



Meta-analyses

An anti-inflammatory diet as a potential intervention for depressive disorders: A systematic review and meta-analysis



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SUMMARY

Background & aims: There is a large body of evidence which supports the role of inflammation in the pathophysiology of mental health disorders, including depression. Dietary patterns have been shown to modulate the inflammatory state, thus highlighting their potential as a therapeutic tool in disorders with an inflammatory basis. Here we conduct a systematic review and meta-analysis of current literature addressing whether there is a link between the inflammatory potential of a diet and risk of depression or depressive symptoms.

Methods: A systematic literature search was performed to identify studies that reported an association between the inflammatory potential of the diet and risk of depressive symptoms or diagnosis of depression. Random effect models were used to meta-analyse effect sizes. Quality assessment, publication bias, sensitivity and subgroup analyses were also performed.

Results: Eleven studies, with a total of 101,950 participants at baseline (age range: 16–72 years old), were eligible for review. A significant association between a pro-inflammatory diet and increased risk of depression diagnosis or symptoms was evident, relative to those on an anti-inflammatory diet (OR: 1.40, 95% confidence intervals: 1.21–1.62, $P < 0.001$). No publication bias was detected; however, some study heterogeneity was evident ($I^2 = 63\%$, $P < 0.001$). Subgroup analyses suggested the main source of study heterogeneity was the study design (cross-sectional or longitudinal) and the effect measure used (odds ratio, hazard ratio or relative risk).

Conclusion: These results provide an association between pro-inflammatory diet and risk of depression. Thus, adopting an anti-inflammatory diet may be an effective intervention or preventative means of reducing depression risk and symptoms.

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1. Introduction

Ranked the single largest contributor to non-fatal health loss, depression affects an estimated 322 million people globally, equivalent to 4.4% of the population [1]. In recent years, links between chronic inflammation and a range of neurological diseases have been established, including depression [2,3]. For example, previous meta-analyses have revealed increased pro-inflammatory peripheral cytokine levels in those with depression, compared to non-depressed individuals [4,5]. Further, anti-inflammatory therapies have been shown to reduce depressive symptoms in inflammatory-related conditions, such as arthritis and cancers [3].

Evidence has also emerged that proposes an interaction between inflammatory status and responsiveness to certain related medications. For example, one study measuring levels of blood C-reactive protein (CRP), a proxy for peripheral inflammation, predicted differential responses to escitalopram and nortriptyline in those with major depressive disorder (MDD) [6]. Collectively, these studies exemplify the inflammatory component of depression pathogenesis and highlight the potential of reducing symptoms through anti-inflammatory interventions.

Extensive research has found diet to modulate inflammatory factors, with numerous studies finding a variety of specific dietary nutrients to have a range of anti-inflammatory properties. For example, consumption of wholegrains has been associated with lower inflammatory markers (CRP), whereas lower wholegrain intake has been shown to increase inflammatory marker (interleukin-6; IL-6) concentrations [7–10]. Results from the ATTICA study have highlighted increased intake of choline, a nutrient found

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in high quantities in eggs, broccoli and cauliflower, and betaine is associated with lower peripheral inflammatory levels, such as CRP, IL-6 and tumour necrosis factor alpha (TNF- α) [11]. In addition to specific nutrients, a link between dietary patterns and inflammation has also been established [12].

Over recent years studies have investigated the role of diet in the development of depression due to its influence on inflammatory pathways, however, results remain inconclusive. For example, Akbaraly and colleagues found a pro-inflammatory diet may increase the risk of depression in females and not males [13], whereas others have found the reverse to be true [14]. Further, many of these studies often contain restricted populations, for example middle-aged Australian women [15] or Iranian adolescents [16], therefore results are not generalizable to a wider population.

Thus, the aim of this study was to conduct a systematic review and meta-analysis examining current literature regarding depression and the inflammatory potential of the diet to determine if diet could be an effective treatment for depression.

2. Methods

This review was performed in accordance to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [17] to answer the following question: does a pro-inflammatory diet associate with depression or depressive symptoms, compared to an anti-inflammatory diet in adults? A standardised review protocol has not been published.

