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depression and anxiety: a systematic
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The beneficial effects of nuts on depression and anxiety: a systematic review of randomized controlled trials

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Abstract

Background Nuts are nutrient dense, and their neuroprotective benefits are beginning to be established. Besides increasing evidence of their potential in delaying cognitive decline, human studies have attempted to explore the protective benefits of nut consumption on neuropsychiatric conditions, such as mood disorders. The present study systematically reviewed randomized controlled trials (RCTs) investigating the effects of nuts on depression and anxiety.

Method Seven electronic databases (Cochrane, EBSCOhost, ProQuest, PsycINFO, PubMed, Scopus, and Web of Science) were searched from inception to February 2024 for randomized controlled trials comparing nut consumption with control interventions. Studies assessing depression and/or anxiety outcomes following nut intake were included, encompassing both short- and long-term interventions. Trials involving adults with or without underlying health conditions were reported. Data extracted included study characteristics, participant demographics, health status, study design, type and quantity of nuts consumed, intervention duration, and mental health outcome measures. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and methodological quality was assessed using the Revised Cochrane Risk of Bias tool for randomized trials.

Results Six articles comprising 4,303 participants met the inclusion criteria. Two studies reported improvements in mood outcomes following nut interventions, including reduced anxiety with peanut consumption ($p=0.001$) and reduced depression scores ($p<0.01$) following an almond-based intervention, whereas the remaining studies reported no significant differences between intervention and control groups. Improvements in depression-related outcomes were observed specifically among participants with type 2 diabetes mellitus.

Conclusion Based on a limited number of randomised controlled trials, the current evidence provides mixed support for the potential role of nut consumption in improving depression and anxiety outcomes. More randomised controlled trials with longer intervention durations and standardised outcome measures are needed to clarify the role of nut consumption in depression and anxiety.

Keywords Nuts · Depression · Anxiety · Randomized controlled trials

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Introduction

Globally, neuropsychiatric conditions are important causes of disability, accounting for approximately one-third of the years lost to disability (YLD) among adults aged ≥ 15 years [1]. World Health Organization (WHO) ranks depression as the single largest contributor to global disability, which is 7.5% all years lived with disability, while anxiety ranks 6th (3.4%) [2]. Approximately 20% of adults experience depressive episodes at least once during their lifetime [3]. Depressive symptoms within a population create concern because many other health problems are often related to or can develop because of depression. Psychiatric illnesses, such as mood disorders, often result from a combination of biological, psychological, and lifestyle factors. Currently, effective prevention and treatment strategies are available, suggesting that this burden can be reduced.

While food is typically considered to provide energy and building materials to the body, its potential to exert beneficial effects on the brain has been gaining attention [4]. Diet and nutrition can exert its influences through certain physiological responses, such as inflammation, oxidative stress, or hormonal factors in mitigating the risk of developing depression [5]. Over the last 10 years, nutritional psychiatry has provided important insights into the effects of food and diet on mood and cognition. The health benefits of tree nuts and legumes, for instance, are evident in studies associating nut intake with a reduced risk of cardiovascular diseases (CVDs) [6] and diabetes [7], as well as beneficial effects on oxidative stress, inflammation, metabolic syndrome [8], and blood pressure [9, 10]. Nuts are excellent sources of minerals (e.g., potassium, magnesium, and calcium), vitamin E, polyphenols, fiber, and unsaturated fatty acids [11], which are associated with better mental health. Furthermore, magnesium, selenium, and tryptophan in nuts play modulatory roles in the serotonergic system [12–14], and well-established links exist between abnormalities in serotonergic function and depression pathophysiology. The polyphenols found in nuts are beneficial because of their antioxidant capacity; therefore, they have received attention for their neuroprotective effects [15]. Based on evidence of a link between disturbances in oxidative metabolism and higher levels of depression, a diet rich in naturally occurring polyphenols could be an effective means of delaying or preventing diseases related to oxidative stress, such as depression and anxiety [16].

