REVIEW

Unsaturated Fatty Acids in Mental Disorders: An Umbrella Review of Meta-Analyses

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ABSTRACT

Unsaturated fatty acids might be involved in the prevention of and improvement in mental disorders, but the evidence on these associations has not been comprehensively assessed. This umbrella review aimed to appraise the credibility of published evidence evaluating the associations between unsaturated fatty acids and mental disorders. In this umbrella review, systematic reviews and meta-analyses of studies comparing unsaturated fatty acids (including supplementation, dietary intake, and blood concentrations) in participants with mental disorders with healthy individuals were included. We reanalyzed summary estimates, between-study heterogeneity, predictive intervals, publication bias, small-study effects, and excess significance bias for each meta-analysis. Ninety-five meta-analyses from 29 systematic reviews were included, encompassing 43 studies on supplementation interventions, 32 studies on dietary factors, and 20 studies on blood biomarkers. Suggestive evidence was only observed for dietary intake, in which higher intake of fish was associated with reduced risk of depression (RR: 0.78; 95% CI: 0.69, 0.89) and Alzheimer disease (RR: 0.74; 95% CI: 0.63, 0.87), and higher intake of total PUFAs might be associated with a lower risk of mild cognitive impairment (RR: 0.71; 95% CI: 0.61, 0.84). Evidence showed that PUFA supplementation was favorable but had weak credibility in anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), dementia, mild cognitive impairment, Huntington's disease, and schizophrenia (*P*-random effects <0.001–0.040). There was also weak evidence on the effect of decreased circulating n–3 (ω-3) PUFAs among patients on risk of ADHD, ASD, bipolar disorder, and schizophrenia (*P*-random effects $<10^{-6}$–0.037). Our results suggest that higher levels of unsaturated fatty acids may relieve symptoms or reduce the risk of various mental disorders; however, the strength of the associations and credibility of the evidence were generally weak. Future high-quality research is needed to identify whether PUFA interventions should be prioritized to alleviate mental disorders. *Adv Nutr* 2022;0:1–20.

Statement of Significance: The credibility of published evidence on the association between unsaturated fatty acids and mental disorders remains controversial. Our findings suggest the overall credibility of evidence is low, in which suggestive/weak evidence indicates the protective effect of high consumption of unsaturated fatty acids or fish and weak evidence indicates the broad differences in circulating unsaturated fatty acids and the potential value of omega-3 polyunsaturated fatty acid supplementation interventions for various mental disorders.

Keywords: mental disorders, unsaturated fatty acids, n–3 PUFA, umbrella review, meta-analysis

Introduction

Currently, mental disorders remain among the top 10 leading causes of disease burden worldwide (1). The Global Burden of Diseases Study (GBD) 2019 showed that the proportion of global disability-adjusted life-years (DALYs) attributed to mental disorders increased from 3.1% to 4.9% between 1990 and 2019 (1). In 2020, only 52% of the WHO's 194 member states met the target related to mental health promotion and prevention programs, which was considerably below the 80% target (2). The global conflict between the increasing burden of mental disorders and the insufficient investment in mental health highlights the growing need to evaluate effective prevention and management strategies for mental disorders (1–3).

Unsaturated fatty acids, as one of the most important dietary nutrients, might be associated with neurodevelopment

and brain function, as well as behavior and mental health (4, 5). Characterized by the number and position of double carbon bonds, unsaturated fatty acids include MUFAs, n–3 PUFAs [including α-linolenic acid (ALA; 18:3n−3), EPA, and DHA], and n–6 PUFAs [including linoleic acid (LA; 18:2n–6) and arachidonic acid (AA; 20:4n−6)]. In early life, obtaining adequate DHA and AA from the mother is essential for the myelination and proper neurodevelopment of the fetus (6, 7). In addition, n–3 PUFAs and n–6 PUFAs are highly enriched in brain tissue (8) and participate in numerous biological processes in the brain (e.g., metabolism, neurotransmission, synaptogenesis, and inflammation) (4, 5, 9, 10). Various mental disorders such as Alzheimer disease (AD), dementia, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), mood disorders, and schizophrenia have been suggested to be associated with altered levels and functions related to unsaturated fatty acids in the brain (8, 11–15).

To date, a large number of meta-analyses have been conducted to assess the role of unsaturated fatty acids in mental disorders from multiple perspectives, but the available evidence remains controversial. The assessment of various kinds of bias (e.g., publication bias, reporting bias, residual confounding bias, and researcher allegiance) in these meta-analyses was often insufficient (16), which might result in overestimated efficacy or false significance (17, 18). Moreover, the appraisal of the evidence has not been formally determined across different mental disorders. To overcome these limitations, we conducted an umbrella review of the relevant meta-analyses, which have increasingly consolidated the highest level of evidence on this topic (19). We aimed to systemically assess the role of unsaturated fatty acids as alternative or complementary (adjunctive) interventions, dietary factors, or peripheral biomarkers for various mental disorders, and generate hierarchies of evidence.

Methods

Literature search strategy and eligibility criteria

We conducted an umbrella review to systematically review and evaluate all available systematic reviews and meta-analyses on the topic of unsaturated fatty acids in mental disorders. PubMed, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews were searched for papers published between database inception and 20 April 2022, and no language restriction was applied. The complete search strategy is provided in the **Supplemental Methods**. In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20), 2 investigators (XG and XS) independently screened titles, abstracts, and full texts to identify potentially relevant systematic reviews (**Figure 1**). We also manually searched the reference lists from relevant studies to reduce missing records in database searches. In case of discrepancies, a third investigator (FZ) was involved, and consensus was reached by discussion.

We included systematic reviews and meta-analyses that evaluated the role of unsaturated fatty acids as interventions, risk factors, or biomarkers for all types of mental disorders and evaluations of unsaturated fatty acids, including but not limited to nutritional supplements, dietary intake, or blood concentrations. For eligible systematic reviews, mental disorders should be assessed using structured psychiatric diagnostic interviews or validated or commonly used rating scales. Systematic reviews without study-level effect sizes and 95% CIs were excluded. When 2 or more systematic reviews existed for the same association or comparison, we included the most recent systematic review with the largest number of individual studies providing study-level estimates, in agreement with umbrella review methodology (21). For systematic reviews that did not report sufficient data for reanalysis, we contacted the corresponding authors to obtain the necessary data.

Data extraction and quality assessment

From each included systematic review, we extracted information on the first author, publication year, number of included studies, outcomes, reported unsaturated fatty acids, and summary meta-analytic estimates. The following information was extracted from each individual study: publication year, study design (i.e., cohort design, case–control design, or clinical trial design), population (i.e., children, adolescents, middle-aged adults, or older adults), sample size, reported unsaturated fatty acids, outcomes and corresponding assessment criteria, and maximally adjusted study-specific estimates [i.e., mean difference (MD), standardized mean difference (SMD; including Hedges' *g* and Cohen's *d*), OR, or RR] with 95% CIs.

The methodological quality of the included systematic reviews was critically appraised using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews), a 16-item rating scale with good interrater reliability and usability (22). AMSTAR 2 is not intended to generate an overall score; instead, it rates the confidence of systematic reviews into 4 broad categories (high, moderate, low, and critically low) based on review design, literature screening, data extraction, and individual study quality assessment (22).

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Supplemental Methods, Supplemental Results, and Supplemental Table 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: AA, arachidonic acid; AD, Alzheimer disease; ADHD, attention-deficit/hyperactivity disorder; ALA, α-linolenic acid; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews; ASD, autism spectrum disorder; BP, bipolar disorder; LA, linoleic acid; MD, mean difference; SMD, standardized mean difference; WMD, weighted mean difference.

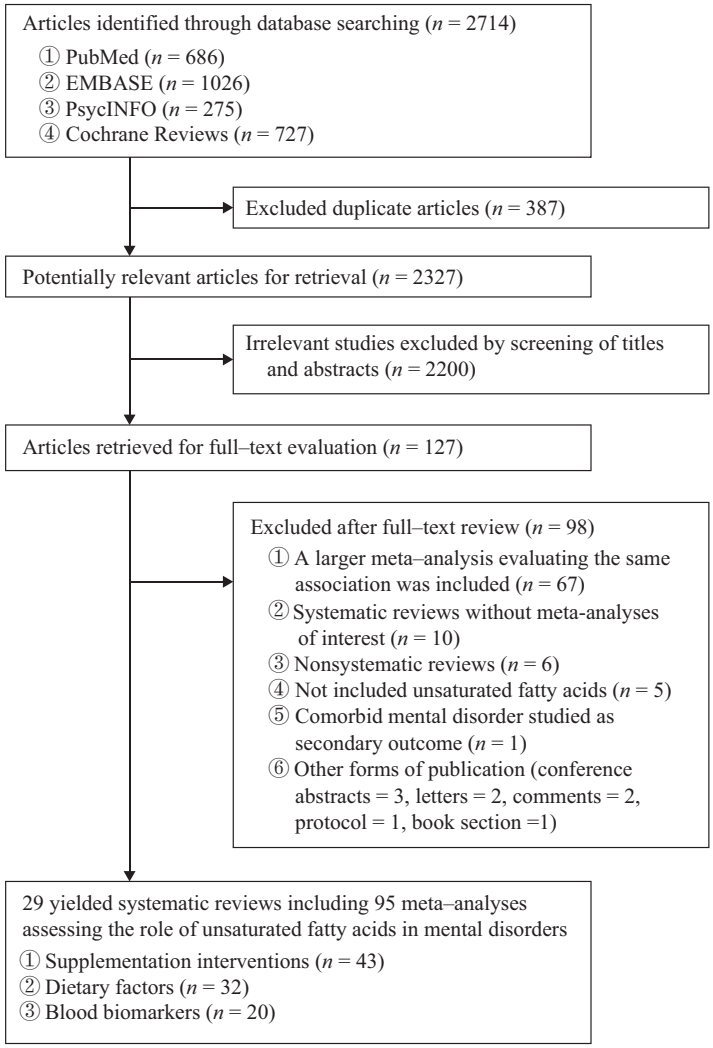

FIGURE 1 Study selection profile.

