Association between dietary patterns and depression

Umbrella Review

Association between dietary patterns and depression: an umbrella review of meta-analyses of observational studies and intervention trials

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Context: *Depression is the most common causes of disease burden worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet. *2018;392:1789–1858).* ***Objective:*** *An umbrella review has been performed to assess the strength and validity of the available observational and trial evidence for the association between a variety of dietary patterns and depression.* ***Data Sources:*** *MEDLINE/PubMed, Scopus, Web of Science, EMBASE, PsycINFO, and Cochrane Database were searched.* ***Data Extraction:*** *The Joanna Briggs Institute Umbrella Review Methodology was used.* ***Data Analysis:*** *The review included 19 articles, covering a relatively wide range of dietary patterns: healthy dietary patterns (n = 8), Mediterranean diet (MedDiet) (n = 6), Dietary Inflammatory Index (DII) (n = 5), Western diet (n = 4), Dietary Approaches to Stop Hypertension (DASH) (n = 2), vegetarian diets (n = 4), and other dietary interventions (n = 2). The methodological quality of the included meta-analyses was generally low or critically low. The strength of the evidence was generally weak, although convincing or suggestive evidence was found for an inverse relationship between MedDiet/DII and depression. Higher adherence to the MedDiet and lower DII score were significantly associated with lower risk of depression.* ***Conclusion:*** *Considering the generally high*

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heterogeneity and low quality of the available evidence, further studies adopting more coherent and uniform methodologies are needed.
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INTRODUCTION

Depression is estimated to affect more than 300 million people worldwide and, according to the World Health Organization (WHO), is one of the leading causes of disability.[1] On average, it more frequently affects women than men, and it first appears during the late teens to mid-20s.[2] Depression is a psychiatric disorder that goes beyond the normal human experiences of sadness, including a broad range of symptoms such as feeling worthless, losing interest in most or all activities, having thoughts of suicide, experiencing a significant reduction or increase in appetite or sleep, and having difficulty concentrating.[3] Depressive symptoms are often distressing to the individual and can lead to an inability to function normally, such as at work or in maintaining relationships.[4]

Although scientists agree in considering that depression is the result of a complex interaction of social, psychological, and biological factors, due to the clinical and etiological heterogeneity it is difficult to clarify its pathophysiology.[5] An increasing body of scientific evidence suggests a relationship between dietary patterns and depression,[6–8] and many meta-analyses[9–11] have found that adherence to healthy diets is associated with lower risk of depression and less severe depressive symptoms. These findings could be important for the prevention and treatment of depression, but the quality, the precision, and the strength of the evidence need improvement.[12] In fact, meta-analyses are powerful tools, but they have a possible bias associated with variation in quality and empirical validation. It has been reported that more than half of all published meta-analyses are flawed or useless, and that the production of poor quality and redundant meta-analyses may contribute to the spread of misleading dietary concepts.[13,14]

Assessment of the quality and credibility of the existing evidence for a relationship between dietary patterns and depression may have implications for both clinical practice and public health. An umbrella review is a review of systematic reviews and meta-analyses that provides a comprehensive and systematic assessment of the available scientific literature for a specific research topic and offers insight into the strength of the evidence and the extent of potential bias.[15] Recently, Xu et al[16] conducted an umbrella review of meta-analyses of prospective cohort studies that investigated the association between various dietary factors (foods, nutrients, and diets) and depression, finding high heterogeneity. The aim of the present umbrella review was to focus only on dietary patterns (as a whole), including all available evidence from existing meta-analyses of both observational (prospective cohort and cross-sectional studies) and intervention studies; a set of predefined criteria was applied to assessment of the strength and validity of the evidence, thus enabling development of an overview of the validity of the potential associations studied and assessing possible hints of bias.

METHODS

The current umbrella review was registered in the PROSPERO International Prospective Register of Systematic Reviews database (ID number: CRD42020223376, at www.crd.york.ac.uk/PROSPERO). This umbrella review of meta-analyses of observational studies and randomized clinical trials was conducted according to the methods recommended by the Cochrane Collaboration[17] (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA guidelines),[18] and the process and results were documented in accordance with the methodology developed by The Joanna Briggs Institute Umbrella Review Methodology.[15] It was designed to answer the following question: "What is the strength and validity of the existing evidence assessing the association between dietary patterns and depression among adults (from both observational research and RCTs)?". This specific research question was developed according to the PICOS (Participants, Interventions, Control, Outcomes, Study Design) principle, and the details are reported in Table 1. Studies that did not report quantitative effect size estimates (effect size and 95% confidence intervals [CIs]) were excluded.

Search strategy

A systematic electronic literature search was independently carried out by 2 authors (V.G. and M.D.) using the following databases: MEDLINE/PubMed, Scopus, Web of Science, EMBASE, PsycINFO, and the Cochrane Database of Systematic Reviews (from database inception to February 2022). The references of the identified articles were manually checked to find any

Table 1 **PICOS criteria for inclusion and exclusion of studies**

Parameter	Inclusion criterion	Exclusion criterion
Population	Adults (>18 y) without comorbidities	Children/adolescents and pregnant women (post-partum depression)
Intervention	All diets or dietary patterns/dietary interventions	Study assessing the effect of single food components
Comparison	No intervention or any diet or dietary patterns/dietary interventions	
Outcome	Depressive symptoms, depression, depressed mood, consumption of anti-depressant medications, depressive feeling	Other outcomes or data combined for depression and other outcomes (for instance depression and anxiety combined)
Study design	Meta-analyses of original studies (both randomized controlled trials and observational studies)	Meta-analyses not published as peer-reviewed meta-analyses in international scientific journals (book, book chapter, thesis). No full-text papers (abstract, conference paper, letter, commentary, note), systematic review without quantitative analysis, meta-analysis not reporting comprehensive data (eg, effect size and 95% confidence intervals)

additional eligible studies. Search terms (both MeSH and text), including diet (and its variants), depression (and its variants), and systematic review/meta-analysis (and their variants) were combined using Boolean operators. A more exhaustive/comprehensive search strategy list, for each database, is provided in Table S1 in the Supporting Information online. Only English articles published in peer-reviewed journals were included. Adherence to any dietary patterns/dietary interventions were eligible. Since the focus of this review was to assess the available evidence for an association between depression and whole-of-diet, rather than individual foods or nutrients, studies focusing only on a single food component (eg, only fish or fruit and vegetables) were not included. Regarding the outcome, all definitions of depression and all methods used to diagnose depression were considered eligible (depressive symptoms, incident/prevalent depression, use of anti-depressant medications, and depressive feeling). Relevant articles were obtained in full and assessed against the inclusion/exclusion criteria. If an article presented meta-analyses for more than 1 dietary pattern/dietary intervention, each of these was included separately.

