VEGETARIANISM AND VEGANISM VERSUS MENTAL HEALTH AND COGNITIVE OUTCOMES. A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Context: Vegetarian and vegan diet become more popular. Although these diets are known to ameliorate health, certain deficiencies might put these people at higher risk. Cognitive and mental health are related diseases with high economic burden.

Objective: A meta-analysis on the relation of vegan or vegetarian diets with cognitive and mental health.

Data Sources: PubMed, Scopus, Science Direct and Proquest databases were examined from the beginning to July 2018.

Study Selection: Only original observational or interventional human studies on pure vegan/vegetarian diets (excluding case-reports, studies without omnivorous control group, multi-lifestyle interventions and eating disorders) were selected by two independent reviewers.

Data Extraction: Raw mean and standard deviation was taken for continuous outcomes while number of events for categorical outcomes.

Results: From 1,249 hits, 13 articles were included on total 17,809 individuals. Most studies were cross-sectional, two prospective and three interventional. Six studies included vegetarians, two vegans and five both. Study quality was rather medium. No significant association was found for the continuous depression score (n=9), stress (n=5), well-being (n=4) or cognitive impairment (n=3). Vegans/vegetarians were at increased depression risk (odds ratio= 2.142[1.105, 4.148], n=2) and had lower anxiety scores (mean difference=-0.847[-1.677, -0.018], n=7). Heterogeneity was large, thus subgroup analyses showed a lot of contrasting significances with higher mental risks mainly in those under 26y and in higher quality studies but no difference whether vegans versus vegetarians were included.

Conclusions: More studies (especially on cognitive health) with overall better quality (e.g. adjusting for confounders) are needed to make clear positive/negative associations.

Keywords: vegetarian diet, vegan, depression, anxiety, stress, memory, well-being, mental health, cognition, dementia.

Systematic Review Registration: PROSPERO registration no. CRD42018097204

Introduction

Cognitive and mental disorders are critical public health issues.[1,2] Among cognitive disorders, dementia is a worldwide problem with a current prevalence of 47.5 million people and the number will double every 20 years.[3] Among mental disorders, depression affects more than 300 million people and it is also linked with cognitive dysfunction and a higher risk for anxiety, stress and many other mental health issues. A poor mental health not only negatively affects a person's emotional and physical health but also productivity with more absenteeism, unemployment, and lower income. Mental health disorders accounted for a total economic burden of more than $1 trillion per year and dementia for $818 billion every year.[2]

Diet has been hypothesized to have an important role not only on physical health but also in cognitive and mental health issues.[4] For example, following a Mediterranean diet can reduce and even prevent cardiovascular disease, breast cancer, depression or cognitive decline.[5,6] Vegetarian and vegan diets have also been widely associated with physical health outcomes, including a lower incidence and/or mortality from ischemic heart disease and incidence from total cancer[7] due to its high content of fiber, folic acid, vitamins C and E, potassium, magnesium, and many phytochemicals and a more unsaturated fat content.[8] Nevertheless, vegetarian and mainly vegan diets, might be deficient in vitamins B12, creatine and omega-3 fatty acids,[9-11] which have been found to be associated with neurodegenerative disease, cognitive impairment and poor mental health.[12-14] Also, the bioavailability of iron and zinc in vegetarian diets is poor because of their higher content of absorption inhibitors such as phytate and polyphenolsand the absence of flesh foods.[15] Such deficiencies might lead to a lower mental health in vegetarians and vegans.[16]

Results in literature have been found to be controversial,[17-29] with some investigations showing positive associations of vegetarian and vegan diets with different mental health and cognitive outcomes[17,19-21] and other studies showing an inverse association.[18,25,29,30] Equivocal results in studies can be partially due to different definitions used to describe vegetarian and vegan diets (with some of the studies including the consumption of fish or chicken also as vegetarian); the special characteristics of the groups studied with a healthier lifestyle (i.e. Seventh Day Adventist)[31] or the variation in the years adopting a vegetarian or vegan diet.

Although the number of vegetarians and vegans worldwide is still low (except for India where around one-third of the population is vegetarian),[32] most recent surveys have shown an increasing number of vegetarians and vegans mostly in high income countries. In fact, the percentage of vegetarians or vegans

represents more than 10% of the total population in countries such as Australia, New Zealand, Israel or Sweden.[33] Taking into account the rise of people adhering to these dietary practices and the controversial literature on mental and cognitive outcomes, we aim to conduct a systematic review and meta-analysis investigating the associations of vegetarianism or veganism with mental and cognitive outcomes.

Methods

Search strategy

The present systematic review and meta-analysis was registered in the PROSPERO database (ID: CRD42018097204) and followed the systematic review methodology proposed in the "Preferred Reporting Items for Systematic reviews and Meta-analyses" (PRISMA) statement (Table S1 in the Supporting Information online).[34,35] A specific question was constructed according to the PICOS (Participants, Interventions, Control, Outcomes, Study Design) principle (Table 1).[36]

A systematic search of the literature was carried out using PubMed, Scopus, Science Direct and Proquest databases (from database inception to July 2018). When possible, the search included Thesaurus (MESH terms in Pubmed). Firstly, the diet terms were combined as follows, "vegetarian" OR "Vegan" OR "Vegetarians" OR "Diet, Vegetarian" OR "Diet, Vegan". Secondly, the mental and cognitive outcome terms were combined as follows, "Cognition" OR "Cognitive" OR "Depression" OR "Executive Function" OR "Anxiety" OR "Memory" OR "Mental health" OR "Psychological stress" OR "Emotion". Finally, both the diet and the mental and cognitive outcome terms were combined with "AND". In Scopus and Science Direct and Proquest these terms had to appear in the title, abstract or keywords. The filters "humans", "articles" and "in English, Spanish, French, Italian and Portuguese" were applied when possible. Two reviewers independently (I.I and N.M) examined each database to obtain publications. Agreement between reviewers was found in 90% of the publications while remaining inter-reviewer discrepancies were resolved by consensus. Relevant articles were obtained in full and assessed against the inclusion and exclusion criteria described below.

Inclusion criteria

The inclusion criteria were as follows: 1) original studies; 2) studies performed in humans; 3) studies written in English, Spanish, French, Italian or Portuguese; 4) studies including vegetarian (lacto-ovo-

vegetarian; ovo-vegetarian or lacto-vegetarian) or vegan diets as exposures; 5) studies including raw data on mental or cognitive outcomes (i.e. mean and standard deviation for continuous variables and cases and events for categorical outcomes). In the present study, vegetarians and particularly lacto-ovo-vegetarians were defined as those who excluded meat, fish and seafood but not milk and dairy products from their diet; vegans were defined as those who excluded any kind of animal product.

Exclusion criteria

The exclusion criteria were as follows: 1) articles that did not provide original data (e.g. systematic reviews, meta-analysis, literature reviews); 2) case reports; 3) articles that did not present data regarding the control group (omnivores), and 4) studies in which several interventions were carried out (i.e. vegetarian or vegan diet combined with an increase in physical activity levels) making it impossible to separate the individual effect of diet and 5) studies with eating disorders as an outcome due to causality.

Data extraction

After reviewing all the relevant literature, depression, anxiety, stress, mental-health/well-being and mood disturbances for mental health and dementia/memory impairment for cognitive measurements were identified as outcomes for the present meta-analysis. For each study that included a mental health or cognitive outcome, relevant data was extracted (see Table 2)[17] including number of participants, sex, mean age, type of diet (e.g. vegetarian, vegan or omnivores diet), instruments used to assess the outcomes, study design and quality assessment. Instruments to assess the outcomes were self-reported or diagnosed by a specialist, with different tools to evaluate **depression**: Depression Anxiety Stress Scales, DASS-Depression (DASS-D), Center for Epidemiologic Studies Depression (CESD), Hamilton Rating Scale for Depression (HRSD) and Edinburgh Post Natal Depression Scales (EPDS); **anxiety**: DASS-Anxiety (DASS-A), State-Trait Anxiety Inventory (STAI); **stress**: DASS-Stress (DASS-S) or 36-Item Short Form Health Survey (SF-36), used to assess depression, anxiety and mental health; **mood disturbances**: Profile of Mood States (PMHS); **mental health**: Positive Mental Health Scale (PMHS) and **dementia/memory impairment**: Mini-Mental Status Examinations (MMSE). Other information extracted was whether the papers included any confounders or used raw data; possible differences between groups in relevant confounders (i.e. vegan and vegetarians were usually more physically active, had a lower Body Mass Index (BMI) and a higher education and were less likely to be married than omnivores); the period of

time for which the vegetarian or vegan diet had been followed; country or countries in which the study took place and predominant ethnicity if reported.

Mean and standard deviation (SD) was taken for continuous outcomes while number of events in each group (i.e. number of depressions diagnosed in vegetarian and vegan vs. omnivores) for categorical outcomes. Only raw data (unadjusted) was used to perform the meta-analyses as only two papers in the present meta-analysis included adjusted data.[23,29] Reporting unadjusted estimates also reduces the bias of selective reporting of adjusted estimates in primary studies and the risk of over-adjustment with multiple confounders. When a study offered information about matched and non-matched data the matched data was taken for our analysis.

Quality assessment

Depending of the study design, the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies"[37] or the "Quality Assessment Tool of Controlled Intervention Studies"[38] provided by the National Heart, Lung, and Blood Institute was used to assess the quality of the included studies. Two reviewers (I.I and N.M) independently assessed and thereafter discussed the quality of the studies. Agreement between reviewers was found in 90% of the publications and inter-reviewer discrepancies were resolved by consensus.

Search summary

A total of 1,249 articles were extracted from Pubmed, Scopus, Proquest and Science Direct. After eliminating all the duplicates, 911 manuscripts were evaluated. Thereafter, 857 records were excluded by title and abstract reading and 54 full-text articles were assessed for eligibility (see Figure 1): 13 articles were discarded because they did not include a pure vegetarian or vegan diet (i.e. flexitarians or self-reported vegetarians reporting to eat fish)[13,30,39-49]; 11 studies had a different objective than the one of our meta-analysis[50-60]; 6 did not include a control group (omnivorous group) to compare the mental or cognitive outcome[61-66]; 4 had eating disorders as a mental health outcome[67-70]; 3 were conducted in unhealthy subjects (i.e. papers in which participants reported to have eating disorders before starting the diet)[71-73], 1 did not provide raw data to extract[60,74]; 2 were not pure diet interventions in which we could separate individual dietary effects[75,76]; 1 was not an original article.[77] The main author was contacted in case the manuscript did not provide raw or adjusted data and to clarify blurred definitions of diets. Also, the main author was contacted in case mixed diets had been

reported in the same group to ask for the separated data if available (i.e. vegetarian, vegan and pescatarian were reported in the same group), which was possible for one study that was included.[29]

Statistical analyses

All analyses were performed using Open Meta [Analyst] software. For continuous outcomes, information on sample size, mean and standard deviation (SD) was taken and for categorical outcomes number of events in each group mean and SD were extracted for meta-analysis. When the SD was not reported in the study, the authors were first contacted and if no response[19], the following formula were applied: Standard Error=SD/√n; SD=interquartile range/1.35. When the mean was not reported in the studies, the median was used.[20] The mean difference (MD) and the relative risks (RRs) or odds ratio (OR) with a 95% CI were calculated for continuous and categorical data respectively. DerSimonian and Laird estimators using random effects models were applied for continuous and categorical data. Effect sizes were calculated for each outcome. When possible, subgroup analyses were conducted.

Sources of heterogeneity were investigated by subgroup analyses comparing results based on age (<=25 years old, 26-45 years old or >45, or NR -not reported-); sex (women, men, mainly women, men and women); the period of time for which the vegetarian or vegan diet had been followed (short term period: <1 year, long term: ≥1 year or NR); diet (vegetarians or vegans), instrument used to assess the mental or cognitive outcome and quality assessment when information was available (<50 score versus >=50 score). The heterogeneity of the studies was tested using the I^2 statistic.[78] This statistic describes the variance between studies as a proportion of the total variance. A value <25% indicated low heterogeneity, from 25 to 50% moderate, from 50 to 75 high heterogeneity, and >75% very high heterogeneity. The associated p-value of the heterogeneity of the studies was also calculated, with a non-significant result indicating absence of heterogeneity.

To investigate publication bias, we conducted funnel plots using RevMan (version 5.2). Additionally, publication bias was assessed by Egger's linear regression test following the indications provided by Peters et al.[79] Therefore, funnel plots and tests were carried out when the meta-analysis had above ten studies because a small number of studies lowers test power to a point where it is too low to distinguish chance from real asymmetry.[80]

Results

Description of the included studies

After applying the exclusion criteria, a total of 13 articles[17-29] was included in this review: 11 covered outcomes of depression (9 as continuous and 2 as categorical); 8 outcomes of anxiety (7 as continuous and 1 as categorical); 5 on stress; 4 included mental health/well-being outcomes (continuous), 3 outcomes of memory impairment/Alzheimer (categorical); 2 outcomes of mood disturbances (continuous), 1 outcomes of neuropsychiatric problems (categorical), 1 outcomes of personality change (Figure 1)[17-29].

Mental health differences between vegetarians/vegans and omnivores

Figure 2 to 7[17-29] show the individual study results and plot the global effect of vegetarianism/veganism on mental health and cognitive outcomes as well as several subgroup analyses. Several specific sub-group analyses were not performed due to a lack of studies (subgroups with only 1 or 2 studies in one of the groups).

Depression (continuous)

As shown in Figure 2a, no statistically significant differences were found between vegetarian or vegan diets and omnivores regarding the incidence of depression (MD = -0.532; 95% CI: -2.047, 0.984). Heterogeneity among studies for depression was very high (I^2 =92.53; p = 0.040).

Results of the subgroup analysis showed a statistically significant higher depression level in vegetarians/vegans under 26 years old (MD= 1.737; 95% CI: 0.757, 2.717; Figure 2b), in female vegetarians/vegans (MD= 2.910; 95% CI: 0.876, 4.944; Figure 2c) or studies with higher quality (MD= 1.418; 95% CI: 0.473, 2.363; Figure 2g). Subgroup analyses on period following the diet (Figure 2d), vegan vs vegetarian (Figure 2e), or used instrument (Figure 2f) did not show significant differences in comparison with the control group. Heterogeneity was more pronounced in those over 25 years old (I^2 =93.22; p<0.001), in studies that included mainly women (I^2 =94.29; p<0.001), short-term studies (I^2 =97.87; p<0.001), studies including vegans (I^2 =95.10; p<0.001), when using instruments different from DASS or CESD (I^2 =98.12; p<0.001) and lower quality studies (I^2 =93.62; p<0.001).

