



Association between 5-hydroxytryptamine transporter gene-linked promoter region polymorphism and the susceptibility of lifelong premature ejaculation: a meta-analysis involving 1,604 subjects

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Abstract: The relationship between 5-hydroxytryptamine transporter-linked promoter region (5-HTTLPR) gene and lifelong premature ejaculation (LPE) risk was discussed widely for the last few years, which was still controversial and remained to be explored. We performed the meta-analysis with 8 reliable research, which were searched in the following databases: PubMed, Embase and Cochrane Library. We also performed random and fixed effects models to evaluate the odds ratios (ORs) and 95% confidence intervals respectively. By pooling all included studies, we found that SS genotype of 5-HTTLPR polymorphism was linked with significantly higher PE risk in Caucasian population (OR =0.635, 95% CI: 0.417–0.958, $I^2=0.311$, $P=0.035$), and S-allele of 5-HTTLPR polymorphism increased the risk of LPE significantly in Asian population (OR =0.656, 95% CI: 0.539–0.799, $I^2=0.435$, $P<0.001$). However, no significant was observed between 5-HTTLPR gene polymorphism and LPE risk in overall studies. Further studies were anticipated to be done.

Keywords: Meta-analysis; sexual dysfunction; premature ejaculation; 5-hydroxytryptamine; single nucleotide polymorphisms

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Introduction

Premature ejaculation (PE) was one of the two most common male sexual dysfunction, prevalence of PE was 20–30% all over the world (1). PE meant that Ejaculation occurs too quickly, either before vaginal penetration or <1–2 min afterwards, and PE could be classified as lifelong premature ejaculation (LPE) and secondary premature ejaculation (SPE). There has been a problem from the first sexual experience, and it's been going on for a lifelong in patients with LPE (1). Ejaculation always occurred within 1 minute of vaginal penetration from the first

sexual experience, which was defined as LPE (2). It not only had a bad influence between the husband and wife, but also impacted the mental health and quality of life (3). Therefore, it was imperative to study premature ejaculation.

The etiology of PE was yet to be determined. PE has been recognized as a psychological block and discussed in relation to many factors in the past, for example: environmental, endocrine, neurobiological and genetic factors (4–6). Genetic factors accounted for around 30% of all etiology (7), which was worth to study.

There is a specific protein transporter located in the cell membrane, called 5-hydroxytryptamine transporter

(5-HTT). The function of 5-HTT is to promote reabsorbing serotonin from the synapse. However, the concentration of 5-hydroxytryptamine (5-HT) in the synaptic cleft is related to ejaculation (8). As we all know, selective serotonin re-uptake inhibitors (SSRIs) could be used to delay the process of ejaculation (9), and has been used as primary therapeutic drug for PE currently (10). European Association of Urology (EAU) has suggested that the first-line treatment of LPE is pharmacotherapy, instead of behavioural treatment. Dapoxetine is the only drug approved for PE except for the USA (11). The 5-hydroxytryptamine transporter-linked promoter region (5-HTTLPR) is a one of the 5-HTT gene, which has an effect on the function of 5-HTT (12). And there are two variant alleles: long (L) and short (S) allele respectively. The former has 44 base pairs (bps) more than the latter (13). And Janssen *et al.* considered that the ejaculation latency time is longer in men with SS and SL genotype than LL genotype (14). However, Safarinejad *et al.* showed a completely opposite view, considered that carriers of SS genotype had increased the risk of PE (15). These studies reported inconsistent and conflicting results, and the strength of evidence was not enough because the sample size was small in these studies. Consequently, we did the meta-analysis of overall currently authoritative articles to delve the possible relationships between 5-HTTLPR gene polymorphism with LPE risk. Then subgroup analysis has been done by ethnicity and control source. We also explored the association between 5-HTTLPR gene polymorphism and SPE risk, but there was not enough evidence to support the strength of the conclusion.

Methods

Search strategy

We performed a systematic search of Embase, PubMed and Cochrane Library databases for studies on 5-HTTLPR polymorphism and the susceptibility of LPE up to Sept, 2019. The key words and medical subject headings used for searching were ‘premature ejaculation’, ‘early ejaculation’, ‘rapid ejaculation’, ‘polymorphism’, ‘serotonin’, ‘5-HT’, and ‘5-HTTLPR’. There was not any restriction on the sample size. We also have done a manual search of all retrieved reference to get the original text and reviewed them.

