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Research Paper

Mushroom intake and depression: A population-based study using data from the US National Health and Nutrition Examination Survey (NHANES), 2005–2016

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ABSTRACT

Background: Mushrooms contain numerous bioactive compounds that may be associated with reduced anxiety including vitamin B12, nerve growth factor, antioxidants, and anti-inflammatory agents. We hypothesized that mushroom consumption is associated with a lower risk of depression in American adults.
Methods: Data from the National Health and Nutrition Examination Survey 2005–2016 was used. Up to two days of 24 h dietary recall were analyzed to assess mushroom intake frequency. Depression was measured using the Patient Health Questionnaire (PHQ-9, score $\geq$ 10). We used multivariable logistic regression models, adjusting for potential confounding factors.
Results: Among 24,699 participants (mean (SE) age: 45.5 (0.3) years), the weighted prevalence of depression was 5.9%. Mushrooms were consumed by 5.2% of participants. Compared with the lowest tertile of mushroom intake, participants in the middle tertile (median intake = 4.9 g/d, number of cases = 16) had lower odds of depression (adjusted OR = 0.31; 95% confidence interval [CI] 0.16, 0.60) while those in the highest tertile did not differ (median intake = 19.6 g/d, adjusted OR = 0.91; 95% CI: 0.47, 1.78, number of cases = 22) (P-trend = 0.42).
Limitations: Cross-sectional data and lack of information on specific types of mushrooms consumed.
Conclusion: Mushroom consumers had a lower odd of depression. However, we did not observe a dose-response relationship.

1. Introduction

Major depression is one of the most common mental health illnesses in the United States (US). According to the National Institute of Mental Health, approximately 17.3 million adults in the US have had at least one major depressive episode (National Institutes of Health, 2019). Mental illnesses such as depression are the third leading cause of hospitalization in the US among adults (Kessler et al., 2007; Parks et al., 2006) and those living with an acute mental illness tend to die on average 25 years earlier than healthy individuals. Depression is a significant public health problem and serious medical illness which is associated with mood disorder symptoms such as feelings of guilt or low self-esteem, and cognitive and physical symptoms such as disturbed sleep, changes in appetite or weight, and poor concentration (American Psychiatric Association, 2013; Marcus et al., 2012). It is a significant contributing factor to the global burden of disease and is also associated with increased rates of chronic diseases, suicide attempts, medical costs, disability, and impaired function (Katon, 2003; Moussavi et al., 2007; Wells et al., 1989).

Evidence from a randomized controlled trial suggested dietary

Abbreviations: PHQ-9, Patient Health Questionnaire; NHANES, National Health and Nutrition Examination Survey; FNDDS, Food and Nutrient Databases for Dietary Studies; NGF, Nerve growth factor; FCID, Food Commodity Intake Database; NDI, National Death Index.

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improvements as an efficacious treatment strategy for treating major depressive episodes (Jacka et al., 2017). In addition, a meta-analysis study also indicated that a dietary pattern characterized by a high intake of fruits, vegetables, whole grains, and antioxidants and low intakes of animal-derived foods was associated with a lower risk of depression (Li et al., 2017).

Mushrooms are low in calories and fat, cholesterol-free, and good a sources of vitamins (e.g., B_1, B_2, B_{12}, and vitamin C) and minerals (selenium and copper)(Breene, 1990; Mattila et al., 2000), and fit well with a healthy eating pattern (O'Neil et al., 2013). Even though mushrooms share some nutritional characteristics with plant-derived foods, they are biologically distinct as fungi. Importantly, mushrooms are a rich dietary source of potent antioxidants glutathione and ergothioneine. Antioxidants and B12 are thought to have anti-depressant effects. Certain species of edible mushrooms such as Hericium erinaceus (Lion's Mane) can stimulate the expression of neurotrophic factors such as nerve growth factor (NGF) synthesis, which could have a potential impact on preventing neuropsychiatric disorders including major depression (Kawagishi et al., 1996; Kawagishi et al., 1994; Ma et al., 2010). Mushrooms also contain anti-inflammatory agents (Elsayed et al., 2014). Inflammation has been linked to depression, and nonsteroidal anti-inflammatory drugs are thought to lower stress and depression (Kohler et al., 2016). White button mushroom buttons, which are the most commonly consumed mushroom variety in the US, also contain potassium, which is believed to reduce anxiety (Mrug et al., 2019).

