Clinical Nutrition 42 (2023) 1728–1736

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Nut consumption is associated with a lower risk of depression in adults: A prospective analysis with data from the UK Biobank cohort

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ARTICLE INFO

Article history:
Received 31 October 2022
Accepted 24 July 2023

Keywords:
Adulthood
Nuts
Mental health
Depressive disorder
Longitudinal

SUMMARY

Background & aims: Evidence on the association between nut consumption and depression is mainly based on cross-sectional studies. This study aims to analyse whether nut consumption is prospectively associated with the risk of depression in adults.

Methods: This study was conducted using the United Kingdom (UK) Biobank resource. Data from middle-aged and older UK adults who participated in this cohort between 2007–2012 (baseline) and 2013–2020 (follow-up) were analysed. Baseline information on nut consumption was obtained with the Oxford WebQ 24-h questionnaire. Depression, defined as a self-reported physician diagnosis of depression or antidepressant use, was assessed at baseline and follow-up. Hazard regression models estimating the predictive ability of nut consumption for the risk of developing depression were adjusted for socio-demographic, lifestyle, and health confounders.

Results: A total of 13,504 participants (mean age 57.5 ± 7.2 years, 50.7% female) free of depression at baseline were included in the analyses. After a mean follow-up of 5.3 ± 2.4 years, 1122 (8.3%) incident cases of depression were identified. Compared with no nut consumption, the daily consumption of >0 to 1 serving of 30 g of nuts was associated with a lower risk of depression (hazard ratio, HR = 0.83; 95% confidence interval, CI: 0.71–0.97) regardless of all potential confounders considered. In stratified analyses, a decreased risk of depression was more clearly observed in UK adults with adequate weight control, a healthy lifestyle, and better health status than in their counterparts ($p < 0.05$).

Conclusions: Low-to-moderate nut consumption (>0 to 1 serving of 30 g/day) was associated with a 17% lower risk of depression during a 5.3-year follow-up compared with no nut consumption in a large sample of middle-aged and older UK adults. This protective association is enhanced in the absence of other known risk factors for depression.

1. Introduction

Depression is among the most common mental disorders, affecting 279.6 million people worldwide in 2019, with a lifetime prevalence ranging from 3.4 to 4.2% [1]. These are probably conservative estimates since the complex clinical picture of depression leads to a high proportion of undiagnosed cases [2]. Although treatments based on antidepressant use may mitigate depressive symptoms [3], not all patients with depression can sustain symptom remission with antidepressant use alone [4,5]. This could be explained because depression pathophysiology involves psychosocial, behavioral, and environmental factors, in addition to genetic and biological interactions [6]. In this sense, complementary lifestyle-oriented approaches have shown

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https://doi.org/10.1016/j.clnu.2023.07.020
0261-5614/

promising effects in preventing depression and alleviating depressive symptoms [7,8]. Therefore, it is recommended that mental health systems emphasize a multidimensional framework focused on lifestyle strategies to prevent depression [9].

Dietary behaviors have received special attention as one of the most feasible and robust strategies to contribute to healthy adult life [10], and specifically, as a modifiable lifestyle risk factor for depression [11]. Scientific evidence from observational studies [12] and clinical trials [7] supports the role of optimal dietary patterns and specific food sources in modulating depression risk and symptom management. In particular, nuts are frequently included in current dietary guidelines [13] and healthy dietary patterns [14] as a food with potential preventive and supportive antidepressant activity [15]. Based on the nutritional research definition [16] nuts are nutrient-dense foods that include a wide variety of types, such as walnuts, almonds, Brazil nuts, cashews, hazelnuts, and pistachios. Peanuts, which are legumes, are also integrated among nuts because they share a similar nutrient profile [16]. Despite their diversity, nuts share essential nutritional properties (i.e., bioactive substances such as phenols or phytosterols, essential micronutrients, fiber, high-quality protein, monounsaturated and polyunsaturated fatty acids, and vitamins) [16,17] that could play a beneficial role in mental health [18]. Specifically, nuts provide a rich variety of bioavailable phytochemicals that might be associated with various mechanisms, such as anti-inflammatory or antioxidant activities, involved in the progression of pathogenic processes [19].

A recent review by our research group synthesized observational and randomized controlled trial studies endorsing that higher nut consumption could be associated with a lower risk of depression and fewer depressive symptoms [18]. However, most of the studies had a cross-sectional design. In the only prospective cohort in the general population with an adequate follow-up period available thus far, low-to-moderate nut consumption was associated with a reduced risk of depression [20]. The objective of this study was to assess the prospective association between nut consumption and depression, defined as a self-reported physician diagnosis of depression or antidepressant use, in a large sample of middle-aged and older adults from the United Kingdom (UK).

2. Materials & methods

This community-based cohort study (Project Application Number 72061) was conducted using the UK Biobank (UK-B) resource [21]. The UK-B project was approved by the North West Multicentre Research Ethics Committee (Ref: 16/NW/0274), in accordance with the principles of the Declaration of Helsinki. All participants provided signed consent forms.

