The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials

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The role of nutrition in mental health is becoming increasingly acknowledged. Along with dietary intake, nutrition can also be obtained from "nutrient supplements", such as polyunsaturated fatty acids (PUFAs), vitamins, minerals, antioxidants, amino acids and pre/probiotic supplements. Recently, a large number of meta-analyses have emerged examining nutrient supplements in the treatment of mental disorders. To produce a meta-review of this top-tier evidence, we identified, synthesized and appraised all meta-analyses of randomized controlled trials (RCTs) reporting on the efficacy and safety of nutrient supplements in common and severe mental disorders. Our systematic search identified 33 meta-analyses of placebo-controlled RCTs, with primary analyses including outcome data from 10,951 individuals. The strongest evidence was found for PUFAs (particularly as eicosapentaenoic acid) as an adjunctive treatment for depression. More nascent evidence suggested that PUFAs may also be beneficial for attention-deficit/hyperactivity disorder, whereas there was no evidence for schizophrenia. Folate-based supplements were widely researched as adjunctive treatments for depression and schizophrenia, with positive effects from RCTs of high-dose methylfolate in major depressive disorder. There was emergent evidence for N-acetylcysteine as a useful adjunctive treatment in mood disorders and schizophrenia. All nutrient supplements had good safety profiles, with no evidence of serious adverse effects or contraindications with psychiatric medications. In conclusion, clinicians should be informed of the nutrient supplements with established efficacy for certain conditions (such as eicosapentaenoic acid in depression), but also made aware of those currently lacking evidentiary support. Future research should aim to determine which individuals may benefit most from evidence-based supplements, to further elucidate the underlying mechanisms.

Key words: Nutrient supplements, polyunsaturated fatty acids, omega-3, eicosapentaenoic acid, methylfolate, vitamin D, N-acetylcysteine, depression, schizophrenia, attention-deficit/hyperactivity disorder, adjunctive treatment

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Abundant evidence now suggests that people with mental disorders typically have an excess consumption of high-fat and high-sugar foods, alongside inadequate intake of nutrient-dense foods, compared to the general population[1-5]. The relationship between poor diet and mental illness appears to persist even when controlling for other factors which could explain the association, such as social deprivation or obesity, and is not explained by reverse causation[1,6].

Furthermore, although the metabolic and hormonal side effects of psychotropic medications can affect food intake[7,8], inadequate nutrition appears to be present even prior to psychiatric diagnoses. For instance, in depression, it seems that poor diet precedes and acts as a risk factor for illness onset[6,9,10]. Similarly, in psychotic disorders, various nutritional deficits are evident even prior to antipsychotic treatment[11].

The importance of diet for maintaining physical health is widely accepted, due to the clear impact of dietary risk factors on cardiometabolic diseases, cancer and premature mortality[12,13]. In parallel, the potential impact of diet on mental disorders is increasingly acknowledged[14,15]. However, along with regular food intake, nutrients can also be consumed in supplement form[16]. Supplements are typically used in attempts to: a) complement an inadequate diet (or low measured plasma levels of a nutrient) to achieve recommended nutrient intakes/levels; b) administer specific nutrients at greater doses than those found in a typical diet, for putative physiological benefits; c) provide nutrients in more bioavailable forms for individuals with genetic differences, or relevant health issues, which may result in poor nutrient absorption. Supplements can be synthetically manufactured or directly food-derived, typically including substances such as vitamins (e.g., folic acid, vitamin D), dietary minerals (e.g., zinc, magnesium), pre/probiotics (from specific strains of gut bacteria), polyunsaturated fatty acids, PUFAs (typically as omega-3 fish oils), or amino acids (e.g., N-acetylcysteine, glycine).

Nutrient supplements are widely used across the population. For instance, in the US, over half of adults take some form of nutrient supplements[17]. There is a lack of evidence that this wide-scale usage reduces the incidence of diseases or premature mortality (indeed, many of the best quality trials – e.g., of vitamins D[18] and E[19,20] – were negative). However, some specific

nutrient supplements are linked to health benefits for specific populations or clinical conditions (for instance, women in pregnancy are advised to supplement with folic acid to reduce the risk of neural tube deficits in offspring[21]; individuals with pernicious anaemia are treated with vitamin B12[22]; oral supplementation with zinc is a first-line treatment for Wilson's disease[23]; and national medical associations have recommended omega-3 fatty acids for patients with myocardial infarction[24]).

Currently, there is an increased academic and clinical interest in the role of nutrient supplements for the treatment of various mental disorders[14-16]. This growth of research is partly attributable to our evolving understanding of the neurobiological underpinnings of mental illness, which implicates certain nutrients as a potential adjunctive treatment for a variety of reasons[25].

First, recent clinical research has found that many mental disorders are associated with heightened levels of central and peripheral markers of oxidative stress and inflammation[26-29], and an association has been reported between the efficacy of both pharmacological and lifestyle interventions for mental illness and changes in these biomarkers[30,31]. Thus, the antioxidant and anti-inflammatory properties of certain nutrient supplements (such as N-acetylcysteine[32] and omega-3 fish oils[33]) indicates that these could be beneficial in the treatment of psychiatric conditions caused or exacerbated by heightened inflammation and oxidative stress.

Second, there are now extensive data from large-scale studies showing that psychotic and mood disorders are associated with significantly reduced serum levels of essential nutrients, including zinc[34,35], folate[36,37] and vitamin D[38,39]. Since these deficits appear to be related to treatment response and clinical outcomes in these populations[11,34,40], there is a possibility that nutrient supplementation could improve outcomes.

Third, there is nascent (but growing) evidence that mental disorders may be linked to dysfunction of the gut microbiome[41,42]. As gut bacteria can be modified through micronutrients and pre/probiotics[43,44], this suggests that some pre/probiotic supplements may serve as potentially useful novel therapeutic options worthy of further investigation[45,46].

Alongside the theoretical potential for nutrient supplements to target certain aspects of mental disorders, there is also a vast amount of clinical trials and meta-analyses examining their use in psychiatric treatment, and some data in prevention[47,48]. However, there remains considerable contention around their role in clinical care. This likely stems from the lack of clear and up-to-date guidance for clinicians and researchers regarding their: a) relative effectiveness for improving clinical outcomes in people with mental illness, and b) safety for use, particularly in conjunction with psychiatric medications.

The aim of this meta-review is to aggregate and evaluate the top-tier evidence for the efficacy and safety of nutrient supplements in the treatment of mental disorders, and to explore the conditions under which they may be effective. To do this, we identified, synthesized and appraised all available data from meta-analyses of randomized controlled trials (RCTs) examining health outcomes and quality of evidence for all nutrient supplements across various mental disorders. Along with providing a clear overview of the efficacy of specific nutrient supplements across different disorders, we also aimed to explore which dosages and symptomatic targets are most appropriate, while additionally reporting on the safety and tolerability for all supplements examined.

METHODS

The search strategy and data synthesis were conducted in line with the PRISMA statement[49], and followed a pre-registered protocol (PROSPERO: CRD42018105880).

Systematic search

The title and keyword search algorithm is presented in Table 1. The systematic search was conducted using Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, Allied and Complementary Medicine (AMED), PsycINFO and Ovid MEDLINE(R), from inception until February 1, 2019.

A search of Google Scholar was conducted using the same key words to identify any additional relevant articles. Reference lists of included articles were also searched.

Table 1 PICO (Participants, Interventions, Comparisons, Outcomes) systematic search strategy

Participants (any mental disorder)
Depression OR depressive OR mental illness* OR mental disorder* OR mood disorder* OR affective disorder* OR anxiety OR panic disorder OR obsessive compulsive OR ADHD OR attention deficit OR attentional deficit OR phobia OR bipolar type OR bipolar disorder* OR psychosis OR psychotic OR schizophr* OR antipsychotic* OR post traumatic* OR personality disorder* OR stress disorder* OR dissociative disorder*
Interventions (any nutrient or nutraceutical)
Vitamin* OR mineral* OR nutrient* OR food supplement* OR meal replacement* OR nutritional supplement* OR health supplement* OR multivitamin* OR omega 3 OR fish oil* OR alpha lipoic acid OR alpha linolenic acid OR alpha linoleic acid OR eicosapentaenoic OR docosahexaenoic OR fatty acid* OR amino acid* OR taurine OR S-adenosyl methionine OR creatine OR acetylcysteine OR cysteine OR probiotic* OR tryptophan OR tocopherol OR alphatocopherol OR carotene OR retinol OR thiamine OR riboflavin OR niacin OR niacinamide OR nicotinic acid OR pantothenic OR pyridox* OR biotin OR methylfolate OR 5-MTH* OR levomefolic acid OR folate OR folinic acid OR folic acid OR inositol OR cyanocobalamin OR methylcobalamin OR cobalamin OR ascorbic acid OR cholecalciferol OR iron OR ferrous OR tocopherols OR trace element OR calcium OR phosphorus OR magnesium OR potassium OR manganese OR zinc OR selenium OR boron OR chromium OR lycopene OR isoflav* OR flavonoid* OR bioflavonoid* OR micronutrient OR carnitine
Comparator (placebo controlled trials)
Random* OR placebo OR control* or adjunc* or clinical trial*
Outcomes (any from meta-analyses)
Meta-analy* OR metaanaly* OR meta reg* OR metareg* OR systematic review*

Eligibility criteria

Eligibility criteria were organized in accordance with the PICO (Participants, Interventions, Comparisons, Outcomes) reporting structure, as described below.

