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Inverse association between caffeine intake and depressive symptoms in US adults: data from National Health and Nutrition Examination Survey (NHANES) 2005–2006

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ABSTRACT

The objective of this study was to examine the association between caffeine consumption and depressive symptoms. We used data from the 2005–06 National Health and Nutritional Examination Surveys (NHANES). A total of 4737 individuals aged ≥ 18 years who answered the caffeine intake and PHQ-9 questionnaires were selected for this study. Depressive symptoms were assessed using the 9-item Patient Health Questionnaire (PHQ-9) with total scores between 0 and 27. Those with PHQ-9 total scores ≥ 10 were considered as having clinically relevant depression. To investigate the association of caffeine intake and PHQ-9 scores, a multiple logistic regression was used in different models. The overall weighted prevalence of depression was 5.5% (4.3% in men and 6.6% in women). After controlling for potential confounders (age, sex, family PIR, education, marital status, disease history, sleep disorders, thyroid problems, physical activity, social support, smoking, total energy, and cholesterol, retinol, vitamin A, beta-carotene, beta-criptoxanthin, vitamin B1, iron, and phosphorus levels), a significant nonlinear inverse association between caffeine consumption and PHQ-9 scores was observed. In conclusion, caffeine's psychostimulant properties appear to protect against depressive symptoms; however, additional prospective studies are required to ascertain whether or not caffeine consumption can lead to a decrease in depressive symptoms.

1. Introduction

Depression is a chronic and recurrent condition that presents a major public health problem. The World Health Organization (WHO) has estimated that approximately 4.4% of the global population suffers from depressive disorder, and ranked depression as the single largest contributor to global disability and non-fatal health loss (WHO, 2017). Depression is the most prevalent psychiatric illness in the United States, and researchers estimate that the 12-month and lifetime prevalence of MDD was 10.4% and 20.6%, respectively (Hasin et al., 2018). Another study based on data from the U.S. National Health and Nutrition Examination Survey from 2005–2008 reported that among adults, the prevalence of depressive symptoms and severe depression was 22% and 0.6%, respectively (Shim et al., 2011). Depression is an important independent risk factor for many conditions, including coronary heart disease (CHD) (Carney and Freedland, 2017), hypertension (Gangwisch et al., 2010), diabetes (Knol et al., 2006) and suicide (Won et al., 2016). Given considerable negative impacts of depression on society and people, identifying risk factors for depression is a public health priority. It has been suggested that neurobiological, psychological, social, and genetic factors are involved in the pathogenesis of depression (Raison et al., 2006). For instance age, sex, ethnicity, family history of mood disorders, and chronic illness have been linked to the risk of depression (Sullivan et al., 2000; Kessler et al., 2003; Clarke and Currie, 2009).

Dietary is another potential modifiable factor for depression (Jacka et al., 2011), and increasing attention has been focused on the role of caffeine–one of the world's most frequently ingested psychoactive substance (Heckman et al., 2010). Approximately 85% of the US population (aged ≥ 2 years) and 73% of U.S. children are reported consuming at least one caffeinated beverage per day (Mitchell et al., 2014) and on a given day (Branum et al., 2014), respectively.

Caffeine is a substance with a bioavailability of nearly 100% being rapidly and completely absorbed in the gastrointestinal tract (Blanchard and Sawers, 1983a, 1983b) and distributed to all areas of the body. It passes through all the biological membranes (e.g., the blood-brain barrier and the placenta) owing to its sufficiently hydrophobic nature (Lachance et al., 1983; Ikeda et al., 1982). Some effects due to the intake of caffeine, includes reduced sleeping hours, accelerated aggression, headache, and increased daytime sleepiness (Kang et al., 2012; Roehrs and Roth, 2008). Although caffeine is a widely consumed substance with prominent effects on the central nervous

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system (Deslandes et al., 2005), its impact on depression is still less understood.