The neuroprotective effects of nuts have predominantly been studied by examining their influence on cognition [6, 17–19]. However, a number of cross-sectional studies [20–22] and randomized controlled trials (RCTs) have revealed an association between nut consumption and depression and anxiety [23–26]. Given that food consumption is often

confounded by dietary and lifestyle practices, RCTs can elucidate the distinct benefits of nut consumption. Therefore, this systematic review used RCTs to clarify whether nuts have beneficial effects on depression and anxiety in adults regardless of health conditions.

Materials and methods

Study search

The present review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (i.e., PRISMA) [27] and was registered in a systematic review registry (PROSPERO Registration No. CRD42022308131). Two investigators independently searched for studies published in the seven databases (Cochrane, EBSCOhost, ProQuest, PsychInfo, PubMed, Scopus and Web of Science) from their inception to February 2024. These databases were selected to capture literature across medicine, nutrition, and psychology. A search strategy was developed based on the research question, incorporating Medical Subject Headings (MeSH) and relevant keywords related to nuts, depression, anxiety, and randomized controlled trials. The search terms included (nut* OR nuts OR almond* OR Prunus Dulcis OR cashew* OR Anacardium OR hazelnut* OR Corylus OR macadamia* OR Pistacia* OR pistachio OR Walnut* OR Juglans OR pecan* OR Carya OR peanut* OR Arachis OR pine nut* OR Pinus OR Brazil nut* or Bertholletia); (depression* OR depressions OR depressive symptoms OR depressive symptom OR symptom, depressive OR symptoms, depressive OR emotional depression OR depression, emotional OR depressions, emotional OR emotional depressions); and (anxiety* OR hypervigilance OR nervousness OR social anxiety OR anxieties, social OR anxiety, social OR social anxieties).

A total of 478 articles were identified in the initial search. All records retrieved from the database searches were imported into EndNote (X9). Duplicates were removed and a manual search for the reference lists of the publications identified in the database searches was performed. The title and abstract of each article were independently screened for suitability by two investigators using the inclusion and exclusion criteria and the search strategies mentioned here.

Inclusion criteria

Studies were included if they met the criteria for randomized controlled trials or interventions

Titles and abstracts were screened for eligibility. Published research evaluating the effects of nuts on depression and

anxiety among human participants were included. Both short- and long-duration trials were considered. Studies conducted on any participant, regardless of their background medical illness (e.g., CVD, type 2 diabetes mellitus [T2DM], or obesity), were included if depression or anxiety scores were part of the outcome measures. Only studies published in English in peer-reviewed journals were included. Relevant studies were also identified through a careful review of the reference lists. Studies were excluded if they were not RCTs, were non-English language papers, editorials, news articles, expert opinions, theses, and letters to the editor. Cross-sectional studies evaluating the association between nut intake and depression, or anxiety were also excluded.

Data extraction

Data were independently extracted from full-text articles screened by the authors and compiled using a data collection table. Conflicts were resolved through further discussion with a third author. The data collected included author, year and place of publication, title, objective, study design, sampling method, sample size, screening method, health condition, quantity and type of nuts, duration of intervention, and measures of depression or anxiety.

Quality assessment

The quality of individual studies was determined using the Revised Cochrane Risk of Bias tool for randomized trials (ROB2) [28]. ROB2 was used to identify the risk of bias in randomized controlled trial findings based on five domains: randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result.

Results

Description of the included studies

Of the 478 articles identified in the initial search, 353 remained after the removal of duplicates. Title and abstract screening identified 41 articles as potentially eligible for inclusion. Of these, 35 were excluded after full-text assessment because they did not meet the predefined inclusion criteria. The reasons for exclusion after full text assessment: (1) depression or anxiety scores were not used as an outcome measure; (2) the dietary exposure was insufficiently characterized, as the type and/or quantity of nuts consumed was not reported, limiting meaningful interpretation and synthesis of findings; (3) the studies were not

RCTs; and (4) the studies did not contain relevant data (Fig. 1).