Participants

We included studies of individuals with common and severe mental disorders, i.e., depressive disorders, bipolar disorder (type I and II), schizophrenia and other psychotic disorders, anxiety and stress-related disorders, dissociative disorders, personality disorders, and attention-deficit/hyperactivity disorder (ADHD). Studies of individuals who met criteria for being at "ultra-high risk" or "clinical high risk" for developing a psychotic disorder were also included.

All studies of the above conditions were eligible provided that at least 75% of the sample had a confirmed mental illness or at-risk state, ascertained by either clinical diagnostic history or reaching established thresholds on validated screening measures. Studies examining mental health outcomes of nutrient supplementation in the general population were only included if data from a mental illness subgroup (with 75% of the sample meeting the above criteria) were available. Studies examining nutrient supplements only for ameliorating the malnutrition associated with eating disorders or substance abuse disorders were excluded. Studies examining neurodevelopmental disorders (e.g., autism, intellectual disability) or neurodegenerative disorders (e.g., dementia) were also not included.

Interventions

All nutrient supplements were considered for this meta-review, used either as adjunctive treatment or monotherapy. Nutrient supplements were defined as vitamins, minerals, macronutrients, fatty acids or amino acids (including oral supplement forms of precursors to these) commonly found in the human diet. Meta-analyses of dietary modification interventions and herbal supplements were not included.

Comparisons

As this study aimed to provide a meta-review of the top-tier evidence, only meta-analyses of RCTs were included.

Outcomes

All data on physical and/or mental health outcomes (including changes in clinical measures, response rates, and adverse effects) from meta-analyses of RCTs examining nutritional supplements for any eligible disorder were included in this meta-review. A meta-analysis was classified as eligible if: a) it had clearly stated inclusion, intervention and comparison criteria aligned with the participant, intervention and comparison criteria listed above; b) it reported a systematic search with a screening procedure; c) it had used systematic data extraction and reported pooled continuous or categorical outcome data from more than one study.

Where overlapping meta-analyses of a given nutritional supplement for a specific outcome/disorder existed, the most recently updated meta-analysis was used, as long as it captured more than 75% of the trials in the earlier version. Where older meta-analyses presented unique findings, through inclusion of a greater number of studies or use of particular subgroup analyses, these data were used as secondary analyses for our meta-review.

Quality assessment of included meta-analyses

The quality of eligible meta-analyses was assessed using "A Measurement Tool to Assess Systematic Reviews" Version 2 (AMSTAR-2)[50], an updated version of the original AMSTAR designed to better capture review quality and confidence in findings.

AMSTAR-2 assesses 16 constructs, which all indicate the quality of a systematic review/meta-analysis. Seven of these were identified as "critical domains", which can be used to determine the overall confidence in review findings[50]. For the purposes of our meta-review, the included meta-analyses were scored on all the 16 AMSTAR-2 items, but also received a separate score for the number of "critical domains" they adhered to.

Data extraction and analysis

Primary analyses focused on the effects of nutrient supplementation on measures of physical or mental health outcomes from eligible meta-analyses. For each nutritional supplement used for each disorder, we manually extracted effect size data as standardized mean differences (SMDs) with 95% confidence intervals (CIs) compared to placebo conditions, along with the reported probability of the compared effects being due to chance (p value). Data were initially extracted by five authors (KA, ST, WM, MS, DS), and then cross-checked for quality with duplicate data extraction by four independent authors (JF, BS, JC, FS).

In line with conventional interpretations, SMDs were classified as negligible (<0.2), small (0.2-0.4), moderate (0.4-0.8), or large (>0.8). In cases where meta-analyses had provided effect sizes corrected for publication bias, these were reported alongside the main effects observed, and interpreted as the primary findings from the analysis. In cases where continuous outcomes were reported as weighted mean differences or raw mean differences, these were recalculated into an SMD (Hedges' g) using Comprehensive Meta-Analysis 3.0. Where original meta-analyses had reported beneficial effects of nutrient supplementation as negative value effect sizes (to represent a reduction in symptoms), these were re-coded to positive – such that all effect sizes

presented here are positive values when indicating benefit from nutrient supplementation compared to placebo, or negative values when placebo was associated with better outcomes than nutrient supplementation. Where meta-analyses had applied fixed-effects models to calculate the effect sizes of nutritional supplementation compared to placebo, these were also recalculated using a random-effects model, such that SMDs across supplements/disorders could be meaningfully compared.

The results of secondary analyses, focusing on safety and tolerability, were typically reported as categorical outcomes (relative rates of adverse events or discontinuation in active vs. placebo conditions). These were extracted as either odds ratios (ORs) or risk ratios (RRs), in line with the originally reported outcomes.

For both primary and secondary analyses, we also extracted the number of participants (N), along with the number of trials/comparisons (n) from which the pooled effect size was derived. Additionally, heterogeneity was quantified using the I^2 statistic, and categorized as low (I^2<25%), moderate (I^2=25-50%) or high (I^2>50%).

Where reported, all relevant study characteristics were also extracted, specifically with regards to the nutritional supplement used (including type, dose and co-factors), the sample and the diagnostic details, and any relevant subgroup analyses implemented (e.g., separating high/low quality trials, specific patient subsamples, or dosage levels).

The potential impact of publication bias was assessed wherever there were sufficient data for appropriate analyses, and the adjusted effect sizes (when controlling for small study bias) are presented alongside the main findings.

RESULTS

Systematic search results

The search returned 1,194 results, which were reduced to 737 after duplicates were removed. One further potentially eligible article was retrieved from the additional search of Google Scholar. Title and abstract screening removed 597 articles, while 141 articles were retrieved and reviewed in full. Of these, 108 were ineligible. Thus, in total, eligible data from 33 independent meta-analyses of RCTs of nutrient supplementation in mental disorders were included for this meta-review (see Figure 1).

Meta-analyses examined RCTs of PUFAs, vitamins, minerals, amino acid supplements and pre/probiotics, with primary analyses including outcome data from a total of 10,951 individuals. All meta-analyses were based on nutrient supplementation administered in conjunction with "usual care" (without specifying treatment regimens) or as an adjunctive treatment to a specific class of psychotropics (e.g., selective serotonin reuptake inhibitors (SSRIs) in depression, or antipsychotics in schizophrenia). Only one of the meta-analyses reported on a nutrient supplement as monotherapy for a mental disorder (i.e., omega-3 fatty acids for depression[51]), whereas no others specifically excluded patients taking medications. No meta-analyses directly compared nutrient supplementation to psychotropic medications. All studies[51-82] were placebo-controlled.

Specific psychiatric conditions (and reported outcomes) considered in this meta-review included: schizophrenia (examining total symptoms along with positive, negative, general and depressive symptoms, and tardive dyskinesia)[52-59]; states at risk for psychosis (examining attenuated psychosis symptoms, negative symptoms, transition to psychosis, and functioning)[60-63]; depressive disorders (including any clinical depression, diagnosed major depressive disorder (MDD), depression in pregnancy, in old age, or as a comorbidity to chronic health conditions)[51,59,64-73]; anxiety and stress-related conditions (including generalized anxiety disorder, obsessive-compulsive disorder (OCD) and trichotillomania)[68,72,74]; bipolar disorder type I and II (examining overall symptoms, bipolar mania, bipolar depression, functional impairments, and quality of life)[56,68,72,75,76]; and ADHD (including composite symptoms, hyperactivity-impulsivity, inattention, behavioural comorbidities such as aggression, and cognitive functioning)[77-82].

Quality assessment of the included meta-analyses

The quality assessment of the meta-analyses is provided alongside the respective outcomes in Figures 2-7. Individual meta-analyses fulfilled between 4 and 16 of the AMSTAR-2 criteria (median: 12, mean: 12). The majority of the meta-analyses (25 out of 33) adhered to five or more of the seven "critical domains", but only five of them adhered to all the domains[52,58,64,78,80]. Twenty-six of the 33 included meta-analyses were published in 2016-2019.

Efficacy and safety of nutrient supplementation for mental disorders

Figures 2-7 show the efficacy of nutrient supplementation (as determined by meta-analyses) for all clinical outcomes reported across different psychiatric conditions, including depressive disorders (Figure 2), anxiety disorders (Figure 3), schizophrenia (Figure 4), states at risk for psychosis (Figure 5), bipolar disorder (Figure 6), and ADHD (Figure 7). The overall quality of meta-analyses is also displayed in these figures. Nutrient supplements with sufficient data (i.e., from meta-analyses with >400 participants) are highlighted in Table 2. For all nutrients assessed, the specifics of these findings, along with data on safety and tolerability, are detailed below.

