Systematic Review and Meta-Analysis

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5HTTLPR polymorphism and postpartum depression risk

A meta-analysis

Jianming Li, PhD[a,b,c], Yongjun Chen, PhD[c], Qin Xiang, PhD[a,b], Ju Xiang, PhD[a,b], Yonghong Tang, PhD[c,*], Liang Tang, PhD[a,b,*]

Abstract

Objective: Postpartum depression (PPD) is an episode of major depressive disorder that affecting women of childbearing age. 5-HTTLPR is 1 of the most extensively investigated polymorphisms in PPD. However, the previous results were inconsistent and inclusive. Hence, we performed a meta-analysis to precisely evaluate the association between 5-HTTLPR polymorphism and PPD susceptibility.

Methods: The studies were retrieved through databases including PubMed, web of science, EMASE, and CNKI. The odd ratios (ORs) and 95% confidence interval (CIs) were applied for evaluating the genetic association between 5-HTTLPR (L/S) polymorphism and PPD risk.

Results: Six studies with 519 cases and 737 controls were enrolled in the present study. The frequencies of allelic (OR = 0.72, 95% CI = 0.60–0.85, $P = .0001$) and dominant (OR = 0.57, 95%CI = 0.44–0.73, $P = .004$) models of 5-HTTLPR polymorphism significantly decreased in patients with PPD than those in the healthy controls. Subgroup analysis based on ethnicity revealed that the allelic (OR = 0.71, 95%CI = 0.60–0.85, $P = .0001$) and dominant (OR = 0.51, 95%CI = 0.32–0.79, $P = .003$) models of 5-HTTLPR polymorphism were significantly associated with PPD risk in Asian population ($P > .05$). No evidence was observed between the recessive model of 5-HTTLPR polymorphism and PPD risk ($P > .05$).

Conclusions: The allelic and dominant models of 5-HTTLPR polymorphism might be protective factors for PPD. To confirm these results, larger number of association studies or multicenter case–control studies are necessary in the future.

Abbreviations: CI = confidence interval, L = long allele, OR = odd ratio, PPD = postpartum depression, S = short allele.

Keywords: 5-HTTLPR, asian, polymorphism, postpartum depression

Editor: Wen-Jun Tu.

JL and YC contributed equally to this work.

The present study was funded by the National Natural Science Foundation of China (Grant No. 81873780, 61702054); Hunan Natural Science Foundation Youth Program (2019JJ50697, 2018JJ3568); The Changsha Outstanding Innovative Young People Training Scheme (kq1905047, kq1802024); The Foundation of the Education Department of Hunan Province (19A058, 19B072); The Foundation of Health and Family Planning Commission of Hunan Province (20201918); The Application Characteristic Discipline of Hunan Province; The Hunan Key Laboratory Cultivation Base of the Research and Development of Novel Pharmaceutical Preparations (No. 2016TP1029); The clinical research center of neurodegenerative diseases in Hunan province (2018SK4002); The Hunan Provincial Innovation Platform and Talents Program (No. 2018RS3105); The Hunan provincial science and technology department and hunan provincial health and family planning commission (Grant No.[2018]85); The Natural science foundation of hunan province (Grant No.[2017]1); The Key project of hunan provincial commission of health and family planning (Grant No.[2017]144); The hunan province science and technology major project (Grant No. [2016]158); Hunan Provincial Science and Technology Department Clinical Medical Technology Innovation Guide Project (2018SK51711).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

[a] Department of Anatomy, Changsha Medical University, [b] Department of Rehabilitation, Xiangya Boai Rehabilitation Hospital, Changsha, [c] Department of Neurology, Nanhua Affiliated Hospital, University of South China, Hengyang, China.

[*] Correspondence: Liang Tang, Department of Anatomy, Changsha Medical University, Changsha 410219, China (e-mail: tlcool318@163.com); Yonghong Tang, Department of Neurology, Nanhua Affiliated Hospital, University of South China, Hengyang 421001, China (e-mail: tyh6246@163.com).