Characteristics of the included studies

In total, six articles fulfilled the criteria for final inclusion. The reviewed studies consisted of one parallel-group multicenter RCT, one prospective RCT, three parallel-group randomized trials, and one crossover RCT. The trial duration ranged from 8 to 12 weeks [23–25] to three years [26] (Table 1).

Almonds were studied in two trials [23, 25], walnuts in two trials [24, 29], peanuts in one trial [30], and a mixture of walnuts, hazelnuts, and almonds in one trial [26]. The quantity of nuts consumed in these studies ranged from 20 g/day to 60 g/day.

All studies included in this review measured changes in depression or a combination of depression and mood scores, of which two studies included an assessment of anxiety levels.

The participants' ages ranged from 18 to 80 years old. Three studies recruited older participants (60–75 years) [23, 25, 26], whereas the other three focused on younger adults (18–35 years) [24, 29, 30]. Studies included overweight participants [23], patients diagnosed with T2DM [25], individuals at high risk of CVD [26].

A meta-analysis was not performed because of the heterogeneity of the outcome measures and the differences in the types of nuts consumed.

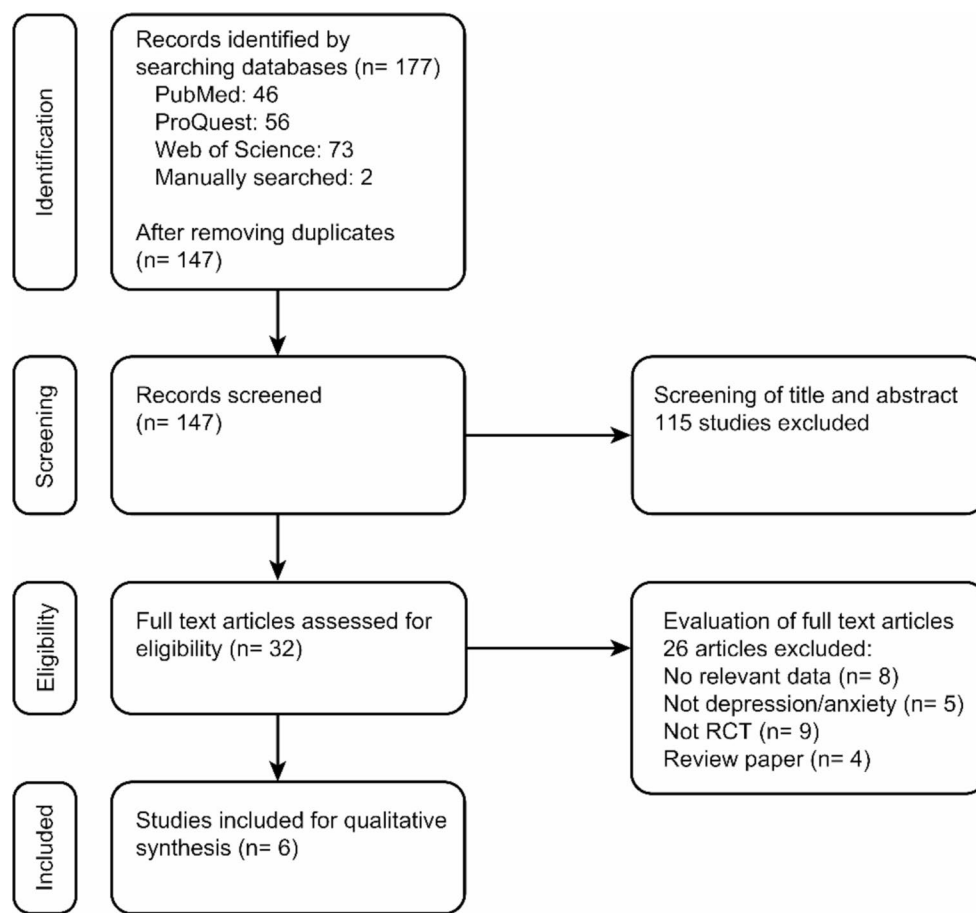
Quality assessment of the included studies

Based on ROB2, five studies received an overall low-risk quality assessment, while one received some concerns due to insufficient reporting. There were minor methodological issues across the studies, such as participants not being blinded because the study foods were presented in their natural form, except in one study that used crushed walnuts in banana bread [24]. There was also a lack of description of the efforts to minimize potential biases and how missing data were dealt with (Table 2).