Depression (categorical)

As shown in Figure 3a, vegetarians and vegans had a higher risk of depression when using a categorical variable (OR = 2.142; 95% CI: 1.105, 4.148) but heterogeneity among studies was high (I^2 =65.4; p = 0.089).

Anxiety (continuous)

Vegetarian and vegan diets were associated with lower levels of anxiety (MD = -0.847; 95% CI: -1.677, -0.018) but heterogeneity among studies was very high (I^2 =92.08; p = 0.001) (Figure 4a).

Results of the subgroup analysis confirmed these lower anxiety levels in vegetarians/vegans 26-45 years old (MD= -3.144; 95% CI: -4.728, -1.561; Figure 4b), in studies including predominantly women (MD= -0.744; 95% CI: -1.461, -0.026; Figure 4c), when not using DASS-A as instrument (MD= -5.940; 95% CI: -7.704, -4.175; Figure 4f) or in lower quality studies (MD= -3.144; 95% CI: -4.728, -1.561; Figure 4g). In contrast, higher levels of anxiety were detected in vegetarian/vegans younger than 26 years (MD= 0.901; 95% CI: 0.143, 1.658; Figure 4b) and higher quality studies (MD= 0.909; 95% CI: 0.158, 1.660; Figure 4g). Subgroup analyses on period of following the diet or vegan versus vegetarian did not show any significant differences with the control group (Figure 4d, Figure 4e). Heterogeneity was more pronounced in those under 26 years old (I^2 =92.27; p<0.001), in studies that included women and men (I^2 =93.86; p<0.001), in studies that did not report the period following the diet (I^2 =94.94; p<0.001), studies including vegetarians (I^2 =93.35; p<0.001), when using DASS as an assessment instrument (I^2 =98.12; p<0.001) and higher quality studies (I^2 =89.79; p<0.001).

Stress (continuous)

Vegetarian and vegan diets did not show any statistically significant associations with stress (MD = -0.422; 95% CI: -1.823, 0.979). Heterogeneity among studies for stress was very high (I^2 =82.71; p = 0.001) (Figure 5a).

Results of the subgroup analysis showed lower stress levels in vegetarians/vegans 26 to 45 years old in comparison with omnivores (MD= -2.178; 95% CI: -3.538, -0.818), and in low quality studies (MD= -2.178; 95% CI: -3.538, -0.818; Figure 5f). In contrast, higher stress levels were found in younger vegetarians/vegans compared to omnivores (MD=1.033; 95% CI: 0.478, 1.587; Figure 5b) and in higher quality studies (MD= 1.005; 95% CI: 0.452, 1.559; Figure 5f). The results did not differ by sex (Figure 5c), the period following the diet (Figure 5d) or

by vegan versus vegetarian (Figure 5e). Subgroup analyses by instrument were not conducted because all studies used DASS-S.

Heterogeneity was more pronounced in adults from 26 to 45 years old (I^2 =49.24; p = 0.139), in studies that included mainly women (I^2 =83.14; p<0.001), in studies that did not report the period following the diet (I^2 =89.31; p<0.001), studies including vegetarians (I^2 =78.17; p = 0.001) and low quality studies (I^2 =49.24; p = 0.139).

Mental health/well-being (continuous)

As shown in Figure 6a, being a vegetarian or vegan was not statistically significantly associated with levels of well-being (MD= -1.319; 95% CI: -2.834, 0.197) and heterogeneity among studies was high (I^2 =73.62; p = 0.004).

Based on subgroup analyses, lower mental health/well-being levels were found in vegetarians/vegans under 26 years old (MD= -1.967; 95% CI: -2.924, -1.011; Figure 6b), when the studies included both men and women (MD= -1.480; 95% CI: -2.134, -0.826; Figure 6c), when the years of diet adherence was not specified (MD= 1.967; 95% CI: -2.924, -1.011; Figure 6d) and in higher quality studies (MD= 1.967; 95% CI: -2.924, -1.011; Figure 6d).

Heterogeneity was more pronounced in those participants under 26 years old (I^2 =55.22; p = 0.107), in studies that included mainly women (I^2 =83.14; p<0.001), in studies that did not report the period following the diet (I^2 =55.22; p = 0.107), studies including vegans (I^2 =81.44; p = 0.005) and in low quality studies (I^2 =84.93; p = 0.001).

Other mental health outcomes

A meta-analysis was not conducted on other mental health outcomes due to the insufficient quantity of studies (n=1 or 2). However, Beezhold et al. concluded that vegetarians reported significantly less negative emotion than omnivores.[19,20] On the contrary, Kapoor et al. reported higher neuropsychiatric problems (psychosis and personality change) in young vegetarians compared to omnivores and Baines found that vegetarians had significantly higher panic attacks or palpitations, deliberate self-harm and other psychosomatic problems.[25]

Memory impairment/dementia

Vegetarian and vegan diets did not show any statistically significant associations with memory impairment when compared to omnivores (OR = 0.825; 95% CI: 0.242, 2.809) and heterogeneity among studies was very high (I^2 =63.13; p = 0.066) (Figure 7a).

Publication Bias

No indication for publication bias was found for studies including depression (Egger *P*=0.230) and anxiety (Egger *P*=0.324). Also, visual inspection of the funnel plot did not suggest publication bias for neither depression nor anxiety as the studies were distributed symmetrically (i.e. inverted funnel shape) around the summary effect size (Supplementary Figure 1 and 2).

Discussion

Overall findings

To date no previous systematic review or meta-analysis has been conducted on the associations between vegetarianism or veganism and mental and cognitive outcomes. We could not find a significant effect of being vegetarian/vegan for the continuous depression score (n=9), stress (n=5), well-being (n=4) or cognitive impairment (n=3) but vegans/vegetarians were at increased depression risk (OR = 2.142; 95% CI: 1.105, 4.148, n=2) and showed higher levels of anxiety in this younger age while older adults had lower anxiety scores (MD = -0.847; 95% CI: -1.677, -0.018, n=7). Heterogeneity was large, thus subgroup analyses showed a lot of contrasting significances. For all tested outcomes, higher mental risks were found in those under 26y and in higher-quality studies. Concerning the instruments used, often no differences existed and only lower anxiety levels were found when not using the specific DASS-A. Inconsistent sex-patterns appeared: more depression symptoms were seen only in female vegetarians/vegans, while lower anxiety symptoms were shown only in studies including predominantly women above the age of 26. Lower wellbeing was only seen in studies including both men and women. Finally, no differences were detected depending on whether vegans versus vegetarians were included or on the amount of years diet adherence.

Vegetarian and vegan diets have been found to be a protecting factor for many chronic diseases such as heart disease, hypertension, type 2 diabetes, obesity, and some cancers such as colorectal and prostate[81]. This might be because of the healthier diet intake with higher fiber, polyunsaturated fats, vitamin C, bioactive molecules and a lower intake of saturated fats. All these nutrients act directly or

indirectly (via other diseases) to an anti-inflammatory status./span>[82] Moreover, vegetarians and vegans seem to have a healthier lifestyle: higher levels of physical activity and lower levels of sedentarism, alcohol and tobacco consumption.[83] Nevertheless, our meta-analyses indicated the potential of negative mental health outcomes in a vegetarian/vegan diet. Despite of benefits, several investigations have indeed identified nutrient deficiencies among vegetarians and vegans[18,84,85] that are related to poorer mental health outcomes.[18,22,25,26]

Subgroup analyses showed clear age-dependent patterns with negative effects at a young age while opposite effects in those older than 25. This might reflect that young people are more vulnerable to deficiencies since their brain and personality are still in development.[86] While women are often more sensitive to mental problems, no such consistent sex-patterns appeared in our study. Similarly, vegan subjects often have more difficulties in preventing nutrient deficiencies but no higher risk for vegans versus vegetarians was detected in subgroup analyses. Since information on the duration of diet adherence was often lacking or imprecise, the lack of subgroup differences depending on diet adherence duration is not surprising.

Possible mechanisms involved in these associations between vegetarian/vegan diets and mental health outcomes

Large heterogeneity was found in the link of vegetarianism and veganism with mental health outcomes: several non-significant findings, lower risk for anxiety but higher risk for depression and age dependent. In general, higher quality studies and studies in populations <25y suggested a higher risk of all types of mental problems in vegetarians and vegans compared to omnivores.

A first possible explanation for these associations is a reverse causal relationship between vegetarianism or veganism and mental health outcomes: individuals who have psychosocial disorders are more eager to follow a vegetarian or vegan diet in order to improve their mental health. Based on age of diet adoption in a German study, the adoption of vegetarian diets was after the onset of mental disorders thus confirming the possibility of reverse causation.[42] Still, one intervention study found an improvement in depression, anxiety and mood after following a vegan diet,[17,20] while another found only improvements in stress but no significant changes in depression, anxiety or mood.[19] These interventions, however, have been conducted for only a short period (less than 4 months) and effects during a longer period have not yet been investigated. As mental health problems often develop at young age, our subgroup analysis showing higher risk in those younger than 25 might reflect this reverse

causation, apart from the fact that young people are more vulnerable to deficiencies. Other possible explanations yielded in the literature are the nutrient deficiencies that are common in vegan diets (such as some amino acids, long chain omega 3 fatty acids, vitamin B6 and B12, zinc and creatine and even too low cholesterol) that could accelerate or worsen pre-existing mental conditions.[8] All these deficiencies have been found to be linked with a higher risk of mental health problems[87, 88]. Several amino-acids like methionine, tryptophan, lysine, arginine, beta-alanine and tryptophan can have a protective effect on depression and on anxiety[89,90] as derived neurotransmitters like dopamine and serotonin are important neurotransmitters in mood regulation.[91] Still the story is more nuanced since the levels of methionine, tryptophan and tyrosine were highest in fish-eaters and vegetarians, followed by meat-eaters, but lowest in vegans.[92] Thus the amino-acid deficiencies would mainly be an explanation for health effects in vegans only.

Another possible explanation could be that vegetarians or vegans belong to a minority group (at least until recently since the prevalence is skyrocketing the last years) and being a minority can induce feelings of lower well-being.[22]

Possible mechanism of the results found in cognitive outcomes

We did not find a statistically significant result between following a vegetarian/vegan diet and cognitive outcomes in the two existing studies, while Giem et al. found a trend toward delayed onset of dementia in vegetarians,[23] Kapoor et al. found higher neuropsychiatric and neurological problems such as memory impairment, personality change, and psychosis in vegetarians. Studies that were not included (because of vegetarian definition problems) were also conflicting: Xu et al. found a higher risk of memory impairment and dementia in vegetarians,[48] while in another study vegetarians responded better than meat-eaters in memory tasks but for other cognitive domains no differences were observed,[14] and macrobiotic (similar to vegan diets but fish eaten occasionally) adolescents performed worse on most cognitive tests than omnivores.[13]

The apparently contradictory results might be explained by differences in vitamin B12 values. Vegetarians had lower vitamin B12 (and 50% had a deficiency) compared to omnivores in Kapoor's study where higher cognitive risks for vegetarians were found. In the macrobiotic study, vitamin B12 levels were indeed associated with lower performance for certain cognitive tests and not all macrobiotic subjects had deficiency. The other studies did not report serum vitamin B12 profiles.[23,48] A second possible mechanism cited in the literature is the role that phytoestrogens play

in cognitive function. Phytoestrogens are the most bioactive components of soy (a product mainly eaten by vegetarians and vegans) that seem to have a neuroprotective effect.[93] Creatine is another nutrient that plays a critical role in brain development and function. Some papers have hypothesized that it aids cognition by improving energy supply and neuroprotection. Creatine is a peptide found mostly in meat, fish and other animal products, and the levels of muscle creatine are known to be lower in vegetarians. After supplementation of creatine, the memory of vegetarians was better than that of meat-eaters. However, at baseline, memory did not differ depending on dietary style, so any hypothesised creatine deficiency in vegetarians did not influence memory, rather it was found that vegetarians were more sensitive to supplementation with creatine.[51]

Strengths and weaknesses of this meta-analysis

To the best of the authors' knowledge, this is the first meta-analysis to examine the association between vegetarianism/veganism and mental health and cognitive outcomes. An advantage is that these outcomes were interpreted quite broadly while both categorical as well as continuous variables were considered. This study also included many subgroup analyses (by diet, age, sex, instrument, period following the diet and quality assessment score) to detect heterogeneity that might reflect more vulnerable subgroups and methodological issues. This allowed us to estimate the total effect size of the vegan and vegetarian diets on mental health and cognitive outcomes with a larger sample size despite the large heterogeneity in the included studies.

A first limitation is that there are no studies including children and most of the studies included a higher percentage of women than men. Secondly, there were only a few interventional studies and some of them with a low-quality score had a short intervention period (i.e. 2 weeks) hindering the detection of long-term consequences on cognition or mental health. Although many studies have described important differences in lifestyle among vegetarians and vegans compared to omnivores (lower BMI, higher levels of physical activity and lower levels of sedentarism, alcohol and tobacco consumption), only two studies took into account key potential confounders.[23,29] Consequently, the meta-analysis was conducted on raw data only. Nevertheless, adjustment for confounders did not drastically change results in these two studies. Moreover, many relevant articles were finally discarded since they wrongly used the term vegan or vegetarian (i.e. they ate fish or poultry) or they self-reported to be vegetarians or vegans but in the food frequency questionnaire meat and fish were occasionally

eaten.[30,40,42,48] The large variety in used instruments/approaches to define vegetarian/vegan limits comparability and power to find significant relationships. Although it might be interesting to test the situation in pesco-vegetarians (to see whether outcomes might be due to fish omission), only 3 studies identified pesco-vegetarians and this was always a minority group mixed with those having a pure vegetarian diet. Another group that was discarded in our systematic review was eating disorders as mental health outcome. Although vegetarians and vegans were more likely to suffer from eating disorders compared to omnivores in some studies[39,68], we discarded these due to the fact that vegetarian/vegan diets can be a camouflge of an existing eating disorder.[94] Finally, subgroup analyses were based on a small quantity of studies and might thus be biased or lack power.