Data analysis

We followed the analytic approach that was developed and reproduced in previous umbrella reviews (23–26). The pooled effect size, 95% CI, and *P* value of each meta-analysis were re-estimated in their original form under random-effects models using the DerSimonian and Laird method (27). The statistical significance *P*-value threshold of pooled effect estimates was set at <0.05, and additional *P*-value thresholds were set at $<10^{-3}$ and $<10^{-6}$ to assess the credibility of evidence (28, 29). For between-study heterogeneity, we performed Cochran's *Q* tests (30) ($P < 0.10$ indicated the existence of heterogeneity) and calculated the I^2 statistic (31) ($I^2 \geq 50\%$ represented high inconsistency).

To enable comparison of the effects of various interventions on the same outcome, we further re-estimated unstandardized MDs as SMDs by the method of Cohen and converted all SMDs into equivalent ORs based on Hasselblad and Hedges' method (32–34). Subsequently, we estimated the 95% prediction intervals, which specify the uncertainty as to whether the effect will persist in a future study examining the same research question (35, 36). Prediction intervals excluding the null value (i.e., 1 in the case of RRs or ORs) infer that the effect would be expected in a new study (35, 36). Egger's regression asymmetry test was used to identify potential publication bias (37). The presence of small-study effects was established at an Egger's $P < 0.10$, with the estimate of the largest component study (the study with the smallest SE) being more conservative than the summary estimate based on random-effects models (23–26).

We evaluated the excess significance to examine whether the observed number of studies (O) with nominally statistically significant results ($P < 0.05$) in each meta-analysis was larger than their expected number (E) (38). For each meta-analysis, the expected number of significant studies was estimated from the sum of the statistical power estimates for each individual study (26), using an algorithm from a noncentral *t* distribution and the effect size of the largest

study in each meta-analysis as the plausible power for the tested association (39). For each meta-analysis, the significance threshold of the excess significance bias was set at $P < 0.10$. Excess significance for single meta-analysis was established at $P < 0.10$ (1-sided $P < 0.05$ with O > E, as previously proposed). All statistical analyses were performed using Stata version 14.0 (StataCorp). The *P* values were all 2-tailed.

Determining the credibility of evidence

In accordance with previous umbrella reviews (23–26, 40), the following criteria were used to determine the level of evidence: *1*) $P < 10^{-6}$ based on random-effects meta-analysis, *2*) >1000 participants, *3*) $P < 0.05$ of the largest study, *4*) between-study heterogeneity with $I^2 < 50\%$, *5*) no evidence of small-study effects, *6*) 95% prediction interval that excluded the null value, and *7*) no excess significance bias. Based on the results of statistical analyses, we categorized the credibility of each evidence as class I (convincing evidence that met all criteria), class II (highly suggestive evidence that met 1 to 3 of the criteria), class III (suggestive evidence criteria that required only a $P < 0.001$ by random-effects and >1000 participants), class IV (weak evidence that required only a $P < 0.05$ under random-effects), and no significant evidence ($P \geq 0.05$ under random-effects).

Results

A total of 2714 records were identified through a systematic database search. After duplicate removal and the inspection of titles and abstracts, 127 full-text articles were screened for eligibility. Ultimately, 29 systematic reviews involving 96 meta-analyses met the umbrella review inclusion criteria and were included for reanalysis (**Figure 1**) (11–15, 41–64). Details of the excluded reviews with the reasons for exclusion are provided in the **Supplemental Results**. From the included systematic reviews, we extracted information on the role of the assessed unsaturated fatty acids and mental disorders of interest (**Table 1**). Among these systematic reviews, 43 meta-analyses assessed the efficacy of unsaturated fatty acid supplementation interventions, 32 meta-analyses assessed the effect of unsaturated fatty acid intake, and 20 meta-analyses assessed differences in peripheral unsaturated fatty acid concentrations between healthy controls and patients with mental disorders.

Of the 29 systematic reviews identified, 11 had high-quality ratings according to the AMSTAR 2 scoring system (11, 15, 43, 46, 47, 54, 56–59, 63), 2 had moderate quality ratings (13, 49), and 16 received a low or critically low-quality rating (Table 1) (12, 14, 41, 42, 44, 45, 48, 50–53, 55, 60–62, 64). AMSTAR 2 detected that, in 8 reviews, the methods were not established prior to the conduct of the review and 10 reviews did not provide the list of excluded studies with justification of the exclusions (details are reported in **Supplemental Table 1**).

Unsaturated fatty acid supplementation interventions for mental disorders

A total of 43 meta-analyses assessed the efficacy of unsaturated fatty acid supplementation on improving mental disorders, including AD, mild cognitive impairment, anxiety, bipolar disorder (BP), depression, perinatal depression, postpartum depression, ADHD, ASD, specific learning disorders, Huntington's disease, schizophrenia, and psychosis. However, only 12 reanalyses reported a nominally statistically significant summary effect using random-effects models ($P < 0.05$), and only one 95% prediction interval excluded the null value (**Table 2**). Significant heterogeneity ($I^2 > 50\%$) was observed in all statistically significant comparisons, with the exception of the meta-analysis on the efficacy of an n–3 PUFA or n–6 PUFA supplementation intervention for ASD, Huntington's disease, and schizophrenia (Table 2). The risk of small-study effects bias was observed in 2 comparisons, whereas excess of significance bias was detected in 8 comparisons. However, 17 comparisons consisted of less than 5 individual studies, in which case the power of the test was reduced.

None of the 43 meta-analyses had convincing, highly suggestive, or suggestive strength of evidence according to the quantitative umbrella review criteria. In addition, the strength of the evidence was weak for 10 meta-analyses (Table 2). Weak evidence suggested that n–3 PUFA and n–6 PUFA supplementation could significantly reduce depressive symptoms in patients with depression (SMD: –0.941 to –0.401; equivalent OR: 0.182 to 0.484; *P*-random effects: 0.001–0.026). Weak evidence also suggested that n–3 PUFA and n–6 PUFA supplementation could significantly reduce Aberrant Behavior Checklist total scores in patients with ASD (SMD: –0.183; equivalent OR: 0.718; *P*-random effects: 0.023), and reduce parent-reported core symptoms in patients with ADHD (SMD: –0.167; equivalent OR: 0.739; *P*-random effects: 0.031). For n–3 PUFA supplementation intervention (**Figure 2**), there was weak evidence for its efficacy in reducing Positive and Negative Syndrome Scale total scores in patients with schizophrenia (SMD: –0.295; equivalent OR: 0.586; *P*-random effects: 0.012), efficacy in reducing motor scores in patients with Huntington's disease (MD: –2.225; equivalent OR: 0.025; *P*-random effects: 0.007), efficacy in reducing symptoms of patients with anxiety (Hedges' *g*: –0.374; equivalent OR: 0.508; *P*-random effects: 0.012), and efficacy in improving Mini-Mental State Examination scores in patients with mild cognitive impairment (WMD: 0.852; equivalent OR: 1.646; *P*-random effects: 0.040).

Dietary unsaturated fatty acid intake and the risk of mental disorders

A total of 32 meta-analyses assessing the dietary unsaturated fatty acid intake and the risk of mental disorders, such as AD, dementia, mild cognitive impairment, Parkinson disease, depression, and suicide, were recalculated. Only 5 meta-analyses reported a marginally statistically significant

TABLE 1 Characteristics and quality assessments of eligible meta-analyses evaluating the associations between unsaturated fatty acids and mental disorders[1]