2.1. Study design and participants

The study design and methods of the UK-B are reported in detail elsewhere [21]. Briefly, the UK-B is a large-scale epidemiological study established in 2006–2010 with a large sample of middle-aged and older UK adults recruited (i.e., eligible and consenting) from 22 assessment centres. A total of ~9.2 million individuals registered with the UK National Health Service were invited, and ~5.5% participated in the initial assessment [22]. The sampling population is volunteer-based and is not representative of the UK population [22]. The UK-B dataset for this study included 502,366 adults aged 37–73 years. Of these, 110,977 participants had valid baseline data for nut consumption and depression. After the exclusion of 13,151 individuals who at baseline had a self-reported physician diagnosis of depression or were taking antidepressant medication, 4312 who die during the time-at-risk period, an additional 79,715 individuals with missing data for any of the study variables (only baseline information), and 295 adults with less than one year of follow-up data on depression, a total of 13,504 participants were followed for a mean of 5.3 ± 2.4 years (ranging from 1.0 to 10.7 years) (Figure 1). According to the percentage method [23], the follow-up rate was 13.8%.

2.2. Study variables

The variables and criteria used for defining nut consumption, depression, and covariates based on the UK-B data fields are detailed in Supplementary Tables 1–3. The data for the variables were obtained through May 2021 (the latest withdrawal of participants was updated on May 1, 2023). Baseline assessments (nut consumption, depression, and covariates) were performed between 2007 and 2012 (mean date: 06-08-2011), and longitudinal assessments (depression) were conducted between 2013 and 2020 (mean date: 05-12-2016).

2.2.1. Exposure: nut consumption

The UK-B applied the Oxford WebQ questionnaire, which is a validated online 24-h dietary recall that assesses self-reported nut consumption on the previous day [24]. Participants completed dietary assessments at the end of the recruitment phase (i.e., between 2009 and 2010) and four additional rounds of questionnaires between 2011 and 2012. This dietary assessment tool was designed to be used on multiple occasions to reduce the potential measurement error, which usually occurs when the diet is measured only once [24]. The quantity of each food consumed was calculated by multiplying a portion size assigned for each specific food by the amount consumed [25]. Consistent with recommendations for the use of the Oxford WebQ questionnaire [24], baseline nut consumption was averaged across the five time points to estimate usual consumption. The Oxford WebQ obtained information on nut consumption by asking participants 'Did you eat any crisps, nuts, or savoury snacks yesterday?' with responses of (i) no or (ii) yes. For those who reported yes to the previous question, a list of different types of snack foods and nuts was presented, and the respondents were asked to specify the type and frequency of portion size (~40 g) of nuts consumed daily [25]. Therefore, the mean frequency of nut consumption across the dietary assessment time points was calculated from the original response options (i.e., 1/2, 1, 2, or ≥3 handfuls per day) and multiplied by the original estimate of serving size (40 g) [25].

For the present study, the answers for 'unsalted nuts (e.g., almonds, cashews, pistachios)', 'salted/roasted nuts (e.g., almonds, cashews, pistachios)', 'peanuts, unsalted (monkey nuts)', and 'peanuts, salted/roasted (monkey nuts)' were considered valid for the estimation of total nut consumption [25]. Nuts were considered to include both nuts and peanuts based on a nutritional research definition [16]. For the analyses in this study, nut consumption categories were estimated using the standard conversion of 1 serving equals 30 g [26] because it aligns with the estimated amount supported by scientific evidence [27] and is more commonly used compared to a 40 g serving size [26,28,29]. Therefore, regarding the portions of nuts consumed, the original response options (i.e., 1/2, 1, 2, or ≥3 handfuls of 40 g/day) were combined into three categories: (i) no consumption (reference category), (ii) >0 to 1 serving of 30 g/day (low-to-moderate consumption), and (iii) >1 to 4 servings of 30 g/day (high consumption). This conversion of the categories was proposed because, in addition to facilitating the interpretation of the results, previous evidence supports the recommendation of daily consumption of one serving or less (~12–30 g) of nuts to reduce the risk of adverse cardiovascular and metabolic health outcomes [27,30].

