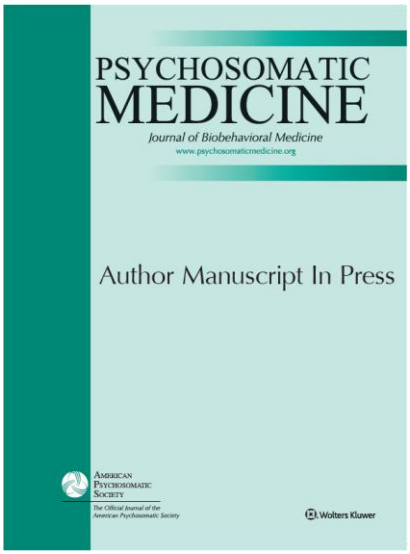

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Authors: Joseph Firth, Wolfgang Marx, Sarah Dash, Rebekah Carney, Scott B. Teasdale, Marco Solmi, Brendon Stubbs, Felipe B. Schuch, André F. Carvalho, Felice Jacka, and Jerome Sarris

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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[1,2], Wolfgang Marx, PhD[3], Sarah Dash, PhD[3,4], Rebekah Carney, PhD[2,5], Scott B Teasdale, PhD[6,7], Marco Solmi, MD[8,9], Brendon Stubbs, PhD[10,11], Felipe B. Schuch, PhD[12,13], André F. Carvalho, MD[14,15], Felice Jacka, PhD[3,16,17], Jerome Sarris, PhD[1,18]

[1] NICM Health Research Institute, Western Sydney University, Australia;

[2] Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of Manchester, UK;

[3] Deakin University, Food & Mood Centre, IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Geelong, Australia

[4] Baker Heart and Diabetes Institute, Metabolic and Vascular Physiology, Australia

[5] Youth Mental Health Research Unit, Greater Manchester Mental Health NHS Foundation Trust, Manchester, UK

[6] School of Psychiatry, Faculty of Medicine, UNSW Sydney, Australia;

[7] Keeping the Body in Mind Program, South Eastern Sydney Local Health District, Sydney, Australia;

[8] University of Padua, Neurosciences Department, Padua, Italy

[9] Padua University Hospital, Psychiatry Unit, Padua, Italy

[10] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom

[11] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

[12] Post Graduate Program in Health and Human Development, La Salle University, Canoas, Brazil;

[13] Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Brazil;

[14] Department of Psychiatry, University of Toronto, Toronto, ON, Canada;

[15] Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada;

[16] Black Dog Institute, Sydney, Australia

[17]Murdoch Childrens Research Institute, Centre for Adolescent Health, Melbourne, Australia

[18]Department of Psychiatry, University of Melbourne, Professorial Unit, The Melbourne Clinic, Melbourne, Australia.

Corresponding author:

Joseph Firth

NICM Health Research Unit, University of Western Sydney, Penrith, NSW 2750, Australia

Tel: +44 (0)161 306 7914

Email: j.firth@westernsydney.edu.au

Co-final author (Felice Jacka and Jerome Sarris)

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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.

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

Results: Sixteen eligible RCTs with outcome data for 45,826 participants were included; the majority of which examined samples with non-clinical depression (N=15 studies). Nonetheless, dietary interventions significantly reduced depressive symptoms (*g*=0.275, 95% C.I.=0.10-0.45, p=0.002). Similar effects were observed among high-quality trials (*g*=0.321, 95% C.I.=0.12-0.53, p=0.002), and when compared to both inactive (*g*=0.308, 95% C.I.=0.02-0.60, p=0.038) and active controls (*g*=0.174, 95% C.I.=0.01-0.34, p=0.035). No effect of dietary interventions was observed for anxiety (k=11, n=2,270, *g*=0.100, 95% C.I.=-0.04-0.24, p=0.148). 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.

Keywords: mental illness; nutrition; nutrients; mood; affective disorders.

Introduction

Depressive disorders affect over 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 due to 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' (CMDs) due to their prevalence across the globe, with approximately 1 in 5 people experiencing one of these conditions over any given year (3). Standard treatments for CMDs comprise psychopharmacological and psychotherapeutic interventions. Whilst these have established efficacy in depression, a substantial proportion of people do not achieve remission using such strategies (4).

Furthermore, sub-clinical symptoms of depression and anxiety are also highly prevalent across the general population, among those without clinically-diagnosed CMDs. 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, pro-inflammatory 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 sub-clinical 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 non-psychiatric 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, are uncertain. Therefore, we aimed to determine the efficacy of dietary interventions for symptoms of depression and anxiety by conducting a meta-analysis of all RCTs examining this therapeutic strategy to date. We also employed sub-group analyses to examine effects of dietary interventions on depression/anxiety in both clinical and non-clinical 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.

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 pre-specified subgroup analyses used in this meta-analysis were prospectively registered with PROSPERO (CRD42018091256).

Search Strategy

The primary search was performed using OVID Medline on 12/03/2018, in line with the pre-registered protocol, using the keyword 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' in order 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-language 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 non-clinical populations, including depression (e.g. major depressive disorder (MDD)) or anxiety, co-morbid 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 randomized controlled trials (RCTs) comparing the effect of dietary interventions to non-dietary control conditions. All 'whole of diet' dietary interventions were eligible, delivered via any format, including individualised dietary counselling, group dietary classes, and standardised dietary prescription. Also, 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. As 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. Multi-component lifestyle interventions were only eligible where comparator conditions had adequately controlled for active non-dietary aspects of the intervention. For instance, multicomponent interventions such as 'exercise with diet' would only be eligible if compared to an 'exercise alone' control condition, so that the effects of the dietary component could be accurately determined. Cross-over trials were only included where between-group differences from the 'first leg' of the cross-over 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-post measures had been collected from both groups). Conversely, 'active control groups' were categorised as any which compared diet to 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, counselling, or exercise, or (c) other forms of activities, such as 'time and attention' matched patient contact.

All studies matching the above 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 over the period of two 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 non-dietary additions), control condition, intervention length (in 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 which used >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 categorised as positive, negative or neutral using the standardised '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 vs 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, in order 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 aforementioned analyses. Furthermore, a Duval and Tweedie's 'trim-and-fill' analysis was applied to the random-effects models, in order to re-calculate the pooled effect size after statistically accounting for any studies which may introduce publication bias (e.g. small studies with large effect sizes). Additionally, a funnel plot of study effect sizes was generated from primary analyses, for a visual inspection of publication bias.