Several previous studies have investigated the association between caffeine intake and depression, but their findings are conflicting intake. Some studies showed a positive association (Richards and Smith, 2015; Benko et al., 2011; Whalen et al., 2008), whereas others found an inverse or lack of association (Smith, 2009; Lucas et al., 2011; Pham et al., 2014), (James et al., 1989; Ruusunen et al., 2010; Ritchie et al., 2014) in addition to and a J-shaped association (Iranpour et al., 2017). Moreover, prior research has limited sample sizes and solely addressed specific age groups or sex, or patients in clinical settings. Thus, the aim of this report was to investigate the association between caffeine intake and depressive symptoms among in a large, nationally representative sample of US adults.

2. Methods

2.1. Database and study subjects

For this cross-sectional study, we used publicly available data from the 2005–06 National Health and Nutritional Examination Surveys (NHANES). The methods and data collection procedure behind of NHANES are described in detail elsewhere (National Center for Health Statistics). Briefly, NHANES are a series of cross-sectional, complex, multi-stage surveys conducted by the Centers for Disease Control and Prevention (CDC) on nationally representative, non-institutionalized U.S. population members in order to provide health and nutrition data. Participants were first interviewed in their homes to collect background information, such as socio-demographic, medical, and family histories. They subsequently visited a mobile examination center (MEC) for the collection of other pertinent data, including anthropometric, blood pressure, laboratory measurements, and so on.

In the present study, we analyzed NHANES data including adults aged ≥ 18 years (N = 5563) collected during the 2005–2006 period. Among the 5563 subjects (2675 men and 2888 women), 4836 had complete data on depressive symptoms and 4737 had complete data on both diet and depressive symptoms. Therefore, we included 4737 subjects with complete dietary and depressive symptoms data in analyses. The ethics approval for NHANES had been obtained by the National Center for Health Statistics Research Ethics Review Board (National Center for Health Statistics, 2012).

2.2. Assessment of depressive symptoms

Depressive symptoms were assessed using the 9-item Patient Health Questionnaire (PHQ-9) depression scale, which consists of nine questions based on DSM-IV symptoms of depression. Each of the nine items is scored from 0 (not at all) to 3 (nearly every day), and Summing scores on nine items yields a total score between 0 and 27 (Kroenke et al., 2001). In this study those with PHQ-9 total scores ≥ 10 were considered as having clinically relevant depression (CRD) (Manea et al., 2012). This definition has shown both sensitivity and specificity of 88% for major depression (Kroencke et al., 2001). PHQ-9 depression scale was included as part of the computer assisted personal interview (CAPI) in MEC (National Center for Health Statistics, 2009).

2.3. Assessment of caffeine and dietary data

Data on caffeine intake (mg/day) and other nutrients and food items including protein (gm), carbohydrate (gm), dietary fiber (gm), total fat (gm), total saturated fatty acids (gm), total monounsaturated fatty acids (gm), total polyunsaturated fatty acids (gm), cholesterol (mg), retinol (mcg), vitamin A (mcg), alpha-carotene (mcg), beta-carotene (mcg), beta-cryptoxanthin (mcg), thiamin (vitamin B1) (mg), riboflavin (vitamin B2) (mg), niacin (mg), vitamin B6 (mg), total folate (mcg), folic acid (mcg), vitamin B12 (mcg), added vitamin B12 (mcg), vitamin C (mg), vitamin K (mcg), calcium (mg), phosphorus (mg), magnesium (mg), iron (mg), zinc (mg), copper (mg), selenium (mcg), alcohol (gm), and energy (kcal) was obtained from the total nutrient file, which contains summed nutrients for an individual from all foods and beverages provided on the dietary recall. Amount of vitamin D (ng/ml) was obtained from the laboratory file. Caffeine intake was calculated from fluid (coffee, tea, and soda) and food sources (chocolate) (National Center for Health Statistics). Participants were categorized based on the quartiles of caffeine intake.

