Effects of risperidone on blood levels of interleukin-6 in schizophrenia
A meta-analysis

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Abstract

Background: To evaluate the association between risperidone use and interleukin-6 (IL-6) levels by conducting a meta-analysis of controlled before-and-after studies.

Methods: Studies were identified through a systematic search of PubMed and Embase. The mean and standardized differences were extracted to calculate the standardized mean differences. IL-6 levels were compared in patients with schizophrenia before and after risperidone treatment.

Results: Ten studies were included in the final meta-analysis. The primary findings from our study suggest that there was a significant decrease in serum IL-6 levels after risperidone treatment ($P = .021$). A subgroup analysis revealed the sources of heterogeneity. The sensitivity analysis indicated that the results were stable, and no publication bias was observed.

Conclusions: The present meta-analysis provides evidence that risperidone can significantly reduce IL-6 levels in schizophrenia. IL-6 is a potential biomarker of the pathophysiology and clinical processes of schizophrenia.

Abbreviations: CNS = central nervous system, CSF = cerebrospinal fluid, IL-6 = interleukin-6, SMD = standardized mean difference.

Keywords: interleukin-6, meta-analysis, risperidone, schizophrenia

1. Introduction

Schizophrenia is a chronic mental disorder with heterogeneous genetic and neurobiological backgrounds; this disorder has an average lifetime prevalence of less than 1%.[1] The physiological and pathological mechanisms of schizophrenia are unclear, but many factors may influence the occurrence of schizophrenia, such as genetic predisposition,[2] maternal infection during pregnancy,[3] and abnormal brain function. Gene-environment interactions play a key role in the risk of schizophrenia. Different environmental factors and inflammatory immune processes have been shown to be involved in the etiology and pathology of schizophrenia.[4] There is evidence that cytokine elevation plays an important role in the pathogenesis of schizophrenia and is closely related to its etiology and pathogenesis. Interleukin-6 (IL-6), a major cytokine, plays several important roles in the central nervous system (CNS), such as regulating brain development and synaptic plasticity, and is also related to sleep and stress.[5] Increased levels of IL-6 in the blood are 1 of the most commonly observed pieces of evidence linking schizophrenia to immunological characteristics.

Antipsychotic medication is the preferred treatment for schizophrenia. Risperidone, the representative second-generation antipsychotic drug, is effective against both positive and negative symptoms of schizophrenia. Adverse reactions to the drug are mild and generally do not include an effect on cognitive function. With these features, risperidone has become a first-line drug for the treatment of schizophrenia. Recent studies have suggested that antipsychotics, including risperidone, may have a direct effect on inflammatory status, such as significant changes in cytokine levels during antipsychotic treatment.[6] However, observations regarding cytokine changes after antipsychotic treatment have been inconsistent among studies, and the effects of risperidone on immune system regulation and cytokines remain unclear.

Therefore, this meta-analysis was designed to assess the effect of risperidone on IL-6 levels in patients with schizophrenia, with

the goal of determining whether IL-6 is a suitable biomarker for evaluating the efficacy of schizophrenia treatments.

2. Materials and methods

We followed the PRISMA guidelines[7,8] for reporting of inclusion criteria, assessment of publication bias, and synthesis of results.

2.1. Literature-search strategy

Ten Relevant studies were identified from PubMed and EMBASE electronic databases until October 2019 without restrictions on geography, type of publication or language. The authors performed a systematic literature review using the Medical Subject Headings terms. The keywords used for the search were antipsychotics, risperidone, schizophrenia, and IL-6. In addition, a manual search was carried out to identify references in the identified studies to identify possible other studies. Finally, we contacted the corresponding author to obtain the original data if the data in the research report is insufficient.

It is important to mention that when we searched literatures with these keywords

risperidone, schizophrenia and IL-6, we only got very limited number of articles. So, we expanded the search scope, add antipsychotic as keyword and got more literatures on the area. However, we only included papers with risperidone, not other antipsychotics as treatment drug in the meta-analysis.

2.2. Inclusion and exclusion criteria

Studies were included if

(1) they involved subjects with schizophrenia-spectrum disorders as defined by the Diagnostic and Statistical Manual of Mental Disorders/International Classification of Diseases;
(2) they employed a pre–post design that involved the administration of antipsychotics (typical, atypical, or mixed); and
(3) they measured the plasma or serum levels of IL-6 in vivo before and after the treatment. When several articles dealt with the same population, we selected the article with the largest sample.

Studies were excluded if

(1) the study design was cross-sectional;
(2) the sample of patients comprised patients with Diagnostic and Statistical Manual of Mental Disorders Axis I disorders other than schizophrenia-spectrum disorders;
(3) cytokine levels were measured using cerebrospinal fluid (CSF); or
(4) cytokine levels were measured using supernatants of leucocytes stimulated in vitro, as such studies vary widely in the conditions of in vitro incubation. If the data were duplicated or the population was examined in more than 1 study, we included only the study with the largest sample size and the most comprehensive outcome evaluation.

