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Review article

The efficacy of nutritional supplements for the adjunctive treatment of schizophrenia in adults: A systematic review and network meta-analysis

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ABSTRACT

Nutritional supplementations have been widely used as adjunctive treatments for schizophrenia. However, among these supplementations, of which the most beneficial is currently unknown. This study aimed to compare and rank the effectiveness of nutritional supplementations in the adjunctive treatments of schizophrenia. The four nutritional supplementations evaluated were: 1) folate acid or vitamin B12; 2) vitamin D; 3) N-acetyl cysteine (NAC); 4) Omega-3 polyunsaturated fatty acid, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). 17 eligible RCTs with 1165 participants were included in this network meta-analysis based on study criteria. NAC supplementation was significantly more efficacious than folic acid or vitamin B12 [MD (95% CI): −6.6 (−10.8, −2.4)] and omega-3 polyunsaturated fatty acid [MD (95% CI): −5.1(−9.9, -0.8)] supplementation in the term of PANSS score changes. There were no significant differences in the PANSS score changes between NAC and vitamin D [MD (95% CI): −5.2 (−10.9, 0.5)] supplementations. The estimated ranking probabilities of treatments showed that NAC might be the most effective adjunctive intervention over all nutritional supplementations. These results indicate that NAC could improve PANSS score and it may be among the most effective nutritional supplementations in schizophrenia patients.

1. Introduction

Schizophrenia is a highly prevalent and serious mental disorder that has a profound impact on patients, their families, and society(GBD 2015 DALYs and HALE Collaborators, 2016). It has a lifetime prevalence of about 0.28% globally (Charlson et al., 2018) and 0.6% in China (Huang et al., 2019), contributing to 13.4 million years of total life lived with disability (YLDs) (Charlson et al., 2018) and a substantial cost for the healthcare system (Kovacs et al., 2018). Antipsychotics are the mainstay of treatment of schizophrenia (Leucht et al., 2013). Even though their therapeutic advantages are well-known, antipsychotics are associated with high costs (Cloutier et al., 2016; Huang et al., 2014) and important negative side-effects that can cause serious disability even death(Kane, 2011). Moreover, the side effects of antipsychotics will result in poor treatment adherence and a high risk of psychotic relapse in patients, which may further lead to impaired social and cognitive functioning, psychiatric hospitalizations, and increased treatment costs (De Berardis et al., 2018). Therefore, more safe and better adherence treatments for schizophrenia need to be developed.

In the past several years, the growing evidence from different studies suggested the links between exposure to nutritional deficiencies and increased risk of schizophrenia. Many epidemiological studies, including prospective studies, have shown associations between prenatal malnutrition(He et al., 2018), deficiencies of vitamins and minerals (Fond et al., 2018; Teasdale et al., 2019; Tomioka et al., 2018), low serum amino acid level (Hons et al., 2021) and dietary fatty acid intake (Hedelin et al., 2010), and the increased risk of schizophrenia. Evidence from birth cohort studies indicated that prenatal famine exposure, as

Abbreviations: n-3 PUFA, omega-3 fatty acid; NAC, N-acetylcysteine; PANSS, Positive and Negative Syndrome Scale.

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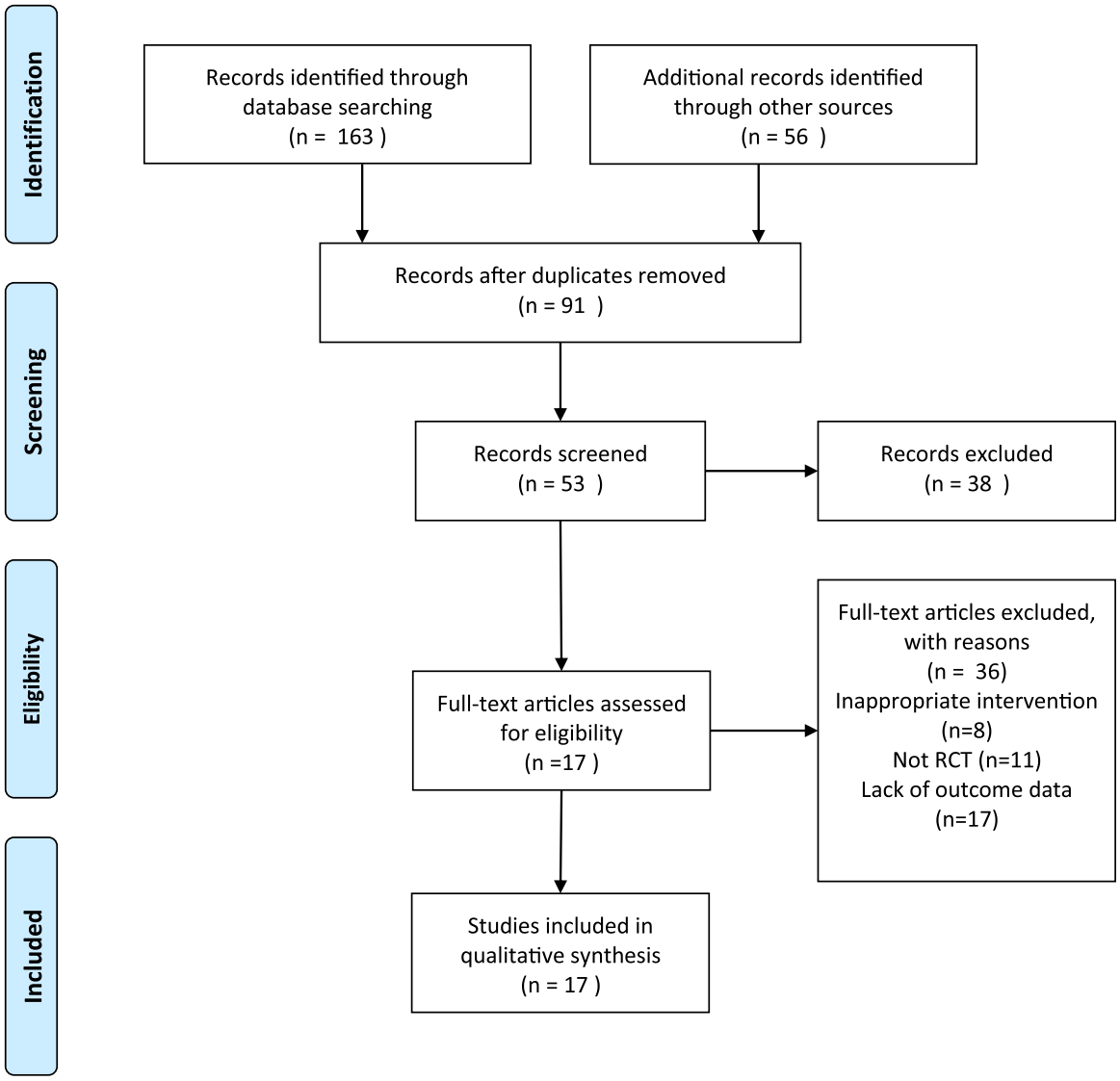

