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Research Article

# Association between the *MTHFR* 677C/T Polymorphism and Susceptibility to Psoriasis: An Updated Meta-Analysis

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## ABSTRACT

The correlation between psoriasis and Methylenetetrahydrofolate Reductase (*MTHFR*) 677C/T polymorphism has been examined in a number of studies. However, the findings remain ambiguous. The present meta-analysis was conducted to comprehensively evaluate this issue. Eligible studies were searched in EMBASE, PubMed, Web of Science, Wan Fang Database, and Chinese National Knowledge Infrastructure (CNKI) up to December 31, 2021. Pooled Odds Ratios (ORs) with 95% Confidence Intervals (CIs) were calculated to estimate the effects of the *MTHFR* 677C/T polymorphism on psoriasis risk in different genetic models. Eleven relevant case-control studies were included in our meta-analysis, involving 2010 psoriasis cases and 1881 healthy controls. Pooled analysis suggested that the *MTHFR* 677C/T polymorphism was associated with increased psoriasis risk in the recessive model (TT *vs.* TC+CC, OR1.69, 95%CI=1.09-2.61, P=0.020). Stratification by ethnicity indicated that the *MTHFR* 677C/T polymorphism was associated with increased psoriasis risk in Asians under the recessive model (TT *vs.* TC+CC, OR=1.64, 95%CI=1.01-2.67, P=0.046) and in Europeans under the allelic model (T *vs.* C, OR=2.57, 95%CI=1.02-6.48, P=0.046). In conclusion, the *MTHFR* 677C/T polymorphism may be associated with an increased psoriasis risk. The TT genotype may increase the risk of psoriasis in Asians. Allele might increase psoriasis risk in Europeans.

**Keywords:** *MTHFR*; Polymorphism; Psoriasis; Meta-analysis

## INTRODUCTION

Psoriasis is a chronic and recurrent inflammatory disease which affects 1%-3% the world's population [1]. The characteristic lesions of psoriasis are red papules or plaques covered with multiple layers of silvery white scales. Due to the chronic course and recurrent attacks, psoriasis can not only influence appearance, but also affect the physical health and psychological status of patients [2].

The precise pathogenesis of psoriasis is still unclear. However, it is widely accepted that multi-factors, including genetic predisposition, environment, and host immune response, were involved in the development and exacerbation of psoriasis [3].

Methylenetetrahydrofolate Reductase *(MTHFR)* is a key enzyme in the folate metabolic pathway. Its main function is to convert 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate with biological functions [4]. The human *MTHFR* gene is located on chromosome 1p36.3, a region in which many Single Nucleotide Polymorphisms (SNPs) have been identified. The polymorphism at position 677 in *MTHFR* gene has been extensively investigated in psoriasis, which substitutes nucleotide C with to T, resulting in the reduced activity of the enzyme and increased homocysteine levels [5].

Despite the fact that *MTHFR* polymorphism has been linked to psoriasis in a number of studies, the results are still inconclusive. This is partly because the studies' sample sizes, statistical power, clinical heterogeneity, and diverse ethnic populations made it difficult to draw firm conclusions. In this study, we quantified the associations between the *MTHFR* polymorphism and psoriasis using a thorough meta-analysis. Additionally, we performed subgroup analyses to evaluate the impacts of the variables that might change this association.

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## MATERIALS AND METHODS

### Search strategy

Eligible studies were independently searched from EMBASE, PubMed, Web of Science, Wan Fang Database, and Chinese National Knowledge Infrastructure (CNKI) by two authors up to 31 December 2021, using the following keywords: ("Methylenetetrahydrofolate Reductase" or "*MTHFR*") and ("psoriatic" or "psoriasis") and ("Single Nucleotide Polymorphism" or "SNP" or "polymorphism" or "mutation" or "variation"). We included only Chinese and English language studies. The reference lists of included studies were manually searched to obtain additional related studies.