There have been few reported epidemiological studies on the association between mushroom consumption and depression, and these have been limited to small (< 100 participants) clinical trials where intervention with the mushrooms species Hericium erinaceus was found to be effective at alleviating the symptoms of depression (Nagano et al., 2010; Okamura et al., 2015; Vigna et al., 2019). To the best of our knowledge, there have been no observational studies on mushroom consumption and depression. Thus, we aim to fill this critical gap in knowledge by investigating the association between mushroom consumption and depression in a nationally representative sample of US adults using the National Health and Nutrition Examination Survey (NHANES) (2005–2016).

2. Methods

2.1. Data source

The NHANES comprises a series of cross-sectional, stratified, multistage probability surveys conducted continually by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The NHANES is a program of studies designed to examine the health and nutritional status of adults and children in the US. Before 1994, the NHANES was conducted periodically; starting in 1999, the survey became a continuous program, with every 2-years constituting 1 cycle that has a developing focus on a variety of health and nutrition measurements to accommodate emerging needs. It is a nationally representative sample of the civilian, non-institutionalized US population located in counties across the US (Centers for Disease Control and Prevention, 2020). The surveys include demographic, socioeconomic status, dietary, and health-related questions. Details on the NHANES Laboratory/Medical Technologists Procedures and Anthropometry Procedures are described elsewhere (Centers for Disease Control and Prevention, 2011). The survey protocol is approved annually by the NCHS Research Ethics Review Board and all participants provided written informed consent (Centers for Disease Control and Prevention, 2011Centers for Disease Control and Prevention, 2016). Details information about the dietary interview portion has been published previously (Ahluwalia et al., 2016). The present study used the NHANES 2005–2016 data.

2.2. Study population

The present cross-sectional study included participants aged 18 years or older from a nationally representative sample of the continuous NHANES 2005–2016 with data on depression screener questions (N = 31,191). As done by a previous study (Dong et al., 2020), individuals who reported implausible daily energy intake levels (< 800 kcal or > 4200 kcal for men and < 500 kcal or > 3500 kcal for women) were excluded from the current analysis (N = 1102). We further excluded participants with missing dietary data or incomplete dietary sampling weight (N = 2591) and antidepressant users (n = 2799) leaving a total of 24,699 participants in the present analysis.

2.3. Mushroom consumption assessment (exposure)

In the NHNAES 2005–2016, all examined participants were eligible for up to two 24 h dietary recall interviews in which respondents reported all foods and beverages consumed during the preceding 24 h. The first dietary recall interview was collected in-person in the Mobile Examination Center (MEC) by trained interviewers. The second interview was collected by telephone 3 to 10 days after the MEC interviews using the computerized US Department of Agriculture (USDA) Automated Multiple-Pass Method (AMPM) to account for day-to-day variation (Centers for Disease Control and Prevention, 2020). The US Department of Agriculture Food and Nutrient Databases for Dietary Studies (FNDDS) was used to determine the nutrient content of foods using individual foods and total nutrients files. Mushroom dietary intake was identified from the 24-recall data based on USDA food codes. Dietary data used for estimating food sources of mushroom intake were derived from 2-day means for those individuals who completed both recall days and from the in-person recall for individuals who only completed a single recall. As done by previous studies (Ba et al., 2021a; O'Neil et al. 2013), mushroom consumption was identified based on the intake of food codes including dishes that were mainly mushrooms (e.g., mushroom soup, mushroom gravy, stuffed mushrooms, or sautéed mushrooms) and those that contain significant amounts of mushrooms (e.g., egg omelet or scrambled eggs with mushrooms, or sausage and rice with mushrooms). In the mixed dishes with mushrooms, the US Environmental Protection Agency-USDA Food Commodity Intake Database (FCID) commodity codes were used to determine the actual amounts of mushroom intake as follow: grams of intake by USDA food code time the commodity weight of mushroom contribution per 100 grams of the USDA food code (O'Neil et al., 2013). According to the NCHS guideline, only individuals with reliable and complete dietary records for mushroom intake were included in the present analysis.

2.4. Depression assessment (outcome)

Starting from 2005 to later years, NHANES has incorporated the Patient Health Questionnaire (PHQ-9). This is a self-reported assessment based on the nine Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) signs and symptoms for depression (Kroenke and Spitzer, 2002; Spitzer et al., 1999). The instrument assesses depressive symptoms over the past two weeks. The nine symptoms response categories "not at all," "several days," "more than half the days," and "nearly every day" were given a score ranging from 0 to 3, respectively. Scores were summed to create a total score ranging from 0 to 27 for each participant. As done by previous studies, depression for this study was defined as a PHQ-9 total score of $\geq$ 10, a cutoff point that has been clinically validated with a sensitivity of 88% and a specificity of 88% and frequently used in clinical and epidemiologic studies to define depression (Beydoun et al., 2013; Kroenke and Spitzer, 2002; Kroenke et al., 2001; Wang et al., 2016).

