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The Effects of Dietary Improvement on Symptoms of Depression and Anxiety: A Meta-Analysis of Randomized Controlled Trials

Joseph Firth, PhD, Wolfgang Marx, PhD, Sarah Dash, PhD, Rebekah Carney, PhD, Scott B. Teasdale, PhD, Marco Solmi, MD, Brendon Stubbs, PhD, Felipe B. Schuch, PhD, André F. Carvalho, MD, Felice Jacka, PhD, and Jerome Sarris, PhD

ABSTRACT

Objective: Poor diet can be detrimental to mental health. However, the overall evidence for the effects of dietary interventions on mood and mental well-being has yet to be assessed. We conducted a systematic review and meta-analysis examining effects of dietary interventions on symptoms of depression and anxiety.

Methods: Major electronic databases were searched through March 2018 for all randomized controlled trials of dietary interventions reporting changes in symptoms of depression and/or anxiety in clinical and nonclinical populations. Random-effects meta-analyses were conducted to determine effect sizes (Hedges' g with 95% confidence intervals [CI]) for dietary interventions compared with control conditions. Potential sources of heterogeneity were explored using subgroups and meta-regression analyses.

Results: Sixteen eligible randomized controlled trials (published in English) with outcome data for 45,826 participants were included; the majority of which examined samples with nonclinical depression (n = 15 studies). Nonetheless, dietary interventions significantly reduced depressive symptoms (g = 0.275, 95% CI = 0.10 to 0.45, p = .002). Similar effects were observed among high-quality trials (g = 0.321, 95% CI = 0.12 to 0.53, p = .002) and when compared with both inactive (g = 0.308, 95% CI = 0.02 to 0.60, p = .038) and active controls (g = 0.174, 95% CI = 0.01 to 0.34, p = .035). No effect of dietary interventions was observed for anxiety (k = 11, n = 2270, g = 0.100, 95% CI = −0.04 to 0.24, p = .148). Studies with female samples observed significantly greater benefits from dietary interventions, for symptoms of both depression and anxiety.

Conclusions: Dietary interventions hold promise as a novel intervention for reducing symptoms of depression across the population. Future research is required to determine the specific components of dietary interventions that improve mental health, explore underlying mechanisms, and establish effective schemes for delivering these interventions in clinical and public health settings.

Registration: PROSPERO Online Protocol: CRD42018091256.

Key words: affective disorders, mental illness, mood, nutrients, nutrition.

Podcast SDC Supplemental Content

From the NICM Health Research Institute (Firth, Sarris), Western Sydney University, Westmead, New South Wales, Australia; Division of Psychology and Mental Health (Firth, Carney), Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom; Deakin University (Marx, Dash, Jacka), Food & Mood Centre, IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Geelong, Victoria, Australia; Baker Heart and Diabetes Institute (Dash), Metabolic and Vascular Physiology, Melbourne, Victoria, Australia; Youth Mental Health Research Unit (Carney), Greater Manchester Mental Health NHS Foundation Trust, Manchester, United Kingdom; School of Psychiatry (Teasdale), Faculty of Medicine, UNSW Sydney, Sydney, New South Wales, Australia; Keeping the Body in Mind Program (Teasdale), South Eastern Sydney Local Health District, Sydney, New South Wales, Australia; Neurosciences Department (Solmi), University of Padua, Padua, Italy; Padua University Hospital (Solmi), Psychiatry Unit, Padua, Italy; Physiotherapy Department (Stubbs), South London and Maudsley NHS Foundation Trust, London, United Kingdom; Department of Psychological Medicine (Stubbs), Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom; Post Graduate Program in Health and Human Development (Schuch), La Salle University, Canoas, Brazil; Hospital de Clínicas de Porto Alegre (Schuch), Federal University of Rio Grande do Sul, Porto Alegre, Brazil; Department of Psychiatry (Carvalho), University of Toronto, Toronto, Ontario, Canada; Centre for Addiction and Mental Health (CAMH) (Carvalho), Toronto, Ontario, Canada; Black Dog Institute (Jacka), Sydney, New South Wales, Australia; Murdoch Childrens Research Institute (Jacka), Centre for Adolescent Health, Melbourne, Victoria, Australia; and Department of Psychiatry (Sarris), University of Melbourne, Professorial Unit, The Melbourne Clinic, Melbourne, Victoria, Australia.

Address correspondence to Joseph Firth, PhD, NICM Health Research Unit, University of Western Sydney, Penrith, NSW 2750, Australia. E-mail: j.firth@westernsydney.edu.au

FJ and JS are co-final authors.

All authors contributed substantially toward the writing of the article and interpretation of the findings. JF conducted statistical analyses.WM, SD, RC, and ST conducted searches and data extraction. MS, BS, FS, FJ, and JS contributed to the intellectual conception of the article and the interpretation of results.

Received for publication August 3, 2018; revision received November 30, 2018.

DOI: 10.1097/PSY.0000000000000673

INTRODUCTION

Depressive disorders affect more than 300 million people around the world and are associated with unemployment, poor physical health, impaired social functioning, and, in its most severe forms, suicide (1). Thus, depressive disorders incur considerable burden not only for individuals but also for society because of the high economic cost from lost productivity and demand on healthcare services (2). The same can be said for anxiety disorders, which, along with depression, are also classified as "common mental disorders" because of their prevalence across the globe, with approximately one in five people experiencing one of these conditions for any given year (3). Standard treatments for common mental disorders comprise psychopharmacological and psychotherapeutic interventions. Although these have established efficacy in depression, a substantial proportion of people do not achieve remission using such strategies (4).

Furthermore, subclinical symptoms of depression and anxiety are also highly prevalent across the general population, among those without clinically diagnosed common mental disorders. These symptoms, although falling short of diagnostic thresholds, still impede upon quality of life and socio-occupational functioning, incurring even further personal and economic burden on a population scale (5). Therefore, new primary and/or adjunctive methods to address symptoms of depression and anxiety across the population are urgently needed.

Emerging evidence suggests that diet may influence the onset of mood disorders and specifically depression. For instance, many studies described in recent systematic reviews have demonstrated associations between measures of diet quality and the probability of and risk for depression (6,7). Moreover, proinflammatory dietary patterns are also associated with a significantly higher incidence of depressive symptoms, even among those without diagnosed mental disorders (8–10). A previous systematic review examined the benefits of various dietary interventions for depressive symptoms and anxiety, but using only narrative synthesis (11). Results generally suggested positive effects of dietary interventions on subclinical depression and anxiety, measured as secondary outcomes (11). However, the previous review did not apply meta-analytic techniques to quantify the findings and the results did not include recent interventions in clinical populations, Thus, it remains unclear if dietary interventions can improve symptoms of depressive and anxiety (in either clinical or nonpsychiatric samples) and the magnitude of any effects. Moreover, the potential influence of moderators such as sex, professional delivery, or the quality of studies on treatment outcomes is uncertain. Therefore, we aimed to determine the efficacy of dietary interventions for symptoms of depression and anxiety by conducting a meta-analysis of all randomized controlled trials (RCTs) examining this therapeutic strategy to date. We also used subgroup analyses to examine effects of dietary interventions on depression/anxiety in both clinical and nonclinical populations and to explore which aspects of these are associated with any potential greater efficacy. The findings of this meta-analysis will provide the first overall estimate of the efficacy of dietary interventions for reducing symptoms of depression and anxiety, along with informing self-management strategies for people with these conditions, and suggest directions for future research.

CI = confidence interval, **MDD** = major depressive disorder, **RCT** = randomized control trial

METHODS

This meta-analysis followed the PRISMA statement for transparent, comprehensive reporting of methodology and results (12). To eliminate researcher bias, the search strategy, inclusion criteria, and data extraction, overall and prespecified subgroup analyses used in this meta-analysis were prospectively registered with PROSPERO (CRD42018091256).