2.4. Assessment of covariates

During the home interview portion of NHANES 2005–2006, an interviewer collected information about socio-demographic, lifestyle, and health-related factors using the Sample Person and Family Demographics questionnaires. Data included age, sex, education, ethnicity, marital status, family PIR (PIR = ratio of family income to poverty threshold, with a PIR value less than 1 indicating an income below the poverty threshold and a PIR greater than 1 indicating an income above the poverty threshold), sleep disorders, social support, physical activity, home status, smoking, and BMI (kg/m^2).

Histories of diseases including asthma, overweight, arthritis, congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, stroke, emphysema, chronic bronchitis, liver condition, chronic bronchitis, thyroid problems, cancer or malignancy, and prostate specific antigen (PSA) test was not normal were ascertained through the question "Has a doctor or other health professional told you that you had [diseases]?". The amount of hemoglobin (g/dl) was obtained from the laboratory file.

2.5. Statistical analysis

Statistical analysis was conducted using the SPSS version 18 (PASW Statistics for Windows, Chicago: SPSS Inc.). We used design-based $\chi 2$ test to examine the associations of categorical variables with caffeine intake (quartile) and PHQ-9 score (binary). We used Student's *t*-test and one-way analysis of variance (ANOVA) to examine statistical differences in daily average dietary factors intake across the quartiles of caffeine intake and the strata of PHQ-9 score.

After preliminary analyses, to control for possible confounding variables, a logistic regression analysis using the Enter method was performed to assess the association of caffeine intake and PHQ-9 score in different models. We used the first quartile of caffeine as the reference group.

Trend tests (*p*-value for trend) were performed by entering the caffeine intake (quartile-categorical) as continuous variable, and re-running the corresponding regression models.

Linear regression analyses were also conducted with the same variables used in the logistic regression models.

To detect effect modification, we conducted subgroup analysis and performed multiple linear regression analysis with the Enter method, investigating the association between caffeine intake and PHQ-9 scores in each category of variables and adjusting for potential confounding variables)age, sex, family PIR, education, marital status, history of disease, sleep disorders, thyroid problems, physical activity, social support, smoking, total energy, cholesterol, retinol, vitamin A, beta-caroten, betacriptoxanthin, vitamin B1, iron, phosphorus). The Wald test was used to obtain the *p*-value for interaction.

Regarding the selection of the variables for inclusion in the model, any variable that had a significant univariate test at the 0.2 level was selected as a candidate for the multivariate analysis. In the iterative process of variable selection, covariates were removed from the model if they were non-significant (at the 0.1 alpha level) and not confounders ("confounding" was evaluated as a change in any remaining parameter estimate that was greater than 15% when compared to the full model) (Bursac et al., 2008). In all analyses, sampling design complexity was

Table 1
Characteristics of participants by PHQ-9 scores and caffeine intake.