Implications for public health

The necessary protein, fat, carbohydrate, vitamin and mineral intake within vegetarian and vegan diets for optimal health is still under investigation. Vegetarians and particularly vegans may require supplementation as the nutrients may not be adequately available from plant sources. Some supplements (such as vitamin B12, zinc or creatine) to improve short term memory and intelligence/reasoning may help in very restricted diets. Otherwise, a well-chosen plant-based diet provides all the necessary protein, fats, carbohydrates, vitamins and minerals for optimal health. Apart from the strict omission of animal-based protein, dietary patterns can also be considered on a continuous scale where the amount of animal-based protein is just limited.[95] The terms semi-vegetarians, flexitarians, and plant-based diets reflect the decrease of animal-based proteins[96], which might perhaps bring the advantages without the difficulties of preventing deficiencies in a vegetarian diet. A 6-19% reduction in the risk of all-cause mortality and cardiovascular disease mortality was found by replacing 3% of energy from animal protein with plant protein.[97]

Implications for further research

Drawing conclusions is difficult when there is a lack of studies, when different instruments/definitions are used or when study quality is low. A major flaw in current literature on this topic is the adjustment for confounders. Future studies should adjust for sociodemographics, physical activity, alcohol and tobacco consumption, weight status and medical history. To draw causal conclusions, well-designed intervention studies are needed as we could only find 3 interventions where often participants differed at baseline, there was low intervention adherence and only short-term interventions. In finding causal

pathways, studies should measure nutrient status as deficiencies are frequent in vegetarian/vegan diets. Moreover, different gradients of plant-based diet should be examined e.g. the role of fish (with omega-3 fats), milk, eggs and quality of plant-based foods (omission of meat or any other animal-product does not guarantee high-nutritious choices). Herein, the duration of diet adherence is seldom examined.

Conclusion

Based on our meta-analysis, following a vegan or vegetarian diet was associated with a higher depression risk and in those under 26y with higher anxiety scores but no differences for the other outcomes were found. Subgroup analyses showed a lot of contrasting significances with higher mental risks mainly in those under 26y and in higher quality studies. Large heterogeneity impeded us to draw definitive conclusions. More studies in mental health and especially on cognitive outcomes with overall better quality are needed to derive clear positive/negative associations.

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All authors revised and provided intellectual input into the final manuscript.

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Table 1. PICOS table

PICOS	
Participants	Children, adolescents or adults, both sexes and all nationalities without chronic diseases
Interventions	Vegetarianism or veganism
Control/comparator group	Omnivores
Outcomes	1. Mental health (depression, anxiety, stress, neuropsychiatric, psychological health and well-being) 2. Cognitive outcomes (attention, memory, orientation, executive functions, social cognition)
Study design	Observational studies with a comparison group (cohort studies, cross-sectional studies, case control studies) and randomized control trial and non- randomized control trials.

Table 2. Characteristics of included studies.

Study	**Participants**	**Mental health and cognitive outcomes**	**Study**	**Other information**	**QA (%)**

											design		
Authors and year	**VEGAN n (age)**[a]	**LOVn (age)**[a]	**OMVn (age)**[a]	**Se**	**Continuous outcome**	**Instrument used**	**Mean±SD**	**Categorical outcome**	**Instrument used**	**Number of events**			
Agarwal et al. (2015)[17]	91 (43.8±10.6) 92 (43.8±10.6) 91 (43.8±10.6)		110 (45.4±11.3) 110 (45.4±11.3) 109 (45.4±11.3)	F/ F/M F/M	Depression Anxiety Mental health	SF-36 SF-36 SF-36	*VEGAN (18.2±3.9) OMN (24.4±5.9) *VEGAN (27.4±6.3) OMN (33.2±10.4) *VEGAN (78.3±16.3) OMN (72.1±18.3)				RCT	Raw data No significant differences between the intervention and control groups for any demographic or clinical measurements except for sex (more men in the intervention group than in control group) Period following the diet[b]: 18 weeks (intervention) Country (predominant ethnicity): USA (Caucasian)	**50**

Baines et al. (2007)[18]		252 (22-27)	8034 (22-27)	F	Mental health	SF-36	*LOV (47.6±10.5) OMN (50.5±9.1)	Depression Anxiety Deliberate self-harm Panic attacks or palpitations	Self-reported according to diagnosis of a doctor Self-reported according to diagnosis of a doctor Self-reported according to diagnosis of a doctor Self-reported according to diagnosis of a doctor	*LOV 51 OMN 1074 *LOV 24 OMN 466 *LOV 25 OMN 249 LOV 46 OMN 249	CS	Raw data Vegetarians were more physically active, had a lower BMI, were more likely to be living in an urban area, unmarried, have a university degree but lower income. No significant differences in smoking or alcohol consumption. Period following the diet[b]: NR Country (predominant ethnicity): Australia (NR)	**43**

Beezhold et al. (2010)[19]		60 (45.0±11.1)	78 (41.0±12.3)	F/	Depression Anxiety Stress Mood disturbances	DASS-D DASS-A DASS-S POMS-total	*LOV (1.7±2.1) OMN (4.8±6.0) *LOV (1.5±1.8) OMN (4.3±4.7) *LOV (5.1±4.0) OMN (8.4±8.1) *LOV (0.1±.15.4) OMN (15.3±27.3)				CS	Raw data Vegetarians were older, more physically active and had a lower BMI than non-vegetarians. No differences: by education or gender among vegetarians and omnivores. Period following the diet[b]: NR Country (predominant ethnicity): USA (NR)	**36**

Beezhold et al. (2012)[20]		13 (NR)	13 (NR)	F/	Depression Anxiety Stress Mood disturbances	DASS-D DASS-A DASS-S POMS-total	LOV (1.0±1.4) OMN (1.0±1.4) LOV (15±23.7) OMN (10.0±14.0) *LOV (8.5±10.3) OMN (14.0±11.8) LOV (5.0±17.0) OMN (3.0±16.3)				Pilot RCT	Raw data Control and intervention groups did not differ by age, gender, BMI, educational level, ethnicity, total PA level or fatty acid intakes Period following the diet[b]: 2 weeks (intervention) Country (predominant ethnicity): USA (NR)	**57**
Beezhold et al. (2015)[21]	283 (37.2±10.3)	109 (32.7±9.5)	228 (34.6±10.8)	F/	Depression Anxiety Stress	DASS-D DASS-A DASS-S	VEGAN (5.4±6.5) LOV (5.4±5.9) OMN (5.4±6.7) *VEGAN (3.4±4.20) LOV (3.9±4.5) OMN (4.7±5.3) *VEGAN (7.5±6.3) LOV				CS	Raw data Vegetarians and vegans were less likely to be married, and they had better lifestyle (higher activity, higher intakes of fruits and vegetables and lower alcohol) and lower education level than omnivores. No significant	**50**

							(9.3±7.5) OMN (10.0±8.2)					differences by sex or smoking. Period following the diet[b]: NR Country (predominant ethnicity): USA (NR)	
Forestell and Nezlek. (2018)[22]		223 (18.9±1.3)	4192 (18.9±1.3)	F/	Depression	CESD	*LOV/VEGAN (17.1±10.6) OMN (14.2±9.5)				CS	Confounder differences: NR Period following the diet[b]: NR Country (predominant ethnicity): USA (Caucasian)	**50**
Giem (1993)[23]	68 (>65)	68 (>65)	136 (>65)	F				Dementia/memory impairment	Physical and neurological examination	*VEGAN 5 *LOV 3 OMN 16	PS	Raw data and adjusted models (sex, age, education, ZIP code, previous diseases, alcohol, smoking and BMI). Cases were matched on age and sex), differences in other confounders: NR. Period following the diet[b]: ≥20 y	**86**

												Country (predominant ethnicity): USA (NR)	
Katcher et al. (2010)[24]	65 (23-65)	44 (21-62)		F/	Mental health	SF-36	VEGAN (76.9±18.5) OMN (76.8±17.9)				NR CT	Raw data Vegan (intervention) were older but no other significant differences between control and intervention group Period following the diet[b]: 22 weeks (intervention) Country (predominant ethnicity): USA (NR)	**43**
Kapoor et al. (2017)[25]		100 (27.7±5.8)	100 (28.8±5.7)	F/				Dementia/memory impairment Depression Personality change Psychosis	MMSE HRSD Diagnosed by a doctor	*LV 7 OMN 2 *LV 31 OMN 12 *LV 5 OMN 1	CS	Raw data Confounder differences: NR. Vegetarians lower mean values of B12 Period following the diet[b]: Since childhood Country (predominant ethnicity): Pakistan (NR)	**57**

									Diagnosed by a doctor	*LV 11 OMN 3			
Lindeman (2010)[26]		42 (29.0 ± 10.8)	197 (29.0 ± 10.8)	F	Depression	ESDS	*LOV (12.5±6.18) OMN (9.6 ±5.7)				CS	Raw data Confounder differences: NR Period following the diet[b]: NR Country (predominant ethnicity): Finland (NR)	**50**
Rodríguez et al. (1998)[27]	20 (23-70)	20 (23-70)	40 (23-70)	F/	Depression Anxiety	CESD IDARE-STAI	*VEGAN (6.1±4.9) *LOV (4.5±4.2) OMN (12.5±10.7) *VEGAN (26.4±4.7) LOV * (29.5±6.3) OMN (33.9±9.6)				CS	Raw data Confounder differences: NR Period following the diet[b]: >3 y Country (predominant ethnicity): Puerto Rico (NR)	**50**
Timko et al. (2012)[28]	35 (26.9 ± 7.9)	111 (26.7 ± 9.1)	265 (23.4 ± 9.7)	F/	Depression	DASS-D	VEGAN (6.5±7.6) LOV				CS	Raw data	**57**

					Anxiety Stress	DASS-A DASS-S	(9.5±10.4) OMN (7.0±7.6) VEGAN (0.6±0.9) LOV (0.5±0.9) OMN (0.4±0.8) VEGAN (11.8±10.3) LOV (11.5±8.8) OMN (10.4±7.7)					Lower BMI and higher smoker rate in vegans and vegetarians than in omnivores. Not significant difference by sex or age. Period following the diet[b]: ≥6 y Country (predominant ethnicity): USA (Caucasian)	
Velten et al. (2018)[29]	52 (23.4±3.8)	227 (21.4 ±3.3)	2204 (21.6 ± 4.0)	F/	Depression Anxiety Stress	DASS-D DASS-A DASS-S	*VEGAN (6.5±5.3) *LOV (5.3±4.8) OMN (4.2±4.3) *VEGAN (5.3±4.5) LOV * (5.3±4.8) OMN (3.4±3.6) *VEGAN (8.5±4.4) LOV * (8.0±4.9) OMN (7.1±4.6)				PS	Raw and adjusted Models (for gender, age, physical activity, mental activity, social irregularity, BMI, alcohol, smoking) Confounder differences: in all tested confounders, depending on the country. Period following the diet[b]: NR Country (predominant ethnicity): Germany and China (NR)	**57**

	69	259	2483		Mental health	PMHS	*VEGAN (16.2±5.5) *LOV (16.9±5.9) OMN (18.3±5.3)						

[a] mean ± standard deviation or (minimum, maximum)

[b] Minimum years following the vegetarian or vegan diet

* Results statistically significant between vegetarians or vegans and omnivores

CESD, Center for Epidemiologic Studies Depression; CS, Cross-sectional study; DASS, Depression Anxiety Stress Scales; DASS-A, DASS-Anxiety; DASS-D, DASS-Depression; DASS-S, DASS-Stress; EPDS, Edinburgh Post Natal Depression Scales; F, Females; HRSD, Hamilton Rating Scale for Depression; IDARE, Spanish version of State-Trait Anxiety Inventory; LOV, lacto-ovo-vegetarians; LV, lacto-vegetarian, M, Males; MMSE, Mini-Mental Status Examinations; NR, Not Reported; NRCT, Non-Randomized Controlled Trial; OMN, omnivores; PMHS, Profile of Mood States; Positive Mental Health Scale; POMS, SF-36, 36-Item Short Form Health Survey; PS, Prospective Study; QA, quality assessment; STAI, State-Trait Anxiety Inventory; y, years

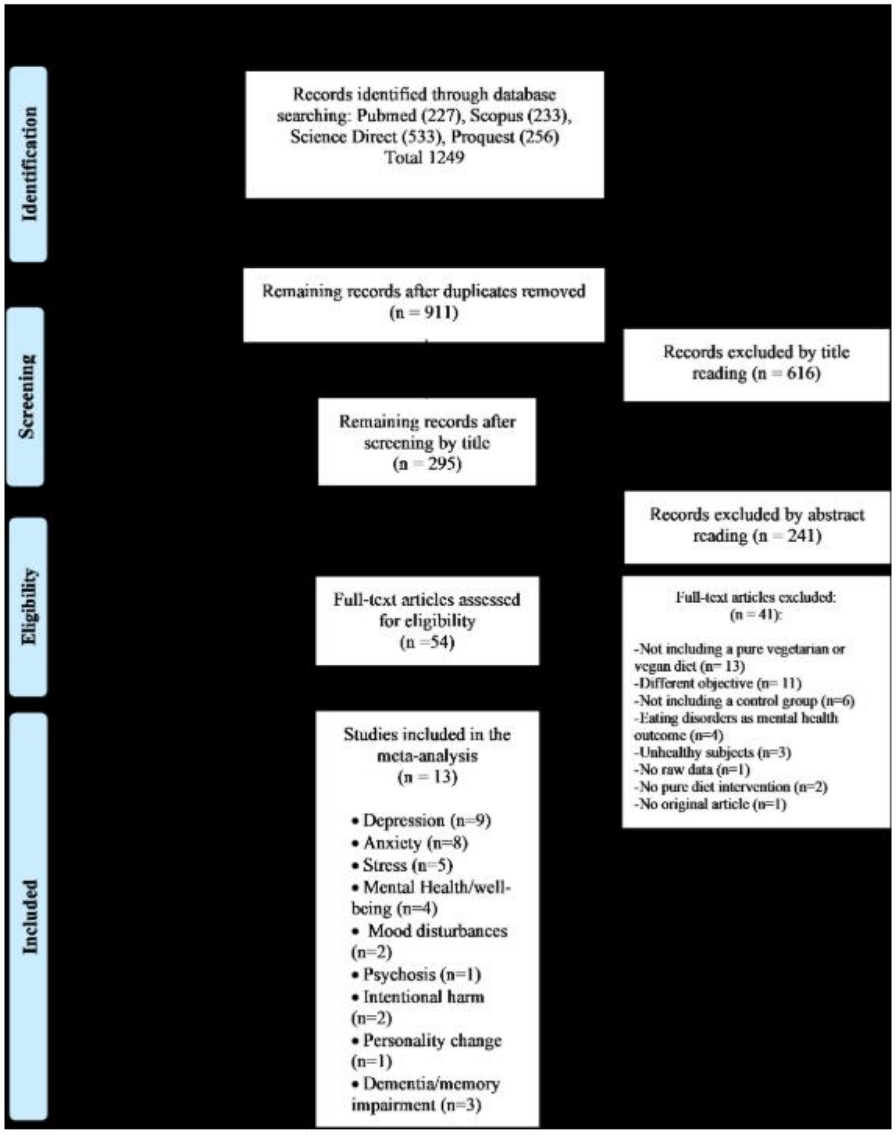


Figure 1. PRISMA flow diagram. Search strategy.

