Invest Clin 64(3): 424 - 436, 2023 https://doi.org/10.54817/IC.v64n3a12

Clinical efficacy and safety of folic acid and vitamin B_{12} for the adjuvant treatment of schizophrenia: a systematic review and meta-analysis.

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Key words: folic acid; meta-analysis; schizophrenia; vitamin B_{12}.

Abstract. Given the different effects of folate and vitamin B_{12} on the adjuvant treatment of schizophrenia (SCH), their efficacy and safety as adjuvant therapies for SCH were systematically evaluated by evidence-based medicine. Publication retrieval was performed using authoritative databases such as the Cochrane Library, PubMed, and Web of Science to screen randomized controlled trials (RCTs). After the quality evaluation and data extraction of included studies, eligible RCTs were systematically reviewed using Review Manager 5.2 software. In total, 14 RCTs were included. The results of the meta-analysis revealed that as the adjuvant therapy for SCH, vitamin B_{12} differed significantly from folate in terms of anxiety relief rate [odds ratio (OR)=1.28, 95% confidence interval (CI) (1.02, 1.61), p=0.03, I^2 =0%, Z=2.13]. However, there were no significant differences in the incidence rate of mania [OR=1.13, 95% CI (0.78,1.65), p=0.65, I^2=36%, Z=0.65], total efficacy [OR=1.06, 95% CI (0.72, 1.56), p=0.77, I^2=0%, Z=0.30] and incidence rate of adverse reactions [OR=1.15, 95% CI (0.88, 1.49), p=0.31, I^2=0%, Z=1.03]. Although folate and vitamin B_{12} exhibit no significant differences in the adjuvant treatment of SCH, vitamin B_{12} exerts markedly fewer side effects than folate drugs, and it is of determinant significance for the clinical adjuvant medication of SCH.

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Eficacia clínica y seguridad del ácido fólico y la vitamina B_{12} como tratamiento adyuvante de la esquizofrenia: una revisión sistemática y metanálisis.

Invest Clin 2023; 64 (3): 424 – 436

Palabras clave: ácido fólico; metanálisis; esquizofrenia; vitamina B_{12}.

Resumen. En vista de los diferentes efectos del folato y la vitamina B_{12} en el tratamiento adyuvante de la esquizofrenia (SCH), su eficacia y seguridad como terapia adyuvante para SCH fueron evaluadas sistemáticamente mediante la medicina basada en la evidencia. La recuperación de publicaciones se realizó en base a bases de datos autorizadas como Cochrane Library, PubMed y Web of Science para la selección de ensayos controlados aleatorios (ECA). Después de la evaluación de la calidad y la extracción de datos de los estudios incluidos, los ECA elegibles se revisaron sistemáticamente mediante el software Review Manager 5.2. En total, se incluyeron 14 ECA. Los resultados del metanálisis revelaron que, como terapia adyuvante para la SCH, la vitamina B_{12} difería significativamente del folato en términos de tasa de alivio de la ansiedad [odds ratio (OR) = 1,28, intervalo de confianza (IC) del 95% (1,02, 1,61), p=0,03, I^2=0%, Z=2,13], pero no hubo diferencias significativas en la tasa de incidencia de manía [OR=1,13, IC 95% (0,78,1,65), p=0,65, I^2=36%, Z= 0,65], eficacia total [OR=1,06, IC 95% (0,72, 1,56), p=0,77, I^2=0%, Z=0,30] y tasa de incidencia de reacciones adversas [OR=1,15, IC 95% (0,88, 1,49), p=0,31, I^2=0%, Z=1,03]. Aunque el folato y la vitamina B_{12} no presentan diferencias significativas en el tratamiento adyuvante de la SCH, la vitamina B_{12} ejerce notablemente menos efectos secundarios que los fármacos de folato y tiene una importancia orientativa para la medicación adyuvante clínica de la SCH.

