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# Association between dietary theobromine with depression: a population-based study

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## Abstract

**Objective:** The purpose of this study is to investigate the possible link between dietary theobromine intake and symptoms of depression.

**Materials and methods:** These results are based on the responses of 3637 people who took part in the National Health and Nutrition Examination Survey in 2017–2018. Participants' daily theobromine intake was determined using a 24-h food questionnaire from the 2017–2018 cycle. Presence of depression was defined as a score of 5 or above on the Patient Health Questionnaire. Association between theobromine intake and depression was examined using a multivariate logistic regression adjusting for several relevant sociodemographic, lifestyle and health-related factors.

**Results:** A total of 6903 participants were included in the study. The results of multivariate logistic regression showed a correlation between depressive symptoms and theobromine intake (OR:1.17, 95%CI:1.02–1.34).

**Conclusions:** Our cross-sectional population based study suggests that increased theobromine intake is associated with increased risk for depression. Nevertheless, more investigations are needed to confirm our findings.

**Keywords:** Depression, Theobromine, NHANES

## Introduction

Depression is a serious condition affecting 246 millions of individuals worldwide [1]. Depression is the most common cause of disability and the fourth most common contribution to the overall illness burden in the world [2]. Antidepressant drugs, psychotherapies, and a variety of brain stimulation methods are all validated therapy options for depression [3]. Antidepressants are one of the most often recommended groups of psychotropic drugs for adolescents in the United States [4]. However, patient adherence was quite poor, with as many as half of patients interrupting their therapy in the first six weeks

[5]. Increasing data also shows that dietary factors have an impact on depression symptoms [6, 7]. Previous studies have reported a protective effect of chocolate against depression [5]. In this regard, one of the primary ingredient of chocolate, theobromine, has been shown to protect cognitive function by regulating neurotransmitter signaling [8]. Despite this, few population-based studies have investigated the link between theobromine in the diet and depression. Therefore, we aimed at examining the association between theobromine consumption and depressive symptoms taking advantage of a large population-based cohort in the United States.

## Materials and methods

### Study population

The National Health and Nutrition Examination Survey, also known as NHANES, is an ongoing survey that is carried out on a rolling basis in order to collect cross-sectional data from the civilian population in the United States that does not reside in institutions [9]. Since 1999,

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the NHANES has been conducting a survey of a nationally representative, complicated, stratified, multi-stage probability sample of the US population [10]. Each wave of the survey has included a different participant. The assessment procedures include a household interview and a physical examination at a mobile examination center (MEC) [11]. In this study, we obtained data from 2017–2018. In NHANES, depressive symptoms were only assessed in patients aged 18 years; therefore, we only included data from this age group.

## Measures

### **Exposure: Theobromine intake**

Participants in the NHANES were asked to take part in an in-person household interview as well as a health examination at a MEC, which included a recall of their dietary intake over the previous 24 h [12]. The Automated Multiple Pass Method, which was utilized in NHANES in order to collect dietary data, has been successfully validated [13]. More details are available at [www.ars.usda.gov/ba/bhnrc/fsrg](http://www.ars.usda.gov/ba/bhnrc/fsrg). Based on the distribution of theobromine intake in NHANES, we defined increased theobromine intake as values above the third quartile (Q3), ie 43 mg/day [8].

### **Outcome: depressive symptoms**

The Patient Health Questionnaire (PHQ-9) is a validated 9-item depression screener that was used to evaluate depressive symptoms. The questions on this screener enquire about the duration and severity of depressive symptoms during the last two weeks [14]. For each question, the score ranged from 0 to 3, and the total score ranged from 0 to 27. Depressive symptoms were then categorised as "none or minimal" (0–4), "mild" (5–9), "moderate" (10–14), "moderately severe" (15–19), or "severe" (20–27) [15]. Depressive symptoms were defined as a score of  $\geq 5$  on the PHQ-9 [8].

## Covariates

Age, gender, race (Mexican American; white; black and other), multimorbidity, education level (below high school; high school and college or above), smoking status (former; never and current), drinking status (never; former; light; moderate and heavy) and the poverty income ratio (PIR) were all taken into consideration when determining socio-demographic characteristics. A never smoker is an adult who has never smoked or has smoked fewer than 100 cigarettes in their lifetime; former smokers are individuals who have reported smoking 100 cigarettes in their lifetime but are not currently smokers; and current smokers are individuals who have smoked 100 cigarettes on some days or

