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The Association between the Serotonin Transporter Promoter (5-HTTLPR) Polymorphism and Panic Disorder: A Meta-Analysis of Case-Control Studies

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Abstract

Background: Case-control studies have reported the association between 5-HTTLPR polymorphism and panic disorder (PD) risk. However, the results are inconclusive and conflicting. To investigate the genetic association of 5-HTTLPR polymorphism and PD risk, we conducted a comprehensive meta-analysis based on previous case-control studies.

Methods: A literature search was performed through PubMed, Embase, the Cochrane Library, and Web of Science databases until March 2024. The strength of the association was assessed by relative risk (RR) and its corresponding 95% confidence interval (CI). A fixed or random effect model was selected based on the results of the heterogeneity test. Further, subgroup analyses were conducted to explore the association of 5-HTTLPR polymorphism and PD risk in different populations.

Results: 14 studies with 2280 PD cases and 2640 healthy controls were identified. Although there was a significant association between 5-HTTLPR polymorphism and PD risk, the significance did not exist after subgroup analyses, either in Asians or Caucasians. In addition, the association between 5-HTTLPR polymorphism and the risk of PD comorbidity with agoraphobia was not observed in the current study.

Conclusions: Our present meta-analysis does not support a direct effect of 5-HTTLPR polymorphism on PD risk as well as the risk for PD comorbidity with agoraphobia according to present results. Further analyses of the effect of genetic networks and more well-designed studies with larger sample sizes are required.

Keywords: 5-HTTLPR polymorphism; panic disorder; agoraphobia; meta

Introduction

Panic disorder (PD), a common psychological problem, is a debilitating anxiety disorder affecting around 5% of the population [1]. The core symptom of PD is re-occurring panic attacks, sudden episodes of intense fear or discomfort along with a number of bodily symptoms, such as palpitations, shortness of breath, numbness, and dizziness [2]. Panic attacks are associated with several comorbid psychiatric and non-psychiatric conditions such as anxiety, depression [3], cardiovascular diseases [4], and impairment of social, work, and family functioning [5]. Agoraphobia is a strong fear or anxiety provoked by real or anticipated exposure to a wide range of situations and is often associated with panic disorder. As such, their etiology has been, and continues to be, a major target of investigation.

PD has been shown to be hereditary [6], but the genes responsible for the disease still remain to be elucidated. A meta-analysis showed genetic factors explain approximately 43% of the variance in the PD, indicating an important role in the pathological PD [6]. Several genes have been studied in relation to panic disorder. These include genes involved in serotonergic signaling, such as the serotonin transporter, several serotonergic receptors, and genes involved in the production and degradation of serotonin. Previous studies have consistently demonstrated serotonin involvement in the neurobiology of PD [7, 8]. The serotonin (5-HT) transporter (5-HTT) gene has been extensively screened for polymorphic variants. The 5-HTT gene-linked polymorphic region (5-HTTLPR), located in the promoter region, has been identified as a functional polymorphism. The polymorphism consists of a 44-base pair (bp) insertion or deletion involving repeat elements 6 to 8 [9]. In vitro, the basal activity of the long (L) variant was found to be more than twice that of the short (S) one in 5-HTT mRNA synthesis and 5-HTT expression [9]. These two different transcriptional efficiencies suggest that 5-HTT gene transcription is modulated by 5-HTTLPR genetic variants. Although an association of panic disorder to functional length polymorphism in 5-HTTLPR has been proposed [10], some association studies have reported no significant difference in 5-HTTLPR allele frequencies between patients with PD and controls [11-14] even in a previous meta-analysis conducted in 2007 showing no evidence to support an association between 5-HTTLPR and PD [15]. Nonetheless, recent studies suggested that 5-HTTLPR polymorphism may be a predictor of response to sertraline in the treatment of PD [16] and the interaction effect between 5-HTTLPR and separation life events on panic disorder and its potential endophenotype was observed [17].

Given that these inconsistent findings suggest functional participation of serotonergic gene polymorphisms in PD, a meta-analytic treatment of the data is timely, particularly as many research groups have begun to search for an “anxiety gene”.

Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18], involving a systematic process that encompassed a thorough literature search, meticulous organization of review documents, rigorous assessment of the quality of each empirical study, comprehensive data synthesis, and meticulous report writing. Additionally, our meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42024529340).

Literature Search

We systematically conducted a literature search across multiple databases, including PubMed (National Library of Medicine, Washington, DC), Embase, Cochrane, and Web of Science, to gather studies specifically investigating the association between 5-HTTLPR and PD. The search spanned from the inception of the databases up to March 2024, utilizing a strategy that combined Medical Subject Headings (MeSH) terms with their corresponding free-text terms. The MeSH terms employed in the search included ‘Serotonin Plasma Membrane Transport Proteins’ and ‘panic disorder’. The complete search strategy is detailed in Table S1. Reference cross-checking: the list of references of the included studies was searched looking for additional studies. Contact with authors: efforts were made to contact all research groups of studies included in the analysis to identify unpublished data.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were established as follows, which delineates the key components: (1) Patients diagnosed with PD according to standard diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders third/fourth edition (DSM- -III/IV) [19, 20] and International Classification of Diseases [21]; (2) Studies that assessed the relationship between 5-HTTPLPR polymorphism and PD risk; (3) The genotype frequency distribution of 5-HTTPLPR could be extracted from the PD group and healthy control group; (4) The genotype frequency distribution in the health control group was consistent with Hardy-Weinberg equilibrium law; (5) The study design was a case-control study. The exclusion criteria were defined as follows: (1) Studies lacking explicit diagnostic and effectiveness criteria; (2) Studies conference abstracts, guidelines, letters/responses to the editors, or opinion articles; and (3) Studies containing incomplete or inaccurate data that precluded meaningful integration.

Study Selection and Data Extraction

Following the criteria for inclusion and exclusion outlined previously, the study selection process was independently conducted by two researchers (Xiaolu Zhang and Linghong Huang). Initially, all potentially relevant studies were imported into EndNote X9 to identify and eliminate duplicate entries. Subsequently, a screening process ensued, involving the review of titles and abstracts to exclude studies that did not meet the predefined eligibility criteria. Finally, full-text articles underwent additional screening. In cases of disagreements, resolution was attained through discussion or consultation with a third researcher, Yingying Zhang. We utilized the Cochrane data extraction form to retrieve the following data and details: (1) Fundamental information including the title, primary author's name, and publication year; (2) Essential characteristics of the study subjects, encompassing age, gender, case numbers in each group, and diagnostic criteria; and (3) Outcome measures, which genotype frequency distribution of 5-HTTPLPR between the PD group and healthy control group.