Pre-specified subgroup analyses were conducted to examine how effects of dietary interventions differed when (i) comparing diet to either waitlist/inactive control conditions, or active control conditions, (ii) in 'clinical' (i.e. patients with diagnosed depressive/anxiety disorder) and 'non clinical' (i.e. people without diagnoses of depression or anxiety), or (iii) comparing interventions that had combined 'diet with exercise' to control groups using 'exercise alone'. Additionally, we conducted a range of post-hoc analyses, in order 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 (in weeks), and study quality (measured with ADA scale).

Results

Included studies and participant details

The full search and screening process is shown in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A537. Following the removal of duplicate articles from the systematic search of electronic databases, 26 papers 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 a further 2 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 to 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 above (categorised as 'high quality') (18-27), and five studies scored below 9 (categorised 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' (CES-D)(32)scale(19, 22); the 'Beck Depression Inventory'(33)(BDI)(16, 21, 27, 28); the 'Hamilton Rating Scale for Depression'(34)(HAM-D)(28); the 'Montgomery Åsberg Depression Rating Scale'(35)(MADRS)(36); the Geriatric Depression Scale(37)(GDS)(23, 29), the Taylor Manifest Anxiety Scale(38)(TMAS)(16), and the subscale scores for depression/anxiety from the following measures: the 'Hospital Anxiety Depression Scale'(39)(HADS)(17, 20, 26); the Short-Form Health Survey(40)(SF-36)(18, 27); the Brief Symptom Inventory(41)(BSI)(24, 25, 28); the Profile Of Mood States(42)(POMS)(17Wardle, 2000 #10083, 30, 31) and the General Well-Being Schedule(43)(GWBS)(31). 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 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% C.I.=0.10 to 0.45, p=0.002). There was significant heterogeneity across the

study data (Q=141.4, p<0.01, I^2=89.4%), and some indication of publication bias (Egger's regression intercept=1.67, p=0.025; 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% C.I.=0.22 to 0.60, p<0.01). 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% C.I.=0.12 to 0.53, p=0.002, Q=131.1, I^2=92.4%).

Pre-Specified 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 on depressive symptoms across 10 dietary interventions that compared to habitual diet alone (or 'inactive' control conditions) was g=0.308 (n=44,319, 95% C.I.=0.02 to 0.6, p=0.038), indicating a small-to-moderate significant effect. Effects were slightly smaller, but still statistically significant, when compared to 'active' control conditions (N=10, n=1,948, g=0.174, 95% C.I.=0.01 to 0.34, p<0.001). Both waitlist-controlled and active-controlled subgroups had high heterogeneity among included studies, with no evidence of publication bias significantly altering the findings (see Table 2).

For pre-specified subgroup analyses on clinical vs. non-clinical 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 to 'social support' (17). Dietary interventions reduced depressive symptoms significantly more than control conditions among the remaining 15 trials in non-clinically depressed individuals (n=45,770, g=0.246, 95% C.I.=0.07-0.423, p=0.006). Additionally, pre-planned 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% C.I.=0.03 to 0.50, p=0.027) 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=1,068, g=0.212, 95% C.I.=0.09 to 0.34, p=0.001) and those aiming to reduce fat intake (N=4, n=43,638, g=0.477, 95% C.I.=0.07 to 0.89, p=0.022). Similar sized effects were observed from interventions primarily aiming to improve nutritional intake (N=9, n=1170, g=0.365, 95% C.I.=-0.02 to 0.75), although this subgroup fell short of statistical significance (p=0.066). 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=0.002), 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=0.328).

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=0.007) 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=0.091). 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=0.027) or 100% male samples (three studies, g=-0.176, 95% CI=-0.43 to 0.07, p=0.17), with significantly greater effects from dietary interventions on depression observed in female sample studies (p=0.021 between subgroups). Exploratory meta-regression analyses examining intervention length (in weeks), study quality (ADA scale) and sample age (mean average, in 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 2,270 individuals found no overall effect of dietary interventions on anxiety compared to control conditions (g=0.100, 95% C.I.=-0.036 to 0.235, p=0.148, 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=2,005, g=0.105, 95% C.I.=-0.06 to 0.27, p=0.219, Q=17.9, I^2=60.92). Furthermore, there were no effects from dietary interventions on anxiety when compared to either active control conditions (N=6, n=1,292, g=0.046, 95% CI=-0.13 to 0.22, p=0.602) or habitual diet/inactive controls (N=7, n=984, g=0.137, 95% C.I.=-0.08 to 0.36, p=0.216), 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=0.676). 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=0.093) 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>0.05). No 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=0.174) or those aiming to reduce bodyweight (N=4, n=1,068, g=0.058, 95% CI=-0.07 to 0.18, p=0.366). 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=0.001) 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=2,235, g=0.273, 95% CI=0.0.02 to 0.53, p=0.034), whereas those which did not report dietitian/nutritionist involvement had no effects (N=2, n=85, g=0.242, 95% CI=-0.17 to 0.67, p=0.247).

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=0.001) whereas those in mostly male samples observed non-significant negative effects (g=-0.19, 95% CI=-0.42 to 0.04, p=0.107). 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% C.I.=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 non-clinical 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. Additionally, our sub-group analyses found that positive effects of dietary interventions for depressive symptoms were observed in both studies using inactive control conditions (g=0.308, p=0.038) and 'active' control conditions (g=0.174, p=0.035), 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. As 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, as we found no significant differences between dietary interventions primarily aimed at (i) reducing bodyweight, (ii) improving nutrition, or (iii) decreasing dietary fat intake. However, this is perhaps unsurprising, as even though 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-fibre, 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 mitochrondial dysfunction, which are disrupted in people with mental disorders (44). Gut microbiota dysbiosis has also been implicated due to emerging research demonstrating involvement of the microbiome in the modulation of stress response, immune function, neurotransmission, and neurogenesis (45). 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 fibre, a high concentration of various polyphenols which appear to be associated with reduced rates of depression in limited observational studies, potentially due to their anti-inflammatory, neuroprotective and prebiotic properties (46, 47). Furthermore, vitamins (e.g. B vitamins), fatty acids (e.g. omega 3 fatty acids), minerals (e.g. zinc, magnesium), and fibre (e.g. resistant starch) as well as other bioactive components (e.g. probiotics), that are typically abundant in healthy dietary patterns, may also be protective from mental illness (45). 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 (48).