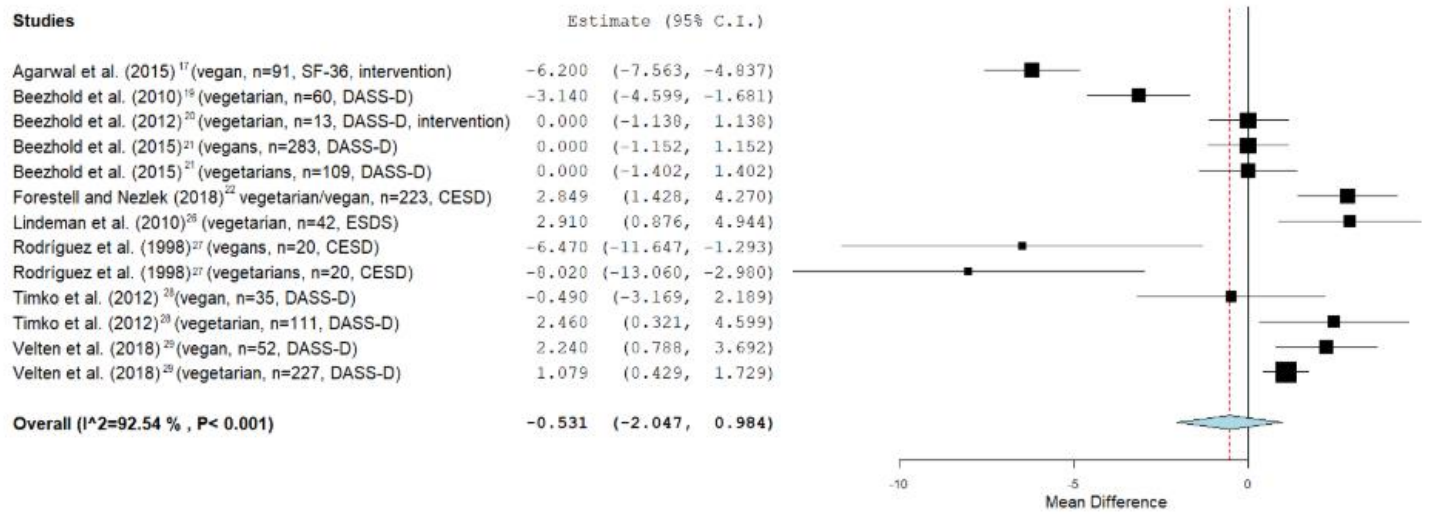


Figure 2. Random effects meta-analysis of the effects of vegetarian and vegan diets on depression (continuous).

Figure 2a. Differences in depression (continuous) between vegetarians and vegans versus omnivores

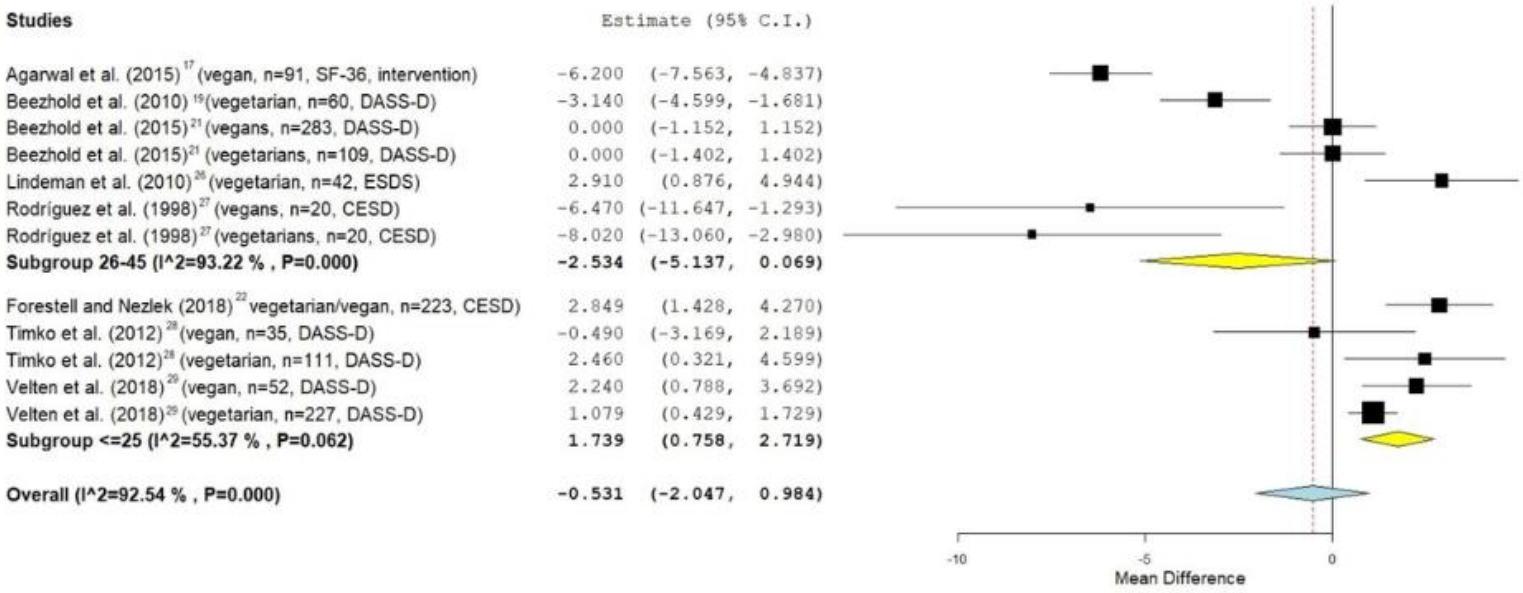


Figure 2b. Subgroup analyses by age (<=25 years old, 26-45 years old or >45, or NR -not reported-)

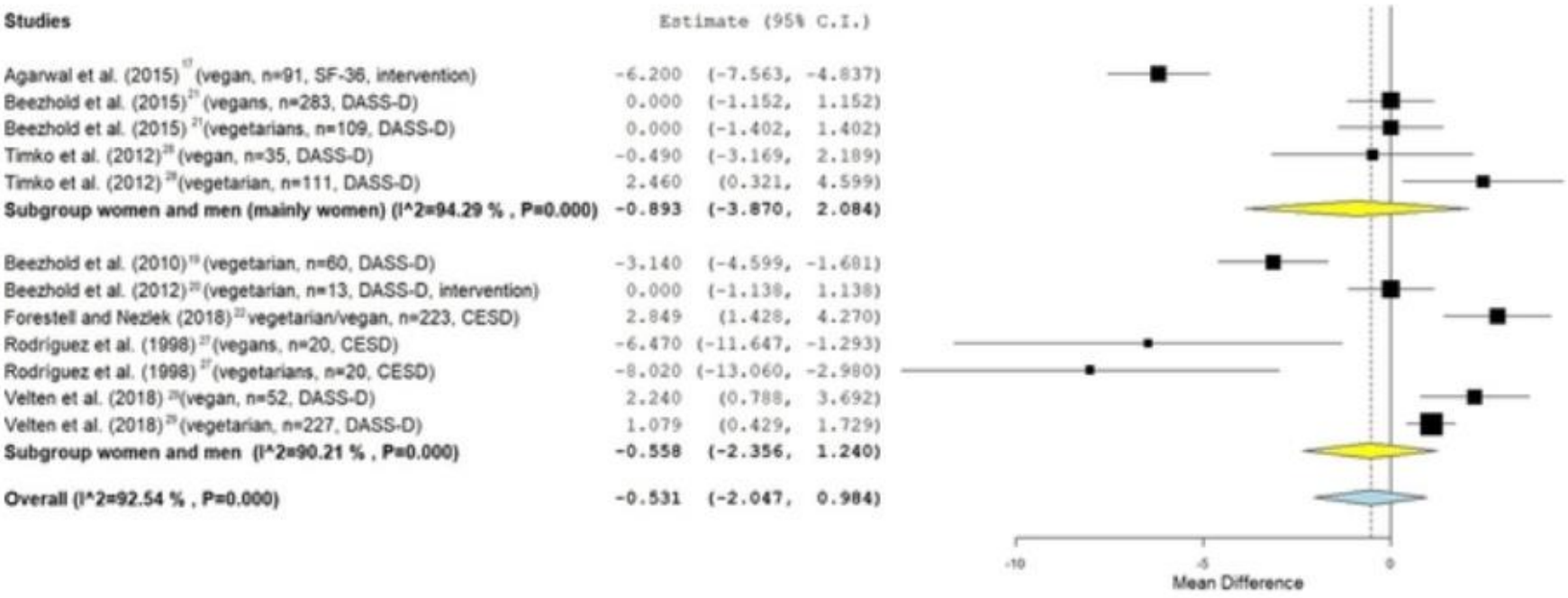


Figure 2c. Subgroup analyses by sex (women, men, women/men, NR -not reported-)

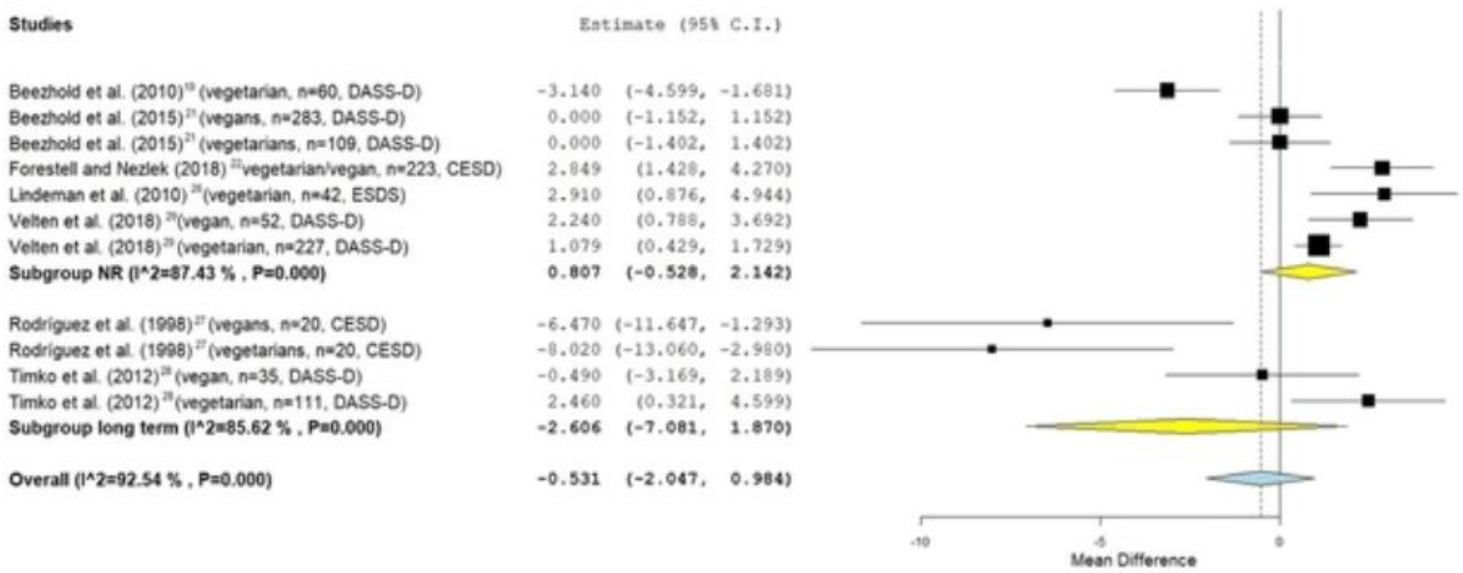


Figure 2d. Subgroup analyses by period following the diet (short term, long term or NR -not reported-)