Vitamins and minerals

Folate-based supplements

The most widely assessed vitamin supplement for mental disorders was vitamin B9, which is also referred to as "folate" when

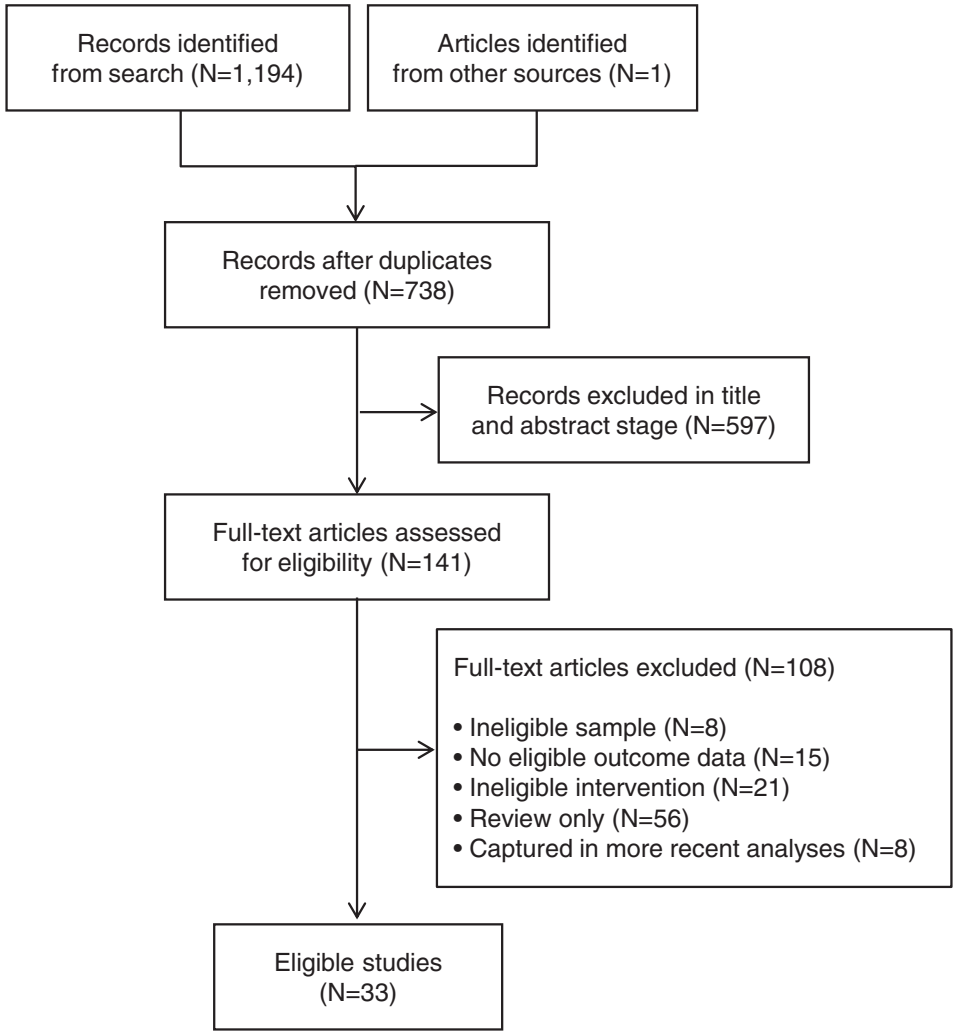

Figure 1 PRISMA flow chart

in dietary form. It can be administered in supplement form as folic acid, folinic acid or methylfolate (which is also known as l-methylfolate, levomefolic acid, or 5-methyltetrahydrofolate).

As an adjunctive to SSRIs in 904 individuals with unipolar depression (mostly MDD), folate-based supplements (including folic acid and methylfolate, administered at varying doses) were associated with significantly greater reductions in depressive symptoms compared to placebo, although there was large heterogeneity between trials (n=7, SMD=0.37, 95% CI: 0.01-0.72, p=0.04, I^2=79%)[67].

When administering vitamin B9 as folic acid (0.5-10 mg/day), no significant effects on depressive symptoms were observed (N=657, n=4, SMD=0.4, 95% CI: –0.08 to 0.88, p=0.1, I^2=83%). Significant effects were observed in the two trials using low dose (<5 mg/day) folic acid (N=190, SMD=0.57, 95% CI: 0.23-0.91, p<0.001, I^2=25%), while no significant benefits were observed from doses of ≥5 mg/day (N=467, n=2, SMD=0.24, 95% CI: –0.56 to 1.03, p=0.56, I^2=76%)[67].

Two RCTs examining a high dose (15 mg/day) of methylfolate (the most bioactive metabolite of folic acid) as an adjunctive treatment for MDD found moderate-to-large benefits for depressive symptoms (N=99, n=2, SMD=0.73, 95% CI: 0.28-1.19, p=0.002, I^2=3%)[67]. There was no evidence of adverse effects or statistical heterogeneity. However, when including the lower-dose trials of methylfolate (7.5 mg/day), no significant effects on depression were observed (N=249, n=3, SMD=0.34, 95% CI: –0.4 to 1.08, p=0.37, I^2=81%).

Seven RCTs (N=340) examined folate-based supplements as an adjunctive treatment for schizophrenia[54]. Vitamin B9 was administered as methylfolate (n=2) or folic acid (n=5), and also in combination with B6 and B12 (n=3). In overall analyses, the small effects of vitamin B9 on total symptoms were not statistically significant (SMD=0.20, 95% CI: –0.02 to 0.41, p=0.08, I^2=0), and subgroup analyses of high-quality studies confirmed the absence of overall effects (N=231, n=3, SMD=0.15, 95% CI: –0.11 to 0.42, p=0.26, I^2=0%). The folate-

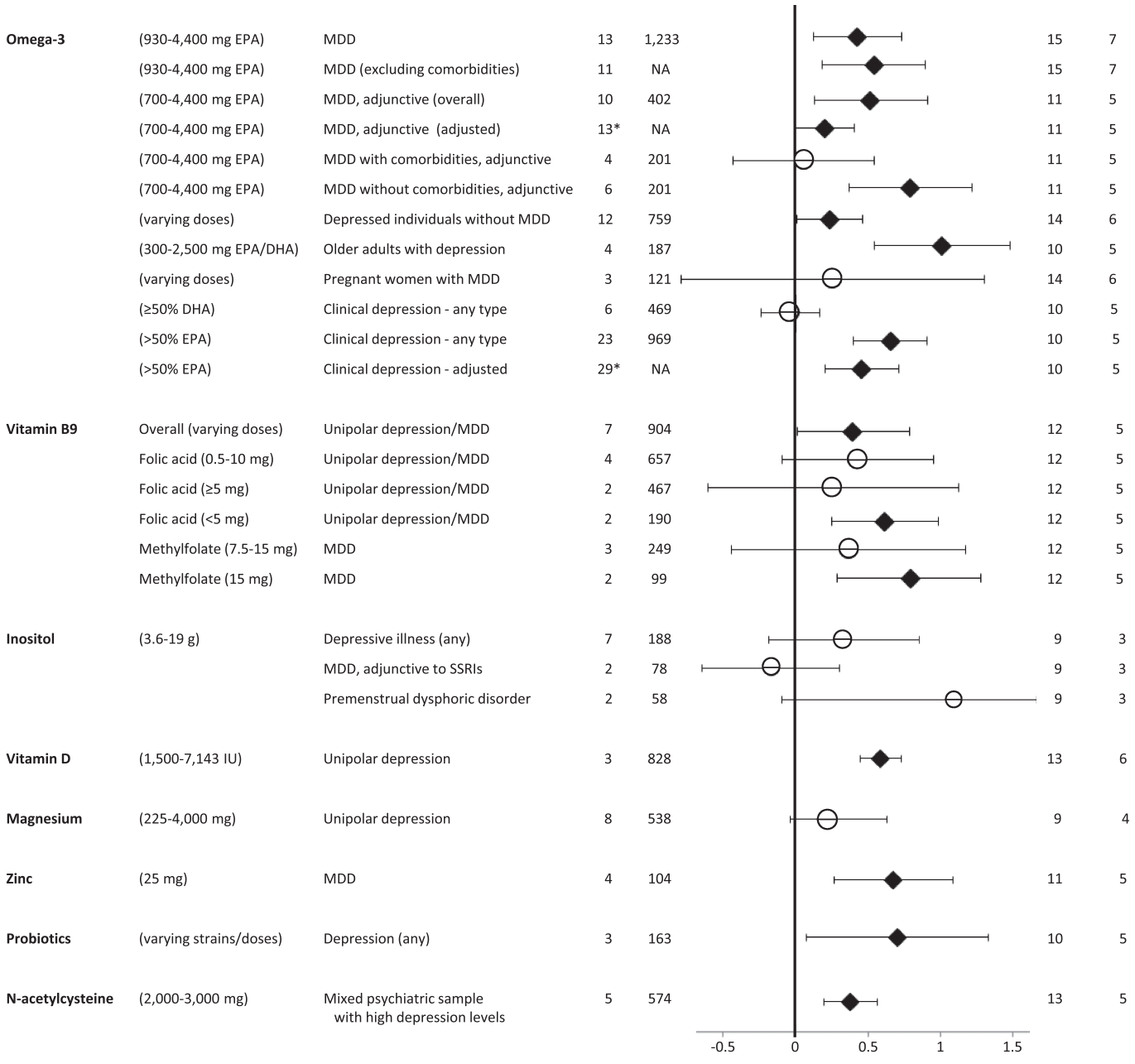

Figure 2 Effects of nutrient supplements in depressive disorders, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo; diamonds represent p≤0.05 compared to placebo; * represents trim-and-fill estimate adjusted for publication bias. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, MDD – major depressive disorder, EPA – eicosapentaenoic acid, DHA – docosahexaenoic acid, SSRIs – selective serotonin reuptake inhibitors, NA – not available.

based supplements were ineffective on total symptom scores when administered as folic acid (N=268, n=5, SMD=0.13, 95% CI: –0.12 to 0.37, p=0.32, I^2=0%), even in combination with other homocysteine-reducing B vitamins (i.e., B6 and B12) (N=219, n=3, SMD=0.18, 95% CI: –0.13 to 0.5, p=0.24, I^2=16%). However, effects on total symptom scores in two trials of high-dose methylfolate (15 mg/day) approached statistical significance (N=72, n=2, SMD=0.45, 95% CI: 0.02-0.92, p=0.06, I^2=0%).