Search Strategy

The primary search was performed using OVID Medline on December 03, 2018, in line with the preregistered protocol, using the key word terms "Diet" with "Mediterranean" or "Therapy" or "Educat*" or "Counsel*" or "Intervention*" or "Treatment*" AND "Randomized Controlled Trial" or "Random Allocation" or "Clinical Trial" or "Control Groups" AND "Depression" or "Anxiety" or "Depressive Disorder." We performed additional searches of Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, Allied and Complementary Medicine (AMED), Embase, Health Management Information Consortium (HMIC), and PsycINFO, using the same keywords, along with a further general search of "Google Scholar" to capture any articles not captured by the main search. The full search details are presented in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A537.

Eligibility Criteria

Only English articles published in peer-reviewed journals were included. We aimed to determine effects of dietary interventions on symptoms of depression and anxiety in all clinical and nonclinical populations, including depression (e.g., major depressive disorder [MDD]) or anxiety, comorbid depression, and anxiety, and in samples with depressive/anxiety symptoms that did not reach clinical thresholds. No restrictions were placed on diagnosis or any other clinical or demographic characteristics of eligible samples.

Eligible studies were RCTs comparing the effect of dietary interventions to nondietary control conditions. All "whole-of-diet" dietary interventions were eligible, delivered via any format, including individualized dietary counseling, group dietary classes, and standardized dietary prescription. In addition, all "types" of diet were eligible, including those primarily aiming to decrease the intake of unhealthy foods, improve nutrient intake, and/or those designed to restrict calorie intake to order induce weight loss. Because we aimed to establish the effects of whole-of-diet interventions for depression and anxiety, rather than examining only individual foods/nutrients, interventions focusing only on a single food component (e.g., eating more fish) were not included. Multicomponent life-style interventions were only eligible where comparator conditions had adequately controlled for active nondietary aspects of the intervention. For instance, multicomponent interventions such as "exercise with diet" would only be eligible if compared with an "exercise alone" control condition, so that the effects of the dietary component could be accurately determined. Crossover trials were only included where between-group differences from the first leg of the crossover trial were reported (so that parallel groups comparisons could be performed from the data).

Studies using both "inactive control groups" and "active control groups" were eligible for inclusion. Inactive control groups were classified as those in which participants maintained their habitual diets and received no additional active intervention during the trial period (or put onto a "waitlist" until pre- and postmeasures had been collected from both groups). Conversely, "active control groups" were categorized as any that compared diet with other active interventions or used comparator conditions designed to control for general "intervention effects" using either (*a*) benign interventions not aiming to treat depression/anxiety, (*b*) psychosocial interventions, e.g., social support, counseling, or exercise, or (*c*) other forms of activities, such as "time and attention"–matched patient contact.

All studies matching the previous criteria and reporting changes in at least one quantitative measure of depression or anxiety with sufficient detail for meta-analysis were included. Two independent investigators judged article eligibility (JF and RC) with any disagreements resolved through discussion. Where study design matched eligibly criteria, but data were insufficiently reported, study authors were contacted twice for 2 months to request the necessary data.

Data Extraction

A systematic extraction form was used to extract the following data from each eligible study:

(i) *Sample information:* sample size (*n*), sex (% females), mean age of participants (years), population sampled health status (diagnostic information or relevant inclusion criteria),
(ii) *Intervention:* primary aim of dietary change (e.g., weight loss or increasing nutritional intake), dietary program summary, individual delivering the intervention (e.g., dietitian or researcher), any additional intervention components (e.g., in-person or remotely delivered nondietary additions), control condition, intervention length (weeks).
(iii) *Effects on depressive or anxiety symptoms*: changes in total depressive/anxiety symptoms before and after dietary and control conditions, using any clinically validated rating scale. For studies that used more than 1 measure of depression, a mean total change was calculated by pooling outcomes from each measure.

Study quality was determined through applying the quality criteria from the Academy of Nutrition and Dietetics (formerly the American Dietetic Association [ADA]) in the ADA quality assessment tool (13). This applies set criteria for examining allocation bias, selection bias, blinding, data collection, trial retention (along with methods of handling dropouts), and interventional adherence. Each study was categorized as positive, negative, or neutral using the standardized "quality consideration questions" described in the ADA Evidence Analysis Manual (13). All studies were included in the meta-analysis, regardless of ADA rating.

Statistical Analyses

Meta-analyses were conducted using Comprehensive Meta-Analysis 2.0 (14), using a random-effects model (15) to account for the expected heterogeneity between studies. The total difference in changes in symptoms of depression and anxiety from dietary interventions versus control conditions were pooled to compute the overall effect size of dietary interventions (as Hedges *g*), with 95% confidence intervals (CI). For RCTs reporting comparisons of dietary interventions with more than one control group, we pooled comparisons with each control group to generate an overall estimated effect of dietary interventions, to make use of all available data. For the one study reporting sex groups separately (16), a combined estimate across both sexes was calculated as Hedges *g* effect size and used for primary analyses. After computing main effects, a sensitivity analysis was applied to investigate effects of dietary interventions in RCTs that had a "positive" ADA rating.

The degree of statistical heterogeneity in the meta-analyses was quantified using Cochran's Q and I^2 values. Risk of publication bias was examined by applying Eggers' regression to all previously mentioned analyses. Furthermore, a Duval and Tweedie's "trim-and-fill" analysis was applied to the random-effects models, to recalculate the pooled effect size after statistically accounting for any studies that may introduce publication bias (e.g., small studies with large effect sizes). In addition, a funnel plot of study effect sizes was generated from primary analyses, for a visual inspection of publication bias.

Prespecified subgroup analyses were conducted to examine how effects of dietary interventions differed when (*a*) comparing diet with either waitlist/inactive control conditions or active control conditions, (*b*) in "clinical" (i.e., patients with diagnosed depressive/anxiety disorder) and "nonclinical" (i.e., people without diagnoses of depression or anxiety), or (*c*) comparing interventions that had combined "diet with exercise" to control groups using exercise alone. In addition, we conducted a range of post hoc analyses, to examine putative factors that may influence the effects of dietary interventions. Specifically, we examined how changes in depressive symptoms were influenced the following factors: studies' sex distribution, mean sample age, type of diet used, how the intervention was delivered, intervention length (weeks), and study quality (measured with ADA scale).

RESULTS

Included Studies and Participant Details

The full search and screening process are shown in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A537. After the removal of duplicate articles from the systematic search of electronic databases, 26 articles were identified as potentially eligible after the title and abstract screening stage. Screening of the full-text versions resulted in 10 of these being excluded, and 16 identified as eligible for inclusion. The additional search of Google Scholar identified further two possible trials, although these were deemed ineligible after full-text screening. Details on the ineligible articles and reasons for exclusion are displayed in Supplement 1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A537.

Therefore, a total of 16 RCTs were included in the analyses; reporting outcome data from 45,826 individuals (median average age = 55 years, range = 21–85 years). The results from the ADA Quality Assessments for each study are displayed in Supplemental Digital Content 2, http://links.lww.com/PSYMED/A538. This showed that only one study scored 12/12 for study quality (17), 10 others met the criteria for positive on ADA scale by scoring 9 or higher (categorized as "high quality") (18–27), and five studies scored lower than 9 (categorized as low/neutral quality) (16,28–31). One reported outcome data in a format not suited for meta-analysis, but the corresponding authors provided the required data for inclusion (23).