### Criteria for inclusion and exclusion

We ran a preliminary screening of all the literature based on titles and abstracts. Based on the inclusion criteria, we read the literature that was identified in the preliminary screen and acquired the final included literature. Studies were included if they met the following criteria: (1) Were case-control studies; (2) Were studies that documented the association between 677C/T polymorphism in the *MTHFR* gene and psoriasis susceptibility; (3) Were studies that had available data to calculate 95% Confidence Intervals (CIs) for Odds Ratios (ORs). Correspondingly, the following studies were excluded for any of the following: (1) Were duplications; (2) Were not case-control studies; (3) Were not related to the association between 677C/T polymorphism in the *MTHFR* gene and psoriasis susceptibility; (4) Lacked the available data to calculate OR and 95%CI; (5) The genotype distributions of healthy controls were not consistent with the Hardy-Weinberg Equilibrium (HWE).

### Data extraction

Eligible studies were extracted by two authors according to the inclusion and exclusion criteria. The following information was extracted by two investigators independently: First author, publication year, country, ethnicity, genotype distribution in cases and controls. Disagreements were settled through discussion between the authors.

### Statistical analysis

The genotype distributions of healthy controls were tested by Pearson's $\chi^2$ test, and $P<0.05$ was regarded as diverging from HWE [6]. Cochran Q-statistics and the $I^2$ test were used to check the heterogeneity between studies [7-8]. $P<0.1$ or $I^2>50\%$ indicated that there was potential heterogeneity. Random-effect model or fixed-effect model was applied to calculate ORs with corresponding 95%CIs according to the presence or absence of heterogeneity. Sensitivity analysis, carried out by sequentially excluding a single individual study, was used to evaluate the robustness of results. Both Begg's funnel plot and Egger's test were performed to investigate the potential publication bias in the present meta-analysis. All statistical tests were conducted using STATA 12.0 software (Stata Corporation, College Station, Texas).

## RESULTS

### Characteristics of included studies

A flow chart displaying the process of selection study or exclusion study is shown in Figure 1. 11 relevant case-control studies were included in this meta-analysis, involving 2010 psoriasis cases and 1881 healthy controls [9-19]. The publication year ranged from 2000 to 2018. The characteristics of the included studies and genotype distributions are summarized in Table 1.

