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MTHFR polymorphisms (rs1801133) and systemic lupus erythematosus risk

A meta-analysis

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Abstract

Background: The relationship between MTHFR (5, 10-methylene tetrahydrofolate reductase) gene polymorphisms and Systemic Lupus Erythematosus (SLE) has been wildly studied, but the results are still conflicting. Therefore, the purpose of this meta and pooled analysis was to identify the role of the MTHFR SNP (single nucleotide polymorphism, rs1801133) in SLE in a large sample of subjects and to assess the risk of SLE.

Methods: Data were collected from EMBASE, PubMed and China National Knowledge Infrastructure from inception to August, 2019. Summary odds ratio (OR) with 95% confidence interval (CI) was applied to assess the association. Subgroup and sensitivity analysis were performed to assess the potential sources of heterogeneity of the pooled estimation.

Results: We identified seven eligible studies involving 882 cases and 991 controls. MTHFR rs1801133 T carrier was significantly associated with increased risk of SLE when comparing to C allele [ORs were 1.766 (1.014–3.075) for T carrier vs CC, $P = .04$]. Furthermore, the results of the subgroup analysis by genotyping methods suggested that T allele significantly contributed to the risk of SLE for both by polymerase chain reaction-TaqMan (PCR-TaqMan) [10.111 (2.634–38.813) for TT vs CC, 3.467 (1.324–9.078) for CT vs CC and 3.744 (1.143–12.264) for TT vs C carrier]. Also the results of the subgroup analysis by ethnicity suggested that T allele significantly contributed to the risk of SLE for Asians [9.679 (4.444–21.082) for TT vs CC, 5.866 (3.021–11.389) for T carrier vs CC and 8.052 (3.861–16.795) for TT vs C carrier].

Conclusion: This cumulative meta-analysis showed that the MTHFR SNP (rs1801133) contributed to susceptibility of SLE. However, more multicentre well-designed case-control studies and larger sample sizes are exceedingly required to validate our findings in the future.

Abbreviations: CI = confidence interval, CNKI = China National Knowledge Infrastructure, Hcy = Homocysteine, HWE = Hardy-Weinberg equilibrium, MAF = minor allele frequency, MTHFR = methylene tetrahydrofolate reductase, OR = odds ratio, PCC = population-based case-control controls, SLE = Systemic Lupus Erythematosus, SNP = single nucleotide polymorphism.

Keywords: meta-analysis, MTHFR polymorphisms, rs1801133, systemic lupus erythematosus

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology that involves multiple organ systems, which is characterized by autoantibody production and immune complex formation leading to intense inflammation and multiple organ damage.[1,2] Although the reasons for the development of SLE are not fully understood, more research shows that genetic factors and environmental factors are involved.[3,4]

It is well known that homocysteine (Hcy) is elevated in patients with SLE,[5] and the availability of folic acid and B vitamins will directly affect the concentration of Hcy. In the folate / HCY metabolic pathway, they are also affected by the functional polymorphism of key enzymes, including MTHFR, which also affect the distribution of intermediates in this pathway and lead to the increase of HCY.[6,7] The human 5, 10-methylene tetrahydrofolate reductase (MTHFR) gene is located at position 36 on the end of the short arm of chromosome 1 (1p36.3) and is composed of 11 exons.[8] Folic acid metabolism of MTHFR enzyme plays an important role and influence in DNA methylation and synthesis. This transition occurs on 5-methyl-10-methyltetrahydrofolic acid to 5-methyltetrahydrofolic acid,

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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which is the main cyclic form of folic acid. The 5-methyltetrahydrofolate product donated a methyl homocysteine in the generation of S-adenosylmethionine methyl used as the main source of DN+ A methylation. MTHFR gene product contributes to maintain cycle of folic acid and methionine levels, so as to prevent the accumulation of homocysteine.[9] Although several single nucleotide polymorphisms (SNPs) in MTHFR gene have been reported in previous studies, this paper mainly studies the most common gene polymorphism of SNP the rs1801133 (677C > T). The C-to-T transition at nucleotide 677 in exon 4 is a point change, converting an alanine (C) to valine (T) substitution, making enzyme less active.[10] Previously published articles refer to wild type CC, CT heterozygous form, and TT homozygous variant. The enzyme activity of subjects with the TT or CT genotype is lower than subjects carrying the CC genotype.[11]