Folate-based supplements had no significant effects on positive symptoms, general psychopathology or depressive symptoms in patients with schizophrenia[54]. However, they reduced

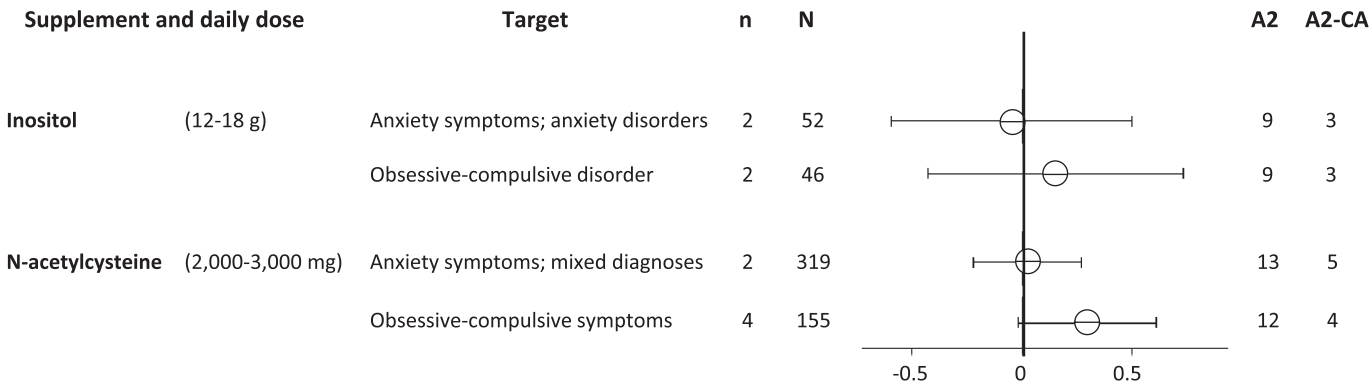

Figure 3 Effects of nutrient supplements in anxiety, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to.

negative symptoms more than placebo (N=281, n=5, SMD=0.25, 95% CI: 0.01-0.49, p=0.04, I^2=0). The effect persisted in high-quality RCTs (N=190, n=2, SMD=0.30, 95% CI: 0.00-0.60, p=0.05, I^2=0), but became non-significant when excluding the RCT using 15 mg/day methylfolate (N=226, n=4, SMD=0.23, 95% CI: –0.04 to 0.50, p=0.10, I^2=0%)[54].

A significantly lower incidence of serious adverse events compared to placebo was observed over the trial periods in patients with schizophrenia (N=241, n=4, RR=0.32, 95% CI: 0.12-0.82, p=0.02, I^2=0%)[54].

Inositol

In an overall analysis of the effects of inositol (3.6-19 g/day, median: 12 g/day) on depressive symptoms across bipolar disorder, unipolar depression and premenstrual dysphoric disorder, no significant difference from placebo was found (N=188, n=7, SMD=0.35, 95% CI: –0.2 to 0.89, p=0.22, I^2=70%)[68]. Inositol was also ineffective when examined as adjunctive to SSRIs in MDD (N=78, n=2, SMD=–0.17, 95% CI: –0.66 to 0.33, p=0.50, I^2=0%) and for depressive symptoms in premenstrual dysphoric disorder (N=58, n=2, SMD=1.15, 95% CI: –0.08 to 2.39, p=0.07, I^2=78%)[68].

In schizophrenia, inositol supplementation (6-12 g/day) was not superior to placebo for total symptom scores (N=66, n=3, SMD=0.155, 95% CI: –0.35 to 0.58, p=0.63, I^2=87.2%)[53]. Among individuals with bipolar disorder, inositol (5.7-19 g/day) had no effect on depressive symptoms (N=42, n=2, SMD=–0.11, 95% CI: –0.75 to 0.52, p=0.72, I^2=0%) or response rates (RR=0.63, 95% CI: 0.35-1.12, p=0.12, I^2=22%)[68]. In anxiety disorders, inositol (12-18 g/day) had no effects on Hamilton Anxiety Rating Scale scores (N=52, n=2, SMD=0.04, 95% CI: –0.58 to 0.51, p=0.89) and symptom scores in OCD samples (N=46, n=2, SMD=0.15, 95% CI: – 0.43 to 0.73, p=0.60)[68].

Discontinuation did not differ between inositol and placebo groups[68]. However, inositol supplementation was associated with a trend towards a higher rate of gastrointestinal upset than placebo (N=183, n=6, SMD=3.26, 95% CI: 0.94-11.34, p=0.06, I^2=0%).

Other vitamins and minerals

Vitamin D was found to significantly reduce depressive symptoms in patients with clinical depression (N=948, n=4, SMD=0.58, 95% CI: 0.45-0.72, p<0.01, I^2=0%). This estimate included data from non-blinded trials using intramuscular injections[69]. Nevertheless, in our re-analysis of data using only double-blind RCTs of oral supplements, similar positive effects were observed at doses of 1,500-7,143 IU/day (N=828, n=3, SMD=0.57, 95% CI: 0.43-0.71, p<0.001, I^2=0%).

Eleven RCTs examined the efficacy of mineral supplementation for depression, using either zinc or magnesium. Zinc was administered at 25 mg/day (elemental) as an adjunctive treatment for MDD, and had moderate significant effects on depressive symptoms (N=104, n=4, SMD=0.66, 95% CI: 0.26-1.06, p=<0.01)[65]. Although there was no evidence of heterogeneity (I^2=0%), all included RCTs were identified as having high risk of attrition bias, due to lack of intent-to-treat analyses[65]. In individuals with depression identified using self-report measures, magnesium supplementation at 225-4,000 mg/day had no effects beyond placebo (N=538, n=8, SMD=0.22, 95% CI: –0.17 to 0.48, I^2=30.9%)[70]. No data on magnesium as an adjunctive treatment in diagnosed MDD are available.

No significant effects on total symptom scores in schizophrenia were observed from pooled analyses of antioxidant vitamins (vitamin C and vitamin E: N=340, n=6, SMD=0.296, 95% CI: –0.39 to 0.98, p=0.40, I^2=40.6%); mineral supplements (zinc and chromium: N=129, n=2, SMD=0.324, 95% CI: –0.48 to 1.13, p=0.43, I^2=0%); or vitamin B6 (N=75, n=3, SMD=0.682, 95% CI: –0.09 to 1.45, p=0.08, I^2=58.4%)[53].

As a therapeutic option for managing side effects of antipsychotics, vitamin E showed no difference from placebo on levels of improvement in tardive dyskinesia[52]. Nevertheless, it did significantly reduce the risk of tardive dyskinesia "worsening" over 1 year (N=85, n=5, RR=0.23, 95% CI: 0.07-0.76), although this result was based on low-quality trials[52].

All vitamin and mineral supplements appeared to have good safety profiles in schizophrenia, with none producing a greater number of adverse events than placebo control conditions[52,53].

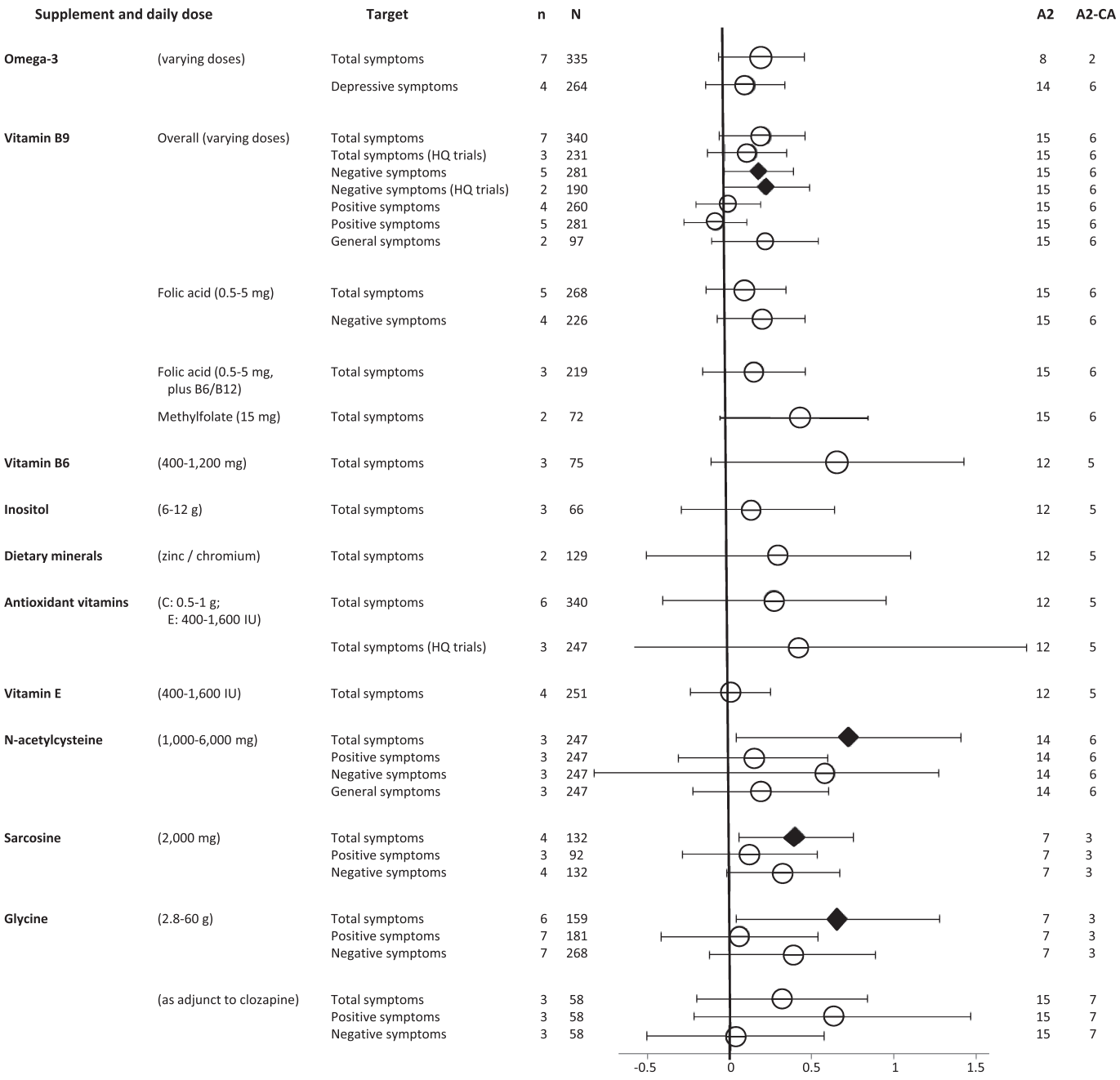

Figure 4 Effects of nutrient supplements in schizophrenia, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo; diamonds represent p≤0.05 compared to placebo. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, HQ – high quality.