Inclusion and exclusion criteria

All studies we have included must meet the follow

requirements: (I) the studies were associated with the theme: the association between 5-HTTLPR gene polymorphism and LPE risk; (II) case-control study; (III) there was similar characteristic between case group and health control in addition to the content of the study; (IV) the studies were consistent in Hardy–Weinberg equilibrium (HWE). These studies were excluded as follow: (I) the data was incomplete; (II) the type of study was abstract, review and comment; (III) the patient with other disease, such as diabetes, hypertension, melancholia or other sexual dysfunction, for example: erectile dysfunction, lukewarm sex.

Data abstraction

The patients were come from all over the world, and there was no repetition of the crowd among the studies. We have collected the relevant information needed for the study as follows: the family name of the lead author, the time of publication, nationality of patients, ethnicity, size of the sample, genotype distributions and the allele frequency in cases/controls. The quality of the included researches were evaluated by The Newcastle-Ottawa Scale (NOS) (16), and the selection, exposure and comparability of study were evaluated.

Statistical analysis

The abstracted data were analyzed with Stata 12.0 software. The publication bias was assessed by Egger’s test and Begg’s funnel plot (17). The stability and the effect of individual study on the overall odds ratios were determined by performing a sensitivity analysis. We also performed the NOS scale of case-control to assess the quality of the included researches. ORs (odds ratios) with 95% confidence intervals (CIs) was measured to evaluate the relativity between LPE risk and the polymorphism of the 5-HTTLPR gene. We calculated the total ORs by dominant model (LL+LS *vs.* SS), recessive model (LL *vs.* LS+SS), homozygote model (LL *vs.* SS), heterozygote model (LS *vs.* SS), and allelic contrast (L-allele *vs.* S-allele) severally. The chi-square based on Q statistic was performed to check the heterogeneity among the studies, and result was recognized as significant at $P < 0.05$. When the $I^2 < 50\%$, indicated that there was no significant heterogeneity and the fixed-effects model (Mantel–Haenszel method) would be used (18). And we performed the random-effects model (DerSimonian and Laird method) when the heterogeneity of the data could not be explained ($P < 0.05$, $I^2 > 50\%$) (19). The Z-test was

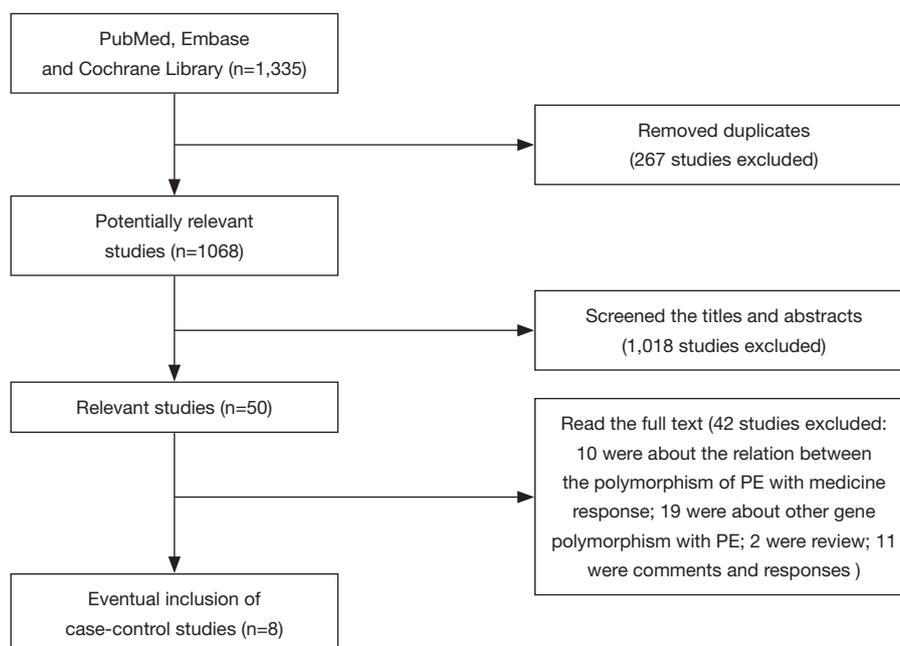


Figure 1 Flowchart illustrating the search strategy for 5-HTTLPR polymorphism and the risk of LPE.

performed to evaluate the meaning of the overall ORs, and statistically significant was observed with $P < 0.05$. We also made the subgroup analysis by the ethnicity of patients and control source respectively.

