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The correlation between methylenetetrahydrofolate reductase gene 677C > T polymorphism and fetal congenital defects: A meta-analysis

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Abstract: Objective To investigate the correlation between the methylenetetrahydrofolate reductase (*MTHFR*) gene 677C> T polymorphism and fetal congenital defects.

Method Original studies relevant to the *MTHFR* gene 677C>T single nucleotide polymorphism and fetal congenital defects were systematically searched in the electronic databases of Medline, EMBSE and China National Knowledge Infrastructure (CNKI). All relevant publications were screened for inclusion in the present work. The correlation between the *MTHFR* gene 677C > T single nucleotide polymorphism and the occurrence of fetal congenital defects was expressed as an odds ratio (OR) and its 95% confidence interval (95% CI). Publication bias was assessed by Begg's funnel plot and Egger's line regression test.

Results Nineteen case-control studies were ultimately included in the present meta-analysis. The pooled results indicated that the general risk of fetal congenital defects was significantly elevated in subjects with the 677T allele of the *MTHFR* gene in dominant (OR=1.07,95%CI:1.03-1.12, P<0.05), homozygous (OR=1.17,95%CI:1.06-1.30, P<0.05) and recessive genetic models (OR=1.16,95%CI:1.03-1.31, P<0.05) through the random effect method. However, significant publication bias was identified upon pooling the individual data and evaluating the correlation.

Conclusion According to the present evidence, the *MTHFR* gene 677C>T single nucleotide polymorphism is correlated with poor pregnancy outcomes, and subjects with the T allele have an increased risk of developing general fetal congenital defects.

Keywords: methylenetetrahydrofolate reductase; pregnancy outcomes; polymorphism; meta-analysis.

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Introduction

The incidence of birth defects in China is about 5.6%, making them the main cause of perinatal and infant deaths [1]. More and more studies have shown that genetic and environmental factors are involved in the occurrence of birth defects [2]. Maternal genetic susceptibility also increases the incidence of both spontaneous abortion and birth defects [3, 4]. In recent years, attention has been paid to polymorphisms in genes closely related to folic acid metabolism, such as *MTHFR* and *MTRR*, and their relationship with fetal congenital malformations, spontaneous abortion and congenital cardiovascular diseases. This field has become a research hotspot in recent years.

The *MTHFR* 677C>T single nucleotide polymorphism is a common polymorphism. The 667 cytosine of MTHFR is replaced by thymine, which transforms the highly conserved alanine (Ala) into valine (Val). This change can affect the protein's activity, resulting in abnormal methylation metabolism of Hcy, hyperhomocysteinemia and other diseases. Previous studies on the MTHFR 677C>T single nucleotide polymorphism and birth defects have been reported [5], but due to the small sample size and low statistical efficiency of each report, there are some contradictions in the results. Therefore, in this study, we used the meta-analysis method to analyze the aforementioned studies and further clarify the correlation between the *MTHFR* 677C > T single nucleotide polymorphism and birth defects.

Material and Methods

Study identification in the databases

Original studies relevant to the *MTHFR* gene 677C>T single nucleotide polymorphism and fetal congenital defects were systematically searched in the electronic databases of Medline, EMBSE and China National Knowledge Infrastructure (CNKI). Case-control or cohort studies relevant to the above topic and published in English or Chinese were systematically searched using the keywords "methylenetetrahydrofolate reductase," "*MTHFR*," "pregnancy," "fetal congenital defects" and "polymorphism." The references of the relevant publications were also reviewed in order to find additional potential studies related to this topic.

Study inclusion and quality assessment

Included studies should meet the following criteria: (1) The publication type is case-control or cohort study; (2) The study was published in Chinese or English; (3) The single nucleotide C and T distributions can be extracted from the original study; (4) Correct single nucleotide polymorphism detection methods were used. Study exclusion criteria were: (1) Other study design besides case-control or cohort; (2) Duplicated publication or data; (3) Single nucleotide C and T distributions were not provided or can't be calculated from the original studies.

The general methodological quality of the included studies was assessed using the Newcastle-Ottawa scale [6], which was used for quality assessment of observation studies by two reviewers (DX Li and EX Wang) independently.