Variables		PHQ-9 score PHQ-9 score < 10 Unweighted sample size (percentage**)	PHQ-9 score ≥ 10 Unweighted sample size (percentage**)	*P*-value*	Caffeine intake(mg) Quartile 1 Unweighted sample size (percentage **)	Quartile2 Unweighted sample size (percentage **)	Quartile3 Unweighted sample size (percentage **)	Quartile 4 Unweighted sample size (percentage **)	*P*-value*
Gender	Male	2209 (49.1)	122 (38.5)	.002	309)46.6(	271)37.2(	602)42.4(	1098)54.4(	< 0.001
	Female	2322 (50.9)	183 (61.5)		425)53.4(	438)62.8(	729)57.6(	865)45.6(	
Race/Ethnicity	Mexican American	955 (7.8)	67 (9.4)	.11	161)9.3(	158)9.5(	348)11.8(	331)5.3(	< 0.001
	Other Hispanic	137 (3.2)	9 (3.4)		19)3.4(	25)3.9(	53)5.0(	47)2.4(	
	Non-Hispanic White	2212 (73.3)	124 (65.0)		217)55.7(	315)67.0(	505)62.7(	1260)82.7(	
	Non-Hispanic Black	1053 (10.8)	95 (17.2)		308)25.6(	184)14.5(	379)15.4(	246)5.0(	
	Other Race - Including Multi-Racial	174 (4.9)	10 (4.9)		29)6.0(	27)5.1(	46)5.1(	79)4.6(	
Marital Status	Married	2289 (57.1)	114 (41.1)	< 0.001	268)42.7(	373)57.0(	613)51.2(	1106)61.3(	< 0.001
	Widowed	348 (5.9)	17 (3.7)		46)5.9(	55)7.6(	105)6.1(	141)5.0(	
	Divorced	379 (9.6)	45 (17.4)		48)9.6(	47)8.3(	91)7.2(	229)11.7(	
	Separated	117 (2.1)	23 (8.3)		20)1.8(	18)1.6(	36)2.3(	62)2.6(	
	Never married	1042 (17.4)	63 (15.7)		271)28.4(	163)19.1(	369)22.8(	281)12.0(	
	Living with partner	354 (8.0)	43 (13.8)		81)11.5(	53)6.5(	117)10.3(	142)7.2(	
History of disease	Yes	2357 (59.3)	212 (78.9)	0.001	310)54.6(	371)61.6(	664)58.5(	1170)62.1(	0.02
	No	1688 (40.7)	64 (21.1)		268)45.4(	250)38.4(	492)41.5(	703)37.9(	
Education	Less than 9th grade	469 (5.9)	45 (9.3)	< 0.001	62)5.6(	81)7.7(	177)8.5(	169)4.4(	0.04
	9–11th grade	598 (10.6)	55 (16.2)		111)12.5(	93)11.3(	191)12.3(	242)9.8(	
	High School grad/GED or equivalent	955 (24.5)	75 (31.8)		133)23.1(	128)21.4(	258)23.5(	498)26.9(	
	Some college or AA degree	1161 (31.5)	82 (34.3)		170)32.0(	168)30.3(	322)31.4(	559)31.9(	
	College graduate or above	860 (27.5)	19 (8.4)		102)26.8(	150)29.1(	208)24.2(	405)26.9(	
Sleep disorders	Yes	803 (34.4)	139 (75.0)	< 0.001	133)33.7(	143)42.5(	225)34.9(	412)37.1(	0.52
	No	1749 (65.5)	49 (25.0)		280)66.3(	233)57.5(	526)65.1(	724)62.8(	
Thyroid problems	Yes	357 (9.5)	46 (19.0)	0.001	42)7.4(	68 (13.1)	105 (10.1)	182 (10.1)	0.55
	No	3680 (90.3)	230 (81.0)		536 (92.6)	551 (86.8)	1048 (89.8)	1689 (89.8)	
Anyone to help with emotional support	Yes	2300 (94.7)	158 (86.3)	.005	244 (88.7)	335 (94.5)	602 (94.0)	1221 (95.2)	0.07
	No	159 (4.6)	28 (13.7)		32 (9.6)	27 (5.2)	42 (5.0)	80 (4.3)	
	SP doesn't need help	21 (0.5)	0 (0)		3 (1.7)	1 (0.1)	6 (0.7)	11 (0.4)	
Average level of physical activity each day	Sits during the day and does not walk about very much	943 (21.7)	119 (40.7)	< 0.001	153 (21.9)	158 (22.5)	281 (23.2)	439 (22.7)	0.08
	Stand or stands or walks about a lot during the day, but does not have to carry or lift things very often	2351 (49.1)	136 (42.8)		400 (48.1)	385 (54.9)	724 (52.7)	931 (45.8)	
	Lift(s) light load or to climb stairs or hills often.	875 (20.4)	29 (9.8)		133 (21.7)	130 (18.0)	226 (16.4)	400 (21.5)	
	Heavy work or {carry/carries} heavy loads	359 (8.7)	19 (5.9)		48 (8.3)	34 (4.5)	99 (7.6)	191 (10.0)	
Home Status	Owned or being bought	2982 (73.2)	161 (56.8)	< 0.001	405 (62.6)	448 (69.7)	829 (68.4)	1407 (76.9)	0.001
	Rented	1394 (24.6)	132 (41.2)		308 (35.7)	233 (27.6)	448 (28.7)	496 (21.2)	
	Other arrangement	121 (2.2)	9 (2.0)		15 (1.7)	24 (2.5)	39 (2.9)	49 (1.9)	
Smoking status	Every day	705 (40.9)	91 (55.8)	.007	80 (40.6)	40 (18.7)	154 (39.4)	504 (45.9)	< 0.001
	Some days	131 (6.6)	16 (8.4)		18 (7.2)	14 (6.2)	43 (10.0)	68 (5.8)	
	Not at all	1062 (52.5)	63 (35.7)		101 (52.2)	161 (75.1)	268 (50.6)	575 (48.3)	
Age	18–44	2400 (50.3)	148 (45.3)	.018	497 (63.5)	388 (49.7)	772 (56.7)	846 (44.3)	< 0.001
	45–69	1442 (38.3)	126 (47.4)		180 (29.4)	164 (28.7)	373 (32.5)	821 (46.2)	
	≥70	689 (11.4)	31 (7.3)		57 (7.2)	157 (21.6)	186 (10.8)	296 (9.6)	
Family PIR	< 100%)	811 (10.5)	105 (29.0)	< 0.001	187 (16.7)	146 (14.2)	270 (13.0)	285 (8.8)	< 0.001