Data extraction and quality assessment

A 2-step process was adopted to identify relevant articles. First, 2 authors (V.G. and M.D.) independently screened the titles and abstracts of the retrieved studies in order to identify potentially eligible studies. Second, full texts of only the potentially eligible studies were retrieved and independently assessed for eligibility by 3 review team members (V.G., D.N., and M.D.). Any disagreements between them over the eligibility of particular studies were resolved through discussion with a senior reviewer (A.O.). Data were independently extracted from each identified meta-analysis by 2 authors (V.G. and D.N.), using a standard data extraction spreadsheet to systematically record qualitative and quantitative data extracted from the included meta-analyses. The spreadsheet was elaborated in Microsoft Excel® for Windows (Redmond, WA, USA, 2007) and was pre-piloted, on 5 randomly selected papers, to ensure methodological concordance among the authors. The following data were extracted: first author and year of publication, number and type of included studies, comparison, number of subjects assigned to each group, study population, outcomes of interest, maximally adjusted effect size measurements (that is, relative risk/hazard ratio, odds ratio, mean difference) along with the corresponding 95% CIs, and the quality of the studies included in each meta-analysis. Data were grouped according to the type of dietary intervention or dietary patterns studied in observational studies. Any discordances between the 3 authors were resolved through discussion; if disagreement persisted, a senior author was consulted (A.O.). Two authors (V.G. and D.N.) independently evaluated the methodological quality of the included meta-analyses. Disagreements were resolved by discussion with a third investigator (M.D.). The "A MeaSurement Tool to Assess systematic Reviews 2" (AMSTAR-2) questionnaire was used to identify the quality of the meta-analyses. The AMSTAR-2 tool has 16 items in total, with an overall rating based on weaknesses in critical domains. Critical domains were as follows: definition of the PICO components (item 1), adequacy of the literature search (items 4 and 5), risk of bias from individual studies being included in the review (item 9), appropriateness of meta-analytical methods (item 11), consideration of risk of bias when presenting the results of the review (item 12), assessment of presence of publication bias (item 15).[19] The overall confidence rate ranged between high (if no or only 1 noncritical weakness), moderate (if more than 1 noncritical weakness), low (if 1

critical weakness), and critically low (if more than 1 critical weakness).[19]

Strengths of evidence assessment and data analysis

All statistical analyses were conducted using Review Manager (RevMan, version 5.3 for Macintosh; The Cochrane Collaboration, Copenhagen, Denmark) and the statistical package PASW 20.0 for Macintosh (SPSS Inc., Chicago, IL). For each included meta-analysis, the following calculations were performed. Pooled effect sizes and their 95% CIs were estimated using both fixed-effects and random-effects models. For the summary random-effects, the 95% prediction interval (PIs) were estimated, which further accounted for the degree of between-study heterogeneity and gave a range for which there was 95% confidence that the effect in a new study examining the same association lay within. Statistical heterogeneity between studies was evaluated using the I^2 statistic[20]; where I^2 exceeded 50% or 75%, the heterogeneity was considered substantial or considerable, respectively.[21] To detect any evidence of small-study effects, the Egger's regression asymmetry test was performed, and the standard error (SE) of the effect size (under random effects) for the largest study of each meta-analysis was calculated.[22] The largest study was defined on the basis of the smallest SE. If the *P*-value for Egger's test was <.10 and the largest study had a smaller effect size than the summary effect size, both criteria for existence of small-study effects were fulfilled.[23] As previously proposed,[24–26] in each meta-analysis observed, associations were categorized as convincing or not, by using the following criteria: significance at $P \leq .05$ and $P \leq .001$; inclusion of >500 or >1000 cases for binary outcomes (>2500 or >5000 total participants if the metric was continuous); absence of considerable heterogeneity ($I^2 < 75\%$); 95% PI excluding the null value and absence of small-study effects. Five categories were identified: (i) *Convincing evidence*: significance threshold reached at $P \leq .001$ for both random- and fixed-effects calculation; >1000 cases (or >5000 total participants if the metric was continuous); no large heterogeneity between studies ($I^2 < 50\%$); 95% PI excluding the null value; no evidence of small-study effects. (ii) *Highly suggestive evidence*: significance threshold reached at $P \leq .001$ for both random- and fixed-effects calculation; >1000 cases (or >5000 total participants if the metric was continuous); not considerable heterogeneity between studies ($I^2 = 50–75\%$). (iii) *Suggestive evidence*: significance threshold reached at $P \leq .001$ for random-effect calculation; 500–1000 cases (or 2500–5000 total participants if the metric was continuous). (iv) *Weak evidence*: significance threshold reached at $P \leq .05$ for random-effects calculation. (v) *No-evidence*: significance threshold not reached ($P > .05$).