Statistical analysis

Stata/SE 11.0 statistical software was applied for analysis of the data. The correlation between the *MTHFR* gene 677C> T polymorphism and fetal congenital defects was expressed as an odds ratio (OR) and its 95% confidence interval (95%CI). Statistical heterogeneity across the included nineteen publications was evaluated by the I^2 test. Publication bias was assessed through Begg's funnel plot and Egger's line regression test.

Results

General characteristics of the 19 publications

After systematically searching the relevant databases, 19 publications [7-25] related to the correlation between the *MTHFR* 677C>T gene polymorphism and fetal congenital defects were included in the present work, **Figure 1**. Of the included studies, ten publications studied Caucasian subjects, seven studied East Asian subjects and two studied mixed populations. The data was published over a time rage of 13 years (from 2004 to 2016). The primary fetal congenital defects studied were neural tube deformity, Down's syndrome, unexplained recurrent spontaneous abortion and congenital heart disease. The methodological quality scores and general characteristics of these 19 publications are shown in **Table 1**.

Dominant genetic model (TT+CT vs CC)

Significant statistical heterogeneity was found to exist across the 19 publications for the dominant genetic model (I^2=60.5%, $P<0.05$). The individual correlations between the *MTHFR* 677C>T gene polymorphism and general fetal congenital defects were pooled through the random effect model. The pooled results indicated that subjects with a TT or CT genotype had an increased risk of developing fetal congenital defects (OR=1.07,95%CI:1.03-1.12, $P<0.05$), **Figure 2.**

Homozygous genetic model (TT vs CC)

In the homozygous genetic model, the data was pooled by the random effect model for statistical heterogeneity (I^2=40.3%, $P<0.05$). The pooled data indicated that the general risk of fetal congenital defects was significantly elevated in subjects with a TT genotype in a homozygous genetic model (OR=1.17, 95%CI:1.06-1.30, $P<0.05$), **Figure 3**.

Recessive genetic model (TT vs CT+CC)

For a recessive genetic model (TT vs CT+CC), the pooled results also showed subjects with the TT genotype had

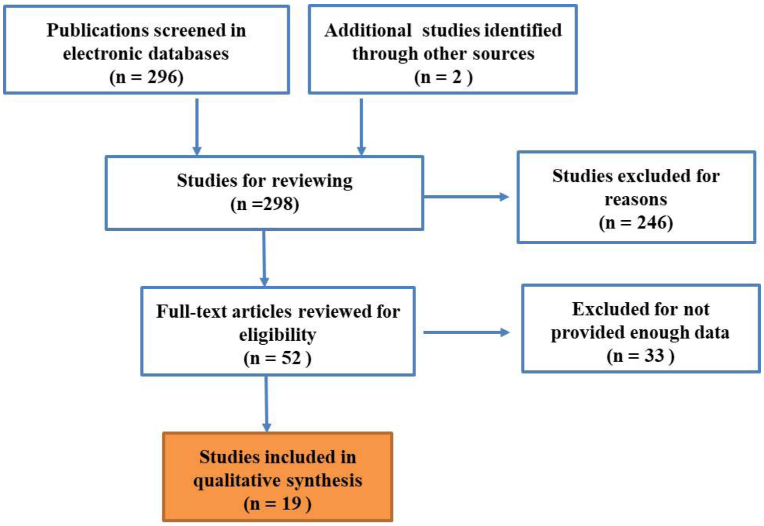

Figure 1: Flow chart of the studies screening in the databases.