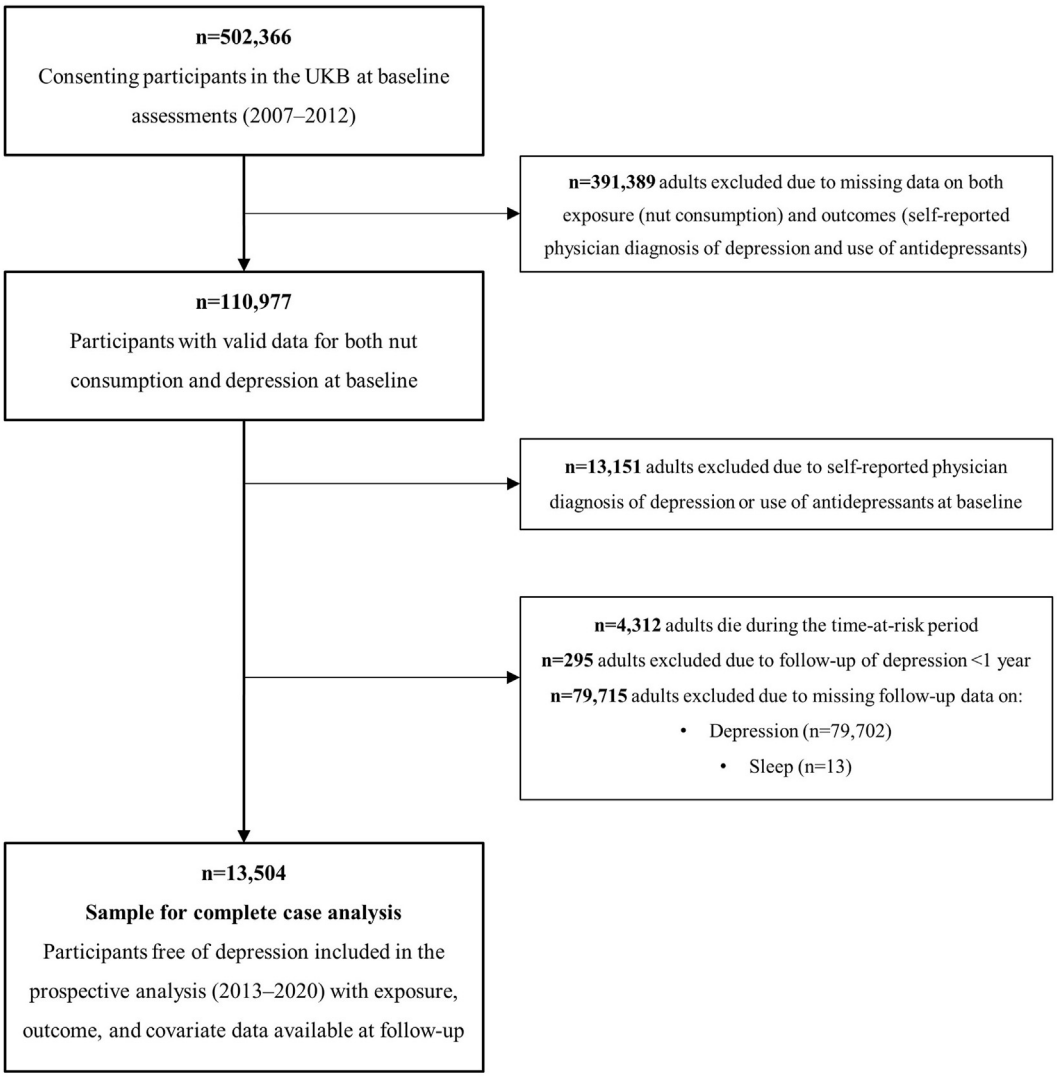

Figure 1. Diagram flow of the study participants in the current study, from the original UK-B cohort.

2.2.2. Outcome: depression

In the UK-B baseline assessments, information on depression was provided through a touchscreen questionnaire and a face-to-face interview conducted by a trained nurse. For the present study, depression was defined with at least one of the following criteria: (i) self-reported physician diagnosis of depression or (ii) use of antidepressants. First, individuals were asked, 'Has a doctor ever told you that you have had any serious medical conditions or disabilities?' with responses of (i) no or (ii) yes (touchscreen questionnaire). Next, those who responded positively were asked in a face-to-face interview to specify the type of medical condition or disability, with depression being a response option. Similarly, individuals were asked, 'Do you regularly take any prescription medications?' with responses of (i) no or (ii) yes (touchscreen questionnaire), and those taking prescription drugs were asked to indicate in a face-to-face interview the type of medication in use, among which one option was antidepressants.

2.2.3. Covariates

Covariates were selected based on recent evidence on the potential determinants of depression and their associations with nut consumption [18,20]. Information on potential confounders of the study associations was derived from the touchscreen questionnaire, the Oxford WebQ questionnaire, and physical measurements assessed at baseline. Self-reported information was obtained for sex (female; male), age (<60 years; ≥60 years), educational or professional qualification (higher level, e.g., university degree or professional qualification; lower level, e.g., high school grade or none of the above), tobacco use (never smoked or former smoker; current smoker), frequency of alcohol consumption (never or occasionally; daily/almost daily), major dietary changes in the last five years (yes; no), diet (healthy diet, i.e., compliance with fruit and vegetable consumption guidelines, ≥5 portions/day; unhealthy diet, i.e., noncompliance with fruit and vegetable consumption guidelines, <5 portions/day) [31,32]; physical activity (sufficiently active, i.e., energy expenditure ≥600 MET-minutes/week; insufficiently active, i.e., energy expenditure <600 MET-minutes/week) [33], sleep duration (low risk, i.e., sleep 7–8 h/day; high risk, i.e., sleep ≤6 or ≥9 h/day) [34], loneliness (lonely feelings, i.e., feels lonely and never, almost or occasionally confide in someone; no lonely feelings), and medical conditions (nonmedical condition; ≥2 medical conditions, e.g., angina, anxiety, cancer, dementia, diabetes, heart attack, hypertension, multiple sclerosis, osteoporosis, Parkinson's disease). Total energy intake was estimated based on the answers to the online 24-h dietary data [24] and determined in total calories (kcal) per day. Moreover, body mass index (BMI) was

calculated as weight divided by the square of the height (kg/m^2), both objectively measured under standardized conditions. The criteria to define the UK-B covariates used in the present study are detailed in Supplementary Table 3.