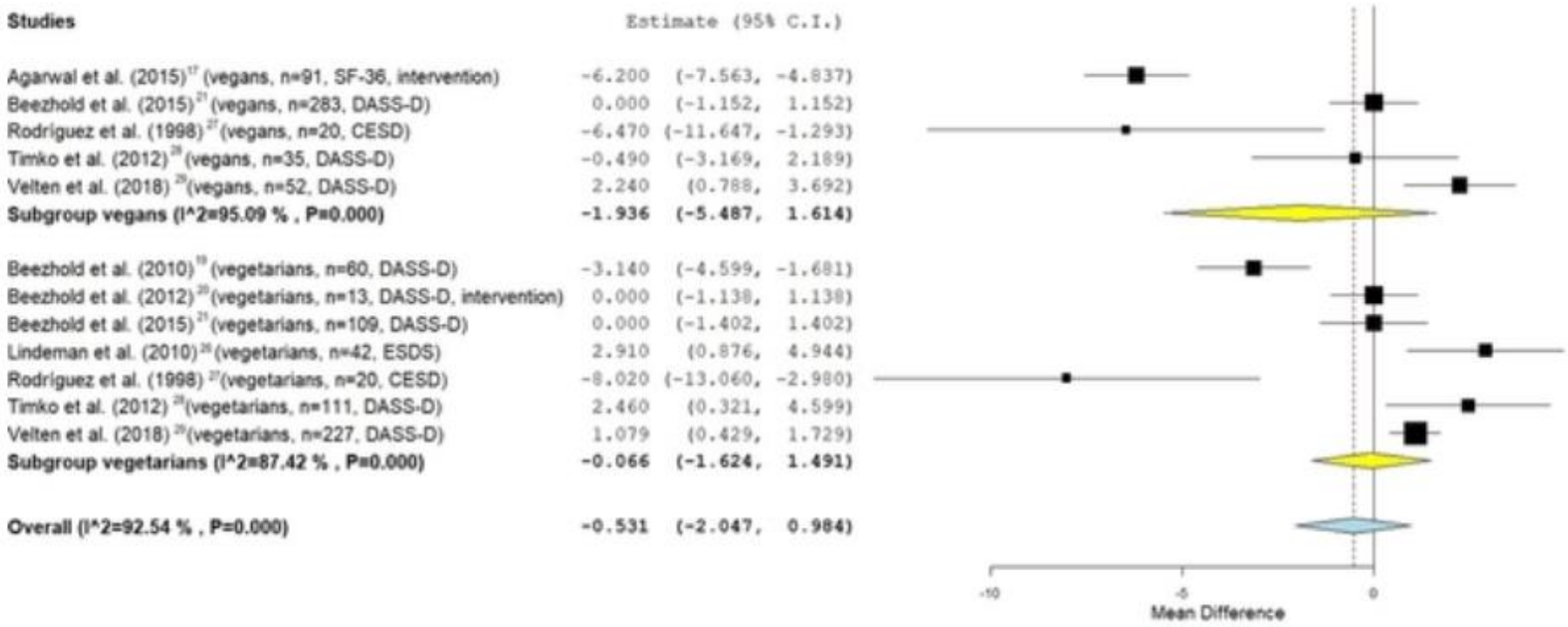


Figure 2e. Subgroup analyses by diet (vegetarians versus vegans)

224x121mm (72 x 72 DPI)

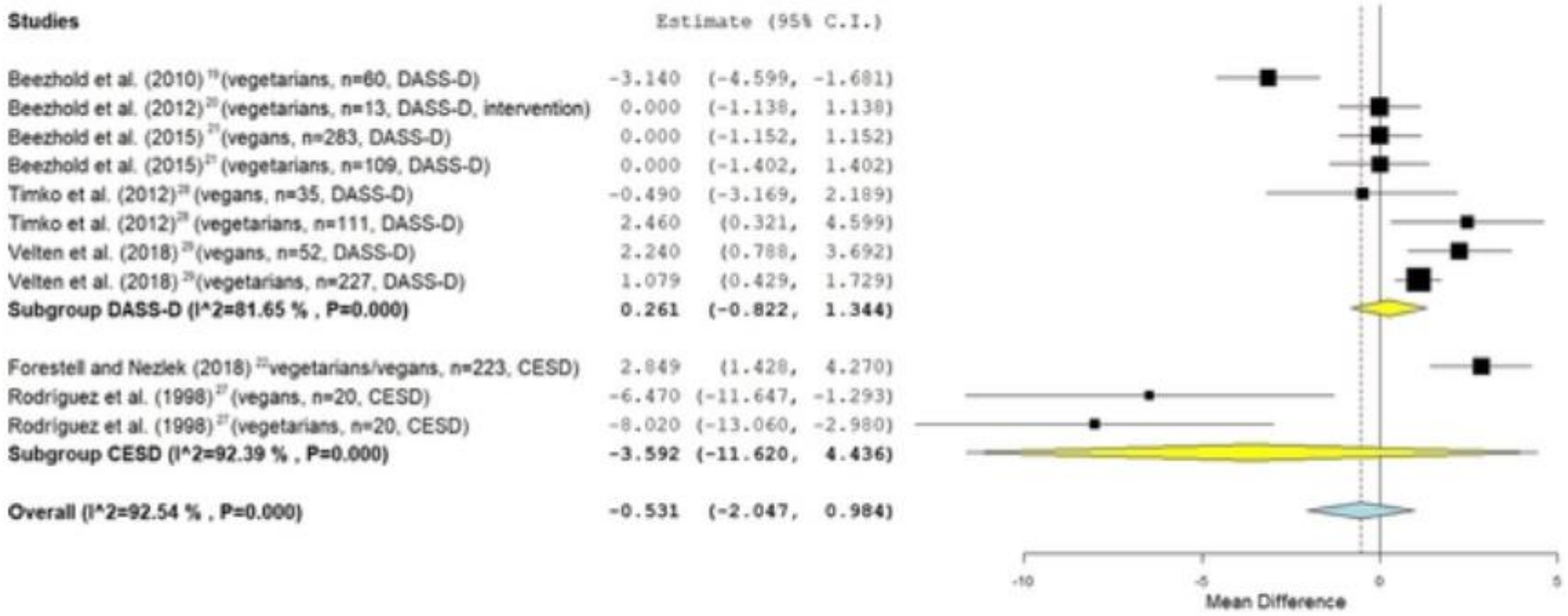


Figure 2f. Subgroup analyses by instrument used (DASS, CESD, others)

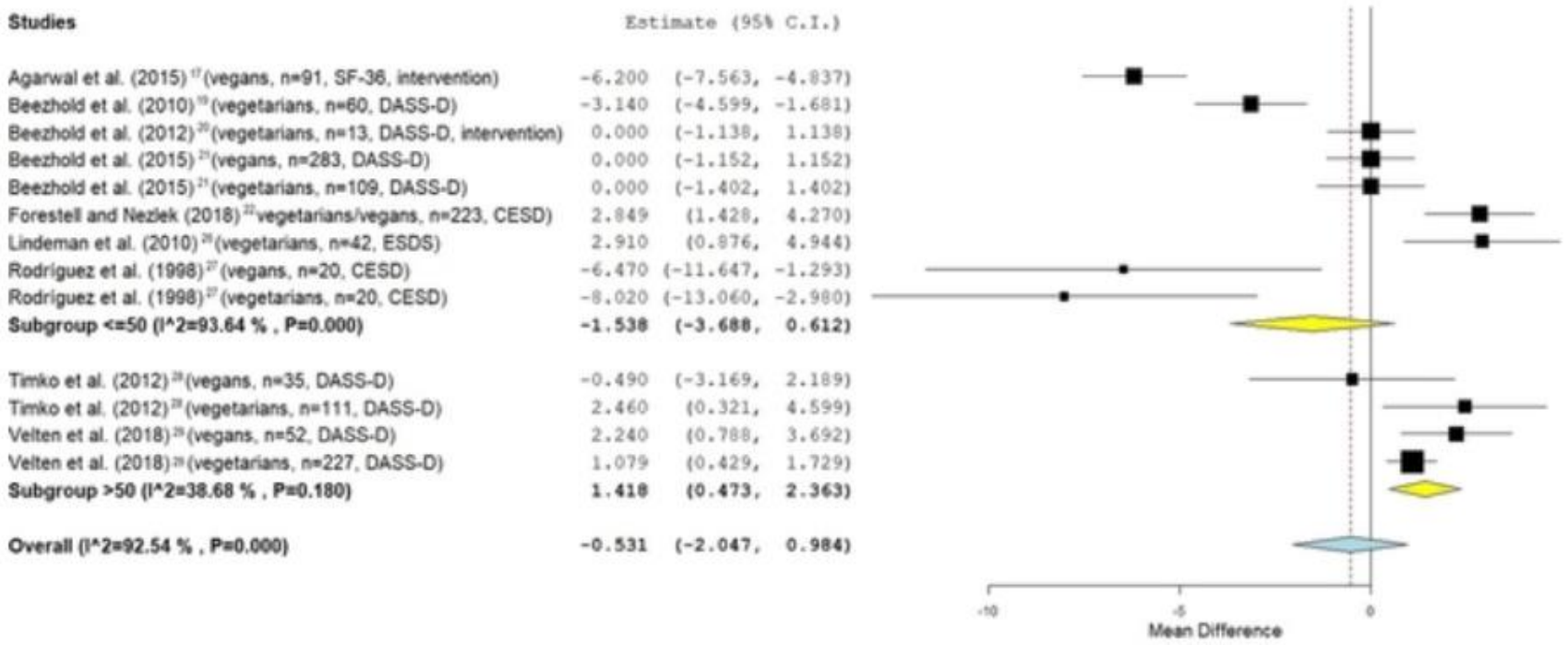


Figure 2g. Subgroup analyses by quality assessment score (<50 score versus >=50 score)

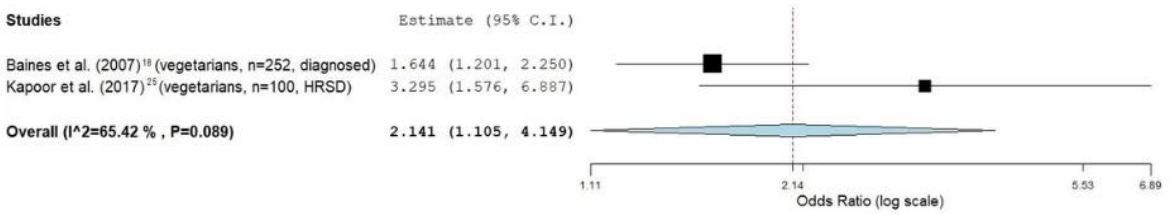


Figure 3. Random effects meta-analysis of the effects of vegetarian and vegan diets on depression (categorical). Differences in depression (categorical) between vegetarians and vegans versus omnivores.

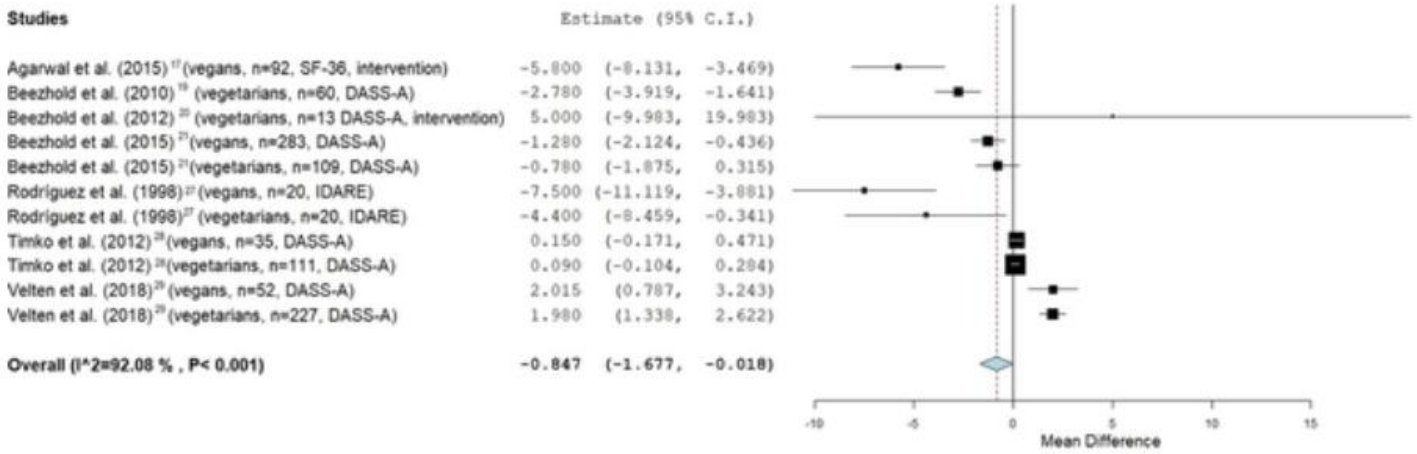


Figure 4. Random effects meta-analysis of the effects of vegetarian and vegan diets on anxiety (continuous). Figure 4a. Differences in anxiety (continuous) between vegetarians and vegans versus omnivores

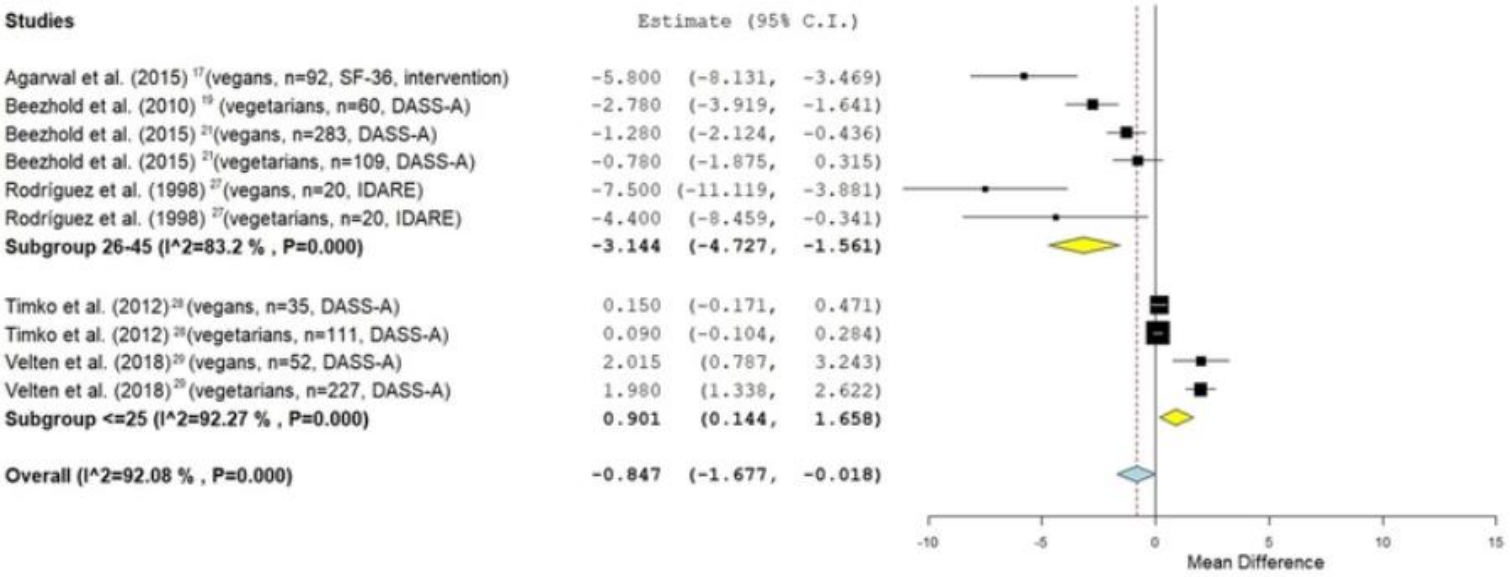


Figure 4b. Subgroup analyses by age (<=25 years old, 26-45 years old, >45 or NR-not reported-)