2.3. Data extraction and quality assessment

Two investigators independently evaluated the eligibility of studies retrieved from the database based on predetermined selection criteria. In addition, the references of the eligible articles were examined to locate studies not found in the computer search. These 2 authors independently extracted the following data from each study: sample size, year of publication, gender ratio of subjects (proportion of males), mean age of subjects, follow-up length, duration of illness, and antipsychotic type.

Articles were screened based on their titles, abstracts, and full texts prior to inclusion in the meta-analysis. The risk of bias was assessed by 2 reviewers working independently using a modified Newcastle-Ottawa classification for observational studies.[9]

2.4. Statistical analyses

Data were entered into Microsoft Excel, and the meta-analysis was conducted using STATA software. Study heterogeneity was estimated with the Cochran Q and I^2 statistics.[10] When the P value was $< .1$ and the I^2 value was $> 50\%$, the data were considered heterogeneous, and a random-effects model was used[11]; these conditions were satisfied in all cases. Effect sizes consisted of the standardized mean difference (SMD) between IL-6 levels before and after treatment. Using Cohen method, the SMD was calculated as the difference between group means divided by the pooled standardized differences.

2.5. Ethics statement

All data sources and statistical analyses were based on previously published studies. Therefore, it did not require patient consent or ethical approval.

3. Results

3.1. Literature search and study characteristics

After preliminary screening, 388 relevant articles were obtained; 318 of those articles were eliminated based on their abstracts. After the full text of each work was read, another 60 studies were excluded for failure to meet the inclusion criteria. A total of 10 controlled before-and-after studies were included.[12–21] Figure 1 shows the article-selection process, and Table 1 shows details on the included studies.

3.2. Risk of bias of selected studies

Overall, the risk of bias in the observational studies was moderate (Table 2) due to missing or unclear descriptions of follow-up time and loss to follow-up.

3.3. Main analysis

The meta-analysis of the 10 controlled before-and-after studies, which included 546 individuals, indicated an association between risperidone use and levels of IL-6 (n = 10 studies; test for overall effect: SMD = -0.506, 95% confidence interval: -0.938 to 0.075, $P = .021$; test for heterogeneity: $\chi^2 = 116.50$, $P < .0001$, $I^2 = 91.4\%$) (Fig. 2).

3.4. Subgroup meta-analysis

A subgroup meta-analysis was performed by region. We found that risperidone reduced IL-6 levels in European patients. In the Asian population, however, risperidone use was not associated with a decrease in IL-6 (Table 3).
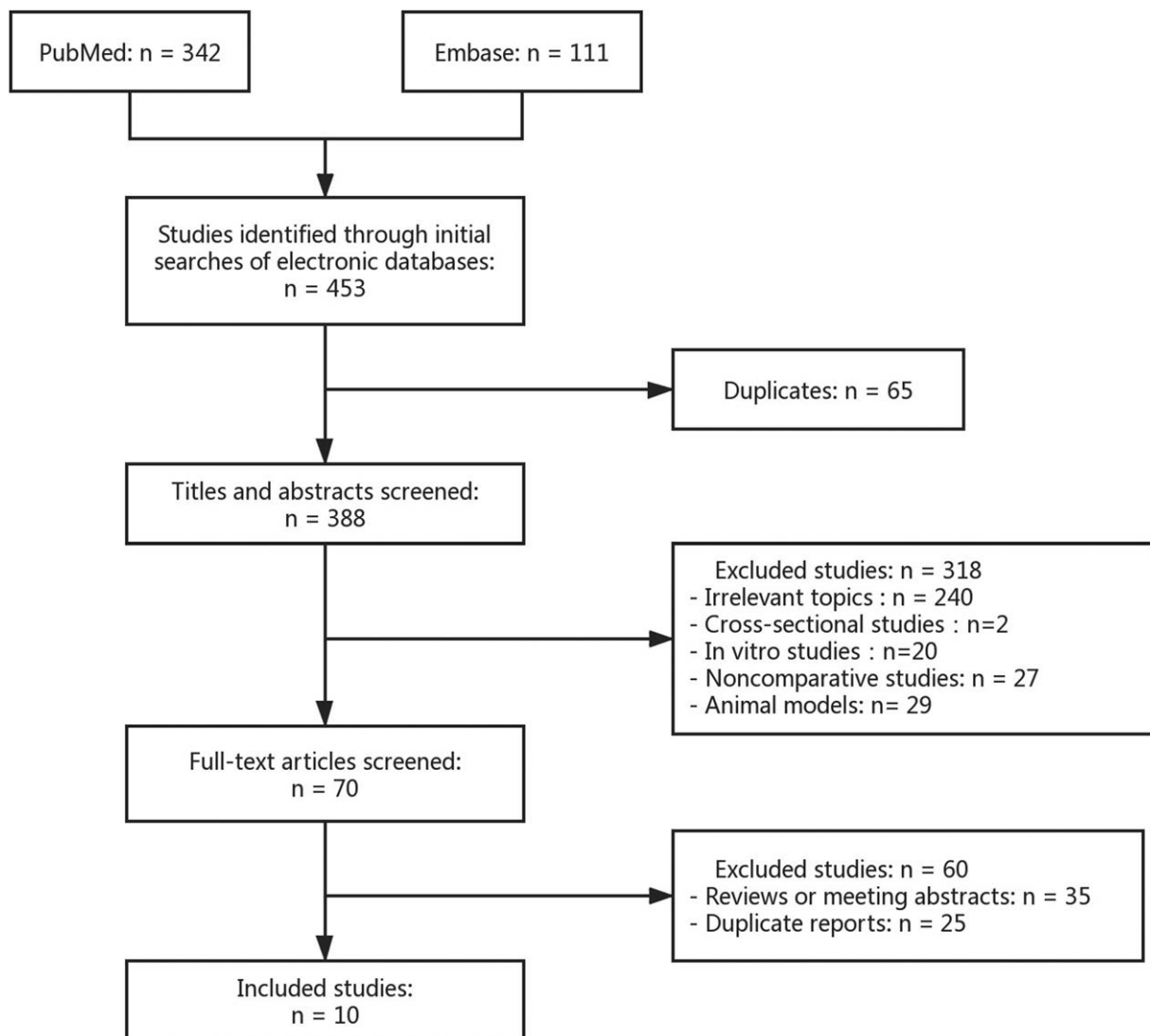
Figure 1. Study selection diagram.