Received: 16-11-2022 Accepted: 15-04-2023

INTRODUCTION

Schizophrenia (SCH) is a chronic mental disorder that involves social, cognitive, and emotional problems and has a lifetime prevalence of 1% in the population. As a chronic disease, SCH is usually accompanied by physical illness, malnutrition, and reduced self-care practices, all of which can cause vitamin deficiency [1]. Nutritional deficiencies often coexist with SCH, which is attributed to the patients' tendency to have higher calorie diets with saturated fat instead of fiber foods such as fruits and vegetables. Previous studies have revealed deficiencies of nutrients, such as folate and vitamin B_{12} in SCH patients resulting from less time on outdoor activities [2,3]. Vitamin B_{12} and folate levels decline in patients with SCH [4]. Alcoholism and drug addictions are viewed as chronic diseases featured by recurrence, in common with SCH. However, the prevalence data of illicit drug addiction worldwide are still lacking. Like SCH, alcoholism, and drug addictions may cause adverse effects on cognitive function and

induce malnutrition [5]. In addition, excessive drinking is a common phenomenon in developed countries, which affects nutrient intake and metabolism, leading to malnutrition, and also causes damage to multiple organs. Although folate and vitamin B_{12} deficiencies are frequently present in chronic alcohol drinkers, the impact of long-term drinking on vitamin B_{12} and folate levels has not yet reached a consensus. Thus, the data about correlations of vitamin D and other vitamin deficiencies with the risk of alcoholism are also insufficient to support the final conclusion [6]. Recently, vitamin B_{12} has been demonstrated to be vital for hemostasis and multiple physiological functions, as well as the pathogenesis of diseases such as cancer, autoimmune disorder, senile dementia, cognitive impairment, and SCH [7]. It was also reported in another study that vitamin B_{12} acts as an essential player in SCH and cognitive function and has immunomodulatory, anti-inflammatory, and antioxidant effects [8]. Homocysteine is thought to be a pro-atherogenic molecule that has toxic effects on endothelium, but its associations with diagnosis and prognostic evaluation of SCH have not been systematically analyzed and summarized [9]. Consistent with vitamin B_{12}, folate is a vitamin B used to modulate cell division. Folate deficiency is closely implicated in megaloblastic anemia, cardiovascular disease, osteoporosis, bone dysplasia, depression, and SCH, and folate insufficiency during pregnancy may cause fetal neural tube developmental defects. SCH involves neurodegenerative processes, although the impact extent of vitamin deficiency on these processes remains unclear[10], and the potential deterioration of such processes resulting from folate and vitamin B_{12} deficiencies cannot be ignored. For this reason, efforts should be made to identify patients at risk of specific vitamin deficiencies and then provide prompt and appropriate interventions.

Consequently motivated, the clinical efficacy and safety of folate and vitamin B12 as adjuvant therapy in SCH were systematically reviewed and meta-analyzed to guide the clinical medication of SCH.

MATERIALS AND METHODS

Retrieval methods

Publication retrieval was performed using databases such as the Cochrane Library, PubMed, Web of Science, and EMBASE, as well as related websites for registration of clinical trial institutions with "schizophrenia", "cognitive impairment", "SCH", "folate", and "vitamin B_{12}" as subject words and trademark names of relevant drugs as free words. In addition, relevant studies published in English were retrieved to avoid bias due to language restrictions (Fig. 1).

Inclusion criteria

The inclusion criteria of studies were as follows: i) studies using randomized controlled trials (RCTs), ii) those with research subjects meeting the diagnostic criteria for SCH following the Minnesota Multiphasic Personality Inventory or schizophrenia scale and also the ICD-11 diagnosis of schizophrenia [11], iii) those researching comparisons of efficacy and safety between folate and vitamin B_{12} as adjuvant therapies for SCH, iv) those mainly evaluating indexes including anxiety relief rate, incidence rate of mania, total efficacy and incidence rate of adverse reactions, v) those whose research subjects had no history of drug abuse, and vi) those including research subjects who underwent 6-12 weeks of treatment and were aged ≥8 years old and lack of folate or vitamin B_{12}.

Exclusion criteria

The exclusion criteria involved: i) studies adopting non-RCTs, ii) repeated studies, iii) studies with incomplete data, or iv) studies published for the second time.

