2.48

Table 3. continued

Diseases	No. of studies (cases/controls)	Homozygous		Heterozygous		Dominant		Recessive		Allelic	
		OR	95% CI	OR	95% CI	OR		OR	95% CI	OR	95% CI
Schizophrenia mothers	1 (143/235)	0.75	0.40, 1.40	0.79	0.50, 1.26	0.78	0.50, 1.21	0.86	0.49, 1.52	0.86	0.64, 1.16
Vascular cognitive impairment	1 (143/140)	4.73	2.13, 10.52	1.01	0.60, 1.70	1.45	0.89, 2.37	4.71	2.24, 9.89	1.79	1.28, 2.52
Diseases of the musculoskeletal system and connective tissue											
Rheumatoid arthritis	4 (332/438)	1.61	1.03, 2.53	1.81	1.30, 2.51	1.89	1.17, 3.05	1.21	0.81, 1.83	1.56	1.00, 2.45
Osteoporosis	3 (1338/1343)	1.43	1.13, 1.81	1.23	1.04, 1.46	1.28	1.09, 1.50	1.26	1.02, 1.57	1.23	1.06, 1.44
Ankylosing spondylitis	3 (374/282)	2.87	1.65, 5.01	1.26	0.89, 1.80	1.59	1.15, 2.18	2.70	1.57, 4.65	1.70	1.32, 2.19
Systemic lupus erythematosus	3 (146/160)	8.61	4.56, 16.27	2.17	1.11, 4.24	4.70	2.73, 8.08	5.93	3.42, 10.27	4.49	2.25, 8.93
Osteonecrosis of the femoral head	1 (243/96)	1.36	0.68, 2.74	1.58	0.79, 3.15	1.47	0.77, 2.81	0.97	0.60, 1.57	1.10	0.78, 1.55
Vertebral fracture	1 (282/197)	1.21	0.54, 2.71	0.86	0.58, 1.27	0.90	0.62, 1.31	1.28	0.58, 2.83	0.97	0.71, 1.32
Gouty arthritis	1 (55/52)	3.21	1.19, 8.64	1.44	0.59, 3.56	2.06	0.94, 4.50	2.73	1.11, 6.75	2.12	1.22, 3.68
Undifferentiated spondyloarthropathy	1 (30/62)	1.76	0.60, 5.13	0.55	0.11, 2.83	1.22	0.48, 3.12	1.89	0.66, 5.43	1.47	0.73, 2.94
Diseases of the genitourinary system											
Male infertility	9 (1816/1612)	2.20	1.79, 2.69	1.38	1.17, 1.62	1.59	1.37, 1.84	1.87	1.57, 2.23	1.52	1.37, 1.68
Diabetic nephropathy	9 (729/645)	3.82	2.74, 5.33	2.02	1.58, 2.58	2.40	1.91, 3.01	2.62	1.94, 3.54	2.11	1.80, 2.49
Renal failure	5 (347/275)	2.34	1.33, 4.12	1.22	0.65, 2.31	1.55	0.81, 2.97	2.38	1.42, 4.00	1.68	1.06, 2.66
Focal segmental glomerulosclerosis	1 (15/238)	1.69	0.36, 7.97	1.27	0.37, 4.37	1.37	0.42, 4.43	1.45	0.39, 5.40	1.27	0.61, 2.67
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism											
Myelodysplastic syndrome	1 (42/126)	1.14	0.34, 3.76	1.41	0.52, 3.83	1.34	0.51, 3.55	0.86	0.36, 2.08	1.03	0.63, 1.69
Diseases of the digestive system											
Ulcerative colitis	4 (598/1271)	1.83	0.82, 4.08	1.29	0.86, 1.93	1.50	0.89, 2.54	1.39	0.81, 2.40	1.38	0.92, 2.09
Cirrhosis	3 (855/721)	2.72	0.70, 10.57	2.45	0.75, 7.93	2.56	0.74, 8.82	1.52	0.77, 2.99	1.80	0.83, 3.90
Chronic hepatitis B	1 (442/549)	0.75	0.53, 1.07	0.93	0.67, 1.28	0.86	0.63, 1.16	0.79	0.60, 1.04	0.86	0.72, 1.03
Non-alcoholic fatty liver disease	1 (212/175)	1.65	0.93, 2.94	1.80	1.15, 2.80	1.75	1.16, 2.64	1.22	0.72, 2.08	1.41	1.05, 1.89
Diseases of the ear and mastoid process											
Sudden deafness	1 (80/100)	1.53	0.62, 3.78	2.15	0.91, 5.11	1.86	0.82, 4.22	0.87	0.47, 1.61	1.12	0.73, 1.70
Diseases of the eye and adnexa											
Diabetic retinopathy	6 (551/556)	4.30	2.67, 6.94	2.53	1.87, 3.42	2.94	2.23, 3.89	2.46	1.81, 3.33	2.20	1.84, 2.63
Primary angle closure	2 (291/426)	1.72	0.38, 7.82	1.41	0.43, 4.62	1.53	0.41, 5.71	1.44	0.57, 3.61	1.44	0.54, 3.81
Central retinal vein occlusion	2 (132/132)	1.14	0.54, 2.40	0.80	0.44, 1.46	0.88	0.50, 1.56	1.33	0.73, 2.46	1.05	0.74, 1.47
Primary open-angle glaucoma	1 (397/201)	1.48	0.56, 3.86	1.26	0.87, 1.83	1.28	0.90, 1.83	1.37	0.53, 3.54	1.24	0.91, 1.68
Diseases of the nervous system											
Parkinson's disease	4 (1203/1186)	0.86	0.66, 1.12	0.99	0.66, 1.50	1.00	0.67, 1.48	0.97	0.76, 1.25	1.01	0.78, 1.29
Migraine	2 (333/240)	1.85	1.15, 2.98	1.32	0.91, 1.93	1.50	1.07, 2.10	1.69	1.07, 2.65	1.48	1.15, 1.91
Diabetic peripheral neuropathy	1 (60/50)	12.64	3.15, 50.79	3.72	1.55, 8.94	4.99	2.17, 11.48	6.19	1.70, 22.62	3.62	2.02, 6.48
Diseases of the respiratory system											
Bronchial asthma	2 (203/221)	2.91	1.73, 4.90	1.29	0.82, 2.03	1.76	1.16, 2.66	2.51	1.60, 3.93	1.82	1.38, 2.39
Diseases of the skin and subcutaneous tissue											
Psoriasis	3 (347/331)	0.77	0.48, 1.24	0.57	0.40, 0.81	0.61	0.44, 0.85	1.07	0.72, 1.59	0.81	0.65, 1.02
Skin lesion in endemic arsenic poisoning	1 (50/35)	1.29	0.42, 3.99	1.54	0.51, 4.61	1.42	0.53, 3.83	0.99	0.40, 2.46	1.14	0.62, 2.10
Vitiligo	1 (1000/1000)	0.58	0.43, 0.76	0.85	0.70, 1.03	0.78	0.65, 0.93	0.63	0.48, 0.82	0.79	0.69, 0.89