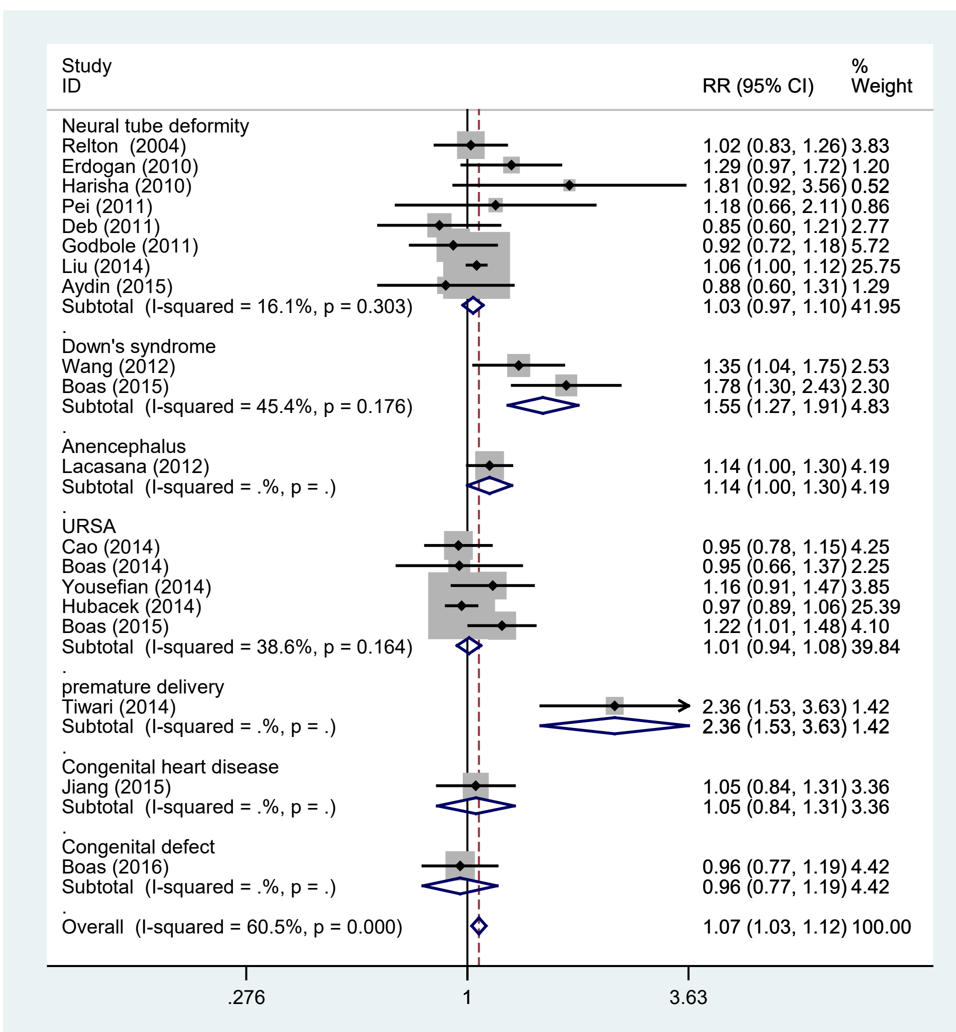

Figure 2: Forest plot of the methylenetetrahydrofolate reductase gene 677C > T polymorphism and fetal congenital defects in a dominant gene model.

Table 1: General information on the included studies for evaluating the correlation between the methylenetetrahydrofolate reductase 677C>T gene polymorphism and fetal congenital defects.

Trials	Year	Country	Ethnicity	Control			Case			Methods	HWE	pregnancy outcomes	NOS score
				CC	CT	TT	CC	CT	TT				
Relton	2004	UK	Caucasian	66	88	15	31	36	15	RFLP	Yes	Neural tube deformity	6
Harisha	2010	India	Caucasian	87	14	1	33	10	2	RFLP	NA	Neural tube deformity	5
Erdogan	2010	Turkey	Caucasian	18	21	9	5	14	7	HRM	NA	Neural tube deformity	6
Deb	2011	Iinda	Caucasian	149	64	9	80	25	6	RFLP	Yes	Neural tube deformity	4
Godbole	2011	Iinda	Caucasian	521	158	5	238	62	5	mass spectrographic analysis	Yes	Neural tube deformity	5
Pei	2011	China	East Asia	42	11	4	40	3	15	RFLP	NA	Neural tube deformity	3
Lacasana	2012	Mexico	Mixed	20	49	22	11	45	42	RFLP	Yes	Anencephaly	6
Wang	2012	China	East Asia	66	44	10	33	43	8	Sequencing	Yes	Down's syndrome	4
Tiwari	2014	India	Caucasian	170	20	4	148	49	12	RFLP	Yes	Premature delivery	4
Cao	2014	China	East Asia	53	83	30	29	43	10	mass spectrographic analysis	Yes	URSA	5
Boas	2014	Brazil	Mixed	97	47	6	59	26	4	RFLP	Yes	URSA	5
Liu	2014	China	East Asia	120	281	171	95	290	188	mass spectrographic analysis	Yes	Neural tube deformity	4
Yousefian	2014	Iran	Caucasian	63	43	10	96	90	18	Taqman	NA	URSA	6
Hubacek	2014	Czech Republic	Caucasian	1068	1116	302	208	214	42	Real-time PCR	Yes	URSA	6
Jiang	2015	China	East Asian	41	48	11	38	46	16	RFLP	Yes	Congenital heart disease	5
Luo	2015	China	East Asia	60	65	10	40	70	15	RFLP	Yes	URSA	5
Aydin	2015	Turkey	Caucasian	15	21	3	16	16	3	Real-time PCR	Yes	Neural tube deformity	4
Sukla	2015	India	Caucasian	141	42	3	86	59	6	RFLP	Yes	Down's syndrome	6
Xiao	2016	China	East Asia	67	66	17	62	50	20	Real-time PCR	Yes	Congenital defect	5