RESULTS

Search results

Figure 1 shows the flow diagram, reporting the selection process. The electronic searches identified 1799 articles in total, of which 313 were identified in the PubMed/Medline, 376 in Scopus, 203 in Web of Science, 702 in EMBASE, 21 in PsychINFO, and 184 in the Cochrane Collaboration database. A total of 921 articles were removed because of duplicates, leaving 878 articles. Of these publications, 848 were excluded on the basis of the title and abstract. Out of 30 potentially eligible articles, 11 were removed after the full-text assessment.[27–37] The reasons for exclusion are shown in Table S2 in the Supporting Information online.[27–37] At the end of the screening process, 19 articles met the inclusion criteria and were included in the analysis.[9–11,38–53]

Characteristics and methodological quality of the included meta-analyses

Table 2 [9–11,38–53] reports the characteristics and methodological quality of the included meta-analyses. Out of the 19 included meta-analyses, 16 were meta-analysis of observational studies, 2 were meta-analysis of RCTs, and 1 meta-analysis included both observational studies and RCTs. The following dietary patterns were analyzed: healthy dietary patterns (n = 8), Mediterranean diet (MedDiet) (n = 6), Dietary Approaches to Stop Hypertension (DASH) (n = 2), vegetarian (n = 4), Dietary Inflammatory Index (DII) (n = 5); Western diet (n = 4), different types of dietary interventions, including very low-calorie diet (VLCD, ie, <800 kcal/d), reducing fat (below 30%) and diets inducing weight loss. The total number of diets covered was higher than the total number of included articles because some of them assessed the association between several types of diets and depression. One article performed a harmonized meta-analysis.[46] In that case, the authors performed a consortium study (MooDFOOD project) including 5 different cohort studies (the Invecchiare in Chianti study [InCHIANTI]); the Longitudinal Aging Study Amsterdam (LASA); Netherlands Study of Depression and Anxiety (NESDA); Healthy Life in an Urban Setting (HELIUS); the Whitehall II study; and an external cohort, the Australian Longitudinal Study on Women's Health (ALSWH)]. Starting from the respective food frequency questionnaires adopted in each cohort, authors estimated adherence to Mediterranean

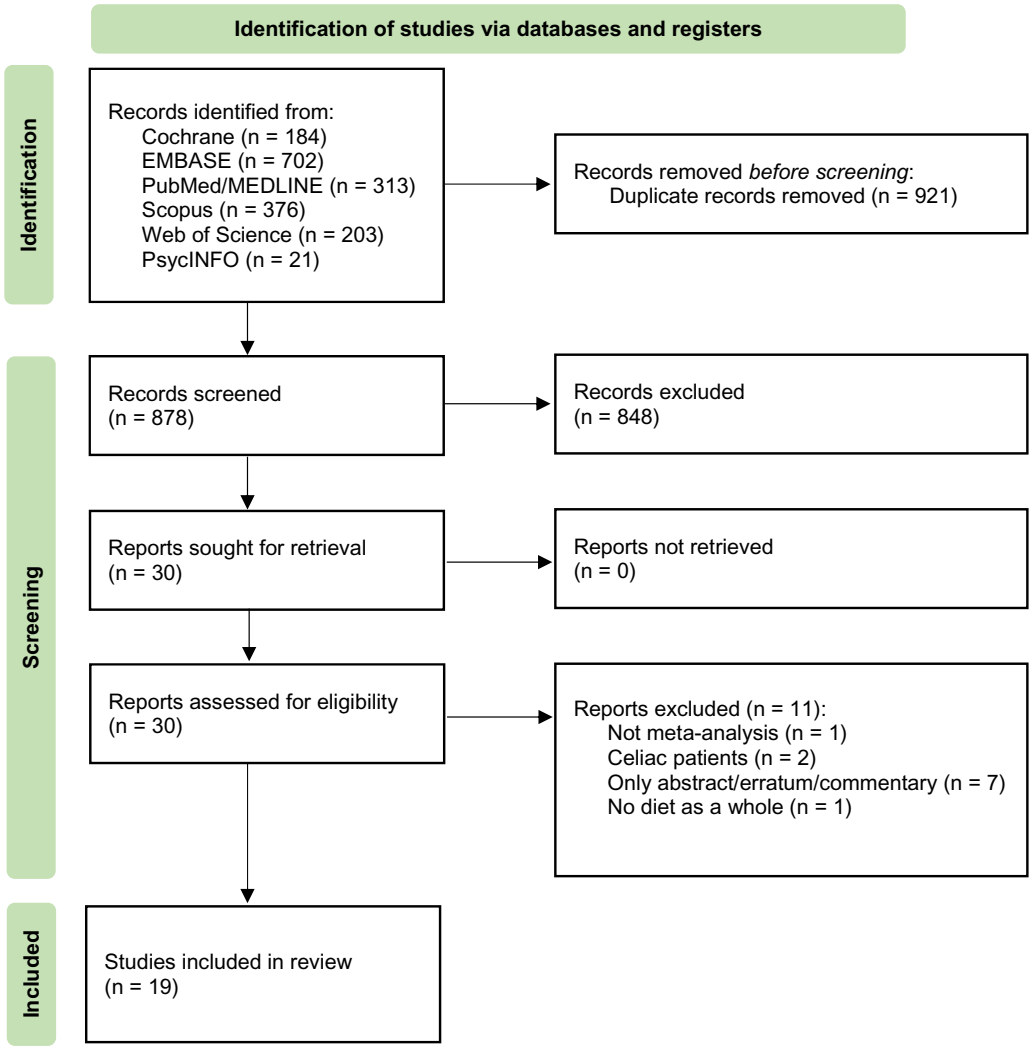

Figure 1 **PRISMA flow diagram of the literature selection process.**

diet using a unique scale (Mediterranean Diet Score). A similar approach was used in this meta-analysis also for the DASH and Alternative Healthy Eating Index (AHEI-2010).