CI, confidence interval; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase; OR, odds ratio; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase; OR, odds ratio.

[a]The cases included esophageal, gastric, colorectal, lung and breast cancers.

Table 4. Summarized OR and 95% CI for the association of the *MTHFR* A1298C polymorphism with disease

Diseases	No. of studies (cases/controls)	Homozygous		Heterozygous		Dominant		Recessive		Allelic	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
The diseases of circulatory system											
Stroke	9 (1212/1213)	1.36	0.57, 3.22	1.21	0.79, 1.87	1.19	0.80, 1.77	1.09	0.74, 1.61	1.20	0.86, 1.66
Essential hypertension	3 (1708/903)	0.75	0.46, 1.23	1.00	0.69, 1.46	0.98	0.70, 1.39	0.75	0.46, 1.22	1.03	0.88, 1.21
Coronary heart disease	2 (377/235)	0.23	0.07, 0.74	0.59	0.38, 0.90	0.54	0.36, 0.81	0.25	0.08, 0.78	0.53	0.37, 0.76
Venous thrombosis	2 (163/201)	3.04	0.58, 15.84	0.83	0.51, 1.34	0.91	0.57, 1.45	3.20	0.62, 16.60	1.01	0.67, 1.53
Type II diabetes mellitus with vascular complications	1 (66/84)	0.97	0.21, 4.53	1.11	0.47, 2.60	1.08	0.50, 2.34	0.95	0.21, 4.41	1.05	0.54, 2.05
Cerebral vascular stenosis	1 (80/55)					0.77	0.35, 1.71				
Congenital malformations, deformations and chromosomal abnormalities											
Congenital heart disease infants	3 (832/921)	0.95	0.56, 1.64	1.02	0.83, 1.25	1.02	0.83, 1.24	0.95	0.56, 1.63	1.01	0.85, 1.19
Birth defects[a]	1 (89/80)	1.19	0.07, 19.49	2.16	1.13, 4.12	2.12	1.12, 4.01	0.90	0.06, 14.59	1.75	1.01, 3.08
Nonsyndromic cleft lip with or without cleft palate infants	7 (1226/1387)	1.05	0.67, 1.65	1.30	0.83, 2.02	1.19	0.86, 1.66	1.02	0.65, 1.58	1.13	0.86, 1.49
Nonsyndromic cleft lip with or without cleft palate mothers	1 (106/106)	6.53	0.31, 138.31	2.77	1.44, 5.35	2.93	1.52, 5.62	5.10	0.24, 107.4	2.67	1.46, 4.88
Neural tube defects infants	2 (109/200)	1.98	0.39, 10.18	0.96	0.54, 1.72	1.02	0.58, 1.78	1.91	0.38, 9.72	1.05	0.71, 1.56
Neural tube defects parents	4 (143/223)	5.03	1.40, 18.12	0.97	0.40, 2.35	1.05	0.39, 2.84	3.50	1.05, 11.66	1.21	0.66, 2.22
Down syndrome mothers	1 (100/100)					1.97	1.04, 3.75				
Cerebral palsy	5 (848/952)	0.92	0.53, 1.59	0.90	0.72, 1.11	0.91	0.74, 1.12	0.98	0.68, 1.42	0.94	0.80, 1.11
Cancer											