Study, year (ref)	Population	Mental disorders	Outcomes	Outcome assessments	No. of studies (participants, *n*)	Study design	Intervention/ comparison	Effect metrics	AMSTAR 2 rating[2]
Unsaturated fatty acids supplementation									
Xu et al., 2022 (64)	Adults	Schizophrenia	Symptoms	Positive and Negative Syndrome Scale	6 (317)	Randomized controlled studies	EPA/DHA/EPA+DHA vs. placebo	MD	●●○○ Low
Appleton et al., 2021 (56)	Adults	Depression	Depressive symptoms, adverse events, quality of life	Beck Depression Inventory, Montgomery Asberg Depression Rating Scale, Hamilton Depression Rating Scale, and others	34 (1924)	Randomized controlled studies	n–3 fatty acids supplementation vs. placebo	SMD, OR	●●●● High
de Andrade Wobido et al., 2021 (57)	Children	Autism spectrum disorder	Symptoms	Aberrant Behavior Checklist, Social Responsiveness Scale	13 (372)	Clinical trial, community trial	n–3 and n–6 fatty acids supplementation vs. placebo	SMD	●●●● High
Goh et al., 2021 (58)	Adults	Schizophrenia	Symptoms	Positive and Negative Syndrome Scale and General Psychopathology Scale	14 (950)	Randomized controlled studies	n–3 fatty acids supplementation vs. placebo or non-supplementation	SMD	●●●● High
Händel et al., 2021 (59)	Children	Attention-deficit/hyperactivity disorder	Symptoms, behavioral difficulties, quality of life	Multiple psychopathology scales assessed the parent-reported core symptoms, teacher-reported core symptoms, parent-reported behavioral difficulties, teacher-reported behavioral difficulties, quality of life (including diarrhea, gastrointestinal discomfort, and nausea)	31 (1775)	Randomized controlled studies	n–3 and n–6 fatty acids supplementation vs. placebo and/or regular diet	SMD	●●●● High
Suradom et al., 2021 (60)	Pregnant and postpartum women	Depression	Prevention and treatment of depression severity	Edinburgh Postnatal Depression Scale, Postpartum Depression Screening Scale, Center for Epidemiological Studies–Depression Scale	11 (3181)	Randomized controlled studies	n–3 and n–6 fatty acids supplementation vs. placebo	SMD	●●○○ Low
Xu et al., 2021 (61)	Elderly	Mild cognitive impairment	Symptoms	Mini-Mental State Examination	3 (96)	Randomized controlled studies	Unsaturated fatty acids vs. antioxidant or non-supplementation	MD	●○○○ Critically low

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref)	Population	Mental disorders	Outcomes	Outcome assessments	No. of studies (participants, *n*)	Study design	Intervention/ comparison	Effect metrics	AMSTAR 2 rating[2]
Araya-Quintanilla et al., 2020 (52)	The elderly	Alzheimer disease	Symptoms	Narcissistic Personality Inventor, Mini-Mental State Examination, Alzheimer's Disease Assessment Scale–Cognitive section	6 (758)	Randomized controlled studies	n–3 fatty acids supplementation vs. placebo	SMD	●○○○ Critically low
Luo et al., 2020 (53)	Adults	Depression	Depressive symptoms	Hamilton Depression Rating Scale or others	10 (910)	Randomized controlled studies	n–3 and n–6 fatty acids supplementation (≥2000 mg/d and <2000 mg/d) vs. placebo	SMD	●○○○ Critically low
Mocking et al., 2020 (54)	Pregnant and postpartum women	Perinatal and postpartum depression	Depressive symptoms	Edinburgh Postnatal Depression Scale; Hamilton Depression Rating Scale; Montgomery-Asberg Depression Rating Scale, or others	18 (4052)	Randomized controlled studies	n–3 and n–6 fatty acids supplementation vs. placebo or regular diet	SMD	●●●● High
Zhang et al., 2020 (55)	The elderly	Mild cognition decline	Cognition	Mini-Mental State Examination	7 (434)	Randomized controlled studies	n–3 and n–6 fatty acids supplementation vs. placebo	WMD	●○○○ Critically low
Devoe et al., 2019 (48)	Youth (age between 13 and 33)	Psychosis	Symptoms	Scale for the Assessment of Positive Symptoms, Brief Psychiatric Rating Scale, the Positive and Negative Syndrome Scale, the Scale of Prodromal Symptoms, and the Comprehensive Assessment of At-Risk Mental States	3 (347)	Randomized controlled studies	n–3 fatty acids supplementation vs. placebo	SMD	●●○○ Low
Morsy et al., 2019 (49)	Adults	Huntington's disease	Total motor score; total motor score-4	Unified Huntington disease rating scale (UHDRS) or other evaluations	4 (782)	Randomized controlled studies	Ethyl-EPA vs. placebo	MD	●●●○ Medium
Zhang et al., 2019 (51)	Children	Depression	Depressive symptoms	The Children's Depression Rating Scale (CDRS), revised CDRS, Beck Depression Inventory, and Children's Depression Inventory	4 (153)	Randomized controlled studies	n–3 fatty acids supplementation vs. placebo	SMD	●○○○ Critically low

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref)	Population	Mental disorders	Outcomes	Outcome assessments	No. of studies (participants, *n*)	Study design	Intervention/ comparison	Effect metrics	AMSTAR 2 rating[2]
Su et al., 2018 (47)	Adults	Anxiety	Symptoms	Clinician-administered post-traumatic stress disorder scale, Child Behavior Checklist anxiety subscale, children's Yale-Brown obsessive-compulsive scale, depression, anxiety, and stress scales, generalized anxiety disorder questionnaire, Hospital Anxiety and Depression Scale anxiety subscale, Hamilton anxiety rating scale, impact of event scale–revised, and Yale-Brown obsessive-compulsive scale	19 (1203)	Clinical trials	n–3 fatty acids supplementation vs. placebo or education	Hedges' *g*	●●●● High
Rosenblat et al., 2016 (45)	Adults	Bipolar depression	Symptoms	Bipolar Depression Rating Scale, Clinical Global Impressions Scale, Clinical Global Impressions Scale–Improvement–Bipolar, Clinical Global Impressions Scale–Improvement–Depression, Clinical Global Impressions Scale–Improvement–Mania, Clinical Global Impressions Scale–Severity–Bipolar, Clinical Global Impressions Scale–Severity–Depression, Clinical Global Impressions Scale–Severity–Mania, Hamilton Depression Rating Scale, Inventory of Depressive Symptomatology–Clinical Rating Scale, Montgomery–Asberg Depression Rating Scale, Quality of Life Enjoyment and Satisfaction Scale, Social and Occupational Functioning Assessment Scale, and Young Mania Rating Scale	4 (140)	Randomized controlled studies	n–3 fatty acids supplementation vs. placebo	SMD	●●○○ Low

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref)	Population	Mental disorders	Outcomes	Outcome assessments	No. of studies (participants, *n*)	Study design	Intervention/ comparison	Effect metrics	AMSTAR 2 rating[2]
Tan et al., 2016 (46)	Children	Specific learning disorders	Adverse effects (gastrointestinal disturbances)	—	2 (116)	Randomized controlled studies, quasi-RCTs	PUFA vs. placebo	RR	●●●● High
Cooper et al., 2015 (42)	Children	Attention-deficit/hyperactivity disorder	Symptoms and brain functions	Wechsler Intelligence Scale for Children, test of variables of attention, digit span backwards (recalling a string of numbers backwards), immediate or delayed word recall, Wide Range Achievement Test, or others	24 (8658)	Randomized controlled studies	n–3 fatty acids supplementation vs. placebo	SMD	●○○○ Critically low
Yang et al., 2015 (43)	Women	Depression	Depressive symptoms	Comprehensive evaluation (including Montgomery–Asberg Depression Rating Scale, Hamilton Depression Rating Scale, Clinical Global Impression, Beck Depression Inventory, or Geriatric Depression Scale)	8 (267)	Randomized controlled studies	DHA and EPA vs. placebo	SMD	●●●● High
Dietary unsaturated fatty acids intake									
Kosti et al., 2022 (63)	The elderly	Dementia, Alzheimer disease	Risk of dementia/Alzheimer disease	Cambridge Mental Disorders of the Elderly Examination, Clinical Dementia Rating Diagnostic and Statistical Manual of Mental Disorders-III-Revised, Geriatric Mental State Schedule, Mini-Mental State Examination Wechsler Memory Scale Revised	9 (440,572)	Cohort	Highest intake of fish vs. reference group	RR	●●●● High
Zhu et al., 2021 (62)	The elderly	Alzheimer disease	Risk of Alzheimer disease	NR	14 (54,177)	Cohort	Highest intake of n–3 fatty acids vs. reference group	RR	●●○○ Low
Qu et al., 2019 (50)	Adults	Parkinson disease	Risk of Parkinson disease	NR	9 (778,571)	Cohort, case-control	Highest intake of n–3 and n–6 fatty acids vs. reference group	RR	●○○○ Critically low

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref)	Population	Mental disorders	Outcomes	Outcome assessments	No. of studies (participants, *n*)	Study design	Intervention/ comparison	Effect metrics	AMSTAR 2 rating[2]
Grosso et al., 2016 (44)	Adults	Depression	Risk of depression	Center for Epidemiologic Studies–Depression, Composite International Diagnostic Interview Short Form, Depression, Anxiety and Stress Scales, Geriatric Depression Scale, Edinburgh Post-partum Depression Scale, and Munich-Composite International Diagnostic Interview	16:15 (255,076)	Cohort, case-control	Highest intake of n–3 fatty acids and fish vs. reference group	RR	●○○○ Critically low
Zhang et al., 2016 (15)	The elderly	Alzheimer disease; cognitive decline; dementia; mild cognitive impairment; Parkinson disease	Risk of cognitive impairment	NR	21 (181,580)	Cohort	Highest intake of n–3 fatty acids and fish vs. reference group	RR	●●●● High
Tsai et al., 2014 (41)	Adults	Suicide	Suicide mortality	—	3 (205,357)	Cohort	Highest intake of n–3 or n–6 fatty acids vs. reference group	RR	●○○○ Critically low
Circulating unsaturated fatty acids									
Mazahery et al., 2017 (11)	Children	Autism spectrum disorder	Circulating n–3, n–6 fatty acids and ratios between n–3/n–6 fatty acids	—	15 (1193)	Case-control	Autism spectrum disorder vs. typically developing control	SMD	●●●● High
McNamara et al., 2016 (12)	Youth	Bipolar disorder	Circulating n–3 and n–6 fatty acids	—	6 (265)	Case-control	Bipolar disorder vs. typically developing control	SMD	●○○○ Critically low
Zhang et al., 2016 (15)	The elderly	Alzheimer disease; dementia; cognitive decline	Risk of cognitive impairment	—	21 (181,580)	Cohort	A 1% increment of blood DHA concentrations	RR	●●●● High
Hawkey et al., 2014 (13)	Children	Attention-deficit/hyperactivity disorder	Circulating n–3 fatty acids	—	9 (586)	Case-control	Attention-deficit/hyperactivity disorder vs. typically developing control	Hedges' *g*	●●●○ Medium
van der Kemp et al., 2012 (14)	The elderly	Schizophrenia	Circulating n–3 and n–6 fatty acids	—	14 (873)	Cohort, case-control	Schizophrenia vs. typically developing control	Cohen's *d*	●○○○ Critically low