A great variability was observed in the included studies in the definitions of specific dietary patterns or dietary interventions. For instance, both healthy dietary patterns and Western diet were defined based on an a priori or a posteriori factor, on cluster or principal components analysis. Similarly, adherence to the MedDiet was quantified by means of a variety of MedDiet scales; and of the 4 meta-analyses of vegetarian diets, 1 considered vegans and vegetarians diets together,[38] while the others differentiated between the 2.[41,43,47] On the other hand, very low or no heterogeneity was found when DASH or DII were considered, since in both cases a univocal diet scale is in place. Regarding depression, it was generally defined as diagnosis of depressive disorders or depressive symptoms, without any restriction on the methods used for the assessment. In this respect, a great heterogeneity was found for diagnostic methods (validated tools, clinical interview, self-reported diagnosis, consultation of medical records, or antidepressant drug use). Regarding dietary patterns, in all except 4 meta-analyses,[38,40,42,43] the authors compared the highest vs lowest adherence (or vice versa in 2 studies[50,51]). In these 4 meta-analyses, 3 compared different dietary patterns (eg, pre- vs post-dietary intervention, no intervention vs intervention, and vegetarian vs omnivorous), whereas another compared depressed vs no depressed subjects. Table S3 in the Supporting Information online[9–11,38–53] further details the characteristics of the included meta-analyses, reporting pooled effect sizes, prediction intervals, heterogeneity, and *P*-values.

The largest population (>100 000 subjects) was observed in observational studies, particularly in meta-analyses of the vegetarian diet,[38,41] healthy dietary patterns,[11] and DII.[50] In contrast, the smallest population

Table 2. **Characteristics and quantitative synthesis of meta-analyses reporting associations between dietary patterns and depression**

Reference	n of studies/ study design	Comparison	Diet assessment	Outcome	Outcome measurement	Study population (age ≥ 18 y)	Quality/risk of bias assessment	n events	N total	AMSTAR-2	Strength of evidence
Healthy dietary patterns											
Lai et al, 2014[9]	13/9 CS, 4 C	High vs low adherence[a]	Validated FFQ and 24h-DR	Depression	CES-D, HADS, self-reported clinical diagnosis or ADs, ICD-10, Structured Clinical Interview for DSM 4th edition	M/F	ADA	2833[e]	83 226	Moderate	Suggestive
Lassale et al, 2019[10]	6/3 CS, 3 C	High vs low adherence (HEI/aHEI)	24h-DR, DQES, FFQ	Depressive outcomes	BDI, CES-D, DASS, HADS, K10, PHQ-9, self-reported	M/F	NOS	4643	51 716	Moderate	Weak
Li et al, 2017[44]	21/6 CS, 11 C, 4 CC	High vs low adherence	FFQ	Depression	NA	M/F	NOS	9100	62 138	Critically low	Suggestive
Matison et al, 2021[45]	7 C	High vs low adherence	24h-DR, DQES, FFQ	Depression	GDS, CES-D	M/F	NOS	7980[c]	75 963	High	No evidence
Molendijk et al, 2018[11 i]	12 C	High vs low adherence	24h-DR, DQES, FFQ	Depression/ depressive symptoms	ADs, CES–D, EPDS, GDS, K10, self-diagnosis	M/F	Criteria set by authors	NA	105 494	Low	Weak
Nicolaou et al, 2019[46]	6 CS	High vs low adherence (aHEI)	FFQ	Depressive symptoms	CES-D, IDS-Self Report, PHQ-9	M/F	None	4932	23 107	Critically low	Weak
Nicolaou et al, 2019[46]	3 C	High vs low adherence (aHEI)	FFQ	Depressive symptoms	CES-D, IDS-Self Report, PHQ-9	M/F	None	2966	13 295	Critically low	No evidence
Wu et al, 2020[52]	18/11 CS, 6 C, 1 RCT	High vs low adherence	FFQ, 24h-DR, diet-history questionnaire	Depression	NA	Elderly M/F (≥65 y)	JBI CAC	NA	45 972	Critically low	Weak
Wu et al, 2020[53]	8/6 CS, 2 C	High vs low adherence (aHEI)	FFQ, 24h-DR	Depression	CES-D, HADS, BDI, Self-reported physician diagnosis + ADs	M/F	ADA	NA	NA	Low	Weak
Mediterranean Diet (MedDiet)											
Lassale et al, 2019[10]	6/2 CS, 4 C	High vs low adherence	MDS, rMED, aMED	Depressive outcomes	BDI, CES-D, DASS, HADS, K10, PHQ-9, self-reported	M/F	NOS	1954[d]	41 289	Moderate	Highly suggestive
Matison et al, 2021[45]	3 C	High vs low adherence	24h-DR, FFQ	Depression	GDS, CES-D	M/F	NOS	1219	10 343	High	No evidence
Molendijk et al, 2018[11 i]	5 C	High vs low adherence	24h-DR, DQES, FFQ	Depression/ depressive symptoms	ADs, CES–D, EPDS, GDS, K10, self-diagnosis	M/F	Criteria set by authors	NA	38 366	Low	Weak
Nicolaou et al, 2019[46]	6 CS	High vs low adherence	FFQ	Depressive symptoms	CES-D, IDS-Self Report, PHQ-9	M/F	None	4932	23 107	Critically low	Convincing
Nicolaou et al, 2019[46]	3 C	High vs low adherence	FFQ	Depressive symptoms	CES-D, IDS-Self Report, PHQ-9	M/F	None	2966	13 295	Critically low	Highly suggestive
Psaltopoulou et al, 2013[48]	9/8 C, 1 CC	High vs low adherence	A variety of scores converted to 0–9 range of the MDS	Depression	ZDRS, interview, HADS, CES-D, GDS, diagnosis + ADs	M/F	NOS	2203	17 064	Critically low	Weak

(continued)