Quality Assessment of the Included Studies

To evaluate potential bias and the overall quality of the included studies, we employed the Newcastle–Ottawa Scale (NOS), a widely utilized tool for assessing the methodological quality or risk of bias in case-control studies, according to Cochrane recommendations [22-24]. The evaluation of publication bias in the included studies was independently conducted by two researchers (Xiaolu Zhang and Linghong Huang), with any discrepancies resolved through consultation or discussion with a third researcher (Yingying Zhang). Each included study underwent an evaluation based on specific criteria. For case-control studies, these criteria included selection (scored from 0 to 4), comparability (scored from 0 to 2), and exposure (scored from 0 to 3). For cohort studies, the criteria consisted of selection (scored from 0 to 4), comparability (scored from 0 to 2), and outcome (scored from 0 to 3). The results were then interpreted according to commonly accepted standards and categorized into the following groups: very high risk of bias (0–3 NOS points), high risk of bias (4–6 NOS points), and low risk of bias (7–9 NOS points) [24].

Data Analysis

All statistical analyses were conducted using Stata version 16.0. The meta-analysis with the allele comparison model (S vs. L), the codominant model (SS vs. LL), the recessive model (SS vs. L+ (SL + LL)), and the dominant model (S + (SS + SL) vs. LL) for the unknown inherited model of PD. The pooled relative risk (RR) and its corresponding 95% confidence interval (CI)were used to evaluate the strength of the association between 5-HTTLPR polymorphism and PD risk. Z test was used to determine the statistical significance of RRs. In addition to the overall analysis, subgroup analysis was conducted in Asian and Caucasian populations. Heterogeneity was evaluated by quantifying the proportion of variation attributed to confounding variables, employing I^2 statistics. An I^2 value exceeding 50% indicated a significant degree of heterogeneity among the included studies. In such instances, a random-effects model was employed, and a sensitivity analysis was conducted to identify the source of this heterogeneity. Conversely, when I^2 was below 50%, a fixed-effects model was applied.

Additionally, suspicion of publication bias was raised with Egger's test if the p-value was below 0.05.

Results

Literature Search Results

Following the search strategy, a total of 535 records were initially identified from the four databases, with an additional four records recognized through relative reviews. After removing 165 duplicates, the remaining 370 records were screened. leading to the removal of 34 records categorized as meta-analyses, reviews, guidelines, or conference abstracts. Subsequently, a review of the titles and abstracts of the remaining records led to the removal of 280 records based on the predefined criteria for inclusion and exclusion mentioned earlier. Full-text articles were evaluated, and 42 records were excluded due to unavailability of full texts and relevant outcomes. Ultimately, the present study incorporated a total of 14 studies. The detailed selection process is displayed in Figure 1.

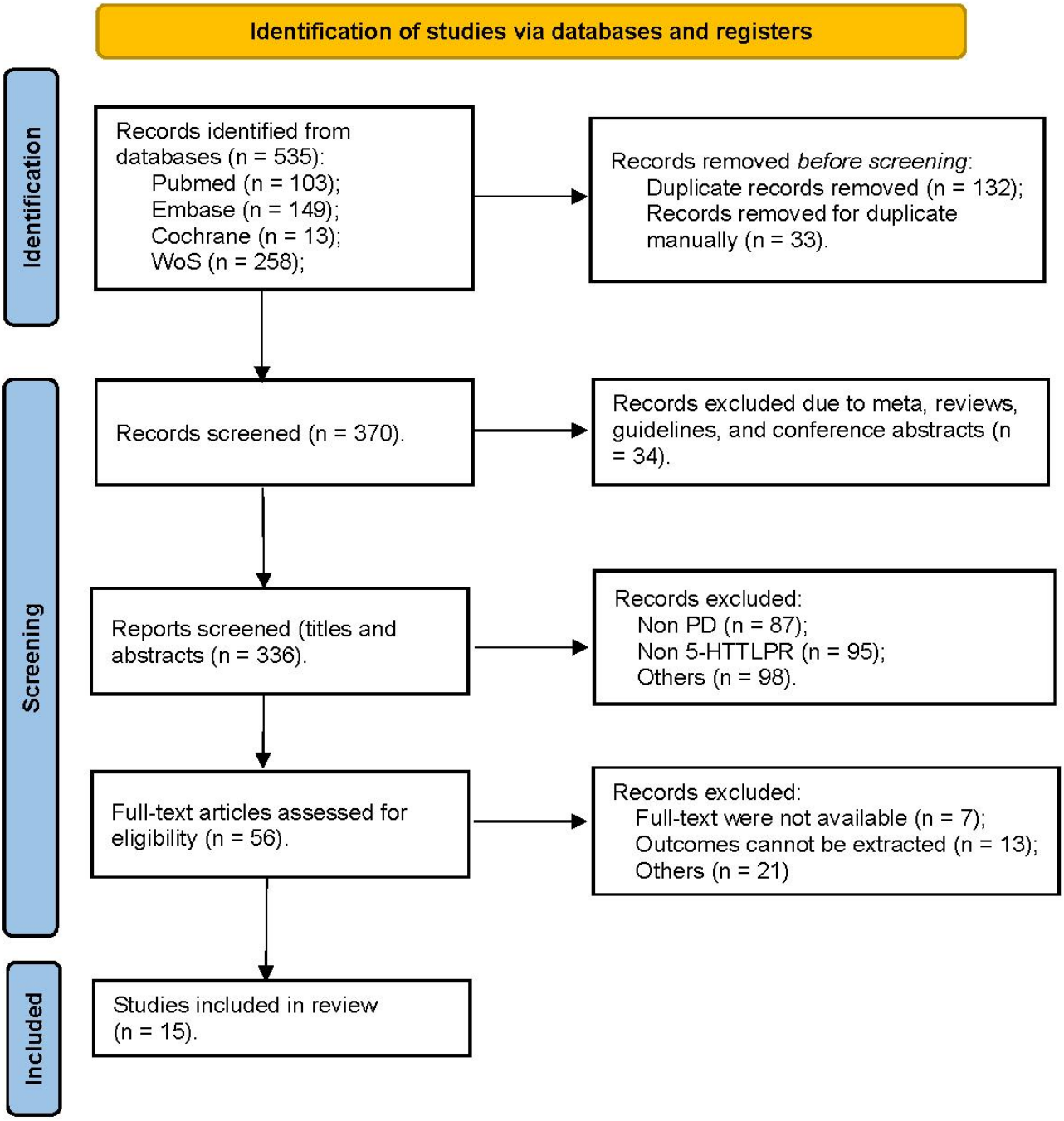


Figure 1: Flow diagram for searching and selecting qualifying studies incorporating in the meta-analysis.