When we performed subgroup analysis based on patients' conditions, we observed that risperidone was not associated with decreased IL-6 in patients with acute schizophrenia, refractory schizophrenia, or first-episode schizophrenia (Table 3).

Another subgroup meta-analysis was performed by follow-up length. We found that psychiatric patients who took risperidone had decreased levels of IL-6 in the short term. No statistical heterogeneity was observed in the long-term group (Fig. 3, Table 3).

3.5. Sensitivity analysis

To assess the robustness of our analysis, we performed a sensitivity analysis by recalculating the combined results of the original analysis, excluding 1 study per iteration. The results showed that excluding any 1 study did not change the overall results (Fig. 4).

3.6. Publication bias

Begg rank correlation test and Egger linear regression test indicated no evidence of publication bias among the studies

[Begg, $P > z = .755$; Egger, $P = .939$, 95% confidence interval -10.96–10.22] (Figs. 5 and 6).

4. Discussion

To the best of our knowledge, this is the first meta-analysis performed to describe the effects of risperidone on IL-6 levels in controlled before-and-after studies. The primary findings from our study consistently suggest a significant decrease in serum IL-6 after risperidone treatment. We also found that, in some cases, the changes in IL-6 levels could be impacted by region or follow-up length.

Our findings are also consistent with current research on risperidone. Noto et al[22] compared antipsychotic-naive first-episode psychosis patients with healthy people and found that treatment with risperidone significantly suppressed the immune inflammatory response system and compensatory immune-regulatory reflex system; in particular, the inflammation marker IL-6 was significantly reduced. In the present study, although heterogeneity was observed, the findings were stable and robust

Summarized characteristics of the included studies.

Study	Sample size	Year of publication	Gender (% male)	Participants' mean age	Follow-up length	Mean duration of illness	Antipsychotic type
Maes et al [10]	17	2000	47	48.6	4 mo	NA	Clozapine; risperidone
Kim et al [11]	19	2001	57.9	28.4	4 wk	30 mo	Risperidone
Pae et al [12]	35	2006	60	37.7	2 mo	6.0 yr	Risperidone; olanzapine; quetiapine
Kim et al [13]	53	2009	45	33.9	6 wk	74.9 mo	Risperidone; amisulpride; olanzapine; aripiprazole
Zhang et al [14]	78	2009	77	43.8	12 wk	21.6 yr	Risperidone; haloperidol
Lin et al [15]	34	2011	47	34.65	1 mo	8.57 yr	Clozapine; risperidone; olanzapine
Borovcanin et al (FEP) [16]	88	2013	41	33.64	30 d	0.28 yr	Haloperidol; zuclopenthixol; chlorpromazine; fluphenazine; levopromazine; thioridazine; clozapine; risperidone; olanzapine
Borovcanin et al (SC in relapse) [16]	45	2013	38	35.95	30 d	7.31 yr	Haloperidol; zuclopenthixol; chlorpromazine; fluphenazine; levopromazine; thioridazine; clozapine; risperidone; olanzapine
Ding et al [17]	69	2014	53.6	27.48	4 wk	9.68 months	Risperidone
Noto et al [18]	55	2014	65.50%	24.75	10 wk	NA	Risperidone
Song et al [19]	62	2014	53	24.7	6 mo	7.1 mo	Risperidone