Table 2. **Continued**

Reference	n of studies/ study design	Comparison	Diet assessment	Outcome	Outcome measurement	Study population (age ≥ 18 y)	Quality/risk of bias assessment	n events	N total	AMSTAR-2	Strength of evidence
Shafiei et al, 2019[49]	4 C	High vs low adherence	9-component MedDiet pattern, 11-component MedDiet pattern, and 14-item MedDiet questionnaire	Depression	CES-D, GDS, HADS, ZDRS, diagnosis + ADs	M/F	NOS	903[c]	31 746	Low	No evidence
Shafiei et al, 2019[49]	9 CS	High vs low adherence	9-component MedDiet pattern, 11-component MedDiet pattern, and 14-item MedDiet questionnaire	Depression	CES-D, GDS, HADS, ZDRS, diagnosis + ADs	M/F	NOS	NA	9409	Low	Weak
DASH											
Lassale et al, 2019[10]	4/3 CS, 1 C	High vs low adherence	24h-DR, DQES, FFQ	Depressive outcomes	BDI, CES-D, DASS, HADS, K10, PHQ-9, self-reported	M/F	NOS	587[c]	20 472	Moderate	No evidence
Nicolaou et al, 2019[46]	6 CS	High vs low adherence	FFQ	Depressive symptoms	CES-D, IDS-self report, PHQ-9	M/F	None	4932	23 107	Critically low	No evidence
Nicolaou et al, 2019[46]	3 C	High vs low adherence	FFQ	Depressive symptoms	CES-D, IDS-Self Report, PHQ-9	M/F	None	2966	13 295	Critically low	Weak
Vegetarian diets											
Askari et al, 2020[38]	10/6 CS, 4 C	Depression vs no depression	FFQ, customized questionnaires	Depression	M-CIDI, HADS, CES-D, EPDA, GDS, DASS	M/F vegetarians	NOS	NA	122 391	Low	No evidence
Fazelian et al, 2022[41]	6 CS	Semi-vegetarian vs omnivore	24h-DR, FFQ, brief questions about regular diet	Depression	GDS, CES-D, DSM, HADS, EPDS, DASS, CIDI	M/F	NOS	NA	106 004	Moderate	Weak
Fazelian et al, 2022[41]	2 CS	Vegan vs omnivore	FFQ about regular diet	Depression	DASS, CES-D	M/F	NOS	NA	91 272	Moderate	No evidence
Iguacel et al, 2020[43]	2 CS	Vegetarian/ vegan vs omnivores	NA	Depression	DASS, SF-36, CES-D	M/F	NHBLI	1168	8486	Moderate	Weak
Iguacel et al, 2020[43]	5/3 CS, 1 C, 1 RCT	Vegan vs omnivores	NA	Depression	DASS, SF-36, CES-D	M/F	NHBLI	NA	3127	Moderate	Weak
Iguacel et al, 2020[43]	7/5 CS, 1 C, 1 RCT	Vegetarian vs omnivores	NA	Depression	DASS, SF-36, CES-D	M/F	NHBLI	NA	3607	Moderate	No evidence
Ocklenburg and Borawski, 2021[47]	NA	Vegetarian vs omnivores	NA	Depression/ Depressive symptoms	DASS, SF-36, CES-D, PHQ-9	M/F	NOS	8057	41 832	Critically low	Weak
Dietary Inflammatory Index (DII)											
Chen et al, 2022[39]	8 CS	High vs low DII	FFQ, 24h-DR	Depression/ depressive symptoms	CES-D, DASS, PHQ-9, HADS, BDI	M/F	NOS	6432[b]	52 360	Low	Highly suggestive

(continued)

Table 2. **Continued**

Reference	n of studies/ study design	Comparison	Diet assessment	Outcome	Outcome measurement	Study population (age ≥ 18 y)	Quality/risk of bias assessment	n events	N total	AMSTAR-2	Strength of evidence
Chen et al, 2022[39]	5 C	High vs low DII	FFQ, 24h-DR	Depression/ depressive symptoms	CES-D, DASS, PHQ-9, HADS, BDI	M/F	NOS	5854	55 392	Low	Highly suggestive
Lassale et al, 2019[10]	9/5 C, 4 CS	Low vs high DII	24h-DR, DQES, FFQ	Depressive outcomes	BDI, CES-D, DASS, HADS, K10, PHQ-9, self-reported	M/F	NOS	6152	65 666	Moderate	Highly suggestive
Matison et al, 2021[45]	3 C	High vs low DII	24h-DR, FFQ	Depression	GDS, CES-D, self-reported	M/F	NOS	1244[b]	7826	High	Weak
Tolkien et al, 2019[50]	11/7 C, 4 CS	High vs low DII[f]	FFQ	Depression/ depressive symptoms	CES-D, PHQ-9, HADS, DASS, diagnosis + ADs, self-reported + ADs	M/F	NOS	NA	101 950	Low	Weak
Wang et al, 2019[51]	6/4 C, 2 CS	High vs low DII	FFQ, 24h-DR	Depression	CES-D, PHQ-9, self-reported diagnosis	M/F	STROBE	4864[b]	49 584	Critically low	Convincing
Western diet											
Lai et al, 2014[9]	4/2 CS, 2 C	High vs low adherence	Validated FFQ and 24h-DR	Depression	CES-D, HADS, self-reported clinical diagnosis or ADs, ICD-10, Structured Clinical Interview for DSM 4th edition	M/F	ADA	1000[b]	60 868	Moderate	No evidence
Li et al, 2017[44]	17/5 CS, 9 C, 3 CC	High vs low adherence	FFQ	Depression	NA	M/F	NOS	7331	40 975	Critically low	Weak
Matison et al, 2021[45]	7 C	High vs low adherence	24h-DR, FFQ	Depression	GDS, CES-D, self-reported	M/F	NOS	4956[c]	79 917	High	Weak
Molendijk et al, 2018[11 i]	10 C	High vs low adherence	24h-DR, DQES, FFQ	Depression/ depressive symptoms	ADs, CES–D, EPDS, GDS, K10, self-diagnosis	M/F	Criteria set by authors	NA	84 870	Low	No evidence
Other diets											
Ein et al, 2019[40]	9 RCT	Pre vs post VLCD intervention	6 studies performed a long intervention (range 8–16 wk), 3 a short intervention (range 6 d–8 wk)	Depressive symptoms	BDI, POMS, SM-D, HADS	M/F	Criteria set by authors	345	345	Critically low	Weak

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Table 2. **Continued**

Reference	n of studies/ study design	Comparison	Diet assessment	Outcome	Outcome measurement	Study population (age $\geq$ 18 y)	Quality/risk of bias assessment	n events	N total	AMSTAR-2	Strength of evidence
Firth et al, 2019[42]	16 RCT	No dietary intervention vs dietary intervention	Diets aimed to improve nutrition were based on MedDiet recommendations. Diets aimed to reduce % of fat intake focused on reducing fat consumption. Diets aimed to induce weight loss were based on caloric restrictions. Interventions ranged between 10 d and 3 y.	Depressive symptoms	SF-36, CES-D, HADS, GDS, BSI, BDI, POMS	M/F	ADA	18 746	27 080	Moderate	Weak

[a] This meta-analysis included studies assessing adherence to a healthy diet defined a posteriori, and adherence to the MedDiet measured using different scores.