Results

Studies characteristics

A total of 1,068 potentially relevant articles were searched by systematic retrieval from the PubMed, Embase and Cochrane Library databases. As showed in *Figure 1*, full texts of 50 original articles on 5-HTTLPR gene polymorphism related to LPE were retrieved after screening the titles and abstracts. We excluded 42 studies: 10 were about the relation between the polymorphism of PE with medicine response; 19 were about other single nucleotide polymorphisms (SNPs) with PE; 2 were review; 11 were comments and responses. Finally, our meta contained 8 studies, a total of 898 LPE patients and 706 health controls (14,15,20-25). The basic characteristics of all studies were showed in *Table 1*. All studies were consistent with the Hardy-Weinberg equilibrium (HWE). In these studies, 4 were conducted on Caucasian descendants, 3 on Asian descendants, and only one was conducted on African population. The same genotyping method by polymerase chain reaction based

(PCR)-restriction fragment length polymorphism (PFLP) was used in all articles we have included.

Meta-analysis

Table 2 listed the main results of the meta-analysis of 5-HTTLPR gene polymorphism and the susceptibility of LPE, as well as the results of subgroup analysis.

Relationship between 5-HTTLPR polymorphism and susceptibility of LPE

The pooled studies indicated that there was no significant relationship between the two over the different genetic models (*Figure 2*). According to the high heterogeneity ($I^2 > 50\%$) in all models, the subgroup analyses were performed as followed.

Relationship between 5-HTTLPR polymorphism and the population risk classified by ethnicity

In this part, we found that there was significant association between 5-HTTLPR polymorphism and the risk of LPE in Caucasian population. The homozygous genetic models showed the significant result (OR =0.635, 95% CI: 0.417–0.958, $I^2=0.311$, $P=0.035$) in *Figure 3*, and we

Table 1 Main characters of studies included in this meta-analysis

First author	Year	Country	Ethnicity	Control source	Sample size cases/controls	Cases			Controls			Genotype methods
						LL	LS	SS	LL	LS	SS	
Janssen <i>et al.</i>	2009	Netherlands	Caucasian	HB	89/92	27	43	19	27	41	24	PCR-RFLP
Ozbek <i>et al.</i>	2009	Turkey	Caucasian	PB	69/69	11	21	37	12	37	20	PCR-RFLP
Safarinejad <i>et al.</i>	2009	Iran	Caucasian	PB	82/82	24	29	29	35	30	17	PCR-RFLP
Luo <i>et al.</i>	2011	China	Asian	HB	119/90	24	34	61	25	31	34	PCR-RFLP
Zuccarello <i>et al.</i>	2012	Italy	Caucasian	PB	89/100	22	49	18	33	51	16	PCR-RFLP
Huang <i>et al.</i>	2016	China	Asian	PB	114/101	18	61	35	22	48	31	PCR-RFLP
Salem <i>et al.</i>	2017	Egypt	African	HB	60/20	16	25	19	10	8	2	PCR-RFLP
Kham <i>et al.</i>	2018	Pakistan	Asian	PB	271/152	108	97	66	30	72	50	PCR-RFLP

HB, hospital based; PB, population based; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

also found positive result in Asians population in allelic genetic model (OR =0.656, 95% CI: 0.539–0.799, $I^2=0.435$, $P<0.001$) (Figure 4). In addition, we also found significant association between the risk of LPE in African population and 5-HTTLPR gene polymorphism in Homozygous model (OR =0.168, 95% CI: 0.032–0.884, $I^2=0$, $P=0.035$) and allelic contrast (OR =0.388, 95% CI: 0.180–0.834, $I^2=0$, $P=0.015$), which indicated that people with SS genotype and S allele were more likely to get LPE in different country. There's only one study (24) described the relationship in African population. So there's not enough evidence to show the relationship.

Relationship between 5-HTTLPR polymorphism and PB and HB population risk

People in population based (PB) were more likely to get LPE in allelic genetic model (OR =0.746, 95% CI: 0.576–0.967, $I^2=0.562$, $P=0.027$) (Figure 5). Otherwise, no significantly different associations could be observed in different genetic models in hospital based (HB).

Relationship between 5-HTTLPR polymorphism and SPE population risk

In subgroup analysis, 2 studies (22,25) were further divided the PE into LPE and SPE. The results also showed that no significantly different associations could be observed in SPE (Figure 6).

Sensitivity analysis and publication bias

We performed a sensitivity analysis to evaluate the effect of a single study on the total results, which showed that there was not any study impacted the pooled ORs significantly. This demonstrated that combining results were reliable (Figure 7). We also evaluated the publication bias by Egger's test and Begg's funnel plot as shown in Figure 8, the shapes of all models were symmetric, which indicated that no evidence could be used to affirm that there was publication bias.

Discussion

This was a meta-analysis of 5-HTTLPR polymorphism and the susceptibility of LPE. We found that SS genotype of 5-HTTLPR gene polymorphism increased susceptibility to LPE in Caucasian population, which was similar to the result by Zhu *et al.* (26), moreover, the risk of LPE also has increased with S-allele in Asian. However, we didn't find a significant association between 5-HTTLPR gene polymorphism and LPE in overall studies. These results were different with Zhu *et al.* In addition, for the people from PB, S-allele also increased susceptibility to LPE. So we suggested that SS genotype and S-allele of 5-HTTLPR gene polymorphism were risk factors for LPE.