NA = not available, FEP = first episode psychosis, SC = schizophrenia.

based on our sensitivity analysis. There are several plausible mechanisms by which risperidone may decrease IL-6 levels. Accumulating evidence has shown that astrocytes can amplify inflammatory responses in the CNS, a phenomenon that is closely related to the neurobiology and progression of neuropsychiatric disorders.[23,24] Bobermin et al[25] observed that risperidone had an anti-inflammatory effect on C6 astroglia, decreasing the release of IL-6. Moreover, De Souza et al[26] found that risperidone inhibited IL-6-induced S100B secretion, reducing the secretion rate below the basal level. Noto et al[27] suggest that circulating levels of IL-6 and IL-10 might regulate the expression of the AKT1, DROSHA, NDEL1, DISC1, and MBP genes. Thus, risperidone treatment may modulate gene expression in the course of schizophrenia treatment. In recent years, scientists have found in biochemical studies of the central nervous system that IL-6 is produced by neurons, astrocytes and microglia and acts as a neurotrophic factor in the central nervous system.[28] However, a recent study of Mamun et al[29] shows that risperidone can attenuate the activation of microglia in the brain, which may reduce the levels of IL-6, and proposes that risperidone may contribute to the improvement in brain diseases.

Our overall study shows that treatment with risperidone can lead to a decrease in IL-6 levels; although a high I^2 (85.6%) was present for overall risperidone use, we identified the sources of heterogeneity by performing subgroup analyses. In the subgroup analysis by follow-up length, we found that no heterogeneity was observed in the long-term follow-up studies; all of the heterogeneity was derived from the short-term studies. One study in the meta-analysis found a significant decrease in IL-6 levels after short-term risperidone treatment: Song et al[30] found significant changes in cytokine levels after a mean of 4 weeks of antipsychotic treatment. Other researchers have reported similar

Risk of bias of observational studies.

| Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-Up long enough for outcomes to occur	Adequacy of follow-up of cohorts
Maes et al [10]	somewhat representative	no description	secure record	yes	NA	record linkage	no	complete follow-up
Kim et al [11]	somewhat representative	NA	secure record	yes	NA	record linkage	no	lost to follow-up unlikely to introduce bias
Pae et al [12]	somewhat representative	NA	secure record	yes	NA	record linkage	no	lost to follow-up unlikely to introduce bias
Kim et al [13]	somewhat representative	drawn from the same community	secure record	yes	NA	record linkage	no	lost to follow-up unlikely to introduce bias
Zhang et al [14]	somewhat representative	drawn from the same community	secure record	yes	NA	independent blind assessment	no	complete follow-up
Lin et al [15]	somewhat representative	drawn from a different source	secure record	yes	NA	record linkage	no	complete follow-up
Borovcanin et al [16]	somewhat representative	no description	secure record	yes	NA	record linkage	no	complete follow-up
Ding et al [17]	somewhat representative	no description	secure record	yes	NA	record linkage	no	lost to follow-up unlikely to introduce bias
Noto et al [18]	somewhat representative	no description	secure record	yes	NA	record linkage	no	complete follow-up
Song et al [19]	somewhat representative	no description	secure record	yes	NA	record linkage	no	lost to follow-up unlikely to introduce bias