Our results showed that dietary interventions which 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, as there is robust evidence from epidemiological data that overweight status is consistently associated with an elevated risk of depression (49, 50). 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 over the trial also had the greatest improvements in measures of psychological well-being (16, 25, 31). Previous trials of multi-component weight-loss interventions (which were ineligible for our meta-analysis) have also shown that reductions in depressive symptoms following health behaviour programs are significantly correlated with reductions in bodyweight (51). The leading hypothesis for why obesity is associated with depression is through inflammation, as this is a core feature of depressive illness(52) and excessive adipose tissue increases the production of pro-inflammatory cytokines (53). Indeed, recent pre-clinical research has shed further light on pathways through which obesogenic diets impacts on mental health; demonstrating that dietary-induced obesity reduces insulin signalling in the brain and increases neuroinflammation – resulting in depressive-like behaviours in rodent models (54). 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 BMI 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 non-clinical 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 over 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 pre-clinical studies indicating poor diet can also influence brain health and function in absence of obesity(55).

None of our pre-specified 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 non-clinical 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 the majority of evidence of dietary interventions reducing depressive symptoms only applies to non-clinical 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 (56). However, this study was ineligible for our meta-analysis due to the intervention also including fish oil supplements (an active treatment for depression) (57), thus making it impossible to determine if 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 to the social support condition (58). 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 appears to improve depression even when used alongside other more established self-management strategies, such as physical activity (51), as pooled data from studies examining 'diet plus exercise' combinations showed significant additional benefits compared to 'exercise alone'. However, this result should be interpreted with caution due to 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 which use dietitians have significantly better effects on weight-management in SMI compared to those which use other types of health professionals (59, 60).

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 towards a negative effect (see Figure 2). Again, as 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 this data. However, these findings could be potentially be explained by three sex-specific factors. First, since females have a higher presence of mood disorders across the population, this may create greater scope for a significant benefit from dietary interventions (61). 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 (62). Third, sociocultural sex differences in expectations surrounding diet and health beliefs may influence outcomes of dietary interventions. For example, men rate certain health behaviours, including diet, as less important than women, have lower nutrition knowledge, and women seek nutrition counselling more frequently than men (63, 64). Thus, women may be more likely than males to adopt health behaviours 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. As depressive symptoms were used as as secondary outcomes in the majority of studies here, and conducted in non-clinical 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, to those studies which 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 to the counselling control group (17), whereas the two trials which 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 cardio-metabolic complications) and substance abuse, both of which could modify the impact of dietary interventions on mental well-being.

Summary and Conclusions

In conclusion, 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. As 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 in order to develop more refined, targeted and thus perhaps more effective interventions. Additionally, given the potentially accumulative effects of diet and exercise together, future research should explore the modification of diet in concert with multiple other lifestyle modifications to provide a more integrated approach (65). Finally, further research

should also be directed towards 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.

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Figure Legends

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% confidence intervals.

Figure 2. Meta-analysis showing differential effects of dietary interventions in male vs. 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% confidence intervals.

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% confidence intervals.

Table 1. Details of included studies

	Sample details	N= Diet/ Control	Age	Study aims	Design	Dietary intervention details	Other intervention aspects	Relevant Outcome Measures
Agarwal et al. 2015	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 weeks of workplace dietary intervention vs. 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.	Participants also advised to take a multivitamin	SF-36 (Depression and Anxiety subscales).

					Workplace cafeterias also provided foods suitable for the low-fat vegan diet.		
Assaf et al. 2015	Healthy postmenopausal women aged 50-79y	n/r 17,335 / 25,698	Assess the effect of a low-fat diet intervention on HRQoL, depressive symptoms, and cognition.	2-arm randomized controlled cross-over 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	Men with hyperlipidemia who had participated in Oslo Diet and Antismoking	70 253/252	Examine whether dietary counselling influences health behaviours and psychological health in high risk males	3-year prospective follow-up of a lifestyle intervention using a 2x2 RCT comparing dietary advice combined with a placebo/n-3	Dietary counselling 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 subjects encouraged to reduce calories. Participants met with	Half of subjects in both diet and control conditions also randomised to receive n-3	HADS

	Study			25y after taking part in a lifestyle program.	PUFA supplement vs. no dietary advice with placebo/n-3 PUFA supplement.	nutritionist every 6 months.	PUFA, the other half placebo capsules.	
End evelt et al. 2010	Older, community dwelling adults (75y+) at nutritional risk according to the Mini-Nutritional Assessment-sf (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 vs. medical treatment with only educational materials on nutritional vs a non-randomized untreated group (which was not included in the meta-analyses).	The dietary intensive treatment group received five meetings, providing individualised treatment from a dietitian, with intensity based on severity of under-nutrition. The medical treatment group received a booklet on nutrition education for older adults from a primary care physician.	None	GDS

Forster et al. 2012	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, 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. 200	Untreated hypercholesterolaemic	60/ 60	48.4/ 48	Assess the effect on mood of both separate and combined	Randomised double-blind placebo-controlled cross over trial	Instructed to adhere to a Mediterranean diet for 12 weeks. Max 10% kcal from saturated fat and trans fats, less than	Randomised to receive either simvasta	BSI

3	men; 35-64y; BMI <32; otherwise healthy			effects of a Mediterranean diet intervention and treatment with simvastatin.	comparing Mediterranean diet intervention (+ simvastatin/placebo) and habitual diet (+ simvastatin/placebo).	250mg/d cholesterol, 4g/d n-3 fatty acids, increased fruit, vegetables and fibre intake and advised to consume lean meat, low-fat dairy, fish twice per week. Free food exchanges supplied (eg margarine).	tin or placebo.	
Imayama et al. 2011	Obese females; 50-75y; BMI >25 (>23 asian-american); <100min/wk physical activity; post-menopa	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-month 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 Diabetes Prevention Program (DPP) lifestyle and Look AHEAD (Action for Health in Diabetes) trial, with goals of: calorie intake 1200-2000 kcal/day based on weight, <30% calories from fat, 10% weight loss within 24wks, and maintenance for the remainder. Small group sessions 2x/wk	Exercise intervention 45min/day of mod-vig aerobic exercise, 5 days/wk including 3 supervised sessions	BSI-18

	usal not on HRT; no serious medical conditions or adverse health behaviours.					and communication with dietitians 2x per month via email/phone. Sessions include strategies and skills to achieve caloric and weight loss goals including self-monitoring, goal setting, coping strategies and problem solving.	by an exercise physiologist.	
Jacka et al. 2017	Adults 18y+ with moderate to severe depression according to DSM-IV, MADRS ≥ 18,	33/34	40.3	Assess the effect of a dietary intervention as a treatment for major depression.	2-arm randomized controlled cross-over study comparing Mediterranean diet to social support over 12 weeks.	Personalised 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