Characteristics of the Included Studies

Table 1 presents a comprehensive overview of the eligible studies, delineating key characteristics such as the country of origin, diagnostic criteria, sample ethnicity, PD kinds, and outcome indicators. Specifically, the analysis encompasses 14 case-control studies [10, 11, 16, 17, 25-34], including 2280 patients (mainly included 1536 PD, and 515 PD combined with agoraphobia, and 229 others (specific PD such as social phobia)) and 2640 healthy controls. All the included studies used DSM to diagnose PD except for one study [28]. Regarding the allele and stratified analyses, no evidence of significant deviation of Hardy-Weinberg equilibrium was found (all $p > 0.05$). Among the included studies, 7 studies recruited samples from Asians (Japanese [25-27, 33], Korean [17, 31],

and Chinese [16]), 7 studies recruited samples from Caucasians (German [11, 32, 34], Polonaise [28], Spanish [29], Danish [30], and Estonian [10], while one study not only included the Germany sample but also included the Italian sample [11])).

Table 1: The main characteristics of the included studies in the meta-analysis

Included studies	Country	Diagnostic criteria	Ethnicity	PD kinds	PD group			Control group			HW equilibrium	
					SS	SS	SL	LL	SL	LL	χ2	p
Ishiguro et al (1997)	Japan	DSM-Ⅳ	Japanese	PD+Agoraphobia	51	13	2	114	32	4	0.89	0.346
Matsushita et al (1997)	Japan	DSM-III	Japanese	PD	44	35	7	125	78	10	0.24	0.623
Decket et al (1997)	Germany	DSM-III	GermanItalian	PD	1213	4432	2928	1612	4244	3223		
Ohara et al (1998)	Japan	DSM-IV	Japanese	PDPhobia	1410	86	01	62	40	8	0.19	0.661
Samochowiec et al (2004)	Polish	The CIDI	Polonaise	Panic attacksPD+AgoraphobiaSocial phobiaSpecific phobia	101135	40392231	45362630	20	97	85	1.03	0.311
Martínez-Barrondo et al (2005)	Spain	DSM-IV	Spanish	PD	18	42	32	36	74	64	2.80	0.094
Olesen et al (2005)	Denmark	DSM-IV	Danish	PD	15	56	33	18	53	37	0.02	0.894
Maron et al (2005)	Estonia	DSM-IV	Estonian	PDAgoraphobia	119	7234	7544	34	101	80	0.05	0.821
Kim et al (2006)	Korea	DSM-IV	Korean	PDPD+Agoraphobia	159124	7756	87	141	76	10	0.01	0.953
Pfleiderer et al (2010)	Germany	DSM-IV	German	PD	3	11	6	1	10	9	0.73	0.394
Choe et al (2013)	Korea	DSM-IV	Korean	PD	109	71	11	97	63	6	1.20	0.273
Watanabe et al (2017)	Japan	DSM-IV	Japanese	PDPD+Agoraphobia	7355	4232	42	71	41	7	0.11	0.739
Schiele et al (2020)	Germany	DSM-IV	German	PD	14	59	36	66	263	207	1.58	0.209
Zou et al (2020)	China	DSM-IV	Chinese	PD	148	63	22	121	90	20	0.31	0.578

CIDI, Composite International Diagnostic Interview; PD, panic disorder; HW, Hardy-Weinberg.

Quality Assessment of the Included Studies

The evaluation of bias risk revealed that, among the papers included in the analysis, the mean quality score based on NOS was 7.4, for the 14 case-control studies, with scores ranging from 6-9. All these studies were classified as having a low risk of bias. Detailed information is available in Table 2, which outlines the Methodological Quality of Prospective Case-Control Studies according to the NOS criteria [24].

Table 2: Methodological Quality of Prospective Case-control Studies Based on the NOS.

Included studies	Study population selection	Comparability between group	Comparability between group	Levels
Ishiguro et al (1997)	☆☆☆	☆☆	☆☆	7☆
Matsushita et al (1997)	☆☆☆	☆☆	☆☆☆	8☆
Decket et al (1997)	☆☆☆	☆☆☆	☆☆	8☆
Ohara et al (1998)	☆☆	☆☆	☆☆☆	7☆
Samochowiec et al (2004)	☆☆☆	☆	☆☆	6☆
Martínez-Barrondo et al (2005)	☆☆	☆	☆☆☆	6☆
Olesen et al (2005)	☆☆☆	☆☆	☆☆	7☆

Maron et al (2005)	☆☆☆	☆☆	☆☆☆	8☆
Kim et al (2006)	☆☆☆	☆☆	☆☆	7☆
Pfleiderer et al (2010)	☆☆☆	☆☆	☆☆	7☆
Choe et al (2013)	☆☆☆☆	☆☆	☆☆	8☆
Watanabe et al (2017)	☆☆☆☆	☆☆☆	☆☆	9☆
Schiele et al (2020)	☆☆☆	☆☆	☆☆	7☆
Zou et al (2020)	☆☆☆☆	☆☆	☆☆	8☆

Meta-Analysis

The association between 5-HTTLPR polymorphism and PD risk

In the present study, 12 [10, 11, 17, 26-34] studies determined the effect of 5-HTTLPR l/s polymorphism on PD risk, including 2051 PD patients and 2289 healthy controls. Results are shown in Table 2. I^2 and p-value based on Q-test to evaluate heterogeneity across the included studies. Obvious heterogeneity was observed in overall comparisons under genetic models including S vs. L (I^2 = 52.5%, p = 0.014), SS vs. SS/LL (I^2 = 80.6%, $p < 0.001$), and SS/SL vs. LL (I^2 = 77.6%, $p < 0.001$). Thus, the random effect model (REM) was used to synthesize the data for these meta-analyses. The remaining genetic model SS vs. LL (I^2 = 33.8%, p = 0.112) used a fixed effect model to synthesize the data. For overall analysis, there was a significant association between 5-HTTLPR polymorphism and PD under the genetic model S vs. L (RR = 1.13, 95% CI (1.07, 1.19), $p < 0.001$). However, no significant associations between 5-HTTLPR polymorphism and PD under the remanent genetic models (more details please see Table 3). The results of this analysis are shown in the forest plots (Figure S1-S4). In the stratified analyses of the Asian population [17, 26, 27, 31, 33] and the Caucasian population [10, 11, 28-30, 32, 34], this polymorphism was no longer significantly associated with PD risk under each genetic model in the Asian population. In the Caucasian population, the significant association between 5-HTTLPR polymorphism and PD was only observed in the genetic model S vs. L (RR = 1.24, 95% CI (1.16, 1.33), $p < 0.001$).