[b] 1 included study did not report n of events.

[c] 2 included studies did not report n of events.

[d] 3 included studies did not report n of events.

[e] 4 included studies did not report n of events.

[f] 2 included studies assessed inflammation using the blood level of interleukins.

[g] The meta-analysis did not provide adequate data to estimate the summary effect size; the random-effects summary effect size as presented by the authors of the original meta-analysis were reported.

Abbreviations: ADs, antidepressant drugs; ADA, American Dietetic Association quality assessment tool; aHEI, alternative healthy eating index; aMED, alternate Mediterranean Diet scale; AMSTAR-2, A MeaSurement Tool to Assess systematic Reviews 2; BDI, Beck Depression Inventory; BSI, Brief Symptoms Inventory; C, cohort; CC, case–control; CES-D, Center for Epidemiologic Studies Depression Scale; CIDI, composite international diagnostic interview; CS, cross-sectional; DASS, Depression Anxiety and Stress Scale; DII, dietary inflammatory index; DQES, dietary questionnaire for epidemiological studies; DSM, Diagnostic and Statistical Manual of Mental Disorders; EPDS, Edinburgh Postpartum Depression Scale; FFQ, Food Frequency Questionnaire; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HEI, healthy eating index; ICD, Composite International Diagnostic; IDS, Inventory of Depressive Symptomatology; K10, Kessler Psychological Distress Scale; M-CIDI, Munich Composite International Diagnostic Interview; MDS, Mediterranean Diet score; JBI CAC, Joanna Briggs Institute Critical Appraisal Checklist; NA, not available; NOS, Newcastle–Ottawa Scale; NHBLI, National Heart, Lung, and Blood Institute quality assessment tool; PCA, principal component analysis; PHQ-9, Patient Health Questionnaire 9-item depression module; POMS, profile of mood – Depression Scale; RCT, randomized controlled trial; rMED, relative Mediterranean Diet scale; SF-36, Short-Form 36 Health survey; SM-D, subject mood – depression; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology; VLCD, very-low-calorie diet; ZDRS, Zung self-rating depression scale; 24h-DR, 24-hour dietary recall