2.1. Search strategy

A systematic literature search of the PubMed and Scopus databases were performed to identify relevant studies, from inception and up to 3rd October 2018, by two independent reviewers (K.T. and S.B.). The following search terms were used: inflammat* AND diet AND depress*. Searches were limited to journal articles written in English. Relevant references within retrieved studies and an earlier review [18] were also manually searched.

2.2. Inclusion and exclusion criteria

Studies that met the following criteria were included: (i) measured the inflammatory potential of the diet; (ii) measured the incidence of depression or depressive symptoms; (iii) reported effect size and confidence intervals (CI) for the association between an inflammatory diet and depression. Exclusion criteria included: (i) inflammatory potential of the diet was not measured; (ii) depression or depressive symptoms were not reported; (iii) duplicate study population.

2.3. Data extraction

Data and characteristics extracted from each study included: study design, location, number of subjects at baseline, percentage of females, baseline age, length of study follow-up, assessment of depression, assessment of inflammatory potential of the diet, effect sizes for the association between a pro-inflammatory diet and depressive symptoms with 95% CI's and model adjustments. Since the majority of articles reported sex-specific effects, where possible, separate effect sizes for males and females were extracted.

Studies reported different effects: odds ratio (OR), hazard ratio (HR) and relative risk (RR) effects. These were combined, and results presented as OR representing the likelihood of depression or depressive symptoms in the highest inflammatory diet group, compared to the lowest inflammatory diet group. Differences in reported effects were explored during sub-group analysis.

Where studies had stratified subjects into groups (tertiles, quartiles and quintiles), the pro-inflammatory diet was defined as the highest grouping and the anti-inflammatory diet was defined as the lowest grouping.

Where multiple model testing was applied, the model with the most adjustments was extracted for analysis.

When studies utilised the same study population, the study with the largest number of participants at baseline was selected and the others discarded from the meta-analysis. This resulted in a study involving Iranian adolescents being preferred in one article ($n = 300$) [19], as opposed to another ($n = 299$) [16]. Further, we selected the study by Wirth and colleagues to represent the National Health and Nutrition Examination Survey (NHANES) population ($n = 18,875$) [20], as opposed to those by other research groups ($n = 11,592$ – $11,624$) [21,22].

2.4. Quality assessment

The Newcastle–Ottawa Scale (NOS) for cohort studies was used to assess study quality and risk of bias in studies [23], by two independent reviewers (S.B and C.M.). We modified the original scale to fit our analysis (Supplementary material). Specifically, the scale was divided into three categories (selection, comparability and outcome). A maximum score of 7 or 8 points were available for cross-sectional and longitudinal studies respectively. Total scores were converted to percentages, to account for differences in total scores available, and scores of $\geq 75\%$ were considered to be of high quality, whereas those with $<75\%$ were classed as lower quality.

2.5. Statistical analysis

Meta-analysis was performed using the *metafor* package in R [24]. Due to the anticipated variability in methodologies between studies, we utilised random effect models throughout.

Heterogeneity between studies was assessed using the I^2 index which represents the percentage of variation across studies due to inconsistency rather than chance.

Potential publication bias was assessed through visual examination of funnel plots and through the Egger's regression test [25].

Sensitivity analysis was performed through two approaches. The first was the leave-1-method, which simultaneously applies the random effect models whilst leaving a single study out at a time. Secondly, subgroup analysis was performed to investigate the overall results based on the following categorical variables: sex (male, female or mixed populations), study design (cross-sectional or longitudinal), average age at baseline (<50 or ≥ 50 years old), inflammatory dietary assessment (Dietary Inflammatory Index; DII or cytokine measures), study follow-up period (<10 or ≥ 10 years), study effect measure (odds ratio, hazard ratio or relative risk) and quality score (high quality or lower quality).

3. Results

3.1. Study selection

The search strategy returned 1173 potential articles for inclusion of which 1147 were excluded based on title and/or abstract screening (Fig. 1). Fourteen articles remained for full-text screening, of which 3 [16,21,22] were excluded as they contained a duplicate study population. Thus, 11 articles containing 17 populations (6 males, 9 females and 2 mixed sex), were the focus of this meta-analysis.