Acute lymphoblastic leukemia	10 (1107/1454)	0.94	0.62, 1.43	0.97	0.81, 1.15	1.00	0.79, 1.27	0.96	0.63, 1.45	0.97	0.84, 1.12
Gastric cancer	9 (2736/3492)	0.83	0.66, 1.06	1.07	0.96, 1.20	1.02	0.85, 1.22	0.85	0.68, 1.06	0.99	0.85, 1.17
Colorectal cancer	8 (1523/2499)	0.88	0.61, 1.27	0.94	0.82, 1.09	0.93	0.81, 1.07	0.89	0.62, 1.29	0.94	0.84, 1.06
Breast cancer	10 (5446/5864)	1.21	1.01, 1.45	0.98	0.90, 1.06	1.00	0.93, 1.08	1.20	1.01, 1.43	1.03	0.96, 1.09
Esophageal cancer	6 (1054/1392)	1.41	0.77, 2.58	1.11	0.78, 1.58	1.13	0.86, 1.50	1.42	0.77, 2.59	1.14	0.87, 1.49
Lung cancer	6 (1779/2112)	1.36	0.96, 1.92	1.03	0.90, 1.19	1.06	0.92, 1.21	1.28	0.92, 1.77	1.07	0.96, 1.20
Liver cancer	4 (1494/2501)	0.52	0.34, 0.79	1.08	0.93, 1.48	1.01	0.88, 1.16	0.51	0.33, 0.77	0.95	0.84, 1.07
Intestinal cancer	2 (368/670)	0.69	0.28, 1.71	0.79	0.59, 1.05)	0.78	0.59, 1.03	0.71	0.29, 1.74	0.80	0.63, 1.03
Meningioma	2 (917/920)	1.06	0.77, 1.46	0.99	0.81, 1.21	1.00	0.83, 1.20	1.07	0.78, 1.45	1.01	0.88, 1.17
Bladder cancer	2 (551/575)	0.85	0.35, 2.07	0.98	0.76, 1.27	0.97	0.75, 1.25	0.85	0.35, 2.07	0.97	0.77, 1.21
Prostate cancer	2 (435/656)	1.22	0.60, 2.49	0.98	0.75, 1.27	0.99	0.77, 1.29	1.22	0.61, 2.47	1.02	0.81, 1.27
Nasopharyngeal cancer	2 (1061/1021)	1.19	0.75, 1.88	1.21	0.74, 1.99	1.21	0.74, 1.98	1.10	0.76, 1.58	1.15	1.00, 1.32
Endometrial cancer	1 (1036/1019)	1.10	0.68, 1.77	1.08	0.89, 1.31	1.08	0.90, 1.30	1.07	0.67, 1.72	1.07	0.91, 1.26
Cervical cancer	1 (157/199)	0.11	0.02, 0.89	1.84	1.18, 2.88	1.51	0.98, 2.32	0.09	0.01, 0.71	1.12	0.78, 1.61
Pancreatic cancer	1 (163/337)	0.49	0.10, 2.34	0.84	0.54, 1.31	0.81	0.53, 1.25	0.51	0.11, 2.43	0.81	0.55, 1.19
Oral cancer	1 (620/620)	0.70	0.39, 1.25	0.94	0.74, 1.20	0.91	0.72, 1.14	0.71	0.40, 1.27	0.89	0.73, 1.09
Laryngeal cancer	1 (207/400)	1.84	0.58, 5.79	0.78	0.53, 1.15	0.83	0.57, 1.22	1.96	0.62, 6.16	0.92	0.66, 1.28
Endocrine, nutritional and metabolic diseases											
Type II diabetes mellitus	4 (1546/1247)	1.01	0.68, 1.51	1.06	0.84, 1.34	1.08	0.92, 1.27	1.02	0.67, 1.56	1.06	0.93, 1.22
Hyperuricemia	1 (116/110)	0.91	0.22, 3.75	0.84	0.46, 1.55	0.85	0.48, 1.52	0.95	0.23, 3.88	0.88	0.53, 1.46
Graves' disease	1 (186/235)	3.84	0.76, 19.33	0.96	0.60, 1.51	1.06	0.68, 1.65	3.88	0.78, 19.47	1.16	0.78, 1.72