every day in their lifetime [16]. Never drinkers reported consuming less than 12 drinks; ever drinkers reported having more than 12 drinks in their lives but not in the preceding year; and current drinkers were further categorized as light, moderate, or heavy current drinkers. Heavy current drinkers were defined as women drinking 3 drinks per day and men drinking 4 drinks per day, with 5 or more binge drinking days per month; moderate drinkers were classified as women drinking 2 drinks per day and men drinking 3 drinks per day, with 2 binge drinking days per month. People who drank just a little: did not satisfy the standards outlined above [17]. As a measure of socioeconomic status, the PIR, which is the ratio of total family income to the poverty threshold, was used: low ( $PIR < 1.35$ ), medium ( $1.35 \leq PIR < 3.0$ ), and high ( $PIR \geq 3.0$ ) [18]. The presence of diabetes mellitus was defined as the need for the administration of insulin or oral antidiabetic medication treatment. Prediabetes is defined in this study by impaired fasting glucose and impaired glucose tolerance [19]. Body mass index (BMI) was determined by dividing weight in kilograms by the square of height in meters and was classified as underweight ( $BMI = 18.5$ ), normal weight ( $BMI = 18.5–24.9$ ), overweight ( $BMI = 25–29.9$ ), and obese ( $BMI > 30.0$ ) were the four BMI categories. Multimorbidity, defined as the presence of two or more chronic conditions in a person, has been linked to depression [20, 21]. Cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), asthma, arthritis, cancer, stroke, hypertension, hyperlipidemia, diabetes, and obesity were chosen based on their clinical importance and the availability in NHANES [20]. We used a backward stepwise regression to identify our final model with depression (ie  $> 5$  on the PHQ9) as our dependent variable. Improvement in the model was assessed using the Akaike Information Criteria (AIC). Two variables, [PIR, education], were excluded due to high collinearity.

## Statistical analyses

All statistical analyses were performed with R, version 4.0.5 (R Project for Statistical Computing) using the survey package, version 4.1–1 and with Free Software Foundation statistics software, version 1.3. In all tests,  $P < 0.05$  (2-sided) was considered to indicate statistical significance. The categorical variables were summarized as percent and frequency, while continuous variables were summarized as mean and 95% confidence intervals (CIs). Categorical data were compared using the  $\chi^2$  test or Fisher's exact test, while continuous data

were compared using Student's t-test. The analyses were restricted to participants who had complete data records.

## Results

### Population characteristics

Figure 1 depicts the recruitment and inclusion/exclusion criteria for the study. The study included 6903 representative U.S. participants. Participants with depressive symptoms were younger than those without symptoms ( $49.0 \pm 18.3$  years versus  $51.7 \pm 18.0$  years,  $P < 0.05$ ) (Table 1). Moreover, participants with increased theobromine intake ( $\geq 43$  mg/day) reported more depressive symptoms (34.9% vs 31.3% for low intake group,  $P < 0.05$ ). In addition, the proportion of patients with depressive symptoms was higher in women and individuals with white ethnicity, lower family income, college or higher education, as well as multimorbidity. Similar differences were noted in never smokers and mild alcohol users.

### Multivariate regression analysis

In a multivariate regression model including [gender, age, race, smoke, alcohol, multimorbidity], a higher

theobromine intake was associated with increased risk of depression (OR:1.17, 95%CI:1.02–1.34, AIC 319.528; Table 2). A subgroup analysis revealed that in participants aged  $< 60$  years [ $p < 0.001$ ], without multimorbidity [ $p < 0.001$ ], obesity [ $p < 0.05$ ] or cancer [ $p = 0.002$ ], higher theobromine intake was associated with increased risk for depression (Table 3).