On the one hand, 5-HTTLPR polymorphism was related to many diseases. The bio-psycho-social model emphasized that the influence of stress environment on children's question behavior was restricted by the biological

Table 2 Meta-analysis results

Variables	Dominant genetic model (LL+LS vs. SS)			Recessive genetic model (LL vs. LS+SS)			Homozygous model (LL vs. SS)			Heterozygous model (LS vs. SS)			Allelic contrast model (L-allele vs. S-allele)			
	N	I ² (%)	OR (95% CI)	P	I ² (%)	OR (95% CI)	P	I ² (%)	OR (95% CI)	P	I ² (%)	OR (95% CI)	P	I ² (%)	OR (95% CI)	P
Overall	8	67.6	0.732 (0.483–1.110)	0.142	75.5	0.827 (0.511–1.339)	0.440	75.9	0.707 (0.391–1.278)	0.251	44.3	0.787 (0.617–1.002)	0.052	65.4	0.830 (0.647–1.066)	0.144
Ethnicities																
Asian	3	72.3	0.977 (0.550–1.733)	0.935	88.3	1.085 (0.397–2.970)	0.873	86.9	1.042 (0.356–3.055)	0.94	7.0	0.920 (0.665–1.273)	0.615	43.5	0.656 (0.539–0.799)	<0.001
Caucasia	4	60.9	0.638 (0.362–1.124)	0.12	0	0.754 (0.536–1.059)	0.103	31.1	0.635 (0.417–0.958)	0.035	61.7	0.669 (0.360–1.243)	0.203	49.3	0.882 (0.715–1.088)	0.240
Africa	1	0.0	0.240 (0.050–1.140)	0.073	0	0.364 (0.128–1.036)	0.058	0.0	0.168 (0.032–0.884)	0.035	0.0	0.329 (0.063–1.731)	0.189	0.0	0.388 (0.180–0.834)	0.015
Source of control																
HB	3	62.7	0.681 (0.313–1.482)	0.333	34.4	0.734 (0.485–1.109)	0.142	63.4	0.594 (0.237–1.488)	0.266	43.9	0.784 (0.496–1.238)	0.296	76.6	1.071 (0.592–1.939)	0.820
PB	5	74.7	0.748 (0.432–1.296)	0.301	82.6	0.924 (0.463–1.846)	0.823	81.9	0.776 (0.345–1.750)	0.542	55.6	0.738 (0.471–1.155)	0.183	56.2	0.746 (0.576–0.967)	0.027
SPE vs. Con	2	0.0	0.852 (0.484–1.500)	0.578	0.0	0.793 (0.447–1.405)	0.426	0.0	0.772 (0.388–1.538)	0.462	0.0	0.924 (0.493–1.732)	0.805	0.0	0.853 (0.594–1.224)	0.384

N, number; OR, odds ratio; CI, confidence interval; PH, pherogeneity; HB, hospital based; PB, population based.

genetic basis, especially the 5-HT system, which was related to psychological function such as depression, and had important influence on it (27). Deuschle *et al.* found that the risk of insomnia were higher in people with S allele, instead of control group (28). In 2010, a meta-analysis examined studies from European and East Asian populations, confirming that there was a correlation between 5-HTTLPR and depression (29). On the other hand, there were also many gene polymorphism closely related to PE, Luo *et al.* found that LPE was associated with the 5-HT_{2C} receptor gene polymorphism, and people with the -759T or -697C genotype were more likely to have PE (30). Jern *et al.* found that the polymorphism of 5-HT_{1B} also had a huge influence in the time of ejaculation, and suggested that people with G allele had a shorter time than the control group when having sexual intercourse (31).

However, most of the research was still about the 5-HTTLPR, which was a functional repeat polymorphism. It was on chromosome 17, and was part of the serotonin transporter gene SLC6A4. There were two variant alleles which were called long (L) and short (S) allele. The former had 44 base pairs (bps) more than the latter. The possible mechanism of the relationship between LPE and 5-HTTLPR polymorphism was that the L and S alleles could regulate the transcriptional activity of the 5-HTT promoter respectively, and the transcriptional activities of different genotypes were different. Therefore, we can make the 5-HT indexes different in human body by affecting the concentration of 5-HTT mRNA in human body, the reabsorption of 5-HT at presynaptic membrane and the synthesis of 5-HTT protein, which could affect the intensity and duration on ejaculation by 5-HT signaling pathway. It has been found that the transcriptional activity of short type (S) allele was much lower than long type (L) allele (12,32).

