Journal of Psychology & Psychotherapy
ISSN: 2161-0487

Chen et al., J Psychol Psychother 2015, 5:6
DOI: 10.4172/2161-0487.1000214

Review Article Open Access

The Association of 5-HTTLPR Gene Polymorphisms and Eating Disorder: A Meta-Analysis

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Abstract

Background: Eating disorders (EDs), are characterized by abnormal eating habits, including insufficient or excessive food intake, and are detrimental to an individual's physical and mental health. In this paper, we focus on AN (anorexia nervosa) and BN (bulimia nervosa), which are included in EDs. Some studies reported that there may be an association of 5-HTTLPR gene and eating disorders but without clear conclusion to solidify this relationship. Therefore, the goal of this study is to summarize on the reported data and meta-analytically investigate the relationship between the 5-HTTLPR gene polymorphisms and eating disorders.

Method: We searched through all published papers indexed in MEDLINE, EMBASE, and CNKI from inception to May 2015. All studies that we examined regarding the relationship between 5-HTTLPR polymorphisms and EDs were identified to perform this meta-analysis. Odds ratio (OR) and 95% confidence intervals (CIs) were used to evaluate the EDs risk.

Results: Fourteen studies met the inclusion criteria. We performed this meta-analysis involving 2238 subjects in total (including 1832 EDs patients, 779 AN patients, 722 BN patients and 406 control subjects). The 5-HTTLPR S allele was significantly more common in all EDs patients comparing to controls (S vs. L allele: OR=1.25, 95% CI: 1.02-1.53, P=0.03). This significance was also revealed through the recessive model (SS vs. SL+LL: P=0.008) and the additive model (SS vs. LL: P=0.03). When the comparison was stratified by ethnicity (Caucasian and Asian), it shows that the significance only exists in recessive model among Caucasian population (P=0.03). Subsequently, the EDs patients were divided into two groups (AN and BN) to analyze the association between 5-HTTLPR polymorphism and AN or BN. The results showed that S allele was significantly more frequently discovered in the AN group than in the control group (P=0.006). Other comparison models suggest similar results. Ethnically stratified analysis suggested that 5-HTTLPR polymorphism only correlates with AN among Caucasians, but not Asians. However, no statistical difference was found between BN patients and controls in any comparative analysis.

Conclusion: The 5-HTTLPR S allele can result in increased risk for AN but not BN. Of all the ethnical groups that we studied, Caucasian females appear to be the most likely to become susceptible to EDs/AN under the influence of 5-HTTLPR S allele. These results may be helpful to our clinical practice. However, further studies with larger sample sizes are needed for more reliable and conclusive results.

Keywords: 5-HTTLPR; Polymorphism; Eating disorder; Anorexia nervosa; Bulimia nervosa

Introduction

Eating disorders (EDs) are a category of behavioral disorders commonly found among young females. The onset age of EDs is usually 16-17, and they rarely occur among those over 30 years old. ED females share certain physiological disturbance and physical symptoms, such as distorted consciousness of self-image and abnormal eating pattern. The mortality rate of EDs is 10% ~ 15%, where 2/3 of the deaths result from physical complications and 1/3 from suicide [1]. The spectrum of EDs includes anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorders and so on. Notably, women with EDs may suffer from the gynecological endocrinological conditions, such as infertility and amenorrhea. In consequence, women with EDs have a higher rate of prevalence of amenorrhea and oligomenorrhea than controls [2].

Among the population in upper and middle classes in western countries where the societies are relatively sensitive about body sizes, EDs were traditionally thought as being influenced by culture and social opinions. However, recent family and twin studies indicate that 50% ~ 70% of the illness-driving factors for AN and 28% ~ 83% of that for BN can be traced back to genetic variances [3].