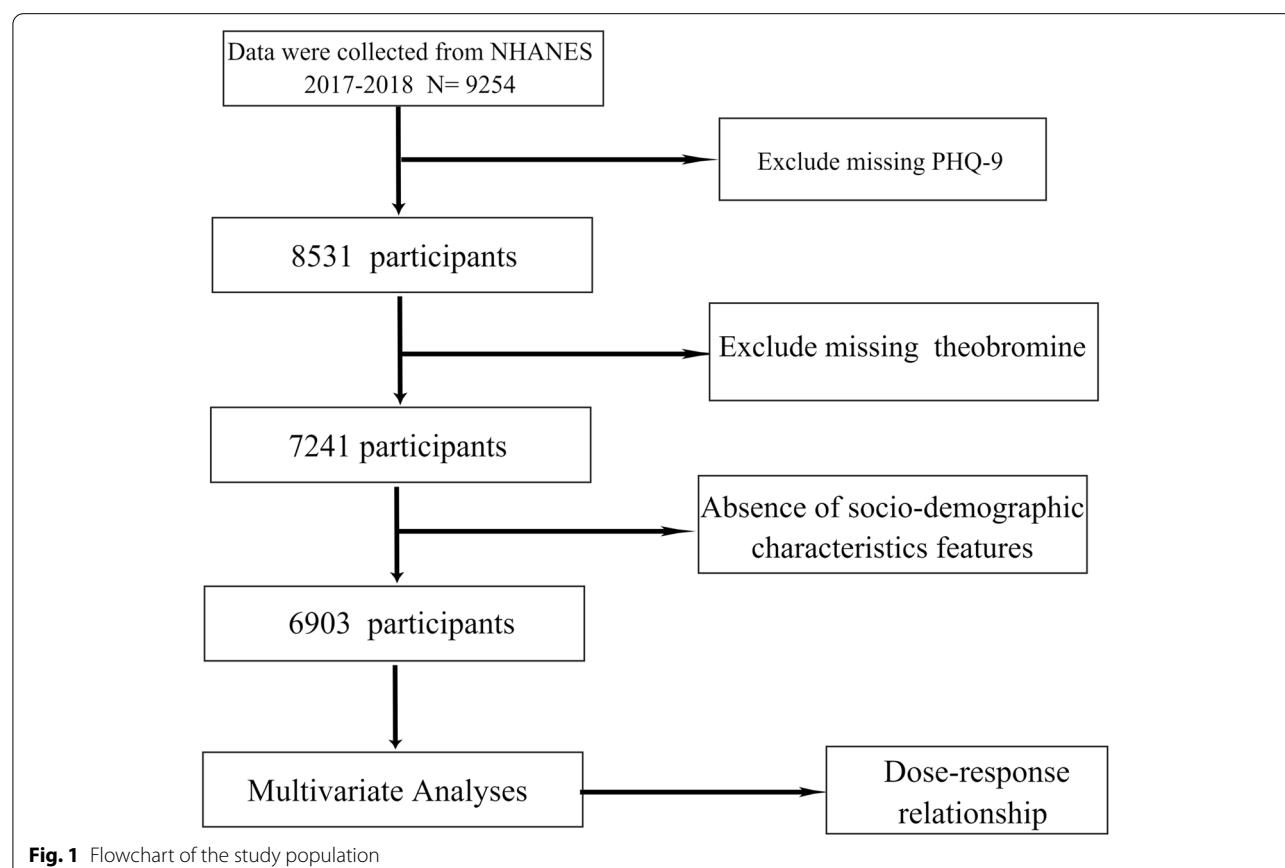
### Relationship between theobromine and depression

A restricted cubic spline (RCS) was used to further clarify the relationship between theobromine and depression after controlling for possible variables. Figure 2 suggests that theobromine is positively correlated with the prevalence of depression.

## Discussion

In this study, we identified an association between increased theobromine consumption and depressive symptoms, even after adjusting for age, sex, race, multimorbidity, smoking status, and alcohol consumption, these relationships were still clearly visible.

Our findings are in the line of previous studies reporting protective effects of theobromine on cognitive function. A wide range of mechanisms have been suggested



