Original Article
Positive association between interleukin-6 -174G/C polymorphism and schizophrenia: a meta-analysis

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Abstract: Interleukin-6 is involved in the pathogenesis of schizophrenia. Several experiments have investigated the association between schizophrenia and IL-6 -174G>C polymorphism, while the conflicting results have been observed inter-and intra-ethnicities. Therefore, this meta-analysis was conducted comprehensively and systemically. In summary, there was significant correlation between the IL-6 -174G>C polymorphism and the risk of Schizophrenia. Here were the results for allelic (C versus G, OR=1.273, 95% CI=1.080-1.501, P=0.004), homozygote (CC versus CG, OR=1.493, 95% CI=1.033-2.158, P=0.033), heterozygote (CG versus GG, OR=1.581, 95% CI=1.224-2.043, P=0.000), dominant (CG/CC versus GG, OR=1.585, 95% CI=1.241-2.024, P=0.000), and recessive (CC versus CG/GG, OR=1.129, 95% CI=0.820-1.554, P=0.457) models. Subgroup analysis showed the significant associations in Caucasian in allelic (C versus G, OR=1. 255, 95% CI=1.055-1.493, P=0.010), heterozygote (CG versus GG, OR=1.626, 95% CI=1.227-2.154, P=0.001, and dominant (CG/CC versus GG, OR=1.613, 95% CI=1.232-2.112, P=0.000) models, while not in Indian Bengalese. Finally, we concluded that the IL-6 rs1800795 allele C was a potential risk factor in schizophrenia, especially for the Caucasian.

Keywords: Schizophrenia, rs1800795, polymorphism, IL-6, interleukin-6

Introduction

Schizophrenia is a serious psychiatric disorder, characterized by delusions, hallucinations, severe cognitive abnormalities, and emotional impairment and behavior dysfunctions [1]. According to a report by Chinese Center for Disease Control and Prevention, the schizophrenia populations had reached to the unprecedented 10 million in China, with an incidence of over 7.81‰ [2]. Correspondingly, from 2010 to 2012, direct medical expenditure on schizophrenia in Guangzhou city were 14.72 million, 25.94 million, and 30.42 million dollars, respectively. While the indirect expense related to schizophrenia were 168.72 million, 184.91 million, and 211.55 million dollars [2]. Despite the remarkable expenditure on schizophrenia [3], the underlying etiopathogenesis remains elusive. To date, it is acknowledged that schizophrenia is strongly associated with the interaction of multiple genes and susceptible environment [4]. Previously, a meta-analysis [5] based on twin studies of schizophrenia was performed to quantitatively estimate the impact of genetic heterogeneity and environment susceptibility on susceptibility to schizophrenia, and concluded that substantial additive genetic heritability in liability to schizophrenia was up to 81%. Subsequently, the genome-wide association studies [6, 7] have also supported that there is a genetic association through comparison of common single nucleotide polymorphisms (SNPs) with the human genome and a cluster of SNPs such as IL-6 -174G>C polymorphism or rs1800795 polymorphism have been identified as susceptible biomarkers for schizophrenia. Up to now, several researches have suggested that the immune system dysregulation is involved in the pathogenesis of schizophrenia. Alterations of the immunoinflamatory-related cytokine concentrations such as IL-6, IL-8, and tumor necrosis factor alpha (TNFα) demonstrated to be responsible for schizophrenia [8].

Cytokines consisted of interferons, interleukins, TNFα, and chemotactic factors are core components associated with inflammatory response, both in the Centre nervous system (CNS) and peripheral environment. Interleukin-6

belongs to the immunoinflamatory super family and is strongly associated with schizophrenia-related immune system disorder [9]. Over the past few years, multiple institutes have reported altered levels of Interleukin-6 in the serum and cerebrospinal fluid of subjects suffering from schizophrenia [10]. Furthermore, Di Nicola M et al. [11] reported that the gene expression of IL-6 in leukocytes was increased when compared with the health subjects and Fung SJ et al. [12] founded the similar result in dorsolateral prefrontal cortex. Additionally, Kalmady S et al. [13] found that there was a significant association between IL-6 -174G>C variation and both hippocampal sizes in the male schizophrenia patients rather than in the female. Thus, Interleukin-6 gene polymorphisms, located in the position-174 of IL-6 promoter sequence, probably exert influence on the risk of schizophrenia through affecting the expression of the Interleukin-6 gene.