How to cite this article: Li J, Chen Y, Xiang Q, Xiang J, Tang Y, Tang L. 5HTTLPR polymorphism and postpartum depression risk: a meta-analysis. Medicine 2020;99:39(e22319).

Received: 18 January 2020 / Received in final form: 4 August 2020 / Accepted: 20 August 2020

http://dx.doi.org/10.1097/MD.0000000000022319

1. Introduction

Postpartum depression (PPD), characterized by depression, restlessness and irritability, is a serious emotional disorder either during pregnancy or within the first 6 months postpartumis. The incidence of PPD is 9.2% to 15.0% in Chinese population and 3.5% to 33.0% in other populations.[1–3] Untreated and unresolved PPD leads to ramifications for the affected individual, their infant as well as their relationship with family members. Published reports have shown that physiological, psychological, individual characteristics such as lower serum 25[OH]D levels,[4] social factors and genetic factors may be important factors leading to PPD.[5–8] However, the exact mechanism of PPD is far from known.

Recent study has suggested that the serotonin (5-HT) system is involved in the pathogenesis of depression.[9] And the serotonin transporter (5-HTT) is located on its presynaptic membrane.[10] 5-HTTLPR, a 5-HTT-based functional polymorphism site, is a promoter-linked polymorphic region. It was revealed that the transcriptional activity may be regulated by this polymorphism in human.[11,12] The 5-HTTLPR gene polymorphism is consisted of 2 alleles, the short allele (S) and the long allele (L), formed by a 44-base pair insertion or deletion.[13] This polymorphism has been reported to affect the expression level of serotonin transporter in human, thereby affect the synaptic serotonin concentration in neurons.[14,15]

Several studies have shown that 5-HTTLPR may contribute to the occurrence of PPD, while the results were inconclusive. Zhang et al has shown that the L/L genotype of 5-HTTLPR polymorphism may reduce the risk of PPD in Chinese population.[16] However, Khabour et al has suggested that 5-HTTLPR (L/S) was not the susceptible factor for the development of PPD in Jordanian women.[17] Similar results were observed in other populations.[18,19]

Considered the inconsistent and inclusive results in individual studies, we conducted on a meta-analysis by including case-control studies in the electric databases to obtain more precise results of the genetic association between the 5HTTLPR polymorphism and PPD risk in the present study.

2. Methods

2.1. Patient and public involvement

There was no patient and public involvement in present meta-analysis. An ethical approval is not necessary for a meta-analysis.

2.2. Literature search strategy

The present study was accorded to the Cochrane collaboration definition and Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines for meta-analysis and systematic review.[20] Literature search was performed in databases including PubMed, web of science, EMASE, and CNKI. The searching terms were used as following: "serotonin transporter gene-linked polymorphic region" or "5HTTLPR" or "Solute Carrier Family 6 (Neurotransmitter Transporter), Member 4" or "solute carrier family 6" and "polymorphism" or "variant" or "single nucleotide polymorphism" or "single nucleotide polymorphism" and "postpartum depression" or "PPD." No years and language were limited. The latest day was May 20, 2019. Related literature was retrieved manually.

2.3. Eligibility criteria

Inclusion criteria

(1) Cases-control designed study.
(2) The data of genotypes were available in case and control populations.
(3) Evaluated the association between 5HTTLPR (L/S) polymorphism and PPD risk.

Exclusion criteria

(1) Duplication, review, conference abstract, letter, case report.
(2) Unavailable genotype frequencies in case and control populations.

2.4. Data extraction and quality assessment

Xiang Q and Xiang J independently screened the included studies according to the eligibility criteria. The essential information including the first name of author, publication year, ethnicity, mean ages, genotyping methods, diagnostic criteria of PPD, number of cases and controls, state of Hardy-Weinberg Equilibrium in controls was extracted. Disagreement was solved by discussion. Newcastle-Ottawa Scale was used to evaluate the quality of individual study.[21] A study with a score of ≥6 was enrolled in the present study.