**Fig. 1** Flowchart of the study population

**Table 1** Characteristics of the overall target population according to theobromine

| Variables                 | Total (n = 6903) | No depression (n = 5148) | Depression (n = 1755) | p       |
|---------------------------|------------------|--------------------------|-----------------------|---------|
| Theobromine intake, n (%) |                  |                          |                       | 0.005   |
| < 43 mg/day               | 4677 (67.8)      | 3535 (68.7)              | 1142 (65.1)           |         |
| > = 43 mg/day             | 2226 (32.2)      | 1613 (31.3)              | 613 (34.9)            |         |
| Age, Mean ± SD            | 51.0 ± 18.1      | 51.7 ± 18.0              | 49.0 ± 18.3           | < 0.001 |
| Sex, n (%)                |                  |                          |                       | < 0.001 |
| Female                    | 3563 (51.6)      | 2543 (49.4)              | 1020 (58.1)           |         |
| Male                      | 3340 (48.4)      | 2605 (50.6)              | 735 (41.9)            |         |
| Race, n (%)               |                  |                          |                       | < 0.001 |
| Black                     | 1135 (16.4)      | 895 (17.4)               | 240 (13.7)            |         |
| Mexican American          | 535 (7.8)        | 414 (8)                  | 121 (6.9)             |         |
| Other Race                | 1814 (26.3)      | 1461 (28.4)              | 353 (20.1)            |         |
| White                     | 3419 (49.5)      | 2378 (46.2)              | 1041 (59.3)           |         |
| PIR, n (%)                |                  |                          |                       | < 0.001 |
| Low                       | 1497 (24.3)      | 899 (19.7)               | 598 (37.4)            |         |
| Medium                    | 2021 (32.9)      | 1381 (30.3)              | 640 (40.1)            |         |
| High                      | 2634 (42.8)      | 2275 (49.9)              | 359 (22.5)            |         |
| Education, n (%)          |                  |                          |                       | < 0.001 |
| Below high school         | 824 (11.9)       | 560 (10.9)               | 264 (15.1)            |         |
| High school               | 1593 (23.1)      | 1070 (20.8)              | 523 (29.8)            |         |
| College or above          | 4480 (65.0)      | 3513 (68.3)              | 967 (55.1)            |         |
| Smoke, n (%)              |                  |                          |                       | < 0.001 |
| Former                    | 1570 (22.7)      | 1126 (21.9)              | 444 (25.3)            |         |
| Never                     | 4077 (59.1)      | 3278 (63.7)              | 799 (45.5)            |         |
| Now                       | 1256 (18.2)      | 744 (14.5)               | 512 (29.2)            |         |
| Alcohol user, n (%)       |                  |                          |                       | < 0.001 |
| Heavy                     | 1038 (19.3)      | 672 (16.5)               | 366 (28)              |         |
| Mild                      | 2565 (47.6)      | 1994 (48.8)              | 571 (43.7)            |         |
| Moderate                  | 1005 (18.6)      | 748 (18.3)               | 257 (19.7)            |         |
| Never                     | 783 (14.5)       | 671 (16.4)               | 112 (8.6)             |         |
| Multimorbidity, n (%)     |                  |                          |                       | < 0.001 |
| No                        | 2204 (31.9)      | 1702 (33.1)              | 502 (28.6)            |         |
| Yes                       | 4699 (68.1)      | 3446 (66.9)              | 1253 (71.4)           |         |
| Arthritis, n (%)          |                  |                          |                       | < 0.001 |
| No                        | 4577 (69.5)      | 3592 (72.5)              | 985 (60.3)            |         |
| Yes                       | 2012 (30.5)      | 1364 (27.5)              | 648 (39.7)            |         |
| Obese, n (%)              |                  |                          |                       | < 0.001 |
| No                        | 4115 (59.7)      | 3190 (62.1)              | 925 (52.7)            |         |
| Yes                       | 2774 (40.3)      | 1945 (37.9)              | 829 (47.3)            |         |
| CVD, n (%)                |                  |                          |                       | < 0.001 |
| No                        | 5832 (88.4)      | 4432 (89.2)              | 1400 (85.7)           |         |
| Yes                       | 768 (11.6)       | 534 (10.8)               | 234 (14.3)            |         |
| COPD, n (%)               |                  |                          |                       | < 0.001 |
| No                        | 6397 (96.9)      | 4861 (97.9)              | 1536 (94)             |         |
| Yes                       | 203 (3.1)        | 105 (2.1)                | 98 (6)                |         |
| CKD, n (%)                |                  |                          |                       | 0.008   |
| No                        | 5307 (80.6)      | 4009 (81.3)              | 1298 (78.3)           |         |
| Yes                       | 1281 (19.4)      | 922 (18.7)               | 359 (21.7)            |         |
| Asthma, n (%)             |                  |                          |                       | < 0.001 |
| No                        | 5955 (86.3)      | 4536 (88.1)              | 1419 (80.9)           |         |

**Table 1** (continued)

| Variables                | Total (n = 6903) | No depression (n = 5148) | Depression (n = 1755) | p       |
|--------------------------|------------------|--------------------------|-----------------------|---------|
| Yes                      | 948 (13.7)       | 612 (11.9)               | 336 (19.1)            | < 0.001 |
| Stroke, n (%)            |                  |                          |                       |         |
| No                       | 6314 (95.9)      | 4788 (96.7)              | 1526 (93.4)           | 0.041   |
| Yes                      | 268 (4.1)        | 161 (3.3)                | 107 (6.6)             |         |
| Hypertension, n (%)      |                  |                          |                       | 0.826   |
| No                       | 3959 (57.4)      | 2916 (56.6)              | 1043 (59.4)           |         |
| Yes                      | 2944 (42.6)      | 2232 (43.4)              | 712 (40.6)            | 0.238   |
| Hyperlipidemia, n (%)    |                  |                          |                       |         |
| No                       | 2193 (31.8)      | 1632 (31.7)              | 561 (32)              | < 0.001 |
| Yes                      | 4709 (68.2)      | 3516 (68.3)              | 1193 (68)             |         |
| Diabetes mellitus, n (%) |                  |                          |                       | < 0.001 |
| No                       | 5623 (81.5)      | 4210 (81.8)              | 1413 (80.5)           |         |
| Yes                      | 1280 (18.5)      | 938 (18.2)               | 342 (19.5)            | < 0.001 |
| Cancer, n (%)            |                  |                          |                       |         |
| No                       | 5723 (86.7)      | 4253 (85.6)              | 1470 (90)             | < 0.001 |
| Yes                      | 877 (13.3)       | 713 (14.4)               | 164 (10)              |         |

