

# The Mediterranean dietary pattern and depression risk: A systematic review

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## ABSTRACT

**Background:** Depression is a major global health burden and psychiatry requires evidence-based primary prevention and treatment strategies. Evidence suggests that certain dietary patterns, in particular, components of the Mediterranean diet, possess key biological factors associated with abating depressive risk and disease progression. We sought to evaluate the existing evidence regarding the association between the Mediterranean diet and depressive symptoms by conducting a systematic review.

**Methods:** A search of published studies was conducted using the computer databases Medline, Embase, PsychINFO, Scopus and Google Scholar, for articles in the English language published from inception to April 2018. The search strategy applied the following subject headings and keywords: “Mediterranean diet” OR Mediterranean\* AND “Major depressive disorder” OR Depress\* OR “Negative mood” OR Mood. The NIH quality assessment tool was implemented by reviewers to determine study quality.

**Results:** Results from twenty observational studies and six intervention trials were qualitatively examined. The majority (85%) of observational studies support the evidence that the Mediterranean dietary pattern is associated with reductions in depressive incidence and all intervention studies echoed these findings.

**Limitations:** Methodological disparity in Mediterranean style diets limited comparisons but were overcome by specifying inclusion criteria and compressive appraisal of the data.

**Conclusions:** Modifying diet provides a potential treatment for depression which procures few side effects, lessens disease progression and demonstrates a cost-effective measure that can be implemented globally. Present research has found that more objective measures are necessary to define the Mediterranean diet and highlights the need for longitudinal studies and clinical trials for future research.

## 1. Introduction

Depressive disorders impact over 300 million people globally, with this figure rising (WHO, 2017). Mental health disorders are the leading cause of burden of disease for females, who experience more than double the burden than males. There is a superfluous social and economic cost of depression due to both the high prevalence of the disorder and the high level of morbidity related absenteeism (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015). Current treatment for depression relies primarily on individualised pharmacotherapy, psychotherapy and lifestyle management. As a chronic and often reoccurring condition, depression frequently requires long term antidepressant treatment and up to 50% of these patients do not respond adequately to the initial anti-depressant that is prescribed, or suffer long term side-effects (Hirschfeld, 2000). Although there are known, effective

treatments for depression, fewer than 10% of countries have these resources available to them (WHO, 2017). An important research imperative is the identification of modifiable risk factors that may prevent or abate disease progression (Lai et al., 2014; Quirk et al., 2013).

Evidence suggests that the pro-inflammatory mechanisms which underlie cardiovascular and metabolic diseases, may also underpin depressive disorders (Sanchez-Villegas & Martínez-González, 2013). Low-grade inflammation as a result of pro inflammatory cytokines have the potential to downgrade the expression of brain-derived neurotrophic factor (BDNF), impair neurotransmitter metabolism and instigate endothelial dysfunction, which may trigger the clinical symptoms of depression (Sanchez-Villegas & Martínez-González, 2013). This common pathophysiological mechanism underscores the importance of diet in facilitating or impeding chronic inflammatory diseases like depression, and suggests that dietary patterns which foster cardiometabolic health

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may also be protective against depression.

Diets that are characterised by higher intakes of red and processed meats, dairy and refined carbohydrates are associated with markers of systemic inflammation (Lai et al., 2014; Quirk et al., 2013). Animal studies have demonstrated that several dietary factors are implicated in the upregulation of BDNF levels with positive correlations between intake of omega-3 fatty acids, vitamin E, flavonols and BDNF expression. (Sanchez-Villegas et al., 2011). Studies have looked at dietary nutrients and foods in isolation and their impact on depression, however several limitations exist when nutrients are studied in isolation. Dietary patterns are multifaceted and thus makes it difficult to attribute a single disease, like depression, to a single nutrient or food group (Quirk et al., 2013).

The Mediterranean dietary pattern is largely sourced from green leafy vegetables, fruit and nuts, legumes, olive oil, cereals, red wine, fish and low dietary intakes of meat products and dairy. This dietary pattern has been associated with reduced cognitive decline, improved cognitive performance, fewer depressive symptoms and dampens the risks associated with developing neurodegenerative and mental health disorders (Knight, Bryan, & Murphy, 2017). It is imperative to identify modifiable risk factors early (Quirk et al., 2013) and encourage greater adherence to traditional diets characterised by wholefoods to greater reduce the likelihood of developing depressive disorders (Quirk et al., 2013).

Though the role of diet on cardiometabolic disorders has been rigorously explored, other non-communicable diseases such as depression, are a novel research field with evidence surfacing only in recent years (Sanchez-Villegas & Martínez-González, 2013). The Mediterranean diet may influence the onset of depression by reducing pro inflammatory food groups and increasing omega 3 fatty acids, anti-oxidants, vitamins and minerals (Sanchez-Villegas & Martínez-González, 2013). Dietary modifications should be considered a preventative and helpful adjunct to the current line of treatment in place for depressive disorders.