2.3. Statistical analysis

First, we examined the baseline characteristics of all the study participants and according to the categories of nut consumption in terms of absolute (n) or relative (%) frequency for categorical variables and mean ± standard deviation for continuous variables.

Second, Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for incident depression (outcome) across the nut consumption categories (exposure, with no consumption as the reference category = 1) in complete-case analysis with the person-years of follow-up as the timeline variable. Participants were followed from UK-B baseline assessments to the date of their first self-reported depression or the end of follow-up, whichever occurred first. Cox regression analyses were performed with the exclusion of events in the first one year (one-year landmark). Three models were built with the aim of progressively assessing the confounding influence of the following blocks of covariates: **model 1**, adjusted for sociodemographic characteristics (i.e., sex, age, and educational or professional qualification); **model 2**, previous model adjusted for BMI and lifestyle behaviours (i.e., tobacco use, alcohol consumption, dietary changes in the last five years, diet −fruit and vegetable consumption−, physical activity, sleep duration, and total energy intake); and **model 3**: previous model adjusted for loneliness and the number of medical conditions.

Third, the likelihood ratio test was used to explore the possible first-order interactions between nut consumption and covariates in the association with depression, and stratified analyses aimed at identifying potential moderators of the study association were performed. For this purpose, the cross-products between nut consumption and age (<60 and ≥ 60 years), sex (male and female), educational or professional qualification (high and low), BMI (obese, BMI ≥30 and nonobese, BMI <30 kg/m^2), major dietary changes in the last five years (yes and no), and loneliness (lonely and not lonely) were individually included in hazard regression models, i.e., a unique model was constructed for each interaction covariate tested. Regarding lifestyle habits, a dichotomous variable was created to differentiate individuals with healthy lifestyle behaviours (i.e., nonsmokers or ex-smokers, abstainers or occasional alcohol drinkers, consumers of 5 or more portions of fruits and vegetables, sufficiently physically active individuals, and with 7−8 h' sleep per day) from those with unhealthy behaviours (i.e., smokers, frequent alcohol drinkers, consumers of less than 5 portions of fruits and vegetables, insufficiently physically active individuals, and with ≤6 or ≥9 h' sleep per day). To test for interaction by health status, the presence of two or more medical conditions (e.g., angina, anxiety, cancer, dementia, diabetes, heart attack, hypertension, multiple sclerosis, osteoporosis, Parkinson's disease) *versus* none or one medical condition was the criterion adopted to differentiate those with worse or better health status, respectively. Due to the small number of incident cases of depression in the high nut consumption, stratified analyses were performed collapsing the two categories of nut consumption into a single category.

Fourth, complementary analyses were conducted according to the mode of nut preparation (i.e., unsalted or salted/roasted). Moreover, to test the robustness of our results, the analyses were repeated after excluding individuals with at least one other self-reported mental health disorder (i.e., anxiety or panic attacks, schizophrenia, bipolar disorder, anorexia, bulimia, other eating behaviour disorder, posttraumatic stress disorder, obsessive-compulsive disorder, and insomnia). Finally, sensitivity analysis of censored proportional hazards models including 5.3-year cumulative mortality (n = 4312) was performed. In each hazard regression model, individuals who died during the time-at-risk period were treated as censored [35]. Therefore, we used a composite end point of the first confirmed depression, death, or the conclusion of the follow-up assessments, whichever occurred first.

All statistical analyses were performed using IBM SPSS Statistics software (Version 28.0; IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered to indicate statistical significance. SPSS codes for the statistical analyses are presented in the Supplementary Table 4.

3. Results

A total of 13,514 participants (mean age 57.5 ± 7.2 years, 50.7% female) were included in the analyses. Slightly more than 20% of the included individuals had obesity, 19.2% were insufficiently physically active, and 65% had two or more medical conditions. Table 1 presents the main baseline characteristics of all included participants according to nut consumption categories.

The prospective associations between nut consumption and depression are presented in Table 2. The overall incidence of self-reported depression (physician diagnosis or antidepressant use) was 8.3% (n = 1122 new cases) for a mean follow-up of 5.3 years. In the minimally adjusted model (Model 1), low-to-moderate consumption of nuts (>0 to 1 serving of 30 g/day) was significantly associated with a reduced risk of depression (HR = 0.82; 95% CI: 0.70−0.97) when compared with no nut consumption. This protective association remained statistically significant when the other two blocks of covariates were added to the hazard regression models. Specifically, low-to-moderate nut consumption was associated with a significantly lower incidence of depression in the fully adjusted analysis (Model 3) (HR = 0.83; 95% CI: 0.71−0.97). No significant association was observed between high nut consumption (>1 to 4 servings of 30 g/day) and incident depression compared to nonnut consumption. However, the corresponding HRs were lower than one in all models analysed, which indicates a nonsignificant trend toward a lower risk of depression among those who consume more nuts compared to nonconsumers.

Interactions with *p-values* <0.05 were observed between nut consumption and the covariates BMI, lifestyle behaviours, and health status for the association with risk of depression (Figure 2). As shown in stratified analyses, participants who consumed nuts classified as nonobese, with healthier lifestyle behaviours, with no feelings of loneliness, or with fewer than two medical conditions had a significantly lower risk of depression than nonconsumers (Figure 2). Conversely, no significant associations were observed in those with obesity, unhealthy behaviours, feelings of loneliness, or two or more medical conditions.