With regard to the IL-6 -174G>C polymorphism, the relevant findings are inconsistent across different institutions. In the Polish population, Paul-Samojedny M et al. [14] reported that the rs1800795 genotype GC correlates with increasing risk of paranoid schizophrenia. However, in in Indian Bengalese population Debnath M et al. [15] reported that there were no significant differences in distributions of genotype as well as allele for IL-6 gene variants between the case and control groups. On the other hand, in Chinese not only the case but also the control group were almost comprised of the IL-6 -174G>C genotype GG [16].

There are a series of potential explanations for those inconsistent conclusions, such as small sample problems, genetic background heterogeneity, and publication bias. Therefore, we, comprehensively and systemically, performed this meta-analysis to synthesize the results of conflicting studies to investigate the association between IL-6 -174G>C gene polymorphism and the risk of schizophrenia.

Materials and methods

Literature search

All studies that investigated the association of the -174G>C polymorphism in the IL-6 gene with the risk of schizophrenia published before August 2015 were considered in the meta-analysis. The studies were identified by extended computer-based search of the PubMed and EMBASE database. A number of Chinese databases including SinoMed and China National Knowledge Infrastructure were also searched. As a search criterion, the combination of following terms was used: ('IL-6' or 'interleukin-6') and ('schizophrenia' or 'affective disorder' or 'bipolar') and ('polymorphisms' or 'single nucleotide polymorphism' or 'SNP' or 'variation'). There were no language restrictions in our study selection. In addition, all references cited in the studies were also checked to identify more eligible published work.

Study selection

The inclusion criteria of our meta-analysis were as follows: (1) case-control study; (2) examining the association between schizophrenia and the IL-6 gene polymorphisms; (3) reporting of sufficient data and the odds ratio (OR) of alleles and genotype can be determined; (4) genotype frequencies in controls followed the Hardy-Weinberg equilibrium. Exclusion criteria: (1) abstracts, case reports and review articles or not case-control studies; (2) studies deficient in the original data needed for statistical analysis; (3) duplicated reports.

Data extraction

Two investigators independently extracted the datum from the included publications. Any disagreement was resolved through discussion until the two authors reached a consensus on all items. From each eligible study the following information was extracted: first author, journal, year of publication, country of origin, ethnicity, sample size, study design, characteristics of patients, alleles and genotype of IL-6 -174G/C, evidence of Hardy-Weinberg equilibrium.