In these studies we have included, just one study discussed the relationship with Chinese and suggested that triallelic way should be used in studying 5-HTTLPR (20). In addition, Safarinejad *et al.* and Zuccarello *et al.* also used triallelic approach to study 5-HTTLPR. They discussed the SNP rs25531 (A/G) and made a distinction between L_G and L_A. Safarinejad *et al.* thought that men who carried S/S, L_G/L_G or S/L_G had higher risk of PE (15). But Zuccarello *et al.* found that there were not any relationship between the two (25). So the further research was required to confirm the correlation between LPE and 5-HTTLPR polymorphism.

Firstly, we analyzed the association between the case group and health volunteers, and we discovered that the

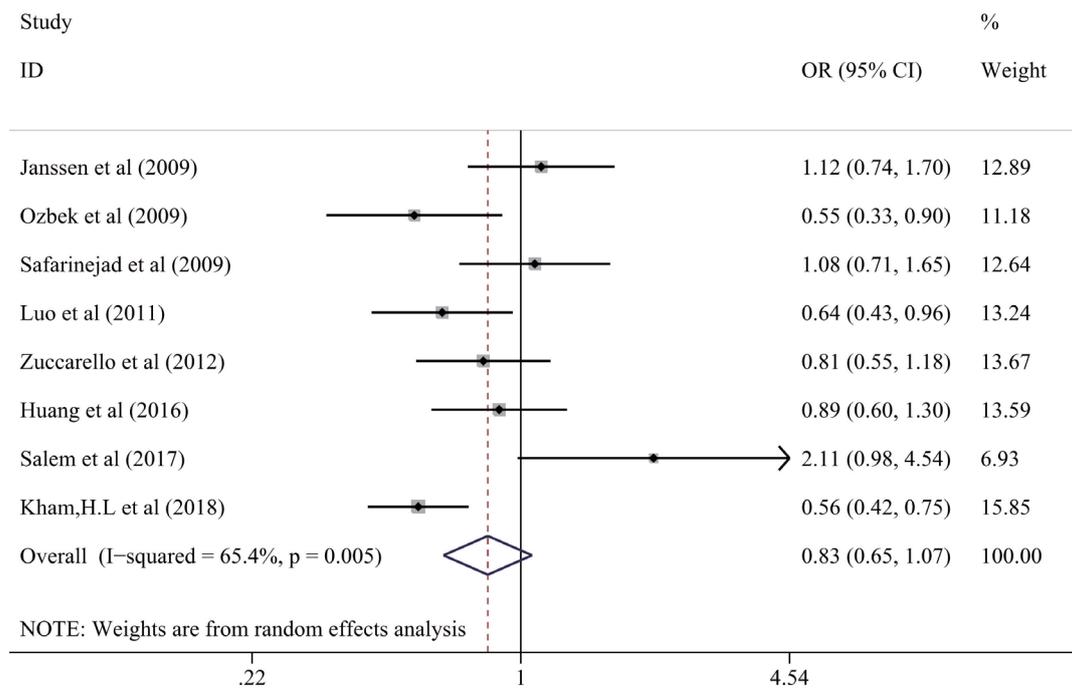


Figure 2 Forest plot of 5-HTTLPR polymorphism and LPE (allelic genetic contrast L-allele vs. S-allele).