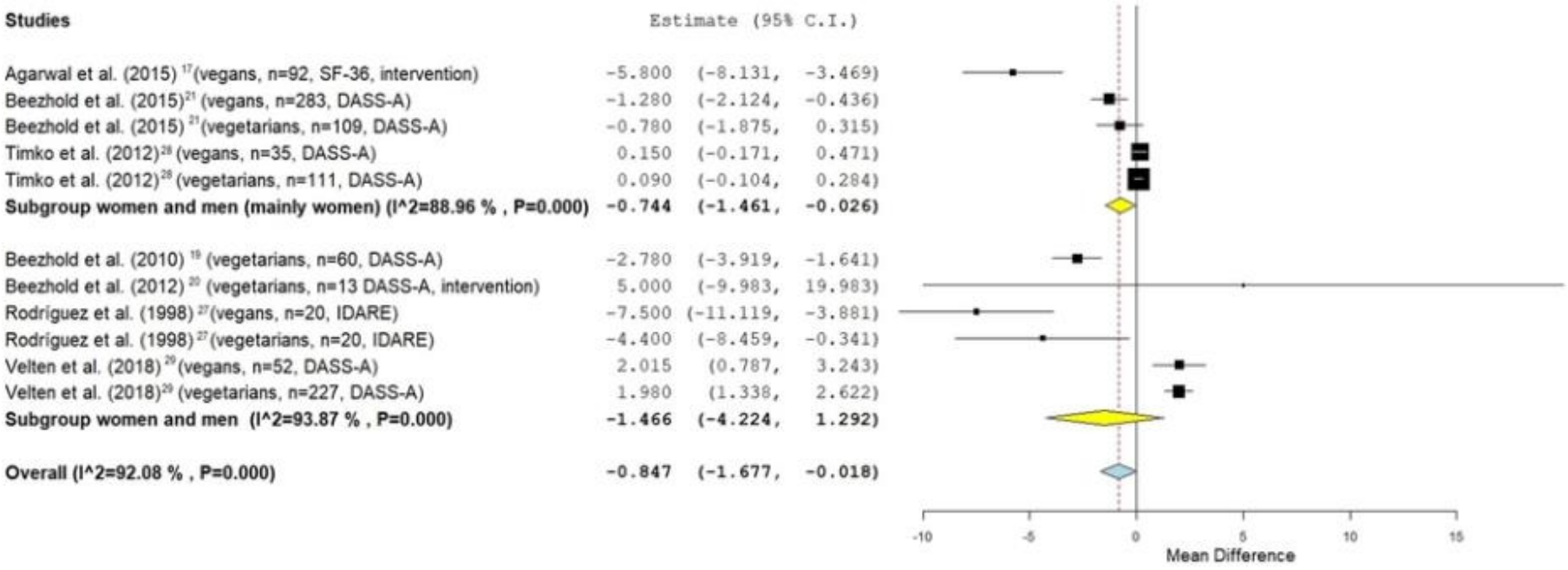


Figure 4c. Subgroup analyses by sex (women, men, women/men, NR)

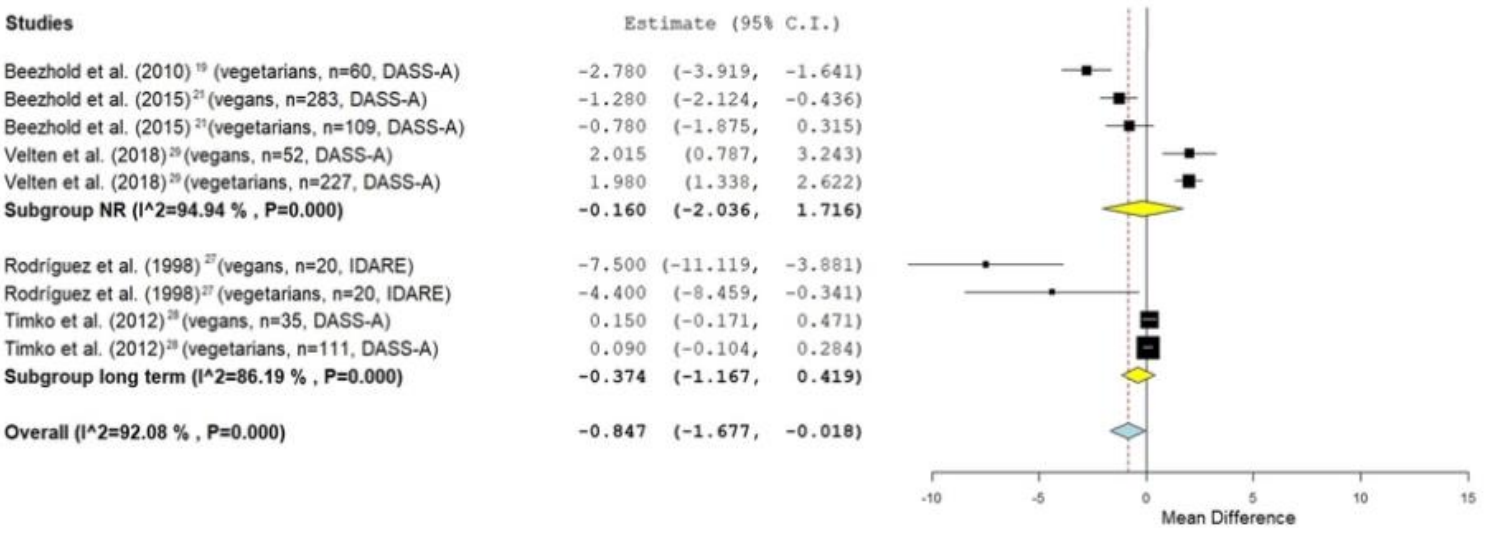


Figure 4d. Subgroup analyses by period following the diet (short term, long term or NR -not reported-)

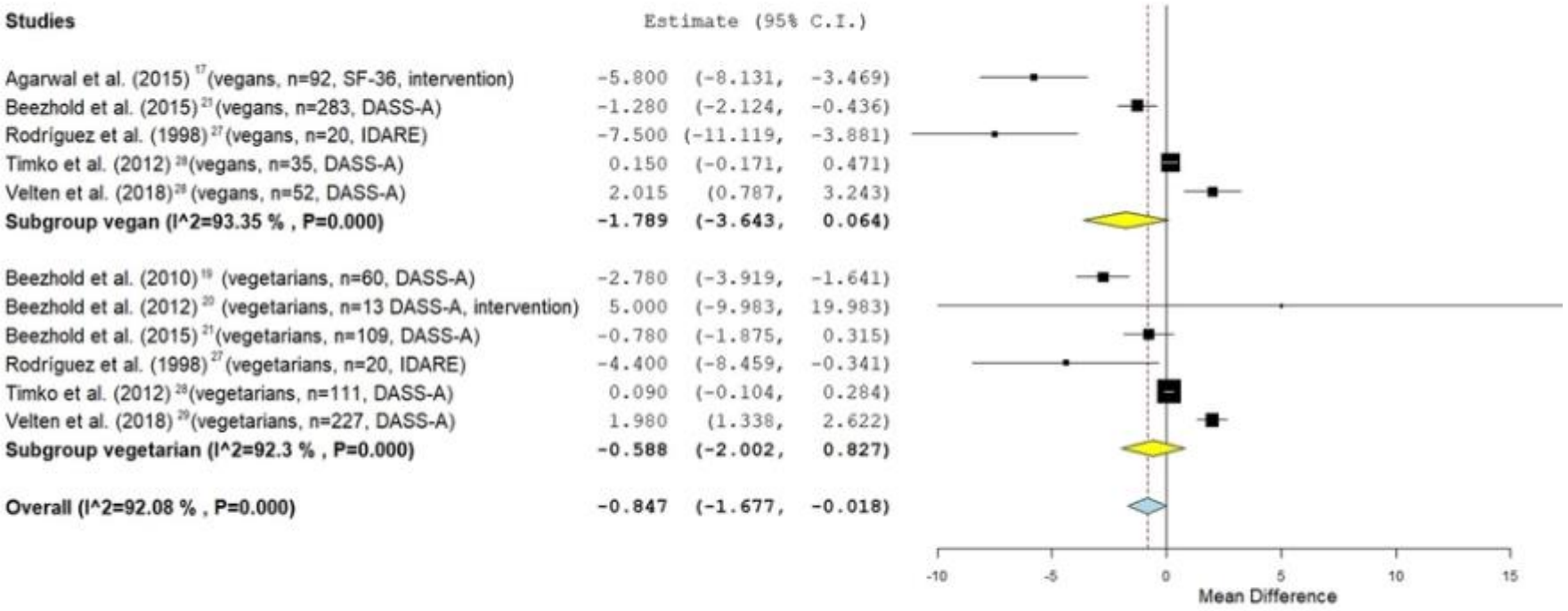


Figure 4e. Subgroup analyses by diet (vegetarians versus vegans)

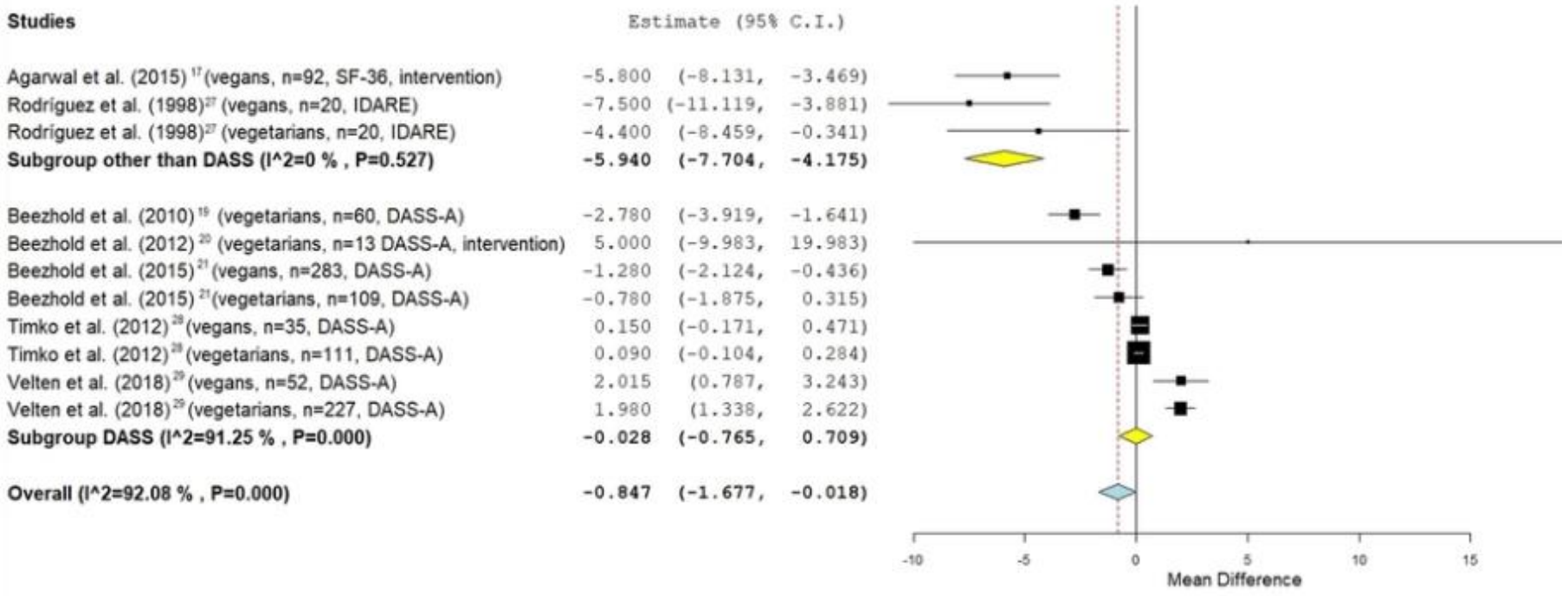


Figure 4f. Subgroup analyses by instrument used (DASS, others)

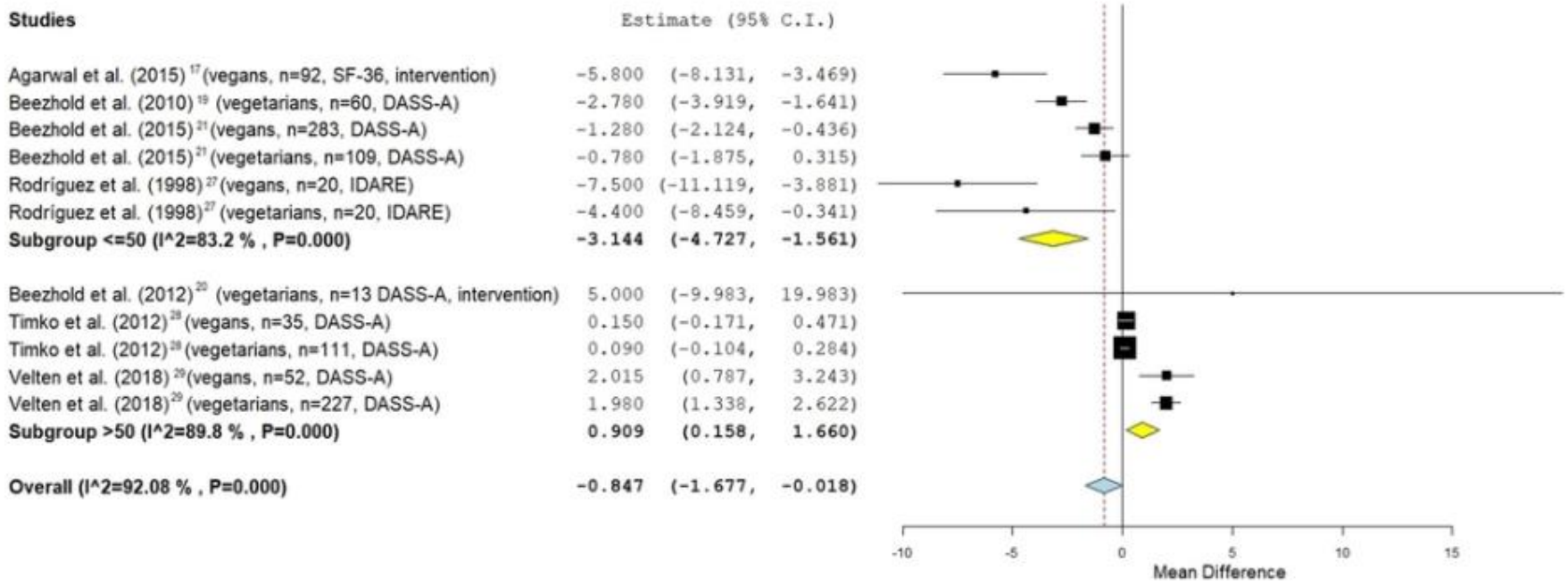


Figure 4g. Subgroup analyses by quality assessment score (<=50 score versus >50 score)