[1] AMSTAR 2, A Measurement Tool to Assess Systematic Reviews; MD, mean difference; NR, not reported; RCT, randomized controlled trial; ref, reference; SMD, standardized mean difference; WMD, weighted mean difference.
[2] AMSTAR 2 used 16 items to assess methodological quality of systematic reviews on the basis of the validity of review design, literature screening, data extraction, and individual study quality assessment. Details of the quality assessment for eligible reviews were provided in Supplemental Table 1.

TABLE 2 Quantitative synthesis and evidence grading for meta-analyses of unsaturated fatty acids supplementation interventions for participants with mental disorders[1]

Study, year (ref)	Mental disorders	Outcomes	Unsaturated fatty acids supplementation	No. of studies (participants, *n*)	Original effect metrics	Random-effects summary estimate (95% CI)	Random-effects *P*	I^2, %	Converted as equivalent OR (95% CI)	95% Prediction interval	Egger's test> *P*	Largest study estimate (95% CI)	Significant studies		Grading
													O/E	*P*	
Xu et al., 2022 (64)	Schizophrenia	Positive and Negative Syndrome Scale total scores	EPA/DHA/EPA+DHA	6 (317)	MD	−3.274 (−5.449, −1.098)	0.003	22.2	0.326 (0.061, 1.751)	(0.001, 144.492)	0.22	1.11 (0.49, 2.52)	1/0.33	0.29	Not significant
Appleton et al., 2021 (56)	Depression	Depressive symptoms	Total n–3 PUFAs	33 (1848)	SMD	−0.401 (−0.642, −0.160)	0.001	80.7	0.484 (0.313, 0.748)	(0.052, 4.482)	0.05	0.83 (0.59, 1.18)	10/2.16	$<10^{-3}$	Weak
		Quality of life	Total n–3 PUFAs	12 (476)	SMD	−0.376 (−0.816, 0.063)	0.093	78.9	0.506 (0.228, 1.121)	(0.029, 8.799)	0.26	1.63 (0.72, 3.68)	5/1.52	0.01	Not significant
		Adverse events	Total n–3 PUFAs	24 (1503)	OR	1.267 (0.977, 1.644)	0.075	5.7	—	(0.840, 1.912)	0.48	1.26 (0.83, 1.91)	2/1.70	0.69	Not significant
de Andrade Wobido et al., 2021 (57)	Autism spectrum disorder	Aberrant Behavior Checklist	Total n–3 and n–6 PUFAs	5 (183)	SMD	−0.183 (−0.341, −0.025)	0.023	0.0	0.718 (0.540, 0.955)	(0.531, 0.970)	0.80	0.79 (0.31, 2.03)	1/1.46	—	Weak
		Social Responsiveness Scale	Total n–3 and n–6 PUFAs	5 (238)	SMD	−0.059 (−0.239, 0.122)	0.524	46.2	0.953 (0.691, 1.314)	(0.337, 2.694)	<0.01	1.88 (1.36, 4.83)	1/4.11	—	Not significant
Goh et al., 2021 (58)	Schizophrenia	Positive and Negative Syndrome Scale total scores	Total n–3 PUFAs	9 (443)	SMD	−0.295 (−0.527, −0.064)	0.012	28.1	0.586 (0.386, 0.891)	(0.230, 1.497)	0.81	1.18 (0.55, 2.52)	3/0.55	0.01	Weak
		Positive and Negative Syndrome Scale–Positive scale	Total n–3 PUFAs	6 (266)	SMD	−0.105 (−0.349, 0.139)	0.400	0.0	0.827 (0.531, 1.287)	(0.442, 1.547)	0.86	0.82 (0.38, 1.75)	0/0.38	—	Not significant
		Positive and Negative Syndrome Scale–Negative scale	Total n–3 PUFAs	3 (195)	SMD	1.193 (−0.654, 3.039)	0.205	96.7	8.661 (0.306, 245.036)	(<0.001, >1000)	0.08	0.67 (0.31, 1.46)	1/0.42	0.37	Not significant
		Positive and Negative Syndrome Scale–General Psychopathology scale	Total n–3 PUFAs	2 (145)	SMD	−0.388 (−1.103, 0.327)	0.287	77.7	0.495 (0.136, 1.806)	—	—	0.93 (0.44, 2.03)	1/0.10	0.10	Not significant
Händel et al., 2021 (59)[2]	Attention-deficit/ hyperactivity disorder	Parent-reported core symptoms	Total n–3 and n–6 PUFAs	24 (1754)	SMD	−0.167 (−0.318, −0.015)	0.031	60.7	0.739 (0.562, 0.972)	(0.245, 2.228)	0.04	1.54 (1.36, 3.24)	8/1.04	0.05	Weak
		Teacher-reported core symptoms	Total n–3 and n–6 PUFAs	10 (640)	SMD	−0.062 (−0.310, 0.186)	0.626	55.0	0.894 (0.571, 1.401)	(0.241, 3.324)	0.26	1.14 (0.59, 2.22)	2/0.58	0.11	Not significant
		Parent-reported behavioral difficulties	Total n–3 and n–6 PUFAs	7 (682)	SMD	−0.014 (−0.169, 0.141)	0.859	0.0	0.975 (0.736, 1.291)	(0.675, 1.409)	0.73	0.74 (0.41, 1.31)	0/0.89	—	Not significant
		Teacher-reported behavioral difficulties	Total n–3 and n–6 PUFAs	5 (377)	SMD	−0.041 (−0.346, 0.264)	0.791	49.1	0.928 (0.534, 1.612)	(0.178, 4.824)	0.38	0.96 (0.49, 1.88)	1/0.25	0.23	Not significant
		Quality of life	Total n–3 and n–6 PUFAs	2 (191)	SMD	0.014 (−0.288, 0.316)	0.929	0.0	1.025 (0.593, 1.771)	—	—	0.98 (0.52, 1.88)	0/0.10	—	Not significant
Suradom et al., 2021 (60)	Depression	Prevention of depression severity	Total n–3 and n–6 PUFAs	10 (1027)	SMD	−0.033 (−0.201, 0.134)	0.697	23.2	0.942 (0.695, 1.275)	(0.493, 1.797)	0.45	1.20 (0.71, 2.03)	1/0.78	0.56	Not significant
		Treatment of depression severity	Total n-3 and n-6 PUFAs	4 (209)	SMD	−0.138 (−0.543, 0.268)	0.506	30.7	0.780 (0.374, 1.623)	(0.070, 8.640)	0.31	1.54 (0.56, 4.18)	0/0.55	—	Not significant
Xu et al., 2021 (61)	Mild cognitive impairment	Mini-Mental State Examination	Unsaturated fatty acids	3 (96)	MD	0.658 (−0.008, 1.325)	0.053	59.8	3.293 (0.986, 10.995)	(<0.001, >1000)	0.44	1.10 (0.33, 3.64)	2/0.16	0.01	Not significant

(*Continued*)

TABLE 2 (*Continued*)