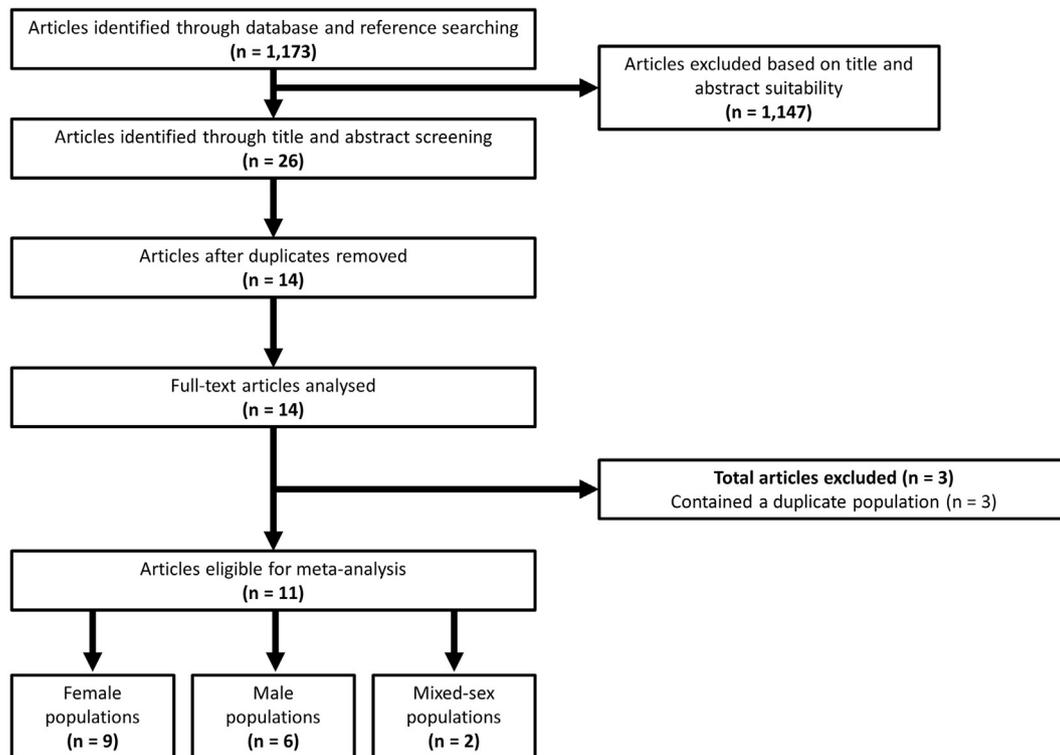


Fig. 1. Flow chart demonstrating the search strategy for the meta-analysis.

3.2. Quality assessment

Included studies were assessed using a modified NOS (Supplementary material). Eight studies [13–15,19,26–29] were determined to be of high quality and of low risk of bias, whereas three [20,30,31] had lower quality (Supplementary Table 1).

3.3. Study characteristics

In total, the included studies contained 101,950 participants at baseline with ages ranging from 16 to 74 years old (Table 1). Most studies reported separate effects for male and female participants, whereas two studies reported effects for mixed sex [26,30]. Seven

studies [13–15,26–28,30] were longitudinal, with follow-up periods of 5–13 years, while 4 were cross-sectional [19,20,29,31].

Details regarding the definition and criteria for depression and depressive symptoms, the assessment of the inflammatory diet used, and the model adjustments used for each study can be found in Table 2. Briefly, most studies assessed the inflammatory potential of the diet using the DII [13–15,19,20,26,28,29,31], whereas two studies based their dietary inflammatory potential through blood cytokine quantifications [27,30]. Two studies [27,28] diagnosed depression by either self-reported physician diagnosis or antidepressant use. The other studies measured depressive symptoms using a variety of methods, including the Centre for Epidemiological Studies Depression Scale (CES-D) [13–15,26,29,30], Patient Health Questionnaire 9 (PHQ-9) [20], Depression Anxiety and

Table 1
Characteristics of studies included in the meta-analysis.