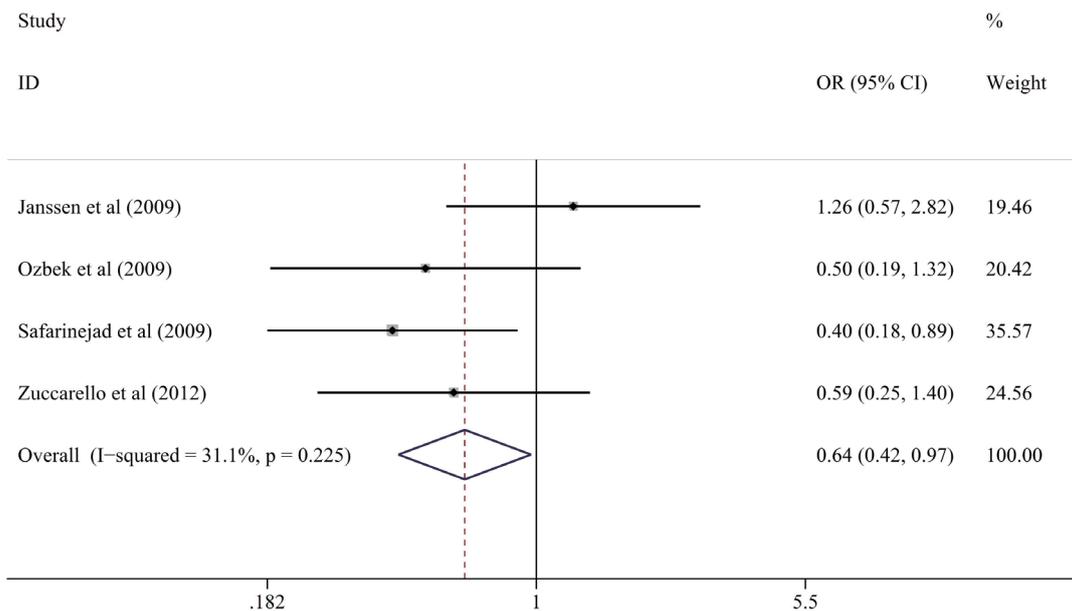


Figure 3 Caucasian population subgroup meta-analysis was held for the association between 5-HTTLPR polymorphism and LPE (homozygous genetic model LL vs. SS).

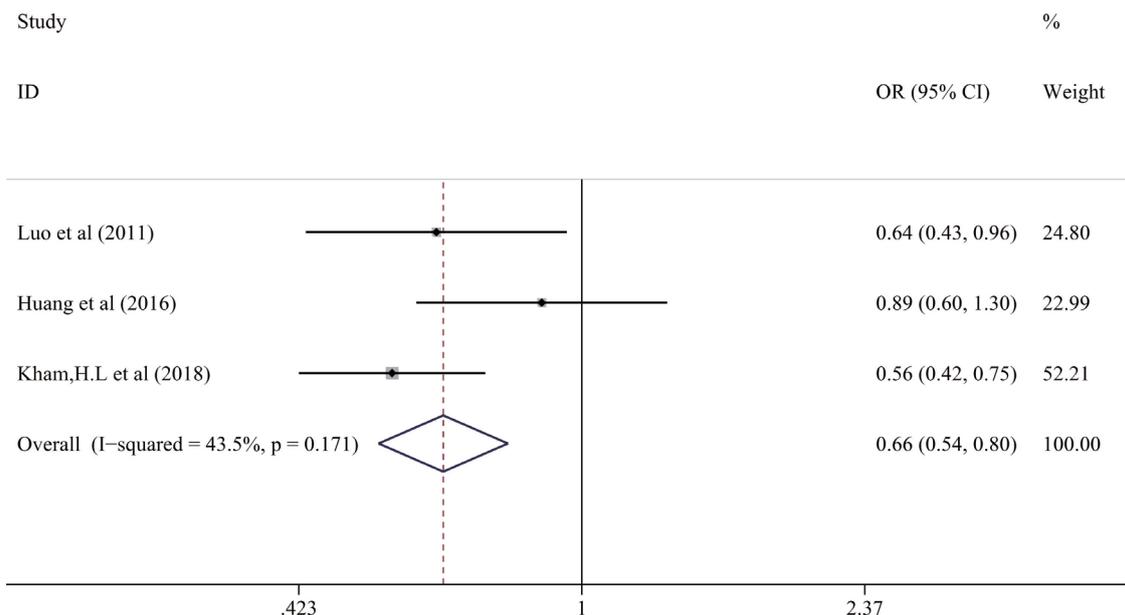


Figure 4 Asian population subgroup meta-analysis was held for the association between 5-HTTLPR polymorphism and LPE (allelic genetic contrast L-allele vs. S-allele).