(*continued on next page*)

Table 1 (*continued*)

Variables		PHQ-9 score PHQ-9 score < 10 Unweighted sample size (percentage**)	PHQ-9 score ≥ 10 Unweighted sample size (percentage**)	*P*-value*	Caffeine intake(mg) Quartile 1 Unweighted sample size (percentage **)	Quartile2 Unweighted sample size (percentage **)	Quartile3 Unweighted sample size (percentage **)	Quartile 4 Unweighted sample size (percentage **)	*P*-value*
	Between 101% and 200%	1054 (19.1)	84 (26.5)		170 (21.4)	179 (22.8)	327 (22.3)	433 (16.8)	
	Above 201%	2464 (70.4)	102 (44.5)		348 (61.9)	350 (63.0)	668 (64.7)	1168 (74.4)	
BMI (kg/m**2)	< 20	247 (5.6)	16 (3.7)	.06	46 (5.8)	45 (6.3)	68 (5.1)	91 (5.3)	0.12
	20 to < 25	1216 (28.2)	81 (27.8)		194 (29.4)	202 (30.2)	377 (31.4)	497 (25.9)	
	25 to < 30	1527 (33.0)	76 (24.2)		212 (29.2)	252 (32.9)	414 (29.2)	702 (34.9)	
	≥ 30	1497 (33.2)	126 (44.3)		273 (35.6)	206 (30.6)	456 (34.3)	657 (33.9)	
Hemoglobin (g/dL)	< 12	321)4.5(	30)5.9(	.25	70 (5.6)	77 (7.6)	110 (6.0)	83 (2.7)	< 0.001
	≥ 12	4030)95.5(	263)94.1(		633 (94.4)	596 (92.4)	1159 (94.0)	1830 (97.3)	

* *P*-value was based on design-based χ2 test.
** weighted percentage

taken into account by specifying primary sampling units (PSUs), strata, and weights using the complex samples module in SPSS. We used two year MEC exam weights for all sample estimations, and masked variance units to estimate variances (Johnson et al., 2013; Vallance et al., 2011; Loprinzi and Cardinal, 2011). Statistical significance level was set at $p < 0.05$.

3. Results

The overall weighted prevalence of depression overall was 5.5%, with 4.3% and 6.6% being in men and women, respectively. Characteristics of the study subjects according to PHQ-9 scores and caffeine intake are presented in Table 1.