A systematic review recently conducted (Molendijk, Moler, Ortuño Sánchez-Pedreño, Van der Does, & Angel Martínez-González, 2018) looked at the diet quality scores of several different dietary patterns and its impression on depressive disorders. This systematic review provides insight on the association between a single dietary pattern, the Mediterranean dietary pattern, and depression, which to our knowledge has not yet been conducted. Given the rising rate of depression globally, there is a need to identify a clear dietary pattern that will offer insight on impending treatment opportunities for depression. The aim of this systematic review is to investigate the relationship between depression and the Mediterranean diet, and to identify future interventions that may facilitate the treatment and management of depressive symptoms.

## 2. Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

### 2.1. Search strategy

A comprehensive search of published studies was conducted using the computer databases Medline, Embase, PsychINFO, Scopus and Google Scholar. A search was conducted for articles in the English language published between inception to February 20th 2018 and search alerts were created to include any relevant articles thereafter. The final search was conducted in April 2018. The search strategy applied the following subject headings: “Mediterranean diet” OR Mediterranean\* AND “Major depressive disorder” OR Depress\* OR “Negative mood” OR Mood. “Negative mood” was included in the search terms as it can be a useful indicator of depressive symptoms and a common precursor of depressive episodes. References cited in articles identified for inclusion were manually searched and assessed for

eligibility.

### 2.2. Selection of studies

To be eligible for inclusion in the current review, studies had to be: i) human studies, (ii) over 18 years, (iii) observational or interventional design with control group, (iv) examined associations of the Mediterranean dietary pattern and included measurements of all dietary components by using a 24-h dietary recall, food record, food-frequency questionnaire (FFQ), or similar instrument, and (v) included depression through a validated screening tool, clinical diagnosis by a trained interviewer or prescription of antidepressants as a proxy for clinical diagnosis. Articles were excluded if they were (i) non-human, (ii) published in languages other than English, (iii) investigated isolated nutrients or individual food items as primary variables of interest, (iv) individuals with comorbid health conditions that may confound the diet-depression relation, and (v) were not original research publications. Due to methodological disparity surrounding the Mediterranean dietary pattern, for this systematic review the Mediterranean diet intervention had to include at minimum a high consumption of plant-based foods such as vegetables and fruits, in addition to at least one of the following; nuts, legumes, cereals, fish or olive oil. Studies were deemed eligible if they incorporated the Mediterranean diet despite omitting depression as the primary outcome, but found findings which were significant to depressive incidence (Sanchez-Villegas et al., 2011). Studies which created a modified Mediterranean diet that included red meat and eggs were excluded (Jacka et al., 2017).

Studies were screened for title, abstract and full-text for eligibility. Search and selection of articles was performed by one author (AA) and second author (HB) independently screened the articles and any differences related to study eligibility were resolved between authors.

### 2.3. Quality assessment

All studies included in the review were assessed according to the National Heart, Lung and Blood Institute (NIH) quality assessment tools (NIH National Heart, 2019). Longitudinal and cross-sectional studies were assessed according to observational study criteria. Treatment intervention trials were assessed according to a separate set of trial intervention criteria. The fourteen criteria used to assess study quality are listed in the supplementary material under “Study Quality Assessment Tools”.

Each of the fourteen criteria items were scored as follows: ‘YES’, ‘NO’, ‘CD’, OR ‘NR’ and rated (%) based on the amount of YES scores attained. Critical appraisal involved considering the risk of potential for selector or allocation bias, measurement bias, information bias or confounding factors. Each study was reviewed by two authors (AA and HB) with an inter-rater reliability set to > 70%. Studies were defined as high quality if the total quality score for all quality scores were above the mean.