**Table 2** Association of theobromine with depression

| Variables                 | OR [95%CI]         | P-value |
|---------------------------|--------------------|---------|
| <b>Theobromine intake</b> |                    |         |
| < 43 mg/day               | 1(Ref)             |         |
| ≥ 43 mg/day               | 1.17 (1.02 ~ 1.34) | 0.023   |
| <b>Age</b>                | 0.98 (0.98 ~ 0.98) | < 0.001 |
| <b>Sex</b>                |                    |         |
| Female                    | 1(Ref)             |         |
| Male                      | 0.79 (0.69 ~ 0.9)  | 0.001   |
| <b>Smoke</b>              |                    |         |
| Former                    | 1(Ref)             |         |
| Never                     | 0.55 (0.46 ~ 0.65) | < 0.001 |
| Now                       | 0.92 (0.75 ~ 1.13) | 0.423   |
| <b>Alcohol user</b>       |                    |         |
| Heavy                     | 1(Ref)             |         |
| Mild                      | 0.69 (0.58 ~ 0.83) | < 0.001 |
| Moderate                  | 0.74 (0.6 ~ 0.91)  | 0.004   |
| Never                     | 0.48 (0.37 ~ 0.62) | < 0.001 |
| <b>Multimorbidity</b>     |                    |         |
| No                        | 1(Ref)             |         |
| Yes                       | 1.65 (1.41 ~ 1.93) | < 0.001 |
| <b>Race</b>               |                    |         |
| Black                     | 1(Ref)             |         |
| Mexican American          | 0.83 (0.62 ~ 1.12) | 0.224   |
| White                     | 1.53 (1.26 ~ 1.85) | < 0.001 |
| Other Race                | 1.09 (0.88 ~ 1.35) | 0.429   |

in the literature such as improved neurotransmission, upregulation of brain derived neurotrophic factors and modulation of calcium and phosphodiesterase homeostasis [22]. Furthermore, experimental findings showed how theobromine is able to cross the blood brain barrier where it regulates the activity of neurotransmitter receptors, such as adenosine receptors, which have been linked to depressive and anxiety states [23, 24]. Other adenosine receptor independent effects were reported such as the reduction of cellular oxidative stress and upregulation of gene expression [PRDX1, PRDX6] [24].

Our findings contrast with previous studies reporting that increased consumption of caffeine, which is also a methylxanthine, is associated with decreased risk of depression [23, 25, 26]. Indeed, a study conducted in the United Kingdom found that unemployed individuals consuming caffeine on a regular basis were more likely to report depressive symptoms [27]. Although belonging to the same group, pharmacological differences are noted between caffeine and theobromine and may therefore explain the opposite effects on mood but also on blood pressure [24, 25]. Caffeine is metabolised to theobromine in the liver and studies conducted in the rat and in humans, show that theobromine has a higher half-life than caffeine, which is more rapidly degraded [24, 28]. Hence, it is believed that the beneficial effect of caffeine is mediated through its metabolites, such as theobromine [24, 25]. It is also hypothesised that the effects of caffeine are more CNS specific, resulting in symptoms such as alertness, while theobromine exerts its effect primarily via peripheral changes [25]. However, the differences between the two