Quality evaluation of studies

Evaluation was performed as required: i) whether patients were ranked randomly

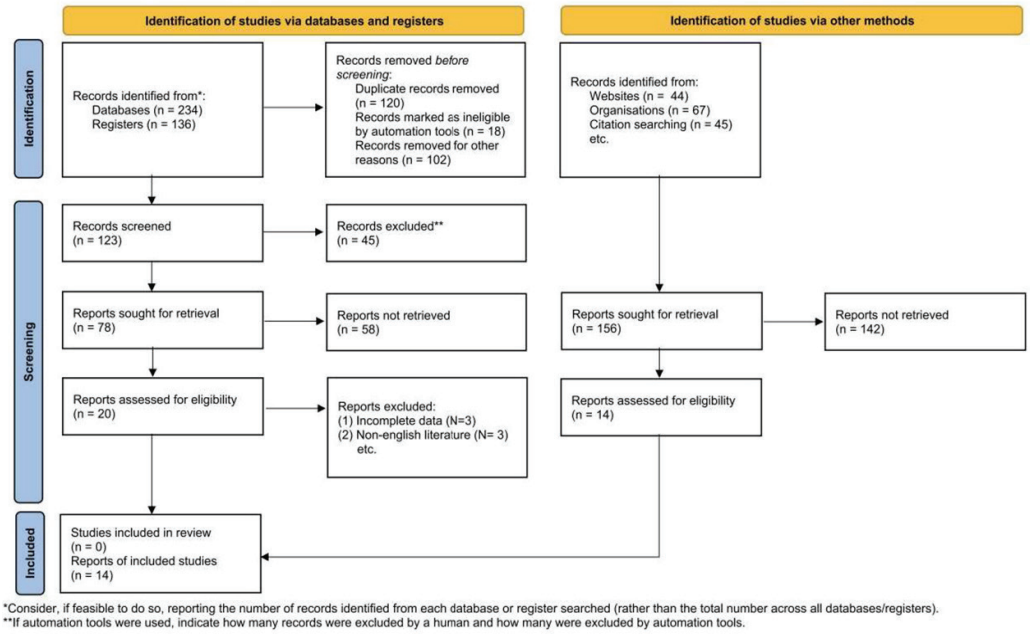

Fig. 1. Flow chart of literature retrieval.

("yes" =2, "unclear" =1, "no" =0), ii) random hiding ("yes" =2, "unclear" =1, "no" =0), iii) blind trial ("yes" =2, "clear" =1, "no" =0), and iv) withdrawal or not withdrawal ("yes" =1, "no" =0). Data involving author information and country, Jadad score, type, patient's age and gender, the dose of study drugs, number of cycles, effective treatment, total efficacy score after treatment, and adverse reactions were extracted. Then two commentators were responsible for comparing these data, where inconsistencies were discussed, and missing information was supplemented as far as possible.

Bias analysis of studies

Two investigators independently conducted data extraction and cross-checking to ensure the data's accuracy. Quality evaluation was conducted for RCTs with the Cochrane Handbook 5.0.2 as a reference. As for the included studies, the presence or absence of publication bias was evaluated using a funnel chart (performed through the Egger's test), which illustrated that all studies were within the triangle area, without obvious publication bias (Figs. 2 and 3).

Statistical analysis

The Review Manager 5.2 software [Cochrane Information Management System (IMS)] provided by Cochrane Collaboration was utilized for statistical analysis using the hazard ratio of binary variables. The meta-analysis analyzed the efficacy and incidence rate of adverse reactions using relative risk (RR) and 95% confidence interval (CI). Besides, the chi-square test (the significance level was set at $p<0.05$) and *t*-test expressed by *Z* and P values for the hypothesis test were applied, and $p<0.05$ was considered statistically significant. The hypothesis test results were displayed in the forest plot, and the χ^2 test was employed to analyze heterogeneity, divided into low, medium, and high heterogeneity and represented by I^2=25%, 50%, and 75%, respectively. The inverted funnel chart was used and displayed no obvious publication bias.

RESULTS

Basic information of included patients

A total of 123 studies were obtained by the preliminary retrieval based on databases such as PubMed, Cochrane Library, Web of