Nut intake

All six studies reported the type of nut consumed by the participants. A few studies have combined nuts with prescribed diets. There was a comparison of an almond-enriched diet to a nut-free diet [23]. Comparisons were also made between an almond-based low-carbohydrate diet (LCD) to a low-fat diet (LFD) [25]. The PREDIMED study assigned participants to Mediterranean Diet (MD) with olive oil, MD with nuts, or control groups. The MD with nuts group consumed

Fig. 1 PRISMA flowchart depicting the study selection process



a mixture of walnuts, hazelnuts, and almonds [26]. In one walnut study, participants in the treatment group were fed ground walnuts in banana bread [24], whereas those in the control group were fed banana bread without walnuts. Participants who consumed skin-roasted peanuts were compared with those who consumed peanut butter and a control butter group [30]. Regarding quantity of nuts consumed, there was a mixture of nuts, with a mean of approximately 30 g/day: (15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds) [26]. The other average intake values were 56 g/day of almonds [25], 56–60 g/day of walnuts [24, 29], 25 g/day of peanuts [30], and 49 g/day of almonds [23] calculated using the Harris–Benedict equations based on sex, age, initial body weight, and physical activity [31].

Outcome measures

Each study used a combination of outcome measures. Three studies [23, 24, 29] used the Profile of Mood States (POMS) [32]. The POMS covers six mood domains: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia and Confusion- Bewilderment. The scores were computed by adding the five negative domain scores and subtracting the vigor score to derive the total mood

disturbance (TMD) score, with higher scores indicating a higher degree of mood disturbance. Other measures used include the Visual Analog Scale (VAS) [33], which consists of three dimensions (alertness, calmness, and contentment), and The Patient Reported Outcomes Measurement Information System (PROMIS) short- form v1.0-Depression 8b [34]. PROMIS consists of eight items assessing four areas: negative mood, negative views of self, negative social cognition, and decreased positive affect. Raw scores were converted to T-scores ranging from 0 to 81.3, with higher scores indicating higher levels of depression. In the PREDIMED study, a diagnosis of depression by a physician or the habitual use of antidepressants indicated depression. The 21-item Depression, Anxiety and Stress Scale (DASS21) [35] and Hospital Anxiety and Depression Scale (HADS [36] were used to assess depression and anxiety. The DASS21 consists of three separate constructs (depression, anxiety, and stress) that measure the severity and frequency of the extent to which participants had experienced each state over the past week. The HADS measures symptoms of depression and anxiety using a two-factor structure. The anxiety subscale focuses on symptoms of generalized anxiety disorder, whereas the depression subscale is based on the anhedonic state as the central psychopathological feature of depression.

Table 1 Characteristics of the included studies

Author, year, country	Study population	Health condition	Design	Nut type and amount	Comparison group	Duration of intervention	Outcome measure	Findings
Coates et al., 2020, Australia	n=128, [M=65 y]	Overweight adults	Parallel-arm RCT	Almonds [calculated using Harris Benedict equations]	Nut-free diet with carbohydrate-rich snack foods	12 weeks [6 days a week]	POMS Bond-Lader VAS: Alertness Content Calm	No significant difference between groups over 12 weeks
Herselman et al., 2022 Australia	n=80, [M=22 y]	Healthy adults	Parallel-arm RCT	Walnuts [56 g]	Refrain from nuts/fatty fish	16 weeks	DASS21; POMS	No significant differences between groups over time on POMS.
Parilli-Moser et al., 2021, Spain	n=63, [M=23 y]	Healthy adults	Parallel-arm RCT	Peanuts [25 g]	Peanut butter and control butter	6 months	HADS Depression Anxiety	Significant reductions in anxiety scores between groups over time, p=0.001
Pribis, 2016, USA	n=64, [M=20 y]	Healthy university students	Cross-over RCT	Walnuts [60 g]	Banana bread	8 weeks	POMS	Overall, no significant differences between groups over time; Significant difference between the walnut and control groups among males, p=0.043
Ren, et al., 2020, China	n=45, [M=73 y]	Diagnosed with T2DM	Parallel-arm, prospective RCT,	Almonds [56 g]	Low-fat diet	3 months	PROMIS	Lower depression scores in the almond group compared to control at 3 months, p<0.01*
Sanchez-Villegas et al., 2013, Spain	n=3923 [M=67 y]	High risk of CVD	Parallel-arm, multi-center RCT	Mixed nuts, 30 g: 15 g walnuts, 7.5 g hazelnuts, 7.5 g almonds	Low-fat diet	3 years	Depression diagnosis made by a physician	Overall, no significant differences between groups over time; Significant difference between the MD nut groups and control group for participants with T2DM, p=0.04*