Study	Location (cohort)	Design	Follow-up, years	Subjects at baseline, n	Females, %	Age at baseline
Lucas et al., 2014 [27]	USA (Nurses' Health Study)	Longitudinal	12	43,685	100	62.6 ± 7.0
Sanchez-Villages et al., 2015 [28]	Spain (Seguimiento Universidad de Navarra)	Longitudinal	8.5	15,093	59	38.3 ± 12.1
Akbaraly et al., 2016 [13]	UK (Whitehall II)	Longitudinal	5	4246	25	60.9 ± 5.9
Shivappa et al., 2016 [15]	Australia (Australian Longitudinal Study on Women's Health)	Longitudinal	12	6438	100	52.0 ± 1.4
Wirth et al., 2017 [20]	USA (National Health and Nutrition Examination Survey)	Cross-sectional	N/A	18,875	51	46.4
Adjibade et al., 2017 [14]	France (Supplementation en Vitamines et Minéraux Antioxydants)	Longitudinal	12.6	3523	58	49.5 ± 6.2
Phillips et al., 2018 [29]	Ireland (Cork and Kerry Diabetes and Heart Disease Study)	Cross-sectional	N/A	1992	51	59.7 ± 5.5
Shivappa et al., 2018 [19]	Iran	Cross-sectional	N/A	300	100	16.2 ± 1.0
Shivappa et al., 2018 [26]	USA (Osteoarthritis Initiative)	Longitudinal	8	3608	57	61.4 ± 9.2
Vermeulen et al., 2018 [30]	Italy (InCHIANTI)	Longitudinal	9	827	58	73.8 ± 6.8
Haghighatdoost et al., 2018 [31]	Iran (Study on the Epidemiology of Psychological, Alimentary Health and Nutrition)	Cross-sectional	N/A	3363	59	36.2 ± 9.2

Table 2
Study specific case definition, methods of inflammatory diet assessment and effect size model adjustments.

Study	Case definition	Criteria for case	Assessment of inflammatory diet	Food parameters derived	Model adjustments
Lucas et al., 2014 [27]	Depression	Self-reported physician-diagnosed depression and regular antidepressant use (strict definition)	Measured CRP, IL-6 and TNF- α receptor 2	39	Age, BMI, total energy intake, smoking, physical activity, menopause status, HRT, marital status, retired, education, husband education, ethnicity, multivitamin use, reported diagnosis of cancer, high blood pressure, hypercholesterolemia, heart disease, diabetes, MHI-5 score at baseline, alcohol intake, caffeine intake
Sanchez-Villages et al., 2015 [28]	Depression	Use of antidepressants and/or physician diagnosis	DII	28	Age, BMI, smoking, physical activity during leisure time, use of vitamin supplements, total energy intake, presence of diseases at baseline (CVD, diabetes, hypertension and dyslipidaemia)
Akbaraly et al., 2016 [13]	Recurrent depressive symptoms	CES-D score ≥ 16 or treated by antidepressants	DII	27	Age, ethnicity, total energy intake, socio-economic status, marital status, smoking habits, physical activity, alcohol intake, coronary heart diseases, type 2 diabetes, hypertension, HDL-cholesterol, use of lipid-lowering drugs, central obesity, cognitive impairment
Shivappa et al., 2016 [15]	Depressive symptoms	CES-D-10 score ≥ 10	DII	26	Total energy intake, highest qualification completed, marital status, menopause status, night sweats, major personal illness or injury, smoking, physical activity, BMI, depression diagnosis or treatment
Wirth et al., 2017 [20]	Depressive symptoms	PHQ-9 score ≥ 10	DII	26	Race, education, marital status, perceived health, current infection status, family history of smoking, smoking status, past cancer diagnosis, arthritis, age, average nightly sleep duration
Adjibade et al., 2017 [14]	Depressive symptoms	CES-D (French) score ≥ 17 in men and ≥ 23 in women	DII	36	Age, intervention group during trial phase, education level, marital status, socio-professional status, energy intake without alcohol, number of 24-h dietary records, interval between the 2 CES-D measurements, smoking status, physical activity, BMI, cancer or cardiovascular events during follow-up
Phillips et al., 2018 [29]	Depressive symptoms	CES-D score ≥ 16	DII	26	Age, BMI, physical activity, smoking, alcohol consumption, antidepressant use, history of depression
Shivappa et al., 2018 [26]	Depressive symptoms	CES-D score ≥ 16	DII	24	Age, sex, race, BMI, education, smoking habits, yearly income, Charlson Comorbidity Index, PASE score, CES-D at baseline, statins use, NSAIDs or cortisone use.
Shivappa et al., 2018 [19]	At least mild level of depressive symptoms	DASS-21 (Persian) score > 9	DII	31	Age, energy, physical activity, BMI, smoking, presence of chronic disease, diet supplement use, salary, marital status
Vermeulen et al., 2018 [30]	Depression	CED-D score ≥ 20	Measured CRP, IL6 and TNF- α	10	Sex, age, marital status, education in years, depressive symptoms at baseline, IADL, smoking status, physical activity, antidepressant use, anti-inflammatory drugs, CVD, diabetes, waist circumference
Haghighatdoost et al., 2018 [31]	Highest tertile of Mental Health Disorders profile	Factor analysis using HADS and GHQ-12 scores	DII	27	Age, marital status, education, BMI, smoking, physical activity, anti-psychotropic medicine use, suffering from gastrointestinal disorders