Statistical analysis

We calculated the ORs and their 95% confidence intervals (95% CIs) to assess the association between IL-6 -174G/C polymorphisms and schizophrenia risk. The pooled ORs were performed for allele frequency comparison (C vs G), heterozygote model (CG vs GG), homozygote model (CC vs GG), dominant model (CG/CC vs GG), and recessive model (CC vs CG/GG) models to evaluated the relationship between IL-6 -174G/C polymorphism and schizophrenia.
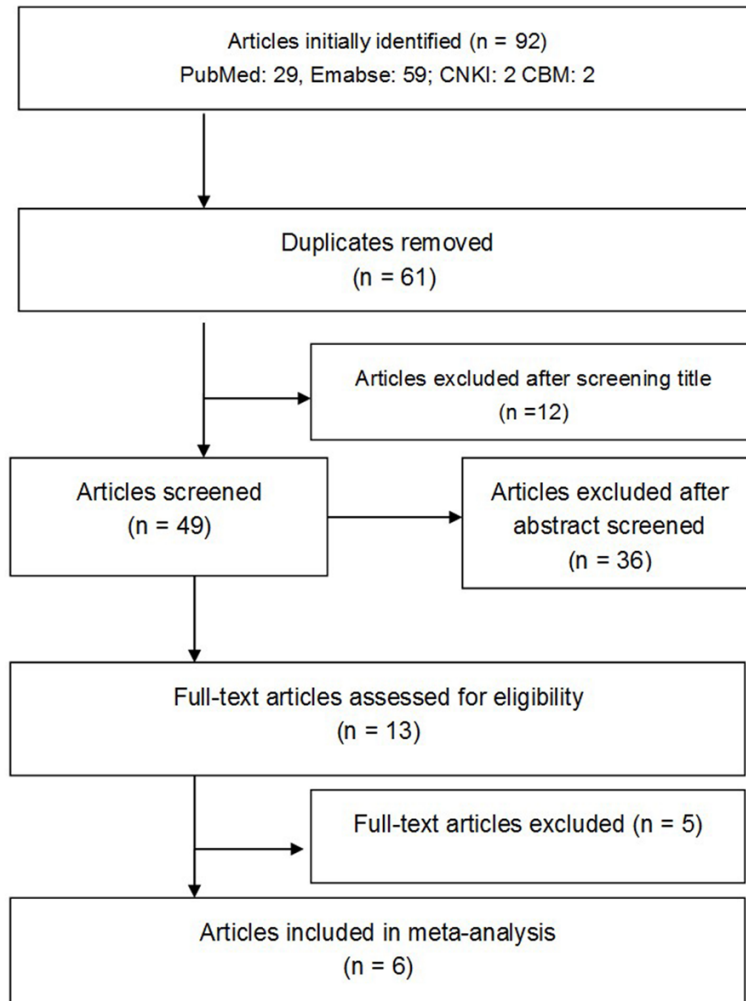
Figure 1. Flowchart of searching literatures that meet the inclusion criteria.

porated in this meta-analysis (**Figure 1**). In those studies, only 2 studies were conducted in Indian Bengalese population [13, 15] and 4 experiments were conducted in Caucasian [10, 14, 17, 18]. There were 593 cases and 771 controls in this meta-analysis. All DNA samples were extracted from leukocyte, and the patients were diagnosed by psychiatrist using Structured Clinical Interview. The descriptive characteristics of eligible studies were demonstrated in **Table 1**. The genotype distributions in the control groups were satisfied with Hardy-Weinberg equilibrium (HWE).

Quantitative data synthesis

Overall, there was significant correlation between the IL-6 (-174G>C) polymorphism and increasing risk to schizophrenia. Here were the results for allelic (C versus G, OR=1.273, 95% CI=1.080-1.501, P= 0.004), homozygote (CC versus CG, OR=1.493, 95% CI= 1.033-2.158, P=0.033), heterozygote (CG versus GG, OR=1.581, 95% CI=1.224-2.043, P=0.000), dominant (CG/CC versus GG, OR=1.585, 95% CI=1.241-2.024, P=0.000), and recessive (CC versus CG/GG, OR=1.129, 95% CI=0.820-1.554, P=0.457) models. When stratified by ethnicity, the significant associations were detected in Caucasian in allelic (C versus G, OR=1. 255, 95% CI=1.055-1.493, P=0.010), heterozygote (CG versus GG, OR= 1.626, 95% CI=1.227-2.154, P=0.001, and dominant (CG/CC versus GG, OR=1.613, 95% CI=1.232-2.112, P=0.000) models, while the corresponding result were not statistically detected in Indian Bengalese population. The pooled ORs coupled with 95% CI based on allele contrast, heterozygote and homozygote models are demonstrated in **Table 2**. Correspondingly, the pooled results of dominant and recessive models are demonstrated in **Figure 2** and **Figure 3**, respectively.

The heterogeneity between studies was tested using the Q-statistic and quantified by calculating the inconsistency index I^2. ORs were pooled by the fixed effect model if the I^2 value is <50% or P>0.10; otherwise, the random effect model was adopted. Sensitivity analyses were performed to examine the effect of excluding specific studies. We also performed subgroup analysis according to the ethnicity of the study population. Analyses were performed using Stata 12.0. All statistical tests were 2-sided.