Study, year (ref)	Mental disorders	Outcomes	Unsaturated fatty acids supplementation	No. of studies (participants, *n*)	Original effect metrics	Random-effects summary estimate (95% CI)	Random-effects *P*	I^2, %	Converted as equivalent OR (95% CI)	95% Prediction interval	Egger's test> *P*	Largest study estimate (95% CI)	Significant studies		Grading
Araya-Quintanilla et al., 2020 (52)	Alzheimer disease	Narcissistic Personality Inventor	Total n–3 PUFAs	2 (543)	SMD	−0.342 (−1.077, 0.393)	0.362	93.7	0.539 (0.142, 2.037)	—	—	0.28 (0.19, 0.41)	1/1.99	—	Not significant
		Mini-Mental State Examination	Total n–3 PUFAs	3 (283)	SMD	0.582 (−0.434, 1.597)	0.262	0.0	2.865 (0.456, 18.016)	(<0.001, >1000)	0.79	2.06 (0.19, 22.09)	0/1.34	—	Not significant
		Alzheimer's Disease Assessment Scale–Cognitive section	Total n–3 PUFAs	3 (239)	SMD	1.096 (−1.031, 3.224)	0.312	96.9	7.275 (0.155, 342.043)	(<0.001, >1000)	0.11	216.09 (99.23, 470.60)	1/2.99	—	Not significant
Luo et al., 2020 (53)[2]	Depression	Depressive symptoms	Total n–3 and n–6 PUFAs (≥2000 mg/d)	4 (160)	SMD	−0.941 (−1.581, −0.301)	0.004	66.9	0.182 (0.057, 0.580)	(0.001, 22.190)	0.05	0.54 (0.24, 1.18)	3/0.73	0.02	Weak
		Depressive symptoms	Total n-3 and n-6 PUFAs (<2000 mg/d)	7 (985)	SMD	−0.630 (−1.186, −0.075)	0.026	90.8	0.319 (0.117, 0.874)	(0.010, 9.976)	0.13	0.82 (0.58, 1.16)	2/0.68	0.14	Weak
Mocking et al., 2020 (54)	Perinatal depression	Depressive symptoms	Total n–3 and n–6 PUFAs	14 (3781)	SMD	−0.072 (−0.188, 0.045)	0.227	19.0	0.879 (0.712, 1.084)	(0.571, 1.352)	0.95	0.83 (0.67, 1.04)	1/1.71	0.68	Not significant
	Postpartum depression	Depressive symptoms	Total n–3 and n–6 PUFAs	4 (423)	SMD	−0.656 (−1.690, 0.378)	0.213	92.7	0.305 (0.047, 1.982)	(<0.001, >1000)	0.10	0.03 (0.01, 0.06)	2/3.99	—	Not significant
Zhang et al., 2020 (55)	Mild cognitive impairment	Mini-Mental State Examination	Total n–3 PUFAs	7 (434)	WMD	0.852 (0.039, 1.665)	0.040	52.2	1.646 (1.009, 2.685)	(0.424, 6.395)	0.55	0.98 (0.59, 1.62)	1/0.35	0.30	Weak
Devoe et al., 2019 (48)	Psychosis	Attenuated psychotic symptoms	Total n–3 PUFAs	3 (347)	SMD	−0.309 (−0.878, 0.261)	0.288	81.1	0.572 (0.204, 1.604)	(<0.001, >1000)	0.74	0.91 (0.57, 1.46)	1/0.17	0.16	Not significant
Morsy et al., 2019 (49)	Huntington disease	Total motor score	Ethyl-EPA	2 (285)	MD	−2.720 (−4.763, −0.677)	0.009	0.0	0.071 (0.001, 3.786)	—	—	0.52 (0.35, 0.79	2/1.42	1.00	Not significant
		Total motor score-4	Ethyl-EPA	2 (285)	MD	−2.225 (−3.843, −0.607)	0.007	9.7	0.025 (0.008, 0.080)	—	—	0.01 (0.01, 0.03)	2/1.99	1.00	Weak
Zhang et al., 2019 (51)	Depression in children	Depressive symptoms	Total n–3 PUFAs	4 (153)	SMD	−0.119 (−0.533, 0.296)	0.575	30.5	0.807 (0.381, 1.709)	(0.069, 9.412)	0.03	1.22 (0.43, 3.49)	1/0.25	0.23	Not significant
Su et al., 2018 (47)[2]	Anxiety	Symptoms	Total n–3 PUFAs	19 (1203)	Hedges' *g*	−0.374 (−0.666, −0.081)	0.012	89.9	0.508 (0.300, 0.863)	(0.049, 5.300)	0.10	1.29 (0.88, 1.87)	6/2.11	0.01	Weak
Rosenblat et al., 2016 (45)	Bipolar depression	Depressive symptoms	Total n–3 PUFAs	4 (140)	SMD	−0.364 (−0.735, 0.007)	0.054	8.3	0.517 (0.265, 1.012)	(0.092, 2.895)	0.79	0.48 (0.20, 1.14)	0/0.83	—	Not significant
Tan et al., 2016 (46)	Specific learning disorders	Adverse effects	PUFAs	2 (116)	RR	1.402 (0.237, 8.281)	0.710	0.0	1.402 (0.237, 8.281)	—	—	2.05 (0.19, 21.7)	0/0.63	—	Not significant
Cooper et al., 2015 (42)[2]	Attention-deficit/hyperactivity disorder	Attention (omission errors)	Total n–3 PUFAs	6 (387)	SMD	−0.129 (−0.327, 0.069)	0.200	0.0	0.792 (0.554, 1.132)	(0.477, 1.314)	0.82	0.76 (0.43, 1.3)	0/0.54	—	Not significant
		IQ	Total n–3 PUFAs	5 (706)	SMD	0.139 (−0.07, 0.351)	0.200	23.3	1.286 (0.876, 1.888)	(0.513, 3.221)	0.96	1.00 (0.55, 1.82)	1/0.25	0.23	Not significant
		Inhibition	Total n–3 PUFAs	12 (951)	SMD	−0.037 (−0.217, 0.143)	0.687	38.9	0.935 (0.675, 1.295)	(0.396, 2.208)	0.49	0.74 (0.43, 1.27)	1/1.36	—	Not significant
		Mean reaction time	Total n–3 PUFAs	11 (1107)	SMD	−0.001 (−0.118, 0.117)	0.997	12.8	0.999 (0.808, 1.236)	(0.684, 1.460)	0.86	1.29 (0.89, 1.85)	1/1.16	—	Not significant
		Reaction time variability	Total n–3 PUFAs	2 (114)	SMD	0.290 (−0.709, 1.289)	0.569	82.1	1.691 (0.277, 10.319)	—	—	0.68 (0.25, 1.92)	1/0.24	0.22	Not significant
		Reading	Total n–3 PUFAs	8 (1433)	SMD	0.014 (−0.062, 0.090)	0.722	0.0	1.025 (0.894, 1.176)	(0.864, 1.218)	0.22	1.04 (0.79, 1.34)	0/0.42	—	Not significant
		Short-term memory	Total n–3 PUFAs	14 (2188)	SMD	0.067 (−0.013, 0.147)	0.101	28.5	1.129 (0.976, 1.306)	(0.793, 1.608)	0.41	1.00 (0.72, 1.39)	2/0.70	0.15	Not significant
		Spelling	Total n–3 PUFAs	6 (974)	SMD	0.031 (−0.090, 0.153)	0.614	5.1	1.058 (0.849, 1.319)	(0.738, 1.517)	0.90	0.95 (0.66, 1.34)	0/0.32	—	Not significant
		Working memory	Total n–3 PUFAs	8 (1410)	SMD	0.089 (−0.007, 0.185)	0.068	3.6	1.175 (0.988, 1.397)	(0.917, 1.505)	0.02	0.96 (0.74, 1.27)	1/0.42	0.35	Not significant
Yang et al., 2015 (43)[2]	Depression in women	Depressive symptoms	EPA+DHA	8 (267)	SMD	−0.648 (−1.120, −0.175)	0.007	78.4	0.310 (0.132, 0.728)	(0.018, 5.344)	0.09	0.53 (0.24, 1.20)	6/1.70	<0.01	Weak

[1] All summary estimates were recalculated based on a random-effects model using the method of DerSimonian and Laird. The 95% prediction interval and Egger's test were not evaluated if available studies were <3. For excess of significance, the *P* value was not evaluated if the observed number of studies was smaller than expected. E, expected number of studies with positive finding; MD, mean difference; O, observed number of studies with positive finding; ref, reference; SMD, standardized mean difference; WMD, weighted mean difference.
[2] The direction of comparison was normalized to supplementation group versus non-supplementation group.