PUFAs

Depression and bipolar disorder

PUFAs have been the most widely assessed nutritional supplement across the various psychiatric conditions, administered as omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and omega-6 fatty acids, such as linoleic acid (LA).

Across 13 independent RCTs in 1,233 people with MDD, omega-3 supplements (mean: 1,422 mg/day of EPA) reduced depressive symptoms (SMD=0.398, 95% CI: 0.114-0.682, p= 0.006, I^2 not available), with no evidence of publication bias[64]. When used specifically as an adjunctive to antidepressants in MDD, omega-3 supplements (930-4,400 mg/day of EPA) also produced moderate effects on depressive symptoms (N=448,

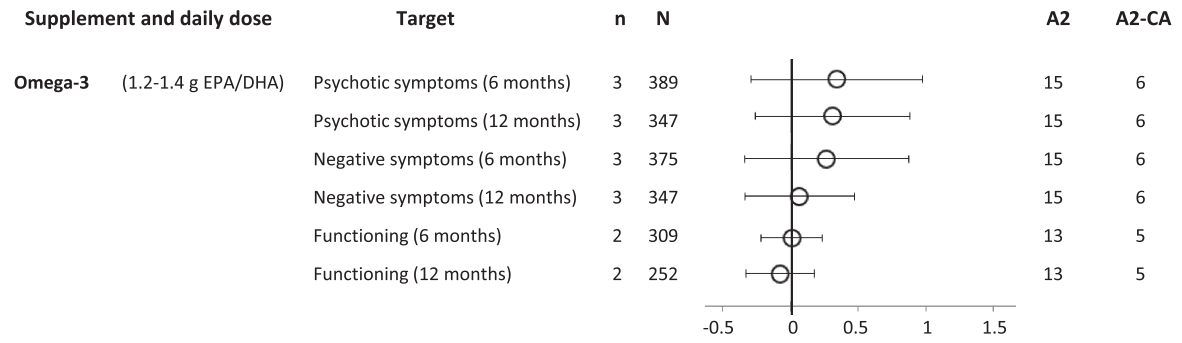

Figure 5 Effects of nutrient supplements in states at risk for psychosis, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, EPA – eicosapentaeonoic acid, DHA – docosahexaenoic acid.

n=11, SMD=0.608, 95% CI: 0.154-1.062, p=0.009, I^2=82%), although there was some indication of publication bias[75]. A subsequent analysis of omega-3 as an adjunctive to antidepressants in MDD produced similar results (N=402, n=10, SMD=0.48, 95% CI: 0.11-0.84, p=0.01, I^2=64%), although again showing evidence of significant publication bias[65]. Adjusting for publication bias produced smaller (but still significant) estimates of effects of omega-3 as an adjunctive treatment for MDD (SMD=0.19, 95% CI: 0.00-0.38, p=0.049).

Subgroup analyses found that omega-3 supplements were only effective as an adjunctive treatment for MDD in cohorts with no reported comorbidities (N=201, n=6, SMD=0.74, 95% CI: 0.34-1.13, p<0.01, I^2=42%), whereas there was no indication of efficacy in samples where MDD occurred in comorbidity with cardiometabolic or neurological diseases (N=201, n=4, SMD=0.05, 95% CI: –0.4 to 0.5, p=0.82, I^2=45%)[65]. Furthermore, omega-3 was ineffective for the treatment of MDD in pregnant women (N=121, n=3, SMD=0.24, 95% CI: –0.73 to 1.21, p=0.63, I^2=85%)[59]. A further subgroup analysis of individuals with indicated depression (but no diagnosis of MDD) found small positive effects of omega-3 for depressive symptoms (N=759, n=12, SMD=0.22, 95% CI: 0.01-0.43, p<0.05, I^2=46%).

In analyses examining different formulations of omega-3 for individuals with any clinical depression, omega-3 supplements containing ≥50% DHA had no benefits beyond placebo (N=469, n=6, SMD=–0.028, 95% CI: –0.21 to 0.16, p>0.1)[51]. However, omega-3 supplements containing >50% EPA had moderately large positive effects on depressive symptoms (N=969, n=23,

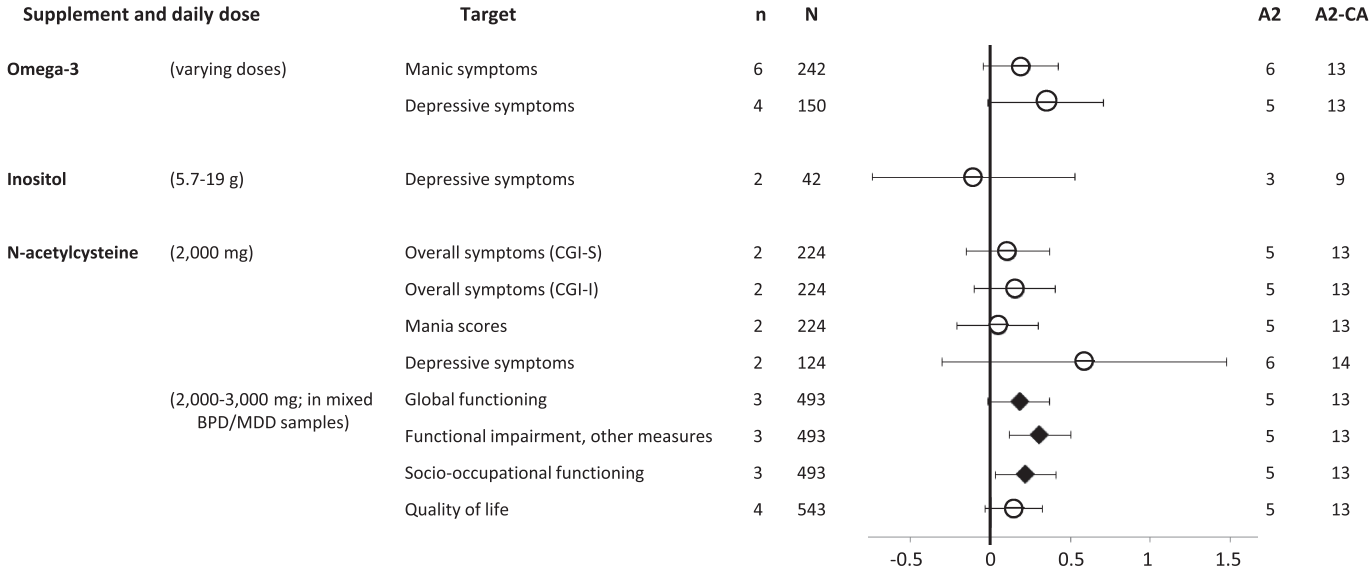

Figure 6 Effects of nutrient supplements in bipolar disorder, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo; diamonds represent p≤0.05 compared to placebo. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, BPD – bipolar disorder, MDD – major depressive disorder, CGI-S – Clinical Global Impression - Severity, CGI-I – Clinical Global Impression - Improvement.