Fig 1. Diagram for the search and selection process of articles included in this review.

well as childhood malnutrition, was associated with a significantly increased risk of schizophrenia in adulthood (He et al., 2018; Venables and Raine, 2012). Results from experimental studies suggested that nutrition deficiency may result in a significant alteration in the metabolic pathways(Chen et al., 2020), increased level of oxidized damage (Canever et al., 2018), as well as epigenetic changes in nuclear receptor genes in the brain (Maekawa et al., 2017). Studies using lifestyle interventions, including education (Holt et al., 2019), motivation(Ringen et al., 2018), behavioral skills(Holt et al., 2019), new and modified foods (Kelly et al., 2019), and supportive interactions, have shown promising results in the treatment of schizophrenia. However, it has proven to be challenging, with limited methodologically compliance and accuracy (Aucoin et al., 2020). Another common approach to treat malnutrition in schizophrenia patients is the use of nutritional supplementations, including omega-3 fatty acid(n-3 PUFA) (Pawelczyk et al., 2017; Pawelczyk et al., 2018), N-acetylcysteine(NAC)(Klauser et al., 2018; Yang et al., 2019), L-methylfolate (Roffman et al., 2018), folate plus vitamin B12 (Roffman et al., 2013) and vitamin D (Krivoy et al., 2017). Further, even in the absence of malnutrition, nutritional supplementations were recommended as one of the primary prevention strategies (Freedman et al., 2018) as well as add-on therapies for schizophrenia (Ghaderi et al., 2019a; Pawelczyk et al., 2016). There was evidence that, in appropriate dosage, those add-on therapies were characterized by low cost, high safety, sustainable compliance, and effectiveness for reducing clinical symptoms in schizophrenia patients (Allott et al., 2019; Firth et al., 2019; Sarris, 2019). The major mechanisms underlying the beneficial effects of these nutritional supplementations on schizophrenia may be via their anti-inflammatory and antioxidant functions, such as reducing the expression of pro-inflammatory markers, regulating the transcription factor NF-κB and inhibiting the formation of reactive oxidative species (ROS)(Mitra et al., 2017). Among these nutritional supplementations, n-3 PUFA intervention was found to significantly improve the schizophrenia symptom severity measured by the Positive and Negative Syndrome Scale (PANSS) and it was also associated with an improvement in general psychopathology, measured through PANSS, depressive symptoms, the level of functioning and clinical global impression (Pawelczyk et al., 2016). Vitamin D and probiotic co-supplementation were found to be associated with a significant improvement in the general and total PANSS scores(Ghaderi et al., 2019a) and B-vitamin supplementation may have specific neuroprotective properties in attention/vigilance(Allott et al., 2019). Moreover, NAC was found to significantly improve PANSS total, negative and disorganized thought symptom scores, but failed to improve PANSS positive symptoms and BACS cognitive scores(Breier et al., 2018) even though the results were inconsistent (Klauser et al., 2018; Sepehrmanesh et al., 2018). These results indicated that nutritional supplements

Table 1
The characteristics of the studies included in this study

Study (Author, Year)	Country	Sample size (Experiments/ Control)			Duration (Weeks)	Experimental group		Control group	
			Type of the patients	Age (Years)		Intervention	Changes of PANSS score	Intervention	Changes of PANSS score
BERK et al. 2008	Austria	69/71	Chronic schizophrenia	36.6 ±10.9	24	NAC 2g/d	-8.8 ±14.57	Placebo	-2.9 ±14.15
RAPADO-CASTRO et al. 2015	Austria	59/62	Chronic schizophrenia	36.4 ±10.4	24	NAC 2g/d	-9.38 ±10.33	Placebo	-4.84 ±12.64
ALLOTT et al. 2019	Austria	52/48	First-episode schizophrenia	19.9 ±2.7	12	Folic acid 5mg/ d+ vitamin B12 0.4mg/d+ vitamin B6 50mg/d	-4.76 ±13.98	Placebo	-5.41 ±14.13
QIAO et al. 2018	China	28/22	Chronic schizophrenia	32.0 ±10.2	12	EPA 0.54g/d+DHA 0.36g/d	-26.1 ±18.92	Placebo	-26.77 ±15.87
PEET et al. 2001b	India	12/14	Chronic schizophrenia	34 (20,60) *	12	EPA 2g/d	-25.8 ±9.48	Placebo	-22.2 ±17.26
FAROKHNIA et al. 2013	Iran	21/21	Chronic schizophrenia	32.8 ±6.5	8	NAC 2g/d	-56.09 ±9.83	Placebo	-44.42 ±11.46
JAMILIAN et al. 2014	Iran	30/30	Chronic schizophrenia	31.5 ±7.9	8	EPA 1g/d	-47±8.34	Placebo	-45.83 ±8.45
GHADERI et al. 2019	Iran	30/30	Chronic schizophrenia	44.0 ± 7.2	12	Vitamin D3 50000IU/2 week + probiotics 8*10^9CFU/d	-7.4±8.7	Placebo	-1.9±7.5
KRIVOY et al. 2017	Israel	24/23	Chronic schizophrenia	40.9 ±1.5	8	Vitamin D 2000IU/ d	-8.9±7.3	Placebo	-10±10.2
LEVINE et al. 2006	Israel	20/22	Chronic schizophrenia	40 (19,59) *	12	Folic acid 2mg/ d+ pyridoxine 25mg/d+ vitamin B12 400 μg/d	-7.4±1.4	Placebo	-4.3±2
PAWEŁCZYK et al. 2016	Poland	36/35	First-episode schizophrenia	23.2 ±4.8	26	EPA 2.2g/d	-19.27 ±1.38	Placebo	-14.42 ±1.4
PEET et al. 2001a	United Kingdom	31/14	Chronic schizophrenia	34.3 ±10.9	12	EPA/DHA 2g/d	-11.15 ±15.95	Placebo	-10.3 ±18.42
FENTON et al. 2001	United States	37/38	Chronic schizophrenia	40.0 ±10.0	16	EPA 3g/d	-5±16	Placebo	-6±18
HILL M et al. 2011	United States	17/15	Chronic schizophrenia	46 (18,68) *	12	Folic acid 1mg/d	-2.3±8.9	Placebo	-4.6±13
ROFFMAN et al. 2013	United States	93/46	Chronic schizophrenia	45.5 ±1.3	16	Folic acid 2mg/ d+ vitamin B12 400 μg/d	-0.21 ±0.69	Placebo	-0.22 ±0.66
ROFFMAN et al. 2018	United States	29/26	Chronic schizophrenia	45.5 ±10.9	12	L- methyl folate 15mg/d	-4.7 ±9.07	Placebo	-1.5±8.54
BREIER et al. 2018	United States	30/30	First-episode schizophrenia	23.6 ±4.7	52	NAC 3.6g/d	-9.42 ±2.19	Placebo	-0.33 ±2.27