**Table 3** Subgroup analyses

| Subgroup                     | Theobromine intake | N total | N event_ % | OR_95CI            | P value | P for interaction |
|------------------------------|--------------------|---------|------------|--------------------|---------|-------------------|
| Age: < 40 year               |                    |         |            |                    |         | 0.001             |
|                              | < 43 mg/day        | 1300    | 352 (27.1) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 755     | 263 (34.8) | 1.42 (1.17 ~ 1.72) | < 0.001 |                   |
| Age: 40-60 year              |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 1527    | 323 (21.2) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 689     | 175 (25.4) | 1.31 (1.06 ~ 1.63) | 0.012   |                   |
| Age: > 60 year               |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 1850    | 467 (25.2) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 782     | 175 (22.4) | 0.86 (0.71 ~ 1.06) | 0.153   |                   |
| Female                       |                    |         |            |                    |         | 0.145             |
|                              | < 43 mg/day        | 2528    | 682 (27)   | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 1035    | 338 (32.7) | 1.29 (1.11 ~ 1.51) | 0.001   |                   |
| Male                         |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 2149    | 460 (21.4) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 1191    | 275 (23.1) | 1.07 (0.91 ~ 1.27) | 0.408   |                   |
| PIR: high                    |                    |         |            |                    |         | 0.535             |
|                              | < 43 mg/day        | 1854    | 250 (13.5) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 780     | 109 (14)   | 1.05 (0.82 ~ 1.34) | 0.684   |                   |
| PIR:low                      |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 947     | 362 (38.2) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 550     | 236 (42.9) | 1.14 (0.92 ~ 1.42) | 0.235   |                   |
| PIR:medium                   |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 1400    | 441 (31.5) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 621     | 199 (32)   | 1.05 (0.86 ~ 1.29) | 0.633   |                   |
| Education: Below high school |                    |         |            |                    |         | 0.903             |
|                              | < 43 mg/day        | 509     | 160 (31.4) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 315     | 104 (33)   | 1.06 (0.78 ~ 1.43) | 0.707   |                   |
| Education:High school        |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 1015    | 320 (31.5) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 578     | 203 (35.1) | 1.11 (0.89 ~ 1.38) | 0.343   |                   |
| Education: College or above  |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 3151    | 661 (21)   | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 1329    | 306 (23)   | 1.12 (0.96 ~ 1.31) | 0.15    |                   |
| Smoke:former                 |                    |         |            |                    |         | 0.219             |
|                              | < 43 mg/day        | 1052    | 282 (26.8) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 518     | 162 (31.3) | 1.24 (0.98 ~ 1.56) | 0.074   |                   |
| Smoke: never                 |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 2836    | 536 (18.9) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 1241    | 263 (21.2) | 1.11 (0.94 ~ 1.31) | 0.212   |                   |
| Smoke: now                   |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 789     | 324 (41.1) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 467     | 188 (40.3) | 0.97 (0.77 ~ 1.23) | 0.83    |                   |
| Alcohol.user: heavy          |                    |         |            |                    |         | 0.522             |
|                              | < 43 mg/day        | 641     | 216 (33.7) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 397     | 150 (37.8) | 1.14 (0.87 ~ 1.48) | 0.342   |                   |
| Alcohol.user: mild           |                    |         |            |                    |         |                   |
|                              | < 43 mg/day        | 1736    | 376 (21.7) | 1(Ref)             |         |                   |
|                              | > = 43 mg/day      | 829     | 195 (23.5) | 1.1 (0.9 ~ 1.34)   | 0.35    |                   |