	75< diet screening tool							
Jenkinson et al. 2009	Adults 45y+; BMI >28; knee pain but otherwise healthy	122/109/82/76	61	Determine if individualised interventions of diet and/or exercise reduces knee pain in overweight adults.	2-year RCT comparing a diet intervention (D), exercise intervention (E), combined diet and exercise (DE) and advice alone (C).	Individualised dietary advice following review of a 7-day food diary to create a deficit of 2.5MJ/600kcal per day in line with healthy eating principles (reduced salt/sugar, increased fruit/vegetables/fibre, smaller portion size) to achieve weight loss of 0.5-1kg per week. Advice and newsletters provided and home visits 1x per month for 6m, 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
Kaskow et al.	Adults 50y+, with ≥11 on	31/29	62.7 4/65	Assess the benefits of Problem Solving	2-arm RCT comparing PST-PC vs. dietary	Coaching in healthy eating based on general nutrition guidelines e.g US Department of	None	HAM-D, BDI, BSI-

2014a	the Center for Epidemiologic Studies Depression (CES-D) scale and experienced a significant traumatic event, recruited from larger 'Prevention of Depression in Older	.66	Therapy-Primary Care (PST-PC) compared to a dietary education intervention in people with subsyndromal depression and psychological trauma.	education (DIET) and followed up over 2 years.	Agriculture Food Pyramid. Help with weekly menus, shopping lists, food coupons, and discussions around access, cost and culturally specific foods. Initial 1 hour session followed by 30 mins across 6-8 sessions and semi-annual boosters over 15 months.	A

	African Americans'							
Kaskow et al. 2014b	Veterans 50y+ with ≥11 on the Center for Epidemiologic Studies Depression (CES-D) scale	11/12	63.1	Assess the benefits of Problem solving therapy compared to an attention-only dietary education intervention.	2-arm RCT comparing problem solving therapy vs dietary education intervention.	Over 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)
Kiernan et al. 2001	Adults 25-49y; men BMI 28-34; women BMI 24-30 but	71/79	38.5	Examine the effect of a dietary weight loss programme on psychological health.	12m RCT comparing dietary intervention, to controls and a diet+exercsise programme using pre-post	Dietary changes as recommended by the National Cholesterol Education Program Step 1(low saturated fat, low cholesterol diet). Participants attended weekly classes with a	Additional diet and exercise arm which contained	TMAS, BDI

	otherwise healthy				repeated measures design.	dietician for 3m, then every other week for 3m and monthly for last 6m.	supervised aerobic exercise 3x/wk.	
Mc Millan et al. 2011	Young female adults 18-30, recruited from general population	12/13	21.1	Examine the effects of a 10-day, nutrient rich diet on mood and cognition.	Randomised, single-blind, parallel group trial.	Diet change group participants were required to increase intake of fruits, vegetables, fatty fish, nuts, seeds, low fat dairy, wholegrain cereals, to combine protein, healthy fats and carbohydrates at each meals and reduce refined foods (i.e. refined sugars, soft drinks, pre-packed foods). Participants completed a daily food fairy to support compliance.	Calorie intake was not restricted.	POMS (Depression and Anxiety subscales)

Nieman et al. 2000	Obese females; 25-70y; BMI 25-50; good health with no known diseases and not on a diet or exercise programme; no current emotional/ mood problems	22/26/21/22	45.6	Compare mood in obese v non-obese women and assess the impact of 12 week moderate energy restriction and/or exercise on mood state.	4-arm RCT comparing effect of 12 weeks exercise (E), energy restriction diet (D), both E&D interventions and control (C) using a pre-post repeated measures design.	Calorie restriction diet consisting of 4.19- to 5.44-MJ/day (1200-1300 kcal). Diet based on dietary exchanges (two fruit, three vegetable, two milk, six bread, two fat, five lean protein and 0.42MJ/100kcal of optional food). Taught about portion size, food exchange, recording diet intake using a daily exchange checklist. Compliance measured by random, 24-hour recall.	Also an exercise (E) and combined exercise and diet arm (E&D), with participants required to walk five times per week for 45mins at 60-80% max HR. Four sessions per week	GWBS and POMS (Depression,Anxiety and Well being measure)

						were had supervision and one without.		
Scheier et al. 2005	Younger women within 2 months 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-week educational, illness-related intervention, nutritional intervention vs. standard medical care.	Participants completed four monthly two-hour 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.	Adults with mild-moderat	59/61/56	53	Assess whether cholesterol-lowering	3-arm randomized trial comparing 12 weeks of	Participants completed 8 individual and group sessions with a dietician and psychologist. The	None	BDI, POMS (Dep

2000	e levels of elevated serum cholesterol (>2.5mM)	diets adversely affect mood and cognitive functioning.	low-fat or Mediterranean diet intervention vs wait list controls.	low-fat diet was asked to reduce energy from fats, particularly saturated fats. The Mediterranean diet group were asked to increase fruit, vegetables, oily fish, fat as 30% of energy, substituting saturated fats for monounsaturated. Individualised and group-based support was provided. Participants were given free-spreading fats and oils to encourage compliance	ression and Anxiety subscales)

ACT, acceptance and commitment therapy; ADHD, attention deficit hyperactivity disorder; BA, behavioural activation; BDI-II, beck depression inventory II; BMI, Body Mass Index; BSI, Brief Symptom Inventory; CBM, cognitive bias modification; CBT, cognitive behavioural therapy ; CES-D, Center for Epidemiological Studies – Depression; DASS, Depression Anxiety Stress Scale; DSM-IV, Diagnostic and Statistical Manual 4th ed.; GDS, Geriatric Depression Scale; GWBS, General Well-Being Schedule; HADS, hospital anxiety depression scale; HAM-D, hamilton rating scale for depression; HR, Heart Rate; HRT, Hormone Replacement Therapy; HRQoL, Health Related Quality of

Life; MADRS, Montgomery Asberg Depression Rating Scale; PHQ, patient health questionnaire; POMS, Profile of Mood States; PTSD, post-traumatic stress disorder; PUFA, Polyunsaturated Fatty Acid; RCT, Randomised Controlled Trial; SF-36, Short Form Health Survey; SR, self-reported; TMAS, Taylor Manifest Anxiety Scale.