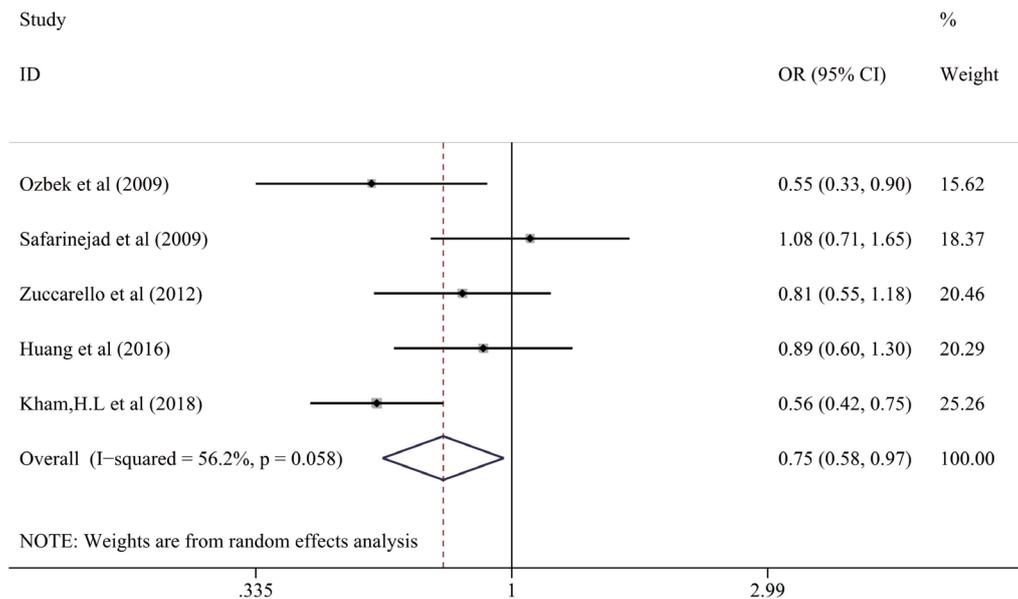


Figure 5 Population based subgroup meta-analysis was held for the association between 5-HTTLPR polymorphism and LPE (allelic genetic contrast L-allele vs. S-allele).

risk of LPE was not associated with the 5-HTTLPR gene polymorphism in five genetic models, which is different with Zhu *et al.* (26). So we performed subgroup analysis to explore the relationship, the result showed SS genotype was

a risk factor of LPE in Caucasian. In addition, we also found that S-allele also could increase the risk of LPE in Asian. So we suggested that SS genotype and S-allele might be a risk factor for LPE, but needed more large sample statistics

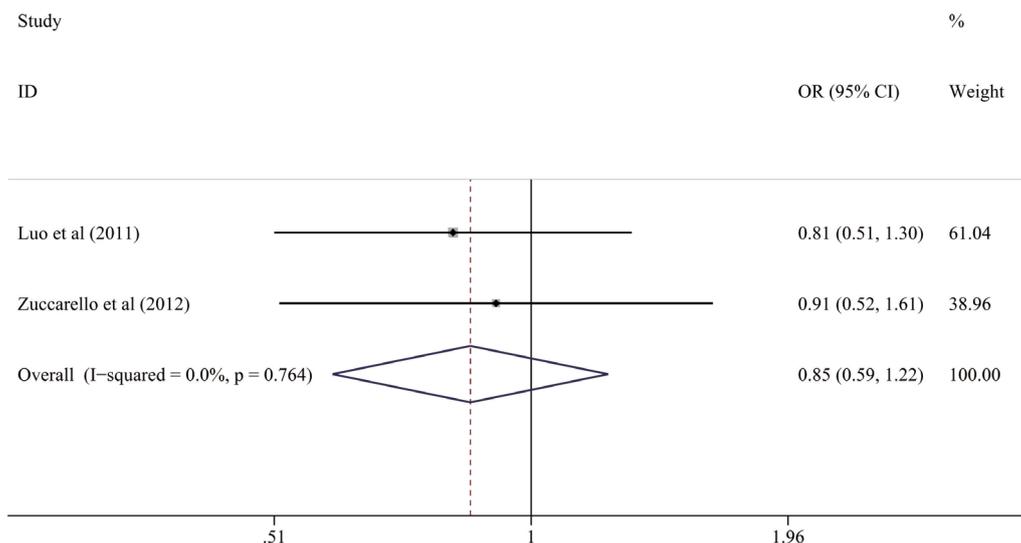


Figure 6 Forest plot of 5-HTTLPR polymorphism and SPE (allelic genetic contrast L-allele vs. S-allele).

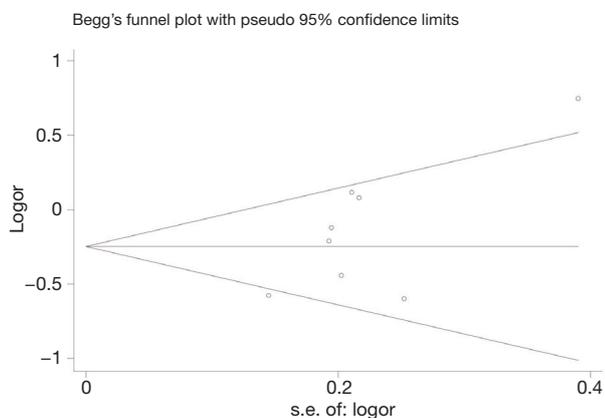


Figure 7 Sensitivity analysis (allelic contrast L-allele vs. S-allele).