2.5. Covariates assessment

Dietary intake was assessed using up to 2-days of 24 h recall from each participant. Data were available from separate files as appropriate such as the total nutrients dataset (i.e., total energy and caffeine intake), individual foods records, and Food Pattern Equivalents Database (FPED), which included standard serving size information for 5 major pyramid food groups such as fruit, vegetables, meat, grains, dairy, and beans as well as solid fat and added sugar. Based on previous studies (Ba et al., 2021a; O'Neil et al., 2013) the following covariates were included in our analysis to reduce potential confounding such as alcohol intake (g/d), fish (oz/d), caffeine (mg/d), total energy (kcal/d), fiber (g/d), fat (g)/1000 kcal/d), and carbohydrate (g)/1000 kcal/d) energy-adjusted.

Information on age, sex (men/women), ethnicity-race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), education (college degree or above/non-college degree), marital status (never married/married), the ratio of family income to the poverty level (< 2, ≥ 2), smoking status (never smoker, ever smoker), cancer, thyroid problem, liver condition (each, yes or no) were obtained by self-reported. Comorbidities including conditions such as history of CVD, diabetes, cancer, thyroid problem, liver conditions were included as covariates because they have been shown to be associated with the outcome(depression) (de Groot et al., 2001; Glassman and Shapiro, 1998; Simon, 2001; Wang et al., 2020), and their presence may alter the dietary behavior of an individual. We recategorized marital status into two groups by combining married and living with a partner as "married", widowed/divorced/separated, and never married as "not married". The body measurement (including weight and height) was measured at the time of physical examination by trained nurses. The body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters squared (m^2) and was categorized into 3 groups: normal weight (< 24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese (≥ 30 kg/m^2). Participants who had smoked < 100 cigarettes in their lifetimes were considered non-smokers; participants who had smoked ≥ 100 cigarettes in their lifetimes were considered former smokers if they answered negatively to the question, "Do you smoke now?" and current smokers if they answered affirmatively as done by previous researchers (Wildman et al., 2005). The smoking status was later categorized as "never smoker" and "ever smoker" by combing former and current smokers. Physical activity was assessed via self-reported using the Global Physical Activity Questionnaire (GPAQ) (World Health Organization, 2012). The GPAQ includes different components of physical activity, such as intensity, duration, and frequency (Du et al., 2019). Measures of physical activity were calculated based on the 3 domains in which physical activity is performed such as leisure-time physical activity (i.e., sports and recreational activities), transportation-related physical activity (i.e., bicycling and walking), and domestic physical activity (i.e., work-related physical activities). The total physical activity score in metabolic equivalents of task (MET)-minutes/week was calculated by summing the total MET-minutes from each domain. The total Met-minute/wk scores were categorized into three groups: < 500 (somewhat active), 500–999 (active), ≥ 1000 (very active). History of CVD includes a self-reported diagnosis of CVD or use of anti-hypertensive drugs in the past 30 days prior to the survey interview. Similarly, a history of diabetes includes a self-reported diagnosis of diabetes or use of anti-diabetic drugs. Participants were categorized as medication users if they were taking one or more of the following drug classes: statins, and opioids in the past 30 days prior to the survey interview.

2.6. Statistical analysis

SAS statistical software version 9.4 (Cary, NC) was used to conduct all statistical analyses using 2-sided $P < .05$ was considered as the level of significance. Univariable analyses were performed to assess the statistical significance of differences in weighted percentages for categorical variables using the Rao-Scott $\chi 2$ test and weighted means for continuous variables using analysis of variance to describe the characteristics of the study participants. The multivariable logistic regression models with appropriate sampling weight, cluster, strata using SAS surveylogistic procedure were used to assess the association of mushroom consumption with depression, adjusting for potential confounders such as total energy intake, demographics, lifestyle, and other dietary factors. We also conducted multivariable linear regression models using SAS surveyreg procedure to examine the association of mushroom consumption with depression score as a continuous variable adjusting for the same covariates mentioned above. As done by a previous study from our group (Ba et al., 2021a), we performed a single imputation using the fully conditional specification method for missing values for demographic and lifestyle variables. For the present study, mushroom intake was categorized into tertile (lowest, middle, and highest) and was later categorized into two groups: (1) no mushroom intake, and (2) more than 0 g/d. We assessed linear trends were for significance by using the median intake of each tertile and modeled as a single continuous variable in the multivariable-adjusted model. To address potential effect modification, the interaction between mushroom intake and age, sex, alcohol intake, CVD, cancer, and smoking associations with depression were statistically tested by introducing interaction-terms into the multivariable surveylogistic regression model.