Table 2. Effects of dietary interventions on symptoms of depression

	Sample		**Meta-analysis**			Heterogeneity		
	Studies	Diet/ Control n=	**Hedge's *g***	**95% CI**	**P value**	Q-value	P value	I^2
Main Analysis	16	18746/27080	0.275	0.100 0.450	0.002	141.4	<0.01	89.39
High Quality Studies	11	18567/26902	0.321	0.116 0.526	0.002	131.08	<0.01	92.37
Diet vs. Active Control	10	1027/921	0.174	0.012 0.335	0.035	22.8	0.007	60.56
Diet vs. Inactive Control	10	18022/26297	0.308	0.017 0.599	0.038	115.9	<0.01	92.24
Non-clinical depression	15	18715/27055	0.246	0.070 0.423	0.006	132.69	<0.01	89.4
Diet + Exercise vs Exercise alone	2	139/137	0.265	0.030 0.500	0.027	0.008	0.928	0.000
Comparative Subgroup Analyses for Depression Outcomes								
Aim: Improving Nutrition	9	560/610	0.365	-0.024 0.753	.066	71.9	<0.01	88.9
Aim: Reducing % Fat Intake	4	17601/26307	0.477	0.069 0.884	.022	53.1	<0.01	94.35
Aim: Inducing Weight Loss	4	585/483	0.212	0.087 0.338	.001	2.21	0.529	0.00
Nutrition Professional	12	18618/26890	0.329	0.124 0.535	.002	136.83	<0.01	91.96
No nutrition professional	4	128/190	0.124	-0.124 0.371	0.328	3.487	0.322	13.961
>75% female sample	8	17706/26314	0.195	0.055 .336	.007	18.97	0.008	63.10
>75% male sample	4	366/362	-0.208	-.449 .033	.091	5.17	0.160	41.93
100% female sample	6	17739/26141	0.164	0.019 .310	.027	18.97	0.008	63.10
100% male sample	3	353/352	-0.176	-.427 .074	.168	5.17	0.16	41.93

Table 3. Effects of dietary interventions on symptoms of anxiety

	Sample		Meta-analysis			Heterogeneity		
	Studies	Diet/ Control n=	**Hedge's *g***	**95% CI**	**P value**	Q-value	P value	I^2
Main Analysis	11	1213/1057	0.100	-0.036 0.235	0.148	18.5	0.046	46.07
High Quality Studies	8	1083/922	0.105	-0.062 0.271	0.219	17.9	0.012	60.92
Diet vs. Active Control	6	690/602	0.046	-0.128 0.220	0.602	9.653	0.086	48.2
Diet vs. Inactive Control	7	528/456	0.137	-0.080 0.355	0.216	10.95	0.090	45.22
Diet + Exercise vs Exercise alone	2	139/137	0.050	-0.185 .285	0.676	0.045	0.833	0.000
Comparative Subgroup Analyses for Anxiety Outcomes								
Aim: Improving Nutrition	6	440/429	0.397	-.173 0.967	.173	61.8	<0.01	91.9
Aim: Reducing % Fat Intake	2	188/195	0.349	0.148 0.550	0.001	0.401	0.526	0.00
Aim: Inducing Weight Loss	4	585/483	0.058	-0.067 0.183	0.366	1.60	0.659	0.00
Nutrition Professional	9	1170/1065	0.273	0.020 0.526	0.034	69.37	0.000	87.0
No nutrition professional	2	43/42	0.248	-0.171 0.667	0.247	0.123	0.726	0.00
>75% female	6	493/472	0.211	0.085 0.337	0.001	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

OVID MEDLINE SEARCH STRATEGY (ADAPTED FROM OPIE ET AL., 2015) PERFORMED ON 12TH MARCH 2018

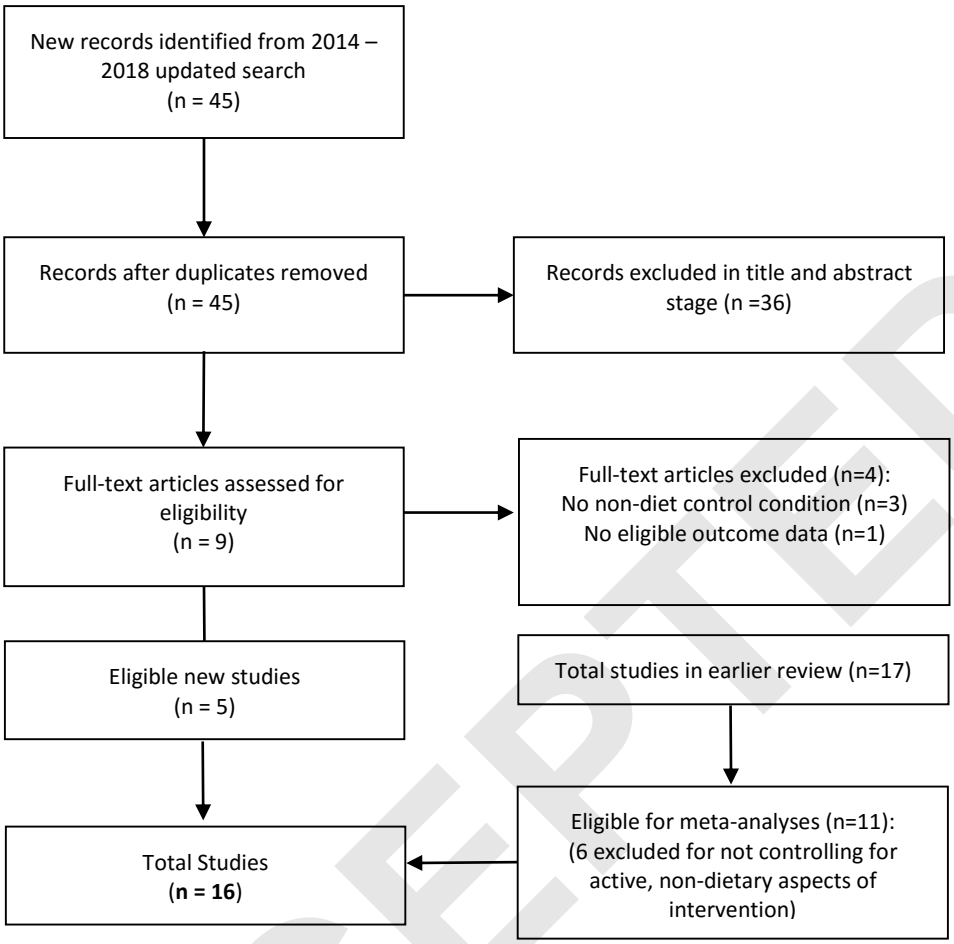
Diet Interventions
Diet/
Diet, Mediterranean/
Diet Therapy/
(diet$ adj1 (educat$ or counsel$ or intervention$ or treatment$)).mp

Intervention Style
Randomized Controlled Trial/
randomised controlled trial.mp.
Random Allocation/
Clinical Trial/
Control Groups/

Outcomes
Depression/
Anxiety/
Depressive Disorder, Major/ or Depressive Disorder/

Note: Additional searches were conducted 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 identical keywords.