2.5. Methods for quantitative synthesis

STATA 12.0 (StataCorp, College Station, TX) and Revman 5 (Cochrane Collaboration, London, UK) software were used in quantitative synthesis. The pooled odd ratios (ORs) and 95% Confidence interval (CI) of the allelic (L vs S), dominant (LS + LL vs SS) and recessive (LL vs LS + SS) models of 5HTTLPR polymorphism and PPD risk were evaluated by Z test. $P < .05$ was significant difference. The statistical heterogeneity between studies was evaluated by a chi-square-based Cochran Q test and Higgins I-squared statistic. $I^2\% > 50\%$ or $P < .05$ indicated significant heterogeneity. A random or fixed model was used to calculate the ORs and the 95% CIs. An I^2 value more than 50% was regarded as significant heterogeneity among these studies and a random-effect model (Mantel-Haenszel) was used. Otherwise, a fixed model was used. Subgroup analysis was conducted on ethnicity of Asian and Caucasian. Sensitivity analysis which excluded the influence of a single study on the overall risk estimate by excluding one study at a time was confirmed. Begg funnel plots and Egger regression test were used to evaluate publication bias ($P < .05$ suggests bias).

3. Results

3.1. The characters of eligible studies

The Figure 1 has shown the flowchart of searching the publications through the databases. A total of 672 publications were retrieved. After screening the title, abstract, and context of each study, 247 were excluded for being duplicated records. 302 were excluded for being irrelevant articles. 117 were removed for being abstract, meeting, letters or reviews. Finally, 6 studies involving 519 patients with PPD and 737 healthy controls investigating the relationship between the 5HTTLPR polymorphism and PPD risk in all ethnic groups were enrolled in the present meta-analysis[16–19,22,23] (Fig. 1). Among these studies, 5

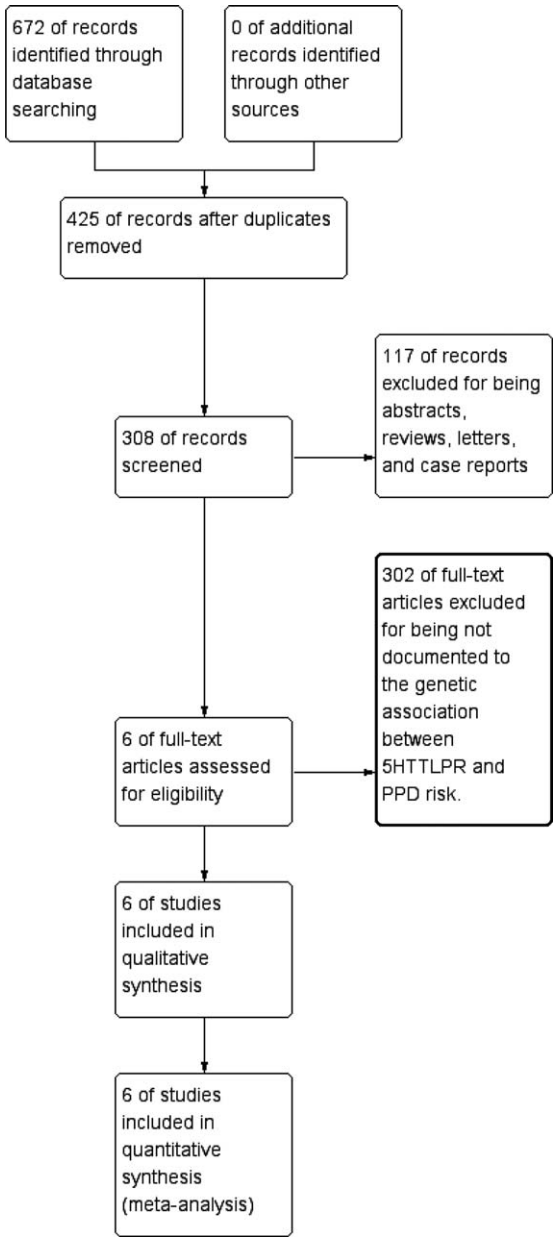

Figure 1. PRISMA flow chart of studies inclusion and exclusion. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

were in Asian, 1 was in Caucasian. The Newcastle-Ottawa Scale scores of the included studies were higher than 6 (Table 1 and Table s1, Supplemental Digital Content, http://links.lww.com/MD/E909).