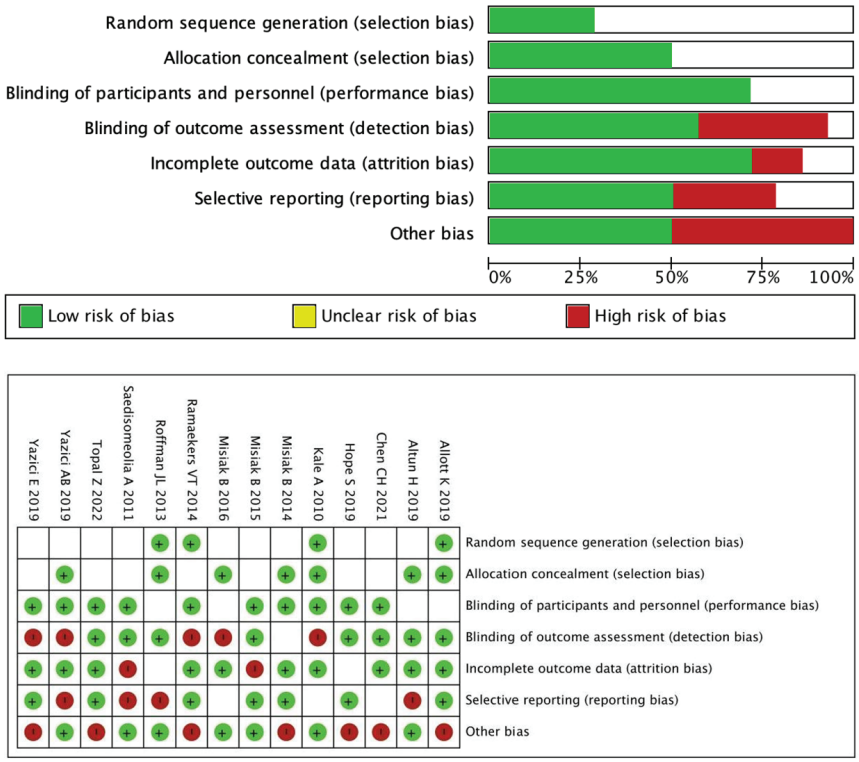

Fig. 2. Quality evaluation chart of literatures.

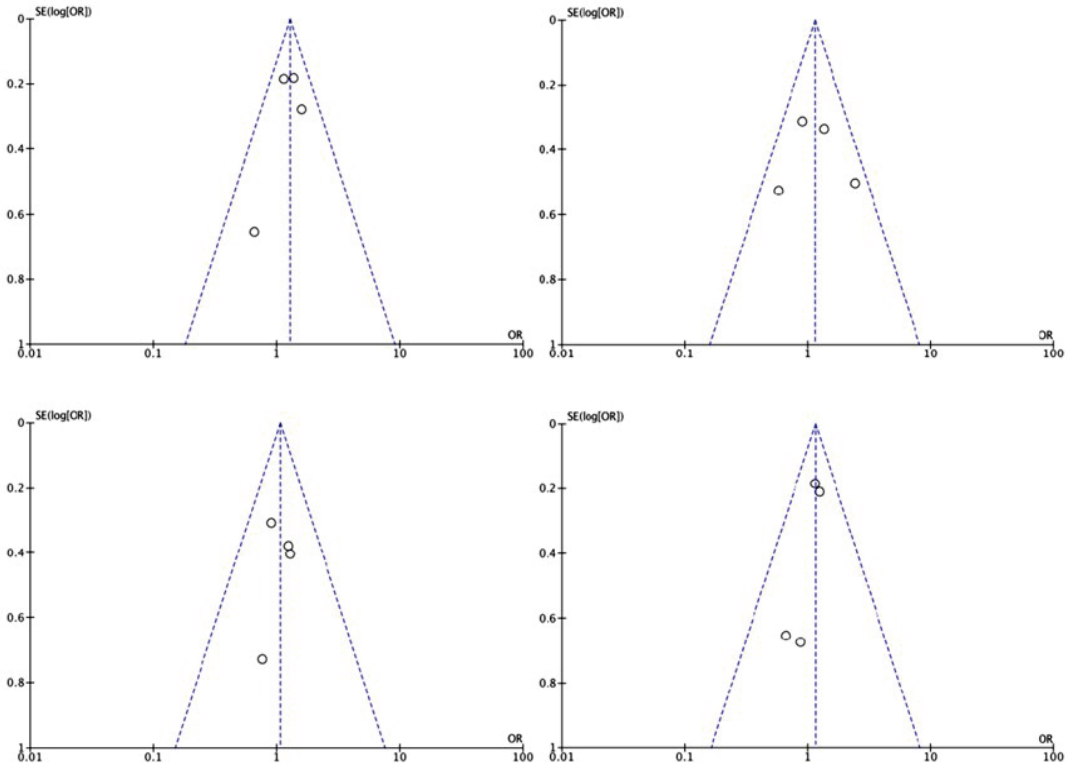

Fig. 3. Funnel chart for analysis of literature publication bias.