RFLP: Restriction Fragment Length Polymorphism
HRM: High-Resolution Melting
URSA: Unexplained Recurrent Spontaneous Abortion

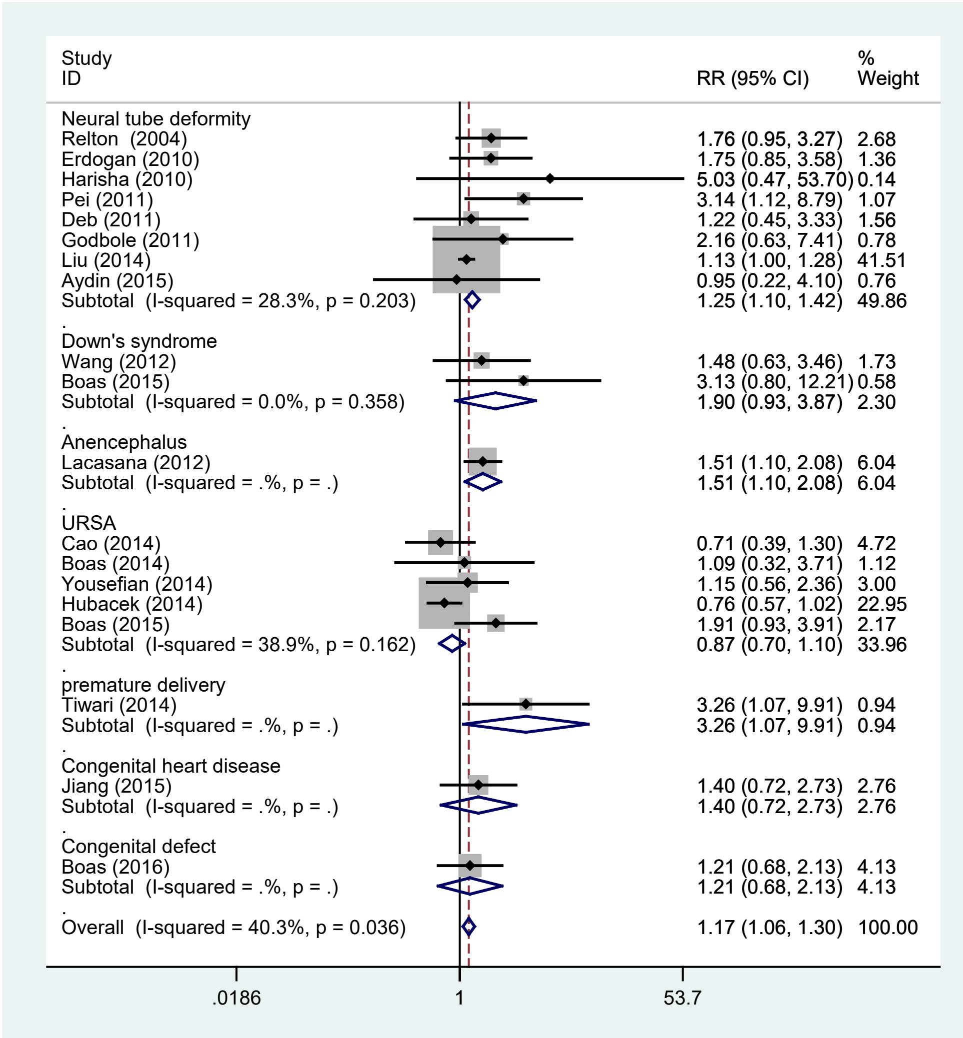

Figure 3: Forest plot of the methylenetetrahydrofolate reductase gene 677C > T polymorphism and fetal congenital defects in a homozygous genetic model.