Considering the role of MTHFR in SLE, a large volume of observational studies had been investigated the association of the MTHFR gene polymorphism and SLE susceptibility. However, the results are conflicting. This may be caused by insufficient power, small effect of the MTHFR gene polymorphisms on SLE susceptibility, and false positive results. Meta-analysis can summarize different research results and is a powerful research tool. It can not only overcome the problems of complex traits, small scale of genetic research and lack of statistical ability, but also provide more reliable results than a single case-control study.[12] We therefore performed a meta-analysis to clarify the inconsistency among studies and to establish a comprehensive picture of the association between the MTHFR gene polymorphisms and SLE susceptibility.

2. Materials and methods

2.1. Search strategy

To identify all pertinent studies, we searched EMBASE, PubMed and and China National Knowledge Infrastructure (CNKI) before 28 August, 2019. The key words and subject terms used were as follows: 'MTHFR', 'Systemic Lupus Erythematosus' and 'genetic polymorphisms', and limited the studies to those involving humans. In addition, we retrieved all eligible articles and checked their references to find other possible studies. There was no language, time period, sample size, type of report and other restrictions. We did not consider case reports, interim analyses, abstracts, reviews, or unpublished reports. When there is more than one study that involves overlapping population, only the latest and largest report was included.

2.2. Inclusion and exclusion criteria

The data from the eligible studies were selected if they satisfy the following inclusion criteria:

(1) the nested case-control or cross-sectional or cohort study design for human;
(2) the same MTHFR SNP have to be studied at least 1 study;
(3) studies should provide sufficient data for estimating OR and corresponding 95% CI;
(4) the study reported sufficient data to calculate the number of each allele identified.

The major exclusion criteria were as follows:

(1) duplicated studies;
(2) there was no sufficient data to support integrity of the data upon extraction;
(3) abstract, comment, review and editorial.

2.3. Data extraction

Huangyan Zhou and Min Yuan extracted data from included studies independently according to the criteria mentioned above. Disagreement was resolved by discussion or contacting the author for further information. For each study, the following information were collected: first author, year of publication, ethnicity, country of origin, genotype frequency of cases and controls, numbers of cases and controls and source of controls (population-based case-control controls, PCC), genotyping methods, minor allele frequency (MAF) in controls, evidence of Hardy-Weinberg equilibrium (HWE) in the control group, and others (Table 1).

2.4. Statistical analysis

We imported data into STATA, version 12.0 (STATA Corporation, College Station, TX). The data were quantified. Heterogeneity between the trials was assessed with I^2 score (I^2) test and Q statistic test.[13] When $P > .10$ for the Q statistic test considered a lack of heterogeneity, the pooled OR was described by the fixed-effect model (Mantel–Haenszel method),[14] on the contrary, the random-effects model (the DerSimonian and Laird method) would be used.[15] Heterogeneity was also carried out using stratified analysis with genotyping methods (PCR TaqMan/ PCR-RFLP), and ethnicity of participant (Caucasian/ Asian/ Mix). Among other things, the causes of heterogeneity also were explored in this context.

In addition, regarding MTHFR polymorphism, we first assessed HWE ($P < .05$ was considered as a deviation from HWE) in the controls for each study using goodness-of-fit test (chi-square or Fisher's exact test).[16] Moreover, ORs, with the corresponding 95% CIs and Z-test were used, and the $P < .05$ indicated statistical significance for the strength of the association between SLE and the MTHFR polymorphism. The pooled ORs were performed for homozygote (TT vs CC), heterozygote (CT vs CC), dominant model (TT + CT vs CC) and recessive model (TT vs CC + CT).

The sensitivity analysis was conducted by removing one study at a time to evaluate the quality and consistency of the meta-analysis results. Modified Begg funnel plot and Egger bias test were used to statistically assess publication bias ($P < .05$ was considered representation of statistically significant publication bias). This statistic is useful when deciding whether there is too much heterogeneity to combine the studies and derive a pooled estimate.