3.2. Combined results

As presented in Table 2, the frequencies of the L allele (OR = 0.72, 95%CI = 0.60–0.85, $P = .0001$) and dominant (OR = 0.57, 95% CI = 0.44–0.73, $P = .004$) models of 5HTTLPR polymorphism were significantly lower in PPD population than those in the control group. No evidence supported the association between the recessive model of 5HTTLPR polymorphism and PPD susceptibility ($P > .05$) (Fig. 2).

The effect of the 5HTTLPR polymorphism on PPD was further evaluated using stratification analysis on ethnicity. In the 5 studies consisting of 504 cases and 624 controls, the L allele (OR = 0.71, 95%CI = 0.60- 0.85, $P = .0001$) and dominant (OR = 0.51, 95%CI = 0.32–0.79, $P = .003$) models of 5HTTLPR polymorphism significantly decreased PPD risk in Asian population (Table 2).

3.3. Test for heterogeneity

Significant between-study heterogeneity existed in the dominant model of 5HTTLPR polymorphism ($I^2\% = 58\%$, $P = .03$). However, this significant difference of heterogeneity was detected only in Asian population ($I^2\% = 63\%$, $P = .03$) in the subgroup analysis based on ethnicity. These heterogeneities in overall and subgroup analysis were conducted by Xiu et al[18] and Peng et al[22] After removal of these 2 studies, the significant between-study heterogeneity disappeared ($I^2\% = 29\%$, $P = .24$), which indicate these 2 studies may mainly influence the results (Table 2).

3.4. Sensitive analysis and publish bias

The data showed that no individual study altered the pooled ORs qualitatively, which provided the evidence of the stability of the meta-analysis (Fig. 3). The shape of Begg funnel plots and Egger linear regression tests showed no publication bias (Fig. 4, Table 3).

4. Discussion

The level of serotonin in the synaptic cleft of neurons and the function of serotonin receptor plays an important role in the pathological process of depression, but whether the function is aggressive or low is still inconclusive.[24,25] The 5-HTT gene is a key factor in affecting risk of depression and other psychiatric

Table 1

The characters of included studies.

First author	Year	Ethnicity	Age (case/control)	Genotyping methods	Diagnostic criteria	Case (LL/LS/SS)	Control (LL/LS/SS)	NOS
Khabour	2013	Jordanian	NA	PCR-RFLP	EPDS > 13	36/59/35	62/124/54	6
Liu	2016	Chinese	28.8 ± 5.1/29.8 ± 4.4	PCR-RFLP	EPDS > 11	33/53/69	39/70/36	7
Peng	2015	Chinese	26.5 ± 3.2/27.1 ± 2.9	PCR-RFLP	EPDS > 15	16/12/32	12/34/14	7
Zhang	2014	Chinese	28.0 ± 4.47/NA	PCR-RFLP	EPDS > 15	2/9/28	3/19/17	7
Zhang	2015	Chinese	28.57 ± 6.8/26.18 ± 7.2	PCR-RFLP	EPDS > 15	5/46/69	19/47/74	7
Zimmermann-Peruzatto	2012	Brazilian	NA	PCR-RFLP	BDI > 18	3/10/2	37/57/19	7

BDI = Beck depression inventory, EPDS = Edinburgh Postnatal Depression Scale, L = long allele, NA = not available, NOS = Newcastle–Ottawa Scale, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, S = short allele.

Table 2

The association between 5HTTLPR polymorphism and PDD risk.