* data expressed as Mean (Range). NAC, N-acetyl cysteine; EPA, eicosatetraenoic acid; DHA, Docosahexaenoic Acid.

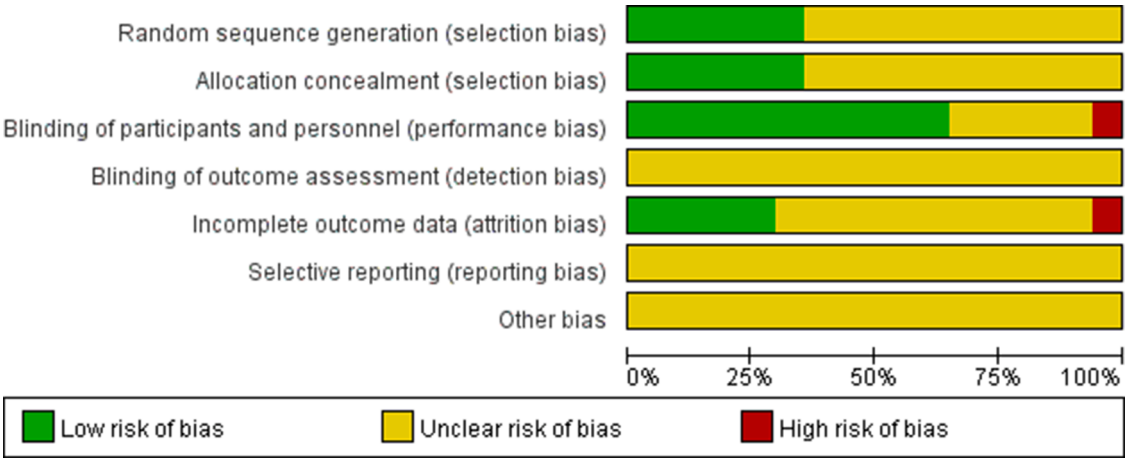

Fig 2. Risk of bias graph per type of bias assessed.