Table 3: Summary of meta-analyses results of the association between 5-HTTLPR polymorphism and PD risk.

Groups	studies	Model	Test of association			
			I2	p	RR (95% CI)	p
overall analysis						
S vs. L	12	REM	52.5%	0.014	1.13 (1.07,1.19)	< 0.001
SS vs. LL	12	FEM	33.8%	0.112	0.97 (0.92, 1.03)	0.325
SS vs. SL/LL	12	REM	80.6%	< 0.001	0.89 (0.71, 1.11)	0.297
SS/SL vs. LL	12	REM	77.6%	< 0.001	1.04 (0.98, 1.10)	0.162
Subgroup analysis						
Asians						
S vs. L	5	FEM	39.6%	0.157	1.05 (1.01, 1.09)	0.053
SS vs. LL	5	FEM	29.1%	0.227	1.00 (0.96, 1.04)	0.989
SS vs. SL/LL	5	REM	38.0%	0.168	1.04 (0.93, 1.17)	0.465
SS/SL vs. LL	5	REM	13.2%	0.330	1.00 (0.98, 1.03)	0.846
Caucasians						
S vs. L	7	FEM	0%	0.939	1.24 (1.15, 1.33)	< 0.001

SS vs. LL	7	FEM	16.6%	0.299	0.88 (0.72, 1.09)	0.253
SS vs. SL/LL	7	REM	85.2%	<0.001	0.75 (0.40, 1.41)	0.371
SS/SL vs. LL	7	REM	78.3%	<0.001	1.07 (0.93, 1.24)	0.355

Sensitivity Analysis and Publication Bias

To examine the influence of each study on the overall RRs, we carried out sensitivity analysis by excluding one individual study from the overall pooled analysis sequentially. Our results of sensitivity analysis revealed that the pooled RRs and its corresponding 95% CIs were generally similar when we removed any study under all the four genetic models. Hence, our results were relatively stable and credible.

Funnel plot and Egger's test were conducted to assess the publication bias qualitatively and quantitatively. Although the shape of the funnel plots was slightly asymmetry (Figure S5), the results of Egger's test did not present any clear evidence of obvious publication bias under any genetic model (for SS vs. LL, $p = 0.574$; for SS vs. SL/LL, $p = 0.346$; for SS/SL vs. LL, $p = 0.458$) except for the genetic model for S vs. L, $p = 0.003$.

The association between 5-HTTLPR polymorphism and the risk of PD comorbidity with Agoraphobia

5 studies [10, 25, 28, 31, 33] determined the effect of 5-HTTLPRL S/L polymorphism on the risk of PD comorbidity with agoraphobia, including 515 PD patients and 943 healthy controls. Heterogeneity could be neglectable in overall comparisons under genetic models (Table 4). The results indicated that there was no significant association between 5-HTTLPR polymorphism and the risk of PD comorbidity with agoraphobia under each genetic model. Due to the limited number of the included studies, only Egger's test was conducted to assess the publication bias. The results of Egger's test did not present any clear evidence of obvious publication bias under any genetic model (all p >0.05).

Table 4: Summary of meta-analyses results of the association between 5-HTTLPR polymorphism and the risk of PD comorbidity with agoraphobia.

Groups	studies	Model	Heterogeneity			Test of association		Egger
			I2		p	RR (95% CI)	p	p
S vs. L	5	REM	50.6%		0.008	1.02 (0.95,1.10)	0.561	0.485
SS vs. LL	5	FEM	28.8%		0.230	1.00 (0.94, 1.06)	0.492	0.652
SS vs. SL/LL	5	FEM	23.0%		0.268	1.08 (0.97, 1.20)	0.897	0.910
SS/SL vs. LL	5	FEM	18.9%		0.295	1.01 (0.97, 1.04)	0.738	0.219

Discussion

In this study, we conducted a meta-analysis of the association between 5-HTTLPR polymorphisms and PD risk. 14 eligible papers were included, including 1,431 cases in the PD group and 2,148 cases in the control group. The results showed that 5-HTTLPR polymorphism was significantly associated with PD risk under the genetic model S vs. L. However, this association was not oobserved in other genetic model including SS vs. LL, SS vs. SL/LL, and SS/SL vs. LL. The association between 5-HTTLPR polymorphism and risk of PD comorbidity with agoraphobia was further assessed but the significant association was not observed.

Although there is growing interest in defining the genetic basis for PD, and research has led to increasing knowledge on PD and genetics, there is still not enough evidence to reach a clear conclusion about the role and extent of genetic influence in the etiology of PD. For the pathophysiology of PD, the serotonergic system has been considered as performing a role as inferred by serotonergic