Table 4. Continued

Diseases	No. of studies (cases/controls)	Homozygous		Heterozygous		Dominant		Recessive		Allelic	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Pregnancy, stillbirth and the puerperium											
Unexplained recurrent pregnancy loss	6 (470/507)	1.12	0.65, 1.93	1.42	0.93, 2.16	1.51	1.10, 2.06	1.84	0.83, 4.08	1.46	1.12, 1.92
Hypertension in pregnancy	4 (250/350)	1.19	0.64, 2.22	1.16	0.82, 1.64	1.16	0.83, 1.61	1.10	0.60, 2.01	1.12	0.86, 1.45
Premature birth	2 (321/391)	0.14	0.02, 1.12	0.72	0.52, 0.99	0.68	0.50, 0.94	0.16	0.02, 1.24	0.70	0.53, 0.92
Adverse pregnancy outcomes	1 (84/87)	7.33	1.55, 34.74	1.49	0.77, 2.90	0.92	0.49, 1.72	6.40	1.38, 29.84	2.12	1.26, 3.56
Adverse obstetric history	1 (53/57)	1.08	0.27, 4.36	2.07	0.89, 4.83	1.79	0.82, 3.90	0.85	0.22, 3.35	1.42	0.76, 2.66
Mental and behavioral disease											
Schizophrenia	4 (813/866)	1.42	0.95, 2.14	1.09	0.89, 1.34	1.06	0.76, 1.49	1.41	0.94, 2.11	1.09	0.82, 1.46
Depression	1 (152/152)	0.94	0.13, 6.80	0.75	0.43, 1.32	0.76	0.44, 1.32	1.00	0.14, 7.19	0.80	0.49, 1.31
Schizophrenia mothers	1 (143/235)	3.89	0.95, 15.91	1.56	0.99, 2.46	1.67	1.07, 2.60	3.39	0.83, 13.76	1.63	1.11, 2.39
Autism	1 (200/200)	3.28	1.68, 6.41	1.04	0.54, 2.02	1.90	1.17, 3.07	3.27	1.68, 6.36	2.28	1.55, 2.34
Diseases of the musculoskeletal system and connective tissue											
Rheumatoid arthritis	3 (280/379)	0.72	0.30, 1.76	0.79	0.57, 1.10	0.79	0.57, 1.09	0.85	0.36, 2.04	0.83	0.64, 1.09
Osteoporosis	1 (92/169)	1.25	0.38, 4.11	0.80	0.45, 1.45	0.86	0.50, 1.50	1.33	0.41, 4.32	0.94	0.59, 1.50
Ankylosing spondylitis	1 (114/100)	1.00	0.29, 3.49	0.90	0.52, 1.56	0.91	0.53, 1.56	1.06	0.31, 3.57	0.95	0.63, 1.44
Systemic lupus erythematosus	1 (52/78)	2.37	0.38, 14.84	1.09	0.46, 2.59	1.23	0.55, 1.76	2.33	0.38, 14.43	1.33	0.66, 2.68
Osteonecrosis of the femoral head	1 (243/96)	1.44	0.16, 13.08	0.65	0.37, 1.13	0.68	0.40, 1.17	1.59	0.18, 14.41	0.75	0.46, 1.22
Diseases of the genitourinary system											
Male infertility	3 (540/387)	1.21	0.58, 2.55	1.31	0.98, 1.76	1.30	0.98, 1.73	1.09	0.53, 2.28	1.22	0.96, 1.56
Diabetic nephropathy	1 (64/84)	1.29	0.31, 5.43	0.83	0.33, 2.07	0.94	0.42, 2.08	1.33	0.32, 5.55	1.02	0.52, 2.01
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism											
Myelodysplastic syndrome	1 (42/126)	3.76	0.81, 17.37	1.64	0.32, 8.40	2.91	0.64, 13.22	2.56	1.18, 5.54	2.36	1.23, 4.52
Diseases of the digestive system											
Ulcerative colitis	2 (470/1149)	1.25	0.26, 5.98	1.11	0.88, 1.40	1.13	0.71, 1.77	1.23	0.28, 5.37	1.13	0.66, 1.97
Diseases of the eye and adnexa											
Diabetic retinopathy	1 (44/84)	0.97	0.17, 5.57	1.11	0.42, 2.90	1.08	0.45, 2.59	0.95	0.17, 5.42	1.05	0.49, 2.23
Diseases of the skin and subcutaneous tissue											
Psoriasis	1 (123/129)	2.00	0.18, 22.43	0.79	0.44, 1.42	0.82	0.46, 1.46	2.12	0.19, 23.64	0.89	0.53, 1.49
Vitiligo	1 (1000/1000)	1.46	0.80, 2.65	1.07	0.87, 1.30	1.09	0.90, 1.32	1.43	0.79, 2.59	1.10	0.93, 1.31

CI, confidence interval; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase; OR, odds ratio.