an increased risk of developing general fetal congenital defects (OR=1.16,95%CI:1.03-1.31, P<0.05) in a random effect model (I^2=39.9%), **Figure 4**.

Subgroup analysis

To investigate different fetal congenital defects and subject ethnicities, we performed subgroup analysis. The correlations between the methylenetetrahydrofolate reductase 677C>T gene polymorphism and different fetal congenital defects or different ethnicities are shown in **Table 2**. In different genetic models, the correlations between the methylenetetrahydrofolate reductase 677C>T gene polymorphism and fetal congenital defects were quite different. However, the *MTHFR* 677C>T gene polymorphism was significantly correlated with anencephaly in various genetic models.

Publication bias evaluation

Publication bias was evaluated by Begg's funnel plot and Egger's line regression test. The funnel plot was asymmetric at its bottom, indicating potential publication bias in all genetic models **(Figure 5).** The Egger's line regression test indicated significant publication bias in the homologous and recessive genetic models, but not in the dominant genetic model, **Table 3**.

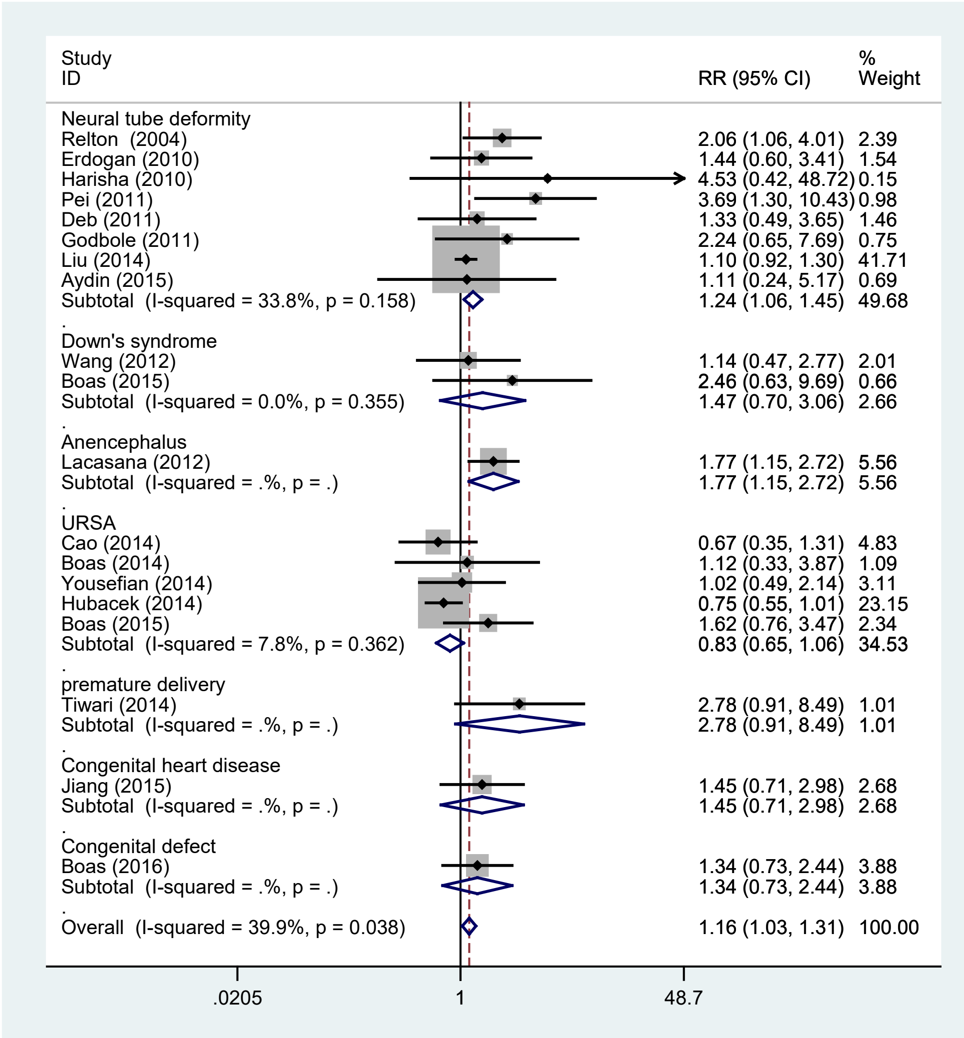

Figure 4: Forest plot of the methylenetetrahydrofolate reductase gene 677C > T polymorphism and fetal congenital defects in a recessive genetic model.

Discussion