treatment studies [35, 36], and brain imaging studies. It is well known that 5-HTT (an integral membrane protein of 630 amino acids, containing 12 transmembrane domains) could regulate the concentration of 5- HT in synapses and further change the excitatory of synapses. As the gene encodes 5-HTT, polymorphisms in the 5-HTTLPR of this gene were reported to be associated with varying degrees of transcriptional activity, and further lead to varying degrees of protein formation. Compared with the L allele, the S allele of the 5-HTTLPR polymorphism was found to reduce the serotonin transporter gene expression and function, resulting in decreased serotonin reuptake [37]. It has been shown that 5-HTTLPR L/S alleles may result in an alteration in 5-HT and 5-HTT early in brain development, possibly affecting the development of PD. Although many clinical studies tried to explore the association between 5-HTTLPR polymorphism and PD risk, the results were inconsistent. Our meta-analysis represents a comprehensive and systematic assessment of the relation of 5-HTTLPR polymorphism with PD risk. So far, there are about 14 population-based studies reported to evaluate the association between 5-HTTLPR polymorphism and PD risk. However, the results were inconsistent. A previous meta-analysis conducted by Blaya et al. explored the effect of this polymorphism in 2007 and did not provide evidence to support an association between 5-HTTLR and PD [15]. Compared with the previous one, out meta-analysis examined the pooled RRs and its corresponding 95% CIs under four genetic models for the unknown inherited model, while their results were only based on allele frequency distribution (S vs. L). Thus, we believed that our meta-analysis explored the effect of 5-HTTLPR polymorphism on PD risk in a different way. In our present meta-analysis, although the pooled RRs and 95%CIs under different comparison models did not show strongly significant association of 5-HTTLPR polymorphism on PD risk in a different way. In details, the significant association of 5-HTTLPR polymorphism on PD risk was observed in the genetic model S vs. L, not other genetic models such as SS vs. LL, SS vs. SL/LL, and SS/LL vs. LL. Heterogeneity across studies may have a significant impact on results. The included studies may cause heterogeneity under the genetic moedel S vs. L (overall I^2 = 52.5%), in the stratified analyses this polymorphism was no longer significantly associated with PD risk under each genetic model in the Asian population with less heterogeneity (I^2 = 39.6%), while the significant association was only observed in the Caucasian population without heterogeneity (I^2 = 39.6%). Therefore, we hypothesized that 5-HTTLPR polymorphism may not have a direct effect on the risk of PD, more studies are needed to evaluate the effect of this polymorphism on PD.

Moreover, we also evaluated the association between 5-HTTLPR polymorphism and the risk of PD comorbidity with agoraphobia. The severity of agoraphobic symptoms is statistically correlated with the severity of panic symptoms, which indicates that panic and agoraphobic symptoms are strongly associated [38]. However, the causal relationship between the two symptoms remains not known. A twin study demonstrated that genetic factors play a role in the variation and covariation of PD and agoraphobia, and the genetic correlation between PD and agoraphobia was very high at 0.83 [39]. Nonetheless, the results of the current study failed to establish the association between 5-HTTLPR polymorphism and the risk of PD comorbidity with agoraphobia, which was consistent with the results of previous meta-analysis [15]. An explanation for the non-significant association between 5-HTTLPR and PD risk as well as the risk of PD comorbidity with agoraphobia was that of gene-environment (GxE) interactions in emotional disorders. An interaction effect between the 5-HTTLPR and the environment is not of a general nature but is restricted to some specific environmental factors [40-42]. Stein et al. (2008) found a statistically significant interaction between 5-HTTLPR polymorphism and childhood (emotional or physical) maltreatment levels [43]. Specifically, SS individuals with higher levels of maltreatment had significantly higher levels of anxiety sensitivity [43]. Another possible explanation for these non-significant association results observed in the meta-analysis might be of that previous studies did not take into account an important single nucleotide polymorphism (SNP; rs25531(A/G)), which is known to further modulate the mRNA expression of the SLC6A4 gene [44]. In detail, SNP rs25531 has been identified within the L allele, further dividing the L allele into L_A and L_G and thus leading to a tri-allelic genotyping classification (S, L_A, and L_G) [45, 46]. The 5-HTT protein transcription level of L_G is almost equivalent to that of S, with both being lower than L_A. Hence, if this genotype is not taken into account, L_G may have been misclassified as a "high expression" variant in previous studies. Further studies are needed to assess the association between 5-HTTLPR polymorphism and PD risk while taking SNP rs25531 into account.

Limitations

There are some limitations in this study, such as the relatively small number of included studies. For instance, the inconsistency of the diagnostic criteria for PD among studies such as DSM-III, DSM-IV, and CIDI, which might lead to heterogeneity among the included studies, and then influence the association between 5-HTTLPR polymorphism. Besides, the fact that the symptoms of PD patients may be regulated by a combination of different genes and it is difficult for a single gene to comprehensively explain the onset of PD. Therefore, it is necessary to conduct more homogeneous and high-quality studies to further validate the results.