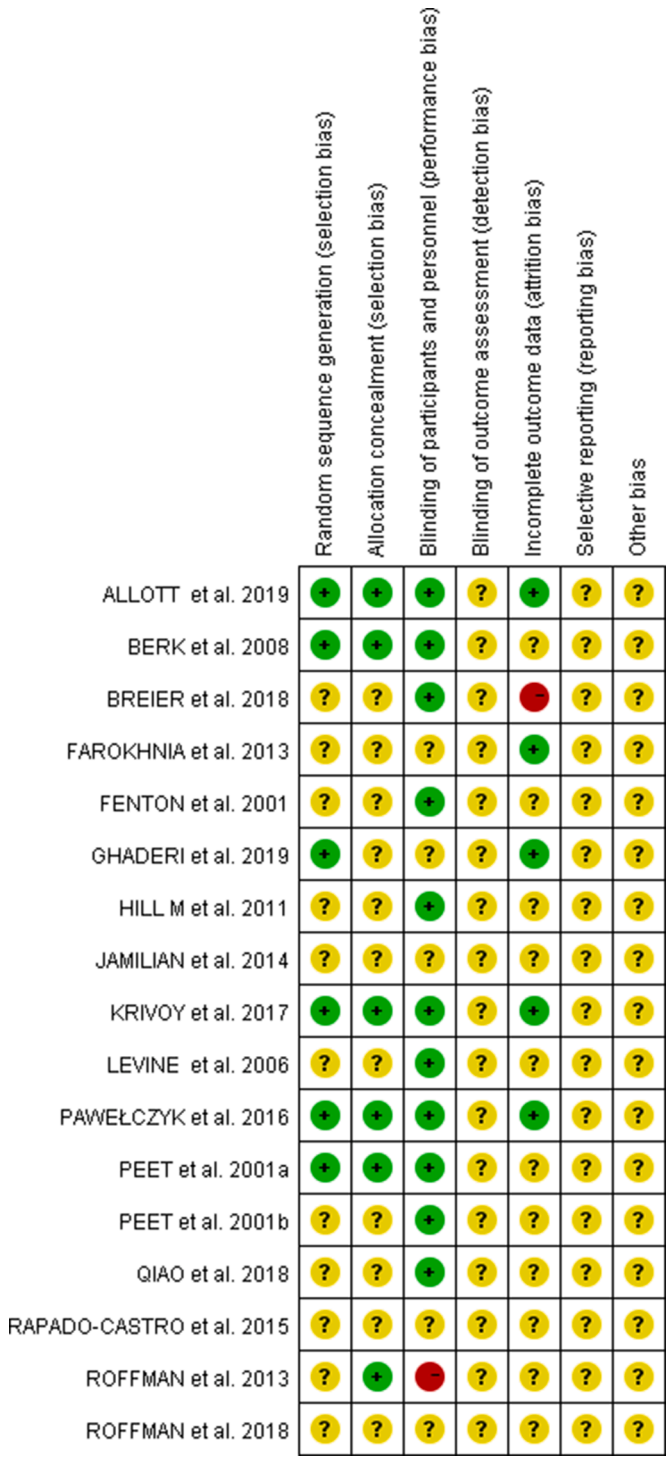

Fig 3. Diagram of bias in the included studies.

may be feasible adjunctive treatments for schizophrenia.

Several earlier systematic reviews and meta-analyses have been published to assess the effects of nutritional supplementations on the clinical symptoms of schizophrenia(Chen et al., 2015; Chia et al., 2015; Firth et al., 2017; Ghaderi et al., 2019b). However, because of the lack of evidence from direct comparisons of different nutritional supplementation in schizophrenia patients, these traditional meta-analysis studies may fail to provide an overall treatment hierarchy of these supplementations. Therefore, which nutritional supplementation is the most effective in the treatment of schizophrenia remains unclear. As network meta-analyses allow comparisons of efficacy among different treatment settings(Mills et al., 2013), in the present study, we conducted a network meta-analysis to compare the effectiveness of different nutritional supplementations in the Adjunctive treatment of schizophrenia. As previous studies indicated that NAC, Omega-3 PUFA, vitamin D, and B-vitamin supplements (especially folic acid and vitamin B12) were useful adjunctive treatments in schizophrenia(Firth et al., 2019), in this study, we choose these supplementations and compare and rank their effectiveness. As folic acid and vitamin B12 may exert their function mainly through homocysteine reduction(Levine et al., 2006), we combined them as a single intervention. We aimed to identify the nutritional supplementations that can best reduce the clinical symptoms in schizophrenia patients.

2. Materials and methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for network meta-analysis (Hutton et al., 2015).

2.1. Search strategy and selection criteria

Six electronic databases, including PubMed, EMBASE, Web of Science, CNKI (China National Knowledge Infrastructure), Wanfang Data (a database for Chinese publications), and Cochrane Center Register of Controlled Trials were searched from inception to April 10th, 2021. The medical subject heading terms used in the literature search were as follows: “Schizophrenia”, “folic acid”, “L-methylfolic acid”, “vitamin B12”, “vitamin D”, “N-acetylcysteine”, “NAC”, “eicosapentaenoic acid”, “EPA”, “docosahexaenoic acid”, “DHA” , “ω- 3 unsaturated fatty acids”, “PUFA”, “PANSS”, “negative symptoms”, “positive symptoms”, “treatment”, “clinical trial”, “Meta-analysis" (supplementary data 1). The language of literature was restricted to Chinese and English, and the references of the articles were also screened for relevant articles. Three authors independently screened abstracts, and then the relevant full-text articles. Disagreements were resolved through consensus or third-party arbitration.

We included randomized controlled trials (RCTs) with a parallel-group involving adults (≥18 years) who were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-V) or International Classification of Diseases 10 (ICD-10). All the studies should use the Positive and Negative Syndrome Scale (PANSS) for schizophrenia to evaluate the severity of symptoms. As the PANSS total score is the standard primary efficacy measure in acute treatment studies of schizophrenia and the significant cross-factor correlations between PANSS factors may result in a problem often referred to as pseudospecificity (Hopkins et al., 2018), in this study, we only used the changes of PANSS total score as the outcome to assess the effectiveness of nutritional supplementations. We included studies that compared at least one nutritional intervention with placebo. The exclusion criteria were as follows:1) studies did not report PANSS score; 2) conference abstracts without full text; 3) case reports, cross-sectional or cohort studies.

2.2. Data extraction and outcomes

Three authors independently extracted the data from each article with a data collection form. The characteristics of the data consisted of the first author, year of publication, the country in which the trial was conducted, the number and sex of trial participants, length of study, intervention and control measures, and the changes of PANSS score.

2.3. Methodological Quality

The quality of the studies included was evaluated by the Cochrane Risk of Bias tool by two reviewers separately (Balshem et al., 2011). Three authors assessed each study independently against the six criteria,