NA = not available.
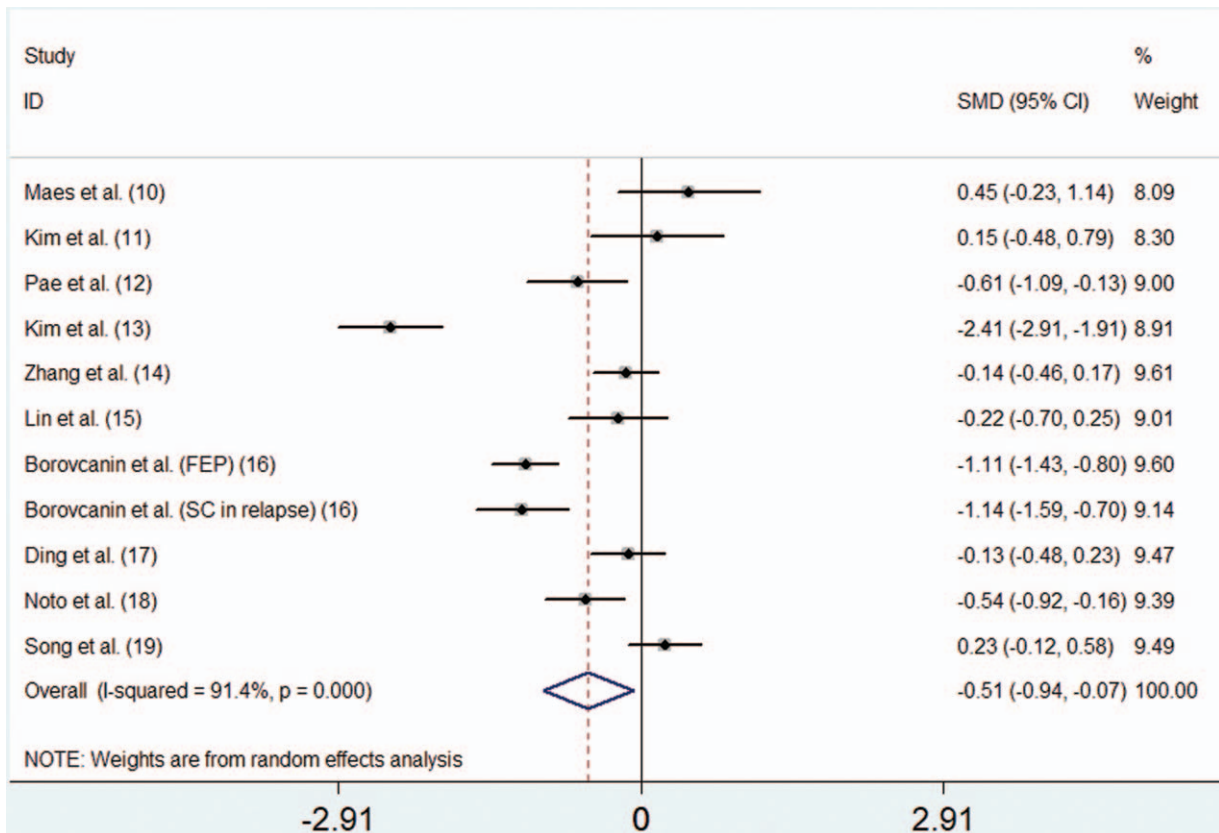
Figure 2. Forest plot of SMDs with CIs for risperidone use and levels of IL-6. CIs = confidence intervals, IL-6 = interleukin-6, SMD = standardized mean difference.

findings; for example, 1 study observed decreased IL-6 levels within 9 days of antipsychotic treatment, and by 8 weeks, there was no significant difference between patients and control subjects.[31] Taken together, these findings suggest that IL-6 levels may be normalized to some extent shortly after risperidone treatment. Through a subgroup analysis by study region, we found that studies conducted in Europe showed significant decreases in IL-6 levels. In the Asian subgroup, however, it was not clear whether risperidone use had any effect on IL-6 levels. To the best of our knowledge, there are no studies compare Asian and Europe schizophrenia patients about serum IL-6 after risperidone treatment currently, and we hope to have opportuni-

ty to do this work in the future. Overall, this analysis suggested that risperidone could significantly reduce the level of IL-6 in the European population, which could contribute to its effectiveness in treating schizophrenia. In the subgroup analysis by patient pathology, there was still considerable heterogeneity among acute schizophrenia, resistant schizophrenia and first-episode schizophrenia. It is not clear whether patients' condition can affect changes in IL-6 levels. A previous meta-analysis found evidence for cytokine alterations in schizophrenia but did not find an effect of clinical status, which was classified as acute, nonacute, or mixed.[32] A study by Miller et al[33] considered the effects of antipsychotic therapy on disease progression and the

Table 3

Subgroup analyses of the association between risperidone use and IL-6 levels.

Subgroup	No. of studies	SMD (95% CI)	P- value	Study heterogeneity	
				I^2(%),	P- value
Region					
Asia	7	−0.442	.141	92.7	.000
Europe	4	−0.641	.027	85.6	.000
Pathology					
Acute SCZ	5	−0.649	.129	93.9	.000
FEP	4	−0.389	.199	91.2	.000
Resistant SCZ	2	−0.366	.647	93.2	.000
Follow-up length					
Long term	2	0.278	.083	0.00	.566
Short term	9	−0.685	.003	90.9	.000