There were statistically significant differences in socio-demographic, lifestyle, and health-related factors between the low (< 10) and high (≥ 10) PHQ-9 score group ($p < 0.05$, with exception of race/ethnicity and hemoglobin ($p = 0.11$, $p = 0.25$, respectively). Except for thyroid problems, sleep disorders, and BMI ($p = 0.55$, $p = 0.52$, and $p = 0.12$, respectively), statistically significant differences were found for caffeine intake levels regarding socio-demographic, lifestyle and health-related factors ($p < 0.05$).

The associations of certain nutrients intake with PHQ-9 score are shown in Table 2. Except for carbohydrate, total saturated fatty acids, and beta-cryptoxanthin ($p = 0.06$, $p = 0.17$, and $p = 0.17$, respectively), intakes of most macro- and micronutrient were significantly different intake between the low and high PHQ-9 score group.

Approximately intakes of two-thirds of studied nutrients were significantly different across caffeine intake levels, while a lack of difference was observed for others namely intakes of dietary fiber, beta-carotene, total folate, folic acid, vitamin B12, added vitamin B12, vitamin K, calcium, iron, zinc, and copper.

Results of multivariable logistic regression analyses of caffeine intakes (quartile) in relation to PHQ scores (binary) are displayed in Table 3. There was no significant association between caffeine intake and PHQ-9 score in non-adjusted model and model 1 (adjusted for age, sex, family PIR, education, marital status). (Table 4)

In Model 2 (adjusted for Model 1 plus history of disease, sleep disorders, thyroid problems, physical activity, social support, smoking) and Model 3 (adjusted for Model 2 plus total energy, cholesterol, retinol, vitamin A, beta-caroten, betacriptoxanthin, vitamin B1, iron, phosphorus), there was a significant inverse association between caffeine intake and PHQ-9 score in every quartile of caffeine.

Similar results were found from linear regression analyses. while neither non-adjusted model nor model 1 found no significant association between caffeine intake and PHQ-9 scores ($\beta = -0.09$, CI: -0.24 –0.05, $p = 0.20$ and $\beta = -0.002$, CI: -0.17 –0.16, $p = 0.98$, respectively), model 2 and model 3 indicated statistically inverse associations ($\beta = -0.37$, CI: $-0.72-0.02$, $p = 0.03$ and $\beta = -0.36$, CI: -0.74–0.01, $p = 0.05$, respectively).

In subgroup analyses, statistically significant interactions were noted between caffeine intake and thyroid problems, social support, and age in relation to depressive symptoms ($p = 0.04$, $p = 0.002$, $p = 0.03$, respectively), despite the lack of interaction for other variables.

4. Discussion

In a large cross-sectional study of US adults, the prevalence of depressive symptoms was higher among women than among men. In this study, we found an inverse association between caffeine intake and the PHQ-9 score. Such an association appeared to be modified by thyroid problems, social support, and age.

Our finding of inverse association between habitual caffeine intake and depressive symptoms is consistent with the literature. In a large prospective cohort study conducted in the U.S., the risk of clinical depression (physician-diagnosed depression and antidepressant use)