The methylenetetrahydrofolate reductase protein primarily reduces 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate in the folic acid metabolic pathway, thus participating in purine synthesis, pyrimidine synthesis and DNA synthesis *in vivo* as an indirect donor of methyl groups [26]. The normal function of the MTHFR protein is to maintain the efficacy of the folate methionine cycle and ensure the normal progress of DNA synthesis and methylation. If the *MTHFR* gene is mutated, this can lead to the disruption of many basic biochemical processes in the body, as well as hyperhomocysteinemia [27, 28]. The 677C > T polymorphism in the *MTHFR* gene causes alanine to be replaced by valine, leading to a decrease in the heat resistance and activity of the enzyme.

It has been reported that *MTHFR* gene mutations can induce elevated blood Hcy levels, leading to many adverse pregnancy outcomes, such as neural tube defects, congenital heart disease, premature delivery, pregnancy complications, recurrent abortion and Parkinson's disease [29]. To this end, some studies have shown that the MTHFR single nucleotide polymorphism can affect serum Hcy levels and is associated with adverse pregnancy outcomes [30]. However, other studies have shown that subjects with the T genotype have an increased risk of developing fetal congenital defects, such as neural tube deformity and congenital heart disease.

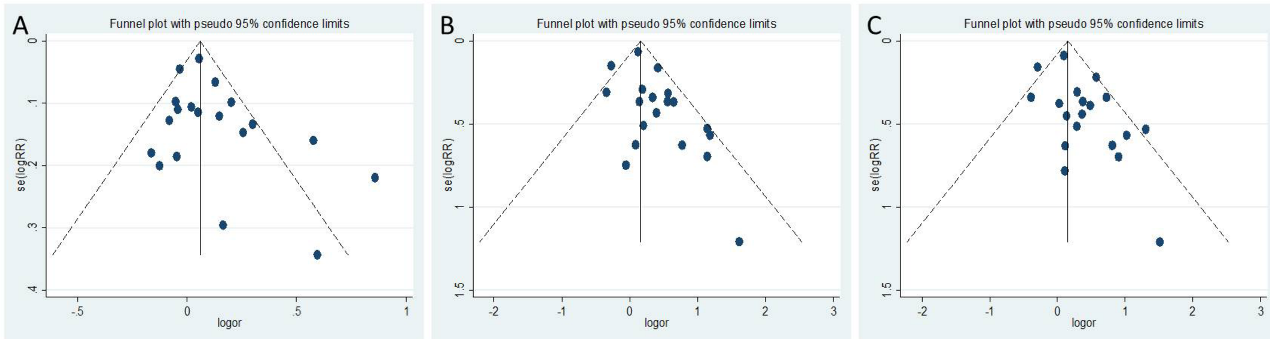

Figure 5: Begg's funnel plot for evaluation of the (MTHFR) gene 677C > T polymorphism and fetal congenital defects. (A: dominant genetic model; B: homologous genetic model; C: recessive genetic model).

Table 2: Subgroup analysis of the correlation between the methylenetetrahydrofolate reductase 677C > T gene polymorphism and fetal congenital defects.