Additionally, the results of complementary analyses did not vary when considering the mode of nut preparation (unsalted or salted/roasted) (Supplementary Table 5). Likewise, proportional hazards models that excluded individuals with other self-reported mental disorders (Supplementary Table 6) and included cumulative mortality at 5.3 years (Supplementary Table 7) showed that the HRs for the incidence of depression were similar to those observed in the main analyses.

4. Discussion

This study analysed the prospective association between nut consumption and the risk of depression in a large sample of middle-aged and older adults in the UK. The main finding is that regular low-to-moderate consumption of nuts (>0 to 1 serving of

Table 1
Baseline characteristics of the UK Biobank cohort by nut consumption categories.

Baseline characteristics	Total (n = 13,504)	Nut consumption categories		
		0 servings per day (n = 9687)	>0 to 1 serving per day (n = 2812)	>1 to 4 servings per day (n = 1005)
Nut consumption, *g/d ± SD (range)*	7.1 ± 15.6 (0–160.0)	–	15.3 ± 7.1 (4.0–30.0)	52.0 ± 21.2 (32.0–160.0)
Female, *n (%)*	6850 (50.7)	4844 (50.0)	1567 (55.7)	439 (43.7)
Age, *years ± SD*	57.5 ± 7.2 (40.0–70.0)	57.4 ± 7.2	58.2 ± 7.0	56.4 ± 7.3
Age over 60 years, *n (%)*	6,296 (46.6)	4440 (45.8)	1455 (51.7)	401 (39.9)
Low educational/professional qualification, *n (%)*	3622 (26.8)	2733 (28.2)	641 (22.8)	248 (24.7)
Current smoking status, *n (%)*	661 (4.9)	491 (5.1)	111 (3.9)	59 (5.9)
Daily/almost daily alcohol intake, *n (%)*	3190 (23.6)	2211 (22.8)	706 (25.1)	273 (27.2)
Major dietary changes-5 years, *n (%)*	5379 (39.8)	3869 (39.9)	1092 (38.8)	418 (41.6)
Unhealthy diet[a], *n (%)*	5262 (39.0)	3965 (40.9)	933 (33.2)	364 (36.2)
Total energy intake, *kcal/d ± SD*	2122.2 ± 590.5	2067.4 ± 575.8	2171.5 ± 537.7	2512.8 ± 701.2
BMI, *kg/m^2 ± SD*	27.0 ± 4.3	27.2 ± 4.4	26.4 ± 4.1	27.0 ± 4.3
Obesity (BMI ≥30.0 kg/m^2), *n (%)*	2819 (20.9)	2152 (22.2)	472 (16.8)	195 (19.4)
Free-time physical activity, *MET-min/week ± SD*	2320.8 ± 2271.5	2298.0 ± 2280.1	2389.9 ± 2249.9	2347.5 ± 2246.3
Insufficiently active (<600 MET-min/week), *n (%)*	2587 (19.2)	1927 (19.9)	476 (16.9)	184 (18.3)
High-risk sleep duration[b], *n (%)*	3718 (27.5)	2667 (27.5)	767 (27.3)	284 (28.3)
Loneliness, *n (%)*	634 (4.7)	456 (4.7)	118 (4.2)	60 (6.0)
Number of medical conditions[c], *mean ± SD*	2.4 ± 1.5	2.4 ± 1.5	2.4 ± 1.5	2.3 ± 1.6
Two or more medical conditions[c], *n (%)*	8776 (65.0)	6270 (64.7)	1868 (66.4)	638 (63.5)

Values are *means ± standard deviations (SD)* or *n (%)*.
[a] Unhealthy diet was based on eating less than 5 portions of a variety of fruit and vegetables every day, i.e., not complying with fruit and vegetable guidelines [31,32].
[b] High-risk sleep duration was defined as ≤6 or ≥9 h/day [34].
[c] Self-reported medical condition diagnosed by a doctor including cancer and other serious medical conditions or disabilities (e.g., angina, anxiety, dementia, diabetes, heart attack, hypertension, multiple sclerosis, osteoporosis, or Parkinson's disease, detailed in data-coding 6 of UK-B data-field 20002, Supplementary Table 3).

Table 2
Prospective (5.3-year follow-up) associations between nut consumption and incident depression.

	Total, *n* (incident cases of depression[a])	Model 1	Model 2	Model 3
Total	13,480 (1122)			
Nut consumption				
0 servings/day	9687 (840)	1.00	1.00	1.00
>0 to 1 serving of 30 g/day	2812 (193)	**0.82 (0.70, 0.97)**	**0.83 (0.71, 0.97)**	**0.83 (0.71, 0.97)**
>1 to 4 servings of 30g/day	1005 (89)	0.97 (0.78, 1.21)	0.93 (0.75, 1.17)	0.94 (0.75, 1.17)