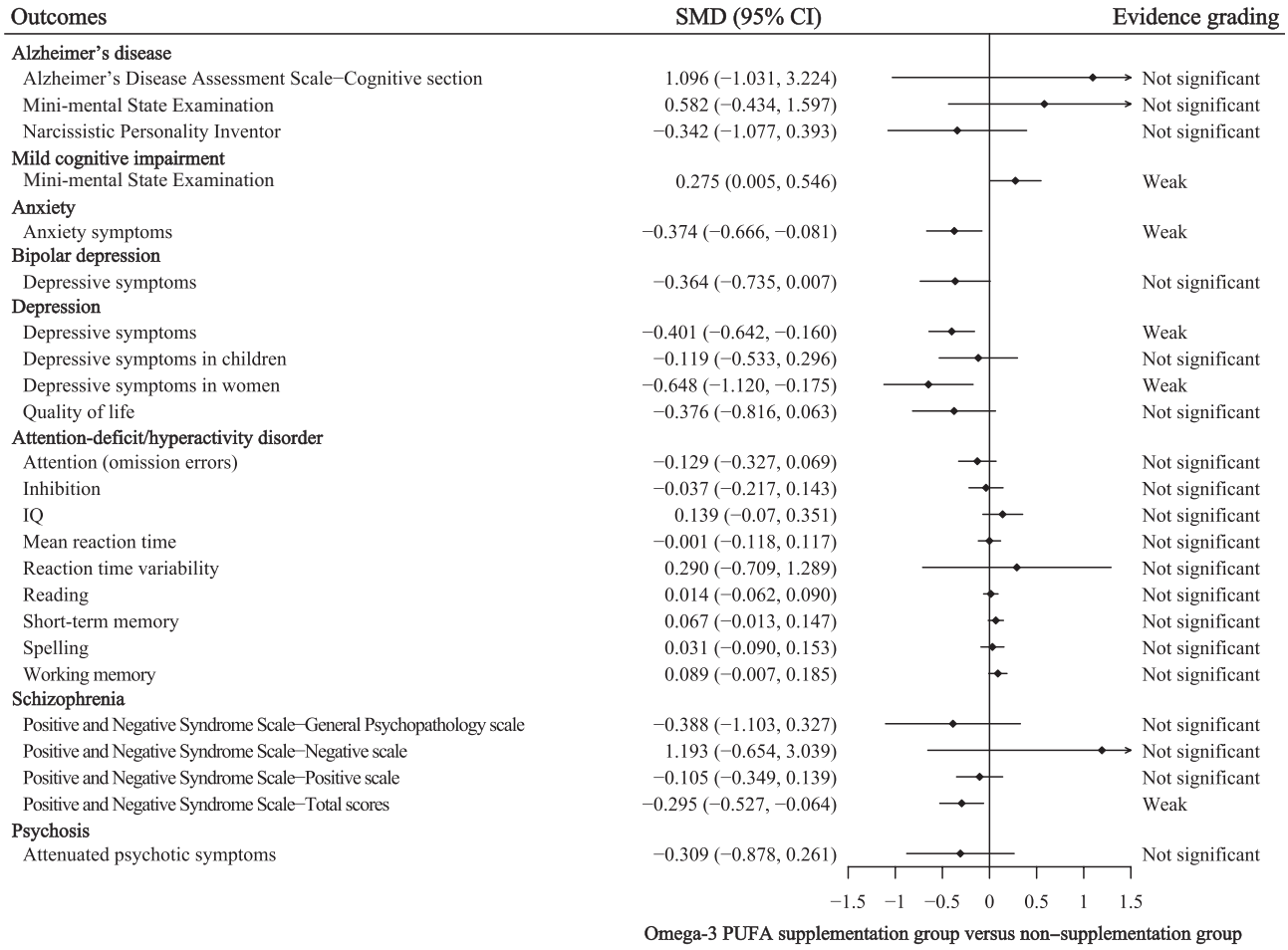

FIGURE 2 Efficacy of n–3 unsaturated fatty acid supplementation interventions for mental disorders with evidence grading. SMD, standardized mean difference.

summary effect using random-effects models ($P < 0.05$), and all 95% prediction intervals of the meta-analyses included the null value, which indicated no associations (**Table 3**). Significant heterogeneity ($I^2 > 50\%$) was observed in associations of fish consumption with risk of depression and intake of EPA and DHA with risk of depression (Table 3). The risk of small-study effects bias was only observed in 2 associations, whereas excess of significance bias was detected in 2 associations. However, most associations (26/32) consisted of fewer than 5 individual studies, in which case the power of the test was reduced.

Three meta-analyses had suggestive strength of the associations according to the quantitative umbrella review criteria, and the strength of the evidence was weak for 2 meta-analyses (Table 3). Suggestive evidence indicated that a higher intake of fish could reduce the risk of depression (pooled RR: 0.780; *P*-random effects: <0.001) and AD (pooled RR: 0.737; *P*-random effects < 0.001), and a higher intake of dietary PUFAs was associated with a lower risk of mild cognitive impairment (pooled RR: 0.714; *P*-random effects < 0.001). Moreover, weak evidence showed that a higher intake of dietary EPA and DHA was associated with a lower risk of depression (pooled RR: 0.782; *P*-random effects: 0.003), and a higher intake of fish might reduce the risk of dementia (pooled RR: 0.798; *P*-random effects: 0.003).

Unsaturated fatty acids as biomarkers for mental disorders

A total of 20 meta-analyses assessed the difference in circulating unsaturated fatty acids between healthy controls and patients with mental disorders, including AD, dementia, mild cognitive impairment, ADHD, ASD, BP, and schizophrenia. Eight meta-analyses reported a nominally statistically significant summary effect using random-effects models ($P < 0.05$), and 3 meta-analyses had 95% prediction intervals excluding the null value (**Table 4**). Significant heterogeneity ($I^2 > 50\%$) was observed in 5 statistically significant comparisons, with the exception of the comparison of circulating DHA between patients with BP and controls, the comparison of circulating total n–3 PUFAs between patients with ADHD and controls, and the comparison of circulating docosapentaenoic acid (DPA; 22:5n−3) between patients with schizophrenia and

TABLE 3 Quantitative synthesis and evidence grading for meta-analyses evaluating the associations between unsaturated fatty acids intake and risk of mental disorders[1]

Study, year (ref)	Mental disorders	Composition	No. of studies (participants, *n*)	Effect metrics	Random-effects summary estimate (95% CI)	Random-effects *P*	I^2, %	95% Prediction interval	Egger's test *P*	Largest study estimate (95% CI)	Significant studies		Grading
											O/E	*P*	
Kosti et al., 2022 (63)	Dementia	Higher intake of fish	9 (45,643)	RR	0.798 (0.688, 0.925)	0.003	0.0	(0.563, 1.129)	0.08	0.84 (0.71, 1.00)	4/3.50	0.74	Weak
	Alzheimer disease	Higher intake of fish	8 (444,022)	RR	0.737 (0.626, 0.867)	$<10^{-3}$	0.0	(0.479, 1.134)	0.71	0.69 (0.60, 0.80)	5/6.49	—	Suggestive
Zhu et al., 2021 (62)	Alzheimer disease	Higher intake of total n−3 PUFAs	4 (11,977)	RR	0.883 (0.662, 1.177)	0.396	60.7	(0.370, 2.11)	0.12	1.07 (0.91, 1.25)	1/0.41	0.35	Not significant
		Higher intake of total n−6 PUFAs	2 (3427)	RR	0.826 (0.549, 1.241)	0.358	55.9	—	—	0.76 (0.55, 1.06)	0/1.69	—	Not significant
		Higher intake of PUFAs	3 (8084)	RR	0.905 (0.741, 1.105)	0.326	0.0	(0.584, 1.403)	0.68	1.09 (0.79, 1.50)	0/0.43	—	Not significant
		Higher intake of MUFA	4 (8899)	RR	1.154 (0.800, 1.664)	0.442	64.50	(0.380, 3.507)	0.78	0.91 (0.77, 1.07)	1/0.56	0.45	Not significant
		Higher intake of DHA	3 (3892)	RR	0.778 (0.477, 1.267)	0.313	76.20	(0.003, 185.619)	0.67	0.73 (0.57, 0.95)	2/1.66	1.00	Not significant
		Higher intake of EPA	3 (3892)	RR	0.888 (0.658, 1.198)	0.436	45.08	(0.046, 16.999)	0.15	0.74 (0.57, 0.95)	1/1.58	—	Not significant
Qu et al., 2019 (50)	Parkinson disease	Higher intake of total n−3 PUFAs	3 (300,321)	RR	0.763 (0.487, 1.194)	0.236	62.2	(0.006, 104.092)	0.50	0.93 (0.76, 1.14)	1/0.39	0.34	Not significant
		Higher intake of total n−6 PUFAs	3 (300,321)	RR	0.990 (0.667, 1.468)	0.959	55.9	(0.015, 66.907)	0.29	1.23 (1.02, 1.49)	1/1.29	—	Not significant
		Higher intake of PUFAs	4 (326,686)	RR	0.864 (0.592, 1.261)	0.449	74.0	(0.173, 4.320)	0.18	1.23 (1.02, 1.49)	2/1.57	0.65	Not significant
		Higher intake of MUFA	5 (327,054)	RR	1.033 (0.865, 1.235)	0.719	0.0	(0.774, 1.380)	0.24	1.13 (0.94, 1.55)	0/1.00	—	Not significant
		Higher intake of ALA	3 (300,513)	RR	0.726 (0.480, 1.099)	0.130	64.6	(0.008, 70.002)	0.22	0.93 (0.77, 1.13)	1/0.39	0.34	Not significant
		Higher intake of LA	3 (300,513)	RR	0.930 (0.614, 1.409)	0.732	65.6	(0.009, 94.012)	0.05	1.23 (1.02, 1.49)	1/1.33	—	Not significant
		Higher intake of AA	2 (299,985)	RR	1.426 (0.753, 2.700)	0.277	80.1	—	—	1.08 (0.90, 1.30)	1/0.36	0.32	Not significant
		Higher ratio of n−3 to n−6 PUFAs	2 (299,985)	RR	0.890 (0.754, 1.051)	0.170	0.0	—	—	0.87 (0.73, 1.04)	0/0.82	—	Not significant
Grosso et al., 2016 (44)	Depression	Higher intake of total n−3 PUFAs	8 (25,923)	RR	0.873 (0.722, 1.055)	0.160	30.9	(0.569, 1.339)	0.86	0.74 (0.58, 0.95)	2/4.57	—	Not significant
		Higher intake of EPA and DHA	7 (77,143)	RR	0.782 (0.667, 0.918)	0.003	50.4	(0.508, 1.206)	0.63	0.65 (0.53, 0.80)	3/6.35	—	Weak
		Higher intake of fish	21 (200,422)	RR	0.780 (0.688, 0.885)	$<10^{-3}$	61.4	(0.489, 1.244)	0.90	0.76 (0.64, 0.91)	8/15.08	—	Suggestive
Zhang et al., 2016 (15)	Alzheimer disease	Higher intake of PUFAs	2 (6844)	RR	0.872 (0.334, 2.278)	0.779	27.9	—	—	1.07 (0.82, 1.39)	0/0.15	—	Not significant
		Higher intake of DHA	3 (6476)	RR	0.546 (0.242, 1.233)	0.145	90.53	(<0.001, >1000)	0.11	1.10 (0.93, 1.31)	2/0.31	0.03	Not significant
	Dementia	Higher intake of PUFAs	2 (6844)	RR	0.870 (0.355, 2.131)	0.760	25.09	—	—	1.04 (0.83, 1.29)	0/0.12	—	Not significant
		Higher intake of DHA	2 (5661)	RR	0.804 (0.511, 1.263)	0.344	90.81	—	—	1.00 (0.89, 1.14)	1/0.10	0.10	Not significant
	Mild cognitive impairment	Higher intake of PUFAs	3 (3386)	RR	0.714 (0.607, 0.841)	$<10^{-3}$	0.0	(0.248, 2.056)	0.70	0.72 (0.61, 0.85)	1/1.05	—	Suggestive
	Parkinson disease	Higher intake of DHA	4 (141,551)	RR	1.001 (0.974, 1.029)	0.931	0.0	(0.943, 1.063)	0.51	1.01 (0.97, 1.04)	0/0.20	—	Not significant