Genetic factors in the eating disorder were mostly reported in the serotonin system. As commonly known, serotonin is involved in mood and appetite regulation [4]. One putative gene in this system involved in eating disorders is the serotonin transporter gene (SLC6A4) since it regulates serotonin reuptake from the synaptic cleft. Most studies investigated the association between SLC6A4 variants and eating disorders referring to the polymorphism of 43 base pair insertion/deletion polymorphism in the promoter region (5-HTTLPR) [5]. 5-HTTLPR consists of a short form (S) and a long form (L). S allele leads to reduced transcriptional efficiency compared with the L allele, which might be the reasons for 5-HTTLPR playing an important role in human's psychological features [6]. The human 5-HTT protein is

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Received August 26, 2015; **Accepted** October 19, 2015; **Published** October 26, 2015

Citation: Chen W, Qian J, Pu D, Ge H, Wu J (2015) The Association of 5-HTTLPR Gene Polymorphisms and Eating Disorder: A Meta-Analysis. J Psychol Psychother 5: 214. doi: 10.4172/2161-0487.1000214

encoded by 5-HTTLPR, which is located on chromosome 17q11.1 to 17q.12. Molecular biological studies support the 5-HTTLPR stress-sensitivity hypothesis [7], that is 5-HTTLPR and stress jointly convey stable changes in serotonin transporter (SERT) expression [8]. The S carriers tend to exhibit lower expression of 5-HTT resulting from reduced reuptake of 5-HT from the synapse, and this may result in stronger psychopathological reactions to stressful experiences than those with L allele [9].

Past studies explored the association between 5-HTTLPR and EDs (including AN and BN), but their results were inconsistent. The present meta-analysis attempts to further clear the relationship between 5-HTTLPR polymorphism and EDs systematically.

Materials and Method

Literature search

To clarify the relationship between 5-HTTLPR and EDs, we screened all related papers up until May 2015 in EMBASE, Pubmed, CNKI (Chinese National Knowledge Infrastructure) and PsychINFO of web knowledge. The keywords we used for searching were "5-HTTLPR", "gene", "Eating disorder", "Anorexia Nervosa", and "Bulimia nervosa". We also screened articles in the reference list to cover as many studies as we can.

Inclusion criteria of studies in the meta-analysis

After reviewing multiple related reviews, we made the following inclusion and exclusion criteria [3,10].

The following are our inclusion criteria: a) published papers; b) case-control or case only studies; c) only English or Chinese papers; d) the participants for studies are unrelated; e) we can get the genetic frequencies of the 5-HTTLPR.

The following are the exclusion criteria: a) The key data is incomplete; b) the participants in paper were also included by other criteria; c) the participants are related (for example, family members).

Data extraction

We have also included the following general information in our table: name of first author, diagnosis, country, diagnosis criteria, and number of samples and control group. For studies not including controls, we use the data of control group from other studies which have similar participants (ethnic) in them: Steiger's study published in 2008 [11] gets control group from his study published in 2009 [12], because they came from a same eating disorder program. The data of the control group in Fumeron's study [13] were applied in three studies of Frieling [14], Urwin [15], Wonderlich [16], because they are mainly causasians.

Statistical analysis

The individual and pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated (The OR and CI were calculated by RevMan http://handbook.cochrane.org). Hardy-Weinberg equilibrium (allele and genotype frequencies in a population will remain constant from generation to generation in the absence of other evolutionary influences) was examined in all studies included in the meta-analysis. Four comparisons were used in this study [17]: S allele vs. L allele (allelic contrast), SS vs. LL+SL genotype (recessive model), SS+SL genotype vs. LL genotype (dominant model), and SS vs. LL (additive model). The present study considers EDs as a whole, AN and BN. Stratified analysis was conducted by ethnicity (Caucasian and Asian) when data were eligible. A random-effects model was used for analysis where there was a significant heterogeneity (I^2>50%) between studies. Otherwise, a fixed-effect model was used for results without obvious heterogeneity.

Data were meta-analyzed by the Cochrane Collaboration Review Manager software (RevMan version 5). P<0.05 was considered to be statistically significant in this trial unless otherwise specified.