Genetic models	Subgroups	Number of studies	Test of association				Test of heterogeneity	
			OR	95% CI	*P*-value	Model	*P* value	I^2 (%)
Allelic	Total	6	0.72	[0.60, 0.85]	.0001	F	.23	27
	Asian	5	0.71	[0.60, 0.85]	.0001	F	.15	40
	Caucasian	1	0.83	[0.39, 1.78]	.63	–	–	–
Dominant	Total	6	0.57	[0.44, 0.73]	.004	R	.03	58
	Asian	5	0.51	[0.32, 0.79]	.003	R	.03	63
	Caucasian	1	1.31	[0.27, 6.30]	.73	–	–	–
Recessive	Total	6	0.82	[0.61, 1.10]	.19	F	.14	39
	Asian	5	0.84	[0.62, 1.14]	.27	F	.10	48
	Caucasian	1	0.51	[0.14, 1.93]	.32	–	–	–

– = not available, CI = confidence interval, F = fixed model, OR = odds ratio, R = random model.

conditions.[26,27] The human 5-HTT gene (also known as solute carrier family 6) is located on chromosome 17q11.1-q12. 5HTTLPR is located about 1 kb upstream of the 5HTT gene transcriptional promoter, and contains a 44 base pair insertion (L allele) or deletion (S allele). Studies have shown that the S allele has lower transcriptional activity than the L allele and carriers of the S allele are more likely to fall into a state of long-term alertness, threatening and reflection, increasing their susceptibility to affective disorders.[28,29] A previous study has reported that the 5-HTTLPR was a susceptible factor for the onset of depression after PM implantation.[30] Many reports have revealed that the 5HTTLPR polymorphism was associated with schizophrenia,[31] personality traits,[32] mood disorders,[33] obsessive-compulsive disorder,[34] generalized anxiety[35] and depression,[36] while the results were inconclusive. Inconsistent results were also found between the 5HTTLPR polymorphism and PPD susceptibility.