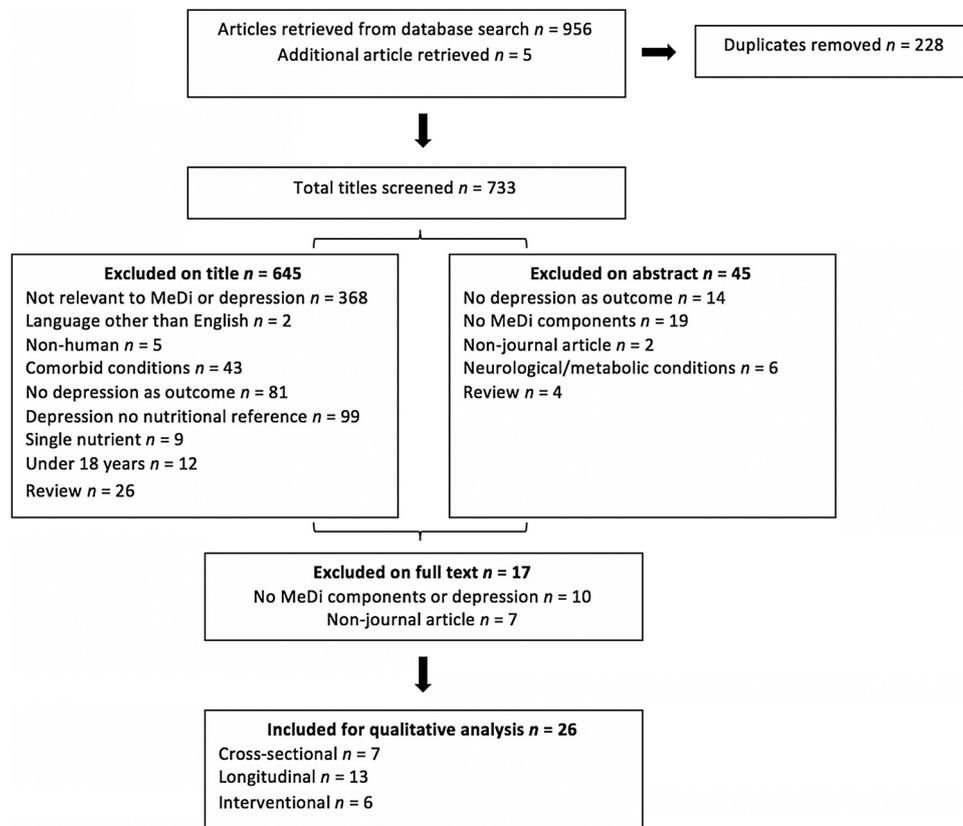
### 2.4. Data extraction

For each article eligible for inclusion, the following information was collected where provided: names of authors, publication year, first year of study, country of study, sample characteristics, study design, dietary assessment instruments, depressive measure, main findings and adjusted confounding factors.

## 3. Results

### 3.1. Identification and selection of included manuscripts

The search generated 956 articles, of which 228 were duplicates. Citations from included literature publications yielded an additional 5 articles. The title and abstracts of the remaining 733 articles were



**Fig. 1.** Flow of Studies Included in Systematic Review.

This figure illustrates the flow of studies in the review process from database search to studies included in the qualitative assessment.

screened, of which 690 failed to meet preliminary criteria. The full texts of the remaining 43 articles were screened in further detail, and based on a concise appraisal of the full articles, a further 17 texts failed to meet eligibility criteria, leaving a final integer of 26 articles included in this systematic review. The flow of the studies through the review process is reported in Fig. 1.

### 3.2. Quality assessment of included studies

Cross-sectional study designs are limited in their ability to establish causal relationships and it is not known whether depression and diet may incite bi-directional causality. Longitudinal studies appraised in this systematic review were of higher quality with majority demonstrating lower scores as a result of low participation and retention rate. Highest rating studies had these measures clearly stated and performed as indicated (Akbaraly, Sabia, Shipley, Batty, & Kivimaki, 2013; Sanchez-Villegas et al., 2015). Assessment of intervention trials demonstrated majority to be fair quality, with the overall scoring around the 65% mark. Studies of good quality (rating no higher than 75%), were randomized, double-blinded studies; reporting that all randomized participants were analyzed in the group to which they were originally assigned (Knight, Bryan, Wilson, Hodgson, & Murphy, 2015; Parletta et al., 2017). The lowest rating study scored 50% as it failed to demonstrate adequate randomization, blinding to group allocation and assessment in addition to a high drop-out rate (Sanchez-Villegas et al., 2011). Quality assessment scores are summarized in Tables 2–4 in supplementary material.

### 3.3. Study design and cohort characteristics

Thirteen of the overall 26 studies in this systematic review investigated the relationship between Mediterranean dietary adherence

and depression using a longitudinal study design. Majority of these studies were mixed cohorts whilst only two studies investigated female specific cohorts (Chocano-Bedoya et al., 2013; Rienks, Dobson, & Mishra, 2013). Majority of longitudinal studies assessed depressive symptoms via a validated scale such as the Centre for Epidemiological Studies Depression Scale (CES-D) (Adjibade et al., 2017; Akbaraly et al., 2009, 2013; Le Port et al., 2012; Rienks et al., 2013; Skarupski, Tangney, Li, Evans, & Morris, 2013; Vermeulen et al., 2016). Sample sizes ranged from 79 to 5731 and age was the most common confounder adjusted for, with all studies reporting the age range or mean of participants.

Seven studies investigated the cross-sectional relationship between dietary patterns and depression; with one study having a sex specific cohort of women (Jacka et al., 2010). The most commonly used cross-sectional measure for depressive symptoms were validated self-report surveys, again predominantly CES-D (Crichton, Bryan, Hodgson, & Murphy, 2013; Miki et al., 2015; Nanri et al., 2010; Sugawara et al., 2012). Sample sizes ranged from 669 to 50605 and age was the most common confounder adjusted for, with all studies reporting the age range or mean of participants.

Treatment intervention trials make up six of the studies appraised in this review. Three trials included participants which had been screened for diagnosed or self-reported depression (Ibarra et al., 2015; Opie, O'Neil, Jacka, Pizzinga, & Itsiopoulos, 2017; Parletta et al., 2017) to measure symptomatic progression and one study used healthy volunteers with no prior diagnosis or report of depressive symptoms (Sanchez-Villegas & Martínez-González, 2013) to identify factors associated with the development of depression. Another two studies included both healthy volunteers and those diagnosed with depression at baseline (Knight et al., 2015; Sanchez-Villegas et al., 2011). The majority of studies had a sample size less than 1000 (Ibarra et al., 2015; Knight et al., 2015; Opie et al., 2017; Parletta et al., 2017; Sanchez-