*p<0.01, CVD cardiovascular disease, DASS21 21-item Depression, Anxiety and Stress scale, MD Mediterranean diet HADS Hospital Anxiety and Depression Scale, POMS Profile of Mood States, PROMIS Patient Reported Outcomes Measurement Information System, RCT Randomized controlled trial, T2DM Type 2 diabetes mellitus, VAS Visual Analogue Scale, y=years

Table 2 Risk of bias results using the Revised Cochrane Risk of Bias tool for randomized controlled trials evaluating the effects of nuts on depression and anxiety

Author, year	D1	D2	D3	D4	D5	Overall
Coates et al., 2020	✓	✓	✓	✓	✓	✓
Herselman et al., 2022	✓	✓	✓	✓	✓	✓
Pribis, 2016	✓	✓	✓	✓	†	†
Parilli-Moser et al., 2021	✓	✓	✓	✓	✓	✓
Ren et al., 2020	✓	✓	✓	✓	✓	✓
Sanchez-Villegas et al., 2013	✓	✓	✓	✓	✓	✓

✓ = low risk, †= some concerns, D1 randomization process, D2 deviations from the intended interventions, D3 missing outcome data, D4 outcome measurement, D5 selection of reported results

Overall findings of included studies

Two studies [25, 30] reported improvements in mood scores, including one peanut intervention [30] and one almond intervention study [25]. Peanut consumers showed significant improvements in both depression and anxiety scores; however, significant group differences were observed only for anxiety (p=0.001) [30]. In the almond study, significant reductions in depression scores were

observed for those consuming an almond-based LCD compared with baseline (p<0.01); although depression scores did not differ from those in the LFD group [25].

In contrast, no differences were observed between walnut consumers and non-consumers in overall TMD scores [24]. However, a borderline interaction effect (p=0.052) was reported for depression scores among walnut consumers measured using the DASS21 [29]. The other almond study [23] reported no significant differences in mood

scores between groups measured using the POMS. Similarly, participants who consumed mixed nuts did not show improvements in depression scores [26].

Health status

Three of the studies included healthy participants. No differences were observed between walnut consumers and non-consumers regarding the overall TMD scores [24], and no significant improvements were observed in any of the six POMS domains. However, there was a nearly significant interaction effect ($p=0.052$) on depression scores of walnut consumers over 16 weeks [29]. Healthy peanut consumers showed significant improvements in depression and anxiety over six months, although significant group differences were only observed for anxiety ($p=0.001$) [30].

Among participants with T2DM, significant changes in depression scores were observed after three months of consuming an almond-based LCD compared to baseline ($p<0.01$); depression scores did not differ from those in the LFD group [25]. Conversely, for participants with a higher risk of CVD [26], depression scores did not improve after three years of intervention, although an inverse association was observed in those in the MD nut group compared to those in the control group (multivariate hazard ratio=0.78). When the analysis was restricted to those with T2DM, significant reductions in depression risk were observed in the MD nut group compared with the control group.

Based on the POMS scores, mood did not improve in overweight participants [23]. In contrast, there was a trend towards improved alertness based on the VAS results in the almond-enriched diet group compared to the control group at 12 weeks. However, the improvement in alertness score was not statistically significant ($p=0.067$).