As a secondary analysis, we conducted a nutritional substitution analysis to compare the health effect of substituting 1-serving/d of mushroom for 1-serving/d of red or processed meat. As done by a previous study, 1-serving of red or processed meat was defined as 3.5-ounce equivalents and 1-serving of mushrooms as 70 g (Rehm et al., 2016). Red or processed meat includes such as beef, veal, pork, lamb, cured, and organs meat. The association of substituting 1-serving/d of mushroom for 1-serving/d of red or processed meat with depression was assessed by including both as continuous variables in the same multivariable surveylogistic regression models by adjusting for the covariates used in model 2 plus BMI, ratio of family income to poverty, smoking status, physical activity, and other dietary variables, including poultry (svg/d), fish (svg/d), eggs (svg/d), nuts/legumes/soy (svg/d), fruit (svg/d), dark green/red-orange vegetables (svg/d), dairy (svg/d), solid fat, added sugar, total energy, caffeine, and alcohol intake. The difference in their regression coefficients, variances, and covariance was used to estimate the OR and 95% CIs for the substitution effect (Bernstein et al., 2010; Halton et al., 2006).

To further test for the robustness of our results, we conducted a series of sensitivity analyses. First, to address potential residual confounding, we further adjusted for a propensity score that reflected associations of mushroom consumption with potential confounding covariates used in model 3b plus the survey weight. Second, because several major chronic diseases are strongly associated with depression (Simon, 2001), we conducted a sensitivity analysis by excluding participants with a history of CVD, diabetes, cancer, thyroid problem, and liver condition.

Survey analysis procedures (e.g., proc surveymeans, proc surveyfreq, proc surveyreg, proc surveylogistic, SAS institute) were used to account for the sampling weights, clustering, and stratification of the complex sampling design as specified in the instructions for using NHANES data to ensure nationally representative estimates (Centers for Disease Control and Prevention, 2020). The multivariable surveylogistic regression results were presented as adjusted odds ratio (OR) with 95% confidence intervals (95% CIs).

3. Results

Among 24,699 US adults (12,268 men and 10,304 women) included in the current analysis, the mean (SE) age was 45.5(0.3) years; about half of the study participants were men (50.2%), and more than half were non-Hispanic Whites (66.1%). The overall weighted prevalence of depression and mushroom consumers during our study period were 5.9%, (95% CI: 5.4, 6.5%) and 5.2 %, (95% CI: 4.7, 5.7), respectively.

Compared with mushroom non-consumers, mushroom consumers were more likely to be females, non-Hispanic white, college graduate or above, and had a higher proportion of ratio of family income to poverty level ≥ 2.0 (Table 1).

In the full adjusted model, compared with the lowest tertile of mushroom intake, participants in the middle tertile (median intake = 4.9 g/d, number of cases = 16) had lower odds of depression (adjusted OR = 0.31; 95% CI: 0.16, 0.60) while those in the highest tertile did not differ (median intake = 19.6 g/d, adjusted OR = 0.91; 95% CI: 0.47, 1.78, number of cases = 22) (*P*-trend = 0.42) (Table 2).

We observed a similar significant association between mushroom intake and depression when depression score was analyzed as a continuous variable for the middle tertile, but not for the highest tertile for all the models (Table 3).

When mushroom intake was further divided into two groups (mushroom consumer, non-consumer), mushroom consumption was associated with lower odds of depression (adjusted OR = 0.57; 95% CI: 0.34, 0.96; Table 4). Further adjustment of the propensity score in the full adjusted model, the association between mushroom intake and lower odds of depression remained statistically significant. A significant association between mushroom and lower odds of depression was also found after excluding participants with major chronic diseases.

In the nutritional substitution model, replacing red or processed meat with mushrooms was not associated with depression. The adjusted OR was 0.61 (95% CI: 0.15, 2.48) when 1-serving/d of mushroom was substituted for an equivalent amount of 1-serving/d of red or processed meat. Lastly, none of the interaction terms were found to be statistically significant ($P_{\text{interaction}} > .05$ for all).