**Table 1**  
Cohort Characteristics Included in the Review.

Author (year)	First year of Study	Country	n = M:F Age (Years)	Type of Study	Diet Measure	Depression Measure	Main Findings
Crichton et al. (2013)	-	Australia	n = 1183 432:751 Age = 40-65	Cross-sectional Study	Self-completed quantified and validated FFQ	CES-D to measure depression.	MeDi adherence was not related to cognitive function. Intakes of plant based foods were positively associated with physical function and general health, and negatively associated with trait anxiety, depression and perceived stress. High intake of vegetables, mushrooms, seaweeds, soybean products, green tea, potatoes, fruits, and small fish with bones, as well as a low intake of rice was inversely associated with depression. A healthy Japanese dietary pattern characterised by high intakes of vegetables, mushroom, fruit and soy products was associated with fewer depressive symptoms.
Miki et al. (2015)	2012	Japan	n = 2006 1792: 214 Age = 19-69	Cross-sectional Study	Brief self-administered diet history questionnaire (BDHQ)	CES-D to measure depression	An a priori healthy diet quality score was inversely related to depression in both women and men. A traditional Norwegian dietary pattern was also associated with reduced depression in women and a Western-type diet was associated with increased anxiety in men and women.
Nanri et al. (2010)	2006	Japan	n = 521 309: 212 Age = 21-67	Cross-sectional Study	BDHQ	CES-D to measure depression	After adjusting for potential confounders, the dietary patterns were not related to the risk of depression for either "Healthy", "Western", "Bread and confectionary" or "Alcohol and accompanying".
Jacka et al. (2011)	1997	Australia	n = 5731 2477 :3254 Age = 46-49 & 74-79	Cross-sectional Study	Self-administered, optically readable validated FFQ of 169 food items	Depression and anxiety measured using the Hospital and Depression Scale (HADS)	The Mediterranean diet pattern was positively related with the cognitive function and a significant relation was noted with MMSE scores. However, no relationship was observed between the Mediterranean dietary pattern and GDS.
Sugawara et al. (2012)	2011	Japan	n = 791 303:488 Age = 22-86	Cross Sectional Study	BDHQ	Depressive symptoms were assessed using CES-D	Western dietary pattern was associated with higher GHQ-12 scores. No association was noted with a "Modern" diet and depression. Depressive and anxiety disorders as outcomes had inverse relationships with the traditional diet, which were further strengthened by adjustments for socioeconomic and lifestyle factors.
Hernández-Galliot and Goñi (2017)	2014	Spain	n = 79 36:41 Age = 75 +	Cross-sectional Survey	Trained dieticians using 3 non-consecutive 24-h diet recalls collected face to face food consumption data	Cognitive function was determined by the Mini Mental State Examination (MMSE), and depressive symptoms were assessed by the Geriatric Depression Scale (GDS)	Potential protective role of the MDP with regard to prevention of depressive disorders. Inverse dose-response relationships were found for fruit and nuts, the monounsaturated- to saturated-fat-to acids ratio, and legumes.
Jacka et al. (2010)	1994	Australia	n = 1046 Female cohort Age = 20 - 93	Cross-sectional Study	Cancer Council Victoria validated FFQ. Consisting of 74 foods and 6 alcoholic beverages	The Structured Clinical Interview for DSM-IV was used as a diagnostic tool for depression and 12-item version of the General Health Questionnaire (GHQ)	Greater adherence to the MeDi at midlife was associated with a lower risk of incident depressive symptoms, particularly in men. After adjustment of potential confounders, adherence to the MeDi was significantly associated with reduced incident depressive symptoms in men but not in women.
Sanchez-Villegas et al. (2009)	1999	Spain	n = 10 094 Age = 18-101	Prospective Cohort Study	Semi- quantitative FFQ of 136 food items previously validated in Spain	DSM-IV was used as a diagnostic tool for depression	A "typical Tuscan dietary pattern" was consistently associated with lower CES-D scores over a 9-year period in the Tuscan population.
Adjibade et al. (2017)	1994	United Kingdom	n = 3, 523 1.492: 2031 Age = 35-60	Prospective Cohort Study	MeDi adherence using repeated 24-h dietary records	CES-D was used to measure depressive symptoms.	
Vermeulen et al. (2016)	1998	Italy	n = 1362 Age = 18-102	Longitudinal Cohort Study	Validated FFQ of North-Central Italy and European Prospective Investigation into Cancer and Nutrition, consisting of 248 questions and 188 food items	CES-D scale was used to detect depressive	
	1999	Spain					

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**Table 1** (continued)