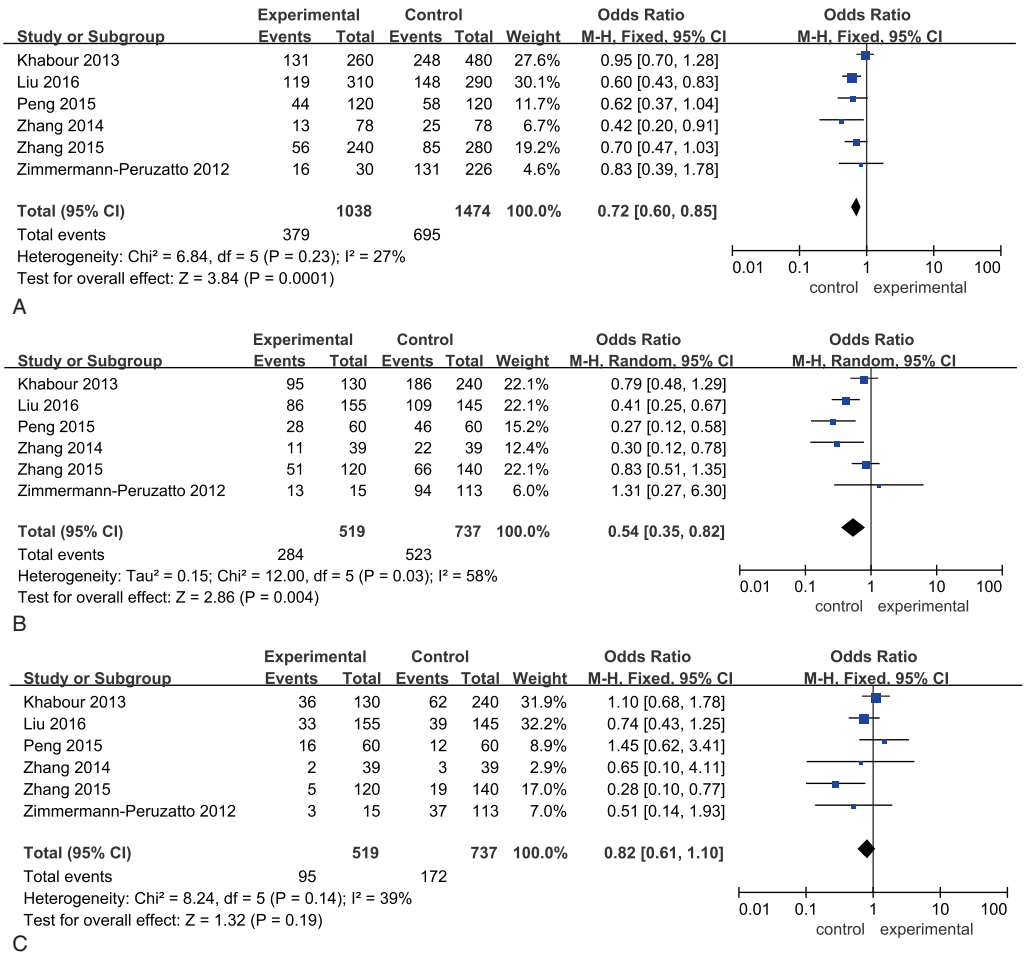

Figure 2. Forest plots of odds ratios for the association between 5HTTLPR and PPD. A: allelic model; B: dominant model; C: recessive model.