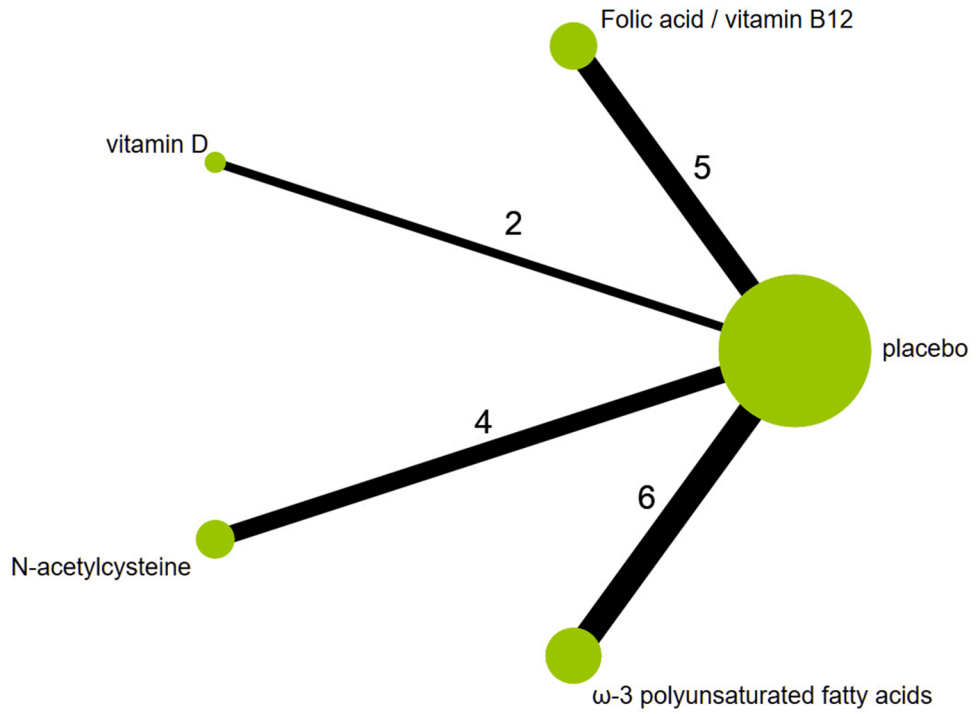

Fig 4. Evidence network of eligible comparisons for network meta-analysis. The numbers along the link lines indicate the number of trials or pairs of trial arms. The width of the lines represents the cumulative number of RCTs for each comparison.

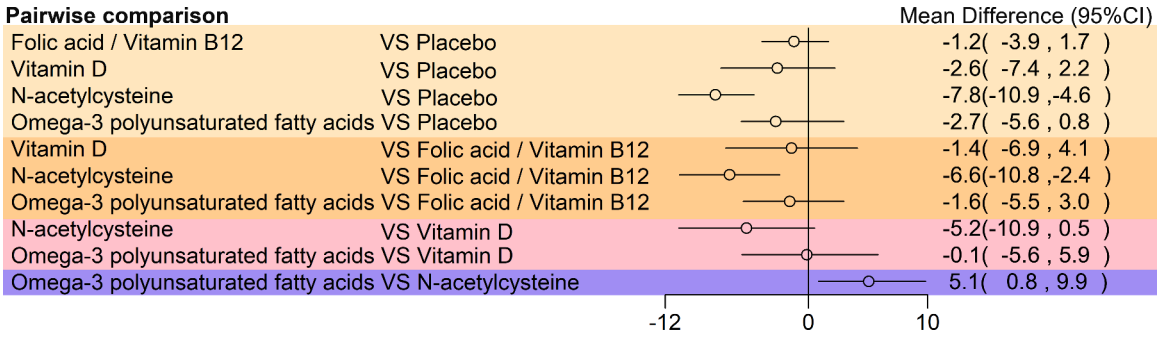

Fig 5. Pairwise meta-analysis of the efficacy of different nutritional supplements.

including 1) random sequence and allocation concealment; 2) blinding of participants and personnel; 3) blinding of outcome assessment; 4) incomplete outcome data; 5) selective reporting; 6) other bias (Cumpston et al., 2019). For any disagreement, the risk of bias was discussed by consensus.

2.3. Network meta-analysis

Bayesian network meta-analysis with random-effect hierarchical models (Faggion et al., 2014) was performed using software R 3.6.1. Standard meta-analyses of direct pair-wise comparisons were also conducted and compared to results from the network meta-analysis. The results were weighted by the inverse of the variances of the means for treatment effects in the meta-analysis. The function mtc. run was used to generate samples through the Markov chain Monte Carlo sampler. The mean difference (MD)with 95% credible interval (CI) was calculated by Markov chain Monte Carlo methods. A total of 5000 simulations were set up initially for each chain as the "burn-in" period, yielding 15,000 iterations to obtain the mean difference (MD) of model parameters while three Markov chains run simultaneously. The model convergence was evaluated by the Brooks-Gelman-Rubin plots method, trace plot, and density plot (supplementary data 2)(Wu et al., 2013). In addition, the rank probabilities were calculated to obtain the hierarchy of each treatment. The matrix of rank probabilities and the plot of rank probabilities were generated by the "gemtc" package simultaneously. From the direct plot of rank probabilities and cumulative rank plot, we could easily find the ranking of each nutritional intervention and the proportion of each ranking, respectively (Du et al., 2017). The mtc.anohe command of the "gemtc" package was applied to evaluate the global heterogeneity via the heterogeneity variance parameter I^2.

3. Results

3.1. Literature search results and characteristics of included studies

A total of 219 studies were identified through a systematic search, which included 128 repeated records (Figure 1). Amongst them, 38 records were excluded because of reviews, letters, case reports, and so on. Then the remaining studies were further carefully scrutinized, and finally, 17 RCTs were eligible for this meta-analysis (Figure 1).

The characteristics of the included studies are presented in Table 1. The studies were published between 2001 and 2019, and about half of

(A)

Placebo				
1.2 (-1.7, 3.91)	**Folic acid / Vit B12**			
2.6 (-2.24, 7.36)	1.4 (-4.1, 6.9)	**Vit D**		
7.8 (4.6, 10.9)	**6.6 (2.4, 10.8)**	5.2 (-0.5, 10.9)	**NAC**	
2.73 (-0.8, 5.64)	1.6 (-3.0, 5.5)	0.13 (-5.9, 5.6)	**-5.1 (-9.9, -0.8)**	**ω-3 PUFA**

(B)