Table 2
Dietary intakes according to PHQ-9 scores and caffeine intake

Nutrients	PHQ-9 score PHQ-9 < 10 Mean ± SD	PHQ-9 ≥ 10 Mean ± SD	*P*-value[a]	caffeine intake(mg) Quartile 1 Mean ± SD	Quartile2 Mean ± SD	Quartile3 Mean ± SD	Quartile 4 Mean ± SD	*P*-value[b]
Vitamin D (ng/mL)	21.99 ± 0.466	19.60 ± 0.846	0.004	20.2 ± 0.9	21.8 ± 0.6	21.2 ± 0.5	22.5 ± 0.4	0.01
Energy (kcal)	2249.1 ± 28.7	2057.3 ± 101.0	0.050	2033.8 ± 42.5	2084.6 ± 64.5	2121.3 ± 45.1	2371.7 ± 39.1	<0.001
Protein (gm)	86.1 ± 0.9	73.5 ± 3.7	0.002	80.6 ± 1.9	80.7 ± 2.7	82.2 ± 2.08	89.1 ± 1.2	.004
Carbohydrate (gm)	268.2 ± 3.5	248.6 ± 11.2	0.06	241.8 ± 6.2	258.8 ± 8.1	257.1 ± 4.7	279.1 ± 4.4	<0.001
Dietary fiber (gm)	15.8 ± 0.2	13.1 ± 0.6	0.002	14.8 ± 0.6	16.6 ± 0.4	14.8 ± 0.4	16.0 ± 0.2	0.06
Total fat (gm)	85.7 ± 1.5	76.0 ± 4.3	0.03	76.4 ± 2.5	77.9 ± 2.6	78.8 ± 1.9	91.6 ± 1.8	<0.001
Total saturated fatty acids (gm)	28.6 ± 0.5	26.1 ± 1.8	0.17	25.2 ± 1.02	26.4 ± 0.7	26.5 ± 0.6	30.5 ± 0.6	<0.001
Total monounsaturated fatty acids (gm)	31.6 ± 0.5	28.1 ± 1.4	0.02	27.9 ± 0.8	28.4 ± 1.07	29.3 ± 0.7	33.7 ± 0.6	<0.001
Total polyunsaturated fatty acids (gm)	18.1 ± 0.3	15.3 ± 0.7	0.004	16.5 ± 0.5	16.3 ± 0.6	16.2 ± 0.4	19.4 ± 0.4	<0.001
Cholesterol (mg)	297.7 ± 3.7	266.7 ± 15.2	0.04	281.2 ± 10.0	282.2 ± 11.5	277.4 ± 7.6	310.8 ± 6.9	0.04
Retinol (mcg)	449.1 ± 11.1	352.7 ± 35.7	0.01	415.5 ± 31.7	497.4 ± 22.3	399.8 ± 13.7	457.7 ± 15.2	0.006
Vitamin A, RAE (mcg)	628.8 ± 11.4	470.0 ± 39.0	0.001	602.3 ± 43.5	703.1 ± 33.7	565.8 ± 19.7	629.6 ± 14.5	0.01
Alpha-carotene (mcg)	367.6 ± 20.0	238.4 ± 33.6	0.002	399.6 ± 49.9	420.04 ± 72.7	305.04 ± 30.7	364.01 ± 20.1	0.10
Beta-carotene (mcg)	1905.5 ± 51.7	1233.6 ± 134.4	<0.001	1956.9 ± 164.9	2182.5 ± 238.8	1773.2 ± 139.8	1821.6 ± 58.5	0.51
Beta-cryptoxanthin (mcg)	130.6 ± 5.0	103.2 ± 20.0	0.17	169.7 ± 16.2	149.2 ± 7.9	127.3 ± 9.2	116.7 ± 7.7	0.03
Thiamin (Vitamin B1) (mg)	1.7 ± .02	1.4 ± 0.07	<0.001	1.6 ± 0.09	1.6 ± 0.04	1.5 ± 0.03	1.7 ± 0.03	0.01
Riboflavin (Vitamin B2) (mg)	2.3 ± 0.03	1.9 ± 0.1	0.006	2.04 ± 0.09	2.1 ± 0.06	1.9 ± 0.04	2.5 ± 0.03	<0.001
Niacin (mg)	26.2 ± 0.3	22.1 ± 1.1	0.002	23.4 ± 0.6	24.1 ± 0.9	24.4 ± 0.6	27.7 ± 0.5	0.001
Vitamin B6 (mg)	2.06 ± 0.03	1.6 ± 0.09	0.001	1.9 ± 0.08	2.04 ± 0.08	1.9 ± 0.04	2.1 ± 0.04	0.02
Total folate (mcg)	416.6 ± 5.4	339.05 ± 18.1	<0.001	389.2 ± 11.5	426.2 ± 18.2	391.1 ± 11.3	424.02 ± 7.9	0.08
Folic acid (mcg)	197.6 ± 4.3	146.1 ± 7.1	<0.001	179.8 ± 8.1	212.8 ± 10.6	196.3 ± 10.04	193.2 ± 5.1	0.12
Vitamin B12 (mcg)	5.6 ± 0.1	4.5 ± 0.3	0.01	5.4 ± 0.3	5.6 ± 0.2	5.4 ± 0.2	5.7 ± 0.1	0.47
Added vitamin B12 (mcg)	1.04 ± 0.05	0.58 ± 0.09	0.001	0.9 ± 0.1	1.2 ± 0.1	0.9 ± 0.09	1.01 ± 0.06	0.33
Vitamin C (mg)	87.4 ± 1.8	71.4 ± 8.03	0.04	112.0 ± 5.2	104.2 ± 6.2	81.8 ± 3.4	79.2 ± 2.9	<0.001
Vitamin K (mcg)	97.9 ± 2.7	77.08 ± 77.08	0.01	98.8 ± 6.5	106.03 ± 11.8	90.8 ± 5.5	96.8 ± 2.4	0.50
Calcium (mg)	965.2 ± 16.3	811.3 ± 56.1	0.008	1001.9 ± 46.8	990.3 ± 35.6	910.1 ± 22.8	960.9 ± 24.01	0.30
Phosphorus (mg)	1378.9 ± 16.5	1173.6 ± 58.4	0.001	1307.4 ± 44.7	1315.6 ± 36.9	1295.5 ± 27.8	1425.7 ± 21.7	0.006
Magnesium (mg)	305.3 ± 3.1	256.4 ± 12.9	0.001	280.6 ± 8.5	299.3 ± 8.1	274.5 ± 6.0	321.05 ± 5.09	<0.001
Iron (mg)	16.4 ± 0.1	13.2 ± 0.4	<0.001	15.1 ± 0.4	16.8 ± 0.6	15.7 ± 0.3	16.6 ± 0.2	0.06
Zinc (mg)	13.05 ± 0.2	10.7 ± 0.4	0.003	12.7 ± 1.2	12.2 ± 0.3	12.9 ± 0.8	13.1 ± 0.2	0.48
Copper (mg)	1.4 ± 0.01	1.1 ± 0.05	<0.001	1.3 ± 0.06	1.4 ± 0.05	1.3 ± 0.04	1.4 ± 0.02	0.14
Selenium (mcg)	113.9 ± 1.5	94.08 ± 5.1	0.001	107.7 ± 2.8	106.7 ± 3.6	109.5 ± 3.2	116.8 ± 1.7	0.02