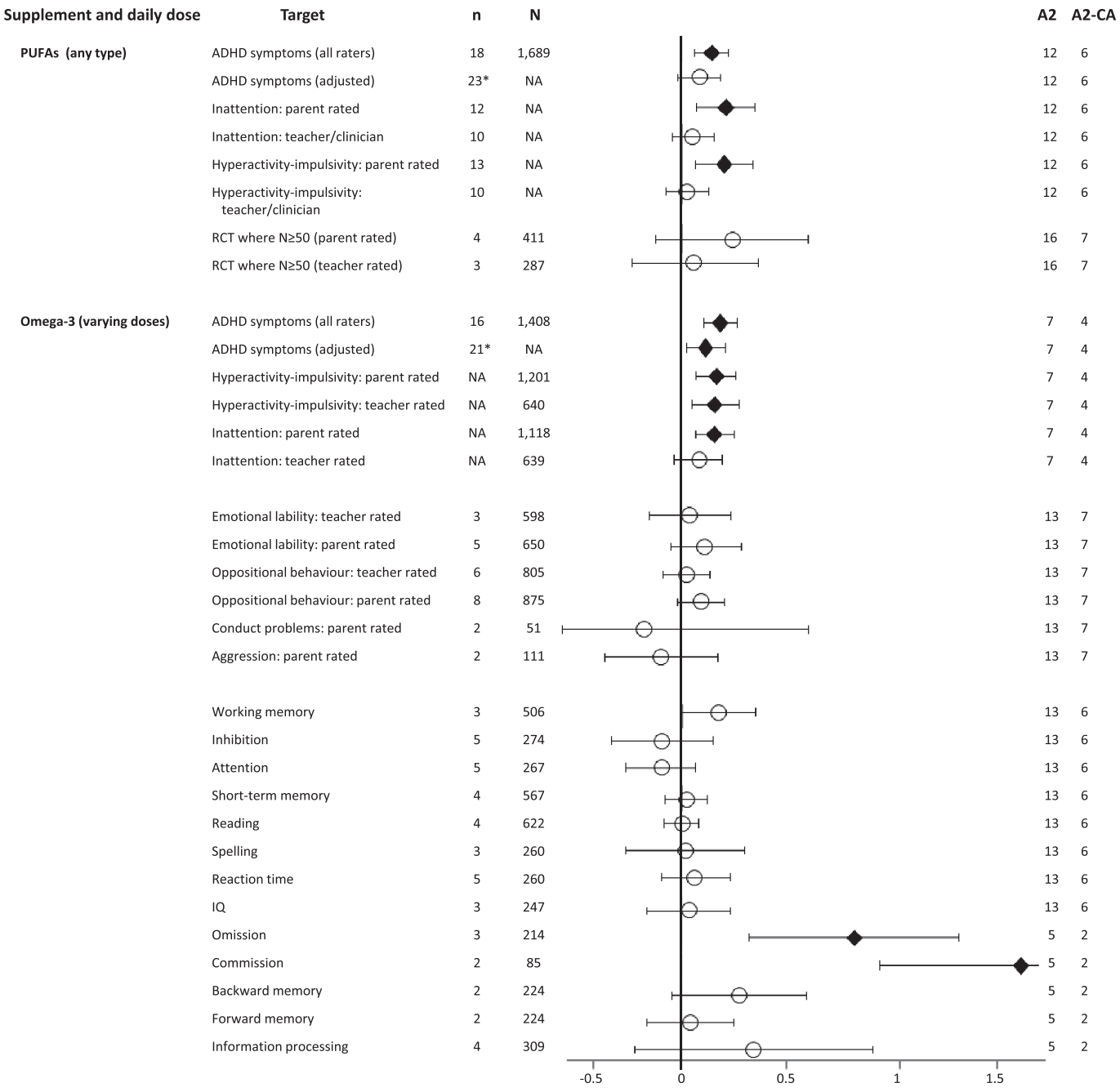

Figure 7 Effects of nutrient supplements in attention-deficit/hyperactivity disorder (ADHD), shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo; diamonds represent p≤0.05 compared to placebo; * represents trim-and-fill estimate adjusted for publication bias. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, PUFAs – polyunsaturated fatty acids, NA – not available, RCTs – randomized controlled trials.

SMD=0.61, 95% CI: 0.38-0.85, p<0.001). Again, publication bias was evident, and the estimated positive effects of high-EPA omega-3 was reduced, but still significant, after adjusting for this (SMD=0.42, 95% CI: 0.18-0.65, p<0.001).

Further subgroup analyses of EPA formulas indicated slightly larger effects on depressive symptoms in studies using >12 week treatment periods (N=274, n=4, SMD=1.07, p<0.01) compared to those using ≤12 week periods (N=695, n=19, SMD=0.55, p<0.001), and for those using omega-3 as an adjunctive treatment (N=535, n=15, SMD=0.72, p<0.001) rather than as a monotherapy for depression (N=434, n=8, SMD=0.44, p=0.017)[51].

An analysis in people aged ≥65 years with clinical depression (either diagnosed or meeting thresholds on validated self-report measures) found that omega-3 (averaging 1.3 g/day of EPA/DHA)

Table 2 Key evidence summaries for nutrient supplements with sufficient data (i.e., meta-analyses with >400 participants)

Treatment	Key findings	Indicated usage	Considerations
Depression			
Omega-3	Small-to-moderate positive effects from high-EPA formulas in clinical depression generally, as well as an adjunctive to SSRIs in MDD	>50% EPA formulas providing 2,200 mg EPA/day	• Small but significant effects observed in high-quality meta-analyses even after adjusting for publication bias • Significant heterogeneity in overall analyses • No benefits for MDD in comorbidity to other conditions • No benefits from DHA-predominant formulas
Folate-based supplements	Small overall benefits for unipolar depression, with greatest effects from high-dose methylfolate in treatment-resistant MDD	15 mg/day of methylfolate as adjunctive treatment in MDD	• Overall effects across folate trials become largely non-significant after excluding 15 mg/day methylfolate • Moderate effects of high-dose methylfolate observed only in few small-scale RCTs
Vitamin D	Moderate improvements in major depression, with low heterogeneity between studies	50,000 IU per week as adjunctive treatment	• Examined in only one meta-analysis of four RCTs, with low confidence in findings • All RCTs from China and Iran (given vitamin D levels are influenced by sunlight exposure/region, replication is required in other settings)
Magnesium	No significant benefits for major depression		• Multiple critical flaws in meta-analyses reduce confidence in findings
NAC	Small-to-moderate reductions in depressive symptoms across various psychiatric diagnoses	2,000 mg/day	• Preliminary evidence: low confidence in findings and significant heterogeneity
ADHD			
Omega-3	Small positive effects for total ADHD symptoms, along with hyperactivity-impulsivity and inattention subdomains; no effects on comorbid emotional/behavioural problems	High EPA formulas providing up to 2,513 mg EPA/day	• Low confidence in review findings and negligible effects after adjusting for publication bias • Examined mostly as monotherapy in youths reaching clinical thresholds from self-report measure; difficult to determine efficacy in conjunction with medications
Bipolar disorder			
NAC	Small positive effects for measures of functional impairment; effects on bipolar symptoms examined in <400 patients	2,000 mg/day	• Significant heterogeneity and low confidence in analyses
Schizophrenia			
Omega 3	No significant effects on symptoms of schizophrenia		• Low confidence in review findings • Subsequent research indicates potential benefit in first-episode psychosis
Folate-based supplements	No effects of adjunctive folate supplements on total symptom scores; significant reductions observed for negative symptoms, particularly in methylfolate trials	15 mg/day of methylfolate as adjunctive treatment	• Effects on negative symptoms become largely non-significant after excluding methylfolate trials • Moderate effects of high-dose methylfolate observed only in few small-scale RCTs

EPA – eicosapentaenoic acid, SSRIs – selective serotonin reuptake inhibitors, MDD – major depressive disorder, ADHD – attention-deficit/hyperactivity disorder, DHA – docosahexaenoic acid, RCT – randomized controlled trial, NAC – N-acetylcysteine

had large, significant effects on depressive symptoms compared to placebo (SMD=0.94, 95% CI: 0.5-1.37, p<0.001, I^2=32.7%), although with only a limited number of small studies (N=187, n=4).

Across all placebo-controlled trials of omega-3 PUFAs in people with bipolar disorder, effects on mania were not significant (N=242, n=6, SMD=0.198, 95% CI: –0.037 to 0.433, p=0.10, I^2=0%) although there were small positive effects on depression (N=305, n=6, SMD=0.338, 95% CI: 0.035-0.641, p=0.029, I^2=30%)[75]. An analysis including only double-blind trials found similar positive effects for bipolar depression, although falling just short of statistical significance (N=150, n=4, SMD=0.36, 95% CI: –0.01 to 0.73, p=0.051, I^2=8%)[76]. The majority of studies were identified as low risk of bias, and showed no indication that omega-3 increased rates of adverse events or mania/hypomania

in bipolar disorder[76].

Schizophrenia and states at risk for psychosis

As an adjunctive treatment for people with schizophrenia, the effect of omega-3 (2-3 g/day of EPA) fell short of statistical significance for total symptom scores (N=335, n=7, SMD=0.242, 95% CI: –0.028 to 0.512, p=0.08, I^2=33.8%)[55]. Omega-3 supplements revealed no significant effects on depressive symptoms in people with schizophrenia (N=264, n=4, SMD=0.14, 95% CI: –0.11 to 0.39, p=0.28, I^2=8%)[59].

Three trials (N=512) examining the impact of omega-3 (1,200-1,400 mg/day) as a monotherapy to prevent transition to psychosis in young people meeting "at risk" criteria showed no indication of benefit (all p>0.1) compared to placebo over 26 weeks (OR=0.64, 95% CI: 0.15-2.68) or 52 weeks (OR=0.64, 95% CI: 0.18-2.26)[60].

In youth at risk of psychosis, PUFA supplements were also ineffective for reducing attenuated psychotic symptoms (N=347, n=3, SMD=0.31, 95% CI: –0.26 to 0.88, I^2=80%)[61], negative symptoms (N=347, n=3, SMD=0.06, 95% CI: –0.35 to 0.46, I^2=63%)[62], and functional disability (N=252, n=2, SMD=-0.08, 95% CI: –0.33 to 0.17)[63] over 52 weeks. Similar null effects were also observed over shorter (i.e., 12 and 26 week) time frames[61-63].

Examination of safety profiles found that EPA was well tolerated in psychotic disorders and did not cause adverse effects other than mild gastrointestinal upset[55]. In the at-risk groups, trial attrition in omega-3 treatment conditions was no different to the placebo control conditions[60].

ADHD

In young people and children with ADHD, overall analyses of any PUFA supplementation (including any omega-3 and omega-6 supplements, at varying doses) showed significant effects beyond placebo for composite ADHD symptom scores (N=1,689, n=18, SMD=0.192, 95% CI: 0.086-0.297, p<0.001, I^2=19.3%)[77]. However, after adjusting for publication bias, the effects of PUFAs on composite symptom scores fell short of significance (SMD=0.118, 95% CI: –0.014 to 0.250, p=0.08).