CI = confidence interval, No. = number, SMD = standardized mean difference, SCZ = schizophrenia, FEP = first episode psychosis.
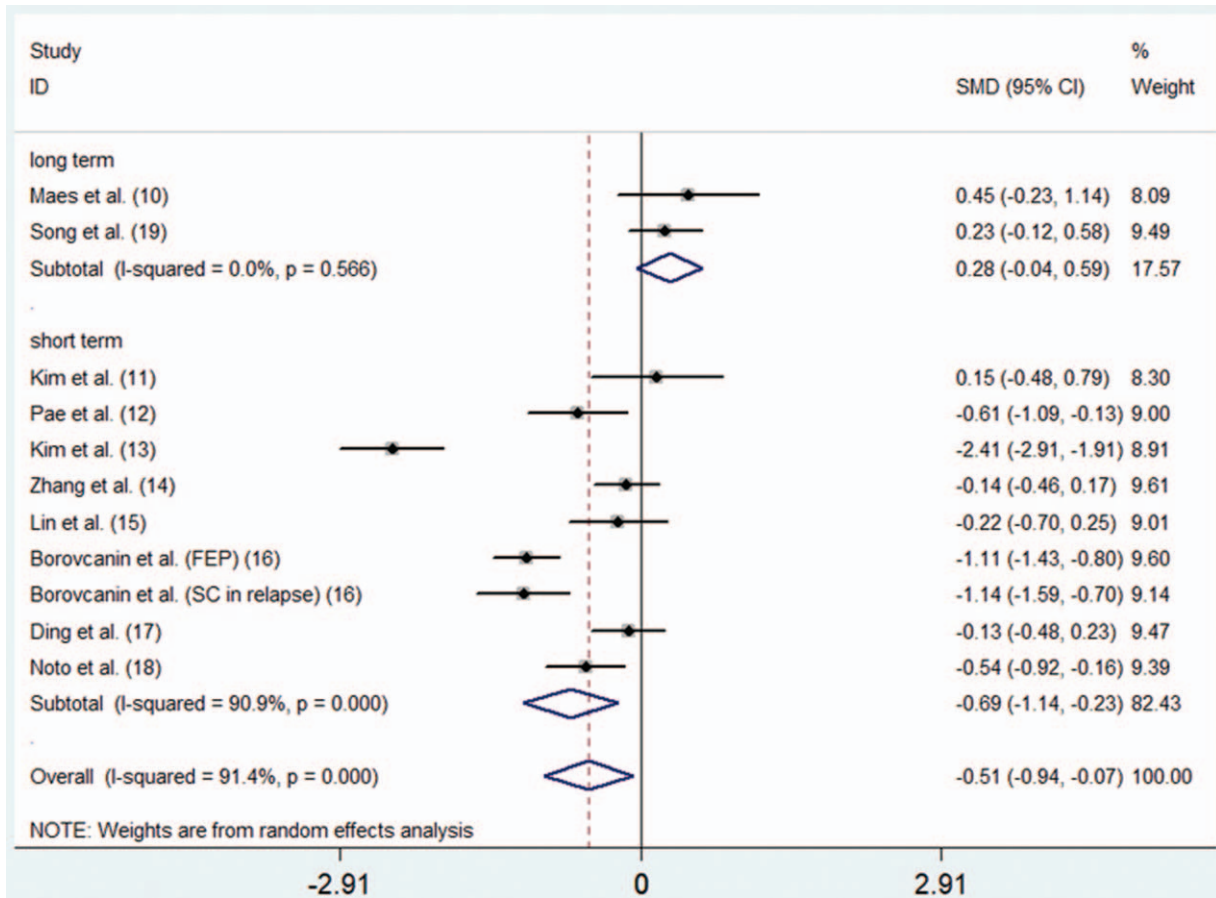
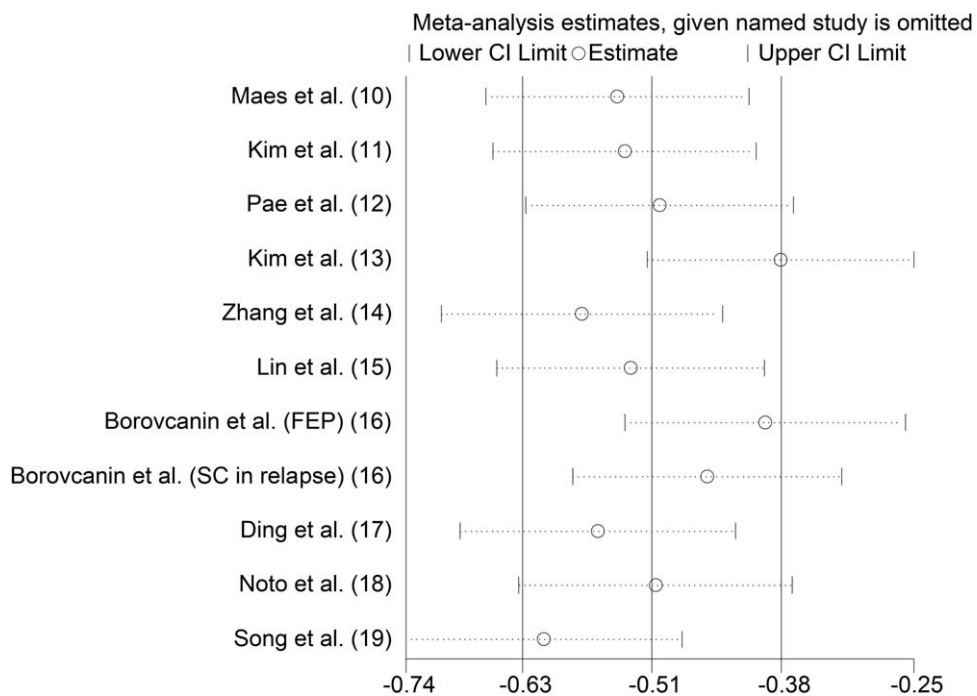**Figure 3.** Forest plot for subgroup meta-analysis by follow-up length.