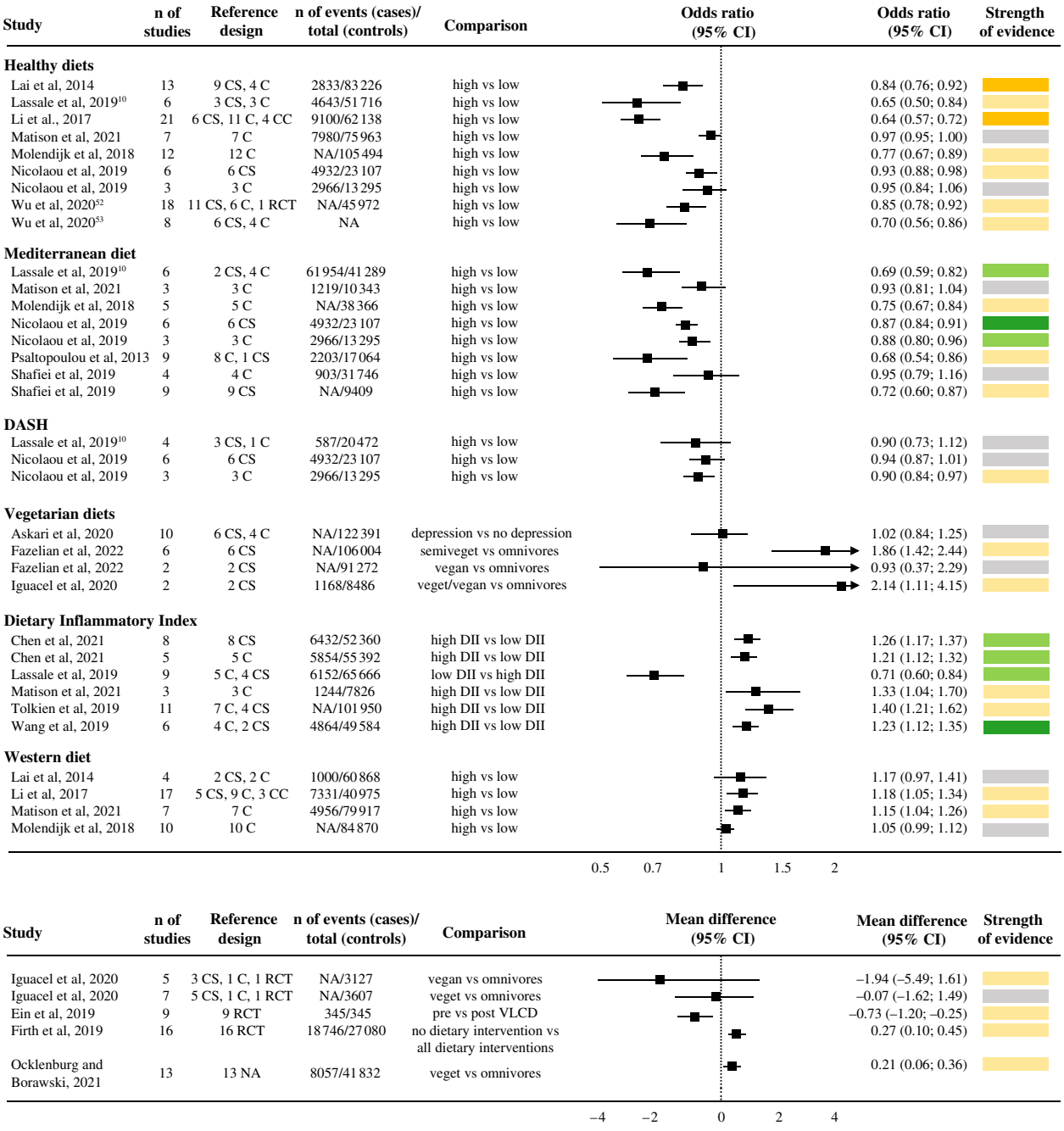

Figure 2 **Summary and strength of evidence of all meta-analyses reporting association betweendietary patterns and depression in adults.** Dark green = convincing evidence; light green = highly suggestive evidence; orange = suggestive evidence; yellow = weak evidence; gray = no evidence. *Abbreviations:* C, cohort; CC, case–control; CS, cross-sectional; DII, Dietary Inflammatory Index; NA, not available; RCT, randomized controlled trial; veget, vegetarian; VLCD, very-low calorie diet

observed in a very-low-calorie diet intervention meta-analysis (n = 345 subjects).[40] All but 2[11,15] of the meta-analyses assessed the quality of the included original studies with a validated scale. In the harmonized meta-analysis of Nicolaou et al,[46] a quality score was not used, since the data were obtained from a consortium project and not from a systematic review. However, 17 out of 19 studies used validated tools, and 9 out of 19 of them did not account for risk of bias when interpreting/discussing the results of the meta-analysis (see Table S4 in the Supporting Information online[9–11,38–53]).

The methodological quality of the included meta-analyses, determined by the AMSTAR-2 questionnaire, was high-to-moderate in 6 articles, low in 6, and critically low in 7 articles (see Table 2). For each included meta-analysis, the complete AMSTAR-2 evaluation is

reported in detail in Table S4 in the Supporting Information online.[9–11,38–53]

Strength of evidence

Figure 2, [9–11,38–53] shows the strength of evidence for each meta-analysis, estimated on the basis of the following criteria: level of significance for both random- and fixed-effect calculations, sample size, heterogeneity, 95% PI, and the presence of small study effects. Detailed information on the assessment of the strength of the evidence is reported in Tables S5 and S6 in the Supporting Information online.[9–11,38–53]

Among all the dietary patterns evaluated, a higher adherence to the MedDiet and lower DII (indicating a lower adherence to an inflammatory diet) were associated with a lower risk of depression with the highest level of evidence (see Figure 2 [9–11,38–53]). Looking at the MedDiet, 1 meta-analysis, which only included cross-sectional data, found convincing evidence[46] (random effect size: .87 [95% CI; .84; .91)], while 2[10,46] found highly suggestive evidence. The first 1 only included prospective data (.88 [95% CI; .80; .96)], whereas the second pooled both cross-sectional and prospective data (0.69 [95% CI; 0.59; 0.82]). As for the DII, it was found that a pro-inflammatory diet as estimated by a higher DII score was associated with an increased risk of depression in a meta-analysis that included both cross-sectional and cohort studies; furthermore, highly suggestive evidence was found that higher DII score is associated with an increased risk of prevalent (1.26 [95% CI; 1.17; 1.37]) and incident depression (1.21 [95% CI; 1.12; 1.32]) in a meta-analysis that estimated the risk stratified by study design.[39] Moreover, highly suggestive evidence was also found that a lower DII score is associated with lower incidence of depression (.71 [95% CI; .60; .84]).[10]

The relationship between healthy dietary patterns and risk of depression was assessed in 8 articles, for a total of 9 unique meta-analyses (1 article reported separately the effect size for cross-sectional and prospective cohort studies). Of these, 2[9,44] reported suggestive evidence for an association between healthy dietary patterns and depression (.84 [95% CI; .76; .92] and .64 [95% CI; .57; .72], respectively), while the other 7 reported weak or no evidence. Regarding DASH, vegetarian and Western diets, the strength of evidence was graded as weak. In addition, in the meta-analysis on the vegetarian diet,[43] both observational data and RCTs were included in the pooled analysis, and this may have biased the results. Weak evidence was also found for the 2 meta-analyses of RCTs on VLCD,[40] and all dietary interventions vs no intervention.[42]

DISCUSSION

The current umbrella review provides an overview and assesses the quality and strength of the available meta-analytic evidence on the association between dietary patterns and risk of depression. The overall analysis comprised 19 meta-analyses of both observational studies and RCTs. Approximately 70% (13 out 19) of the included meta-analyses had low methodological quality, and therefore the strength of evidence in these studies, assessed using evidence classification criteria, was weak. Among all the dietary patterns/dietary interventions analyzed, the largest number of meta-analyses was found for healthy dietary patterns (as a whole), followed by MedDiet. The most consistent evidence was reported for MedDiet and DII, with convincing evidence that a MedDiet or a diet with a low pro-inflammatory score is associated with a reduced risk of depression. Regarding healthy dietary patterns, highly suggestive evidence was also found, but these results should be interpreted with caution, since a high heterogeneity was detected, both in the definition of "healthy", and in the dietary patterns included in each meta-analysis. Finally, weak or no evidence was reported for the DASH, vegetarian, and Western diets, as well as for the meta-analyses of RCTs on VLCD and other dietary interventions.