Results

Study characteristics

The initial search yielded twenty-four papers and the abstracts were carefully reviewed in order to investigate if they fulfill the inclusion criteria. Of the twenty-four articles, four were excluded because they were reviews [10,18-20]. One paper was excluded because the participants were all patients with obesity [21]. One was excluded because the participants were adolescent and young adult female twins and female non-twin siblings [22]. Four [11,15,23,24] were excluded because they did not meet the inclusion criteria (details can be found in the following discussions section). Finally, fourteen papers are included in this study (Table 1). The information from these studies is summarized in Table 2.

Meta-analysis

Fourteen studies [11,13-16,19,25-32], involving 1832 EDs patients and 406 controls, were eligible for analysis (Figure 1). In the comparison of allele contrast, it is shown that S allele is more frequent in ED patients than in controls (S allele vs. L allele: OR=1.25, 95% CI 1.02-1.53, P=0.03). The significance also exists in the recessive model (SS vs. LL+SL, P=0.008, Figure 2) and additive model (SS vs. LL, 0.03). But in dominant model (SS+SL vs. LL), there was no statistical significance

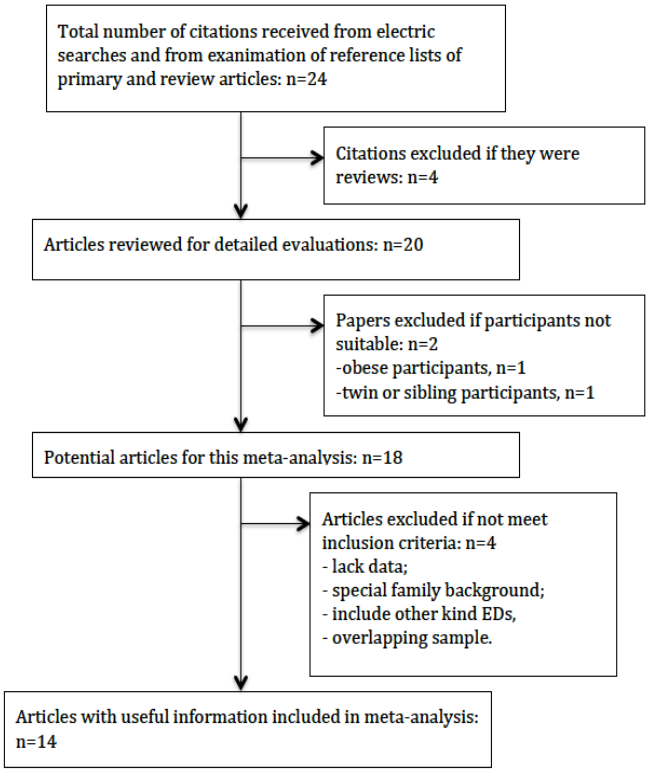

Figure 1: Studies identified with criteria for inclusion and exclusion.

Author	Classification	Country	Diagnostic and assessment criteria	Sample size	
				Case	Control
Steiger [12]	EDs	Canada	EDE	185	93
Steiger [11]	BN, EDNOS	Canada	DSM-IV-TR, EDE, EDE-Q, CES-D, BASIS-32, BIS-11	111	
Rybakowski [30]	AN	Poland	DSM-IV, TCI	132	93
Frieling [14]	AN and BN	Germany	DSM-IV, SCID-I, SCID-II; EDI-2	40	
Wondelich [16]	BN	US	DSM-IV, SCID-IP, DAPP-BQ, IBS, EDEQ-4; MAST/AD; IDS-SR; STAI; MOCI	178	
Monteleone [24]	BN	Italy	DSM-IV, SCID-I, SCID-II, MINI, TCI-R	125	94
Matsushita [26]	ED	Japan	DSM-IV	195	
	AN			77	
	BN			118	
Lauzurica [32]	BN	Spain	DSM-IV	102	
Fumeron [13]	AN	France	DSM-IV	67	
Sundaramurthy [27]	AN	UK	DSM-IV	138	90
Di Bella [29]	AN and BN	Italy	DSM-IV	106	
Castellini [19]	ED	Italy	DSM-IV	201	
	AN			113	
	BN			88	
Yue [28]	AN	China	HAMD, HAMA, EDE-Q, Y-COBS, EDI-II	198	
Chen [25]	AN	China	HAMD, HAMA, EDE-Q, Y-COBS, SCID-II	54	36