**Table 3** (continued)

| Subgroup               | Theobromine intake | N total | N event_%   | OR_95CI            | P value | P for interaction |
|------------------------|--------------------|---------|-------------|--------------------|---------|-------------------|
| Alcohol.user: moderate | < 43 mg/day        | 718     | 170 (23.7)  | 1(Ref)             |         |                   |
|                        | > = 43 mg/day      | 287     | 87 (30.3)   | 1.4 (1.04 ~ 1.91)  | 0.029   |                   |
| Alcohol user: never    | < 43 mg/day        | 539     | 70 (13)     | 1(Ref)             |         |                   |
|                        | > = 43 mg/day      | 244     | 42 (17.2)   | 1.39 (0.91 ~ 2.1)  | 0.124   |                   |
| Multimorbidity: no     | < 43 mg/day        | 1435    | 290 (20.2)  | 1(Ref)             |         | 0.008             |
|                        | > = 43 mg/day      | 769     | 212 (27.6)  | 1.45 (1.18 ~ 1.78) | < 0.001 |                   |
| Multimorbidity: yes    | < 43 mg/day        | 3242    | 852 (26.3)  | 1(Ref)             |         |                   |
|                        | > = 43 mg/day      | 1457    | 401 (27.5)  | 1.04 (0.91 ~ 1.2)  | 0.538   |                   |
| Arthriti: no           | < 43 mg/day        | 3109    | 628 (20.2)  | 1(Ref)             |         | 0.067             |
|                        | > = 43 mg/day      | 1468    | 357 (24.3)  | 1.25 (1.08 ~ 1.46) | 0.003   |                   |
| Arthriti: yes          | < 43 mg/day        | 1381    | 444 (32.2)  | 1(Ref)             |         |                   |
|                        | > = 43 mg/day      | 631     | 204 (32.3)  | 0.94 (0.77 ~ 1.16) | 0.581   |                   |
| Obese: no              | < 43 mg/day        | 2749    | 557 (20.3)  | 1(Ref)             |         | < 0.001           |
|                        | > = 43 mg/day      | 1366    | 368 (26.9)  | 1.42 (1.22 ~ 1.65) | < 0.001 |                   |
| Obese: yes             | < 43 mg/day        | 1922    | 584 (30.4)  | 1(Ref)             |         |                   |
|                        | > = 43 mg/day      | 852     | 245 (28.8)  | 0.91 (0.76 ~ 1.09) | 0.32    |                   |
| CVD:no                 | < 43 mg/day        | 3935    | 897 (22.8)  | 1(Ref)             |         | 0.084             |
|                        | > = 43 mg/day      | 1897    | 503 (26.5)  | 1.21 (1.07 ~ 1.38) | 0.003   |                   |
| CVD: yes               | < 43 mg/day        | 566     | 176 (31.1)  | 1(Ref)             |         |                   |
|                        | > = 43 mg/day      | 202     | 58 (28.7)   | 0.79 (0.55 ~ 1.14) | 0.208   |                   |
| COPD:no                | < 43 mg/day        | 4378    | 1015 (23.2) | 1(Ref)             |         | 0.994             |
|                        | > = 43 mg/day      | 2019    | 521 (25.8)  | 1.14 (1.01 ~ 1.28) | 0.04    |                   |
| COPD: yes              | < 43 mg/day        | 123     | 58 (47.2)   | 1(Ref)             |         |                   |
|                        | > = 43 mg/day      | 80      | 40 (50)     | 1.37 (0.74 ~ 2.54) | 0.309   |                   |
| CKD: no                | < 43 mg/day        | 3563    | 842 (23.6)  | 1(Ref)             |         | 0.157             |
|                        | > = 43 mg/day      | 1744    | 456 (26.1)  | 1.12 (0.98 ~ 1.28) | 0.092   |                   |
| CKD:yes                | < 43 mg/day        | 910     | 238 (26.2)  | 1(Ref)             |         |                   |
|                        | > = 43 mg/day      | 371     | 121 (32.6)  | 1.39 (1.06 ~ 1.81) | 0.015   |                   |
| Asthma: no             | < 43 mg/day        | 4051    | 928 (22.9)  | 1(Ref)             |         | 0.953             |
|                        | > = 43 mg/day      | 1904    | 491 (25.8)  | 1.14 (1 ~ 1.29)    | 0.047   |                   |
| Asthma: yes            | < 43 mg/day        | 626     | 214 (34.2)  | 1(Ref)             |         |                   |
|                        | > = 43 mg/day      | 322     | 122 (37.9)  | 1.21 (0.91 ~ 1.61) | 0.18    |                   |

**Table 3** (continued)

| Subgroup            | Theobromine intake | N total | N event_%  | OR_95CI            | P value | P for interaction |
|---------------------|--------------------|---------|------------|--------------------|---------|-------------------|
| Stroke: no          |                    |         |            |                    |         | 0.002             |
|                     | < 43 mg/day        | 4291    | 985 (23)   | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 2023    | 541 (26.7) | 1.21 (1.07 ~ 1.37) | 0.002   |                   |
| Stroke: yes         |                    |         |            |                    |         |                   |
|                     | < 43 mg/day        | 196     | 87 (44.4)  | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 72      | 20 (27.8)  | 0.45 (0.25 ~ 0.82) | 0.009   |                   |
| Hypertension: no    |                    |         |            |                    |         | 0.557             |
|                     | < 43 mg/day        | 2646    | 672 (25.4) | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 1313    | 371 (28.3) | 1.14 (0.98 ~ 1.32) | 0.087   |                   |
| Hypertension:yes    |                    |         |            |                    |         |                   |
|                     | < 43 mg/day        | 2031    | 470 (23.1) | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 913     | 242 (26.5) | 1.21 (1.01 ~ 1.45) | 0.04    |                   |
| Hyperlipidemia: no  |                    |         |            |                    |         | 0.26              |
|                     | < 43 mg/day        | 1440    | 362 (25.1) | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 753     | 199 (26.4) | 1.04 (0.85 ~ 1.28) | 0.672   |                   |
| Hyperlipidemia: yes |                    |         |            |                    |         |                   |
|                     | < 43 mg/day        | 3237    | 780 (24.1) | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 1472    | 413 (28.1) | 1.21 (1.05 ~ 1.39) | 0.008   |                   |
| DM: no              |                    |         |            |                    |         | 0.646             |
|                     | < 43 mg/day        | 3773    | 904 (24)   | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 1850    | 509 (27.5) | 1.17 (1.03 ~ 1.33) | 0.017   |                   |
| DM: yes             |                    |         |            |                    |         |                   |
|                     | < 43 mg/day        | 904     | 238 (26.3) | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 376     | 104 (27.7) | 1.07 (0.82 ~ 1.41) | 0.605   |                   |
| Cancer: no          |                    |         |            |                    |         | 0.029             |
|                     | < 43 mg/day        | 3901    | 954 (24.5) | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 1822    | 516 (28.3) | 1.22 (1.08 ~ 1.39) | 0.002   |                   |
| Cancer: yes         |                    |         |            |                    |         |                   |
|                     | < 43 mg/day        | 600     | 119 (19.8) | 1(Ref)             |         |                   |
|                     | > = 43 mg/day      | 277     | 45 (16.2)  | 0.73 (0.49 ~ 1.09) | 0.125   |                   |