4. Discussion

In this large cross-sectional study of nationally representative of more than 24,000 US adults, we found that those with mushroom

Table 1
Baseline characteristics of the study population, National Health and Nutrition Examination Survey (NHANES) 2005–2016 (*N* = 24,699).

Characteristic	Tertile of Mushroom Intake			
	Lowest Tertile (*n* = 23,680)	Middle Tertile (*n* = 508)	Highest Tertile (*n* = 511)	*P* value‡
Median intake (g/d)	0	4.9	19.6	
Age, mean±SE, years	45.4 ± 0.3	47.7 ± 1.2	46.6±1.3	0.11
Women	11,852 (49.4)	303 (60.8)	276 (53.5)	0.001
Race-Ethnicity %				< 0.0001
Mexican American	4,177 (9.7)	63 (6.6)	57 (5.4)	
Other Hispanic	2,295 (5.4)	28 (2.1)	26 (2.2)	
Non-Hispanic White	9,699 (65.4)	297 (77.5)	308 (80.2)	
Non-Hispanic Black	5,404 (12.4)	71 (6.4)	59 (5.5)	
Other Race	2,105 (7.2)	49 (7.3)	61 (6.7)	
College degree or above	11,951 (59.9)	333 (68.8)	358 (75.3)	< 0.0001
Married	14,084 (62.7)	325 (70.9)	335 (65.8)	0.02
Body mass index (kg/m^2) %				0.10
< 24.9	7,215 (31.6)	162 (33.7)	176 (37.4)	
25–29.9	7,910 (33.5)	177 (36.9)	155 (29.3)	
≥ 30.0	8,564 (34.9)	169 (29.3)	180 (33.3)	
Ratio of family income to poverty ≥ 2.0	12,241 (63.6)	336 (73.5)	344 (80.9)	< 0.0001
Ever smoker	10,170 (43.2)	234 (43.5)	219 (42.3)	0.96
Physical activity MET-min/week				0.01
Somewhat active	4,673 (18.6)	96 (16.1)	93 (16.7)	
Active	3,446 (13.8)	93 (20.9)	87 (15.3)	
Very active	15,561 (67.7)	319 (63.0)	331 (68.0)	
Prescription medications %				
Statins	3,783 (14.5)	103 (15.1)	92 (17.6)	0.35
Opioid	1,056 (4.5)	20 (3.2)	22 (3.5)	0.32
Self-reported diseases %				
History of CVD	8,902 (33.4)	207 (34.3)	189 (34.0)	0.95
History of diabetes	3,209 (10.4)	66 (8.7)	64 (9.1)	0.45
Cancer	2,003 (9.0)	70 (14.4)	55 (11.5)	0.01
Thyroid problem	2,059 (9.1)	64 (13.5)	44 (11.6)	0.03
Liver condition	760 (2.8)	21 (2.9)	16 (4.2)	0.39
Alcohol intake, g/d	9.1 ± 0.3	9.5 ± 1.4	10.1 ± 1.0	0.54
Fish intake, oz/d	0.6±0.02	0.6±0.1	0.9±0.1	0.05
Caffeine intake, mg/d	158.4 ±3.1	166.6±15.5	176.2±10.8	0.15
Energy intake, kcal/d	2070±8	2013±35	2151±45	0.08
Fiber intake, g/d	16.8±0.1	17.1±0.4	18.8±0.5	0.001
Fat intake (g)/1000 kcal/d	37.7±0.1	38.0±0.5	40.0±0.5	< 0.0001
Carbohydrate intake, (g)/1000 kcal/d	121.2±0.3	119.4±1.3	113.1±1.5	< 0.0001

All Ns are unweighted and all proportions and means (SE) are survey-weighted for complex survey design to be nationally representative estimates. The focus should be on the survey-weighted proportions and means (SE) because they represent the US adult population.
‡For categorical variables, P-value was calculated by the Rao-Scott $\chi 2$ test, which is a design adjusted version of the Pearson $\chi 2$ test. For continuous variables, analysis of variance adjusting for sampling weight was used to calculate P-value.
Data are means ± SE unless indicated otherwise.
SE: Standard Error

Table 2
Multivariable surveylogistic regression showing odds ratios (95% confidence intervals) for depression associated with tertile of mushroom intake (*n* = 24,699).