PRISMA Diagram Search of OVID Medline



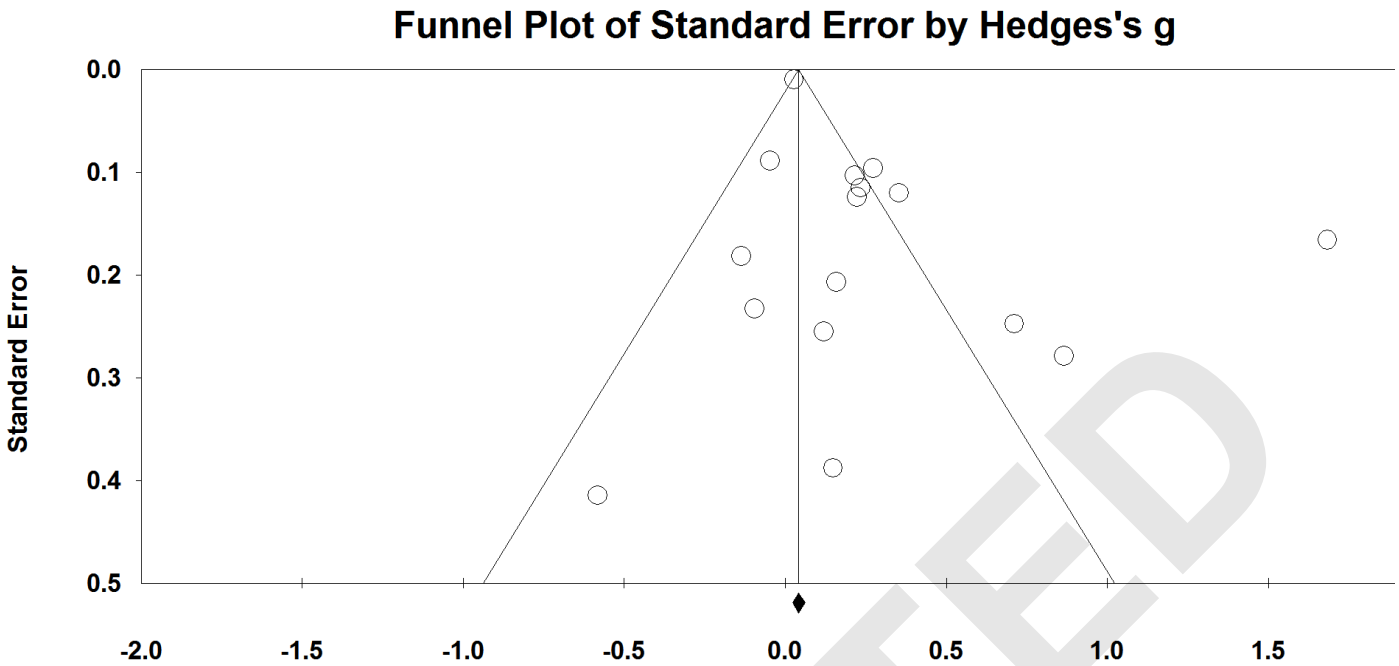
Ineligible studies excluded from full-text screening

Name	Identified from	Title	Reason for Exclusion
Toobert 2007	Opie et al. (2015)'s review	Long-term effects of the Mediterranean lifestyle program: a randomized clinical trial for postmenopausal women with type 2 diabetes	Not controlling for active, non-dietary components of intervention
Ghroubi 2009	Opie et al. (2015)'s review	Physical training combined with dietary measures in the treatment of adult obesity. A comparison of two protocols	Not controlling for active, non-dietary components of intervention
Glasgow 2006	Opie et al. (2015)'s review	Effects of a brief computer-assisted diabetes self-management intervention on dietary, biological and quality-of-life outcomes	Not controlling for active, non-dietary components of intervention
Andersen 2004	Opie et al. (2015)'s review	Psychological, Behavioral, and Immune Changes After a Psychological Intervention: A Clinical Trial	Not controlling for active, non-dietary components of intervention
Merrill 2008	Opie et al. (2015)'s review	Coronary Health Improvement Project (CHIP) is associated with improved nutrient intake and decreased depression	Not controlling for active, non-dietary components of intervention
Garcia-Toro 2012	Opie et al. (2015)'s review	Four hygienic-dietary recommendations as add-on treatment in depression A randomized-controlled trial	Not controlling for active, non-dietary components of intervention
Nam 2016	Updated Search	Lifestyle Intervention for Sleep Disturbances among Overweight or Obese Individuals	Not controlling for active, non-dietary components of intervention