[a]The cases included anenaphalus, hydrocephalus, opened spina bifida, meningocele, cleft lip and palate.

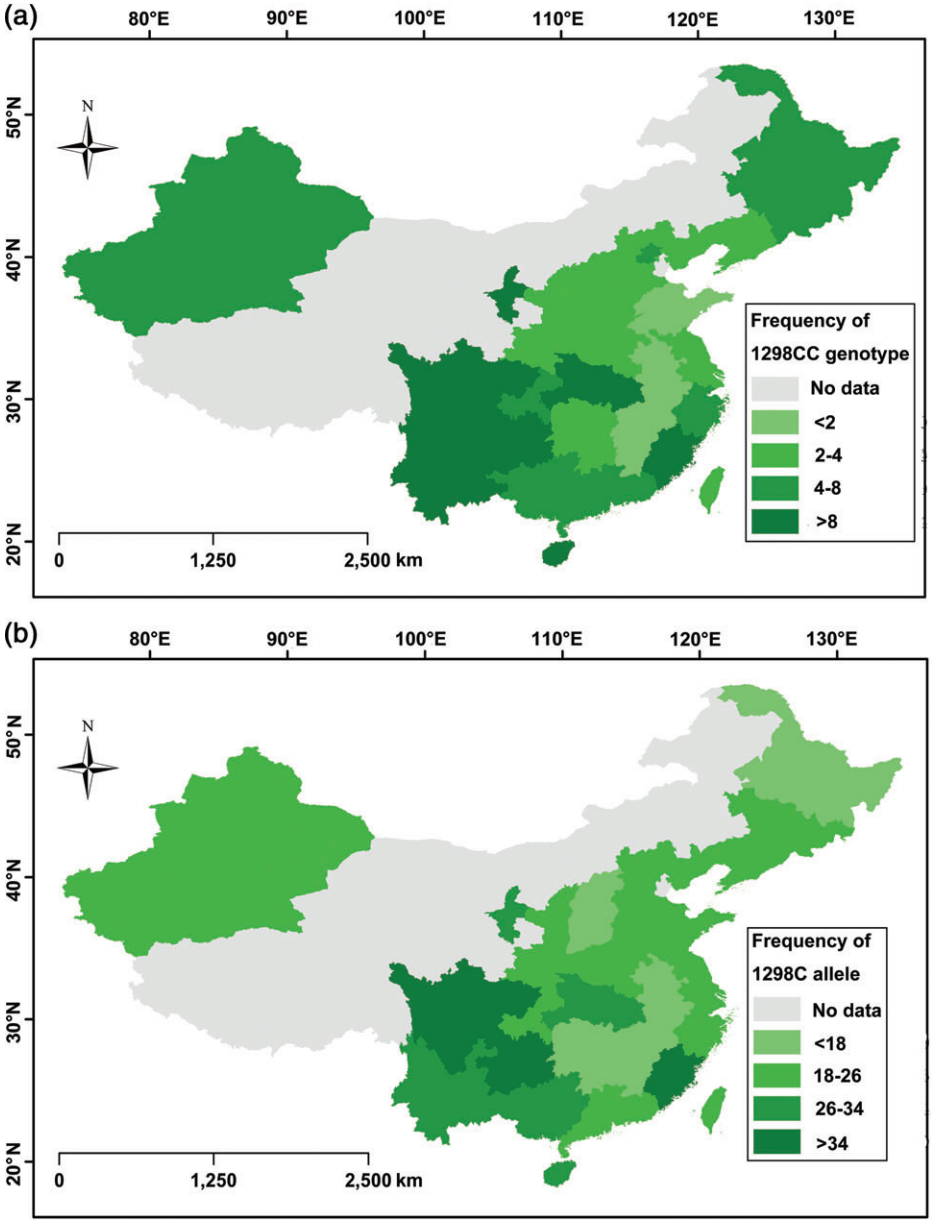

Fig. 2. The pooled frequencies of the methylenetetrahydrofolate reductase (*MTHFR*) 1298CC genotype (a) and 1298C allele (b) in China.

cancers risks were assessed in 3 studies each and a significant association was found for ovarian cancer (OR: 2.69; 95% CI: 1.76–4.12; homozygous; OR: 1.34; 95% CI: 1.04–1.72; heterozygous). Bladder, prostate, cervical, pancreatic, nasopharyngeal cancers and meningioma were investigated in 2 studies each. An increased risk was found for bladder (OR: 2.00; 95% CI: 1.39–2.89; homozygous; OR: 1.34; 95% CI: 1.02–1.74; heterozygous) and pancreatic cancers (OR: 3.88; 95% CI: 2.58–5.86; homozygous; OR: 2.47; 95% CI: 1.74–3.52; heterozygous) but a reduced risk for prostate cancer (OR: 0.48; 95% CI: 0.31–0.75; homozygous; OR: 0.68; 95% CI: 0.51–0.89; heterozygous). Among the significant associations mentioned above, the cumulative evidence was strong only for breast and ovarian cancers. Another 2 associations (pancreatic and bladder cancers) were found to have modest epidemiological credibility, whereas the remaining 3 showed weak credibility.