2.5. Ethics statement

As all analyses in our article were based on previously published studies, no ethical approval or patient consent was required.

3. Results

3.1. Study selection and characteristics

A total of seven eligible studies with 882 cases and 991 controls were included into the meta-analysis based on the inclusion and exclusion criteria.[17–23] A flowchart of the study was shown in Figure 1. The data extracted from each study are presented in

Table 1

Characteristics of studies included in the meta-analysis.

First author (year)	Source of controls	Country	Ethnicity	Sanple size (case/control)	Matching	Genotyping methods	Sample size			MAF in controls	HWE
							CC (case/control)	CT (case/control)	TT (case/control)		
Saeedeh Salimi (2017)	PCC	Iran	Caucasian	150/160	age, sex, and ethnicity	PCR-RFLP	104/110	43/45	3/5	0.17188	0.87928
Yedluri Rupasree (2014)	PCC	India	Caucasian	179/414	age, gender, ethnic and geographical background	PCR-RFLP/AFLP	151/343	28/70	0/1	0.08696	0.187
Carolyn M. Summers (2008)	Unknown	American	Mix	146/144	race and age	PCR-TaqMan	78/80	NA1/50	NA2/14	0.27083	0.14691
Xuebiao Peng (2007)	PCC	China	Asian	40/20	Unknown	PCR-RFLP	8/12	7/5	25/3	0.275	0.09526
M Burzynski1 (2007)	Unknown	Poland	Caucasian	106/141	Unknown	PCR-RFLP	50/61	48/63	8/17	0.34397	0.90571
Xiaoyan Xu (2005)	PCC	China	Asian	54/62	Unknown	PCR-RFLP	16/44	6/8	32/10	0.22581	<0.001
Antonella Afeltra (2005)	PCC	Italy	Caucasian	57/50	age and gender	PCR-TaqMan	19/26	24/20	14/4	0.28	0.95525

NA1 + NA2 = 68. Genotype distributions among the controls of all studies were consistent with HWE ($P > .05$)

HWE = Hardy-Weinberg equilibrium, MAF = minor allele frequency, PCC = population-based case-control, PCR = polymerase chain reaction, PCR-RFLP/AFLP = polymerase chain reaction-restriction fragment length polymorphism/amplified fragment length polymorphism, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

Table 1. Two studies were published in Chinese,[19,21] while the other studies were published in English.[17,18,20,22,23] These 7 case-control studies were published from 2005 to 2017. The distributions of genotypes in the controls of seven studies were in agreement with HWE except for one study.[21] Since one of the researches just presents the data for genotypes of CT + TT and CC.[18] Seven researches were included for analysis for the CT + TT and CC model, and 6 researches were included for other three comparison models.

3.2. Meta-analysis results

As shown in Figure 2, the results of overall analysis indicated that MTHFR rs1801133 T carrier was significantly associated with increased risk of SLE when comparing with C allele [ORs were 1.766 (1.014–3.075) for CC vs T carrier, $P = 0.04$]. In the stratified analysis for genotyping methods, a statistically elevated risk of SLE was revealed by PCR-TaqMan [10.111 (2.634–38.813) for TT vs CC, $P < .05$; 3.467 (1.324–9.078) for CT vs CC, $P = .01$ and 3.744 (1.143–12.264) for TT vs C carrier, $P = .03$]. The positive association was also found in subgroup analysis for ethnicity studies for Asians [9.679 (4.444–21.082) for TT vs CC, $P < .05$; 5.866 (3.021–11.389) for T carrier vs CC, $P < .05$ and 8.052 (3.861–16.795) for TT vs C carrier, $P < .05$]. However, no association was found in Caucasians [1.361 (0.289–6.402) for TT vs CC, 1.135 (0.742–1.735) for CT vs CC, 1.215 (0.701–2.106) for T carrier vs CC, 1.072 (0.382–3.008) for TT vs C carrier] (Table 2).