Results

Search result and study characteristics

In the initial search, 54 potentially relevant articles were retrieved, among which 6 studies meeting the inclusion criteria were finally incor-

Table 1. The descriptive characteristics of studies included in this meta-analysis

Author	Year	Country	Study design	Source of control	Detection method	Score	Ethnicity	Group	HWE	Age Mean/SD (year)	Size	Rs800795 alleles		Rs1800795 genotypes		
												C	G	CC	CG	GG
Monika Paul-Samojedny et al.	2010	Poland	Case control	DSM-IV-TR	PCR-RFLP	8	Caucasian	Case	0.78	44.8/11.6	96	87	105	11	65	120
								Control	0.74	392/19.3	120	104	136	21	62	37
Monojit Debnath et al.	2012	India	Case control	DSM-IV-TR	ABI 3730	8	Indian Bengalese	Case	0.76	Unavailable	100	30	170	5	20	75
								Control	0.91	Unavailable	100	17	183	1	15	84
Zakharyan R et al.	2012	Armenia	Case control	DSM-IV-TR	PCR-SSP	8	Caucasian	Case	0.74	46/9.8	103	78	128	14	50	39
								Control	0.70	37.3/11.3	105	50	160	6	38	61
Dorota Frydecka et al.	2013	Poland	Case control	DSM-IV-TR	Taqman	8	Caucasian	Case	0.56	38.0/11.9	151	150	152	39	72	40
								Control	0.45	38.7/8.8	274	256	292	64	128	82
Sunil Vasu Kalmady et al.	2014	India	Case control	DSM-IV-TR	ABI 3730XL	8	Indian Bengalese	Case	0.96	29.9/57	28	7	49	0	7	21
								Control	0.81	27/5.6	37	12	62	2	8	27
Monika Paul-Samojedny et al.	2014	Poland	Case control	DSM-IV-TR	PCR-RFLP	8	Caucasian	Case	0.56	43/12.6	115	104	126	12	80	23
								Control	0.53	41.3/9	135	108	162	15	78	42

DSM-IV-TR means diagnostic and statistical manual of mental disorders; Score is calculated based on Newcastle-Ottawa scale.

Table 2. Results of allele contrast, heterozygote and homozygote models for the IL-6 -174G>C polymorphism and schizophrenia

Compared models of rs1800795	Test of association			P value	Model	Test of heterogeneity	
	OR	95% CI				p	I^2 (%)
Overall							
C vs G	1.273	1.080	1.501	0.004	F	0.156	37.5
CG vs GG	1.581	1.224	2.043	0.000	F	0.620	0.0
CC vs GG	1.493	1.033	2.158	0.033	F	0.306	16.7
Caucasian							
C vs G	1.255	1.055	1.493	0.010	F	0.152	43.3
CG vs GG	1.626	1.227	2.154	0.001	F	0.371	4.3
CC vs GG	1.440	0.982	2.110	0.062	F	0.254	26.4
Indian							
C vs G	1.452	0.862	2.499	0.161	R	0.118	59.0
CG vs GG	1.377	0.739	2.566	0.313	F	0.678	0.0
CC vs GG	2.406	0.574	10.076	0.230	F	0.195	40.5

Sensitive analysis and publication bias

Trough removing each article of prominent statistical heterogeneity in this meta-analysis, the sensitivity was investigated. No matter which article was rejected, the pooled results did not change remarkably in 5 models. **Figure 4** listed the estimates of sensitive analysis in allelic model. Thus, the stability and credibility of this meta-analysis was guaranteed. Furthermore, this meta-analysis did not perform publication bias for that the number of studies included was less than 10.

Discussion

Immune system plays a vital role in emotional adjustment and cognitive immune system deregulation on the susceptibility to schizophrenia has been increasingly recognized. Not only cerebral cell components such as neurons, microglia, astrocytes but also peripheral immune cells have been involved in inflammation in schizophrenia [19]. Over decades, schizophrenia is speculated to be associated with immunoinflamatory reactions regulated by cytokines [20]. Several institutions have reported the abnormal antioxidant levels and signs of oxidative stress both in peripheral tissue [21-23] and nervous tissue [24, 25] of schizophrenia. Correspondingly, Fillman S et al. [26] reported that these plasma cytokine abnormalities such as elevated IL-6 level were also correlated with cognitive impairment and brain volume loss. In addition, it had been reported that the elevated circulating IL-6 concentrations were responsible for the duration and the treatment resistance of schizophrenia [27, 28]. Furthermore, another study showed a positive correlation between the severity of symptoms and plasma IL-6 levels in schizophrenic patients without taking antipsychotic drugs and the IL-6 levels were significantly decreased after antipsychotic treatment [29]. Obviously, immunological changes are highly associated with schizophrenia. The relevant changes may result from cytokine-level disorders linked with cytokine gene polymorphisms such as IL-6 -174G>C polymorphism.