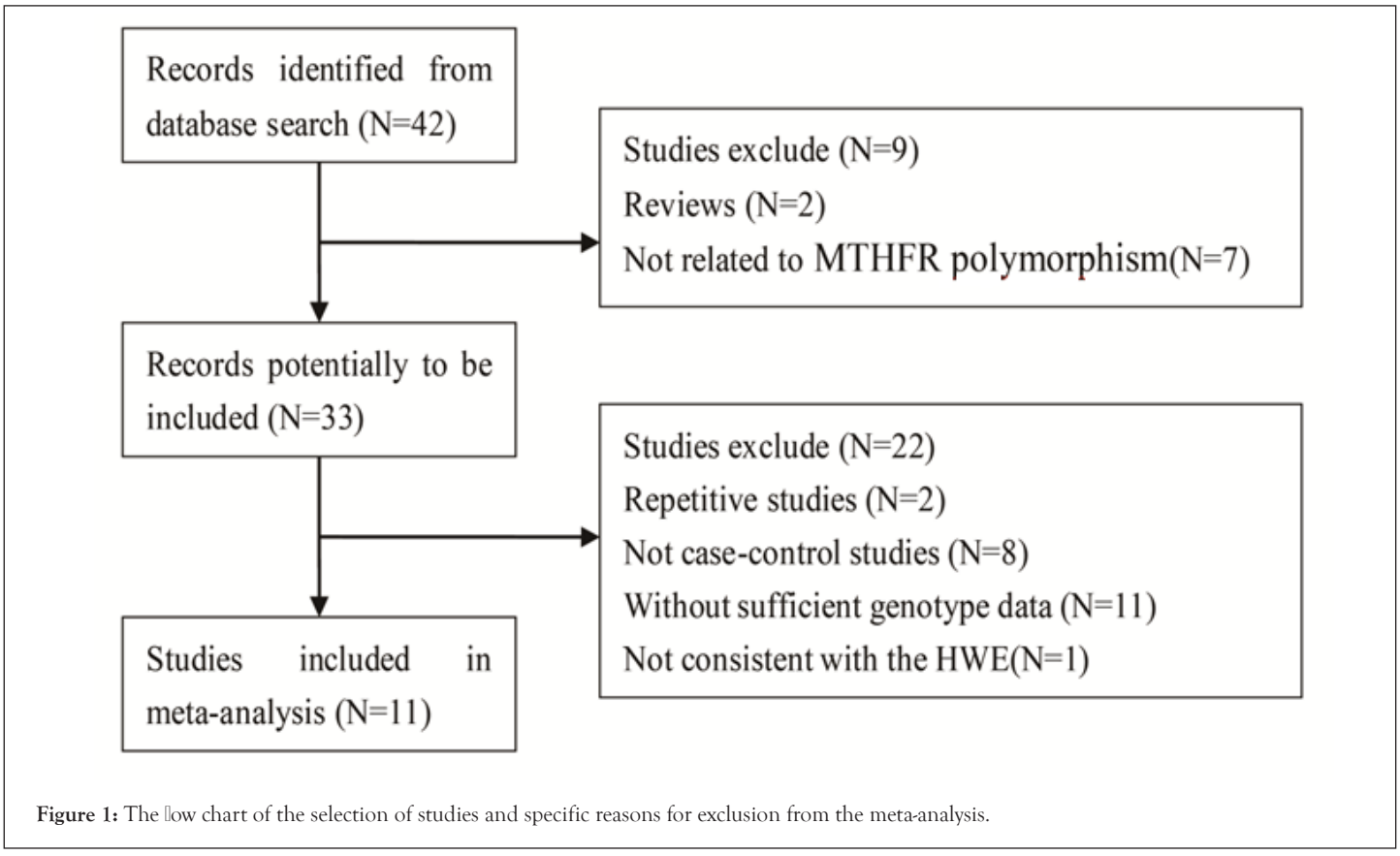


**Figure 1:** The flow chart of the selection of studies and specific reasons for exclusion from the meta-analysis.

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

| Study | Year | Country | Ethnicity | Case | | | Control | | | HWE |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | CC | CT | TT | CC | CT | TT | |
| Baiqiu [16] | 2000 | China | Asian | 8 | 19 | 12 | 26 | 43 | 10 | 0.23 |
| Jie | 2007 | China | Asian | 26 | 59 | 38 | 21 | 73 | 35 | 0.099 |
| Weger [14] | 2008 | Austria | European | 133 | 130 | 47 | 110 | 108 | 29 | 0.752 |
| Vasku [10] | 2009 | Czech | European | 195 | 175 | 40 | 90 | 125 | 29 | 0.147 |
| Dehui [18] | 2012 | China | Asian | 60 | 34 | 14 | 42 | 47 | 13 | 0.979 |
| Liew [11] | 2012 | Malaysia | Asian | 159 | 41 | 0 | 125 | 40 | 2 | 0.543 |
| Xiao-bing | 2014 | China | Asian | 65 | 39 | 16 | 43 | 45 | 12 | 0.966 |
| Asefi [12] | 2014 | Iran | Asian | 50 | 43 | 7 | 64 | 35 | 1 | 0.108 |
| Kilic [15] | 2016 | Turkey | European | 32 | 42 | 10 | 207 | 5 | 0 | 0.862 |
| Izmirli [9] | 2016 | Turkey | European | 34 | 46 | 16 | 39 | 35 | 3 | 0.152 |
| Luo [13] | 2018 | China | Asian | 210 | 169 | 41 | 279 | 129 | 16 | 0.821 |

**Note:** HWE: Hardy-Weinberg Equilibrium.

## Meta-analysis results

Q-test and the $I^2$ test indicated there is obvious heterogeneity between studies in the comparisons of T *vs.* C, TT *vs.* CC, TC *vs.* CC, TT+TC *vs.* CC and TT *vs.* TC+CC (P<0.1 or $I^2$>50%) (Table 2 and Figure 2). Therefore, we used the random effects model to calculate the results. The results of meta-analysis showed that there was no association between *MTHFR* 677C/T polymorphism and psoriasis in the comparisons of T *vs.* C, TT *vs.* CC, TC *vs.* CC and TT+TC *vs.* CC, but a significant association in the comparison of TT *vs.* TC+CC (OR=1.69, 95% CI=1.09-2.61, P=0.020) (Table 2 and Figure 2).