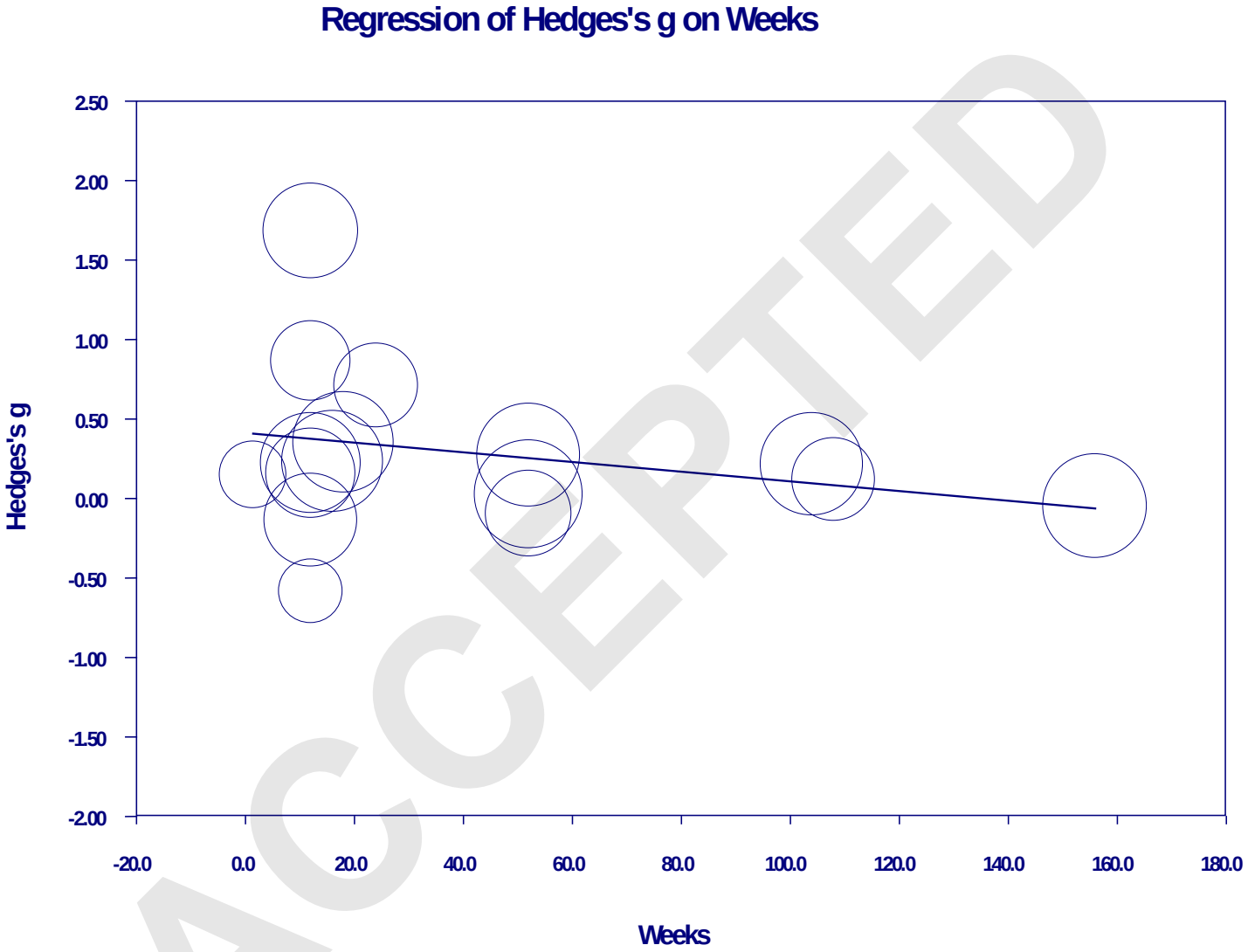
Jimenez 2015	Updated Search	Improving Health-Related Quality of Life in Older African American and Non-Latino White Patients	No eligible outcome data (did not report changes in depression / anxiety)
Perez-Cornago 2014	Updated Search	A decline in inflammation is associated with less depressive symptoms after a dietary intervention in metabolic syndrome patients: a longitudinal study	Lack of non-diet/habitual diet control condition
Breymeyer 2016	Updated Search	Subjective mood and energy levels of healthy weight and overweight/obese healthy adults on high-and low-glycemic load experimental diets	Lack of non-diet/habitual diet control condition
Parletta 2017	Not in main search; identified from google scholar	A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HELFIMED).	Not controlling for active, non-dietary components of intervention
Lee 2015	Not in main search; identified from google scholar	Switching to a 10-day Mediterranean-style diet improves mood and cardiovascular function in a controlled crossover study	No eligible outcome data (crossover study not reporting data from parallel comparisons (i.e. first leg) between diet and control conditions)

Supplemental Table 2. Quality Assessment Scores for Included Studies - adapted from the ADA Quality Criteria Checklist

Author, year COUNTRY	2.1 *Inclusion/ exclusion criteria specified*	2.3 *health & demographics described*	**3.1** *Method of randomisation described (and unbiased)*	**3.2** *Distribution of disease e.g. similar across groups*	**4.3** *Enrolled subjects accounted for?*	5.1 & 5.2 *Blinding?*	6.1 *Protocols described?*	6.3 *Intensity / duration sufficient?*	6.4 *Study retention measured?*	6.4 *Dietary adherence measured?*	6.5 *Co-interventions described?*	7.4 *Measurements based on valid tests?*	**TOTAL "Y"** (out of 12) **Rating** (+, -, ϕ)
Agarwal, 2015 USA	Y	Y	N	Y	Y	N	Y	Y	Y	Y	NA	Y	9 (out of 11) +
Assaf, 2016 USA	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	10 +
Einvik, 2010 NORWAY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	11 +
Endevelt, 2011 ISRAEL	**Y**	**Y**	**N**	**Y**	**N**	**N**	**Y**	**Y**	**N**	**Y**	**NA**	**Y**	**7 (out of 11) ϕ**
Forster, 2012 UK	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	11 (out of 11) +
Hyyppa, 2003 FINLAND	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	10 +
Imayama, 2011 USA	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	11 +
Jacka, 2017 AUSTRALIA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12 +
Jenkinson, 2009 UK	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	10 +
Kasckow, 2014a USA	**Y**	**Y**	**N**	**Y**	**N**	**N**	**N**	**Y**	**Y**	**N**	**Y**	**Y**	**7 ϕ**
Kasckow, 2014b USA	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	11 +
Kiernan, 2001 USA	**Y**	**Y**	**N**	**Y**	**N**	**N**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**8 ϕ**
McMillan, 2011 AUSTRALIA	**N**	**N**	**N**	**Y**	**N**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**7 ϕ**
Nieman, 2000 USA	**Y**	**N**	**N**	**Y**	**N**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**8 ϕ**
Scheier, 2005 USA	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	9 +
Wardle, 2000 UK	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	11 +