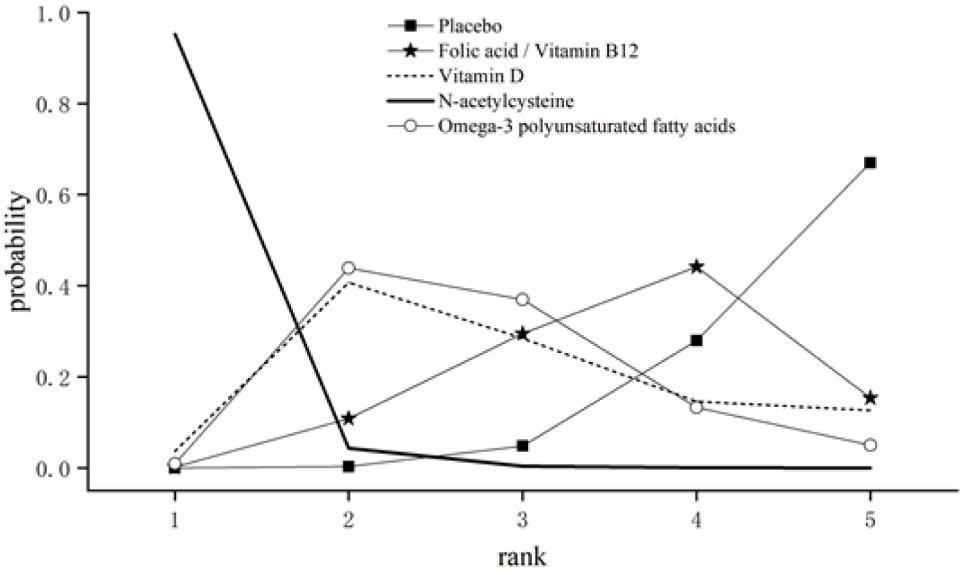

Fig 6. (A) PANSS score-based efficacy ranking league matrix showing the comparative efficacies of the treatments included in this network meta-analysis. Values below the regimens should be read from row to column, and above the treatments should be read from column to row. (B) Rankograms derived from changes of PANSS score for the treatments evaluated in the included RCTs showing the cumulative rank order for each intervention Figure 6.. Network meta-analysis of the efficacy of different nutritional supplements. (A) PANSS score-based efficacy ranking league matrix showing the comparative efficacies of the treatments included in this network meta-analysis. Values below the regimens should be read from row to column. (B) Rankograms derived from changes of PANSS score for the treatments evaluated in the included RCTs show the cumulative rank order for each intervention.

the studies were published within the past 5 years. The sample size of the participants of the studies ranged from 26 to 139, and the total number of participants included in this systematic review was 1165. Among the 17 RCTs, 5 were conducted in the United States (Breier et al., 2018; Hill et al., 2011; Peet et al., 2001; Roffman et al., 2013; Roffman et al., 2018), 3 were conducted in Austria (Allott et al., 2019; Berk et al., 2008; Rapado-Castro et al., 2015), 3 were conducted in Iran(Farokhnia et al., 2013; Ghaderi et al., 2019a; Jamilian et al., 2014), 2 were conducted in Israel(Krivoy et al., 2017; Levine et al., 2006), and each one was conducted in Poland (Pawelczyk et al., 2016), China (Qiao et al., 2018), Indian and United Kingdom (Peet et al., 2001), respectively.

3.2. Assessment of the risk of bias

The methodological quality according to the researchers' decisions on each risk of bias point for each included study is shown in Figs. 2 and 3. Results of the Cochrane risk of bias assessments present an overall medium risk of bias, especially concerning random sequence generation. A slightly higher risk was reported for performance bias and attrition bias. Unclear risks were related to reporting bias, detection bias, and other biases.

3.3. Network structure diagrams

These enrolled studies covered four different nutritional interventions: 1) folate acid or vitamin B12; 2) vitamin D; 3) NAC; 4) Omega-3 polyunsaturated fatty acid, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). The network structure diagrams, which presented the direct association between different nutritional interventions and placebo, were displayed in Figure 4. Besides, the thicknesses of the lines were proportional to the number of comparisons, and the diameters of the circles were proportional to the number of treatments included in the network meta-analysis.

3.4. Pairwise meta-analysis

According to the direct evidence (see Fig. 5), N-acetyl cysteine supplementation was significantly more efficacious than folic acid or vitamin B12 in terms of PANSS score changes [MD (95% CI): −6.6 (−10.8, −2.4)]. There was no significant difference in the PANSS score changes between N-acetyl cysteine and omega-3 polyunsaturated fatty acid, vitamin D [MD (95% CI): −5.1(−9.9, 0.8); −5.2 (−10.9, 0.5), respectively].