Key: CRP = C-reactive protein; IL-6 = interleukin-6; TNF- α = tumour necrosis factor alpha; BMI = body mass index; HRT = hormone replacement therapy; MHI-5 = mental health inventory; DII = Dietary Inflammatory Index; CES-D = Center for Epidemiologic Studies Depression Scale; HDL = high-density lipoproteins; PHQ-9 = Patient Health Questionnaire; PASE = Physical Activity Scale for the Elderly; NSAID = non-steroidal anti-inflammatory drug; DASS-21 = Depression Anxiety and Stress Scale; IADL = Lawton Instrumental Activities of Daily Living; HADS = Hospital Anxiety and Depression Scale; GHQ-12 = General Health Questionnaire.

Stress Scales (DASS-21) [19] and the Hospital Anxiety and Depression Scale (HADS) [31].

3.4. Association between pro-inflammatory diet and depression

Collectively, individuals on the most pro-inflammatory diet had an increased likelihood of being either diagnosed with depression or presenting depressive symptoms, compared to those on with an anti-inflammatory dietary potential (Fig. 2; OR: 1.40, 95% CI: 1.21–1.62, $P < 0.001$). Despite this, significant study heterogeneity was found ($I^2 = 63.3\%$, $P < 0.001$).

Since the majority of studies reported separate effect sizes for males and females, results were also sub-groups based on sex (Fig. 2). Effects were stronger in females (OR: 1.57, 95% CI: 1.23–2.00, $P < 0.001$), as opposed to males (OR: 1.31, 95% CI: 1.03–1.68, $P = 0.029$), whereas studies reporting mixed sex effects only were not significant (OR: 1.14, 95% CI: 0.85–1.51, $P = 0.380$).

3.5. Risk of publication bias

Visual inspection of the funnel plot (Fig. 3) and the Egger's regression test ($Z = 1.20$, $P = 0.229$) suggested there was no presence of publication bias in the analysis.

3.6. Sensitivity and subgroup analyses

The leave-1-out analysis confirmed the robustness of the model since the significance remained after simultaneously removing each study from the model.

To further elaborate on the significant study heterogeneity observed, subgroup analyses was performed, whereby studies were stratified based on: study design, inflammatory dietary assessment, average age at baseline, follow-up period (longitudinal studies only), effect measure and quality score (Table 3).