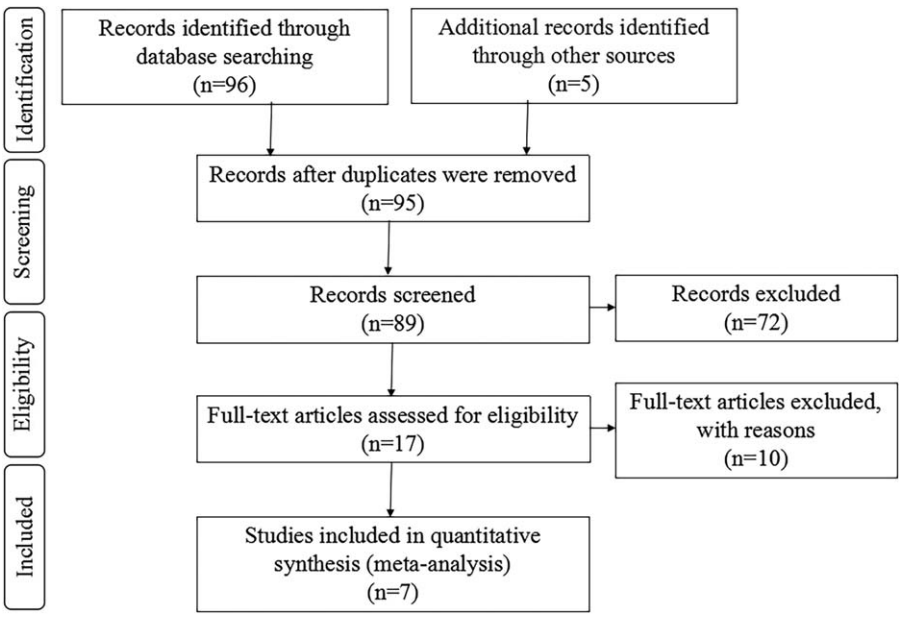

Figure 1. Flow diagram of the studies included in the meta-analysis.