EDs: Eating Disorders; EDE: Eating Disorder Examination (EDE: Fairburn and Cooper, 1993); BN: Bulimia Nervosa; EDNOS: Eating Disorder Not otherwise Sepcificed; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (Text Revision); EDE-Q: Eating Disorder Examination Questionnaire; CES-D: The Center for Epidemiologic Studies Depression Scale; BASIS-32: The Behavior and symptoms Identification Scale; BIS-11: The Barratt Impulsivity Scale-version 11; SCID-I: Structured Clinical Interview for DSM-IV Axis-I disorders; SCL-90R: Symptom Checklist90 Revised; AN: Anorexia Nervosa; EDI-2: Eating Disorder Inventory -2; SCID-IP: Structured Clinical Interview for DSM-IV Patient Edition (First et al, 1997); DAPQ: Dimensional Assessment of Personality Pathology Basic Questionnaire (DAPP- BQ); IBS: Impulsive Behavior Scale; EDE-Q4: Eating Disorder Examination Questionnaire 4; MAST/ AD: Michigam Assessment Screening Test/ Alcohol- Drug; IDS-SR: Inventory for Depressive Symptomatology - Self Report; STAI/SSAI: Spielberger Stait- Trait Anxiety Inventory; MOCI: Maudsley Obsessive- Compulsive Inventory; SCID-II: Structured Clinical Interview for DSM-IV Axis-II disorders; MINI: Mini International Neuropsychiatric Interview; TCI-R: Temperament and Character Inventory Revised; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale; Y-COBS: Y-COBS:e·Brown Obsessive Compulsive Scale.

Table 1: Basic information of included studies.

Disease	N	Comparisons	Models	Subgroups	OR	95% CI	I^2 (%)	P value
EDs	14	S allele vs. L allele	allele contrast	Total	1.25	1.02, 1.53	76	0.03
	11			Caucasian	1.24	0.97, 1.58	78	0.08
	3			Asian	1.29	0.85, 1.97	72	0.23
	14	SS vs. LL+SL	recessive model	Total	1.41	1.09, 1.81	59	0.008
	11			Caucasian	1.43	1.04, 1.96	62	0.03
	3			Asian	1.35	0.84, 2.17	66	0.21
	14	SS+SL vs. LL	dominant model	Total	1.31	0.95, 1.80	70	0.1
	11			Caucasian	1.26	0.89, 1.79	74	0.19
	3			Asian	1.58	0.70, 3.59	51	0.27
	14	SS vs. LL	additive model	Total	1.59	1.05, 2.42	73	0.03
	11			Caucasian	1.58	0.97, 2.56	77	0.07
	3			Asian	1.72	0.69, 4.29	59	0.25
AN	8	S allele vs. L allele	allele contrast	Total	1.35	1.09, 1.67	53	0.006
	5			Caucasian	1.26	1.05, 1.53	13	0.01
	3			Asian	1.42	0.84, 2.42	75	0.19
	8	SS vs. LL+SL	recessive model	Total	1.55	1.16, 2.06	40	0.003
	5			Caucasian	1.51	1.04, 2.19	30	0.03
	3			Asian	1.54	0.91, 2.61	63	0.11
	8	SS+SL vs. LL	dominant model	Total	1.32	1.03, 1.69	6	0.03
	5			Caucasian	1.26	0.97, 1.62	0	0.08
	3			Asian	1.52	0.43, 3.16	60	0.5
	8	SS vs. LL	additive model	Total	1.69	1.13, 2.54	39	0.01
	5			Caucasian	1.6	1.08, 2.36	18	0.02
	3			Asian	1.77	0.42, 7.54	67	0.44
BN	7	S allele vs. L allele	allele contrast		1.24	0.84, 1.81	86	0.27