Author (year)	First year of study	Country	n = M:F Age (years)	Type of Study	Diet Measure	Depression Measure	Main Findings
Sánchez-Villegas et al. (2016)			n = 11 800 Age = 18-101 years	Prospective Cohort Study	Semi- quantitative FFQ of 136 food items previously validated in Spain	Antidepressant use and physician diagnosis was the criterion used to define depression	Participants with the highest adherence to the Mediterranean lifestyle showed a 50% relative risk reduction in depression risk as compared to those participants with the lowest adherence.
Albaraly et al. (2013)	1991	United Kingdom	n = 4215 Age = 35-55	Prospective Cohort Study	Semi- quantitative validated FFQ with 127 food items	CES-D was used to measure depressive symptoms.	AHEI score was inversely associated with depressive symptoms in a dose-response relationship in women but not in men. Women who maintained high AHEI scores during the 10-y period had lower odds of subsequent recurrent depressive symptoms than did women who maintained low AHEI scores.
Albaraly et al. (2009)	1997	United Kingdom	n = 3486 Age = 35-55	Prospective Cohort Study	Semi- quantitative validated FFQ with 127 food items	CES-D scale to measure depressive symptoms.	With adjustments for cofounders, participants in the highest tertile of the whole food pattern had lower odds of CES-D depression 5 years later than those in the lowest tertile. In contrast, high consumption of processed food was associated with an increased odds of CES-D depression scores.
Hodge et al. (2013)	1990	Australia	n = 8,660 Age = 50-69	Prospective Cohort Study	Self- administered 121-item validated FFQ	Kessler (K10) psychological distress scale and DSM-IV for anxiety/depressive diagnosis.	The MeDI score was inversely associated with psychological distress. Stronger adherence to a traditional Australian-style eating pattern was also associated with a lower K10 score at follow- up.
Sánchez-Villegas et al. (2015)	1999	Spain	n = 15 093 Age = 18-101	Longitudinal Cohort Study	Semi- quantitative FFQ of 136 food items previously validated in Spain	A self-reported physician-provided diagnosis of depression using the DSM-IV.	Inverse and significant associations were observed between the three (MDS, PDP and AHEI-2010) diet quality scores and depression risk.
Le Port et al. (2012)	1998	France	n = 12 404 9272: 31.32 Age = 45-60	Longitudinal Cohort Study	Qualitative 35-item validated FFQ of twenty food groups	Depression measured using CES-D.	The low-fat, western, high snack and high fat- sweet diets and low-fat/high snack diets were associated with higher likelihood of depressive symptoms. The highest quartile of traditional diet (fish and fruit consumption) was associated with fewer depressive symptoms in women and the healthy pattern in both men and women.
Rienks et al. (2013)	2001	Australia	n = 6,064 Female Cohort Age = 50-55	Cross-sectional Prospective Study	Validated FFQ of 74 food groups and 6 alcoholic beverages	CES-D to measure depressive symptoms	Higher consumption of the Mediterranean-style diet had a cross-sectional association with lower prevalence of depressive symptoms in 2001 and longitudinally with lower incidence of depressive symptoms in 2004.
Luciano et al. (2012)	2009	Scotland	n = 456 -669 Age = 70-73	Longitudinal Cohort Study	Scottish Collaborative Group 168-item validated FFQ	Depressive symptoms were measured using HADS.	Controlling for confounding factors no interaction effect of depressive symptoms and Mediterranean diet was observed on inflammation. However, a main effect of Mediterranean diet on change in C-reactive protein was significant and the 'Health Aware' diet on ferritin.
Skarupski et al. (2013)	1993	U.S.A	n = 3,502 Age = 56 +	Longitudinal Cohort Study	Validated, semi-quantitative FFQ	CES-D to measure depressive symptoms	Greater adherence to a Mediterranean dietary pattern was associated with a reduced number of newly occurring depressive symptoms. The annual rate of developing depressive symptoms was 98.6% lower among persons in the highest tertile of a MDP compared to lowest tertile group.
Chocano-Bedoya et al. (2013)	1996	U.S.A	n = 50,605 Female cohort Age = 50-77	Prospective Study	131-item semi-quantitative, validated FFQ	Depression was defined with both a clinical diagnosis of depression and antidepressants use. A broad definition included reported use of antidepressants or diagnosis of depression	Women with the highest scores for the Western pattern had 15% higher risk of depression than women with the lowest scores, but after additional

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**Table 1** (continued)

Author (year)	First year of Study	Country	n = M:F Age (years)	Type of Study	Diet Measure	Depression Measure	Main Findings
Ibarra et al. (2015)	-	Spain	n = 51 Age = 18+	RCT	Assigned to a Mediterranean dietary guideline	DSM-IV used for primary depression diagnosis. Hamilton Depression Rating Scale and The Mini International Neuropsychiatric Interview (MINI) were also used.	adjustment for psychological scores at baseline, results were no longer significant. Serum selenium and zinc levels were slightly low at basal point and serum selenium was inversely correlated with severity of depression. Nevertheless, no significant differences in micronutrient levels were observed after the Mediterranean dietary pattern prescription. The MeDi group had greater reduction in depression and improved mental health QoL scores at 3 months which were sustained at 6 months. Reduced depression was correlated with an increased MeDi score, nuts and vegetable diversity.
Parletta et al. (2017)	2014	Australia	n = 152 47:105 Age = 18–65	RCT	A Simple Dietary Questionnaire (SDQ)	Depression measured using DASS-21 and the Assessment of Quality of Life (AQoL)-8D scores were the primary outcome measures.	Participants assigned to MeDi + Nuts showed a significant lower risk of low plasma BDNF values as compared to the control group. Among participants with prevalent depression at baseline, significantly higher BDNF levels were found for those assigned to the MeDi + Nuts.
Sanchez-Villegas et al. (2011)	-	Spain	n = 243 Age = 55-80	RCT	Participants allocated to intervention group had interviews with trained dietitians	Secondary outcome was depressive incidence via self-diagnosis	Modified MeDi group were found to be associated with fewer depressive symptoms. With nutritional counselling support from a qualified dietitian and improvements in diet quality, positive changes can be achieved in a population with depression.
Opie et al. (2017)	2012	Australia	n = 50 Age = 18+	RCT	Modified Mediterranean diet determined by a Dietary Screening Tool, food diary and dietary habits assessed by a dietitian.	Depression diagnosed using DSM-IV and MADRS.	There was an inverse association with depression for participants assigned to a MeDi + nuts although not significant. When restricted to participants with DM type 2, the magnitude of the effect of the intervention with the MeDi + nuts did reach statistical significance.
Sanchez-Villegas et al. (2013)	2003	Spain	n = 3 923 Age = 55-80	RCT	Participants allocated to intervention group had interviews with trained dietitians.	Physician diagnosed depression or report of habitual use of antidepressant drugs.	Mediterranean dietary pattern reduces the onset of cognitive decline and depressive symptoms, and promotes optimal cognitive performance among healthy older adults
Knight et al. (2015)	2013	Australia	n = 166 Age = 65+	RCT	Participants allocated to intervention group had interviews and assistance by trained dietitians.	The CES-D to measure symptoms of depression.	