Age and sex

Depression levels did not differ between walnut consumers and controls in younger adults [24], but improvements were observed for older participants (Ren et al., 2020). Anxiety scores showed improvements for young adults who consumed peanuts.

Sex differences were observed among the younger participants, with male walnut consumers showing significant improvement in TMD scores over eight weeks, while no improvements were observed among female participants.

Intervention duration

This review included four short-term trials (8–16 weeks) [23–25, 29] and two long-term interventions (six months and three years) [26, 30]. Of the four short-term trials, a

significant decline in depression level was observed in one three-month trial [25], and one long-term intervention induced overall improvements in anxiety scores [30].

Discussion

This review synthesised evidence from intervention studies examining the effects of nut consumption on mental health outcomes. Overall, the findings suggest limited and inconsistent evidence that nut consumption may contribute to improvements in mood-related outcomes, particularly symptoms of depression and anxiety. Improvements were reported in two interventions involving peanuts and almonds [25, 30], whereas several other studies [23, 24, 26, 29], including those examining walnuts and mixed nuts within broader dietary patterns, reported no statistically significant changes in depression and anxiety scores. The available evidence suggests that while nut consumption may have potential benefits for depression and anxiety, findings remain inconsistent and may be influenced by differences in study design, populations, and intervention protocols. Nevertheless, nuts may be considered as part of a healthy dietary pattern that supports overall health, primarily for their established cardiometabolic benefits [37], and beneficial effects on oxidative stress, and inflammation [8].

The heterogeneity of findings across studies may reflect methodological differences, including the type and dosage of nuts consumed, intervention duration, and the dietary context in which nuts were consumed. In some studies [25, 26], nuts were incorporated into broader dietary interventions, such as Mediterranean dietary patterns [26], making it difficult to isolate the independent effects of nuts on mental health outcomes. Furthermore, variation in outcome measures and participant characteristics may have contributed to differences in observed effects. For example, improvements were observed in certain subgroups, including older adults [25] and male participants [24] in specific trials, suggesting that demographic factors may moderate the relationship between nut consumption and mood outcomes.

Several underlying mechanisms may explain the observed improvements. Although the nutritional composition of nuts vary, they are generally known for their neuroprotective properties. Peanuts (*Arachis hypogea*) or ground nuts, legumes widely identified in the nut food group, are rich in antioxidants, fibers, proteins, and bioactive compounds [38]. Studies on the gut-brain axis have demonstrated the pathways through which dietary habits and food choices can impact psychiatric illnesses, such as depression and anxiety. Almond consumption increases short-chain fatty acid-producing bacteria [39], which plays a role in the secretion of glucagon-like peptide 1 (GLP-1) [40]. Recent

findings suggest that GLP-1 receptor agonists exert neuroprotective effects in mice [41]. Similar effects have been reported in diabetic mice [42]. Depression and diabetes share pathophysiological factors that disrupt neurogenesis and neurotransmission [43], indicating that nuts may play a role in mitigating depression in humans. This hypothesis was further supported by a review indicating that nuts may be beneficial for insulin sensitivity and that a higher intake of nuts is associated with lower risk of T2DM [44].

Nuts are also known for their high selenium content. Interestingly, reduced concentrations of brain-derived neurotrophic factor (BDNF), a neurotrophic factor that is strongly linked to depression [45], have been associated with selenium deficiency [46]. A more recent hypothesis suggests that BDNF plays a role in depression by mediating the actions of antidepressants [47]. However, human studies have yielded inconsistent results in this regard. For instance, selenium supplementation for six months during pregnancy was found to lower depression scores [48], but no changes in depression levels were observed in another RCT with six months of selenium supplementation [49]. While selenium may be critical in decreasing depression, all tree nuts contain a combination of micronutrients, indicating a synergistic effect. Therefore, when considering the effects of whole foods such as tree nuts and legumes, emphasis remains on the multiple pathways and mechanisms within the neural circuitry.