Depressive symptoms were measured by all 16 studies, whereas anxiety outcomes were measured by only 11 of the 16 eligible trials. Changes in symptoms were assessed using the total scores from the following measures: "Centre for Epidemiological Studies Depression" (19,22,32); the "Beck Depression Inventory" (16,21,27,28,33); the "Hamilton Rating Scale for Depression" (28,34); the "Montgomery-Åsberg Depression Rating Scale" (17,35); the Geriatric Depression Scale (23,29,36), the Taylor Manifest Anxiety Scale (16,37), and the subscale scores for depression/anxiety from the following measures: the "Hospital Anxiety Depression Scale" (17,20,26,38); the Short-Form Health Survey (18,27,39); the Brief Symptom Inventory (24,25,28,40); the Profile Of Mood States (41) (17Wardle, 2000 #10083, 30, 31), and the General Well-Being Schedule (31,42). However, only one study examined the effects of a dietary intervention in a sample with primary diagnosis of clinical depression (17), with all the remaining studies examining effects on comorbid, subclinical, or secondary symptoms of depression/anxiety (see Table 1 for details). Across the different types of diets used by the studies, nine interventions were primarily aimed at improving nutrient intake ($n = 9$), four aimed to decrease fat intake ($n = 4$), and four were designed to reduce bodyweight ($n = 4$). The specifics of dietary interventions differed substantially across studies, and summaries for each are displayed in Table 1. Interventions ranged from 10 days to 3 years in length.

Overall Effects of Dietary Interventions on Depression

Figure 1 displays the pooled effect size from dietary interventions on depressive symptoms, along with individual effects from each

TABLE 1. Details of Included Studies

	Sample Details	Diet/ Control, *n/n*	Age	Study Aims	Design	Dietary Intervention Details	Other Intervention Aspects	Relevant Outcome Measures
Agarwal et al. 2015 (18)	BMI > 25 and/or previous diagnosis of type 2 diabetes	142/150	43.8	Assess the benefits of workplace dietary intervention on mental health.	2-arm cluster randomized trial, comparing 18 wk of workplace dietary intervention versus control settings.	Participants were asked to follow a low-fat vegan diet. Encouragement was provided for the throughout the study in weekly lunch-hour group sessions at work. Group sessions included nutrition education lectures, cooking demonstrations, and discussion. Ongoing support was provided by an interactive online message board. Workplace cafeterias also provided foods suitable for the low-fat vegan diet.	Participants also advised to take a multivitamin	SF-36 (depression and anxiety subscales).
Assaf et al. 2015 (19)	Healthy postmenopausal women aged 50–79 y	17,335/ 25,698	NR	Assess the effect of a low-fat diet intervention on HRQoL, depressive symptoms, and cognition.	2-arm randomized controlled crossover study comparing low-fat diet to no dietary intervention.	During 18 sessions, delivered in a group setting by nutritionists, dietary education was provided to reduce fat intake to 20% of daily energy while increasing fruit, vegetable, and grain intake.	None	CES-D (modified 6-item)
Einvik et al. 2010 (20)	Men with hyperlipidemia who had participated in Oslo Diet and Antismoking Study	253/252	70	Examine whether dietary counseling influences health behaviors and psychological health in high-risk males 25 y after taking part in a life-style program.	Three-year prospective follow-up of a life-style intervention using a 2 × 2 RCT comparing dietary advice combined with a placebo/n-3 PUFA supplement versus no dietary advice with placebo/n-3 PUFA supplement.	Dietary counseling from a clinical nutritionist to increase use of vegetable oils/margarine, fruit and vegetables, and fish, and decrease use of meat and animal fats. Overweight individuals encouraged to reduce calories. Participants met with nutritionist every 6 mo.	Half of individuals in both diet and control conditions also randomized to receive n-3 PUFA, the other half placebo capsules.	HADS

Endevelt et al. 2010 (29)	Older, community dwelling adults (75 y+) at nutritional risk according to the MNA-sf	35/33/59	84.5	Determine the impact of intensive, dietitian-led nutritional intervention on health and nutritional status of malnourished community dwelling older adults.	3-arm, clinical trial comparing effectiveness of an intensive dietary intervention versus medical treatment with only educational materials on nutritional versus a nonrandomized untreated group (which was not included in the meta-analyses).	The dietary intensive treatment group received five meetings, providing individualized treatment from a dietitian, with intensity based on severity of undernutrition. The medical treatment group received a booklet on nutrition education for older adults from a primary care physician.	None	GDS
Forster et al. 2012 (23)	Older adults in South Yorkshire, UK living in the community	72/70/67		Determine the effect of a dietary intervention and micronutrient supplementation on clinical impact of infections, depression, quality of life.	A randomized, placebo-controlled intervention trial comparing effects of dietary intervention, daily micronutrient supplement and placebo.	Dietary intervention group asked to consume at least five portions of fruits and vegetables per day, consume whole grain bread, consume fish twice per week, and consume nuts at least once a week. Pre-prepared salads, vegetables, fruits were provided when available, and menu suggests and portion size information was provided, and a supermarket home delivery service delivered food directly to participants.	Dietary intervention was tailored to participants based on preferences, intention of increasing intake of certain vitamins and minerals.	GDS
Hyyppa et al. 2003 (24)	Untreated hypercholesterolemic men; 35–64 y; BMI <32; otherwise healthy	60/60	48.4/48	Assess the effect on mood of both separate and combined effects of a Mediterranean diet intervention and treatment with simvastatin.	Randomized double-blind placebo-controlled crossover trial comparing Mediterranean diet intervention (+ simvastatin/placebo) and habitual diet (+ simvastatin/placebo).	Instructed to adhere to a Mediterranean diet for 12 wk. Max 10% kcal from saturated fat and trans fats, <250 mg/d cholesterol, 4 g/d n-3 fatty acids, increased fruit, vegetables and fiber intake and advised to consume lean meat, low-fat dairy, fish twice per week. Free-food exchanges supplied (e.g., margarine).	Randomized to receive either simvastatin or placebo.	BSI

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TABLE 1. *(Continued)*

	Sample Details	Diet/ Control, *n/n*	Age	Study Aims	Design	Dietary Intervention Details	Other Intervention Aspects	Relevant Outcome Measures
Imayama et al. 2011 (25)	Obese females; 50–75 y; BMI >25 (>23 Asian-American); <100-min/wk physical activity; postmenopausal not on HRT; no serious medical conditions or adverse health behaviors.	118/117/ 117/87	58	Examine the individual and combined effects of dietary weight loss and exercise interventions on mental health and quality of life.	12-mo RCT comparing dietary weight loss (D), aerobic exercise (E), combined diet and exercise (DE), and inactive controls (C) using a pre-post repeated measures design.	Calorie restriction diet modified from the DPP life-style and Look AHEAD (Action for Health in Diabetes) trial, with goals of: calorie intake 1200–2000 kcal/d based on weight, <30% calories from fat, 10% weight loss within 24 wk, and maintenance for the remainder. Small group sessions 2×/wk and communication with dietitians 2× per month via e-mail/phone. Sessions include strategies and skills to achieve caloric and weight loss goals including self-monitoring, goal setting, coping strategies, and problem-solving.	Exercise intervention 45 min/d of mod-vig aerobic exercise, 5 d/wk including 3 supervised sessions by an exercise physiologist.	BSI-18
Jacka et al. 2017 (17)	Adults 18 y + with moderate to severe depression according to DSM-IV, MADRS ≥18, 75 < diet screening tool	33/34	40.3	Assess the effect of a dietary intervention as a treatment for major depression.	2-arm randomized controlled crossover study comparing Mediterranean diet to social support for 12 wk.	Personalized nutrition intervention delivered by a dietitian based on a modified Mediterranean diet. Intervention included motivational interviewing, goal setting, and the increase of common Mediterranean foods (fruits, nuts, oily fish, olive oil).	Participants provided with food hampers.	MADRS, HADS, POMS