This table illustrates the author; first year of publication; country; number of participants, gender ratio and age range; study design; dietary measure; depressive measure employed; and main findings of all twenty-six studies included in this review.

Villegas et al., 2011); of these a further 33% had a sample size less than 100 participants (Ibarra et al., 2015; Opie et al., 2017). Age was the most common confounder adjusted for, with all studies reporting the age range or mean of participants. Cohort characteristics are summarized in Table 1.

### 3.4. Mediterranean diet and depression

Several observational studies examined the association of the Mediterranean diet and depression in middle aged cohorts. The SUN study cohort demonstrated in two longitudinal studies that the Mediterranean diet exhibited a 50% relative risk reduction in depression incidence when compared to those with lowest adherence and found an inverse dose-response relationship for the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders – fourth edition (DSM-IV) diagnosed depression with fruit, nuts, monounsaturated-to saturated-fatty-acids ratio and legumes (Sanchez-Villegas et al., 2009; Sánchez-Villegas, Ruíz-Canela, Gea, Lahortiga, & Martínez-González, 2016). These plant foods consistently appear to be associated with fewer depressive symptoms (Crichton et al., 2013). An Italian population-based cohort, Vermeulen et al. (2016) longitudinally examined a ‘Typical Tuscan’ diet which was adopted from Tuscany, Italy and was derived from traditional Mediterranean foods. This study found an inverse association between the Tuscan dietary pattern and depressive symptoms over a nine-year period in both men and women. However, one study demonstrated gender specific findings where dietary adherence was significantly associated with reduced incident depression in men but not in women (Adjibade et al., 2017).

Three intervention trials followed a six-month intervention period and found that individuals with depression who were prescribed a modified Mediterranean diet suffered fewer depressive episodes when compared to the control group (Ibarra et al., 2015; Opie et al., 2017; Parletta et al., 2017). Similarly, another two intervention trials examined depression in a cohort of individuals aged 55–80 years, over a three-year period (Sanchez-Villegas et al., 2011, 2013). Sanchez-Villegas and Colleagues (2011) demonstrated that participants who followed a Mediterranean diet supplemented with nuts experienced fewer depressive symptoms and had higher levels of BDNF. These findings have also been exhibited in participants with risk factors for type II diabetes (Sanchez-Villegas & Martínez-González, 2013).

### 3.5. Differences between dietary patterns

Several studies included in this review examined dietary patterns that included components of a Mediterranean dietary pattern and compared these with other Western type diets. Three cross-sectional studies comparing Mediterranean type diets with other dietary patterns were based in Japan (Miki et al., 2015; Nanri et al., 2010; Sugawara et al., 2012). These studies found that Japanese employees who consumed high intakes of vegetables, fruit, soy products, mushrooms and tea had fewer depressive symptoms (Miki et al., 2015; Nanri et al., 2010). Contrastingly, Sugawara et al. (2012) employed a similar study design among a community dwelling population in Japan and found there was no association between several dietary patterns and depression.

Two longitudinal studies based on British office-based civil servants exhibited similar findings when comparing, over a five-year period, a whole food diet sourced from vegetables, fish and fruit to a heavily processed diet (Akbaraly et al., 2009, 2013). These longitudinal studies found that adherence to dietary patterns that are characterised by higher loadings of plant based foods were associated with fewer depressive symptoms (Akbaraly et al., 2009; Le Port et al., 2012). In contrast, high consumption of processed foods were frequently associated with increases in depressive symptoms (Akbaraly et al., 2009; Le Port et al., 2012). Overall, dietary intake of food sources characteristic of the Mediterranean dietary pattern were consistently protective

against depressive symptoms whilst Western diets appear to be more detrimental (Jacka et al., 2010; Jacka, Mykletun, Berk, Bjelland, & Tell, 2011, 2017).