Endocrine, nutritional and metabolic diseases

Type II diabetes mellitus, hyperuricemia, hyperlipidemia and hyperhomocysteinemia were investigated in 30, 5, 3 and 2 studies, respectively. The dominant model was appropriate for all these diseases, and the corresponding pooled ORs were 1.25 (95% CI: 1.08–1.45), 3.45 (95% CI: 2.13–5.57), 1.79 (95% CI: 0.99–3.24) and 2.10 (95% CI: 1.21–3.65), respectively. The cumulative evidence was modest for type II diabetes mellitus and was weak for the other 3 associations. Two studies investigated metabolic syndrome but no association was found.

Pregnancy, stillbirth and the puerperium

Twenty-one studies investigated unexplained recurrent pregnancy loss, yielding pooled ORs of 3.29 (95% CI; 2.43–4.44) and 1.80 (95% CI: 1.38–2.35) in homozygous and heterozygous co-dominant models, respectively. Hypertension in pregnancy was investigated in 16 studies, and the pooled OR was 1.91 (95% CI: 1.38–2.64; dominant). Two studies evaluated premature birth and the pooled ORs were 2.76 (95% CI: 1.84–4.15) and 1.48 (95% CI: 1.04–2.10) in homozygous and heterozygous co-dominant models, respectively. The cumulative evidence was modest for premature birth but was weak for the remaining 2 associations.

Mental and behavioral diseases

Dementia was investigated in 23 studies, yielding a pooled OR of 1.39 (95% CI: 1.22–1.57; dominant). Eight studies focused on depression and 2 on autism, and the corresponding pooled ORs were 1.43 (95% CI: 1.05–1.97) and 2.75 (95% CI: 1.58–4.77) in the recessive model, respectively. Cumulative evidence was moderate for autism and dementia but was weak for depression. Schizophrenia was investigated in 7 studies and no significant association was found.

Diseases of the musculoskeletal system and connective tissue

Rheumatoid arthritis, osteoporosis, systemic lupus erythematosus, and ankylosing spondylitis were investigated in 4, 3, 3 and 3 studies, respectively. An increased risk was found for rheumatoid arthritis (OR: 1.89; 95% CI: 1.17–3.05; dominant), osteoporosis (OR: 1.43; 95% CI: 1.13–1.81; homozygous; OR: 1.23; 95% CI: 1.04–1.46; heterozygous), systemic lupus erythematosus (OR: 8.61; 95% CI: 4.56–16.27; homozygous; OR: 2.17; 95% CI: 1.11–4.24; heterozygous) and ankylosing spondylitis (OR: 1.59; 95% CI: 1.15–2.18; dominant). All of the above significant associations were assessed as having weak cumulative evidence.

Diseases of the genitourinary system

Nine studies investigated infertility, yielding pooled ORs of 2.20 (95% CI: 1.79–2.69) and 1.38 (95% CI: 1.17–1.62) in homozygous and heterozygous co-dominant models, respectively. Nine studies evaluated diabetic nephropathy, yielding pooled ORs of 3.82 (95% CI: 2.74–5.33) and 2.02 (95% CI: 1.58–2.58) in homozygous and heterozygous co-dominant models, respectively. Five studies investigated renal failure, and an increased risk was observed (OR: 2.38; 95% CI: 1.42–4.00; recessive). The cumulative evidence of these associations was moderate for male infertility and diabetic nephropathy but was weak for renal failure.

Diseases of the eye and adnexa

Six studies investigated diabetic retinopathy, and the pooled ORs were 4.30 (95% CI: 2.67–6.94) and 2.53 (95% CI: 1.87–3.42) in homozygous and heterozygous co-dominant models, respectively. The cumulative evidence was moderate. Primary angle closure was evaluated in two studies, and no significant association was observed.

Others

Studies also evaluated the relationships of the C677T polymorphism with diseases of the digestive system, the nervous system, the skin and subcutaneous tissue, the respiratory system, the ear and mastoid process, the blood and blood-forming organs and certain disorders involving the immune mechanism. An elevated risk was found for non-alcohol fatty liver disease, migraine, diabetic peripheral neuropathy and bronchial asthma but a reduced risk for vitiligo. However, these associations were identified based on limited numbers of studies (≤2) and participants.