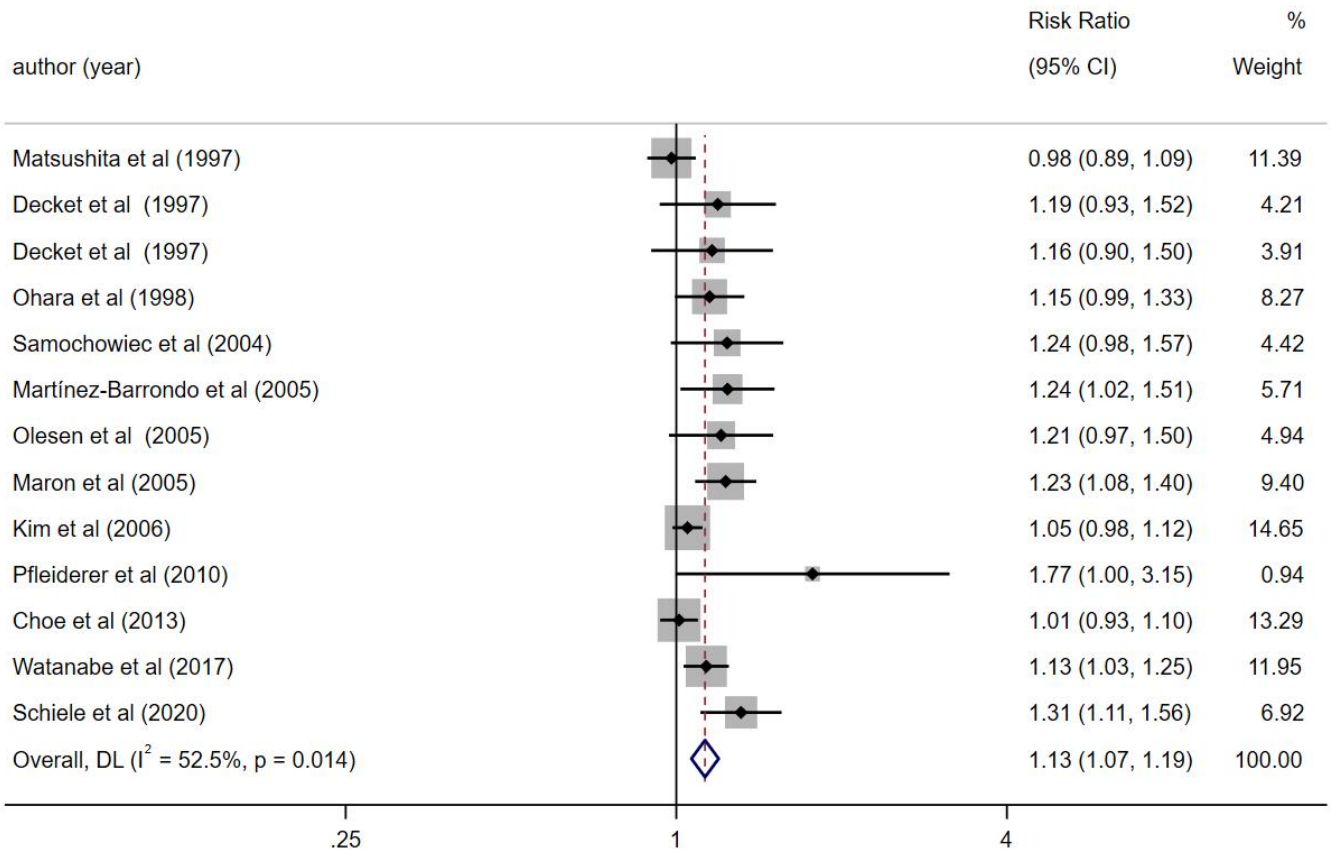
Conclusion

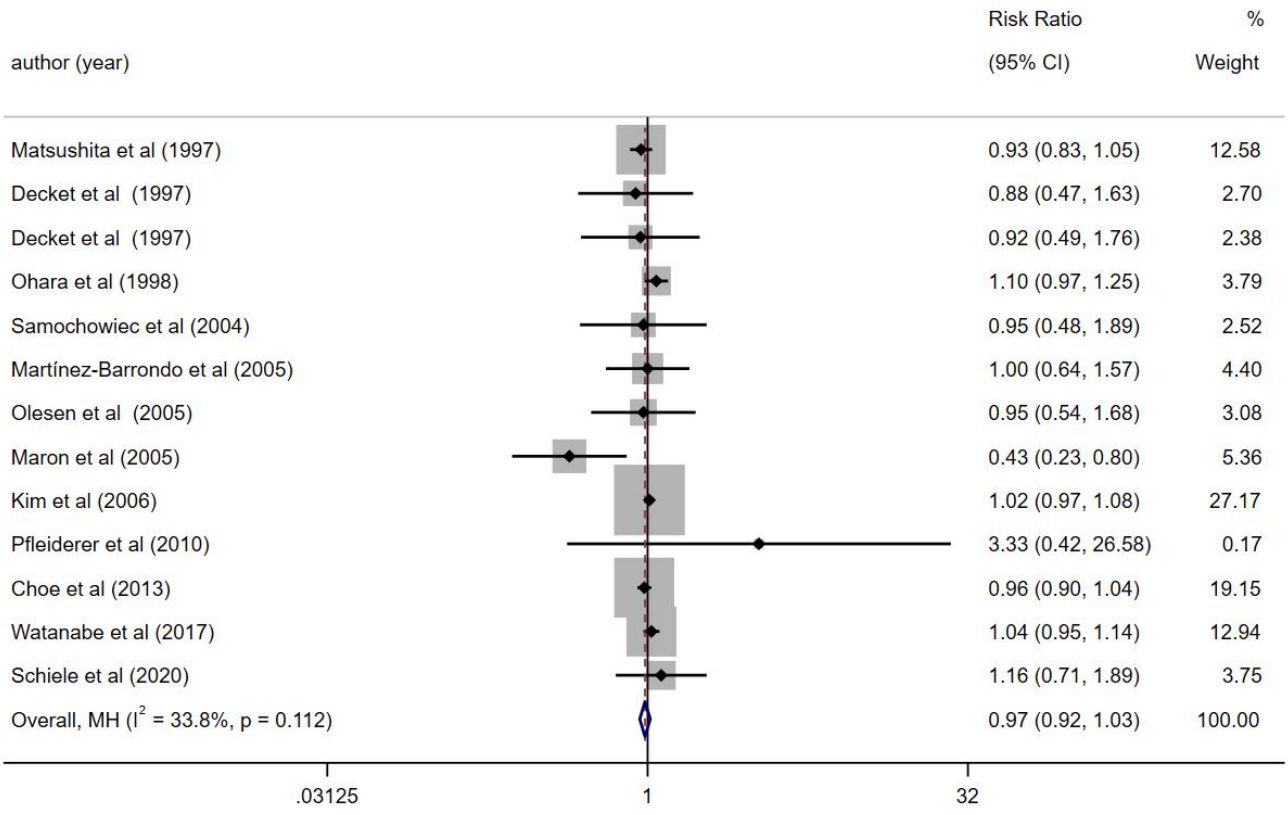
In summary, the results from this systematic review do not support the hypothesis of a significant association between 5-HTTLPR and PD. We also failed to find an association between this polymorphism and the risk of PD comorbidity with agoraphobia. However, more studies are needed in different ethnic populations to evaluate a possible minor effect.