It is also worth noting that Brazil nuts are considered unique compared to other tree nuts because of their high selenium content [50]. One study comparing the effects of Brazil nuts showed a significant improvement in anxiety scores 40 min post-consumption [51]. However, no differences were observed when compared with the controls. Based on these findings, RCTs should be performed to better understand the effects of Brazil nuts on depression, given their nutritional profile and existing evidence of their potential benefits.

The effect of walnuts on mood scores has mainly been observed in men [24]. Walnuts have been identified as one of the most important sources of serotonin, with notable increases in urinary metabolites of the tryptophan pathway leading to melatonin and serotonin synthesis, both of which are urinary markers of nut intake [52]. Tryptophan, a serotonin precursor, is essential for mammals and can be derived only from food [53]. Furthermore, tryptophan levels in foods, such as nuts, appear to link food intake and mood states [12]. Given the biological underpinnings and findings of an observational study of the association between walnuts and mood [22], more RCTs on the effects of walnuts on adults with different health conditions are warranted.

This review incorporated studies that combined nuts with other diets, such as a low-carbohydrate diet and MD.

Although there is strong evidence of the protective effects of MD against neurodegenerative and cognitive decline, some skepticism remains regarding whether the effects are due to the entire dietary pattern or its components [54]. Methodologically, this review was conducted in accordance with established systematic review guidelines, with clearly defined inclusion and exclusion criteria, independent screening, and structured risk of bias assessment using the ROB2 tool. Focusing exclusively on randomized controlled trials strengthens the internal validity of the findings and reduces the influence of confounding factors. However, several limitations should be acknowledged for correct interpretation of these findings. First, the small number of eligible studies limited the ability to draw firm conclusions and precluded the use of meta-analysis. Second, heterogeneity in study populations, nut types, intervention durations, and outcome measures restricted direct comparison and synthesis of results. Third, although broad search terms were used, the review may still be subject to publication bias, as only published studies were included. Finally, refinements to eligibility criteria during the full-text screening stage, while methodologically justified, may introduce some degree of subjectivity, despite being implemented prior to data extraction and analysis.

Future studies could consider if the effects of nuts on depression differ between sexes. Additionally, further studies can also shed some light on the effects of almonds and other nuts, such as Brazil nuts and hazelnuts. Given that depression and anxiety are distinct in its manifestations and underlying mechanisms, more RCT's evaluating the effects of nuts on anxiety are warranted.

Conclusion

This systematic review examined the effects of nut consumption on depression and anxiety based on a limited number of randomized controlled trials with heterogeneous findings. Overall, the evidence suggests potential, but inconsistent, associations between nut consumption and mental health outcomes, with benefits observed in specific contexts rather than across all populations. Some evidence indicates improvements in depressive symptoms among individuals with type 2 diabetes consuming almonds, reductions in anxiety following peanut consumption, and possible sex-specific effects of walnuts; however, these findings are not consistent and should be interpreted with caution. Given the limited number of studies, variability in study design, and inconsistency of results, firm conclusions regarding the mental health benefits of nut consumption cannot yet be drawn. Further well-designed randomized controlled trials are therefore warranted to clarify the effects of different

nut varieties, including less-studied nuts such as hazelnuts and Brazil nuts, which have shown promise in observational research. Future studies should also consider anxiety as a primary outcome, examine different intervention durations, and directly compare nut types using parallel-arm or cross-over designs to better understand their potential and distinct effects on depression and anxiety.

Author contributions Conceptualization: VK, OPB, TKW, CYC; Data curation: VK, KKL; Methodology: OPB; Project administration, VK, KKL; Software: VK, KKL; Writing Original Draft: VK; Manuscript review & editing, TKW, OPB, CYC.

Data availability The data supporting this systematic review are from previously reported studies and datasets, which have been cited. The dataset supporting the conclusions of this article is included within the article and its additional files.

Declarations

Ethics approval This review contains only studies that complied with required ethical standards. All of the eligible articles included in the systematic review had stated that they had obtained informed consent from their participants.

Consent for publication All authors consent to the publication of this manuscript.

Competing interests The authors have no competing interests to declare

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