Science, and EMBASE. Furthermore, relevant references were also retrieved to avoid omission. Fourteen studies adopting RCTs were included (Table 1) [12-25].

Anxiety relief rate in SCH patients undergoing adjuvant therapy with folate and vitamin B_{12}

A heterogeneity test found that a low level of heterogeneity existed in 14 studies adopting RCTs for detecting anxiety relief rates in SCH patients undergoing adjuvant therapy with folate and vitamin B_{12}, so fixed models were utilized for meta-analysis. The experimental group was given folate in combination with vitamin B_{12}, and the control group was only given folate. The two groups had significantly different remission rates of anxiety [odds ratio (OR)=1.28, 95% CI (1.02, 1.61), p=0.03, I^2 =0%, Z=2.13] (Fig. 4).

Incidence rate of mania in SCH patients undergoing adjuvant therapy with folate and vitamin B_{12}

A heterogeneity test was conducted and revealed that 14 studies adopting RCTs for investigating the incidence rate of mania in SCH patients undergoing adjuvant therapy with folate and vitamin B_{12} exhibited a low level of heterogeneity, which could be subject to meta-analysis with fixed models. The results manifested that there was no significant difference in the incidence rate of mania in SCH patients undergoing adjuvant therapy with folate and vitamin B_{12} between the experimental group and the control group [OR=1.13, 95% CI (0.78, 1.65), p=0.65, I^2 =36%, Z=0.65] (Fig. 5).

Total efficacy of folate and vitamin B_{12} in the adjuvant treatment of SCH

A heterogeneity test was performed and manifested that 14 studies adopting RCTs for examining the total efficacy of adjuvant therapy with folate and vitamin B_{12} for SCH showed a low level of heterogeneity, which were subject to meta-analysis with fixed models. The results demonstrated that the total efficacy of adjuvant therapy with folate and vitamin B_{12} for SCH showed no significant difference between the experimental group and the control group [OR=1.06, 95% CI (0.72, 1.56), p=0.77, I^2 =0%, Z=0.30] (Fig. 6).

Incidence rate of adverse reactions of folate and vitamin B_{12} in the adjuvant treatment of SCH

Through a heterogeneity test, it was uncovered that 14 studies adopting RCTs for detecting the incidence rate of adverse reactions of folate and vitamin B_{12} in the adjuvant treatment of SCH had a low level of heterogeneity, so fixed models were used for meta-analysis. The results confirmed that the incidence rate of adverse reactions of adjuvant therapy with folate and vitamin B_{12} for SCH exhibited no significant difference between the experimental group and the control group [OR=1.15, 95% CI (0.88,1.49), p=0.31, I^2 =0%, Z=1.03] (Fig. 7).

DISCUSSION

Folate and vitamin B_{12} have immunomodulatory, anti-inflammatory, and antioxidant properties. It has been reported that the incidence of vitamin D deficiency is raised in patients newly diagnosed with SCH[26]. Another study demonstrated that vitamin B_{12} is not only associated with malnutrition but also correlated with the occurrence of disease and increased incidence rate of autoimmune thyroid diseases. Consequently, the loss of the neuroprotective effect of vitamin B_{12} may be implicated in the pathogenesis of SCH [27]. Like SCH, substance use disorder (SUD) is a chronic disease usually related to malnutrition. In a study about associations of folate and vitamin B_{12} levels with the severity of symptoms in patients with SCH, those with low levels of vitamin B_{12} may be at particular risk of poor prognosis. A previous study also revealed lower folate levels in SCH patients than in healthy controls [28]. Howev-

Table 1
Basic information of patients in 14 literatures adopting RCTs.