	7	SS vs. LL+SL	recessive model		1.3	0.81, 2.09	76	0.28
	7	SS+SL vs. LL	dominant model		1.47	0.79, 2.72	83	0.22
	7	SS vs. LL	additive model		1.71	0.75, 3.89	85	0.2
EDs: eating disorders; AN: anorexia nervosa; BN: bulimia nervosa; OR: odds ratio; CI: confidence interval; I2, Cochrane's x2-based Q statistic test for assessing heterogeneity (>50% indicates substantial heterogeneity).								

Table 2: Meta-analysis of 5-HTTLPR polymorphisms on risk of eating disorders.

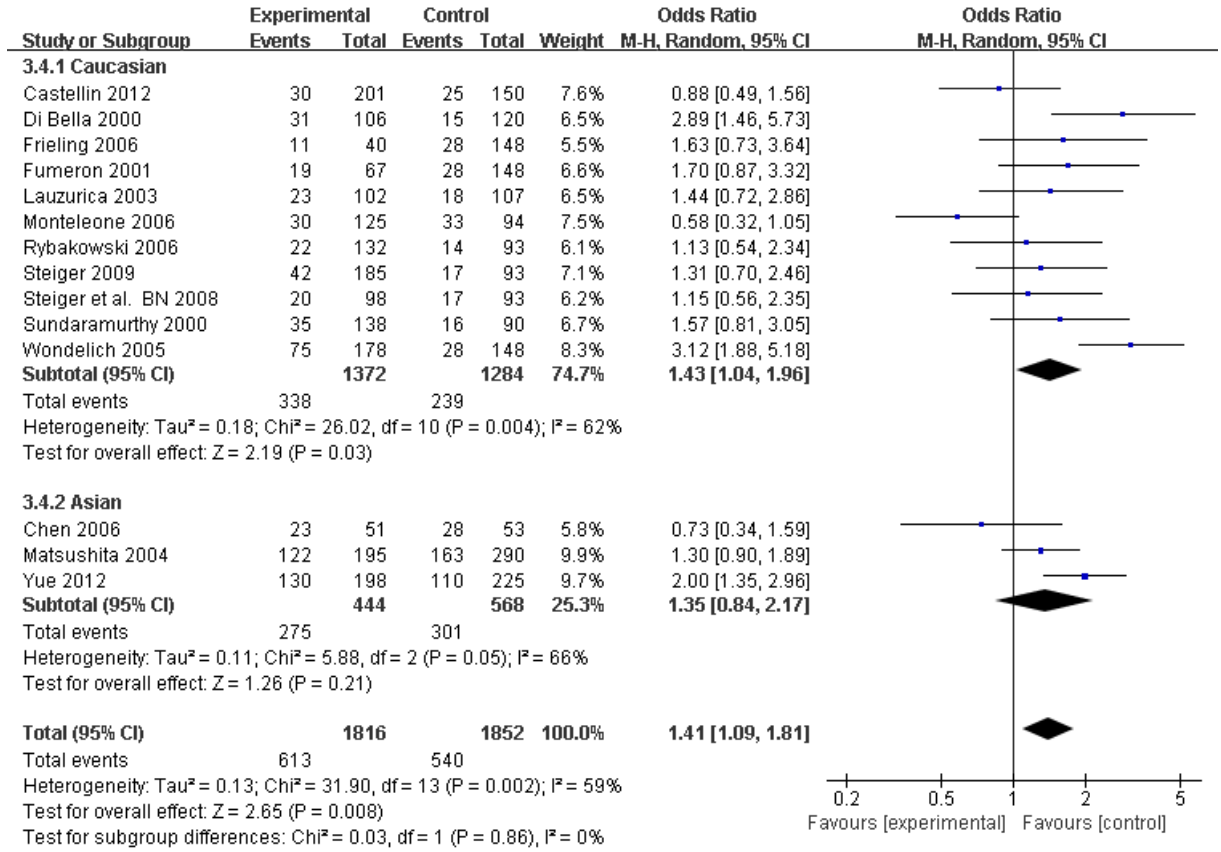

Figure 2: Association between 5-HTTLPR polymorphism and risk of eating disorders in recessive model (SS genotype versus SL+LL genotype).