Jenkinson et al. 2009 (26)	Adults 45 y+; BMI >28; knee pain but otherwise healthy	122/109/82/76	61	Determine whether individualized interventions of diet and/or exercise reduces knee pain in overweight adults.	Two-year RCT comparing a diet intervention (D), exercise intervention (E), combined diet and exercise (DE), and advice alone (C).	Individualized dietary advice following review of a 7-d food diary to create a deficit of 2.5 MJ/600 kcal/d in line with healthy eating principles (reduced salt/sugar, increased fruit/vegetables/fiber, smaller portion size) to achieve weight loss of 0.5–1 kg/wk. Advice and newsletters provided and home visits 1×/mo for 6 mo, then every other month for the remainder.	Exercise arm included strengthening, functional and aerobic exercises demonstrated by the dietitian to be conducted at home.	HADS
Kasckow et al. 2014 (27)	Adults 50 y+, with ≥11 on the CES-D scale and experienced a significant traumatic event, recruited from larger "Prevention of Depression in Older African Americans"	31/29	62.74/65.66	Assess the benefits of PST-PC compared with a dietary education intervention in people with subsyndromal depression and psychological trauma.	2-arm RCT comparing PST-PC versus dietary education (DIET) and followed up for 2 y.	Coaching in healthy eating based on general nutrition guidelines, e.g., US Department of Agriculture Food Pyramid. Help with weekly menus, shopping lists, food coupons, and discussions around access, cost, and culturally specific foods. Initial 1-h session followed by 30 min across 6–8 sessions and semiannual boosters for 15 mo.	None	HAM-D, BDI, BSI-A
Kasckow et al. 2014 (28)	Veterans 50 y + with ≥11 on the CES-D scale	11/12	63.1	Assess the benefits of problem-solving therapy compared with an attention-only dietary education intervention.	2-arm RCT comparing problem-solving therapy with dietary education intervention.	For 6–8 sessions, participants were provided coaching in healthy eating practices using general nutrition guidelines and practical advice. Topics covered cost of food, meal preparation, cultural factors for healthy food, and preparing grocery lists.	None	HAM-D, BDI, SF-36 (depression and anxiety subscales)

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TABLE 1. *(Continued)*

	Sample Details	Diet/ Control, *n*/*n*	Age	Study Aims	Design	Dietary Intervention Details	Other Intervention Aspects	Relevant Outcome Measures
Kiernan et al. 2001 (16)	Adults 25–49 y; men BMI 28–34; women BMI 24–30 but otherwise healthy	71/79	38.5	Examine the effect of a dietary weight loss program on psychological health.	12-month RCT comparing dietary intervention, to controls and a diet + exercise program using pre-post repeated measures design.	Dietary changes as recommended by the National Cholesterol Education Program Step 1 (low saturated fat, low cholesterol diet). Participants attended weekly classes with a dietician for 3 mo, then every other week for 3 mo and monthly for last 6 mo.	Additional diet and exercise arm that contained supervised aerobic exercise 3×/wk.	TMAS, BDI
McMillan et al. 2011 (30)	Young female adults 18–30 y, recruited from general population	12/13	21.1	Examine the effects of a 10-d, nutrient-rich diet on mood and cognition.	Randomized, single-blind, parallel group trial.	Diet change group participants were required to increase intake of fruits, vegetables, fatty fish, nuts, seeds, low-fat dairy, whole grain cereals, to combine protein, healthy fats and carbohydrates at each meals and reduce refined foods (i.e., refined sugars, soft drinks, prepacked foods). Participants completed a daily food fairy to support compliance.	Calorie intake was not restricted.	POMS (depression and anxiety subscales)
Nieman et al. 2000 (31)	Obese females; 25–70 y; BMI 25–50; good health with no known diseases and not on a diet or exercise program; no current emotional/mood problems	22/26/ 21/22	45.6	Compare mood in obese versus nonobese women and assess the impact of 12-wk moderate energy restriction and/or exercise on mood state.	4-arm RCT comparing effect of 12-wk exercise (E), energy restriction diet (D), both E and D interventions, and control (C) using a pre-post repeated measures design.	Calorie restriction diet consisting of 4.19 to 5.44 MJ/d (1200–1300 kcal). Diet based on dietary exchanges (2 fruits, 3 vegetables, 2 milk, 6 breads, 2 fats, 5 lean proteins, and 0.42 MJ/100 kcal of optional food). Taught about portion size, food exchange, recording diet intake using a daily exchange checklist. Compliance measured by random, 24-h recall.	Also an exercise (E) and combined exercise and diet arm (E and D), with participants required to walk 5×/wk for 45 min at 60%–80% max HR. Four sessions per week were had supervision and 1 session without.	GWBS and POMS (depression, anxiety, and well-being measure)

Scheier et al. 2005 (22)	Younger women within 2 mo of completing breast cancer treatment	85/83/84	44.2	Examine whether education/nutrition intervention could enhance physical/ psychological functioning among young women completing breast cancer treatment.	3-arm clinical trial comparing 16-wk educational, illness-related intervention, nutritional intervention versus standard medical care.	Participants completed 4 monthly 2-h sessions. Participants in the education arm received illness and treatment related information. The nutrition group received information on how to follow an eating pattern low in fat and high in fruits and vegetables. A nutrition quiz was administered to assess knowledge of presented material.	None	CES-D (10-item)
Wardle et al. 2000 (21)	Adults with mild-moderate levels of elevated serum cholesterol (>2.5 mM)	59/61/56	53	Assess whether cholesterol-lowering diets adversely affect mood and cognitive functioning.	3-arm randomized trial comparing 12 wk of low-fat or Mediterranean diet intervention versus wait list controls.	Participants completed 8 individual and group sessions with a dietician and psychologist. The low-fat diet was asked to reduce energy from fats, particularly saturated fats. The Mediterranean diet group was asked to increase fruit, vegetables, oily fish, fat as 30% of energy, substituting saturated fats for monounsaturated. Individualized and group-based support was provided. Participants were given free-spreading fats and oils to encourage compliance	None	BDI, POMS (depression and anxiety subscales)

BMI = body mass index; SF-36 = Short-Form Health Survey; HRQoL = health-related quality of life; CES-D = Center for Epidemiological Studies – Depression; ACT = acceptance and commitment therapy; RCT = randomized controlled trial; PUFA = polyunsaturated fatty acid; HADS = Hospital Anxiety Depression Scale; MNA-sf = Mini-Nutritional Assessment-sf; GDS = Geriatric Depression Scale; BSI = Brief Symptom Inventory; HRT = hormone replacement therapy; DPP = Diabetes Prevention Program; MADRS = Montgomery-Åsberg Depression Rating Scale; POMS = Profile Of Mood States; PST-PC = Problem-Solving Therapy Primary Care; HAM-D = Hamilton Rating Scale for Depression; BDI-II = Beck Depression Inventory II; TMAS = Taylor Manifest Anxiety Scale; GWBS = General Well-Being Schedule; NR = not reported.

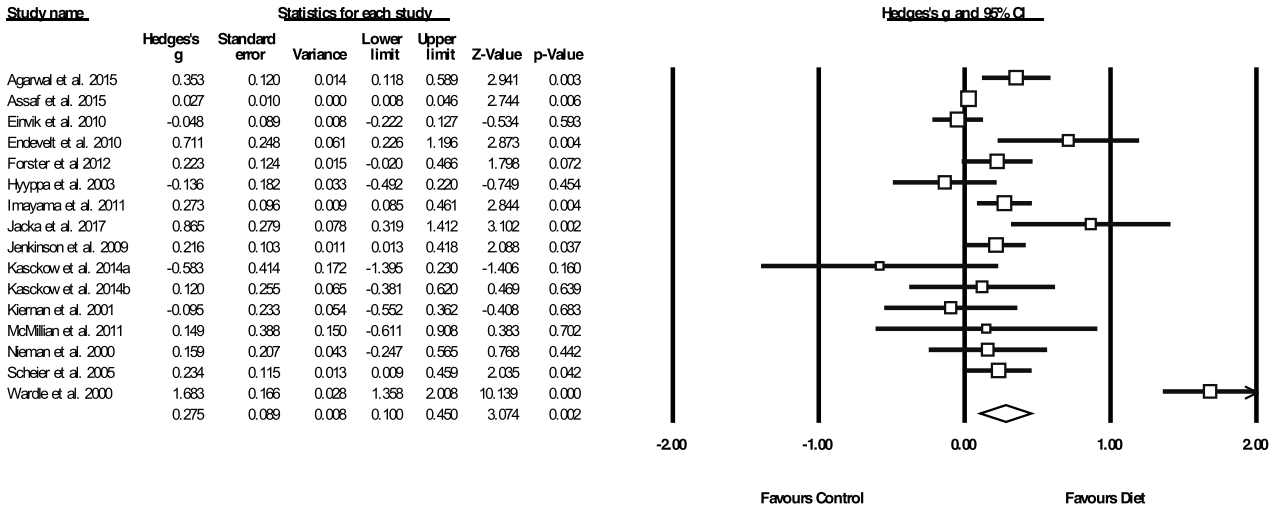


FIGURE 1. Meta-analysis of the effects of dietary interventions on depressive symptoms. Box size represents study weighting. Diamond represents overall effect size and 95% CIs.