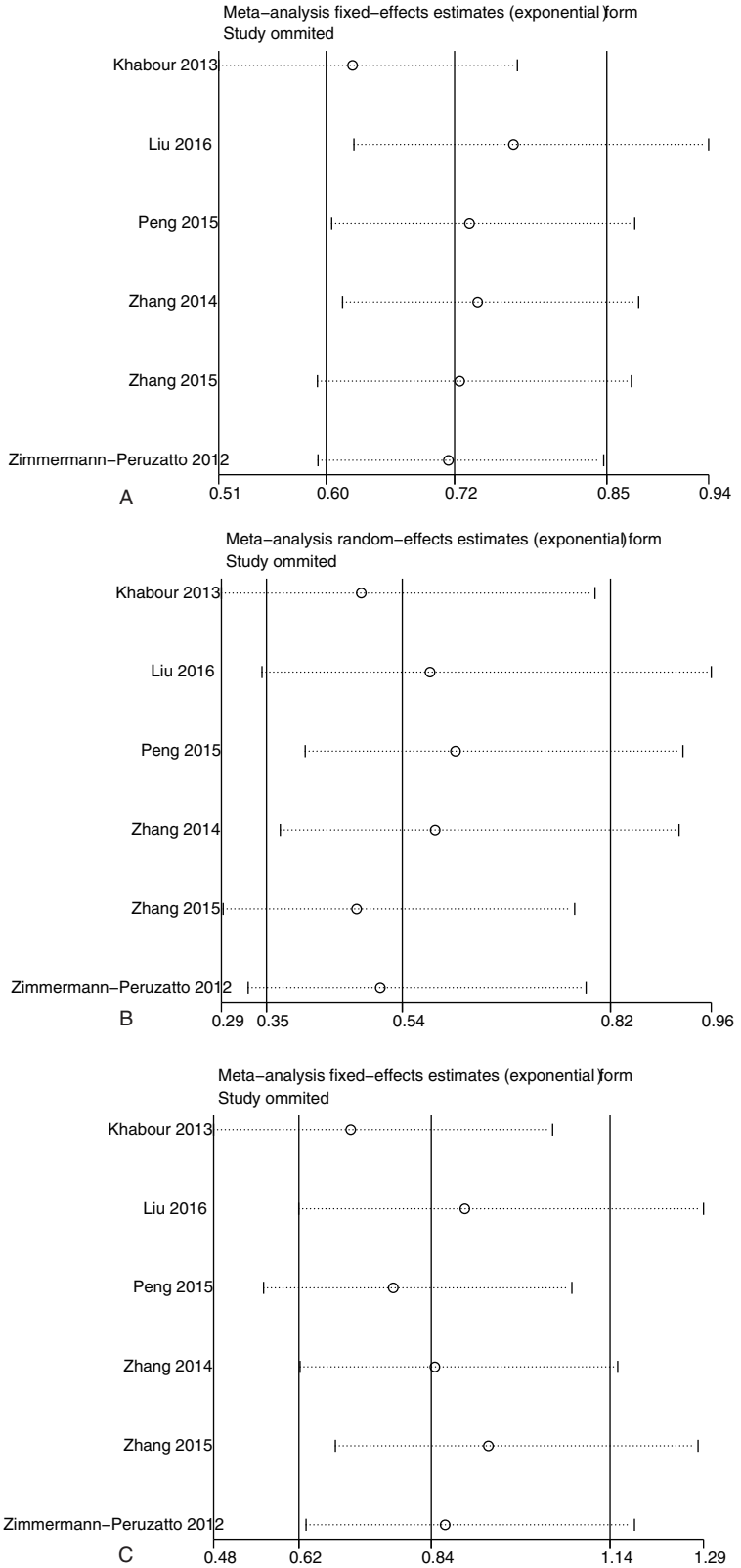

Figure 3. Sensitivity analyses between 5HTTLPR and PPD. A: allelic model; B: dominant model; C: recessive model.