Supplementary Information

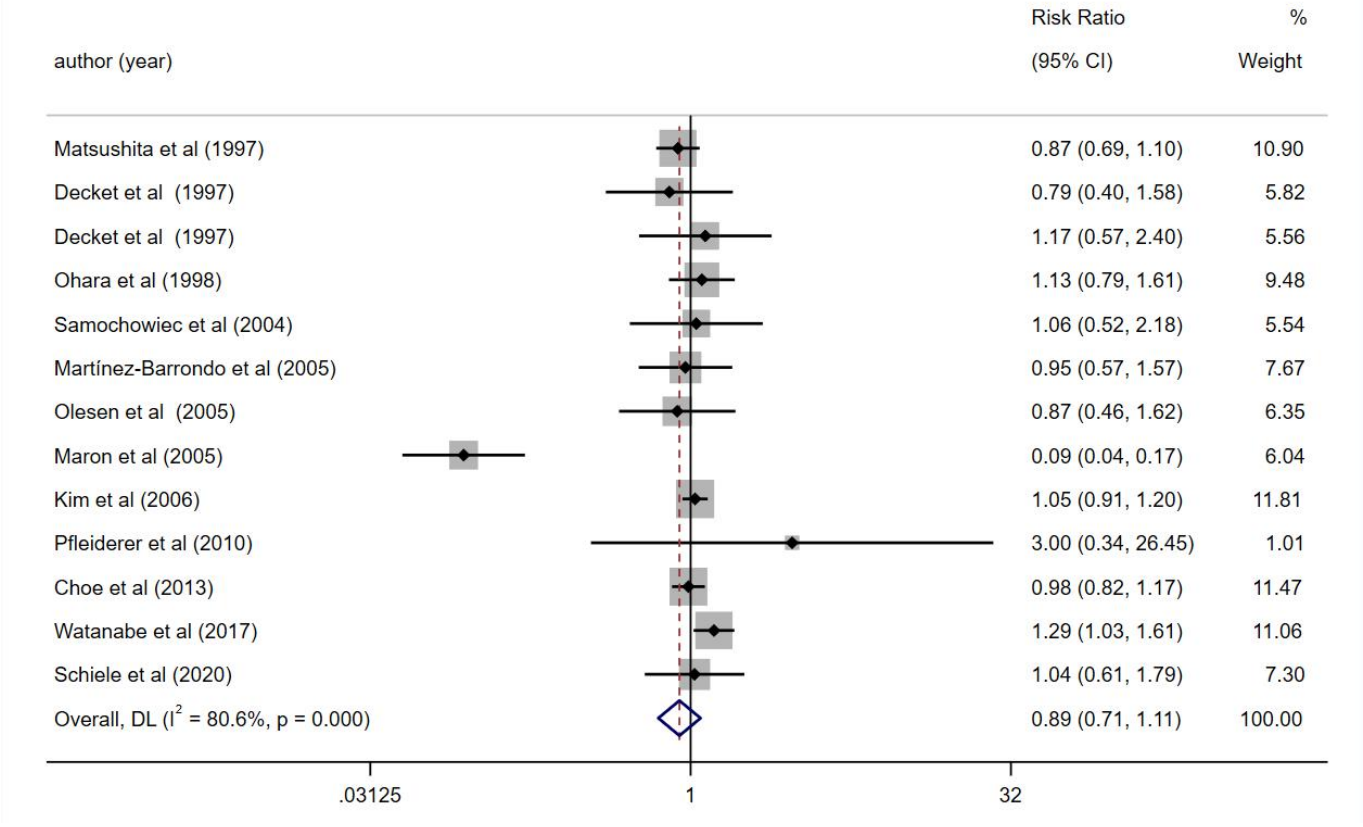
Supplementary Table 1: Literature search strategy of PubMed

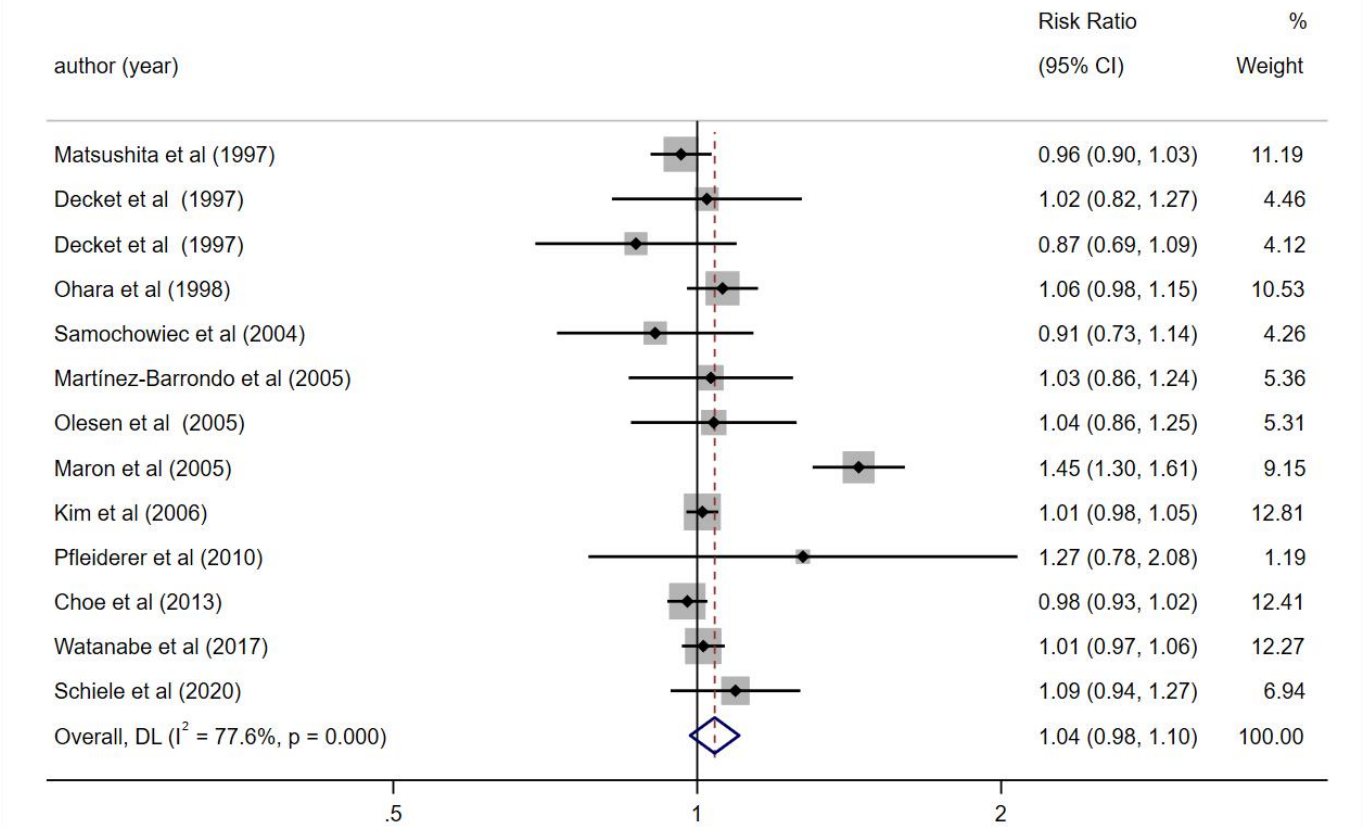
Search number	Query	Records
#1	"Panic Disorder"[Mesh]	7344
#2	((((Panic disorder[Title/Abstract]) OR (Panic disorders[Title/Abstract])) OR (Panic[Title/Abstract])) OR (Panic attack[Title/Abstract])) OR (Panic attacks[Title/Abstract])	17221
#3	("Panic Disorder"[Mesh]) OR (((((Panic disorder[Title/Abstract]) OR (Panic disorders[Title/Abstract])) OR (Panic[Title/Abstract])) OR (Panic attack[Title/Abstract])) OR (Panic attacks[Title/Abstract]))	18114
#4	"Serotonin Plasma Membrane Transport Proteins"[Mesh]	7292
#5	(((((((5-HTTLPR[Title/Abstract]) OR (SERT[Title/Abstract])) OR (5-HTT[Title/Abstract])) OR (SLC6A4[Title/Abstract])) OR (serotonin transporter gene[Title/Abstract])) OR (5 httlpr[Title/Abstract])) OR (5 htt[Title/Abstract])) OR (Serotonin Plasma Membrane Transport Proteins[Title/Abstract])	7379
#6	("Serotonin Plasma Membrane Transport Proteins"[Mesh]) OR (((((((5-HTTLPR[Title/Abstract]) OR (SERT[Title/Abstract])) OR (5-HTT[Title/Abstract])) OR (SLC6A4[Title/Abstract])) OR (serotonin transporter gene[Title/Abstract])) OR (5 httlpr[Title/Abstract])) OR (5 htt[Title/Abstract])) OR (Serotonin Plasma Membrane Transport Proteins[Title/Abstract]))	9630
#7	(("Panic Disorder"[Mesh]) OR (((((Panic disorder[Title/Abstract]) OR (Panic disorders[Title/Abstract])) OR (Panic[Title/Abstract])) OR (Panic attack[Title/Abstract])) OR (Panic attacks[Title/Abstract]))) AND (("Serotonin Plasma Membrane Transport Proteins"[Mesh]) OR (((((((5-HTTLPR[Title/Abstract]) OR (SERT[Title/Abstract])) OR (5-HTT[Title/Abstract])) OR (SLC6A4[Title/Abstract])) OR (serotonin transporter gene[Title/Abstract])) OR (5 httlpr[Title/Abstract])) OR (5 htt[Title/Abstract])) OR (Serotonin Plasma Membrane Transport Proteins[Title/Abstract])))	103