study. Table 2 displays the full results of all meta-analyses. A random-effects meta-analysis of 16 RCTs, reporting outcome data from 45,826 individuals, revealed that dietary interventions significantly reduced depressive symptoms in comparison to control conditions, with a small pooled effect (g = 0.275, 95% CI = 0.10 to 0.45, p = .002). There was significant heterogeneity across the study data (Q = 141.4, p < .01, I^2 = 89.4%) and some indication of publication bias (Egger's regression intercept = 1.67, p = .025; see funnel plot in Supplemental Digital Content 3, http://links.lww.com/PSYMED/A539). Nonetheless, the random-effects trim-and-fill analysis found the estimated effect size to be larger and still statistically significant when accounting for publication bias (recalculated at g = 0.408, 95% CI = 0.2 to 0.60, p < .01). Furthermore, significant effects from dietary interventions on depression were also observed in the sensitivity analysis including only the RCTs with high-quality ratings from the ADA Quality Assessment (n = 11, n = 45,469, g = 0.321, 95% CI = 0.12 to 0.53, p = .002, Q = 131.1, I^2 = 92.4%).

Prespecified Subgroup Analyses for Depression

Table 2 displays full results of all meta-analyses on depression outcomes in primary and subgroup analyses. The pooled effect size (g) on depressive symptoms across 10 dietary interventions that compared with habitual diet alone (or "inactive" control conditions) was 0.308 (n = 44,319, 95% CI = 0.02 to 0.6, p = .038), indicating a

TABLE 2. Effects of Dietary Interventions on Symptoms of Depression

	Sample		Meta-Analysis				Heterogeneity		
	Studies	Diet/Control, *n*/*n*	Hedge's *g*	95% CI		*p*	*Q*	*p*	I^2
Main analysis	16	18,746/27,080	0.275	0.100	0.450	.002	141.4	<.01	89.39
High-quality studies	11	18,567/26,902	0.321	0.116	0.526	.002	131.08	<.01	92.37
Diet versus active control	10	1027/921	0.174	0.012	0.335	.035	22.8	.007	60.56
Diet versus inactive control	10	18,022/26,297	0.308	0.017	0.599	.038	115.9	<.01	92.24
Nonclinical depression	15	18,715/27,055	0.246	0.070	0.423	.006	132.69	<.01	89.4
Diet + exercise versus exercise alone	2	139/137	0.265	0.030	0.500	.027	0.008	.928	0.000
Comparative subgroup analyses for depression outcomes									
Aim: improving nutrition	9	560/610	0.365	−0.024	0.753	.066	71.9	<.01	88.9
Aim: reducing % fat intake	4	17,601/26,307	0.477	0.069	0.884	.022	53.1	<.01	94.35
Aim: inducing weight loss	4	585/483	0.212	0.087	0.338	.001	2.21	.529	0.00
Nutrition professional	12	18,618/26,890	0.329	0.124	0.535	.002	136.83	<.01	91.96
No nutrition professional	4	128/190	0.124	−0.124	0.371	.328	3.487	.322	13.961
>75% female sample	8	17,706/26,314	0.195	0.055	0.336	.007	18.97	.008	63.10
>75% male sample	4	366/362	−0.208	−0.449	0.033	.091	5.17	.160	41.93
100% female sample	6	17,739/26,141	0.164	0.019	0.310	.027	18.97	.008	63.10
100% male sample	3	353/352	−0.176	−0.427	0.074	.168	5.17	.16	41.93

CI = conflict of interest.

small to moderate significant effect. Effects were slightly smaller but still statistically significant, when compared with "active" control conditions (n = 10, n = 1,948, g = 0.174, 95% CI = 0.01 to 0.34, p < .001). Both waitlist- and active-controlled subgroups had high heterogeneity among included studies, with no evidence of publication bias significantly altering the findings (Table 2).

For prespecified subgroup analyses on clinical versus nonclinical populations, only one study used a clinically depressed sample (n = 67), showing significantly greater reduction in depressive symptoms from a 12-week modified Mediterranean diet intervention in comparison with "social support" (17). Dietary interventions reduced depressive symptoms significantly more than control conditions among the remaining 15 trials in nonclinically depressed individuals (n = 45,770, g = 0.246, 95% CI = 0.07 to 0.423, p = .006). In addition, preplanned subgroup analyses comparing "diet plus exercise" combination interventions to exercise alone found a small positive effect on depressive symptoms from the interventions that had the dietary component (g = 0.265, 95% CI = 0.03 to 0.50, p = .027) although this was based only on two studies (n = 276).

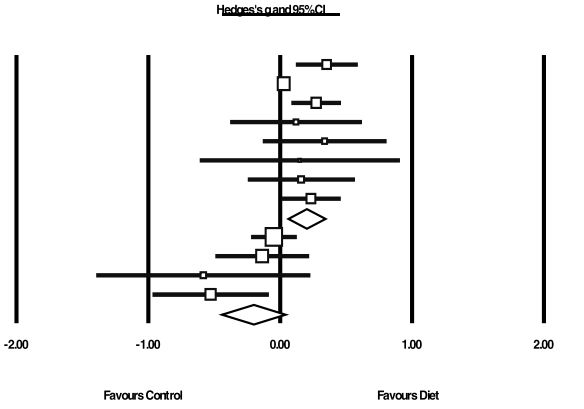
Post hoc Analyses of Factors Influencing Dietary Intervention Effects on Depression

Post hoc subgroup analyses were applied to explore, where possible, how interventional and participant characteristics may affect study findings. Full results are shown in Table 2. Regarding the design of dietary interventions, significant reductions in depression were observed from those primarily aiming to induce bodyweight loss (n = 4, n = 1068, g = 0.212, 95% CI = 0.09 to 0.34, p = .001) and those aiming to reduce fat intake (n = 4, n = 43,638, g = 0.477, 95% CI = 0.07 to 0.89, p = .022). Similar sized effects were observed from interventions primarily aiming to improve nutritional intake (n = 9, n = 1170, g = 0.365, 95% CI = −0.02 to 0.75), although this subgroup fell short of statistical significance (p = .066). Studies specifying the involvement of a nutritional professional (e.g., dietitians or nutritionists) in the delivery of dietary interventions observed a significant effect on depressive symptoms (n = 12, n = 45,508, g = 0.329, 95% CI = 0.12 to 0.54, p = .002), whereas those that were delivered without dietitian/nutritionist professional involvement had no greater effects than control conditions (n = 4, n = 318, g = 0.124, 95% CI = −0.12 to 0.37, p = .328).