Association of the *MTHFR* A1298C polymorphism with disease

The potential relationships of the *MTHFR* A1298C polymorphism with 55 diseases were investigated (Tables 4, S15 and S16, Figs S118–S138). An increased risk was observed for breast cancer (OR: 1.20; 95% CI: 1.01–1.43; recessive) and adverse pregnancy outcome (OR: 6.40; 95% CI: 1.38–29.84; recessive) but a reduced risk for coronary heart disease (OR: 0.23; 95% CI: 0.07–0.74; homozygous; OR: 0.59; 95% CI: 0.38–0.90; heterozygous). Additionally, we found that mothers carrying the 1298 mutant genotype had a 2.93-fold (95% CI: 1.52–5.62; dominant) increased risk of having a non-syndromic cleft lip with or without cleft palate affected child. Also, parents carrying the 1298 CC genotype had a 3.50-fold (95% CI: 1.05–11.66; recessive) increased risk of having a neural tube defects affected child. However, results on most of these associations were based on 1 or 2 studies, and were considered to have weak epidemiological credibility (Tables S17). For the remaining 50 diseases, no significant association was observed.

Discussion

In the present meta-analysis, we have conducted the most comprehensive evaluation of currently available data on geographical and ethnic distribution of the *MTHFR* C677T and A1298C polymorphisms and their associations with many diseases in the Chinese population.

Prior evidence suggested that the distribution of the *MTHFR* C677T polymorphism differs worldwide, with Europeans and North Americans usually having higher 677T frequency than Africans and East Asians (13). We observed that the overall 677T allele frequency was 36.9% in China, which exceeds that of many other countries (13). Further stratified analyses showed that the 677T allele frequency varied markedly among different provinces and ethnicities. Meanwhile, interestingly, along with the increase in the latitude or longitude, the 677T allele frequency across China initially increased gradually and then decreased afterwards. These geographical gradients were also previously reported in

other regions like Pakistani, India, Europe, North America and Eastern Asia (6–8, 10, 28). Several hypotheses have been proposed to explain the distributional variations (7, 29), and the general agreement now is that the distribution pattern of this polymorphism may be caused by both genetic background and natural selection of environmental factors (especially folate intake and ultraviolet radiation) (10).

The *MTHFR* A1298C polymorphism is not as extensively studied as the C677T polymorphism. Globally, the 1298C allele frequency is highest among Asians, followed by Europeans, Africans and Americans (14). Our meta-analysis showed that the overall pooled 1298C allele frequency was 22.4% in China. The prevalence of the 1298C allele also varied among different areas and ethnic groups. More interestingly, contrary to the C677T polymorphism, the distribution of the A1298C polymorphism presented reverse geographical trends. This may be caused by the fact that the occurrence of the 677T and 1298C alleles is usually in *trans* and rarely in *cis* configurations (30). The physical distance that separates the two alleles on the chromosome is short (2.1kb), which reduces the probability of a recombinant event (30). Additionally, the co-occurrence of the 2 alleles could result in a selection disadvantage because of the expression of severe phenotypes including neural tube defects and spontaneous abortions (5).

For gene-disease associations, our review showed that relationships of 103 medical disorders with the *MTHFR* C677T polymorphism had been explored during the past 15 years, with majority of the work relating to cardiovascular diseases, cancers and birth defects. Relation between the C677T polymorphism and 22 diseases in Chinese population had been previously meta-analyzed (31–52). We pooled results for 63 diseases and 42 of them yield significant associations. All results from our current meta-analytical results were consistent with those in the previous meta-analyses (31–41, 43, 45–50) except in terms of acute lymphoblastic leukemia (42), colorectal cancer (51), liver cancer (44) and schizophrenia (52). In the previous meta-analyses, the 677T allele was significantly associated an increased risk of liver cancer (44) and a decreased risk of acute lymphoblastic leukemia (42), colorectal cancer (51) and schizophrenia (52). However, our meta-analyses did not observe any association between the polymorphism and the four diseases. For the *MTHFR* A1298C polymorphism, its associations with 6 diseases in Chinese had been previously meta-analyzed (40, 42, 53–56). In our study, associations of 55 diseases with the polymorphism have been investigated. Twenty-nine of them were meta-analyzed and 3 yield significant results. Among them, only the results for breast cancer were different from the previous meta-analysis (53). Compared with those published meta-analyses (41–56), ours was based on more comprehensive literature searches and included more individual studies and participants, and was thus believed to have more precise estimations. The remaining meta-analyses on 41 diseases with the C677T polymorphism and on 23 diseases with the A198C polymorphism were, to the best of our knowledge, never been published.