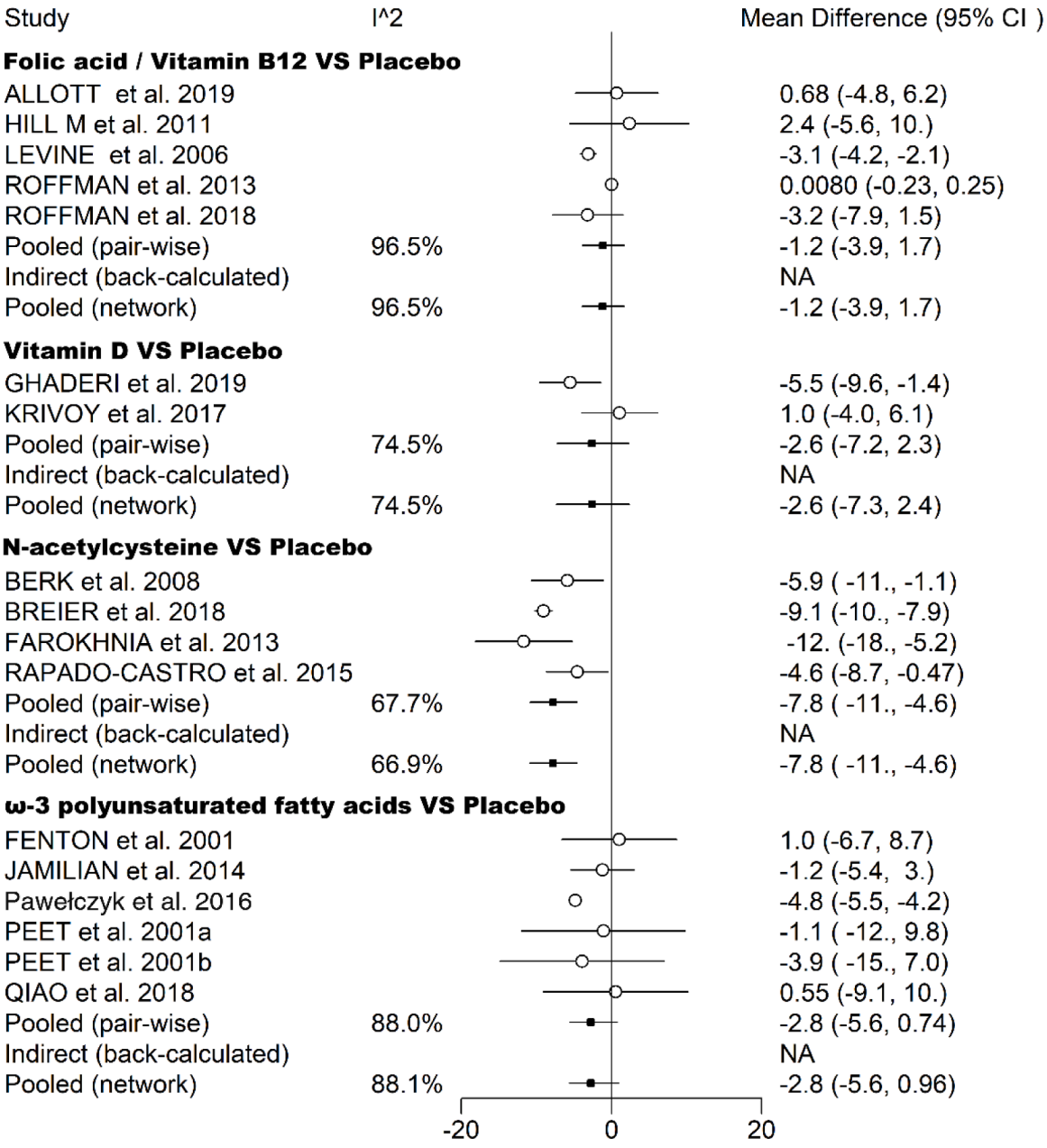

Fig 7. The heterogeneity of the included studies.

3.5. Network meta-analysis

The network meta-analysis results are presented in Fig.6 a. NAC supplement was significantly more efficacious than placebo [MD (95% CI): −7.8 (−10.9, −4.55)], folic acid or vitamin B12 [MD (95% CI): −6.6 (−10.8, −2.4)] and omega-3 polyunsaturated fatty acid [MD (95% CI): −5.1 (−9.9, −0.8)] in terms of PANSS score changes.

The ranking based on cumulative probability plots and the surface under the cumulative ranking curve (SUCRA) value is presented in Fig. 6b. In terms of efficacy, N-acetyl cysteine supplementation ranked first (SUCRA: 95.2%). Though the SUCRA value of omega-3 polyunsaturated fatty acid was higher than that of vitamin D (43.9% vs. 40.7 %), there was a significant difference of PANSS score change between N-acetyl cysteine and of omega-3 polyunsaturated fatty acid supplements, but no significant difference between N-acetyl cysteine and of vitamin D. Therefore, vitamin D and omega-3 fatty acid ranked second and third, respectively.

3.6. Heterogeneity analyses and publication Bias

The global I^2 values suggested the presence of high heterogeneity in MD for PANSS score changes (Figure 7). Substantial heterogeneity for efficacy was present in folic acid (96.5%), vitamin D (74.5%), NAC (66.9%), and omega-3 polyunsaturated fatty acid (88.1 %). Thus, the random-effect models were applied using the Mantel-Haenszel method in the subsequent analyses.

Funnel plots from pairwise meta-analyses are demonstrated in Fig 8. The results from Egger(p=0.35), Begg-Mazumdar (p=0.32), and Thompson-Sharp test (p=0.23) all suggested no significant publication bias in this study.

4. Discussion

The application of nutritional approaches in the adjunctive treatment of psychiatry diseases, including dietary or nutritional supplementations intervention, has evolved with rapidity over the past several

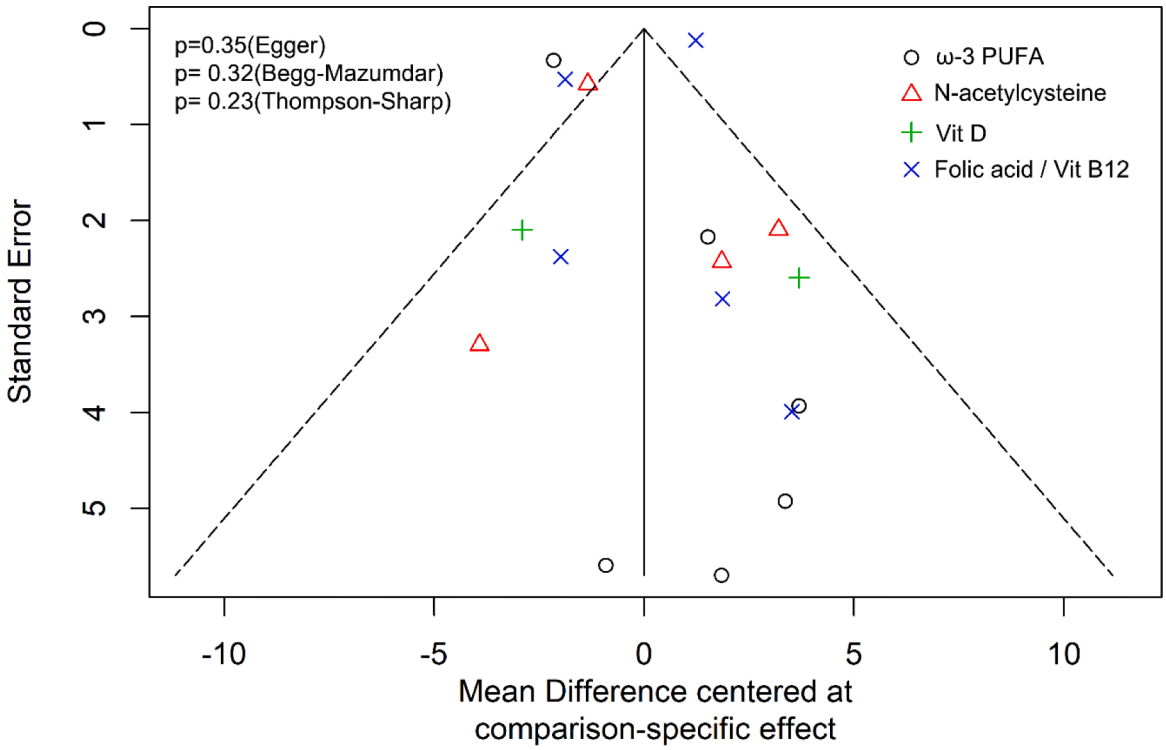

Fig. 8. Comparison-adjusted funnel plots for efficacy.