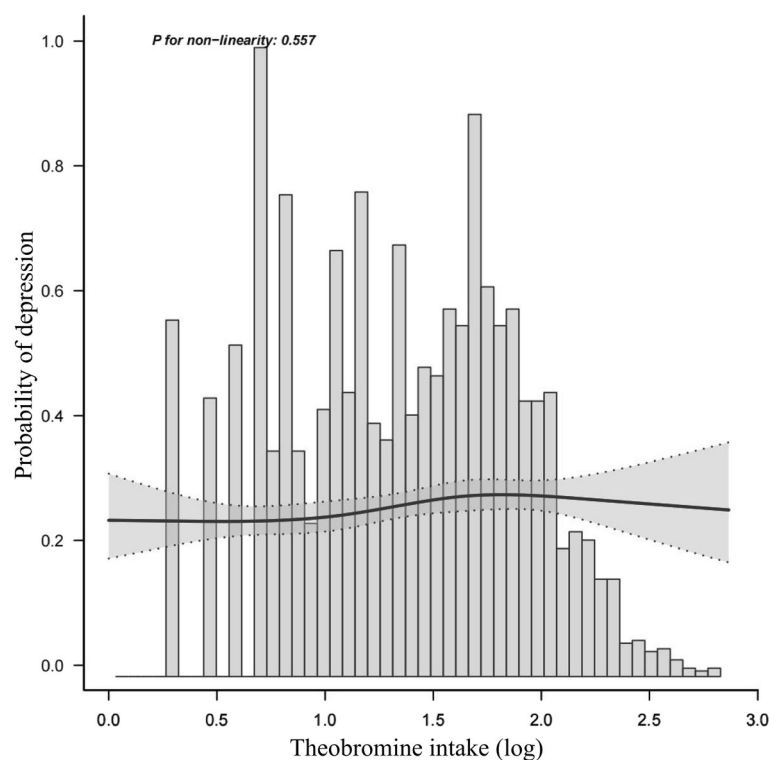
compounds, and their effect on mood stated need to be further explored.

Our subgroup analysis shows that younger participants (i.e. under 60 years old) were more likely to report depression with increased theobromine intake. Previous studies have suggested that young age during pregnancy [especially below 26 years of age] are at increased risk for anxiety and depression [29]. But the pharmacological properties of theobromine may also be affected by recall bias in the elderly, which could not be completely excluded from the questionnaire, and by the effects of oral administration of multiple drugs in the elderly population. Also, our study showed a positive association between theobromine and depressive symptoms in participants without multimorbidity. By

showing an association between theobromine consumption and depression, our study further fuels the debate on the role of nutrition in mental health care and particularly in risk groups. For example, previous studies have found polyunsaturated fatty acids (PUFAs), which may affect depression in elderly Japanese people [30].

However, some limitations remain. Due to the inability of cross-sectional observational studies to establish causality and directionality, our results should be regarded with caution. In addition, the effect of caffeine could not be investigated due to the data paucity. Furthermore, despite thorough adjustments for confounding, residual confounding cannot be ruled out. In particular, recall bias from older adults cannot be completely excluded.





**Fig. 2** Dose-response relationship between theobromine and depression

## Conclusion

Our study suggests that theobromine intake is associated with increased risk for depression in adults, highlighting the importance of nutrition on the cognitive function. Finally, further studies are needed to clarify the link between theobromine and mood states.

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## Authors' contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Availability of data and materials

The National Health and Nutrition Examination Survey (NHANES) data are publicly available at <https://www.cdc.gov/nchs/nhanes> which is publicly available. Accession number: NHANES 2017–2018.

## Declarations

## Ethics approval and consent to participate

An ethics approval and the consent to participate was not necessary.

## Consent for publication

Not applicable.

## Competing interests

No competing interests declared.

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