Values are hazard ratios (95% confidence interval) for incident depression, estimated from Cox regression models. Bold values indicate statistically significant association ($p < 0.05$).
Model 1: adjusted for sex (female or male), age (<60 years or ≥60 years), and educational or professional qualification (high or low); **Model 2:** previous model adjusted for BMI (normal weight/overweight or obese), tobacco use (never/former or current), alcohol consumption (never/occasionally or daily/almost daily), major dietary changes in the last five years (yes or no), dietary pattern (fruit and vegetable consumption, ≥5 or <5 portions/day), physical activity (sufficiently active or insufficiently active), sleep duration (7–8 or ≤6 and ≥ 9 h/day), and total energy intake (kcal/day); and **Model 3:** previous model adjusted for loneliness (lonely or not lonely) and self-reported medical conditions diagnosed by a doctor (nonmedical condition or ≥2 medical conditions).
[a] Incident cases of depression were defined as those participants free of self-reported depression (physician diagnosis or antidepressant use) at baseline assessment and who self-reported depression (physician diagnosis or antidepressant use) during the 5.3-year follow-up.

30 g/day) is associated with a 17% lower risk of depression compared to nonnut consumption after a 5.3-year follow-up, regardless of relevant sociodemographic, lifestyle, and health confounders. In addition, our results highlight the potential role of nut consumption as a healthy dietary behaviour to prevent depression in those free of other known risk factors for depression, such as obesity, unhealthy lifestyle behaviours (smoking, frequent alcohol consumption, low intake of fruits and vegetables, insufficiently active, and inadequate sleep duration), loneliness, and medical conditions such as cardiovascular, metabolic, or mental comorbidities.

In agreement with our results, the authors of a previous cohort study with the general population found that a low-to-moderate (≥30 g/month to 150 g/week) consumption of mixed nuts significantly reduced the risk (23%) of self-reported depression in 15,980 middle-aged Spanish adults followed for 10.4 years [20]. Furthermore, recent pooled analysis from two cohorts with representative samples of older adults from Spain and the Madrid region reported that a low-to-moderate mixed nut consumption (≥3 servings of 30 g/week) was associated with a lower incidence of depression (self-reported or antidepressant use) during a follow-up between 2.3 and 3.2 years [36]. Our study shares more methodological aspects with the SUN cohort [20] than the ENRICA cohorts [36], i.e., a large sample size and a suitable follow-up period, in addition to a mixed nut consumption and similar criteria used to define depression that were identified in both previous studies [20,36].

As an outstanding difference between the SUN and the UK-B cohorts, while in the Spanish cohort the low-to-moderate category of nut intake ranged from 1 serving per month to 5 servings per week [20], our findings in adults from the UK support a daily consumption of >0 to 1 serving of 30 g/day of nuts to reduce the incidence of depression. Thus, considering the recommendation of low-to-moderate and regular nut consumption (1 serving/day or ~12–30 g/day), as presented in dietary guidelines [28,29,37,38], healthy dietary indices [11], and previous studies on the prevention of several health outcomes [27,39,40], our study supports that a daily serving of nuts may reduce the risk of depression. Although previous evidence indicated that the impact of nut consumption on health outcomes could be dose-dependent (the higher the consumption, the greater the benefit) [41], our results are consistent with previous studies [27], indicating that the potential benefits of nuts are achieved only at a certain threshold of nut intake.