(P=0.1). However, when stratified by ethnicity, only recessive model comparison reached statistical significance in the Caucasian population (P=0.03) (Figure 2 and Table 2).

For AN and BN, the results were all statistically significant among all four kinds of comparisons in AN patients comparing to control population by pooling results of eight studies (S allele vs. L allele, allele contrast: OR=1.35, 95% CI 1.09-1.67, P=0.006, Figure 3; SS vs. LL+SL genotype, recessive model: OR=1.55, 95% CI 1.16-2.06, P=0.003; SS+SL genotype vs. LL genotype, dominant model: OR=1.32, 95% CI 1.03-1.69, P=0.03; SS vs. LL, additive model: OR=1.69, 95% CI 1.13-2.54, P=0.01). In contrast, no remarkable difference was found in any of the comparison models of BN subtype by meta-analyzing seven studies (P>0.05). The participants were also stratified by ethnicity, and all the comparison models were statistically significant except for the dominant model in the Caucasian subgroup, while no remarkable difference was found in any comparisons among the Asian subgroup (Table 2).

Discussion

Numerous studies have investigated the correlation between 5-HTTLPR polymorphism and the risk for EDs, but the results from individual studies are inconsistent. Although there have been some published meta-analysis cases [3,10,20,33], the topic was so interesting to the readership that we re-examined the databases and made an update to renew the results of the linkage between 5-HTTLPR polymorphism and EDs, and to obtain potential new findings.

Hinney and colleagues [21] were the first researchers who studied the relationship between 5-HTTLPR polymorphism and AN in 1997. After that, more studies investigating the association of them were carried out. However, the results were controversial. In our research, we discovered that there was no association between 5-HTTLPR and BN. It suggests that including the BN patients in study might be the cause of those controversial results with studies only focusing on AN patients. The result matches the conclusion that AN people have restricted emotional and behavioral features but BN people have impulsive ones [11,12]. These emotional and behavioral differences reflect the genetic differences between AN and BN [34]. Therefore, meta-analysis was performed to gather more reliable evidence. Gorwood [33], Lee [3] and Calati [10] reported that 5-HTTLPR S allele was associated with EDs, especially AN. Polsinelli et al. [20]