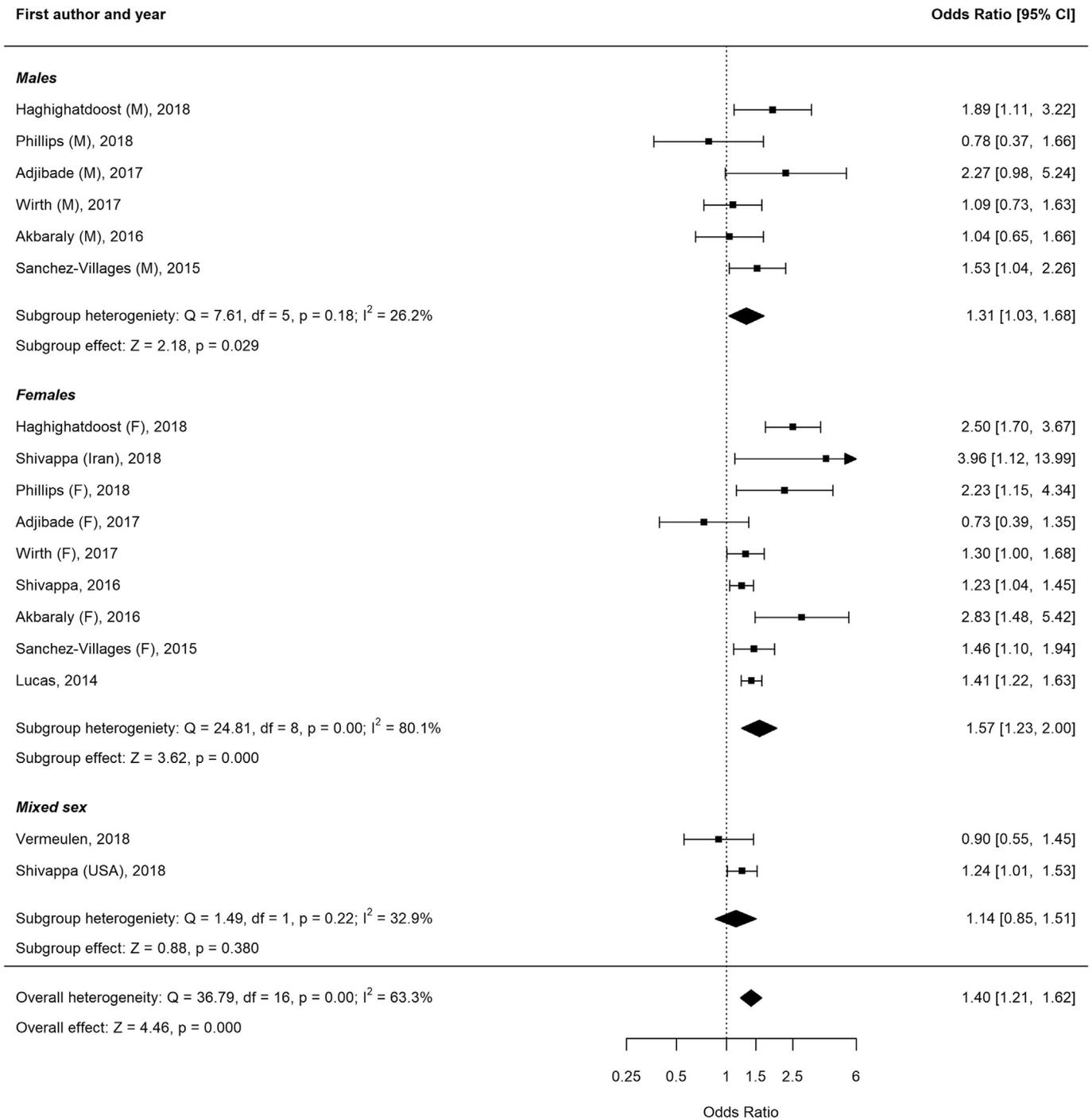


Fig. 2. Random effects meta-analysis and forest plot for the association between a pro-inflammatory diet and depression diagnosis or depressive symptoms. Results are also subgrouped by sex-specific populations.

Overall, model effects were unaffected by the type of study design, average age of participants at baseline, effect measure used or quality score. Further, the significance in longitudinal studies was independent of the follow-up period. Model effects were dependent on the type of inflammatory dietary assessment used, with no significant effect seen in those utilising blood-based cytokine measures, as opposed to using the DII.

Subgroup analysis also suggested the source of potential study heterogeneity may be applicable to the study design and effect measure used (Table 3).

4. Discussion

This meta-analysis of 11 studies, containing a total of 101,950 participants at baseline, suggests that those on a pro-inflammatory diet have a 1.4 increased likelihood of being diagnosed with depression or displaying depressive symptoms, as opposed to those on an anti-inflammatory diet.