The human IL-6 encoding gene is located in the short arm of chromosome 7 (7p21). Four polymorphism sites including IL-6 -174G>C, IL-6 -373A>G IL-6 -572G>C, and IL-6 -597G>A in promoter region have been identified. IL-6 -174G>C polymorphism located in the promoter region, in which the SNP is associated with transcription but is not being translated into messenger RNA. Even though in a normal population a previous meta-analysis [30] concluded that IL-6 -174G>C polymorphism was not significantly associated with plasm IL-6 concentration, in schizophrenic patients Zakharyan R et al. [18] concluded that IL-6 -174G>C polymorphism was linked to elevated IL-6 serum level in Armenian population. Correspondingly, Kalmady SV et al. [13] reported that IL-6 -174G>C polymorphism was involved in reduced hippocampal volume in schizophrenia. Furthermore, IL-6 -174G>C polymorphism was associated with early psychotic symptoms [10]. The corresponding results suggested that IL-6 -174G>C polymorphism was of potential to link with the underlying mechanism of schizophrenia. This meta-analysis, systematically and comprehensively, synthesized the totality of evidence, and found that IL-6 -174G>C polymorphism, due to a G to C transition, was significantly associated with the schizophrenia.

To our best of knowledge, this was the first meta-analysis to investigate the association

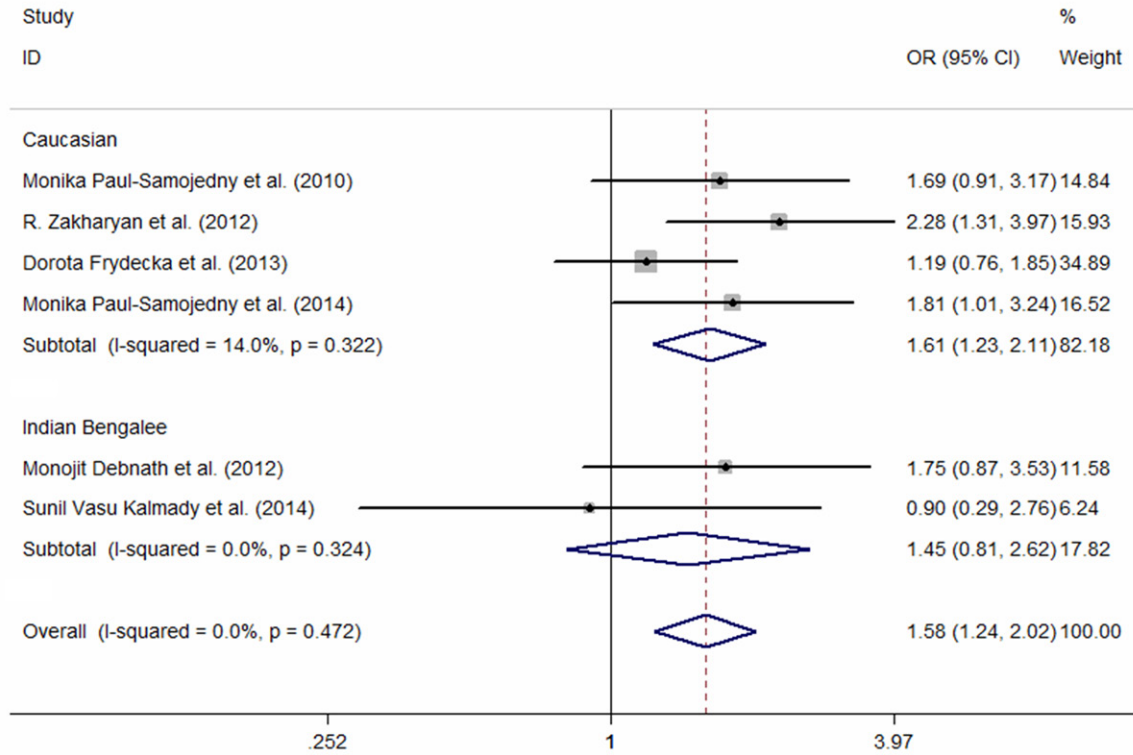# Association between IL-6 -174G/C polymorphism and schizophrenia