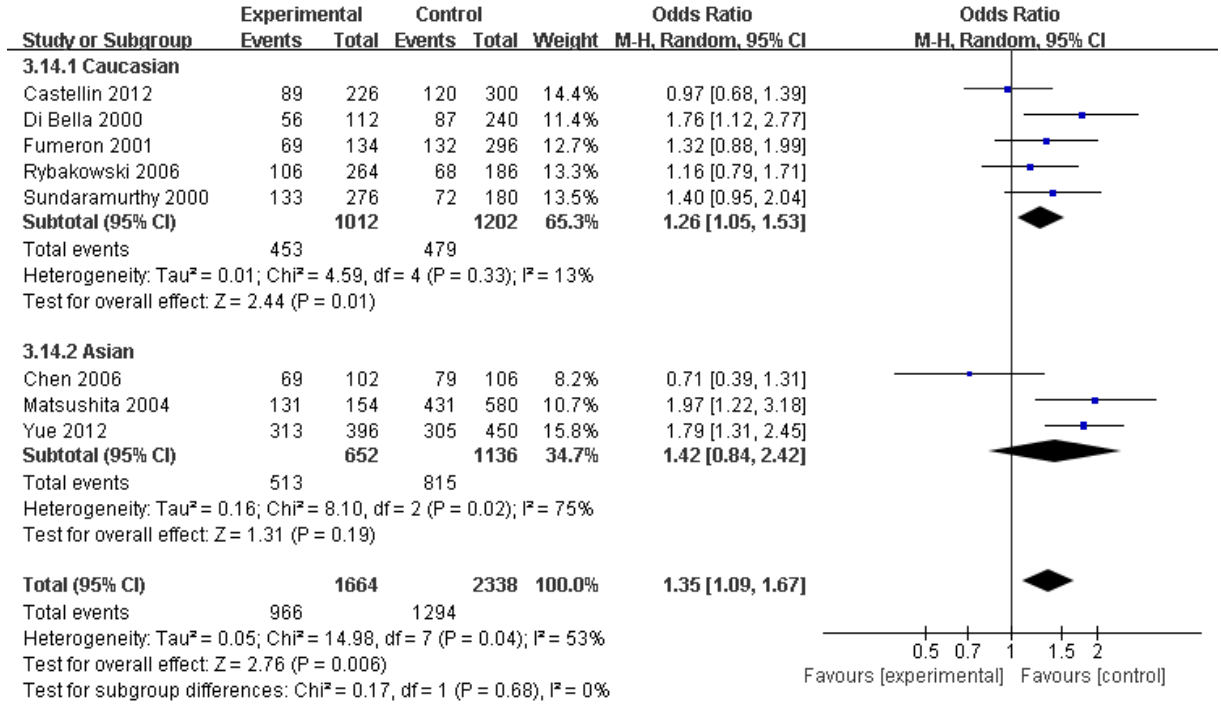

Figure 3: Association between 5-HTTLPR polymorphism and risk of anorexia nervosa in allele contrast (S allele versus L allele).

carried out a meta-analysis (five studies) on the association between 5-HTTLPR and BN, but no significant correlation was found. In the present study, we added three new articles [19,25,28] for meta-analysis to compare with the meta analysis of [10]. we deleted four articles, because the [23] lacks certain specific data: there was no S or L allele frequencies, and the participants in [15] have both parents alive which is not a usual family background for ED patients who always came from incomplete families, [24] includes binge eating disorder patients while this paper only focuses on AN and BN patients. Also, the participants in [11] had been included in another paper of Steiger in 2008 which we have included (we deleted it to avoid repeated inclusion. The pooling result was consistent with the previous meta-analysis, showing that 5-HTTLPR S allele was correlated with EDs as a whole, mainly in allele contrast, recessive model and additive model (P=0.03, 0.008, 0.03), respectively. Subsequently, subtypes of EDs, including AN and BN, were analyzed separately. Results show that 5- HTTLPR S allele was significantly associated with AN (allele contrast: P=0.006, recessive model: P=0.003, dominant model: P=0.03, additive model: P=0.01), but not BN (P>0.05). In addition, the authors conducted further stratified analysis by ethnicity, Caucasian and Asian, finding that all the significance only exists in Caucasian populations, but not among Asians. This result is very interesting and different from previous findings, and implies that there is ethnicity-dependent discrepancy in susceptibility to EDs/AN among people with S allele.

Several limitations might arise in this study. Due to the low incidence of EDs, the sample size is small and number of related studies is low. Besides, although we extracted the data concerning Caucasians and Asians, other ethnic groups such as Africans are not evaluated. Despite these limitations, findings from the present meta-analysis do show a strong association of 5-HTTLPR polymorphism with increase the susceptibility to AN among Caucasian populations. These observations may be used as a starting point for further laboratory and epidemiological investigations aimed at better understanding of the molecular pathways and etiological factors contributing to AN risk.

In conclusion, our data suggest that 5-HTTLPR polymorphism may contribute to individual susceptibility to anorexia nervosa for Caucasians. However, evidence was not sufficient to confirm this association for Asians. Moreover, there was no correlation between 5-HTTLPR polymorphism and bulimia nervosa. More studies are needed to determine the mechanism of 5-HTTLPR gene influencing the risk of developing eating disorders, as well as its genetic and environmental interactions with other risk factors.

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