Our findings are consistent with recent analysis concerning the quality of diet and risk of depression. Specifically, adherence to a higher quality or healthier diet (e.g. the Mediterranean diet) is

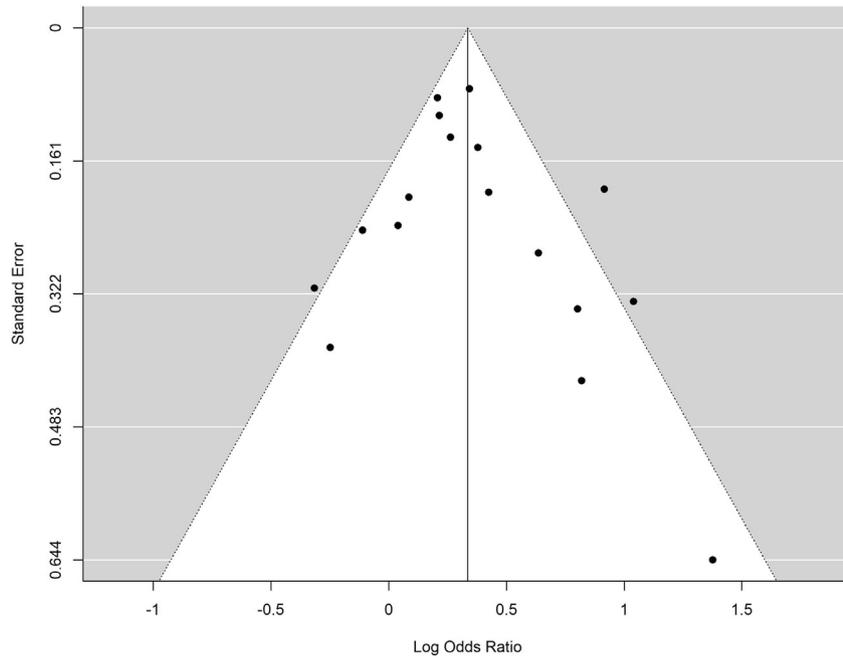


Fig. 3. Funnel plot for the included study populations.

Table 3
Subgroup analysis.

Subgroup factor	Subgroup	Populations	OR (95% CI)	Overall effect		Heterogeneity	
				Z	P	I ²	P
Study design	Cross-sectional	7 [19,20,29,31]	1.61 (1.16–2.24)	2.84	0.005	66.7%	0.007
	Longitudinal	10 [13–15,26–28,30]	1.31 (1.20–1.44)	6.00	<0.001	5.1%	0.051
Inflammatory dietary assessment	DII	15 [13–15,19,20,26,28,29,31]	1.45 (1.21–1.72)	4.15	<0.001	64.3%	0.003
	Cytokine measures	2 [27,30]	1.19 (0.78–1.83)	0.81	0.421	68.3%	0.076
Average age at baseline	<50 years old	9 [14,19,20,28,31]	1.53 (1.20–1.94)	3.45	<0.001	61.5%	0.012
	≥50 years old	8 [13,15,26,27,29,30]	1.30 (1.16–1.44)	4.73	<0.001	14.2%	0.039
Follow-up period (longitudinal only)	<10 years	6 [13,26,28,30]	1.33 (1.10–1.61)	2.98	0.003	36.0%	0.070
	≥10 years	4 [14,15,27]	1.30 (1.12–1.51)	3.39	<0.001	29.5%	0.084
Effect measure	Odds ratio	12 [13,14,19,20,29–31]	1.47 (1.11–1.94)	2.69	0.007	70.2%	0.004
	Hazard ratio	3 [26,28]	1.34 (1.15–1.57)	3.77	<0.001	0.0%	0.515
	Relative risk	2 [15,27]	1.33 (1.16–1.51)	4.14	<0.001	32.2%	0.225
Quality score	High quality	12 [13–15,19,26–29]	1.31 (1.23–1.47)	6.51	<0.001	3.7%	0.030
	Lower quality	5 [20,30,31]	1.43 (1.00–2.04)	1.96	0.050	75.5%	0.004

Key: OR = odds ratio; CI = confidence intervals; DII = Dietary Inflammatory Index.

associated with a lower risk of depressive symptoms in longitudinal and observational cohorts [18,32].

Mechanisms by which a pro-inflammatory diet could increase the risk of depressive symptoms may be through pro-inflammatory nutrients activating the innate immune system that can lead to low-grade inflammation and chronic diseases such as cardiovascular disease (CVD), diabetes and mental health disorders [33,34]. At the molecular and cellular levels there is an increasing abundance of research demonstrating influences of dietary factors on markers of neuronal function and synaptic plasticity [35,36], mechanisms which are all involved in the aetiology of depression [37]. For example, in mice the combination of exercise and an anti-inflammatory (flavonoid-enriched) diet has been found to increase the expression of genes that have positive effects on neuronal plasticity and decrease the expression of genes that are involved in deleterious processes including inflammation [38].