Figure 2. Forest plot describing the meta-analysis under dominant models for the association between the IL-6 polymorphism and increasing risk to schizophrenia(CG/CC versus GG).
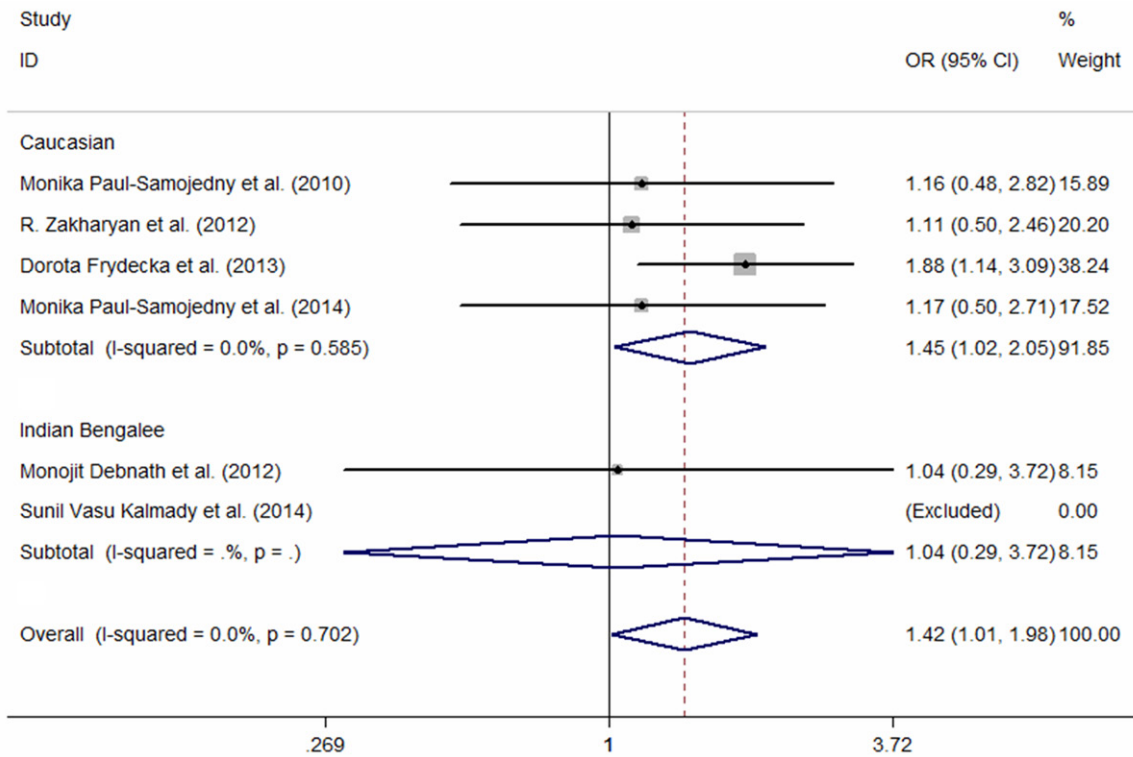