(*Continued*)

TABLE 3 (*Continued*)

Study, year (ref)	Mental disorders	Composition	No. of studies (participants, *n*)	Effect metrics	Random-effects summary estimate (95% CI)	Random-effects *P*	I^2, %	95% Prediction interval	Egger's test *P*	Largest study estimate (95% CI)	Significant studies		Grading
											O/E	*P*	
Tsai et al., 2014 (41)	Suicide	Higher intake of total n–3 PUFAs	3 (205,357)	RR	1.463 (0.950, 2.251)	0.084	10.1	(0.057, 37.437)	0.97	1.47 (0.88, 2.44)	0/0.55	—	Not significant
		Higher intake of total n–6 PUFAs	3 (205,357)	RR	0.887 (0.562, 1.401)	0.607	0.0	(0.0459, 17.149)	0.44	0.82 (0.45, 1.51)	0/0.71	—	Not significant
		Higher intake of EPA and DHA	3 (205,357)	RR	1.241 (0.681, 2.263)	0.481	58.2	(0.002, 786,970)	0.21	0.80 (0.49, 1.28)	0/0.29	—	Not significant
		Higher intake of ALA	3 (205,357)	RR	1.068 (0.734, 1.556)	0.730	0.0	(0.093, 12.222)	0.01	1.27 (0.78, 2.06)	0/0.30	—	Not significant
		Higher intake of LA	3 (205,357)	RR	0.664 (0.418, 1.056)	0.084	0.0	(0.033, 13.410)	0.12	0.54 (0.29, 1.02)	0/2.35	—	Not significant
		Higher intake of AA	3 (205,357)	RR	1.190 (0.824, 1.718)	0.354	0.0	(0.110, 12.895)	0.27	1.09 (0.67, 1.77)	0/0.21	—	Not significant
		Higher intake of fish	3 (205,357)	RR	0.818 (0.283, 2.364)	0.711	73.7	(<0.001, >1000)	0.71	0.55 (0.31, 0.96)	0/2.39	—	Not significant

[1] All summary estimates were recalculated based on a random-effects model using the method of DerSimonian and Laird. The 95% prediction interval and Egger's test were not evaluated if available studies were <3. For excess of significance, the *P* value was not evaluated if the observed number of studies was smaller than expected. AA, arachidonic acid; ALA, α-linolenic acid; E, expected number of studies with positive finding; LA, linoleic acid; MD, mean difference; O, observed number of studies with positive finding; ref, reference; SMD, standardized mean difference.

controls (Table 4). The risk of small-study effects bias was observed in 1 comparison, whereas excess of significance bias was detected in 6 comparisons (Table 4). Among these comparisons, 6 meta-analyses consisted of fewer than 5 individual studies, in which case the power of the test was reduced.

None of the 20 meta-analyses had convincing, highly suggestive, or suggestive strength of efficacy according to the quantitative umbrella review criteria. In addition, the credibility of the evidence was weak for 8 meta-analyses, which suggested differences in circulating unsaturated fatty acids among ADHD, ASD, BP, and schizophrenia patients and healthy controls (*P*-random effects $<10^{-6}$–0.037).

Discussion

This umbrella review included 29 systematic reviews of studies assessing the role of unsaturated fatty acids in numerous mental disorders. Overall, the available evidence has mainly focused on long-chain PUFAs (n–3 PUFAs and n–6 PUFAs), and the effects vary among mental disorders. Current evidence suggests that n–3 PUFA supplementation intervention might have potential value, but the strength of the efficacy and credibility of the evidence were weak overall. Higher intake of unsaturated fatty acids might have protective effects on a limited number of mental disorders (i.e., depression and mild cognitive impairment), and the effect of unsaturated fatty acid intake on many mental disorders has not been evaluated. In addition, we observed broad differences in circulating unsaturated fatty acids between patients with mental disorders and controls. The between-study heterogeneity, limited study populations, prediction intervals including the null value, and risk of excess significance bias were the main factors reducing the overall confidence in the evidence.

Although linking nutrition evidence with practice remains challenging (7, 64–67), the findings of this umbrella review might have clinical practice implications. The availability of a substantial body of experimental evidence generated in unsaturated fatty acid supplementation is a major finding that should inform the establishment of guidelines for the prevention of mental disorders. Mental disorders require complex interdisciplinary treatment grounded in the use of antipsychotic medications (68). However, medical treatment is usually accompanied by a large number of adverse effects, resulting in decreased treatment compliance (69). This has contributed to the development of alternative and complementary (adjunctive) treatments. An ever-growing body of evidence has evaluated the effect of dietary and supplemental unsaturated fatty acids (especially PUFAs) on various mental illnesses, but on the basis of umbrella review criteria none of these effect sizes have reached the maximum in terms of the strength of evidence credibility ratings. Suggestive evidence has shown a protective effect of fish consumption on depression (44) and dietary PUFA intake on mild cognitive impairment (15). Although the credibility in the estimate for efficacy was not optimal, weak evidence supported the efficacy of unsaturated fatty acid supplementation for

TABLE 4 Quantitative synthesis and evidence grading for meta-analyses comparing circulating unsaturated fatty acids between participants with and without mental disorders[1]

Study, year (ref)	Mental disorders	Outcome	No. of studies (participants, *n*)	Original effect metrics	Random-effects summary estimate (95% CI)	Random-effects *P*	I^2, %	Converted as equivalent OR (95% CI)	95% Prediction interval	Egger's test *P*	Largest study estimate (95% CI)	Significant studies		Grading
												O/E	*P*	
Mazahery et al., 2017 (11)	Autism spectrum disorder	Circulating n–3 PUFAs	5 (564)	SMD	−0.164 (−0.536, 0.209)	0.389	73.0	0.744 (0.379, 1.459)	(0.073, 7.573)	0.24	0.51 (0.32, 0.82)	3/2.19	0.66	Not significant
		Circulating n–6 PUFAs	5 (564)	SMD	0.569 (−0.186, 1.323)	0.139	93.2	2.799 (0.715, 10.968)	(0.015, 518.050)	0.09	0.59 (0.37, 0.95)	3/1.54	0.17	Not significant
		Circulating DHA	14 (1291)	SMD	−1.607 (−2.482, −0.732)	$<10^{-3}$	97.3	0.055 (0.011, 0.266)	(0.000, 43.982)	0.11	0.45 (0.28, 0.72)	11/6.78	0.03	Weak
		Circulating EPA	11 (951)	SMD	−0.437 (−0.901, 0.027)	0.065	90.2	0.453 (0.196, 1.050)	(0.019, 10.672)	0.82	1.00 (0.62, 1.60)	3/0.55	0.02	Not significant
		Circulating AA	13 (1211)	SMD	−0.826 (−1.481, −0.172)	0.013	95.5	0.224 (0.068, 0.733)	(0.002, 26.555)	0.82	0.45 (0.28, 0.72)	8/6.29	0.41	Weak
		The ratio of AA to EPA in blood	9 (525)	SMD	0.662 (−0.109, 1.433)	0.093	93.4	3.311 (0.820, 13.367)	(0.023, 470.693)	0.97	5.79 (3.18, 10.33)	5/6.32	—	Not significant
		The ratio of AA to DHA in blood	5 (336)	SMD	−0.080 (−2.223, 2.063)	0.942	98.1	0.865 (0.018, 41.855)	(<0.001, >1000)	0.05	127.84 (58.70, 278.41)	4/4.99	—	Not significant
McNamara et al., 2016 (12)	Bipolar disorder	Circulating DHA	6 (265)	SMD	−0.960 (−1.243, −0.676)	$<10^{-6}$	0.0	0.176 (0.105, 0.294)	(0.085, 0.364)	0.87	0.17 (0.07, 0.44)	4/5.22	—	Weak
		Circulating EPA	6 (265)	SMD	−0.455 (−0.882, −0.027)	0.037	56.9	0.438 (0.202, 0.951)	(0.045, 4.317)	0.27	0.44 (0.20, 1.22)	2/1.96	1.00	Weak
		Circulating LA	4 (199)	SMD	−0.623 (−1.663, 0.418)	0.241	90.3	0.324 (0.049, 2.129)	(<0.001, >1000)	0.28	0.52 (0.19, 1.27)	1/0.94	1.00	Not significant
		Circulating AA	6 (265)	SMD	−0.186 (−0.844, 0.471)	0.579	80.4	0.716 (0.217, 2.361)	(0.013, 40.473)	0.69	0.95 (0.38, 2.43)	3/0.31	<0.01	Not significant
Zhang et al., 2016 (15)	Alzheimer disease	Circulating DHA (a 1% increment of blood DHA concentrations)	3 (1828)	RR	0.785 (0.561, 1.098)	0.157	62.75	—	(0.020, 31.045)	0.16	0.96 (0.88, 1.04)	1/0.16	0.15	Not significant
	Dementia	Circulating DHA (a 1% increment of blood DHA concentrations)	5 (3099)	RR	0.939 (0.864, 1.020)	0.136	57.37	—	(0.744, 1.185)	<0.01	0.99 (0.96, 1.03)	2/0.25	0.02	Not significant
	Mild cognitive impairment	Circulating DHA (a 1% increment of blood DHA concentrations)	2 (2497)	RR	0.846 (0.465, 1.540)	0.585	85.84	—	—	—	1.11 (0.97, 1.26)	1/0.16	0.15	Not significant
Hawkey et al., 2014 (13)[2]	Attention-deficit/hyperactivity disorder	Circulating n–3 PUFAs	9 (586)	Hedges' *g*	−0.409 (−0.563, −0.255)	$<10^{-6}$	0.0	0.492 (0.367, 0.659)	(0.346, 0.700)	0.25	0.59 (0.41, 1.16)	2/1.91	1.00	Weak