Across the 16 RCTs reporting on ADHD symptom domains, significant benefits were observed for both hyperactivity/impulsivity (SMD=0.209, 95% CI: 0.059-0.358, p=0.006) and inattention (SMD=0.162, 95% CI: 0.047-0.276, p=0.006)[77]. Subgroup analyses revealed that significant benefits from PUFAs were only observed on parent-rated measures, with no effects on teacher/clinician rated measures of overall symptoms, hyperactivity/impulsivity or inattention[77]. A subsequent analysis using stricter inclusion criteria of RCTs (and excluding data from trials with less than 50 participants) found no benefits of PUFA supplementation on teacher-rated measures of ADHD symptoms (N=287, n=3, SMD=0.08, 95% CI: –0.32 to 0.47, p=0.56, I^2=0%), and the benefits for parent-rated measures also fell short of statistical significance (N=411, n=4, SMD=0.32, 95% CI: –0.15 to 0.8, p=0.098, I^2=52.4%).

Omega-3 supplements (120-2,513 mg/day; mean: 616 mg/day) reduced composite symptom scores in ADHD significantly more than placebo (N=1,408, n=16, SMD=0.26, 95% CI: 0.15-0.37, p<0.001, I^2=25%)[79]. Although still statistically significant, the magnitude of benefit was negligible when applying a trim and fill analysis to adjust for publication bias (SMD=0.16, 95% CI: 0.03-0.28). Similar small effects were observed for both symptom domains of hyperactivity-impulsivity (SMD=0.26, 95% CI: 0.13-0.39, p<0.001) and inattention (SMD=0.22, 95% CI: 0.1-0.34, p<0.001). Subsequent analyses (although including fewer trials) replicated these findings of small but significant effects of omega-3 supplements on composite scores, hyperactivity-impulsivity and inattention symptoms[80].

With regards to behavioural comorbidities, there was no indication of effects of omega-3 on emotional lability, conduct problems or aggression in young people with ADHD[80]. Only effects on parent-rated oppositional behaviour approached significance in primary analyses (SMD=0.2, 95% CI: 0.03-0.38, p=0.02, I^2=0.2%). A trend for a positive effect on parent-rated oppositional behaviour was also observed when applying strict inclusion criteria (SMD=0.15, 95% CI: –0.006 to 0.31, p=0.06, I^2=8%), and when examining only high-quality trials (SMD=0.2, 95% CI: 0.03-0.38, p=0.02, I^2=0.2%).

As to cognitive dysfunction, the only positive effects of omega-3 in young people with ADHD were observed in individual task scores for errors of omission (N=214, n=3, SMD=1.09, 95% CI: 0.43-1.75, p=0.001, I^2=75%) and errors of commission (N=85, n=2, SMD=2.14, 95% CI: 1.24-3.03, p<0.001, I^2=63%)[81]. A positive trend was detected for composite scores of working memory (N=506, n=3, SMD=0.23, 95% CI: –0.001 to 0.46, p=0.05, I^2=33.9%)[82] and individual task scores for backward memory (N=224, n=2, SMD=0.37, 95% CI: –0.05 to 0.79, p=0.08, I^2=55%).

Omega-3 conferred no benefits in tasks of forward memory (N=224, n=2, SMD=0.06, 95% CI: –0.21 to 0.34, p=0.66, I^2=0%) and information processing (N=309, n=4, SMD=0.46, 95% CI: –0.29 to 1.21, p=0.23, I^2=89%)[81], and did not produce any improvements in composite cognitive scores for overall IQ (N=247, n=3, SMD=0.05, 95% CI: –0.21 to 0.32, p=0.71, I^2=0%), inhibition (N=274, n=5, SMD=–0.12, 95% CI: –0.44 to 0.2, p=0.47, I^2=42.8%), attention (N=267, n=5, SMD=–0.12, 95% CI: –0.33 to 0.1, p=0.28, I^2=0%), short-term memory (N=567, n=4, SMD=0.03, 95% CI: –0.10 to 0.16, p=0.64, I^2=0%), reading (N=622, n=4, SMD=0.01, 95% CI: –0.09 to 0.12, p=0.79, I^2=0%), spelling (N=260, n=3, SMD=0.03, 95% CI: –0.34 to 0.40, p=0.89, I^2=48.9%), or reaction time (N=260, n=5, SMD=0.09, 95% CI: –0.13 to 0.3, p=0.44, I^2=0%)[82].

Amino acids

N-acetylcysteine

N-acetylcysteine is the nutraceutical form of the amino acid cysteine, found in abundance in high protein foods, and acts

as a precursor to glutathione, which has antioxidant activity throughout the body.

It has been the most commonly assessed amino acid supplement across mental disorders. In a mixed sample of 574 psychiatric patients with high levels of depression (comorbid or primary), adjunctive treatment (2-3 g/day) significantly reduced depressive symptoms (n=5, SMD=0.37, 95% CI: 0.19-0.55, p=0.001, I^2=92.64%), but had no effects on perceived quality of life (N=543, n=4, SMD=0.14, 95% CI: –0.04 to 0.32, p=0.14, I^2=68%)[72]. There was high heterogeneity between studies, but no evidence of publication bias.

In people with mood disorders (including bipolar disorder and MDD; N=493, n=3), N-acetylcysteine at 2-3 g/day had small but significant effects compared to placebo on global functioning (SMD=0.19, 95% CI: 0.01-0.39, p=0.04, I^2=64%) and social functioning (SMD=0.22, 95% CI: 0.03-0.41, p=0.02, I^2=67%). It also significantly improved other measures of functional impairment (SMD=0.31, 95% CI: 0.12-0.50, p=0.002, I^2=86%)[72].

Across three RCTs in people with schizophrenia (N=247), adjunctive treatment with N-acetylcysteine significantly reduced total symptom scores (SMD=0.74, 95% CI: 0.06-1.43, p=0.03). Although included trials were rated as high-quality, the overall strength of evidence was weak due to high risk of publication bias and significant heterogeneity in existing data (I^2=84%)[56]. Regarding symptom subgroups, there was a non-significant trend indication of beneficial effects on negative symptoms (SMD=0.59, 95% CI: –0.10 to 2.00, p=0.08, I^2=93%), but no effects beyond placebo for positive symptoms (SMD=0.16, 95% CI: –0.29 to 0.62, p=0.48, I^2=66%) or general symptomatology (SMD=0.2, 95% CI: –0.21 to 0.62, p=0.34, I^2=59%)[56].

As an adjunctive treatment for individuals with bipolar disorder (N=224, n=2), 2 g/day N-acetylcysteine did not differ from placebo in its impact on overall illness severity (Clinical Global Impression - Severity, CGI-S: SMD=0.11, 95% CI: –0.15 to 0.37, p=0.42, I^2=90%, and Clinical Global Impression - Improvement, CGI-I: SMD=0.16, 95% CI: –0.09 to 0.42, p=0.22, I^2=0%) or mania ratings (N=224, n=2, SMD=0.05, 95% CI: –0.2 to 0.31, p=0.68, I^2=0.01%)[72]. N-acetylcysteine was also found to be ineffective on depressive symptoms in people with bipolar disorder (N=124, n=2, SMD=0.59, 95% CI: –0.3 to 1.48, p=0.19, I^2=83%)[56].

In 155 individuals with OCD taking concomitant medications (mostly SSRIs), 2-3 g/day N-acetylcysteine produced a trend-level effect towards reduction in obsessive-compulsive symptoms (n=4, SMD=0.295, 95% CI: –0.018 to 0.608, p=0.064, I^2=65%)[74]. N-acetylcysteine (2-2.4 g/day) also had no significant effects on symptoms of anxiety in a pooled mixed psychiatric sample (N=319, n=2, SMD=0.03, 95% CI: –0.21 to 0.28, p=0.80, I^2=0%)[72].

Across all the above disorders, the rates of discontinuation and severe adverse events from N-acetylcysteine supplementation did not differ significantly from the placebo conditions[56,72,74]. There was no significant difference in rates of mild adverse events (particularly with regards to gastrointestinal upset) in people with schizophrenia (N=186, n=2, OR=1.56, 95% CI: 0.87-2.80, p=0.14, I^2=0)[56], but N-acetylcysteine supplementation was associated with higher rates of mild adverse events in mood disorders (N=574, n=5, OR=1.61, 95% CI: 1.01-2.59, p=0.049)[72].

N-methyl-D-aspartate receptor modulators

The amino acids sarcosine and glycine (which occur naturally in meat, dairy and legumes) have also been assessed as adjunctive treatments for schizophrenia, due to their potential action as N-methyl-D-aspartate (NMDA) receptor modulators[57]. Neither sarcosine (at 2 g/day) or glycine (at 2.8-60 g/day) had any effect on positive symptoms, although both did significantly reduce total psychopathology as an adjunctive to antipsychotic treatment (sarcosine: N=132, n=4, SMD=0.41, 95% CI: 0.06-0.76, p=0.02, I^2 not reported; glycine: N=159, n=6, SMD=0.66, 95% CI: 0.04-1.28, p=0.04, I^2 not reported)[57].

The effects on negative symptoms fell short of statistical significance (sarcosine: N=132, n=4, SMD=0.32, 95% CI: –0.03 to 0.66, p=0.07; glycine: N=268, n=7, SMD=0.39, 95% CI: –0.11 to 0.9, p=0.13)[57]. However, significant benefits for negative symptoms were observed in individuals treated with non-clozapine antipsychotics (sarcosine: N=112, n=3, SMD=0.39, p=0.04; glycine: N=219, n=5, SMD=0.60, p=0.05; CIs and I^2 not provided)[57].

As an adjunctive to clozapine treatment (N=58, n=3)[58], glycine was ineffective for positive (SMD=0.63, 95% CI: –0.21 to 1.48, I^2 not reported), negative (SMD=0.03, 95% CI: –0.51 to 0.57, I^2 not reported) and total symptoms scores (SMD=0.32, 95% CI: –0.2 to 0.84, I^2 not reported). No eligible data were available for effects of sarcosine as an adjunctive to clozapine.