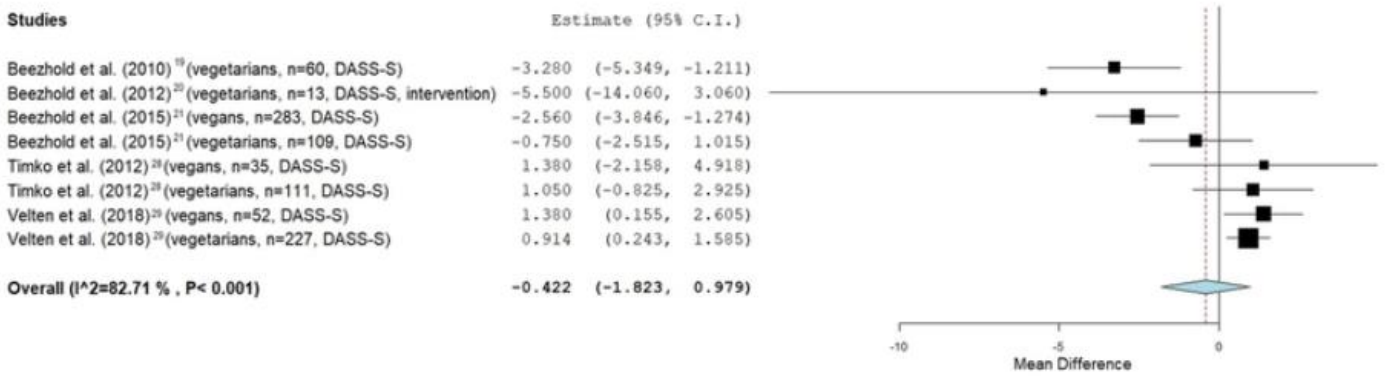


Figure 5. Random effects meta-analysis of the effects of vegetarian and vegan diets on stress (continuous).
Figure 5a. Differences in stress (continuous) between vegetarians and vegans versus omnivores

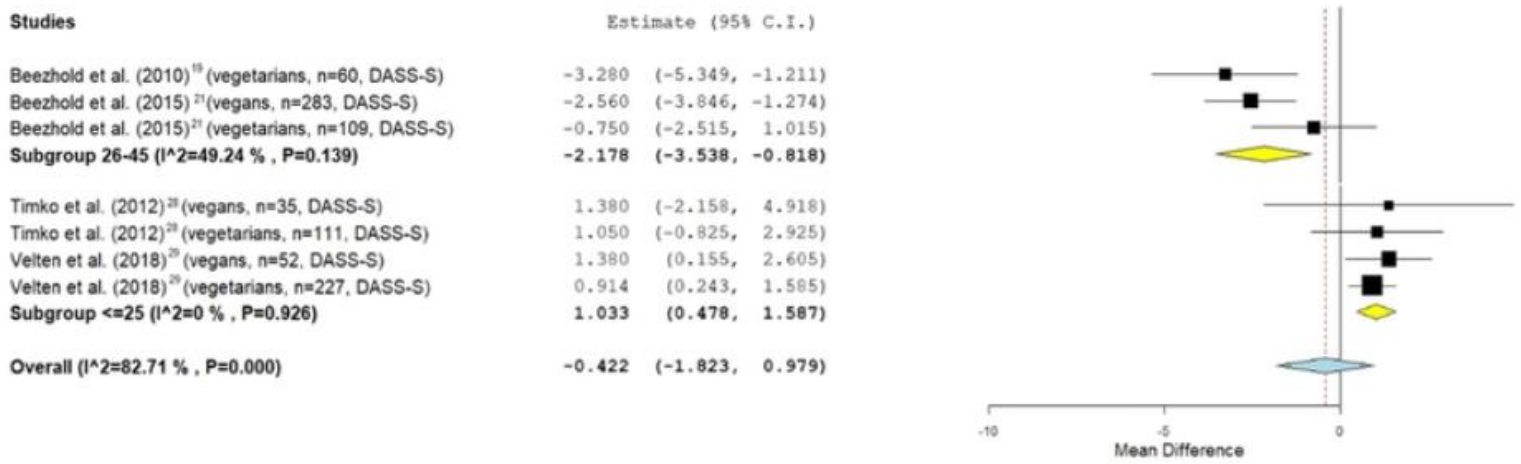


Figure 5b. Subgroup analyses by age (<=25 years old, 25-45 years old, >45 or NR-not reported-)

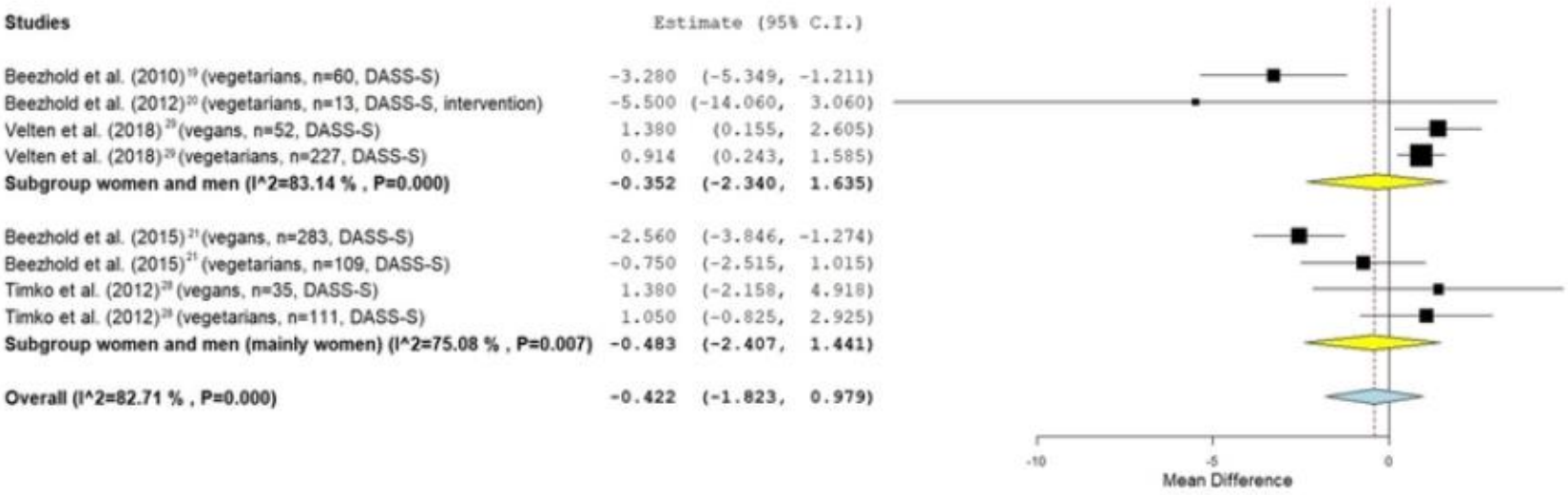


Figure 5c. Subgroup analyses by sex (women, men, women/men, NR-not reported-)

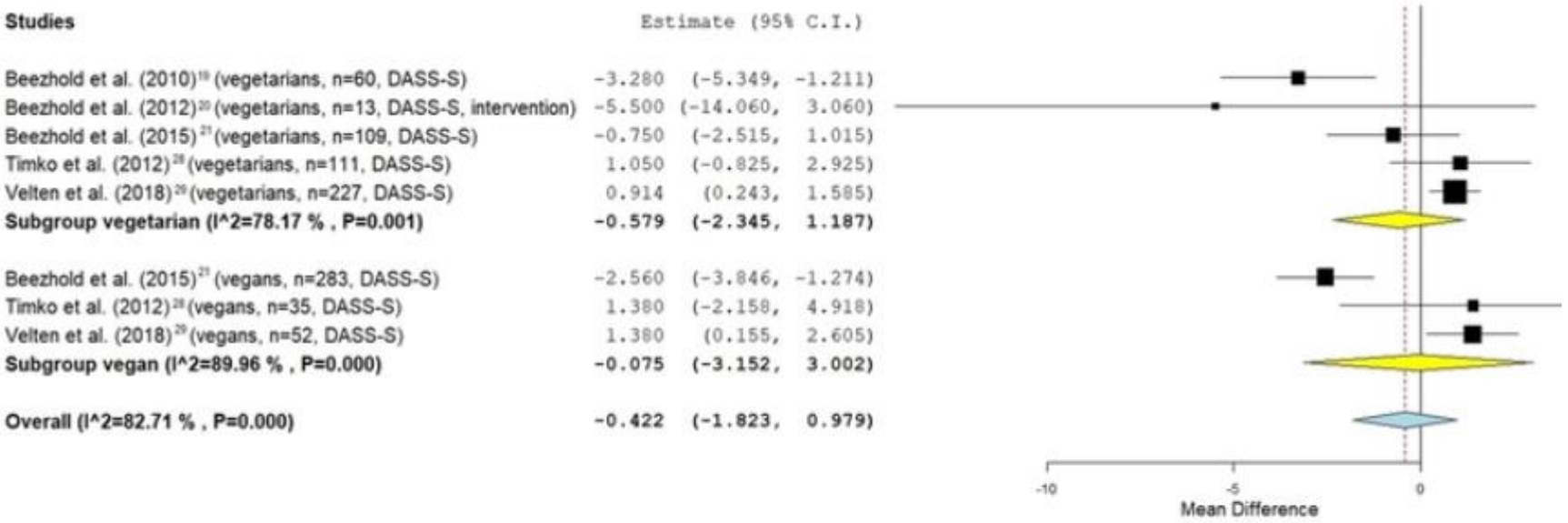


Figure 5d. Subgroup analyses by diet (vegetarians versus vegans)

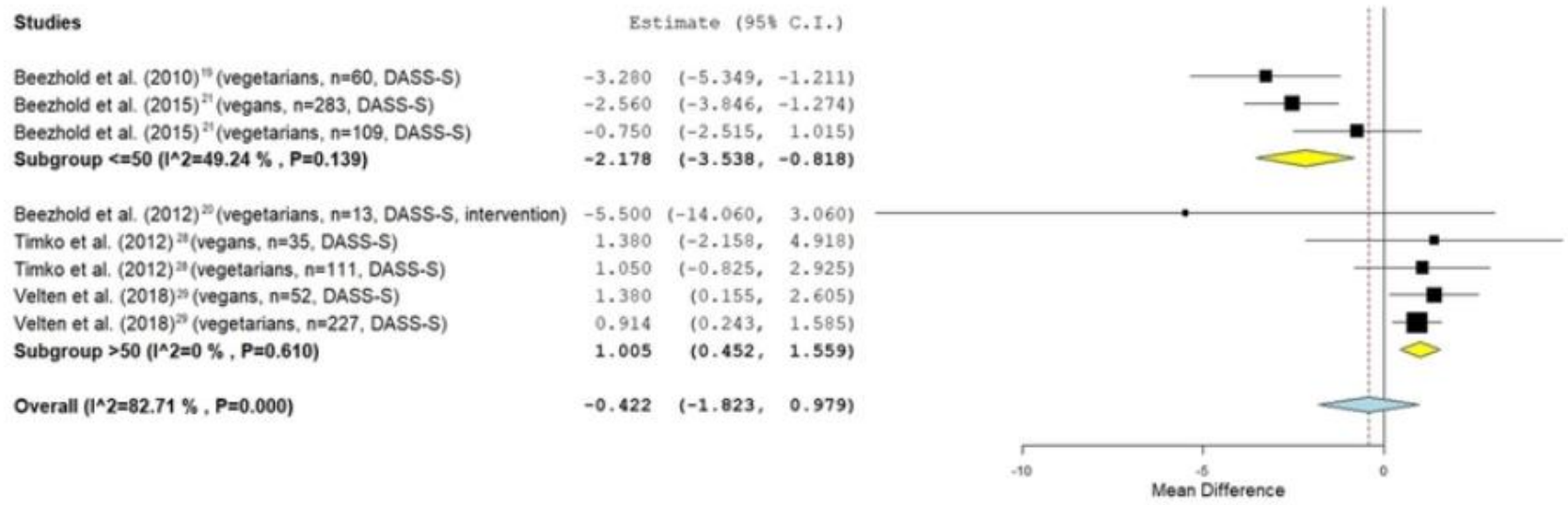


Figure 5e. Subgroup analyses by quality assessment score (<50 score versus >=50 score)

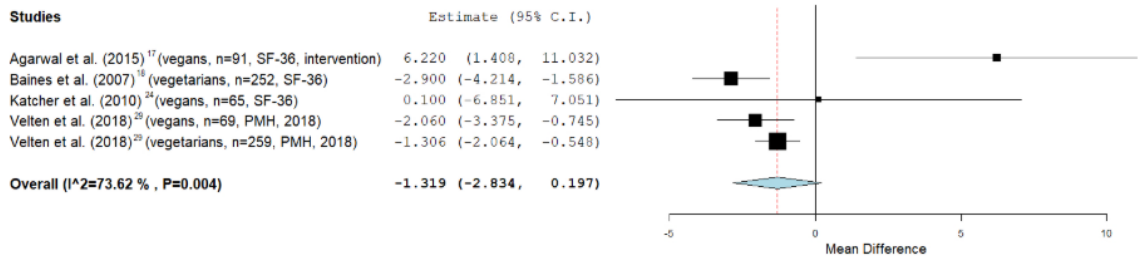


Figure 6. Random effects meta-analysis of the effects of vegetarian and vegan diets on mental health/well-being (continuous). Differences in mental health/well-being (continuous) between vegetarians and vegans versus omnivores.