The results of this analysis further support the use of the DII as a measure of the inflammatory potential of a diet. The DII was developed to provide a tool which could standardise the inflammatory potential of an individual's diet for use in epidemiological

and clinical studies [39]. The current DII database consists of world standard reference values for 45 food parameters derived from a comprehensive review and weighted algorithm scoring of nearly 2000 articles on diet and inflammatory markers and 11 food consumption data sets from different countries. Interestingly, there are efforts to incorporate a Dietary Inflammation Food Grade system on food packages, based on DII scores, which would display user-friendly traffic-light stickers. This approach has tremendous clinical applications and may be a feasible approach to aid with disease treatment.

The use of DII to assess inflammation may also have some restrictions. Scores for the inflammatory potential of food items are derived from an extensive literature search up to December 2010 and based on global means, meaning publication bias and changes in global trends could affect the validity of the tool. However, one third of the findings included are null, demonstrating no bias towards significant results, and there are no anticipated major changes in estimates for global intake of food parameters [39].

The use of randomized control trials (RCTs) would counteract many of the limitations encountered in cohort-based studies and

explore the clinical use of modulating the inflammatory potential of dietary patterns to improve depressive states [40]. This was highlighted in the recent Supporting the Modification of lifestyle In Lowered Emotional States (SMILES) trial, the first RCT directly assessing the impact of a dietary intervention on mental health outcome [41]. Briefly, those placed in the personalised dietary support group demonstrated significant improvements in depressive symptoms, compared to those on social support, over a 12-week period [41]. However, this study failed to analyse the inflammatory potential of their dietary interventions. Thus, future RCTs should consider incorporating these measures, along with a varied dietary intervention group (e.g. pro-, anti- and moderate inflammatory diets).

Lastly, reverse causation must be addressed as it is plausible that mental health status could determine food selection. Papier and colleagues examined the relationship between stress and food selection patterns and found students with mild to moderate stress were up to three times more likely to consume processed food and less likely to consume fruits and vegetables compared to unstressed students [42]. This study demonstrates that adverse mental health can lead to the selection of pro-inflammatory dietary patterns (processed foods) and the avoidance of anti-inflammatory foods (fruits and vegetables) resulting in increased or decreased inflammatory status. Thus, the inter-relationship between an inflammatory diet and depression could lead to a vicious cycle where each may feedback to the other.

Despite the strengths of the current analysis, there are certain limitations that should be noted. Firstly, the included studies contained a varied methodological approach, such as different inflammatory diet measurements and depression scales, which was reflected by the large heterogeneity between studies. Despite this, we utilised random effect models and subgroup analyses to limit and detect such sources of variability. Further, we chose to extract data based on categorical stratification of the inflammatory potential of diets, as opposed to continuous scores, as a means of comparing two extreme groups. Thus, this approach limits the ability to define a threshold when such pro-inflammatory effects are seen. Future work should investigate the levels at which the inflammatory potential of a diet may be detrimental to depression incidence, which would be clinically useful.

The findings from this meta-analysis suggest that a pro-inflammatory diet is associated with the increased likelihood of depression diagnosis or depressive symptoms, which has major implications for the treatment of depression. Future medical and social advice should focus on increasing the awareness of lifestyle changes, such as diet, and their effects on depressive symptoms.

In conclusion, how inflammation causes depression is a promising area of research which needs to be investigated further to help us understand accessible targets for new treatment strategies. However, whilst inflammation's role in depression is not yet fully understood, targeting the diet might provide a promising effective strategy for reducing depressive symptoms.

Author contributions

CM and SB designed the study. SB and KT performed the literature searches and data extraction. SB and CM performed the quality assessment. KT and SB performed statistical analyses. KT wrote the first draft of the manuscript, then all authors contributed to the final version of the manuscript.

Conflict of interest

The authors report no conflicts of interest in this work. This study did not receive any specific funding.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2018.11.007>.

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