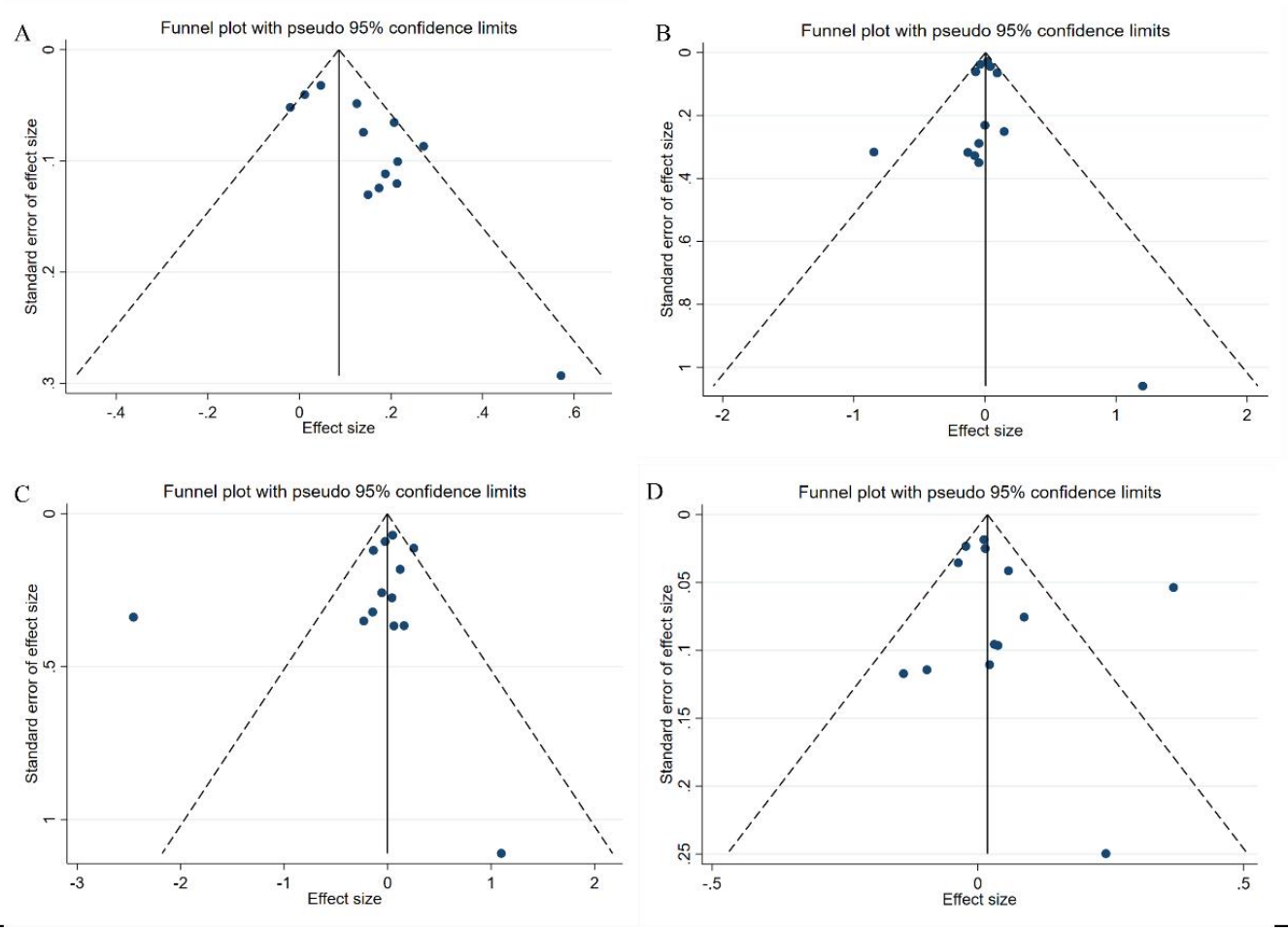


Supplementary Figure 2: Forest plot of the pooled meta-analysis depending on the genetic model SS vs. LL.





Supplementary Figure 4: Forest plot of the pooled meta-analysis depending on the genetic model SS/SL vs. LL.



Supplementary Figure 5: The Funnel plots of the pooled meta-analysis depending on the genetic models. (A), S vs. L; (B), SS vs. LL; (C), SS vs. SS/SL; (D), SS/SL vs. LL.

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