(*Continued*)

TABLE 4 (*Continued*)

Study, year (ref)	Mental disorders	Outcome	No. of studies (participants, *n*)	Original effect metrics	Random-effects summary estimate (95% CI)	Random-effects *P*	I^2, %	Converted as equivalent OR (95% CI)	95% Prediction interval	Egger's test *P*	Largest study estimate (95% CI)	Significant studies		Grading
												O/E	*P*	
van der Kemp et al., 2012 (14)	Schizophrenia	Circulating DHA	6 (194)	Cohen's *d*	−0.871 (−1.290, −0.452)	$<10^{-3}$	68.1	0.207 (0.097, 0.441)	(0.019, 2.269)	0.45	0.485 (0.214, 1.103)	4/1.67	0.06	Weak
		Circulating AA	6 (194)	Cohen's *d*	−0.767 (−1.390, −0.144)	0.016	85.7	0.249 (0.081, 0.771)	(0.005, 12.730)	0.34	0.40 (0.17, 0.91)	4/1.96	0.09	Weak
		Circulating LA	4 (113)	Cohen's *d*	−0.042 (−0.327, 0.244)	0.774	0.0	0.927 (0.553, 1.554)	(0.298, 2.883)	0.57	0.88 (0.39, 2.02)	0/0.21	—	Not significant
		Circulating DPA	4 (113)	Cohen's *d*	−0.924 (−1.225, −0.624)	$<10^{-6}$	0.0	0.188 (0.109, 0.323)	(0.057, 0.619)	0.79	0.18 (0.08, 0.43)	3/0.04	0.63	Weak
		Circulating DTA	3 (78)	Cohen's *d*	−0.113 (−0.478, 0.252)	0.544	12.8	0.815 (0.421, 1.577)	(0.005, 129.249)	0.32	0.51 (0.17, 1.06)	0/0.27	—	Not significant

[1] All summary estimates were recalculated based on a random-effects model using the method of DerSimonian and Laird. The 95% prediction interval and Egger's test were not evaluated if available studies were <3. For excess of significance, the *P* value was not evaluated if the observed number of studies was smaller than expected. AA, arachidonic acid; DPA, docosapentaenoic acid; DTA, docosatetraenoic acid; E, expected number of studies with positive finding; LA, linoleic acid; MD, mean difference; O, observed number of studies with positive finding; ref, reference; SMD, standardized mean difference.
[2] The direction of comparison was normalized to mental disorder group versus control group.

mental disorders, which demonstrated the need for future high-quality randomized controlled trials evaluating the effects of unsaturated fatty acid supplementation interventions on different mental disorders.

n–6 and n–3 PUFAs have opposite effects on inflammatory modulation (4). n–6 PUFAs, particularly AA, are important precursors of eicosanoids (including prostaglandins, thromboxanes, and leukotrienes), which regulate the inflammatory process in immune cells as inflammatory mediators (4, 8). However, EPA and DHA act as competitive inhibitors of n–6 PUFAs causing a reduction in the synthesis of proinflammatory mediators (70). On the basis of evidence grading, the mental health–related favorable effect of unsaturated fatty acid supplementation was mainly limited to n–3 PUFAs, EPA, and DHA. Moreover, n–3 and n–6 PUFAs are implicated in gene expression and regulate several genes involved in lipid metabolism and inflammatory signaling through nuclear receptors (including farnesoid X receptors, liver X receptors, NF-κB, peroxisome proliferator activated receptors, retinoid X receptors, and sterol regulatory element binding protein 1c) (71). However, n–3 PUFAs show a greater potency in modifying nuclear receptor gene expression than n–6 PUFAs (71). n–3 PUFAs downregulate inflammatory genes and lipid synthesis and stimulate fatty acid degradation (71).

PUFAs are highly enriched in the brain (8) and make up approximately 35% of the lipids in brain (72). Adequate brain DHA and ARA are essential for normal cellular processes, such as transmembrane potential, neurotransmission, and the function of ion channels (10, 73). Altered brain fatty acid composition, metabolism, and fatty acid–derived signaling systems have been associated with mental disorders (8, 74, 75). Weak evidence suggested a broad range of circulating unsaturated fatty acid shortfalls in mental disorders (including ASD, ADHD, BP, and schizophrenia), which indicated the disturbance of fatty acid metabolism and a potential decrease in the absorption of unsaturated fatty acids (11–14). Therefore, unsaturated fatty acid supplementation and the intake of an unsaturated fatty acid–enriched diet have potential value in reversing fatty acid–related imbalances in the brain and might have favorable effects on mental health conditions (4, 5, 8, 64).

The main limitations of this umbrella review include those of the included systematic reviews and, in turn, the limitations of the original studies. The most frequently reported review shortcomings, detected by AMSTAR 2, were the absence of the list of excluded studies and the justification for exclusion studies, a thorough discussion of between-study heterogeneity, and adequate investigation and discussion of publication bias. According to the umbrella review criteria, publication bias and excess significance bias cannot be excluded for some comparisons. We were also unable to quantify the differences in the dose of unsaturated fatty acids among the included meta-analyses. These limitations decreased the strength of the associations and credibility of the evidence. Based on the analytic approach of an umbrella review, analyzing numerous outcomes could increase the risk

of making a type I error, and Egger's tests might lack the statistical power to detect bias when few studies are included in the meta-analysis.

Additional limitations were related to the umbrella review methodology because this approach is based on the statistical reanalysis of meta-analyses. By definition, umbrella reviews include only systematic reviews that applied a quantitative approach to data presentation, whereas systematic reviews providing qualitative descriptions of the included studies, without applying meta-analytic techniques, are excluded. However, the absence of a meta-analytical approach is typically motivated by the scarcity of sufficient and homogeneous experimental evidence, which therefore does not reach the minimum clinical and methodological requirements needed for meta-analysis. Another limitation is that we did not analyze whether the efficacy of unsaturated fatty acid supplementation interventions was moderated by the composition and dose of unsaturated fatty acids, the length of follow-up, or by other social, dietary, or lifestyle-related variables (76, 77). The analysis of these variables was not feasible due to the nature of an umbrella review. To avoid data overlapping with exaggerated test power of the actual sample, we excluded a large amount of duplicate or updated studies assessing the same association. Different meta-analyses could have differences in selection criteria and analytical approaches, which might introduce bias to the evaluation of evidence, but we only extracted the main results (i.e., the specific association between unsaturated fatty acids and mental disorders); hence, the latest study with the largest number of individual studies typically provides the most accurate estimate of the true effect size. Finally, based on the aim of this review, we did not include studies evaluating the effects of unsaturated fatty acids on the general population—for example, studies on the neurodevelopment of typically developing children (78–80).

In view of the variability in the strength of the associations and credibility of the evidence, action is required to support further research efforts for different mental disorders. Several initiatives have aimed to improve the capacity of mental health research centers to conduct high-quality nutrition studies. In terms of populations, this review suggests a need for further studies involving children and adolescents, especially in children with mood disorders. A focus on mental health along a continuum from mild psychological distress to a severely disabling condition, as suggested by the Lancet Commission on global mental health and sustainable development (81), seems to be an appropriate and feasible approach, although we note a scarcity of evidence for specific diagnostic conditions, such as sleep disorders. In terms of interventions, considering the effective dose of unsaturated fatty acids, future research efforts should be directed to ascertain which combination and dose is more feasible and effective. In terms of outcomes, the assessment of the long-term effectiveness of n–3 PUFA supplementation would be relevant, including functional and quality-of-life measures, because they were seldom considered by the studies included in this umbrella review.

Given the pressing need for evidence-based answers for people with mental health conditions, and in view of the data on the effect of unsaturated fatty acid supplementation on mental disorders, we recommend that more high-quality studies be conducted to critically evaluate the potential of unsaturated fatty acid supplementation interventions in the prevention and control of mental disorders.

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Data Availability

All data included in this umbrella review were extracted from publicly available systematic reviews.

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