Figure 4. Sensitivity analysis of the association between risperidone use and IL-6 levels. IL-6 = interleukin-6.
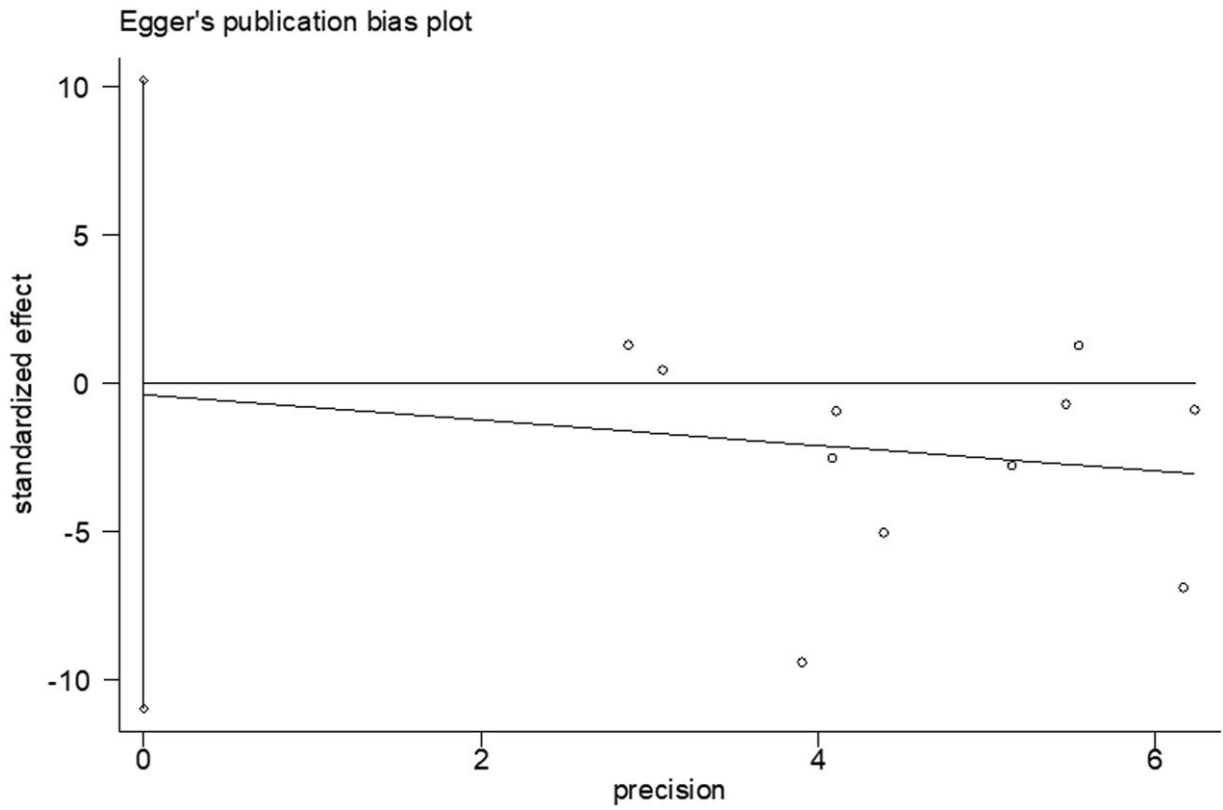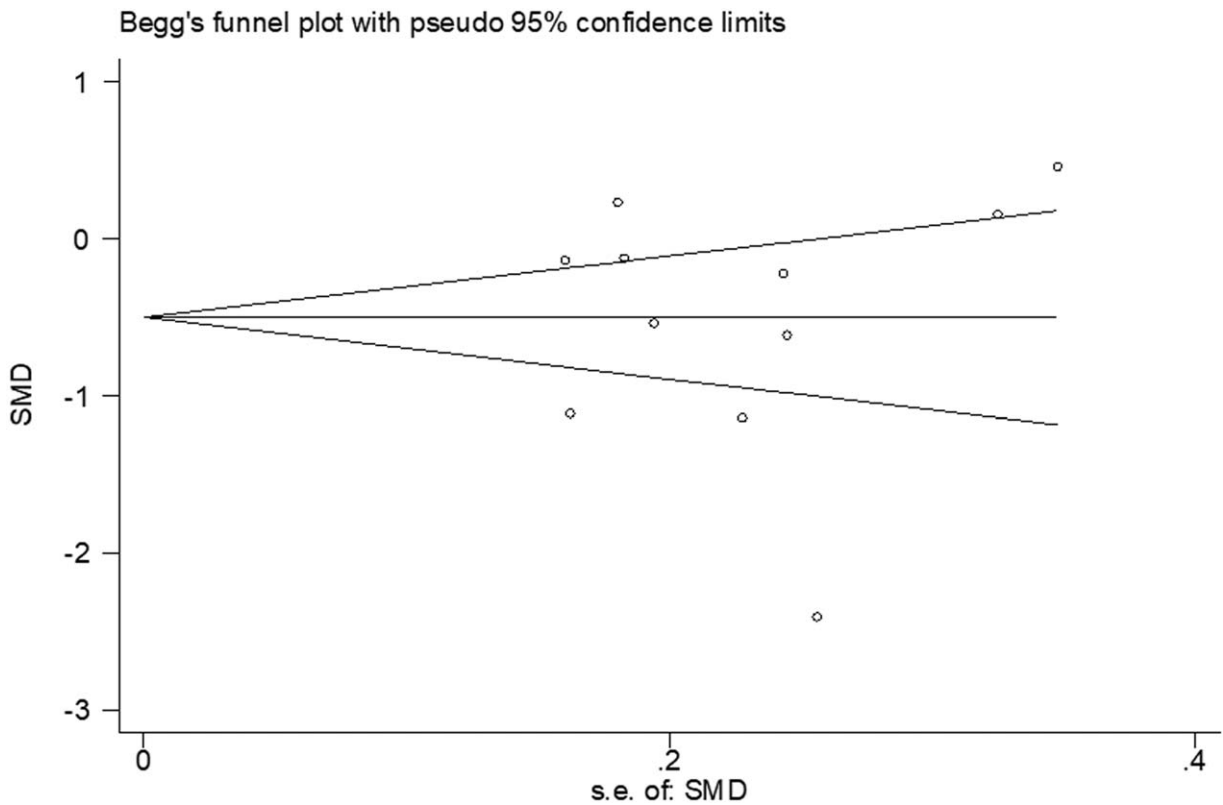
Figure 5. Egger publication bias plot.