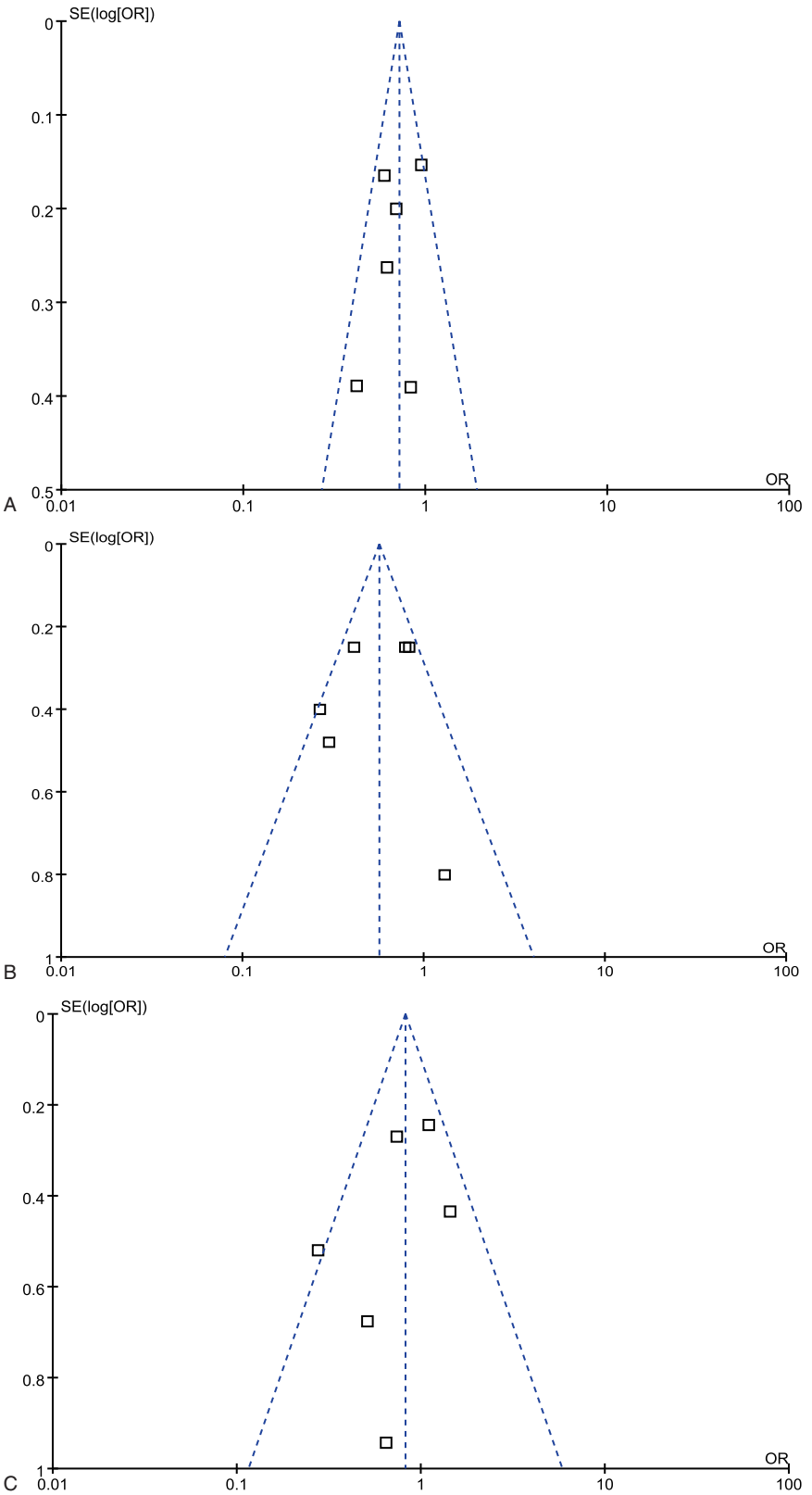

Figure 4. Publication bias of literatures for 5HTTLPR were tested by Begg funnel plot and Egger test. A: allelic model; B: dominant model; C: recessive model.

Table 3

Begg test and Egger test for funnel plot asymmetries of 5HTTLPR (L/S).

Polymorphism (minor allele)	Genetic model	Number of studies	P_{egger}	P_{begg}
5HTTLPR (L)	Allelic	6	.388	.707
	Dominant	6	.690	.452
	Recessive	6	.376	.452

Among the six included articles, only one study showed that the distribution of SS + SL genotype was higher in the case group than that in the control group. While others were in the opposite. The results of the 3 publications conducted by Zhang et al.,[22] Peng et al,[23] and Xiu et al[19] have revealed that the distribution of SS + SL genotype in control group was significantly higher than that in the case group. Therefore, we could not simply draw to the conclusion that the S allele or L allele is a predisposing factor for PPD.

Racial differences among different subjects may be one of the major factors that influence the relationship of 5HTTLPR polymorphism with PPD. Subgroup analyses based on ethnicity has shown the significant association was only within Asian population. Different genetic background in the susceptibility to diseases may contribute to this inconsistent. Notable, only 1 study was conducted in Caucasian population. To confirm this result, lager number of subjects from multiple ethnicity is necessary in the future. In addition, the effects of psychology, physiology, and social environment on PPD should be considered. Nervousness and anxiety due to lack of knowledge about childbirth, the sex of the fetus, and the attitude of husband and family may cause a certain degree of mental burden on the mother.

Limitations should be considered. First, the number of study and subject included in the present study was relatively small, especially in Caucasian population, which may reduce the calculation power. Second, previous studies have adopted different criteria for the diagnosis of PPD, which may be an important influencing factor for the association between 5HTTLPR polymorphism and PPD. Thirdly, further subtle adjusted analysis such as age, smoking, environmental factors, and other lifestyle, should be carried out if more detailed individual information was available.

In conclusion, our meta-analysis supports that the allelic and dominant models of 5HTTLPR polymorphism might be protective factors for PPD in Asian. However, our results need to be confirmed by case–control studies with larger number of subjects.

Author contributions

Data curation: Yongjun Chen, Qin Xiang, Ju Xiang.
Formal analysis: Yongjun Chen, Qin Xiang, Ju Xiang.
Funding acquisition: Yonghong Tang, Liang Tang.
Methodology: Yongjun Chen, Qin Xiang, Ju Xiang.
Project administration: Yonghong Tang.
Software: Qin Xiang, Ju Xiang.
Writing – original draft: Liang Tang.
Writing – review & editing: Yonghong Tang, Liang Tang.

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