Study item	Age	Gender (Male)	Observation index of outcome	Experimental group (N)	Control group (N)	NOS score	Study type
Yazici *et al.* 2019	41.44±12.28	57.14%	Anxiety relief rate, incidence rate of mania, etc.	119/189	109/189	8	RCT
Yazici *et al.* 2019	40.63±13.50	100%	Anxiety relief rate, incidence rate of mania, etc.	24/30	23/28	7	RCT
Altun *et al.* 2018	9.33±1.80	76.67%	Anxiety relief rate, incidence rate of mania, etc.	23/30	25/30	8	RCT
Hope *et al.* 2020	30.0±9.0	55.78%	Anxiety relief rate, incidence rate of mania, etc.	420/ 483	401/483	8	RCT
Allott *et al.* 2019	20.2±3.0	65.40%	Anxiety relief rate, incidence rate of mania, etc.	88/120	76/120	8	RCT
Topal *et al.* 2022	8.5±3.1	73.90%	Anxiety relief rate, incidence rate of mania, etc.	178/203	180/203	7	RCT
Ramaekers *et al.* 2014	19.5±2.56	78.20%	Anxiety relief rate, incidence rate of mania, etc.	12/18	13/18	9	RCT
Chen *et al.* 2021	44.3±10.7	49.60%	Anxiety relief rate, incidence rate of mania, etc.	125/232	117/232	9	RCT
Misiak *et al.* 2014	26.0±5.3	58.97%	Anxiety relief rate, incidence rate of mania, etc.	27/39	31/39	7	RCT
Kale *et al.* 2010	33.57±8.35	56.32%	Anxiety relief rate, incidence rate of mania, etc.	23/31	26/48	8	RCT
Roffman *et al.* 2013	45.3±1.1	71.0%	Anxiety relief rate, incidence rate of mania, etc.	31/56	28/56	8	RCT
Saedisomeolia *et al.* 2011	37.25±16.0	66.44%	Anxiety relief rate, incidence rate of mania, etc.	44/60	41/60	8	RCT
Misiak *et al.* 2016	28.51±8.6	68.44%	Anxiety relief rate, incidence rate of mania, etc.	117/135	121/146	9	RCT
Misiak *et al.* 2015	25.12±4.48	43.22%	Anxiety relief rate, incidence rate of mania, etc.	34/83	36/83	7	RCT

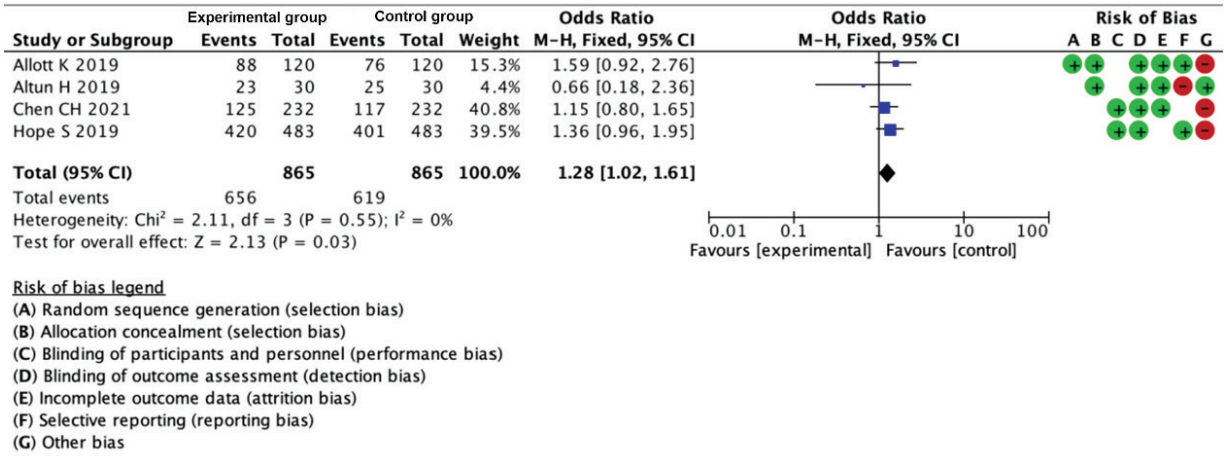

Fig. 4. Meta-analysis of anxiety relief rate in SCH patients undergoing adjuvant therapy between the two groups.