Figure 6. Begg publication bias plot.

correlation between cytokine levels and clinical characteristics; the results of that study suggested that cytokine alterations in schizophrenia might vary with clinical status. Of course, many other factors may have made additional contributions. We will evaluate these factors in the future when the necessary data are available.

Our meta-analysis has several limitations. First, although all studies describing risperidone treatment and IL-6 levels were searched, the search was performed in databases that mainly index English-language material. The number of studies was relatively small, which means some may have been missed because they were published in non-English-language journals or in books or journals not included in computer databases. Second, studies with nonsignificant results, especially those that show a lack of effectiveness, may go unpublished because they are rejected by journals. Although publication bias was controlled by statistical methods, the possibility of publication bias could not be completely excluded. As a result, measures of pooled effects may be overestimated. Third, most studies did not control for known potential confounders that affect cytokine levels, such as age, gender, body mass index, and smoking, and these factors also varied between studies. Fourth, most studies in this meta-analysis did not standardize medication regimens, and different doses of risperidone may have different effects on IL-6 levels. Finally, this analysis was limited to studies conducted in blood rather than CSF, although the latter may have a more direct connection to the CNS. Therefore, further study of the effect of risperidone therapy on IL-6 levels in CSF may help confirm our results.

5. Conclusions

In summary, this meta-analysis provides evidence that risperidone use can significantly reduce IL-6 levels in the body. In addition, the correlation between cytokine levels and psychopathology may provide new immunoregulatory strategies for the treatment of schizophrenia. In summary, IL-6 is a potential biomarker and therapeutic target involved in the pathophysiology and clinical processes of schizophrenia.

In future studies, we should take into account the clinical status, disease duration, and risperidone dose of schizophrenia patients to better assess the impact of changes. Further research is needed on refractory psychiatric patients and CSF biochemistry.

Author contributions

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