Finally, as shown in Figure 2, studies with mostly female samples (i.e., >75% female; eight studies) observed significant positive effects on depressive symptoms from dietary interventions (g = 0.195, 95% CI = 0.06 to 0.37, p = .007), whereas those with mostly male samples (>75% male, four studies) observed a slight worsening of depressive symptoms from dietary interventions, which approached statistical significance (g = −0.208, 95% CI = −0.45 to 0.03 p = .091). This finding persisted when examining only the studies with 100% female samples (six studies, g = 0.164, 95% CI = 0.02 to 0.31, p = .027) or 100% male samples (three

A

Group by >75%male/female	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
female	Agarwal et al. 2015	0.353	0.120	0.014	0.118	0.589	2.941	0.003
female	Assaf et al. 2015	0.027	0.010	0.000	0.008	0.046	2.744	0.006
female	Imayama et al. 2011	0.273	0.096	0.009	0.085	0.461	2.844	0.004
female	Kasckow et al. 2014b	0.120	0.255	0.065	-0.381	0.620	0.469	0.639
female	Kiernan et al. 2001 - female	0.337	0.240	0.057	-0.132	0.807	1.408	0.159
female	McMillian et al. 2011	0.149	0.388	0.150	-0.611	0.908	0.383	0.702
female	Nieman et al. 2000	0.159	0.207	0.043	-0.247	0.565	0.768	0.442
female	Scheier et al. 2005	0.234	0.115	0.013	0.009	0.459	2.035	0.042
female		0.195	0.072	0.005	0.055	0.336	2.721	0.007
male	Einvik et al. 2010	-0.048	0.089	0.008	-0.222	0.127	-0.534	0.593
male	Hyyppa et al. 2003	-0.136	0.182	0.033	-0.492	0.220	-0.749	0.454
male	Kasckow et al. 2014a	-0.583	0.414	0.172	-1.395	0.230	-1.406	0.160
male	Kiernan et al. 2001 - male	-0.527	0.225	0.051	-0.969	-0.086	-2.340	0.019
male		-0.208	0.123	0.015	-0.449	0.033	-1.690	0.091



B

Group by >75%male/female	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
female	Agarwal et al. 2015	0.310	0.120	0.014	0.075	0.545	2.590	0.010
female	Imayama et al. 2011	0.108	0.096	0.009	-0.080	0.296	1.125	0.261
female	Kasckow et al. 2014b	0.297	0.256	0.066	-0.205	0.800	1.160	0.246
female	Kiernan et al. 2001 - female	0.405	0.240	0.058	-0.066	0.876	1.686	0.092
female	McMillian et al. 2011	0.134	0.388	0.150	-0.625	0.894	0.346	0.729
female	Nieman et al. 2000	0.216	0.207	0.043	-0.190	0.622	1.043	0.297
female		0.211	0.064	0.004	0.085	0.337	3.275	0.001
male	Einvik et al. 2010	-0.046	0.089	0.008	-0.220	0.129	-0.513	0.608
male	Hyyppa et al. 2003	-0.302	0.182	0.033	-0.660	0.055	-1.657	0.097
male	Kiernan et al. 2001 - male	-0.416	0.224	0.050	-0.855	0.022	-1.860	0.063
male		-0.190	0.118	0.014	-0.420	0.041	-1.612	0.107

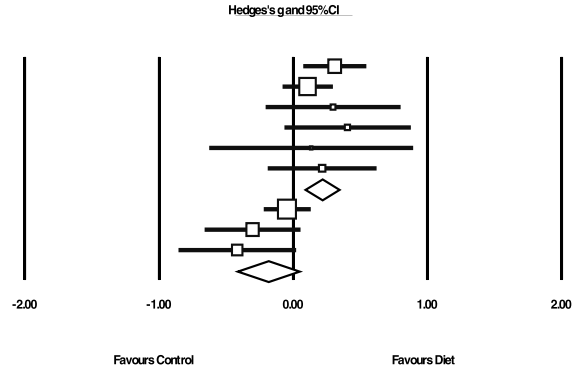


FIGURE 2. Meta-analysis showing differential effects of dietary interventions in male versus female samples, on (A) a symptoms of depression and (B) symptoms of anxiety. Box size represents study weighting. Diamond represents overall effect size and 95% CIs.

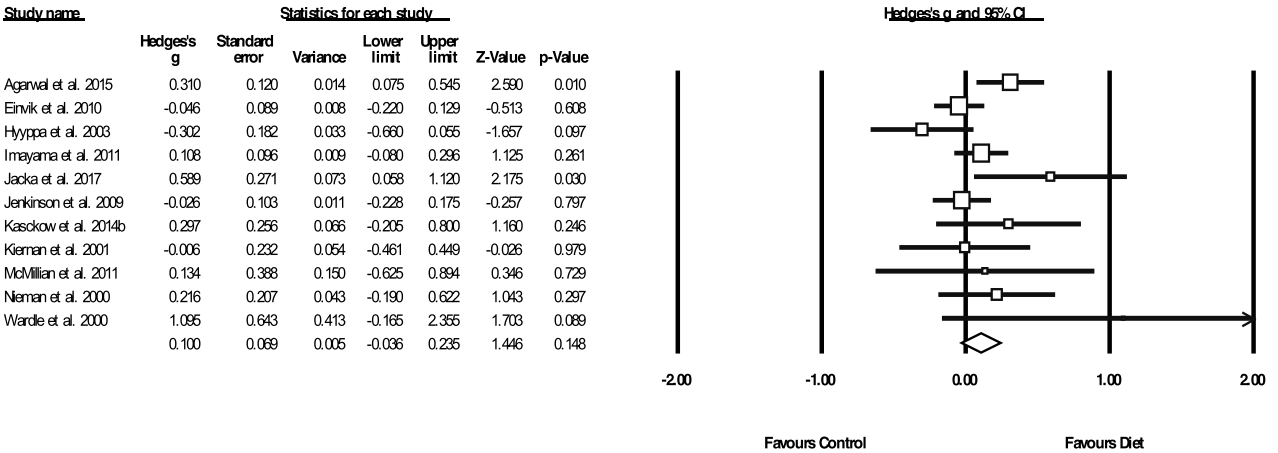


FIGURE 3. Meta-analysis of the effects of dietary interventions on symptoms of anxiety. Box size represents study weighting. Diamond represents overall effect size and 95% CIs.

studies, $g = -0.176$, 95% CI = −0.43 to 0.07, $p = .17$), with significantly greater effects from dietary interventions on depression observed in female sample studies ($p = .021$ between subgroups). Exploratory meta-regression analyses examining intervention length (weeks), study quality (ADA scale) and sample age (mean average, years) found no relationships between these variables and observed effects of diet on depression (full results presented in Supplemental Digital Content 4, http://links.lww.com/PSYMED/A540).

The Effects of Dietary Interventions on Anxiety

As shown in Figure 3, random-effects meta-analysis of 11 RCTs reporting outcome data from 2270 individuals found no overall effect of dietary interventions on anxiety compared with control conditions ($g = 0.100$, 95% CI = −0.036 to 0.235, $p = .148$, $Q = 18.5$, $I^2 = 46.1$). A sensitivity analysis including only studies with high-quality ADA ratings also found no effect of dietary interventions on anxiety ($n = 8$, $n = 2005$, $g = 0.105$, 95% CI = −0.06 to 0.27, $p = .219$, $Q = 17.9$, $I^2 = 60.92$). Furthermore, there were no effects from dietary interventions on anxiety when compared with either active control conditions ($n = 6$, $n = 1{,}292$, $g = 0.046$, 95% CI = −0.13 to 0.22, $p = .602$) or habitual diet/inactive controls ($n = 7$, $n = 984$, $g = 0.137$, 95% CI = −0.08 to 0.36, $p = .216$), and no additional effect of diet on anxiety were observed from studies comparing diet and exercise combinations to exercise alone ($n = 2$, $n = 175$, $g = 0.05$, 95% CI = −0.19 to 0.29, $p = .676$). Full meta-analytic results are displayed in Table 3. Moderate heterogeneity was present across all of the analyses (I^2 = 45.22%–48.2%), and there was some indication of publication bias (Eggers regression intercept = 1.19, $p = .093$) although recalculating the results with trim-and-fill analyses did not change the findings (i.e., no significant benefits from dietary interventions for anxiety outcomes, all $p > .05$). No