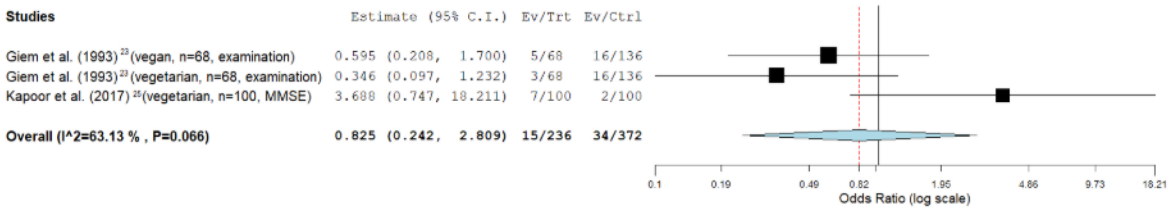
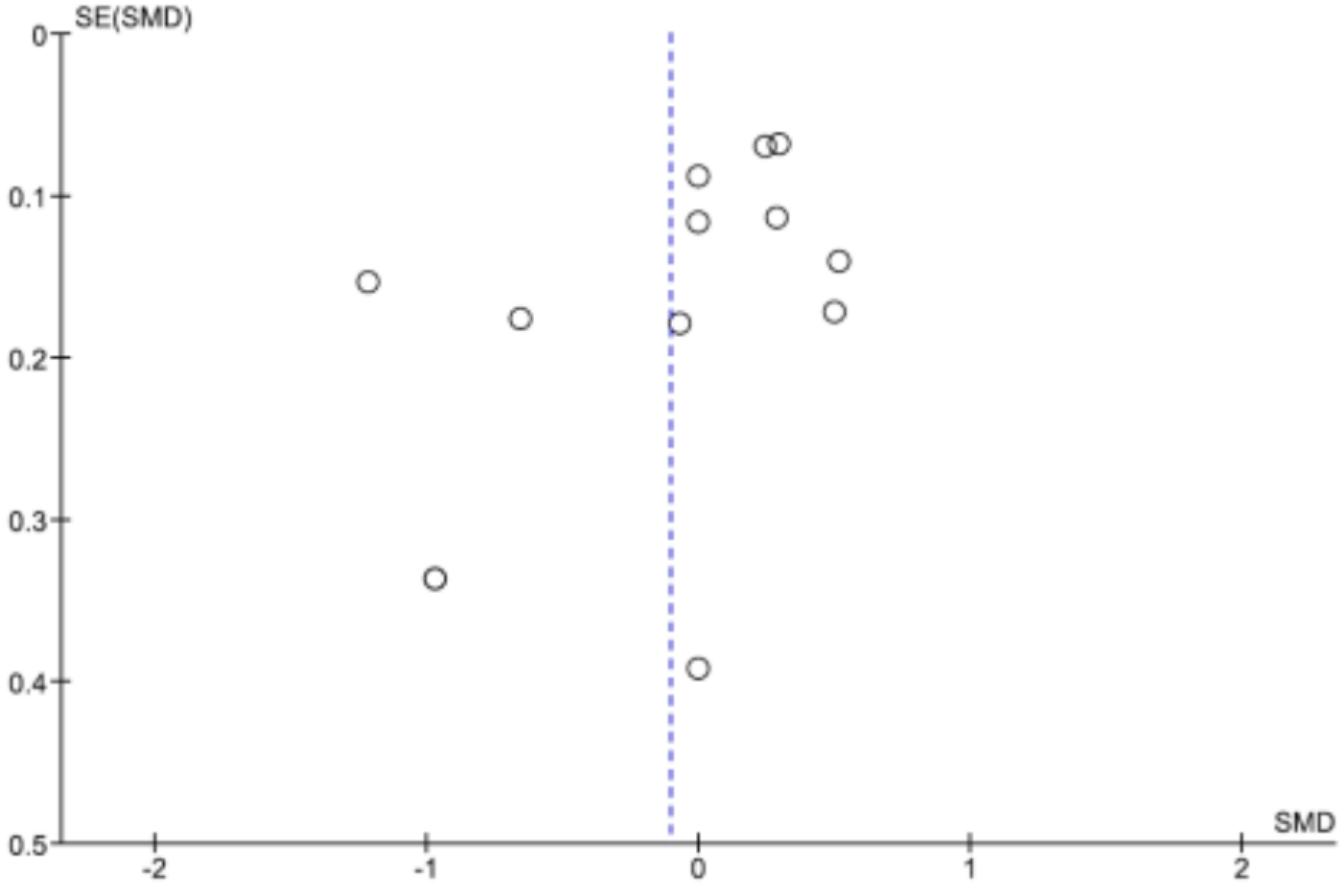


Figure 7. Random effects meta-analysis of the effects of vegetarian and vegan diets on cognitive outcomes (memory impairment/dementia, categorical). Differences in memory impairment/dementia (categorical) between vegetarians and vegans versus omnivores.

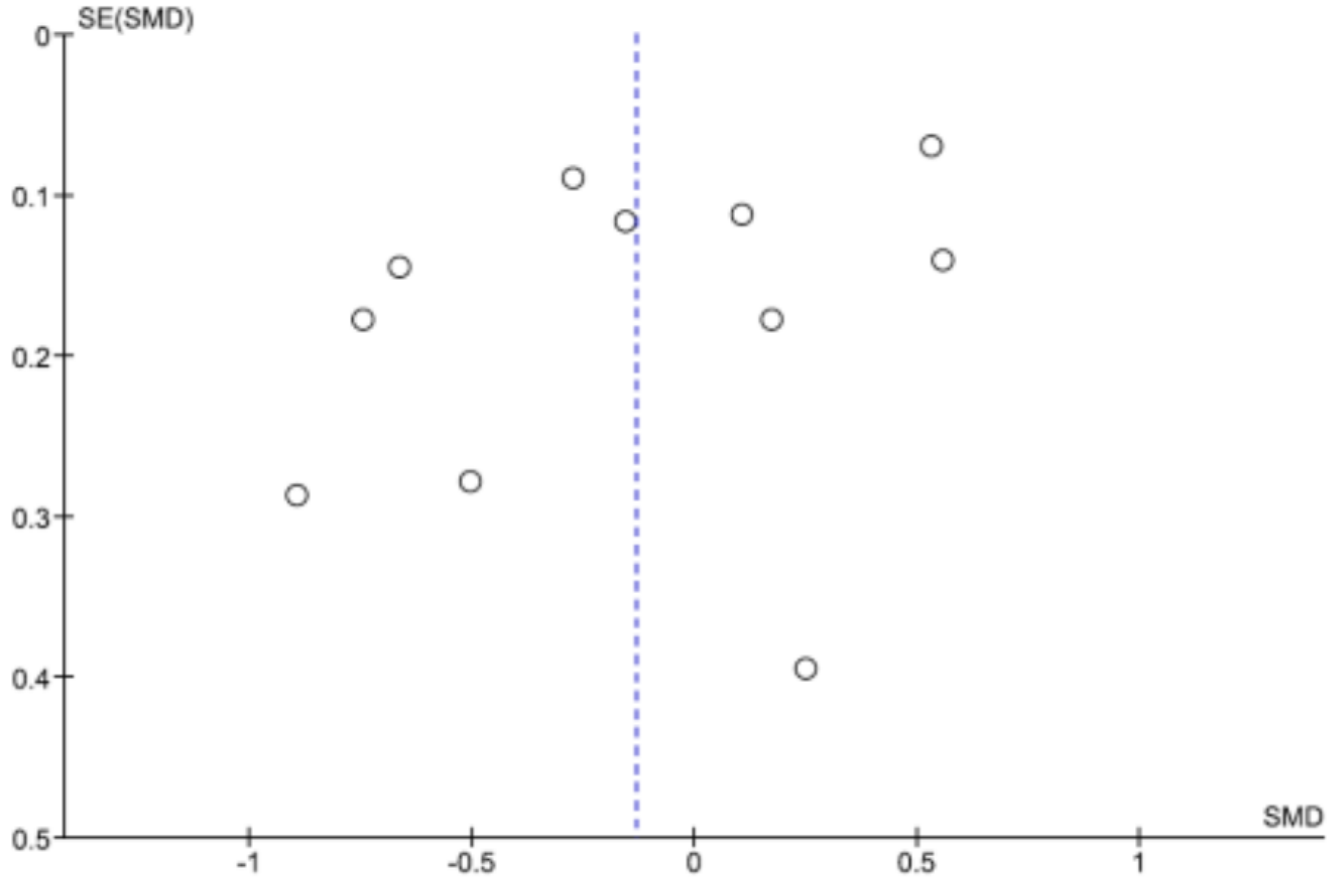
Supporting information

Supplementary Figure 1. Funnel plot of vegetarianism and vegan diets and depression. The effect estimate line is shown as a dashed line.



SMD= standardized mean difference, SE= standard error

Supplementary Figure 2. Funnel plot of vegetarianism and vegan diets and anxiety. The effect estimate line is shown as a dashed line.



SMD= standardized mean difference, SE= standard error

Supplementary table 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 (Title)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 (Abstract)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Table 1 and 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4 and Figure 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 and 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6 and Figure 1

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 and 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Table 1 and 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8, 12 and Supplementary Figure 1 and 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2 and 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1 Figures 2,3,4 and 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2,3,4, and 5

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12 and Supplementary Figure 1 and 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figures 2,3,4 and 5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12 and16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15 and 16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary table 2. Quality assessment for Observational Cohort and Cross-Sectional Studies (NHBLI).

Studies	**Quality assessment criteria**[a]														**Quality score (%)**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Baines et al. 2007[51]	1	1	1	1	0	0	0	1	1	0	0	0	NA	0	**43%**

Beezhold et al. 2010[S2]	1	1	0	1	0	0	0	0	1	0	1	0	NA	0	**36%**
Beezhold et al. 2015[S3]	1	1	1	1	0	0	0	1	1	0	1	0	NA	0	**50%**
Forestell and Nezlek 2018[S4]	1	1	1	1	0	0	0	1	1	0	1	0	NA	0	**50%**
Giem 1993[S5]	1	1	1	1	0	1	1	1	1	0	1	1	1	1	**86%**
Kapoor et al. 2017[S6]	1	1	1	1	0	0	1	0	1	0	1	1	NA	0	**57%**
Linderman 2010[S7]	1	1	1	1	0	0	0	1	1	0	1	0	NA	0	**50%**
Rodríguez et al. 1998[S8]	1	1	NR	1	0	0	1	1	1	0	1	0	NA	0	**50%**
Timko et al. 2012[S9]	1	1	0	1	1	0	1	1	1	0	1	0	NA	0	**57%**
Velten et al. 2018[S10]	1	1	0	1	0	1	1	0	1	0	1	0	0	1	**57%**

[a](1) Was the research question or objective in this paper clearly stated? (2) Was the study population clearly specified and defined? (3) Was the participation rate of eligible persons at least 50%? (4) Were all the subjects selected or recruited from the same or similar populations? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? (5) Was a sample size justification or power description provided? (6) For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? (7) Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (8) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure or exposure measured as continuous variable)? (9) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (10) Was the exposure(s) assessed more than once over time? (11) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (12) Were the outcome assessors blinded to the exposure status of participants? (13) Was loss to follow-up after baseline 20% or less? (14) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Supplementary table 3. Quality assessment for Quality Assessment of Controlled Intervention Studies (NHBLI).

Studies	**Quality assessment criteria**[a]														**Quality score (%)**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Agarwal et al. 2015[S11]	1	1	0	0	0	0	0	1	0	1	1	0	1	1	**50%**
Beezhold et al. 2012[S12]	1	0	0	0	0	0	1	1	1	1	1	0	1	1	**57%**
Katcher et al. 2010[S13]	0	0	0	0	0	0	1	1	0	1	1	0	1	1	**43%**

[a]Criteria Yes No Other (CD, NR, NA)*

1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT? 2. Was the method of randomization adequate (i.e., use of randomly generated assignment)? 3. Was the treatment allocation concealed (so that assignments could not be predicted)? 4. Were study participants and providers blinded to treatment group assignment? 5. Were the people assessing the outcomes blinded to the participants' group assignments? 6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)? 7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment? 8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower? 9. Was there high adherence to the intervention protocols for each treatment group? 10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)? 11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants? 12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power? 13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)? 14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

References

S1 Baines S, Powers J, Brown WJ. How does the health and well-being of young Australian vegetarian and semi-vegetarian women compare with non-vegetarians? Public Health Nutr. 2007; 10: 436-42 PubMed .

S2 Beezhold BL, Johnston CS, Daigle DR. Vegetarian diets are associated with healthy mood states: a cross-sectional study in seventh day adventist adults. Nutr J. 2010; 9: 26.

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S4 Forestell CA, Nezlek JB. Vegetarianism, depression, and the five factor model of personality. Ecol Food Nutr. 2018; 57: 246-59 PubMed .

S5 Giem P, Beeson WL, Fraser GE. The incidence of dementia and intake of animal products: preliminary findings from the Adventist Health Study. Neuroepidemiology. 1993; 12: 28-36 PubMed .

S6 Kapoor A, Baig M, Tunio SA, Memon AS, Karmani H. Neuropsychiatric and neurological problems among Vitamin B12 deficient young vegetarians. Neurosciences (Riyadh). 2017; 22: 228-32.

S7 Lindeman M. The state of mind of vegetarians: Psychological well-being or distress? Ecology and Food Nutrition. 2010; 41: 75-86.

S8 Rodriguez Jimenez J, Rodriguez JR, Gonzalez MJ. [Indicators of anxiety and depression in subjects with different kinds of diet: vegetarians and omnivores]. Bol Asoc Med P R. 1998; 90: 58-68 PubMed .
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