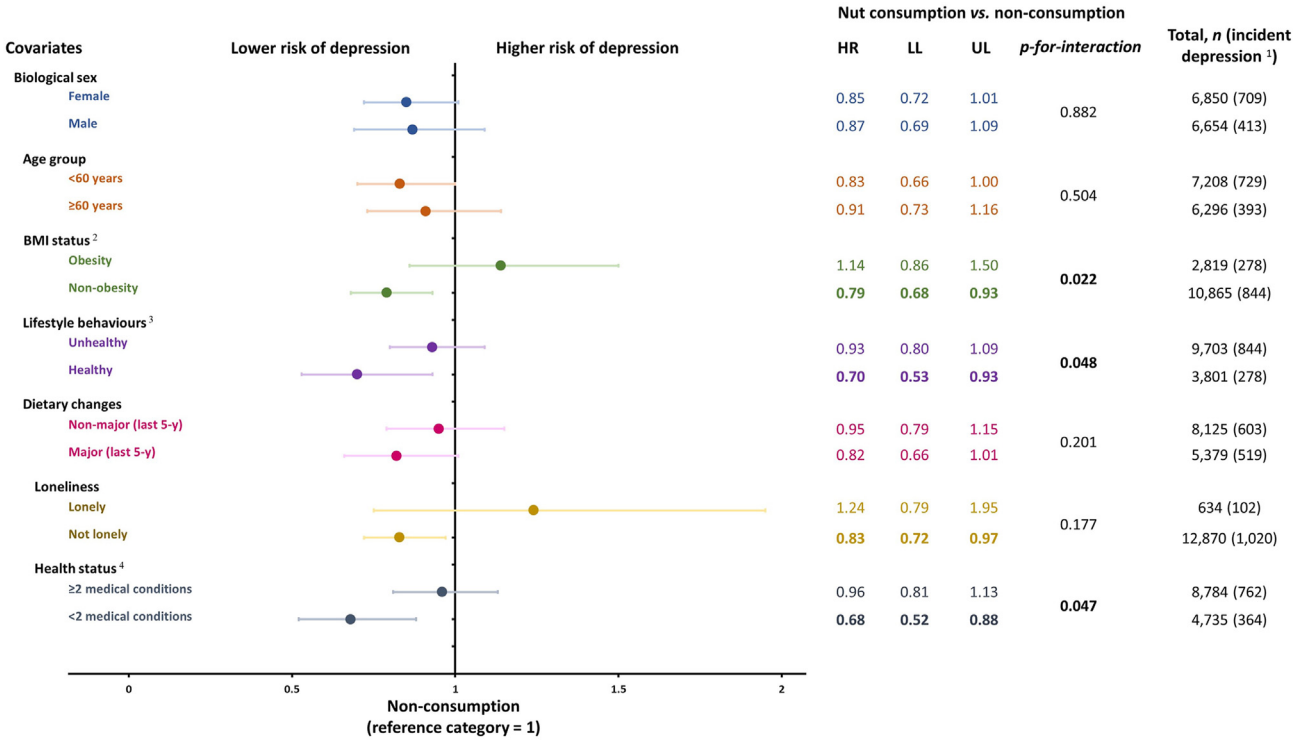

Figure 2. Risk of depression for nut consumption *vs.* nonconsumption, stratified by the covariates of the fully adjusted hazard regression model. Values are hazard ratios (95% confidence interval) for incident depression, estimated from Cox regression model number 3. Bold values indicate a statistically significant association ($p < 0.05$). [1] Incident cases of depression were defined as those participants free of self-reported depression (physician diagnosis or antidepressant use) at baseline assessment and who self-reported depression (physician diagnosis or antidepressant use) during the 5.3-year follow-up. [2] BMI ≥30.0 kg/m^2 was categorized as obesity and BMI between 18.5 and 29.9 kg/m^2 was categorized as normal weight or overweight. [3] Lifestyle behaviours (tobacco use, alcohol consumption, diet, physical activity, and sleep duration) were defined as unhealthy (smoker, frequent alcohol drinker, consumers of less than 5 portions of fruits and vegetables, insufficiently active, and with ≤6 or ≥9 h' sleep per day) or healthy (nonsmoker or ex-smoker, abstainer or drink alcohol only occasionally, consumers of 5 or more portions of fruits and vegetables, sufficiently active, and with 7–8 h sleep per day). [4] Self-reported medical conditions diagnosed by a doctor including cancer and other serious medical conditions or disabilities (e.g., angina, anxiety, dementia, diabetes, heart attack, hypertension, multiple sclerosis, osteoporosis, or Parkinson's disease, detailed in data-coding 6 of UK-B data-field 20002, Supplementary Table 3). Model 3: adjusted for sex (female or male), age (<60 years or ≥60 years), educational/professional qualification (high or low), tobacco use (never/former or current), alcohol intake (never/occasionally or daily/almost daily), major dietary changes in the last five years (yes or no), diet (fruit and vegetable consumption, ≥5 or <5 portions/day), total energy intake (kcal/day), BMI (normal weight/overweight or obese), physical activity (sufficiently active or insufficiently active), sleep duration (7–8 or ≤6 and ≥ 9 h/day), loneliness (lonely or not lonely), and self-reported medical conditions diagnosed by a doctor (nonmedical condition or ≥2 medical conditions).

Therefore, the associations between high nut consumption (32–160 g/day) and depression risk remain inconclusive, and future research is certainly warranted to address the dose–response hypothesis in this association. Furthermore, no differences in the risk of depression were observed according to the mode of nut preparation. Understanding the optimal amount of consumption and mode of preparation of nuts to promote mental health benefits is crucial information to guide the development of more specific dietary recommendations for reducing the risk of depression [16]. Our prospective study establishes associations, not causality, and therefore, long-term clinical trials are needed to provide conclusions regarding optimal nut consumption for preventing depression.

Several mechanisms underlying the potential impact of nuts on mental health have been suggested, such as reducing inflammation and oxidative stress, increasing brain-derived neurotrophic factor levels and tryptophan metabolism, and stimulating the crosstalk between the gut microbiome and brain health [19,42,43]. The anti-inflammatory (downregulation of proinflammatory cytokine expression) and antioxidant (neutralization of reactive oxidative species and enhancement of endogenous antioxidant defences) effects associated with the nutritional composition of nuts (e.g., dietary fibre, omega-3 fatty acids, phenols, polyphenols, and vitamin E) [44,45] could play an important role in reducing the risk of depression [15]. Moreover, nuts are rich in amino acids, including arginine, glutamine, serine, and tryptophan [46], and lower levels of these amino acids have been associated with depression [47]. The metabolites produced along the tryptophan-kynurenine pathway (i.e., kynurenic acid as neuroprotective and quinolinic acid or 3-hydroxykynurenine as neurotoxic) [48] are vital neurobiological mediators in depression [47]. Furthermore, previous studies have reported beneficial associations between a Mediterranean diet enriched with nuts and brain-derived neurotrophic factor [42], a molecule highly expressed in the hippocampus that engages in synaptic plasticity and cellular metabolism, playing a key role in mood [49]. Finally, the gut microbiota, a mediating pathway between diet and brain health that can partially modulate inflammatory activities, serves as another mechanism of action implicated in depression [50].