TABLE 3. Effects of Dietary Interventions on Symptoms of Anxiety

	Sample		Meta-Analysis				Heterogeneity		
	Studies	Diet/Control, *n*/*n*	Hedge's *g*	95% CI		*p*	*Q*	*p*	I^2
Main analysis	11	1213/1057	0.100	−0.036	0.235	.148	18.5	.046	46.07
High-quality studies	8	1083/922	0.105	−0.062	0.271	.219	17.9	.012	60.92
Diet versus active control	6	690/602	0.046	−0.128	0.220	.602	9.653	.086	48.2
Diet versus inactive control	7	528/456	0.137	−0.080	0.355	.216	10.95	.090	45.22
Diet + exercise versus exercise alone	2	139/137	0.050	−0.185	0.285	.676	0.045	.833	0.000
Comparative subgroup analyses for anxiety outcomes									
Aim: improving nutrition	6	440/429	0.397	−0.173	0.967	.173	61.8	<.01	91.9
Aim: reducing % fat intake	2	188/195	0.349	0.148	0.550	.001	0.401	.526	0.00
Aim: inducing weight loss	4	585/483	0.058	−0.067	0.183	.366	1.60	.659	0.00
Nutrition professional	9	1170/1065	0.273	0.020	0.526	.034	69.37	.000	87.0
No nutrition professional	2	43/42	0.248	−0.171	0.667	.247	0.123	.726	0.00
>75% female	6	493/472	0.211	0.085	0.337	.001	2.64	.755	0.000
>75% male	3	353/352	−0.190	−0.420	0.041	.107	3.43	.180	41.68
100% female	4	326/298	0.158	0.001	0.315	.048	1.41	.703	0.000
100% male	3	353/352	−0.190	−0.420	0.041	.107	3.43	.180	41.68

CI = confidence interval.

studies examined effects of dietary interventions in clinical anxiety disorder samples.

Post hoc Analyses of Factors Influencing Dietary Intervention Effects on Anxiety

No significant effects on anxiety were observed from the subgroups of dietary interventions that primarily aimed to improve nutrition (n = 6, n = 869, g = 0.397, 95% CI = −0.17 to 0.97 p = .174) or those aiming to reduce bodyweight (n = 4, n = 1068, g = 0.058, 95% CI = −0.07 to 0.18, p = .366). A significant reduction in anxiety was observed from those aiming to reducing fat intake (g = 0.349, 95% CI = 0.15 to 0.55, p = .001), but the result must be interpreted with caution given the small number of studies in this subgroup (n = 2, n = 383). Studies specifying the involvement of a nutritional professional in dietary interventions did observe a significant, small positive effect on symptoms of anxiety (n = 9, n = 2235, g = 0.273, 95% CI = 0.0.02 to 0.53, p = .034), whereas those who did not report dietitian/nutritionist involvement had no effects (n = 2, n = 85, g = 0.242, 95% CI = −0.17 to 0.67, p = .247).

As with the depression outcomes, subgroups of studies using mostly (>75%) female samples observed significant positive effects on anxiety from dietary interventions (n = 6, n = 965, g = 0.211, 95% CI = 0.09 to 0.34, p = .001), whereas those in mostly male samples observed nonsignificant negative effects (g = −0.19, 95% CI = −0.42 to 0.04, p = .107). Inspection of both individual and pooled study effects revealed that dietary interventions in mostly/entirely female samples consistently had a positive direction of effect on both symptoms of depression (Figure 2A) and anxiety (Figure 2B). Conversely, effects of dietary interventions in the mostly (or entirely) male samples were consistently negative for both depression and anxiety (Figure 2A) and anxiety (Figure 2B).

DISCUSSION

To our knowledge, this is the first meta-analysis to examine the efficacy of dietary interventions for depression and anxiety. Our systematic search identified 16 independent studies, reporting outcomes of dietary intervention RCTs across 45,826 participants. The main analysis found that dietary interventions had a small positive effect on depressive symptoms (g = 0.275, 95% CI = 0.10 to 0.45), which remained significant even after adjusting for study quality and publication bias. However, only one of the 16 trials used a sample with primary diagnosis of clinical depression (17), with all the remaining 15 studies investigating effects of dietary interventions on symptoms of depression in nonclinical depression samples. A further limitation to this is the publication bias found in the primary analysis. However, the effects of dietary interventions were still statistically significant after correcting for this. In addition, our subgroup analyses found that positive effects of dietary interventions for depressive symptoms were observed in both studies using inactive control conditions (g = 0.308, p = .038) and active control conditions (g = 0.174, p = .035), indicating the beneficial effects of dietary interventions on mood extend beyond just general intervention effects.

A final limitation is the significant heterogeneity in the meta-analyses, likely stemming from the broad inclusion criteria. Because substantial heterogeneity was also present in the subgroup analyses, this indicates that significant between-study differences in dietary effect sizes also existed when grouping by specific intervention types. Thus, it was difficult to establish the most effective components of dietary interventions for depression, because we found no significant differences between dietary interventions primarily aimed at (*a*) reducing bodyweight, (*b*) improving nutrition, or (*c*) decreasing dietary fat intake. However, this is perhaps unsurprising, because although the primary aims of the interventions did vary, the actual content of the all dietary intervention generally hold some common features, such as aiming to reduce the intake of "junk" foods (e.g., high-fat, high-sugar discretionary foods and takeaways), while replacing these with high-fiber, nutrient-dense alternatives, such as vegetables.

Implications and Recommendations for Future Research

The mechanisms through which these dietary changes can benefit mental health have yet to be fully established. However, diet may act via several pathways that are implicated in mental health. These include pathways related to oxidative stress, inflammation, and mitochondrial dysfunction, which are disrupted in people with mental disorders (43). Gut microbiota dysbiosis has also been implicated because of emerging research demonstrating involvement of the microbiome in the modulation of stress response, immune function, neurotransmission, and neurogenesis (44). A healthy diet typically contains a wide variety of bioactive compounds that can beneficially interact with these pathways. For example, vegetables and fruits contain, in addition to beneficial vitamins, minerals and fiber, a high concentration of various polyphenols that seem to be associated with reduced rates of depression in limited observational studies, potentially because of their anti-inflammatory, neuroprotective, and prebiotic properties (45,46). Furthermore, vitamins (e.g., B vitamins), fatty acids (e.g., omega 3 fatty acids), minerals (e.g., zinc, magnesium), and fiber (e.g., resistant starch) as well as other bioactive components (e.g., probiotics), which are typically abundant in healthy dietary patterns, may also be protective from mental illness (44). Along with increasing the intake of beneficial nutrients, dietary interventions may also impact on mental well-being by reducing the consumption of unhealthy food associated with increased risk for depression, such as processed meats, refined carbohydrates, and other inflammatory foods (8,9). Unhealthy diets are also high in other compounds that may negatively affect these pathways. For example, elements commonly found in processed foods such as saturated fatty acids, artificial sweeteners, and emulsifiers may alter the gut microbiome, which may activate inflammatory pathways (47).

Our results showed that dietary interventions that primarily targeted weight loss also significantly reduced symptoms of depression. The psychological benefits of weight loss diets observed in our meta-analysis could be linked with reductions in obesity, because there is robust evidence from epidemiological data that overweight status is consistently associated with an elevated risk of depression (48,49). Indeed, all four of the weight loss interventions included in our meta-analysis were conducted in overweight/obese samples. Although only three of these trials examined the correlations between mental health and weight loss, these consistently found that individuals who lost most weight during the trial also had the greatest improvements in measures of psychological well-being (16,25,31). Previous trials of multicomponent weight loss interventions (which were ineligible for our meta-analysis) have also shown that reductions in depressive symptoms following health behavior programs are significantly correlated with

reductions in bodyweight (50). The leading hypothesis for why obesity is associated with depression is through inflammation, because this is a core feature of depressive illness (51) and excessive adipose tissue increases the production of proinflammatory cytokines (52). Indeed, recent preclinical research has shed further light on pathways through which obesogenic diets impacts on mental health, demonstrating that dietary-induced obesity reduces insulin signaling in the brain and increases neuroinflammation, resulting in depressive-like behaviors in rodent models (53). This is supported by recent research in human adolescent samples, which has demonstrated that the protective effects of healthy diet on depression risk is conferred through reduced body mass index and associated inflammation (10). However, it is important to note that the significant effects of weight loss diets on symptoms of depression in this meta-analysis were all observed in nonclinical samples (i.e., individuals with mostly subthreshold depression). In those with clinical depression, the recent SMILES trial showed large positive effects of a dietary intervention in MDD without altering the weight of participants (17). Instead, the trial found that changes in diet quality for the 12-week period correlated closely with changes in depressive symptoms. This is in accordance with the weight of evidence in the extensive observational literature showing that the association between diet quality and major depression exists even independently of body weight (7) and the emerging evidence from preclinical studies indicating poor diet can also influence brain health and function in absence of obesity (54).