## Subgroup analysis

In the subgroup analysis, the included studies were divided into Asian and European populations based on ethnicity. In Asian populations, the results of meta-analysis showed that there was no association between *MTHFR* 677C/T polymorphism and psoriasis in the comparisons of T *vs.* C, TT *vs.* CC, TC *vs.* CC and TT+TC *vs.* CC, but significant association in the comparison of TT *vs.* TC+CC (OR=1.64, 95%CI=1.01-2.67, P=0.046) (Table 2 and Figure 2). In European populations, the results of meta-analysis showed that there was no association between *MTHFR* 677C/T polymorphism and psoriasis in the comparisons of TT *vs.* CC, TC *vs.* CC, TT+TC *vs.* CC and TT *vs.* TC+CC, but a significant association in the comparison of T *vs.* C (OR=2.57, 95%CI=1.02-6.48, P=0.046) (Table 2 and Figure 2).

## Publication bias

Egger's test and Begg's funnel plot (Figure 3) suggested that there was a lack of significant publication bias in all genetic models (all P>0.05).

## Sensitivity analysis

The sensitivity analysis was carried out by sequentially excluding a single individual study. The results were not significantly altered in all genetic models (Figure 4), indicating the stability of our results.

**Table 2:** Meta-analysis of the association between *MTHFR* 677C/T polymorphism and psoriasis susceptibility.

| Comparison | OR | 95%CI | P-value | Heterogeneity | | $P_{Begg's}$ | $P_{Egger's}$ |
|---|---|---|---|---|---|---|---|
| | | | | I2 | P-value | | |
| T *vs.* C | 1.44 | 1.00-2.09 | 0.051 | 91.20% | 0 | | |
| Asian | 1.14 | 0.81-1.60 | 0.455 | 81.70% | 0 | P>0.05 | P>0.05 |
| European | 2.57 | 1.02-6.48 | 0.046 | 96.30% | 0 | | |
| TT *vs.* CC | 1.76 | 0.97-3.19 | 0.063 | 77.60% | 0 | | |
| Asian | 1.54 | 0.75-3.13 | 0.239 | 70.80% | 0.002 | P>0.05 | P>0.05 |
| European | 2.66 | 0.78-9.10 | 0.119 | 87.00% | 0 | | |
| TC *vs.* CC | 1.27 | 0.79-2.03 | 0.331 | 89.70% | 0 | | |
| Asian | 0.93 | 0.61-1.44 | 0.761 | 77.50% | 0 | P>0.05 | P>0.05 |
| European | 2.43 | 0.74-8.04 | 0.145 | 95.80% | 0 | | |
| TT+TC *vs.* CC | 1.41 | 0.87-2.31 | 0.165 | 91.20% | 0 | | |
| Asian | 1.03 | 0.65-1.62 | 0.898 | 81.50% | 0 | P>0.05 | P>0.05 |
| European | 2.76 | 0.81-9.42 | 0.105 | 96.40% | 0 | | |
| TT *vs.* TC+CC | 1.69 | 1.09-2.61 | 0.02 | 65.10% | 0.001 | | |
| Asian | 1.64 | 1.01-2.67 | 0.046 | 50.80% | 0.058 | P>0.05 | P>0.05 |
| European | 2.12 | 0.80-5.58 | 0.128 | 80.60% | 0.001 | | |

**Note:** OR: Odds Ratio; CI: Confidence Interval.


**Figure 2:** Forest plot for the association between the *MTHFR* 677C/T polymorphism and psoriasis susceptibility: T *vs.* C (A), TT *vs.* CC (B), TC *vs.* CC (C), TT+TC *vs.* CC (D), TT *vs.* TC+CC (E). CI: Confidence Interval; OR: Odds Ratio.