Studies have also shown that the Mediterranean dietary pattern may not be the only healthy standard of eating that may exert a beneficial role for individuals with depression. Overall, dietary patterns which have higher intakes of plant based foods and whole grains appear to exhibit a similar impact on depression pathology as those which adhere to the Mediterranean diet (Hodge, Almeida, English, Giles, & Flicker, 2013; Sanchez-Villegas et al., 2015).

### 3.6. Women, aging and depression

A number of studies included in this review collected participants from prespecified demographics which included female only cohorts and aging individuals. Female based cross-sectional studies demonstrate that women who adhere to a dietary pattern characterised by vegetables, fruit, wholegrains, fish and meat suffer fewer depressive symptoms (Jacka et al., 2010; Rienks et al., 2013). These studies also show that greater adherence to Western style diets are associated with poorer health outcomes in women. However, longitudinal analyses in the Women’s Nurses’ Health study, demonstrates that neither a prudent diet characterised by high intakes of plant based foods or a Western diet high in meat and processed foods is associated with any changes in depressive status (Lucas et al., 2014).

Several studies examined the Mediterranean dietary pattern in aging cohorts; however, recall required by participants to remember foods can become particularly challenging in these individuals and as a result, there are inconsistent findings. Two observational studies which examined the Mediterranean diet in aging cohorts found no association with dietary adherence and depression pathology (Hernández-Galiot & Goñi, 2017; Luciano et al., 2012). However, the Chicago Healthy Aging Project reiterates the findings exhibited in middle aged cohorts which suggest that adherence to diets characterised by vegetables, fruits, legumes and wholegrains are associated with reductions in depressive risk (Skarupski et al., 2013). Moreover, greater adherence to Mediterranean style diets have also shown improvements in cognitive performance in addition to fewer depressive symptoms in these individuals (Knight et al., 2015).

## 4. Discussion

In recent years there has been a surge of literature discussing the importance of diet and mental health. This systematic review provides a comprehensive appraisal of the current literature and explores the strength of evidence associated with the Mediterranean dietary pattern for the treatment and prevention of depression. All intervention control trials and majority (85%) of observational studies included in this review support the hypothesis that a Mediterranean dietary pattern characterised by vegetables, fruit, legumes, nuts, cereals, olive oil and fish reduce depressive symptoms or abate its development. Moreover, lower adherence to a Mediterranean diet that is characterised by higher intakes of meat, dairy and processed foods was associated with a greater risk of developing depression. Overall, this systematic review echoes the protective properties of the Mediterranean dietary pattern and provides a potentially therapeutic intervention for individuals with depression.

Research suggests that dietary contribution of several nutrients present in the Mediterranean dietary pattern are implicated in central nervous system membranes, methylation reactions involved in monoamine neurotransmitters, reducing oxidative stress and improving overall inflammatory status (Adjibade et al., 2017; Sanchez-Villegas et al., 2009, 2015). A number of individual dietary components of the Mediterranean diet have been found to be protective against depression; however, these cannot be consumed sustainably in isolation and does not provide a realistic approach for individuals to implement on a

day to day basis. As a result, recent research has shifted towards investigating global dietary patterns that demonstrate synergistic effects on depression pathology. Epidemiological findings are consistent in showing that greater adherence to dietary patterns characterised by a high intake of fruit, vegetables, cereals and legumes and low intake of meat and dairy are associated with a lower risk of depression (Adjibade et al., 2017; Akbaraly et al., 2009; Sanchez-Villegas et al., 2009; Skarupski et al., 2013). Analysis of dietary pattern reflects the cumulative effect of whole nutrient combining and echoes the complexity of diet and its relationship with disease risk.

The Mediterranean diet contains several nutrients that support and foster a healthy mind (Knight et al., 2015). Polyunsaturated fatty acids found mostly in nuts, seed, fish and seed oils are implicated in the dynamic structure of neuronal membranes within the central nervous system and upsurge their permeability of serotonin transport (Sanchez-Villegas et al., 2015). Moreover, folate, B12 and B6 are integral to methylation reactions, such as those involved in serotonin and other monoamine neurotransmitters, which is one pathophysiologic basis for negative mood in depressive disorders (Sanchez-Villegas et al., 2009). The majority of studies included in this review underscore the importance of the Mediterranean dietary pattern for its protective role in depression pathology; however, there are also examples of studies finding no statistically significant association (Chocano-Bedoya et al., 2013; Hernández-Galiot & Goñi, 2017; Luciano et al., 2012; Sugawara et al., 2012). Luciano et al. (2012) did not report effect size suggesting that the study may not have been sufficiently powered and Chocano-Bedoya et al. (2013) lacked external validity by limiting participant recruitment to female nurses. The remaining two studies were cross-sectional in nature (Hernández-Galiot & Goñi, 2017; Sugawara et al., 2012). There are a number of factors that may have contributed to this, including the inability to elucidate a cause-effect relationship and any potential selection bias.