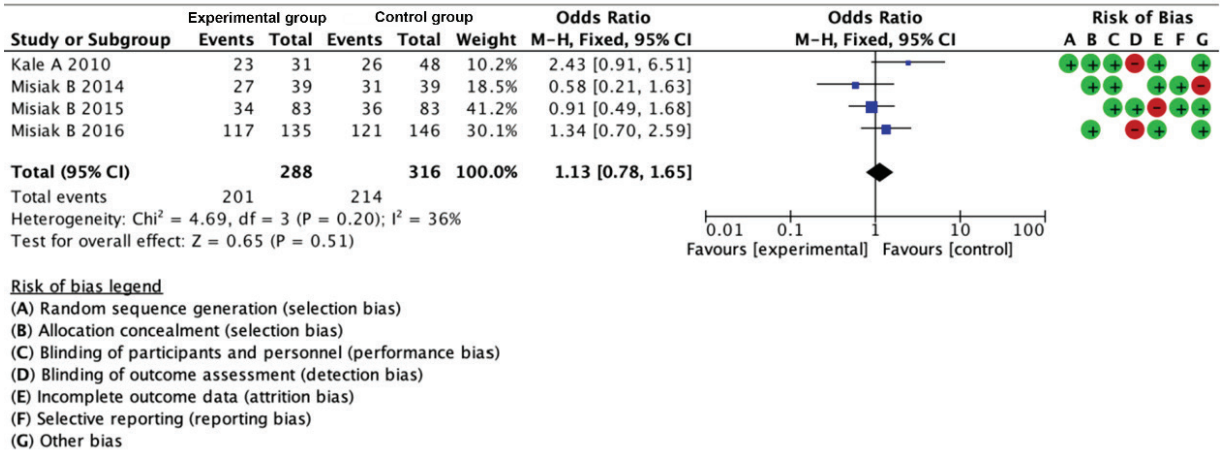

Fig. 5. Meta-analysis of incidence rate of mania in SCH patients undergoing adjuvant therapy between the two groups.

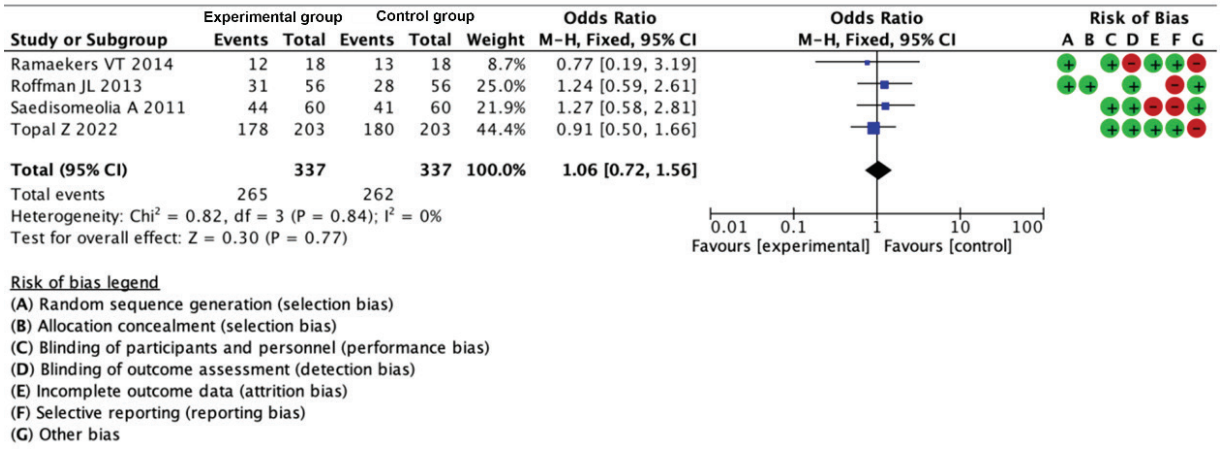

Fig. 6. Meta-analysis of total efficacy of adjuvant therapy for SCH between the two groups.