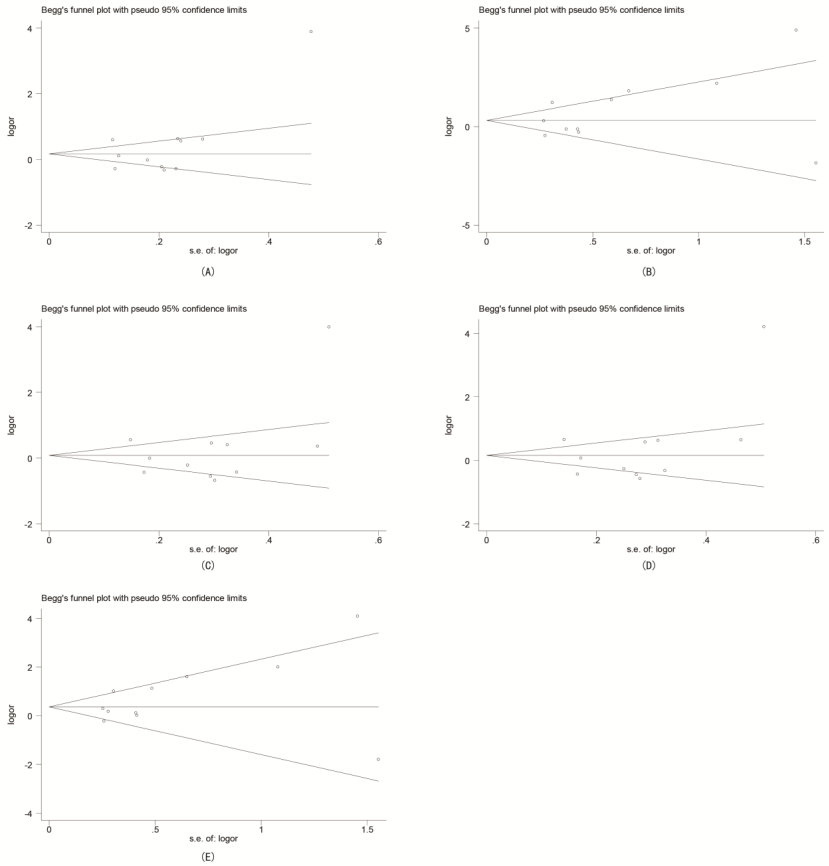


**Figure 3:** Begg's funnel plot test of publication bias for the association between the *MTHFR* 677C/T polymorphism and psoriasis susceptibility: T *vs.* C (A), TT *vs.* CC (B), TC *vs.* CC (C), TT+TC *vs.* CC (D), TT *vs.* TC+CC (E).

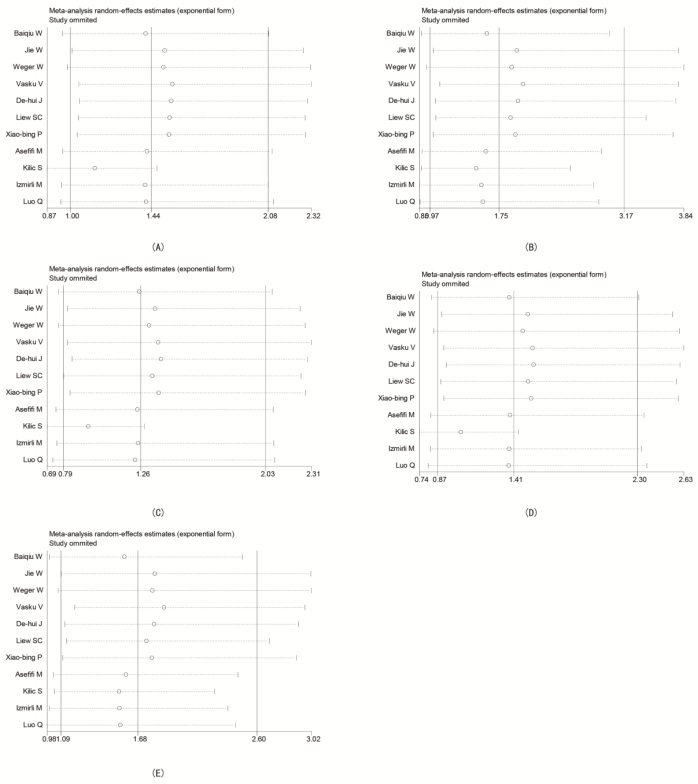


**Figure 4:** Sensitivity analysis of the summary Odds Ratio (OR) on the association between the *MTHFR* 677C/T polymorphism and psoriasis susceptibility: T *vs.* C (A), TT *vs.* CC (B), TC *vs.* CC (C), TT+TC *vs.* CC (D), TT *vs.* TC+CC (E).