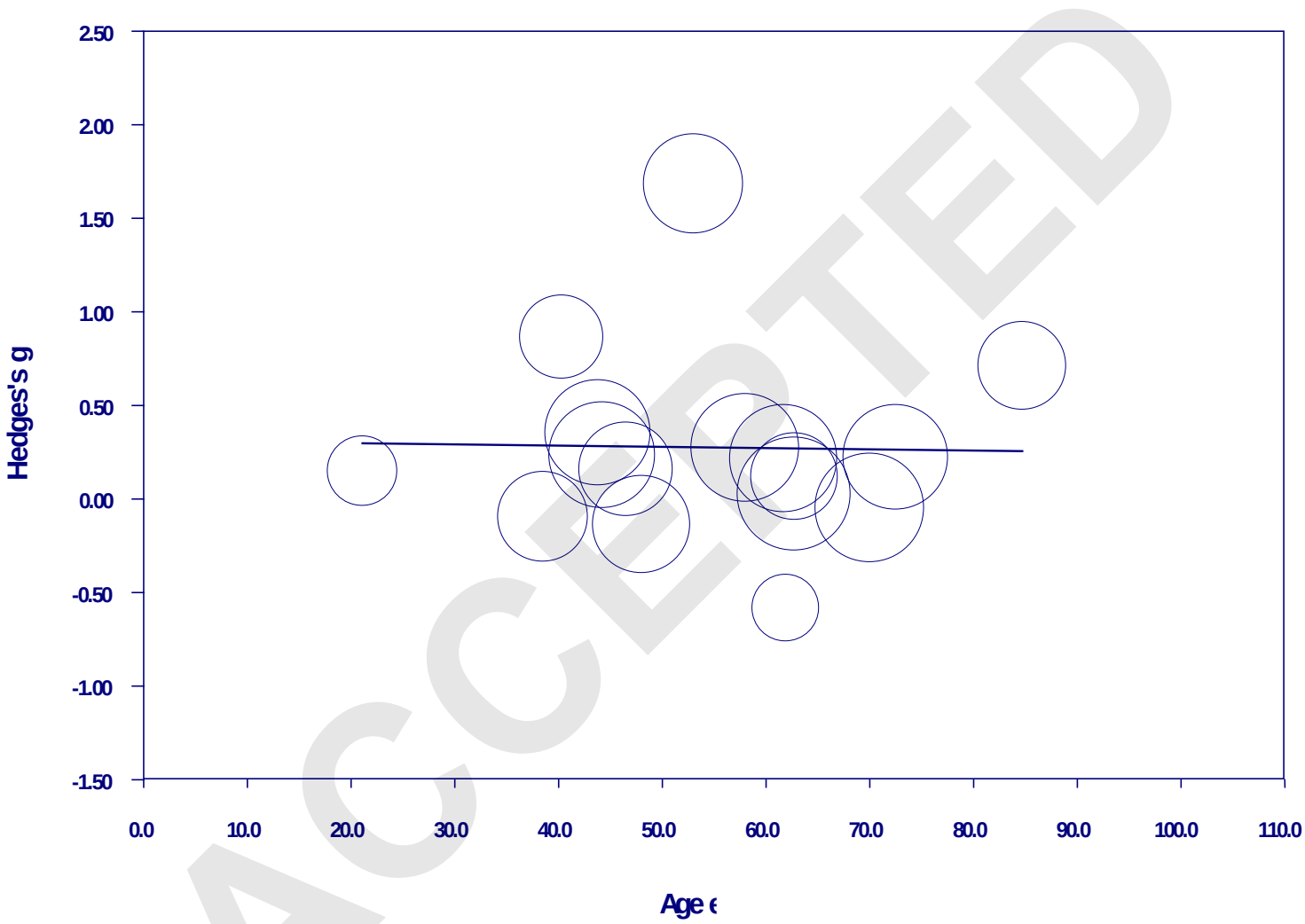


Supplement 3. Funnel Plot demonstrating the significant risk of publication bias for effect sizes of dietary interventions on symptoms of depression.
Note: Findings remained significant after Duval and Tweedie 'trim-and-fill' correction.



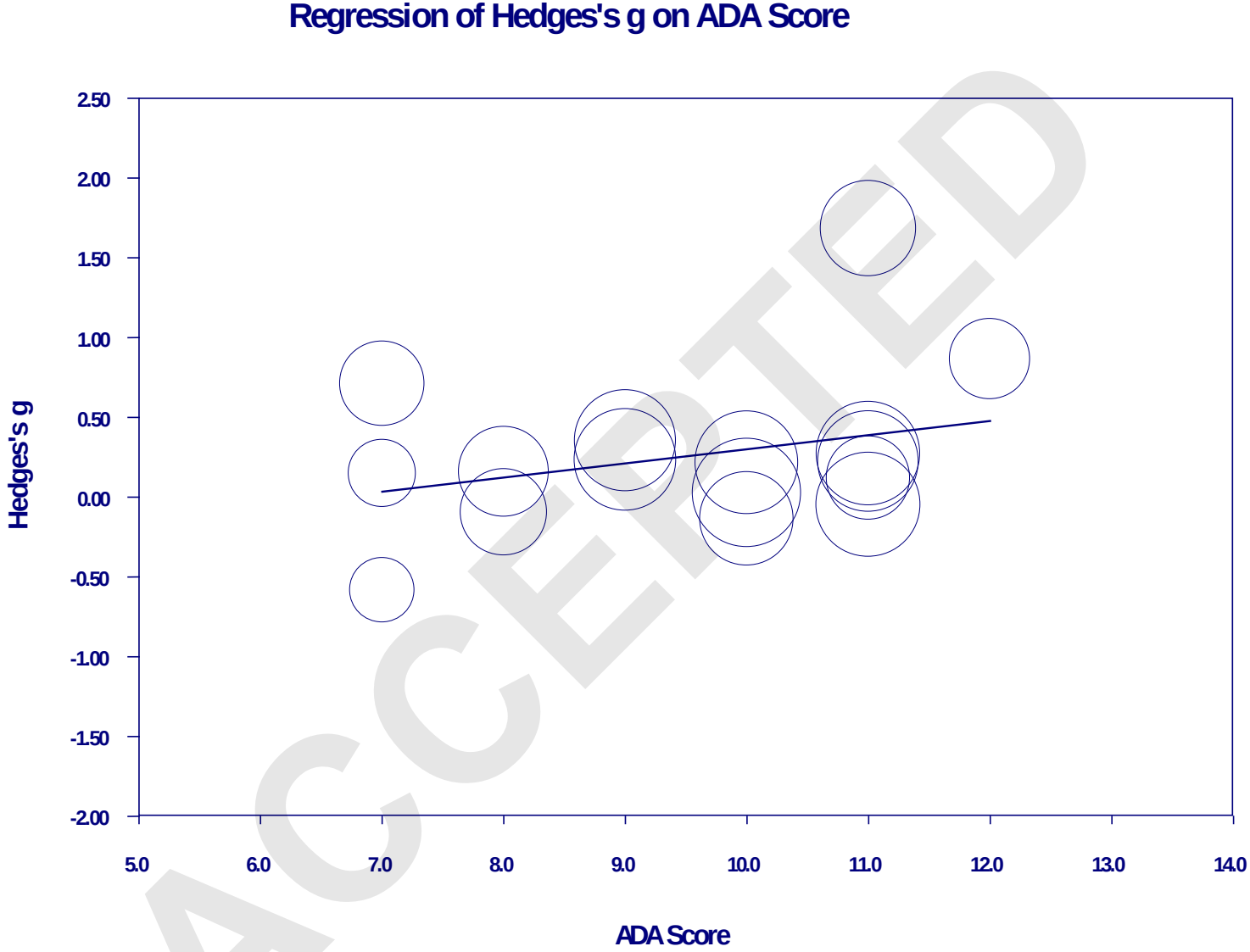
S4a. Meta-regression of effect size for depressive symptoms (Hedge's G) by study length (weeks)

Coeff= -0.003, S.E.=0.002, p=0.126



S4b. Meta-regression of effect size for depressive symptoms (Hedge's G) by mean age (years)

Coeff= -0.0007, S.E.=0.0065, p=0.919



S4c. Meta-regression of effect size for depressive symptoms (Hedge's G) by study quality (ADA Score)

Coeff=-0.0885, S.E.=0.0624, p=0.156