Figure 3. Forest plot describing the meta-analysis under recessive models for the association between the IL-6 polymorphism and increasing risk to schizophrenia (CC versus CG/GG).
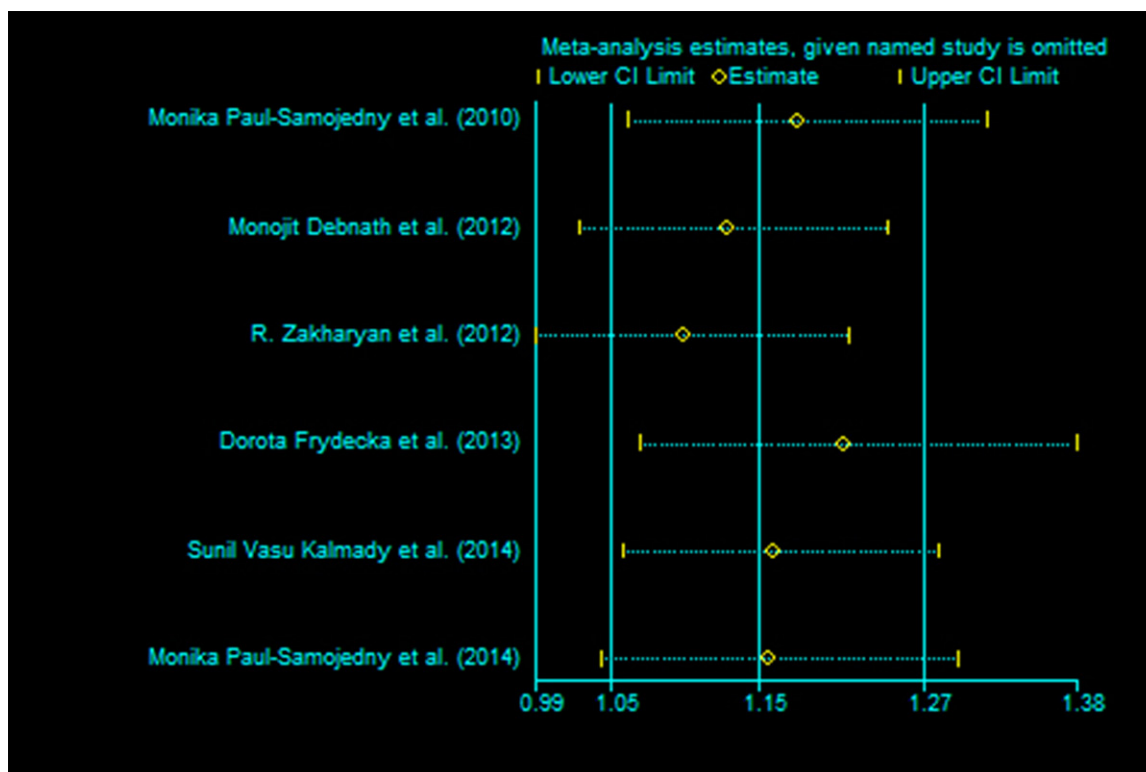
Figure 4. Sensitivity analysis under allelic models for association between the IL-6 polymorphism and increasing risk to schizophrenia.

between the IL-6 -174G>C polymorphism and schizophrenia. In this study, IL-6 -174G>C genotype CC and CG increased the susceptibility to schizophrenia, and the C allele was also positively associated with schizophrenia as a risk factor. The subgroup analysis also suggested the IL-6 -174G>C allele C, genotype CC and CG were statistically marginally significantly associated with schizophrenia within Caucasian, while there was no significant association among Indian Bengalese population. It was well-established that each ethnicity belonged to its unique genetic heterogeneity and environmental susceptibility factors comprised of socioeconomic status, stress and culture background, which might account for the different results. Thus, the interaction of gene-and-gene and gene-and-environment should be paid enough attention.

The current meta-analysis possessed the significant strength for the larger sample size and strict inclusion criteria. However, the following limitations must be taken into account. Firstly, those pooled ORs combined with 95% CI were calculated based on original articles without any adjustment. So we should take the relevant factors such as stress into serious consideration. Secondly, only 6 articles were included and only 2 experiments were conducted in Indian Bengalese population, which, coupled with the relatively small sample size, might misrepresent the underlying associations. Finally, this meta-analysis only included articles in Chinese and English, which, inevitably, missed several important articles. Therefore, the large-scale and well-designed experiment should be conducted to investigate the underlying associations among different ethnicities.

In conclusion, our meta-analysis demonstrated that the C allele of the IL-6 rs1800795 polymorphism might be a potential risk factor in schizophrenia. Given the limited eligible article and the small sample size in this meta-analysis, these results need further investigation.

Disclosure of conflict of interest

None.

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