years(Sarris, 2019). However, concerning nutritional supplementations, results are fairly mixed across the board, and in many cases, there is no emphatic evidence to support the use of these supplementations in various psychiatric disorders(Firth et al., 2019). As nutrient supplementations are widely used by patients with mental disorders, it is critical to assess the efficacy of these supplementations and to determine if a nutrient supplementation is required. The results from this network meta-analysis showed that N-acetyl cysteine (NAC) is more effective than placebo in the adjunctive treatment of schizophrenia, though the quality of the evidence was not high. The estimated ranking based on the cumulative probability showed that NAC supplementation may be the most effective intervention among all nutritional supplementations for schizophrenia. These results may provide some information that could help doctors making initial choices for prescription of nutritional supplementations in the adjunctive treatment of schizophrenia while the quality of the evidence may be limited by the relative paucity of studies, potential for study bias, and lack of clarity regarding the stage of illness effects (early or late-stage supplementation). Moreover, from a clinical perspective, as a 10/15-point difference in PANSS scores means minimal clinical improvement (Leucht et al., 2006) and NAC supplementation only have a mean reduction in PANSS of 8.7 points, the clinicians may report that in the clinical routine they do not 'see' an efficacy superiority of NAC supplementation compared with placebo.

The potential therapeutic effect of NAC on schizophrenia may be due to its pivotal regulatory role in the etiopathogenesis of schizophrenia. NAC is a precursor to the antioxidant glutathione (Tenorio et al., 2021), and it is emerging as a useful agent in the treatment of psychiatric disorders, including schizophrenia (Andrade, 2021; Smaga et al., 2021). NAC has been demonstrated to regulate crucial biological processes that lay at the core of etiopathogenesis of schizophrenia, including attenuating both glutamergic and dopaminergic dysregulation(Zhu et al., 2021), modulating neurotropic and inflammatory pathways(Alam et al., 2019), and inhibiting oxidative stress(Boz et al., 2020). These results indicated that nutritional supplementations with clear target and action mechanisms may be more beneficial for the adjunctive treatment of schizophrenia.

In this study, vitamin D, omega-3 polyunsaturated fatty acid, and folic acid or vitamin B12 supplementations were found to be associated with reduced PANSS scores in schizophrenia, but the results were not significant. Although evidence from observational studies indicated the association between the deficiencies of vitamin D (Valipour et al.,2014; Zhu et al., 2020), omega-3 polyunsaturated fatty acid (Marano et al., 2013; Pawelczyk et al., 2019), and vitamin B12 or folic acid(Cao et al., 2016; Yazici et al., 2019) and increased risk of schizophrenia, the results from randomized control trials (RCTs) were mixed (Ghaderi et al., 2019a; Krivoy et al., 2017; Qiao et al., 2020; Sakuma et al., 2018). These inconsistencies may be due to several reasons. One possible reason is that the available evidence from clinical studies was limited by the low quality and small sample size(Chen et al., 2015; Jeppesen et al., 2020; Sakuma et al., 2018). This was also demonstrated by the high heterogeneity of the studies included in this study. Another reason may be that the effects of nutritional supplements on schizophrenia are stage-specific (Balanza Martinez, 2017; Chen et al., 2015). These nutritional supplementations may have more beneficial effects when they were given at an early stage of the disease(Freedman et al., 2021; Smesny et al., 2017). These results suggested that more large-scale, high-quality RCTs were warranted to confirm the beneficial effects of these nutritional supplements in the treatment of schizophrenia. Furthermore, early intervention research is also needed to find protective nutritional supplements at the crucial developmental stage of schizophrenia.

There were several strengths to consider in our analysis. First, to our best knowledge, our study is the first one to present the overall effects of nutritional supplementations on the PANSS score of schizophrenia patients to date. Second, we applied a network meta-analysis based on Bayesian model, which is thought to be the most appropriate method for multiple treatments(Caldwell et al., 2005), to explore the effect of indirect comparison between different nutritional supplementations. The network technique allows dissection of the individual supplementation to evaluate interested outcomes, especially when very few RCTs have directly compared competing for nutritional supplementations.

Several limitations should also be noted in this study. First, other unpublished literature on relevant websites was not searched and only

trials in English and Chinese were included, and this may lead to potential publication bias and selection bias. Second, we did not investigate the distribution of clinical and methodological variables in detail that we suspected might be potential sources of either heterogeneity or inconsistency in every comparison-specific group of trials, although our pooled estimates were with the random-effect model. Last, in this study, we did not assess the safety of these nutritional supplementations, though it has been demonstrated in other high-quality studies(Firth et al., 2019; Rapado-Castro et al., 2015; Sakuma et al., 2018). Therefore, although this network meta-analysis provides a relatively comprehensive and clear picture of the associations between nutritional supplementation on PANSS score in schizophrenia patients, the application of our results should take into account any limitations of the analysis and the specific clinical situation.

5. Conclusions

In general, our result suggests NAC could improve PANSS score and it may be among the most effective nutritional supplements in schizophrenia patients. More long-term large-scale comparative randomized trials must be performed to confirm the beneficial effects of vitamin D, omega-3 fatty acid, and folic acid or vitamin B12 supplements on PANSS scores in schizophrenia patients.

Declaration of Competing Interest

None of the other authors reported a conflict of interest related to the study.

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