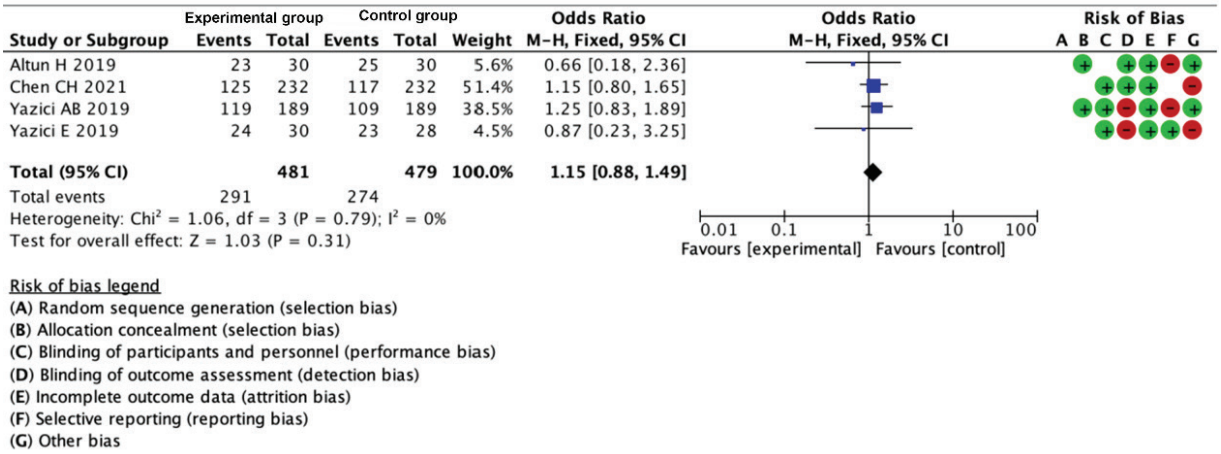

Fig. 7. Meta-analysis of incidence rate of adverse reactions in SCH patients undergoing adjuvant therapy between the two groups.

er, these findings have not been reported in other studies. Consistent with previous studies, folate, and vitamin B_{12} are relatively deficient in older adults, verifying associations with gender and age [29-31].

It has long been considered that abnormal one-carbon metabolism is one of the mechanisms for the neuropathology and psychopathology of SCH [32]. The changes in levels of one-carbon metabolic components (folate and vitamin B_{12}), homocysteine, and docosahexaenoic acid (DHA) are primarily found in patients receiving drug administration. For instance, daily administration of 2 mg folate plus 1 mg vitamin B_{12} for 12 weeks can significantly reduce the serum homocysteine level ($p<0.0001$) [33]. In a relevant study, the impact of change levels of one-carbon metabolic components (folate and vitamin B_{12}) on the severity of SCH was reported, and the subsequent alterations of homocysteine and DHA in phospholipids were also notably correlated with the pathogenesis of SCH [34]. In a study conducted by Satoskar *et al.* [35], the associations of folate and vitamin B_{12} deficiencies with the pathogenesis and prognosis of SCH patients were investigated, and the mechanism of one-carbon metabolism was also further explored. In the study, the clinical efficacy and safety of agents were analyzed between first-episode psychosis (FEP) patients (n=31) and healthy controls (HC, n=48), and folate and vitamin B_{12} were matched with confounding factors such as race, diet, and lifestyle, to reduce variability. Compared with HC, the DHA level in patients with FEP noticeably declined. The unique cohort used in the study provided an extensive mechanism for changing one-carbon metabolism (disturbed folate-vitamin B_{12}-DHA balance). Besides, the increased level of homocysteine contributes to the mechanism research on the neuropathology of SCH, and the data mentioned above may be of great significance for the psychopathology of SCH [36-39].

The limitations of this meta-analysis include: i) Potential publication bias existed because of too few studies and small sample size. ii) There were few studies included and no subgroup analysis for comparison of efficacy. iii) Only therapeutic effects at the end of treatment were evaluated, but long-term effects were not assessed. iii) We only included adult SCH patients over the age of 18, whose results would be inapplicable to adolescents.

Vitamin B_{12} and folate levels are notably lower in patients with SCH [40,41]. Herein, further analysis on the clinical efficacy and

safety of adjuvant therapy with folate and vitamin B_{12} for SCH revealed that vitamin B_{12} differed significantly from folate in terms of anxiety relief rate ($p<0.05$). However, there were no significant differences in the incidence rate of mania, total efficacy, and incidence rate of adverse reactions ($p>0.05$). Although vitamin deficiency commonly occurs in patients with SCH, vitamin B_{12} has notably fewer side effects than folate drugs, which is consistent with the findings of Roffman *et al*. [42]. Hence, this meta-analysis is of great guiding significance for the adjuvant clinical medication of SCH.

ACKNOWLEDGMENTS

This study was not financially supported.

Conflict of interest

The authors declare no conflict of interest.

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Authors' contribution

Study design: KN, XZ; Data collection: YW, YFW; Data analysis: YW, YFW; Writing: KN, XZ. KN and XZ contributed equally to this study.

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