	Tertile of Mushroom Intake			
	Lowest Tertile	Middle Tertile	Highest Tertile	*P*-trend
Median intake (g/d)	0	4.9	19.6	
No. of cases	1,619	16	22	
Model 1	1 (Ref)	0.29 (0.15, 0.58)	0.62 (0.33, 1.17)	0.06
Model 2	1 (Ref)	0.34 (0.17, 0.68)	0.75 (0.39, 1.44)	0.20
Model 3a	1 (Ref)	0.34 (0.17, 0.67)	0.92 (0.47, 1.81)	0.46
Model 3b	1 (Ref)	0.31 (0.16, 0.60)	0.91 (0.47, 1.78)	0.42
Sensitivity analyses[a]				
Propensity score adjustment	1 (Ref)	0.32 (0.16, 0.60)	0.92 (0.48, 1.79)	
Excluding 11,539 participants with major chronic conditions[b]	1 (Ref)	0.24 (0.07, 0.85)	0.77 (0.36, 1.63)	

Model 1: Age and sex (men/women)-adjusted.
Model 2: Model 1 + ethnicity-race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), education (college degree or above/non-college degree), marital status (never married/married) adjusted.
Model 3a: Model 2 + further adjustment of BMI (< 24.9, 25.0–29.9, ≥ 30), ratio of family income to poverty level (< 2, ≥ 2), smoking status (never smoker, ever smoker), fish intake (oz/d), total energy (kcal/d), fat (g)/1000 kcal/d), carbohydrate (g)/1000 kcal/d), fiber (g/d), caffeine (mg/d), alcohol intake (g/d), physical activity MET-min/week (somewhat active, active, very active).
Model 3b: Model 2 + further adjustment of BMI (< 24.9, 25.0–29.9, ≥ 30), ratio of family income to poverty level (< 2, ≥ 2), smoking status (never smoker, ever smoker), physical activity MET-min/week (somewhat active, active, very active), statins (yes or no), history of CVD (yes or no), history of diabetes (yes or no), opioid use, cancer, thyroid problem, liver condition (each, yes or no), fish intake (oz/d), total energy (kcal/d), fat (g)/1000 kcal/d), carbohydrate (g)/1000 kcal/d), fiber (g/d), caffeine (mg/d), alcohol intake (g/d).
[a] Sensitivity analyses based on Model 3b.
[b] Major chronic diseases include history of CVD, diabetes, cancer, thyroid problem, and liver condition.

Table 3
Regression Coefficients (β) (95% confidence intervals) in the association between mushroom intake and depression score on a continuous scale.

	Tertile of Mushroom Intake			
	Lowest Tertile	Middle Tertile	Highest Tertile	*P*-trend
Median intake (g/d)	0	4.9	19.6	
No. of cases	1,619	16	22	
Model 1	1 (Ref)	-0.65 (-0.95, -0.34)	-0.24 (-0.68, 0.20)	0.09
Model 2	1 (Ref)	-0.47 (-0.78, -0.17)	-0.05 (-0.49, 0.40)	0.52
Model 3a	1 (Ref)	-0.42 (-0.74, -0.09)	0.11 (-0.35, 0.57)	0.93
Model 3b	1 (Ref)	-0.42 (-0.73, -0.10)	0.11 (-0.33, 0.54)	0.95

Model 1: Age and sex (men/women)-adjusted.
Model 2: Model 1 + ethnicity-race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), education (college degree or above/non-college degree), marital status (never married/married) adjusted.
Model 3a: Model 2 + further adjustment of BMI (< 24.9, 25.0–29.9, ≥ 30), ratio of family income to poverty level (< 2, ≥ 2), smoking status (never smoker, ever smoker), fish intake (oz/d), total energy (kcal/d), fat (g)/1000 kcal/d), carbohydrate (g)/1000 kcal/d), fiber (g/d), caffeine (mg/d), alcohol intake (g/d), physical activity MET-min/week (somewhat active, active, very active).
Model 3b: Model 2 + further adjustment of BMI (< 24.9, 25.0–-29.9, ≥ 30), ratio of family income to poverty level (< 2, ≥ 2), smoking status (never smoker, ever smoker), physical activity MET-min/week (somewhat active, active, very active), statins (yes or no), history of CVD (yes or no), history of diabetes (yes or no), opioid use, cancer, thyroid problem, liver condition (each yes or no), fish intake (oz/d), total energy (kcal/d), fat (g)/1000 kcal/d), carbohydrate (g)/1000 kcal/d), fiber (g/d), caffeine (mg/d), alcohol intake (g/d).

consumption had lower odds of having depression. The observed association was independent of socio-demographics, major lifestyle risk factors, self-reported diseases, medications use, and other dietary factors. We did not observe a significant dose-response relationship between greater mushroom intake and the odds of depression. Furthermore, in this study, replacing 1-serving of red or processed meat per day with 1-serving of mushrooms per day was not associated with lower odds of depression. These findings highlight the potential clinical and public health importance of mushroom consumption as a means of reducing depression and preventing diseases.