## DISCUSSION

The precise etiology of psoriasis is yet unclear, genetic predisposition, cell-mediated adaptive immune response, cigarette smoking, and other as-yet-unidentified psychosocial factors appear to interact or operate singly in the disease. Recent advances in the large-scale analysis of human genetic loci have generated valuable insights into possible genetic contributions to psoriasis. Many susceptibility genes or loci have been identified for psoriasis by the wide application of Genome-Wide Association Studies (GWASs) [20].

*MTHFR* C677T polymorphism has been studied with conflicting results regarding its potential value for psoriatic patients. Although two meta-analysis was performed in 2015 to investigate the association between *MTHFR* 677C/T polymorphism and psoriasis risk, no significant relationship between *MTHFR* 677C/T polymorphism and psoriasis risk was found [21,22]. In addition, there were only 5 studies and 7 studies in these two meta-analyses, respectively. Due to the emergence of novel studies, an updated meta-analysis on recent evidences is necessarily needed.

In our present meta-analysis, there were 11 studies, 2010 cases and 1881 controls that we evaluated for the possible association between *MTHFR* 677C/T polymorphism and psoriasis risk. Our results indicate that *MTHFR* C677T polymorphism does not correlate with the risk of psoriasis in the comparisons of T *vs.* C, TT *vs.* CC, TC *vs.* CC and TT+TC *vs.* CC under the random-effect model, but there is a significant relationship with susceptibility of psoriasis in the comparison of TT *vs.* TC+CC under the random-effect model, which indicates that TT genotype might increase psoriasis risk than either CC or TC genotype. Subgroup analysis by ethnicity was conducted with the ethnicity being primarily defined as Asian and European. Stratified analysis indicated that *MTHFR* 677C/T polymorphism was associated with increased psoriasis risk in Asian under the recessive model (TT *vs.* TC+CC, OR=1.64, 95%CI=1.01-2.67, P=0.046) and in European under the allelic model (T *vs.* C, OR=2.57, 95% CI=1.02-6.48, P=0.046). Our meta-analysis showed strong evidence to support a connection between the *MTHFR* 677C/T polymorphism and psoriasis risk when compared to earlier meta-analysis [21,22].

The *MTHFR* C677T polymorphism has been implicated in the pathogenesis of esophageal cancer [23], hypertension [24], psychiatric disorders [25], and cervical artery dissections [26]. However, it has not been linked to prostate cancer [27], lung cancer [28], polycystic ovary syndrome [29], osteoporotic fractures [30], open-angle glaucoma [31] and ovarian cancer [32]. When taken as a whole, the findings show that various diseases develop along distinct pathological pathways, and that *MTHFR*'s roles in various pathologies are influenced by the genes it targets.

Additionally, the *MTHFR* C677T polymorphism may, to some extent, quantitatively reflect the severity of psoriasis. According to a cross-sectional study by Karabacak, et al. [33], there may be a link between the *MTHFR* polymorphism and the severity of psoriasis.

In summary, the *MTHFR* C677T polymorphism is a genetic factor in the etiology of psoriasis and may, to some extent, reflect the severity of the disease.

Some advantages were found in our meta-analysis. First, publication bias, a substantial problem for the credibility of the research, was not found in the analysis. Second, the sensitivity analysis suggested that the results were robust. Third, by adding additional studies, we expanded the number of pooled samples. All above-mentioned advantages revealed that the results were relatively reliable. However, some unavoidable limitations of our meta-analysis should not be ignored. First, the results show that there is obvious heterogeneity between the studies, which indicates that there may be ethnic differences in the subjects' genetic background and living environment. Second, the publications included were limited to Asian and European populations, so future work should study other populations. Third, gene linkage effects and gene-environment interaction effects were not analyzed.

## CONCLUSION

Our meta-analysis demonstrated that *MTHFR* 677C/T polymorphism might be associated with increased psoriasis risk. TT genotype might increase psoriasis risk in Asian. Allele might increase psoriasis risk in European. Larger and well-designed studies are still needed to verify these results.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## AUTHORS' CONTRIBUTION

Gang Nie conceived and designed this study. Junhua Qi and Yu Zhang conducted the systematic literature review. Lvya Zhang performed data analyses. Junhua Qi drafted the manuscript. Gang Nie revised manuscript critically. All authors reviewed the manuscript.

## AVAILABILITY OF DATA AND MATERIALS

All the data available upon request to the corresponding author.

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