Additionally, the impact of specific foods on the risk of depression may be based on the synergistic combination of certain risk factors for depression [51]. In stratified analyses, the association between nut consumption and incident depression changed according to lifestyle behaviours, loneliness and the presence of obesity or other chronic comorbidities. Previous evidence on the diet–depression relationship suggests that combining a healthy dietary pattern [52] or specific healthy foods [51] with the simultaneous presence of healthy lifestyle-related behaviours such as regular physical activity could enhance protection against depression. Furthermore, considering the common co-occurrence of depression with obesity [53], loneliness [54] or other diseases [55],

it is reasonable to consider that individuals with these conditions are less likely to benefit from the reduced risk of depression due to the consumption of a particular food such as nuts. Despite our findings highlighting a relevant role of lifestyle and health conditions on the nut consumption and depression relationship, further long-term clinical trials evaluating the multifactorial nature of the mechanisms by which nut consumption is associated with a lower risk of depression in individuals with varied lifestyles and health profiles are needed to draw solid conclusions.

Some limitations of the study should be noted. First, UK-B is not representative of the sampling population, which could affect the magnitude, direction, and generalizability of the results. Compared with the general population, there is evidence of a "healthy volunteer selection bias" in UK-B participants [22]. Second, the high proportion of participants lost to follow-up could lead to selection bias. Third, nut consumption data were self-reported, and some degree of measurement error is expected. Fourth, because we lacked data on nut varieties (e.g., almond, cashew, monkey nut, pistachio, walnut), we were unable to examine the influence of nut types on depression. Fifth, the highest nut consumption category only includes a few cases of depression; therefore, the lack of associations may be due to limited statistical power. Likewise, a small number of participants reported high nut consumption, making them unable to conduct stratified analyses according to nut intake categories. Sixth, although we excluded individuals with depression at baseline (and during the first year of follow-up) and performed sensitivity analyses excluding participants with other mental health disorders, we cannot rule out the possibility that emerging depressive status could alter participants' food choices. Seventh, although our analyses were adjusted for relevant covariates, residual confounding cannot be completely ruled out. Finally, this study assessed self-reported depression, which may affect the prevalence and incidence estimates.

The strengths of this study comprise its prospective design, a large sample size, an adequate time of follow-up and the repeated assessment of nut consumption with a previously validated dietary questionnaire. In addition, to the best of our knowledge, this is the first study to provide evidence on potential moderators between nut consumption and the risk of developing depression according to the mode of preparation of this food. Apart from these, we were able to control for several confounding variables and performed complementary analyses that confirmed the robustness of our results.

5. Conclusions

Our findings indicate that a large sample of middle-aged and older adults from the UK consuming a low-to-moderate and regular frequency of nuts (>0 to 1 serving of 30 g/day) are less likely to develop depression than nonconsumers after a 5.3-year follow-up period, regardless of relevant sociodemographic, lifestyle, and health confounders. This large-scale cohort study shows potential moderators of this association, such as BMI status, lifestyle behaviours (tobacco use, alcohol consumption, diet quality, physical activity, and sleep duration), loneliness, or health status. Since diet is a modifiable lifestyle factor, future long-term clinical trials should evaluate whether nut consumption is an effective strategy to prevent depression in adults. Specifically, understanding the optimal dose and mode of preparation of nuts to promote the greatest mental health benefits will guide the development of more specific dietary recommendations for reducing the risk of depression.

Funding statement

The present study is a part of the "Nuts4Brain Project: The relationship between nut consumption and mental health outcomes throughout adulthood" (grant number PI21/01898), which is funded by the Ministry of Science and Innovation of Spain, the European Union NextGenerationEU program, the Instituto de Salud Carlos III in Spain, and the FEDER Funds. B.B.-P. was supported by a grant from the University of Castilla-La Mancha, Spain, co-financed by the European Social Fund (2020-PREDUCLM-16746). R.F.-R. was supported by a grant from the Spanish Ministry of Education, Culture and Sport (FPU19/00167). A.E.M. is financially supported by a *Beatriz Galindo* contract (BEAGAL18/00093) from the Spanish Ministry of Education, Culture and Sport. This work was also supported by the National Agency for Research and Innovation (POS_EXT_2020_20_1_165371). The funders played no role in the study design, data collection or analysis, decision to publish, or preparation of the manuscript.

Author contributions

B.B.-P.: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. R.F.-R.: Data curation, Writing – review & editing. V.M.-V: Conceptualization, Project Administration, Writing – review & editing, Supervision. M.G.-M.: Data curation, Writing – review & editing. M.M.: Data curation, Visualization, Writing – review & editing. E.J.-L.: Data curation, Writing – review & editing. A.E.M.: Conceptualization, Formal analysis, Funding Acquisition, Methodology, Project Administration, Visualization, Writing – original draft, Supervision.

Data availability statement

The data supporting this study's findings are available from the UK-B website (http://www.ukbiobank.ac.uk). Restrictions apply to the availability of these data, which were used under license for the current study (Application Reference Number: 72061). Details of the study design, method, variables, and ethics governance/framework are available on the UK-B website.

Conflict of interest

The authors declare no conflicts of interest. All authors approved the final version of this manuscript.

Acknowledgments

This research was conducted using the UK-B Resource. We thank all participants in the UK-B study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.07.020.

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