Prebiotics and probiotics

No meta-analyses on the effects of prebiotics or probiotics in mental disorders were identified in our search. However, in groups of individuals with mild to moderate depression (as determined by thresholds on clinically validated scales), probiotic treatments of varying strains and doses reduced depressive symptoms significantly more than placebo (N=163, n=3, SMD= 0.684, 95% CI: 0.0712-1.296, p=0.029)[71].

DISCUSSION

This meta-review aggregated and evaluated all the recent top-tier evidence from meta-analyses of RCTs examining the efficacy and safety of nutritional supplements in mental disorders. We identified 33 eligible meta-analyses published from 2012 onwards (26 since 2016), with primary analyses including 10,951 individuals with psychiatric conditions (specifically depressive disorders, anxiety and stress-related disorders, schizophrenia, states at risk for psychosis, bipolar disorder and ADHD), randomized to either nutritional supplementation (including omega-3 fatty acids, vitamins, minerals, N-acetylcysteine and other amino acids) or placebo control conditions. Although the major-

ity of nutritional supplements assessed did not significantly improve mental health outcomes beyond control conditions (see Figures 2-7), some of them did provide efficacious adjunctive treatment for specific mental disorders under certain conditions.

The nutritional intervention with the strongest evidentiary support is omega-3, in particular EPA. Multiple meta-analyses have demonstrated that it has significant effects in people with depression, including high-quality meta-analyses with good confidence in findings as determined by AMSTAR-2[64]. Meta-analytic data have shown that omega-3 is effective when given adjunctively to antidepressants[51,64]. As a monotherapy intervention, the data are less compelling for omega-3, while DHA or DHA-predominant formulas do not appear to show any obvious benefit in MDD[51,64].

Omega-3 supplementation appears to be of greatest benefit when administered as high-EPA formulas, as significant relationships between EPA dosage and effect sizes are also observed in high-quality meta-analyses of RCTs[59,64]. Emergent data from RCTs further indicate that omega-3 may be most beneficial for patients presenting with raised inflammatory markers[83]. The available meta-analyses suggest that omega-3 supplementation is not effective in patients with depression as a comorbidity to chronic physical conditions[65], including cardiometabolic diseases, a finding which has been replicated in subsequent trials[84]. In light of current adverse event data, omega-3 seems to represent a safe adjunctive treatment.

More research is needed concerning the efficacy of omega-3 supplements in other mental health conditions. For instance, omega-3 was indicated as potentially beneficial for children with ADHD, again with high EPA formulas conferring largest effects[79]. However, the negligible effect sizes after controlling for publication bias, along with the low review quality identified by AMSTAR-2, reduces confidence in findings. Additionally, whereas the existing meta-analytic data have found a lack of significant benefits in people with schizophrenia[55,59], subsequent trials in young people with first-episode psychosis have reported more positive, though mixed, results[85,86], putatively ascribed to neuroprotective effects[87,88].

Adjunctive treatment with folate-based supplements was found to significantly reduce symptoms of MDD and negative symptoms in schizophrenia[54,67]. However, in both cases, AMSTAR-2 ratings indicated low confidence in review findings, and positive overall effects in these meta-analyses were driven largely by RCTs of high-dose (15 mg/day) methylfolate. Methylfolate is readily absorbed, overcoming any genetic predispositions towards folic acid malabsorption, and successfully crossing the blood-brain barrier[89,90]. Indeed, a placebo-controlled trial of methylfolate in schizophrenia reported significant increases in white matter within just 12 weeks, co-occurring with a reduction in negative symptoms[91].

RCTs not captured in our meta-review[92] and retrospective chart analyses[93] have further indicated benefits of methylfolate supplementation in other mental disorders. Considering this, alongside the lack of detrimental side effects (in fact, significantly fewer adverse events in samples receiving treatment compared to placebo[54]), further research on methylfolate as an adjunctive treatment for mental disorders is warranted.

Regarding other vitamins (such as vitamin E, C or D), minerals (zinc and magnesium) or inositol, there is currently a lack of compelling evidence supporting their efficacy for any mental disorder, although the emerging evidence concerning positive effects for vitamin D supplementation in major depression has to be mentioned.

Beyond vitamins, minerals and omega-3 fatty acids, certain amino acids are now emerging as promising adjunctive treatments in mental disorders. Although the evidence is still nascent, N-acetylcysteine in particular (at doses of 2,000 mg/day or higher) was indicated as potentially effective for reducing depressive symptoms and improving functional recovery in mixed psychiatric samples[72]. Furthermore, significant reductions in total symptoms of schizophrenia have been observed when using N-acetylcysteine as an adjunctive treatment, although with substantial heterogeneity between studies, especially in study length (in fact, N-acetylcysteine has a very delayed onset of action of about 6 months[56,94]).

N-acetylcysteine acts as a precursor to glutathione, the primary endogenous antioxidant, neutralizing cellular reactive oxygen and nitrogen[95]. Glutathione production in astrocytes is rate limited by cysteine. Oral glutathione and L-cysteine are broken down by first-pass metabolism, and do not increase brain glutathione levels, unlike oral N-acetylcysteine, which is more easily absorbed, and has been shown to increase brain glutathione in animal models[96]. Additionally, N-acetylcysteine has been shown to increase dopamine release in animal models[96].

N-acetylcysteine may assist in treatment of schizophrenia, bipolar disorder and depression through decreasing oxidative stress and reducing glutamatergic dysfunction[96], but has wider preclinical effects on mitochondria, apoptosis, neurogenesis and telomere lengthening of uncertain clinical significance.

NMDA receptors are activated by binding D-serine or glycine[97]. Sarcosine is a naturally occurring glycine transport inhibitor and can act as a co-agonist of NMDA[98]. As such, D-serine, glycine and sarcosine may improve psychotic symptoms through NDMA modulation[99]. We found reductions in total psychotic symptoms, but not negative symptoms, with glycine and sarcosine. Additionally, we found that glycine was not effective in combination with clozapine. This may be because clozapine already acts as a NMDA receptor glycine site agonist[97].

The role of the gut microbiome in mental health is also a rapidly emerging field of research[99]. Gut microbiota differs significantly between people with mental disorders and healthy controls, and recent faecal transplant studies using germ-free mice indicate that these differences could play a causal role in symptoms of mental illness[41,100,101]. Intervention trials that aim to investigate the effect of probiotic formulations on clinical outcomes in mental disorders are now beginning to emerge[71]. We included one recent meta-analysis that evaluated the pooled effect of probiotic interventions on depressive symptoms: while the primary analysis reported no significant effect, the moderately large effect in the three included studies suggests that

probiotics may be beneficial for those with a clinical diagnosis of depression rather than subclinical symptoms[71]. However, additional trials are required to replicate these results, to evaluate the long-term safety of probiotic interventions, and to elucidate the optimal dosing regimen and the most effective prebiotic and probiotic strains[102].

While this meta-review has highlighted potential roles for the use of nutrient supplements, this should not be intended to replace dietary improvement. The poor physical health of people with mental illness is well documented[103], and excessive and unhealthy dietary intake appears to be a key factor involved[4,5]. Improved diet quality is associated with reduced all-cause mortality[104]. whereas multivitamin and multimineral supplements may not improve life expectancy[18-20].

A meta-analysis of dietary interventions in people with severe mental illness found benefits on a number of physical health aspects[105]. It is unlikely that standard nutrient supplementation will be able to cover all beneficial aspects of improved dietary intake. In addition, whole foods may contain vitamins and minerals in different forms, whereas nutrient supplements may only provide one form. For example, vitamin E occurs naturally in eight forms, but nutrient supplements may only provide one form. Dietary interventions also reduce dietary elements in excess, such as salt, which is a key driver of premature mortality[13].

While improving dietary intake appears to have a clear role in increasing life expectancy and preventing chronic disease, there is currently a lack of studies evaluating this in people with mental disorders. Additionally, although recent meta-analyses of RCTs have demonstrated that dietary improvement reduces symptoms of depression in the general population[106], more well-designed studies are needed to confirm the mental health benefits of dietary interventions for people with diagnosed psychiatric conditions[25].

Our data should be considered in the light of some limitations. First, although meta-analyses of RCTs typically constitute the top-tier of evidence, it is important to acknowledge that many of the outcomes included in this meta-review had significant amounts of heterogeneity between the included studies, or were based on a small number of studies. A next step within this field of research is to move from study-level to patient-level meta-analyses, as this would provide a more personalized picture of the effects of nutrient supplements derived from adequately powered moderator, mediator and subgroup analyses. Additionally, comparing nutrient supplements in the same trial would be desirable.

It is recognized that people with mental disorders commonly take nutritional supplements in combinations. In some instances, research has supported this approach, most commonly in the form of multivitamin/mineral combinations[107]. However, recent research in the area of depression has revealed that "more is not necessarily better" when it comes to complex formulations[108]. Of note, recent large mood disorder clinical trials have revealed that nutrient combinations may not have a more potent effect, and in some cases placebo has been more effective[47,108,109].

In conclusion, there is now a vast body of research examining the efficacy of nutrient supplementation in people with mental disorders, with some nutrients now having demonstrated efficacy under specific conditions, and others with increasingly indicated potential. There is a great need to determine the mechanisms involved, along with examining the effects in specific populations such as young people and those in early stages of illness. A targeted approach is clearly warranted, which may manifest as biomarker-guided treatment, based on key nutrient levels, inflammatory markers, and pharmacogenomics [83,91,110].

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