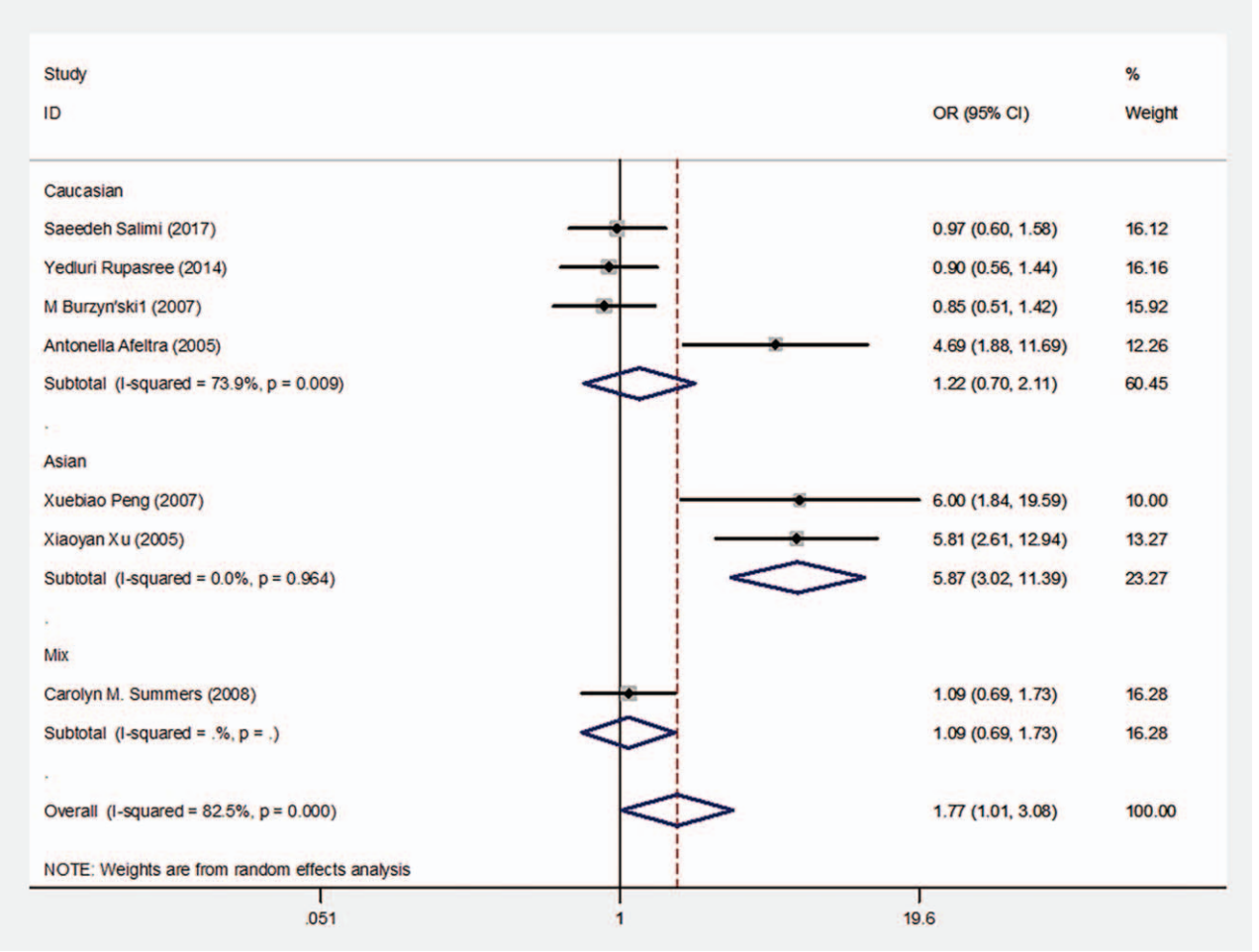

Figure 2. Forest plot of SLE risk associated with rs1801133 polymorphism in different ethnicities (TT + CT vs CC).

Table 2

Pooled ORs and stratification analysis of MTHFR polymorphisms on SLE risk in the meta-analysis.

			Homozygote				Heterozygote		
SNP	**Subgroup**	**N**	**OR (95%CI)**	***P* value**	$P_{heterogeneity}$	**N**	**OR (95%CI)**	***P* value**	$P_{heterogeneity}$
rs1801133 (677C > T)			TT vs CC				CT vs CC		
Total		6	2.845 (0.764–10.600)	.119	0	6	1.225 (0.841–1.784)	.29	.137
Genotyping methods	PCR-RFLP	5	2.162 (0.480–9.728)	.315	0	5	1.016 (0.771–1.339)	.908	.626
	PCR-TaqMan	1	**10.111 (2.634–38.813)**	**.001**	NA	1	**3.467 (1.324–9.078)**	**.011**	NA
Ethnicity									
	Caucasian	4	1.361 (0.289–6.402)	.696	.005	4	1.135 (0.742–1.735)	.559	.09
	Asian	2	**9.679 (4.444–21.082)**	**0**	.694	2	2.078 (0.822–5.252)	.122	.985

			Dominant model				Recessive model		
SNP	**Subgroup**	**N**	**OR (95%CI)**	***P* value**	$P_{heterogeneity}$	**N**	**OR (95%CI)**	***P* value**	$P_{heterogeneity}$
rs1801133 (677C > T)			TT + CT vs CC				TT vs CC + CT		
Total		7	**1.766 (1.014–3.075)**	**.044**	0	6	2.288 (0.735–7.121)	.153	0
Genotyping methods	PCR-RFLP	5	1.692 (0.840–3.410)	.141	0	5	2.024 (0.500–8.191)	.323	0
	PCR-TaqMan	2	2.140 (0.513–8.926)	.296	0.005	1	**3.744 (1.143–12.264)**	**.029**	NA
Ethnicity									
	Caucasian	4	1.215 (0.701–2.106)	.487	0.009	4	1.072 (0.382–3.008)	.895	.089
	Asian	2	**5.866 (3.021–11.389)**	**0**	0.964	2	**8.052 (3.861–16.795)**	**0**	.79
	Mix	1	1.090 (0.686–1.730)	.716	NA				

N = Number of comparisons.

Random-effects model was used when $P_{heterogeneity} < .10$; otherwise, fixed-effects model was used.