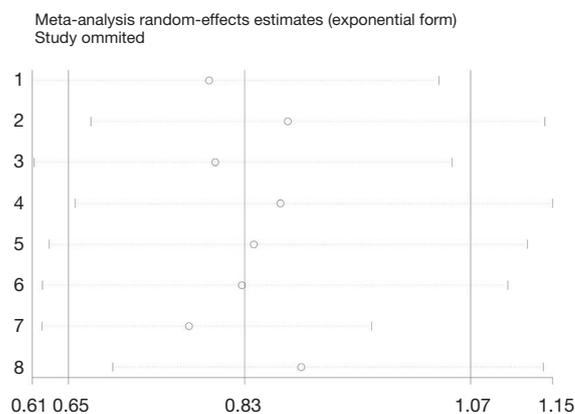


Figure 8 Funnel plot (allelic contrast L-allele vs. S-allele).

to support the conclusion. Otherwise, we also detected the same correlation between 5-HTTLPR polymorphism and susceptibility to LPE in PB population in allelic genetic contrast. Our meta-analysis may help doctor to discover high-risk population of LPE and promote the research of the polymorphism of LPE, it also could be helpful for the treatment of LPE.

LPE is a multifactorial disorder (33). It is mediated by complex interactions of the neurobiological (34), genetic (35), endocrine (36) and psychological (37) factors, which are considered as the significant risk factors for LPE. Endocrine factor might be one of the most vital factors through hormonal regulation of the ejaculatory process. Increasing evidence suggested that testosterone, the key hormone of

male sexuality, is involved in the regulation of ejaculatory reflex (38). Androgens influence ejaculatory reflex by several mechanisms: (I) acting on the various central and peripheral nuclei which are related to the ejaculatory pathways, (II) altering the expression of several mediators which mediate the ejaculatory reflex, and (III) regulating the different pathways which are associated with the contractility of male genital tract (39). Furthermore, recently it was suggested that elevated testosterone and reduced estradiol could enhance the parasympathetic excitation, and as a consequence, ejaculatory latency time will be shortened (38).

Treatment for LPE has progressed since the 1930s. Prazajaculin has been launched in 1932 as the first oral drug

for PE (40). Although dapoxetine had weak ejaculation delaying effect, on-demand use of 30 mg dapoxetine is the first registered oral drug for the treatment of LPE (9). Fortacin topical Spray has been the second registered drug for the treatment of LPE (41). Moreover, there are also many Off-label drugs to treat LPE, especially the selective serotonin reuptake inhibitors (42). Furthermore, on-demand treatment with over the counter topical anesthetics is well established and is effective in delaying ejaculation in men with LPE recently (37). In addition to drug therapy, psychological and psychosexual behavioural therapy has become more and more important for LPE patients (43). It is vital during the management stage to set treatment goals with each patient and partner if appropriate, in order to better guide therapeutic actions.

Combined therapy including pharmacological and non-pharmacological treatment may be the most effective way of treating patients with PE in the future (44). As the effects of PE on a patient and their partner's is multifactorial, exclusive treatment may fail to address certain patient needs. In particular, sole pharmacological treatment may be unable to address significant emotional distress surrounding PE, interpersonal relationships, and unrealistic expectations from patients. Psychological and psychosexual behavioural strategies may similarly fall short in adequately extending IELT in patients or increasing the patient's perceived control over ejaculation. A suggested solution to providing holistic patient care is combination or integrated therapy. A study found that combination therapy of Dapoxetine and psychosexual behavioural treatment was more effective than pharmacological treatment alone in improving IELT in patients with LPE (45), which indicated the promise of combination therapy. A combined treatment of pharmacological, and non-pharmacological management may be superior to pharmacological treatment alone in providing patients with holistic and effective care.

On the one hand, compared with Zhu *et al.*'s research, the data of our study was more abundant and latest. Furthermore, we included 8 studies with 1,604 subjects, containing 898 LPE patients and 706 healthy controls, which made our results more reliable. In addition, we also performed the sensitivity analysis and Begg's test to make our results more credible.

On the other hand, our study also had some disadvantages need to be improved. The size of the sample was still too small to draw any conclusions. So there needed more researches to confirm the conclusion. In our study, the

heterogeneity was significant which reduced the reliability of results. All the same, the heterogeneity was accepted in stratified analysis by ethnicity and suggested strong correlation.

Conclusions

Generally speaking, in our meta-analysis of 8 reliable studies, we found that SS genotype of 5-HTTLPR gene polymorphism increased susceptibility to LPE in Caucasian population, and the S-allele gene was also a risk factor for LPE in Asian. So it can be indicated that SS genotype and S-allele of 5-HTTLPR gene polymorphism were risk factors for LPE. However, no significant correlation was observed between 5-HTTLPR gene polymorphism and LPE in overall studies. More researches were needed to confirm these conclusions.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau.2020.03.39>). The authors have no conflicts of interest to declare.

Ethical Statement: All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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