The observed association between mushroom consumption and lower odds of depression in our study is consistent with the results of previous small clinical trials (Nagano et al., 2010; Okamura et al., 2015; Vigna et al., 2019). A clinical study conducted by Nagano et al. indicated that mushroom consumption has the possibility to reduce depression and anxiety (Nagano et al., 2010). In addition, another recent clinical study that has examined the effect of mushrooms on depression, anxiety, sleep, and eating disorders in 77 volunteers affected by overweight or obesity also indicated a significant decreased in depression, anxiety, and sleep disorders (Vigna et al., 2019). Furthermore, previous epidemiological findings from our group and others suggest that mushroom consumption is associated with a lower risk of chronic diseases, including some cancers (Ba et al., 2021b; Hong et al., 2008; Zhang et al., 2009; Zhang et al., 2017).

A potential biological mechanism regarding the association of mushroom intake with depression observed in our study is plausible and may stem from the antioxidant and neuroprotective properties of specific mushroom components such as ergothioneine. However, our results should be interpreted with caution. We cannot exclude the possibility that the observed association between mushroom intake and depression is a chance finding since no clear dose-response relationships were observed.

Accumulating evidence suggests that oxidative stress resulting from an imbalance between oxidant exposure and antioxidants defense systems plays a significant role in the pathophysiology of numerous

Table 4
Multivariable surveylogistic regression showing odds ratios (95% confidence intervals) for depression associated with mushroom intake (Yes/No) (n = 24,699).

	No Mushroom Intake	Mushroom Intake
No. of cases	1,619	38
Model 1	1 (Ref)	0.45 (0.28, 0.74)
Model 2	1 (Ref)	0.54 (0.33, 0.89)
Model 3a	1 (Ref)	0.60 (0.35, 1.00)
Model 3b	1 (Ref)	0.57 (0.34, 0.96)
Sensitivity analyses[a]		
Propensity score adjustment	1 (Ref)	0.58 (0.34, 0.96)
Excluding 11,539 participants with major chronic conditions[b]	1 (Ref)	0.49 (0.25, 0.95)

Model 1: Age and sex (men/women)-adjusted.
Model 2: Model 1 + ethnicity-race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), education (college degree or above/non-college degree), marital status (never married/married) adjusted.
Model 3a: Model 2 + further adjustment of BMI (< 24.9, 25.0–29.9, ≥ 30), ratio of family income to poverty level (< 2, ≥ 2), smoking status (never smoker, ever smoker), fish intake (oz/d), total energy (kcal/d), fat (g)/1000 kcal/d), carbohydrate (g)/1000 kcal/d), fiber (g/d), caffeine (mg/d), alcohol intake (g/d), physical activity MET-min/week (somewhat active, active, very active).
Model 3b: Model 2 + Further adjustment of BMI (< 24.9, 25.0–29.9, ≥ 30), ratio of family income to poverty level (< 2, ≥ 2), smoking status (never smoker, ever smoker), physical activity MET-min/week (somewhat active, active, very active), statins (yes or no), history of CVD (yes or no), history of diabetes (yes or no), opioid use, cancer, thyroid problem, liver condition (each yes or no), fish intake (oz/d), total energy (kcal/d), fat (g)/1000 kcal/d), carbohydrate (g)/1000 kcal/d), fiber (g/d), caffeine (mg/d), alcohol intake (g/d).
[a] Sensitivity analyses based on Model 3b.
[b] Major chronic diseases include history of CVD, diabetes, cancer, thyroid problem, and liver condition.

neuropsychiatric disorders including schizophrenia, bipolar disorder, and major depression (Ng et al., 2008; Pandya et al., 2013). Consequently, antioxidants have been proposed to play a significant role in the prevention of these disorders (Pandya et al., 2013). Evidence from a previous study using NHANES 2005–2006 data indicated that serum levels of antioxidants, especially total carotenoids (mostly β-carotene and lutein+zeaxanthins) were associated with reduced levels of depressive symptoms among US adults (Beydoun et al., 2013). Antioxidants that mimic glutathione peroxidase activity and zinc have also been found to have anti-depressive effects (Maes et al., 2011).