3.3. Heterogeneity and sensitivity analyses

The results of heterogeneity test were shown in Table 2. As for some studies that had heterogeneity ($P_{heterogeneity} < .10$), the random-effects models were performed; others were analyzed by fixed-effects model. In the sensitivity analysis, the influence of each study on the pooled OR was examined by deleting one at a time. The results indicated that our overall results were stable (Fig. 3).

3.4. Publication bias

Funnel plot, Begg and Egger tests were used to evaluate the publication bias for rs1801133. Most of the results did not show publication bias for rs1801133 (Homozygote model: Begg test $P = .851$, Egger test $P = .939$; heterozygote model: Begg test $P = .188$, Egger test $P = .076$; recessive model: Begg test $P = .176$, Egger test $P = .002$), besides, there is a slight bias for Egger test of dominant model (Begg test $P = .573$, Egger test $P = .858$) (Fig. 4).

4. Discussion

In this meta-analysis of seven studies involving 882 cases and 991 controls, we found that MTHFR polymorphisms was associated with an increased risk of SLE. The MTHFR SNP (rs1801133) contributed to susceptibility of SLE.

MTHFR rs1801133 endowed with a lot of attention in recent years. Previous study has suggested that there was no significant association between rs1801133 and SLE susceptibility.[20] However, evidence showed that rs1801133 polymorphism increased the risk of SLE in this meta-analysis, which was consistent with the results of previous studies.[24] We found that T carries TT + CT significantly increased the risk of SLE, when comparing with common homozygous CC genotype. In the subgroup analysis by genotyping methods, the positive association was also observed in Asian studies. The results indicated that a significant association was observed between the rs1801133 polymorphism and SLE with PCR-TaqMan [homozygote TT vs CC: OR 10.111 (2.634–38.813), heterozygote CT vs CC: OR 3.467 (1.324–9.078), and recessive model TT vs C carrier: OR 3.744 (1.143–12.264)], but not with PCR-RFLP.

In previous studies, risk factors for SLE thrombosis have been identified including the presence of antiphospholipid antibodies,[25] smoking, longer course of disease, older age at diagnosis of SLE[26] and disease activity. However, these known risk factors do not fully explain the thrombotic burden of systemic lupus erythematosus. For example, among the 30% to 40% SLE patients with acute promyelocytic leukemia, only 10% experienced thrombotic events.[27] In addition, 40% of SLE patients with thrombosis were negative for antiphospholipid antibodies.[22] Work by Kaiser et al[24] suggests that the genetic variation of MTHFR (Rs1801133) was associated with the risk of thrombosis in white patients with SLE, which further confirmed the close relationship between MTHFR polymorphism and SLE.

One of the major concerns is the significance of heterogeneity testing by the Q test and I^2 statistics in this meta-analysis. Obvious heterogeneities were observed in overall comparisons. Even if we did subgroup analyses, heterogeneities still cannot eliminate or reduce. Heterogeneity may come from the following sources, such as changes in population characteristics, study design, regional differences, length of follow-up and adjustment of confounding factors. In the meta-analysis, sample size, imperfect matching, multiple risk factors, country of origin and research type are the main sources of heterogeneity. Another important issue is sensitivity analysis for rs1801133. The results were consistent for all of the comparison models, indicating that our results were statistically stable. In this meta-analysis, the Begg funnel plot and Egger test were performed to evaluate publication bias. Both the shape of the funnel plots and statistical results did not show publication bias. Thus, the results were reliable.