Numerous published meta-analyses also have looked at the *MTHFR* polymorphisms and the risk of various disorders among different populations worldwide, which usually reported that the genetic-disease association depended on the ethnicity and geographical location of the studied population. For example, a meta-analysis by Holmes et al. (17) reported that the 677TT genotype was associated with an increased risk of stroke in Asia, but not in America, Australia and New Zealand. Similarly, a meta-analysis on the A1298C polymorphism and cancer risk showed that increased risks of cervical cancer and lymphoma and decreased risk of colorectal cancer were only found in Asians, but not in Caucasians, Africans and Indians (57). The inconsistency of these results may be caused by many factors, with differences in genetic background and lifestyle emerging as the most likely contributors. Therefore, it is of great significance to provide empirical evidence on the gene-disease associations in each area or ethnic group, which is just the primary endeavor of the present study.

While interpreting the findings of our study, the following limitations should be noted. First, although we made every effort to identify all relevant publications, it may be possible that some studies were missed or selected erroneously. Second, in estimating the geographical and ethnic distributions, the sample size of some provinces and all minorities were not large enough, especially for the A1298C polymorphism. This limits our ability to provide more precise estimates. Third, effect of the *MTHFR* gene polymorphisms on diseases may be modified by demographic and environmental factors. For example, our group previously found that the *MTHFR* C677T polymorphism was associated with hypertension only in older subjects (>45 years) (58). Chen et al. observed that significant relationship between the 677TT genotype and ischemic stroke was limited to males (59). Furthermore, multiple gene polymorphisms can interact to contribute to the development of diseases (Table S18). However, in our study all the pooled ORs were based on study-level genotype data, which precludes us from performing more sophisticated analyses incorporating potential confounders (such as age, sex, gene–environment or gene–gene interactions). Fourth, evidence of publication bias in some of our meta-analyses was detected (Tables S12 and S15, Figs S110–S117 and S128–S138). We appraised potential sources of bias using extensive sensitivity analyses, but our study is still limited because latent undetectable bias is always possible. Fifth, the number of 'true' gene-disease associations is probably smaller than the number of statistically significant findings identified in our systematic review (60). The primary reason was that many significant ORs were based on only 1 or 2 studies. Additionally, multiple testing, linkage disequilibrium, reporting bias and other flaws in study design can also contribute to the inconsistency (24). When we applied the Venice criteria, only 2 of the 45 significant associations can be considered to have strong epidemiological credibility. Although the Venice Criteria is a recently developed interim epidemiological grading system and its performances remains to be further validated, the graded

results provide some evidences that some significant findings may be false-positive. Therefore, our results must be interpreted conservatively before further strong evidence is provided by well-designed large studies.

Despite these caveats, our study offers the first comprehensive and systematic assessment of the epidemiological evidence on the distribution of the *MTHFR* polymorphisms and their associations with various diseases among the Chinese population. More importantly, we included many studies published in Chinese language, which might never be read and referenced by foreign researchers. Inclusion of these studies not only enhances the stability of our estimates but also builds a bridge between these important information and non-Chinese readers. Findings from our study can help researchers in this field explore the prevalence of the two polymorphisms in different populations; interpret the prevalence gradient of related disorders and improve the design of future gene-diseases association studies. From a public health perspective, these data can provide implications for Chinese government and policy makers to design regional or ethnic preventive measures and to evaluate the health care costs-benefits ratio. Apart from these, our systematic review points out the limitations and gaps in the existing literature, which provides an important guide for future efforts.

Conclusions

Our study presents the most systematic assessment of the current evidence on geographical and ethnic distribution of the *MTHFR* C677T and A1298C polymorphisms and their associations with diseases among the Chinese population, which otherwise would be impossible to be obtained from fragmented investigations of individual studies or isolated meta-analyses. Findings from this study documented distinctive geographical and ethnic variation in the prevalence of the two polymorphisms in China, although the estimates from several regions and ethnicities were less precise due to small sample size. Moreover, the two polymorphisms were found to be significantly associated with a variety of diseases; however, most of the significant associations were assessed as having moderate or weak epidemiological credibility, thus requiring careful caution in the interpretation of results. These evidence-based genomic data can serve several purposes (e.g. further prevalence study into different populations, improved understanding on gene-disease association especially the C677T and A1298C polymorphism, etc.) and may be integrated into future medical and public health practices. Given the potential for interactions of *MTHFR* genes with environment factors and other genes on diseases, future large studies with accurate measurement of the environmental exposure and other related genes are warranted to explore the gene-environment and gene-gene interactions, and to confirm or refute the associations observed in our meta-analysis. Also, future studies need to improve their methodological quality and the reporting of their findings, in order to increase the credibility of the evidence accumulating over time.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Acknowledgements

This work was supported by the Educational Department of Liaoning Province (Grant 20131015900).

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