None of our prespecified analyses found notable effects from dietary interventions on symptoms of anxiety. This could be due to a "floor effect," whereby the low levels of anxiety in the nonclinical samples examined to date make it difficult to observe any notable effects of dietary interventions. Indeed, in the single trial to use a sample of individuals with diagnosed affective disorders (although of major depression), the participants also had borderline clinical levels of anxiety at baseline, and these symptoms were significantly reduced by the dietary intervention (17). Future RCTs are required to confirm or refute the effects of dietary interventions on those with clinically diagnosed anxiety disorders.

Clinical Implications

A key issue in clinical applicability of our findings is the lack of studies in clinically depressed samples meaning that most evidence of dietary interventions reducing depressive symptoms only applies to nonclinical depression to date. Although the SMILES trial was the first to examine the efficacy of dietary interventions in a clinically depressed sample, another more recent RCT (the HELFIMED trial) has also indicated the efficacy of a Mediterranean diet for treating depression (55). However, this study was ineligible for our meta-analysis because of the intervention also including fish oil supplements (an active treatment for depression) (56), thus making it impossible to determine whether reductions in depression were due to dietary changes or fish oil treatment. Furthermore, a recent economic evaluation of the SMILES trial provides support for the cost-effectiveness of such an approach to treating depression, with participants in the dietary support condition generating substantially reduced societal and health sector costs compared with the social support condition (57). However, it is important to consider that, to date, no trials have yet compared the efficacy of dietary interventions to antidepressant medications. Thus, dietary intervention can only be considered an adjunctive strategy for managing depressive symptoms at this point.

Nonetheless, the significant benefits observed for subclinical/secondary depression are also of considerable value. The benign nature of dietary interventions, along with the established benefits of diet for physical health, suggests that dietary improvement could be an ideal option for low-intensity treatment or for individuals to adopt themselves as a self-management approach for reducing subclinical depressive symptoms. Furthermore, diet seems to improve depression even when used alongside other more established self-management strategies, such as physical activity (50), because pooled data from studies examining "diet plus exercise" combinations showed significant additional benefits compared with exercise alone. However, this result should be interpreted with caution because of the low number of studies included in the subgroup analysis ($n = 2$, $n = 276$). Our subgroup analyses also indicated that interventions delivered by registered dietitians and professional nutritionists have significant benefits for both depression and anxiety, whereas those delivered by other individuals (e.g., research staff) did not. Although preliminary, the finding from this subgroup analysis is in line with a previous research showing that interventions that use dietitians have significantly better effects on weight management in severe mental illness compared with those who use other types of health professionals (58,59).

Our meta-analysis also found that studies using primarily female samples observed significant mental health benefits from dietary interventions (for depression and anxiety), whereas those with male samples did not, even indicating a trend toward a negative effect (Figure 2). Again, because these subgroup analyses consisted of only few studies for each sex ($n = 8$ studies in females, $n = 4$ studies in males), definitive conclusions cannot be drawn from these data. However, these findings could be potentially be explained by three sex-specific factors. First, because females have a higher presence of mood disorders across the population, this may create greater scope for a significant benefit from dietary interventions (60). Second, differences in dietary effects on mood could be linked to sex differences in metabolism and body composition, whereby women may be more responsive to diets that alter glucose or fat metabolism (61). Third, sociocultural sex differences in expectations surrounding diet and health beliefs may influence outcomes of dietary interventions. For example, men rate certain health behaviors, including diet, as less important than women, have lower nutrition knowledge, and women seek nutrition counseling more frequently than men (62,63). Thus, women may be more likely than males to adopt health behaviors as recommended. Future research should examine the extent to which sex differences in adherence to dietary interventions explain the differential effects between sexes.

Beyond sex differences, future research should also aim to determine the influence of several other confounding factors, which have so far been overlooked. One key factor for future research to examine is the interaction between dietary interventions with psychotropic medications. Because depressive symptoms were used as secondary outcomes in most studies here and conducted in nonclinical samples, few studies have examined this to date. However, preliminary insights on this issue can be gained by comparing trials, which excluded individuals taking antidepressants, with those studies that included high proportions of antidepressant users. For instance, the single trial of an MDD sample (in which >75%

of the intervention group were taking antidepressants) observed large, significant benefits of dietary intervention compared with the counseling control group (17), whereas the two trials that specifically excluded individuals taking antidepressants from their analyses observed no significant differences between dietary interventions and problem-solving therapy for symptoms of depression (27,28). Other important confounding factors to be examined in future research include medical comorbidities (particularly cardiometabolic complications) and substance abuse, both of which could modify the impact of dietary interventions on mental well-being.

SUMMARY AND CONCLUSIONS

The consistently significant and positive effects of dietary interventions on depressive symptoms observed across all random-effects meta-analyses, even in high-quality studies, strongly suggests that diet can play a role in the treatment and also self-management of depressive symptoms across the population. Because pooled effect sizes were mostly classified as "small," further research is warranted to distil both the key components and mechanistic actions of diet for mental health to develop more refined, targeted, and thus perhaps more effective interventions. In addition, given the potentially cumulative effects of diet and exercise together, future research should explore the modification of diet in concert with multiple other life-style modifications to provide a more integrated approach (64). Finally, further research should also be directed toward determining cost-effective and sustainable methods for providing dietary interventions within mental healthcare services, along with developing and evaluating public health schemes for dietary improvement across the population.

The authors thank Dr. Elizabeth Williams (Human Nutrition Unit, University of Sheffield) for kindly providing additional data required for the analyses.

Source of Funding and Conflicts of Interest: J.F. is supported by a Blackmores Institute Fellowship. W.M. is funded by a Deakin University Dean's Postdoctoral Research Fellowship. F.N.J. is supported by an NHMRC Career Development Fellowship (2) (APP1108125). J.S. is funded by an NHMRC Research Fellowship (APP1125000). S.T. is funded by the South Eastern Sydney Local Health District in a clinical position. B.S. is supported by the Health Education England and the National Institute for Health Research HEE/NIHR ICA Programme Clinical Lectureship (ICA-CL-2017-03-001). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health and Social Care. F.J. has received grant/research support from the Brain and Behaviour Research Institute, the National Health and Medical Research Council (NHMRC), Australian Rotary Health, the Geelong Medical Research Foundation, the Ian Potter Foundation, Eli Lilly, Meat and Livestock Australia, Woolworths Limited, The Fernwood Foundation, The Wilson Foundation, GMHBA, and The University of Melbourne and has received speakers honoraria from Sanofi-Synthelabo, Janssen Cilag, Servier, Pfizer, Health Ed, Network Nutrition, Angelini Farmaceutica, Eli Lilly, and Metagenics. J.S. has received either presentation honoraria, travel support, clinical trial grants, book royalties, or independent consultancy payments from: Integria Healthcare & MediHerb, Pfizer, Scius Health, Key Pharmaceuticals, Taki Mai, Bioceuticals & Blackmores, Soho-Flordis, Healthworld, HealthEd, HealthMasters, Kantar Consulting, Research Reviews, Elsevier, Chaminade University, International Society for Affective Disorders, Complementary Medicines Australia, SPRIM, Terry White Chemists, ANS, Society for Medicinal Plant and Natural Product Research, Sanofi-Aventis, Omega-3 Centre, the National Health and Medical Research Council, CR Roper Fellowship.

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