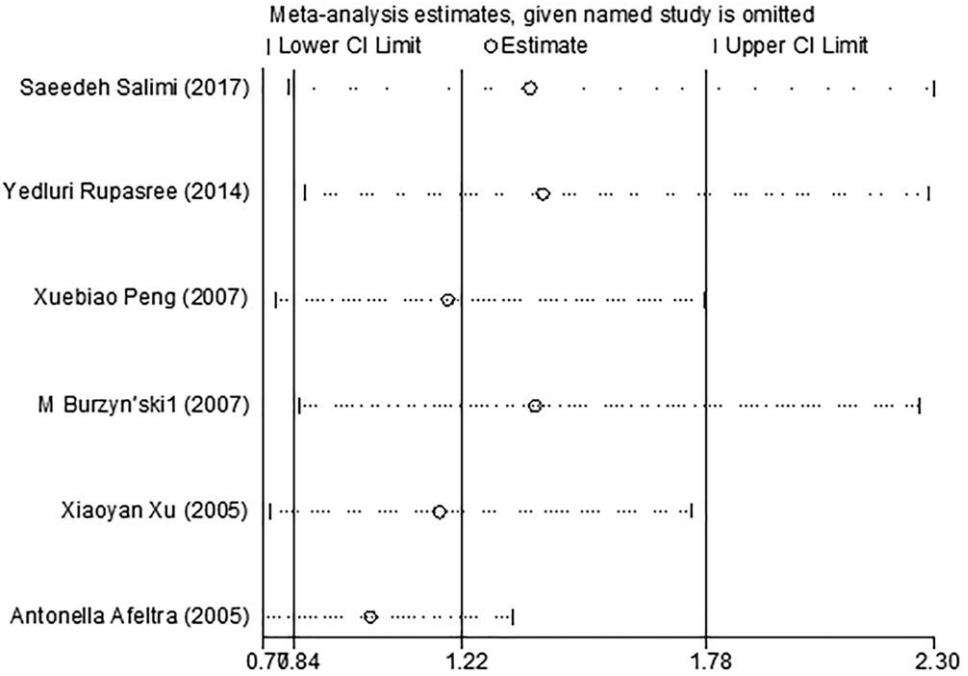

Figure 3. Sensitivity analysis examining the association between the MTHFR polymorphism rs1801133 and SLE risk in dominant model CT vs CC.

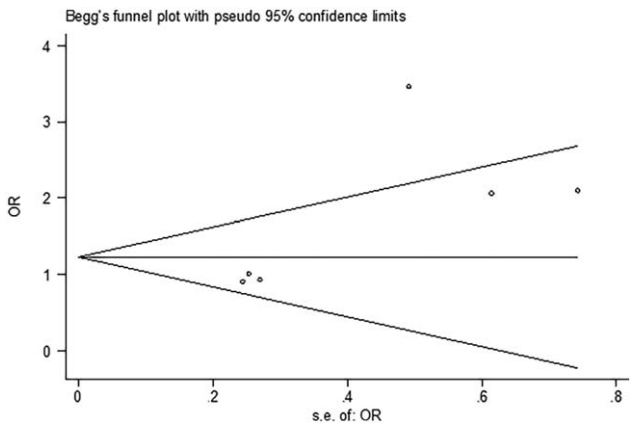

Figure 4. Begg funnel plot for the assessment of potential publication bias (CT vs CC).

Similar to the other meta-analyses, there are still some limitations in the meta-analysis, which should be acknowledged. First, the sample size was relatively small. Second, due to the lack of necessary information, our results were not based on the adjusted evaluation. In order to provide a more precise estimation on the basis of adjustment for the confounders, well designed studies taking the potential confounders such as gender and age into account are warranted. Third, limited data in case-control studies were included. In addition, meta-analyses are types of retrospective studies that may lead to the recall and selection bias if publication bias is present. Moreover, apart from MTHFRSNP (1801133), we have not conducted in-depth study on other risk factors of systemic lupus erythematosus thrombosis, such as antiphospholipid antibodies, which may be the second "hit" factor of systemic lupus erythematosus thrombosis. We hope that in the future research, we can fully take into account the impact of these factors, further improve the accuracy of the study and reduce heterogeneity. Therefore, our results should be interpreted with caution, and more large sample and high-quality research will be urgently needed to explore this conclusion in the future.

5. Conclusion

Overall, this meta-analysis found a significant association between the risk of SLE and the MTHFR polymorphisms. Nevertheless, the results should be explained with great caution, more multicentre well-designed case-control studies and larger sample sizes are exceedingly required to validate our findings in the future.

Author contributions

Min Yuan and Huangyan Zhou conceived, designed the study, and searched the databases, checked these according to the eligible criteria and exclusion criteria, as well as extracted the quantitative data, at last Min Yuan and Huangyan Zhou wrote the draft of the paper. All authors contributed in writing, reviewing, or revising the paper.

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