The Mediterranean diet is considered an ideal standard for healthy eating indebted to its antioxidant and anti-inflammatory properties. A protective mechanism has been established in cardiovascular disease (Ibarra et al., 2015), diabetes (Sanchez-Villegas et al., 2013), metabolic syndrome (Sanchez-Villegas et al., 2015) and more recently depression (Adjibade et al., 2017; Opie et al., 2017; Parletta et al., 2017). There are several identifiable foods within the Western dietary pattern which have been shown to predispose to inflammatory disease through the upregulation of pro-inflammatory cytokines. Western dietary patterns characterised by relatively high consumption of sugar-sweetened soft drinks, refined grains, red meat, and low in wine, olive oil and cruciferous vegetables, were correlated with high inflammatory biomarkers (Akbaraly et al., 2009). Several studies which compared components of the Mediterranean diet to a Western dietary pattern establish that a higher consumption of processed foods was associated with increased depressive symptoms (Akbaraly et al., 2009; Amr & Volpe, 2012; Baskin, Hill, Jacka, O'Neil, & Skouteris, 2015; Dipnall et al., 2015; Jacka et al., 2010, 2011, 2017; Le Port et al., 2012). These findings propose that the relationship between diet and depression, may in part, be mediated by inflammation.

A number of factors were investigated for possible reasons for heterogeneity between the findings of studies. The use of different dietary assessment methods could potentially influence the association between diet and depression. Despite the greater precision associated with 24-h dietary recall (Adjibade et al., 2017; Hernández-Galiot & Goñi, 2017), it does not provide a long-term viewpoint on individual dietary patterns. The majority of studies (69%) utilised Food Frequency Questionnaire's (FFQ) which provide a long-term analysis of food intake; however, it is subject to bias and misclassification errors introduced as a result of food list limitations, memory recall and perceptions of portion sizes. There was also variability in determining dietary compliance with the use of diet quality scores, indexes or other methods among studies. The strength of the diagnostic measures and symptom inventories used will subject the diet- depression relationship

to variability. Depressive inventories are self-reported and therefore possess an inherent predisposition to bias, and many questionnaires also vary in their scoring and classifying of depressive cases. This may be particularly erroneous for older participants with poor cognitive function and recall. Moreover, some studies also relied primarily on habitual intake of anti-depressants as a proxy for depression (Chocano-Bedoya et al., 2013; Sanchez-Villegas et al., 2013, 2015; Sánchez-Villegas et al., 2016) which may inaccurately assume depressive status.

The current review has systematically appraised existing literature and proposes that an overall dietary pattern characterised by high consumptions of fruit, vegetables, legumes, cereals, olive oil, red wine and fish may reduce depression risk. This suggests that there are modifiable risk factors such as diet, involved in the pathogenesis of depression and highlights the importance of dietary guidelines for impending prevention strategies for depression. Further longitudinal studies and intervention control trials with improved methodology of repeated diet measurements, better validation of outcome measures, larger sample sizes and assessment of potential relapses are necessary to better understand the biochemical influence components of the Mediterranean diet has on depression.

#### 4.1. Limitations

It is important to consider some limitations in this systematic review. Firstly, there is methodological disparity concerning the definition of the Mediterranean diet among studies, making it difficult to ascertain a consistent dietary pattern. Furthermore, 77% of the studies included in this review are observational in nature which highlights the concern of reverse causality as a potential source of bias in the relationship between the Mediterranean dietary pattern and depression. Cross-sectional study designs are limited in their ability to establish causal relationships as depression and diet may incite bi-directional causality. Although longitudinal studies may establish with greater assurance whether dietary habits precede depressive symptoms it is still important to consider the complex influences regarding dietary compliance which may confound the diet and depression relationship. Lastly, a meta-analysis was not included in this review as a recent publication conducted a quantitative analysis providing information on several dietary patterns, one of which was a Mediterranean diet, with regard to its impact on depression (Molendijk et al., 2018).

## 5. Conclusion

This review sought to examine the association between the Mediterranean diet and depression, and builds on previously published papers that focus more broadly on numerous dietary patterns. It saw that an extensive analysis of the articles was performed, in an attempt to prove a non-biased, clear and comparative interpretation of the results. The Mediterranean dietary pattern offers a potential alternative or useful adjunct to current treatments in place for depression, which procures few side effects, lessens disease severity and demonstrates a cost-effective measure that can be implemented globally. Future studies should consider conducting head-to head clinical trials comparing mainstream treatment therapies with the Mediterranean diet to extrapolate its therapeutic potential on depressive symptoms. It is expected that forthcoming high quality observational studies and randomized control trials will overcome the current limitations in place to better understand whether a true causal relationship exists between the Mediterranean diet and depression.

## Contributors

AA was involved in conducting the search, screening of articles and drafting the manuscript. AG conceptualized and oversaw the review methodology and assisted in drafting the manuscript. HB double screened the articles and drafted the manuscript. CS conceptualized the

review and drafted the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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### Conflicts of interest

CS has provided clinical consultancy and been on scientific advisory committees for the Australian Commonwealth Scientific and Industrial Research Organisation, Alzheimer's Australia, University of Melbourne and other relationships which are subject to confidentiality clauses. She has been a named Chief Investigator on investigator driven collaborative research projects in partnership with Pfizer, Merck, Bayer and GE. She may accrue revenues from patent in pharmacogenomics prediction of seizure recurrence.

AA, HB, and AG declare no conflicts.

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### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.npbr.2019.05.007>.

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