The MedDiet is a dietary pattern mainly based on limited intake of red and processed meat and high consumption of fruit and vegetables, legumes, fish, whole grains, extra virgin olive oil, and nuts,[54] whereas the DII is a validated measure of the inflammatory potential of the overall diet.[55] The protective effects of higher adherence to the MedDiet and a low DII score for risk of depression may be explained by their anti-inflammatory effects; indeed, previous evidence suggests a proinflammatory status in subjects with depression.[56,57] Their potential anti-inflammatory effect can be due to the high content of antioxidants, such as B-carotene and polyphenols, contained in fruit and vegetables, and olive oil. In particular, a high content of polyphenols seem to have direct neuroprotective effects.[58] Fruit and vegetables are also rich in folate, which is involved in the synthesis of some neurotransmitters, such as dopamine and serotonin, which are both associated with mood regulation.[59] Actually, a deficiency of folates may be associated with an increased level of homocysteine, which in turn is associated with lower concentration of S-adenosylmethionine, the universal methyl donor involved in the synthesis of several neurotransmitters, including dopamine and serotonin.[59] Moreover, fruit and vegetables are high in fibre, which plays an important role in the well-being of the gut microbiota[60] and the interconnection between gut and brain.[57,61] It seems that an alteration of this microbiota

(dysbiosis) increases the release of lipopolysaccharides from bacteria, which in turn activate an anti-inflammatory reaction.[62] In this context, a growing number of studies suggests a beneficial association between probiotics supplementation and the treatment of depression among depressed patients.[63,64] The anti-inflammatory effect might also be due to the long-chain omega-3 polyunsaturated fatty acids of fish and nuts, which might play a role in reducing the level of inflammation and improving the neurotransmission, through improved fluidity of the cellular membranes.[65] Preliminary evidence has suggested that depressed subjects supplemented with omega-3 polyunsaturated fatty acids potentially showed a reduction in plasma noradrenaline and cortisol stimulated by mental stress.[66] On the other hand, the pro-inflammatory properties of foods included in the Western diet (eg, red and processed meat, refined grains, sweets, and ultra-processed foods) may explain the detrimental effect of this dietary pattern.[57,67–70] However, even if most of the available evidence explored the association between single nutrients or food groups and depression,[71–75] in real life, people consume meals composed of a combination of many foods and nutrients that interact with one another. Thus, even though discussing potential beneficial or detrimental effects of individual food components is useful for better understanding of the biological mechanisms, it is also important to consider that there is likely no 1 food/nutrient that is responsible for the final effect. Instead, the dietary pattern as a whole is what should be considered, particularly because it is considered 1 of the lifestyle factors.

This umbrella review highlights several critical aspects in the literature. First, the total number of available review articles is relatively low, probably indicating that this is a relatively new research topic that needs more studies. The second critical aspect is that approximately half of the included articles had low quality in the current assessment. Third, the inclusion/exclusion criteria set by most of the included meta-analyses were not well defined, resulting in high heterogeneity of the dietary patterns considered. Also, depression was very heterogeneously defined: many different scales were used, and in some cases these were not validated. Last, the cut-offs used for assessing both dietary pattern adherence and depression might have led to misclassification of subjects. In future studies, the methods for assessing adherence to various dietary patterns need standardization, as do the assessment and definition of depression: the development of international recommendations for future research is needed. Based on the data retrieved and their analysis, it can be affirmed that future studies need a more coherent and uniform methodology (both in assessing diet and in the diagnosis of depression), with detailed reporting of interventions, participant characteristics, sample sizes, and outcome data. This approach would allow a more precise quantification of the relationship between dietary patterns and depression. In spite of the above-mentioned weakness of the included meta-analyses, the most consistent findings were that a higher adherence to a Mediterranean diet or a low pro-inflammatory diet were associated with a lower risk of depression. None of the included meta-analyses found that dietary patterns had a detrimental effect in terms of depression, except for the Western diet.[9,11,44]

Limitations and strengths

This study has several strengths and limitations. First, since an umbrella review is a systematic review of meta-analyses, it depends on the quality of the included meta-analyses and cannot correct for potential omissions or overlapping of original studies, as with any other systematic review. In addition, as in all umbrella reviews, it is possible that very recent individual studies were not part of the meta-analyses included. Second, based on the same assumption, the quality of this umbrella review and its corresponding conclusions might be affected by the limitations of the meta-analyses included; these meta-analyses were heterogeneous in terms of framing the question and definition of criteria, comparisons, and populations. Dietary exposure was heterogeneously measured in the original studies, and the included meta-analyses did not differentiate between the several possible methods available for assessing dietary patterns (they had different questionnaires for the same dietary patterns, or different analytical approaches, eg, a priori or a posteriori analysis). Moreover, dietary research is intrinsically affected by several methodological challenges, which include measurement and quantification of dietary intakes, but also recall bias, misreporting, misclassification, and measurement error. Third, the current umbrella review was limited by the relatively low number of available meta-analyses, particularly referring to meta-analyses of RCTs. Fourth, due to the relatively low number of observational meta-analyses available and the absence of specific subgroup meta-analysis, it was not possible to specifically assess the association between dietary patterns and different depressive outcomes (eg, separating early-onset or later-life depression, depressive disorder, depressive symptoms, or antidepressant drugs use). Despite these limitations, there are some strengths. All possible dietary patterns or diet interventions in association with depression were included, offering a comprehensive and systematic overview of the available

evidence. Moreover, the quality and the strength of the evidence were both assessed.

CONCLUSIONS

In conclusion, in the present umbrella review all the available meta-analyses on dietary patterns and depression were collected and assessed. This study shed light on the strengths and limitations of the available evidence, and the results suggest that the MedDiet as well as anti-inflammatory diets can be protective against the development of depression. This finding needs to be substantiated by high-quality RCTs. Further studies adopting more coherent and uniform methodology and analyses, and detailed reporting of participant characteristics, sample sizes, and data collection, would allow a better quantification of the association between various dietary patterns and depression.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **Literature search strategy used for each considered database**

Table S2 **Detailed exclusion motivations**

Table S3 **Additional studies' details**

Table S4 **Item-by-item methodological quality of included meta-analyses**

Table S5 **Assessment across the meta-analyses reporting association between dietary patterns and depression**

Table S6 **Bias assessment of meta-analyses reporting association between dietary patterns and depression**

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