Sub-group	Recessive genetic model			Dominant genetic model			Homozygous genetic model		
	OR(95%CI)	I^2	P	OR(95%CI)	I^2	P	OR(95%CI)	I^2	P
Pregnancy outcomes									
Neural tube deformity	1.24(1.06-1.45)	33.8%	<0.05	1.03(0.97-1.10)	16.1%	>0.05	1.25(1.10-1.42)	28.3%	<0.05
Down's syndrome	1.47(0.70-3.06)	0.0%	>0.05	1.55(1.27-1.91)	45.4%	<0.05	1.90(0.93-3.87)	0.0%	>0.05
Anencephaly	1.77(1.15-2.72)	-	<0.05	1.14(1.00-1.30)	-	0.05	1.51(1.10-2.08)	-	<0.05
URSA	0.83(0.65-1.06)	7.8%	>0.05	1.01(0.94-1.08)	38.6%	>0.05	0.87(0.70-1.10)	38.9%	>0.05
Congenital heart disease	1.45(0.71-2.98)	-	>0.05	1.05(0.84-1.31)	-	>0.05	1.40(0.72-2.73)	-	>0.05
Congenital defect	1.34(0.73-2.44)	-	>0.05	0.96(0.77-1.12)	-	>0.05	1.21(0.68-2.13)	-	>0.05
Premature delivery	2.78(0.91-8.49)	-	>0.05	2.36(0.84-1.31)	-	>0.05	3.26(1.07-9.91)	-	<0.05
Ethnicity									
Caucasian	1.06(0.85-1.32)	46.4%	>0.05	1.07(1.00-1.14)	75.4%	0.05	1.09(0.88-1.35)	51.8%	>0.05
East Asia	1.16(1.00-1.35)	33.5%	0.05	1.07(1.02-1.13)	22.4%	<0.05	1.19(1.05-1.35)	33.2%	<0.05

Table 3: Publication analysis by Egger's line regression test in different genetic models.

Genetic model	Coef	Se	t	P
Dominant	0.91	0.58	1.58	0.13
Homologous	0.90	0.39	2.33	0.03
Recessive	1.04	0.42	2.47	0.02

In our present meta-analysis, we included 19 case-control studies and pooled the results for dominant, recessive and homozygous genetic models. The pooled data indicated a significant correlation between the *MTHFR* 677C > T gene polymorphism and fetal congenital defects. **S**ubjects with the T genotype in dominant (OR=1.07,95%CI:1.03-1.12, P<0.05), homozygous (OR=1.17,95%CI:1.06-1.30, P<0.05) and recessive genetic models (OR=1.16,95%CI:1.03-1.31, P<0.05) had significantly increased risks of developing fetal congenital defects or experiencing poor pregnancy outcomes. For further investigation, we performed subgroup analysis according to the fetal congenital defects. For different genetic models, the correlation between the methylenetetrahydrofolate reductase 677C>T gene polymorphism and fetal congenital defects was quite different. In a recessive genetic model, the *MTHFR* 677C>T gene polymorphism was correlated with neural tube deformity and anencephaly. In a dominant genetic model, the *MTHFR* 677C>T gene polymorphism was correlated with Down's syndrome and anencephaly. Finally, for the homozygous genetic model, the *MTHFR* 677C>T gene polymorphism was correlated with neural tube defects, anencephaly and premature birth. Therefore, under different genetic models, the *MTHFR* 677C>T polymorphism may affect different fetal congenital defects, which had not been evaluated in previous publications. However, the *MTHFR* 677C>T gene polymorphism was significantly correlated with anencephaly in all genetic models. This indicates that the *MTHFR* 677C>T gene polymorphism may be an important factor in the development of anencephaly.

Fetal congenital defects or poor pregnancy outcomes represent a group of complex diseases, which are affected by multiple susceptibility genes and many environmental factors. Because of this, only assessing the effect of one single nucleotide polymorphism in one gene may be not enough to completely explain the disease etiology. Therefore, high-throughput analysis of folic acid metabolism-related genes and their correlations with fetal congenital defects or poor pregnancy outcomes is necessary.

The present work also had limitations: (1) Heterogeneity across the included studies was significant, which may decrease statistical power; (2) Only open studies published in English or Chinese were included in the work. Therefore, other suitable studies may have been omitted; (3) The general methodological quality of the included studies was moderate. Therefore, more high-quality relevant studies will be needed to further validate our findings.

Conflict of interest: Authors states no conflict of interest

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