Mushrooms are a potent source of powerful antioxidants and are thus more likely to lower oxidative stress induced by reactive oxygen species (Kalaras et al., 2017). Specifically, they are uniquely high in the antioxidant ergothioneine, which is known to be obtained exclusively through dietary sources with mushrooms having the highest concentration levels (Beelman et al., 2019; Ey et al., 2007). In an animal model orally ingested ergothioneine was shown to cross the blood-brain barrier where it promoted neuronal differentiation and alleviated symptoms of depression (Nakamichi et al., 2016). Another recent animal model suggested that ergothioneine may be a common substance in the microbiota-gut-brain axis that prevents stress related diseases including major depressive disorder(Matsuda et al., 2020).

Notwithstanding the benefits of ergothioneine, the average consumption (mg/d) is relatively low in the US compared to other countries such as Italy, Ireland, France, and Finland (Ramirez-Martinez et al., 2016). Mushrooms also contain other bioactive compounds including fiber-associated monosaccharides, chitin, and β-glucans (Dikeman et al., 2005; Jo Feeney et al., 2014). They are low in energy and high in vitamins, which may play a significant role in healthy eating patterns.

According to a previous NHANES population-based cross-sectional study, mushroom intake was associated with better diet quality (O'Neil et al. 2013).

5. Strengths

Our study has several strengths. Previous epidemiological studies that have examined the effects of mushrooms on depression were limited to small clinical trials with sample sizes ranged from 8 to 77 subjects (Nagano et al., 2010; Okamura et al., 2015; Vigna et al., 2019). To the best of our knowledge, this is the first large scale epidemiological study that used nationally representative US adult population data and examined the association between mushroom consumption and depression. In addition, we used a validated questionnaire for assessing symptoms of depression. Our results are robust to adjustment for a wide spectrum of potential confounders factors, given their potential association with depression and the propensity score adjustment.

6. Limitations

Notwithstanding, the study has some limitations that need to be addressed. First, self-reported 24 h dietary recalls using USDA foods code for recipes may have introduced misclassification bias. This includes misclassification of mushrooms as vegetables and inaccurate assessment of mushroom content in the mixed of dishes. The two 24 h recalls may not have adequately captured the within-person variation in mushroom intake. Such nondifferential measurement error may have underestimated the association between mushroom intake and risk of depression. Second, the cross-sectional nature of the survey does not allow for the determination of the cause-effect relationship. Third, although we controlled for wide ranges of major potential confounders including, demographics, self-reported diseases, medications, major lifestyle, and dietary risk factors in the multivariable logistic models, there could be residual confounding from unmeasured factors which could have impacted the effect size estimates. Fourth, information on the different types of mushrooms was not available in NHANES database, and, therefore, we may have missed the effects of specific types of mushrooms on depression. Lastly, it is possible that the observed association could be due to chance, because we did not have enough cases in the second and third tertile. Despite these limitations, this study may provide important information regarding the potential protective effects of mushrooms in lowering the risk of depression among American adults.

7. Conclusion

In this nationally representative study of US adults, we found that mushroom intake was associated with lower odds of depression. However, our results should be interpreted with caution. We found that compared to the lowest tertile, the middle tertile was associated with depression but not for the highest tertile indicating that the finding could be possibly due to chance. Our findings are consistent with preclinical studies suggestive of potential health benefits from specific bioactive constituents found in mushrooms. Larger prospective cohort studies with repeated measurements of diet are warranted to further replicate our findings and clarify the potential role of mushroom intake in lowering the risk of depression.

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Data availability

Data used for this study are available on the NHANES website: https://wwwn.cdc.gov/nchs/nhanes/.

CRediT authorship contribution statement

Djibril M. Ba: Conceptualization, Investigation, Visualization, Formal analysis, Writing – original draft, Writing – review & editing. **Xiang Gao:** Conceptualization, Investigation, Visualization, Writing – review & editing. **Laila Al-Shaar:** Conceptualization, Investigation, Visualization, Writing – review & editing. **Joshua E. Muscat:** Writing – review & editing. **Vernon M. Chinchilli:** Writing – review & editing. **Robert B. Beelman:** Writing – review & editing. **John P. Richie:** Conceptualization, Investigation, Visualization, Writing – review & editing.

Declaration of Competing Interest

None.

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