[a] *P*-value was based on *t*-test
[b] *P*-value was based on ANOVA test
-Sampling design complexity is taken into account in all analyses.

decreased in a dose-dependent manner with increasing caffeine intake (Lucas et al., 2011). Such a study also reported depression was only associated with caffeinated coffee, not decaffeinated coffee, suggesting that caffeine–a major compound in coffee (Rodrigues and Bragagnolo, 2013)–may be a potentially beneficial contributor. The inverse association between caffeine intake and depression was also evident in some cross-sectional studies in other populations (Smith, 2009; Pham et al., 2014). The UK study of non-working participants has shown caffeine intake from daily caffeinated drinks without including caffeine from other sources (e.g. chocolate or medication) was associated with a reduced risk of depression (Smith, 2009). In that study, either caffeine intake from coffee or tea beverages exhibited similar results. Likewise, Pham et al. 2014 found Japanese men and women with higher caffeine intake (estimated from caffeine contents in green tea and coffee) had a lower prevalence of depressive symptoms assessed by the Japanese version of the Center for Epidemiologic Studies Depression (CES-D). Moreover, a recent systematic review and meta-analysis of fifteen observational studies, there was an inverse association between coffee or tea (the common sources of caffeine) intake and the risk of depression (Kang et al., 2018).

However, some previous studies reported conflicting results. For example, in a cross-sectional study of 2307 secondary school children aged 11–17 years, there was a positive significant association between total weekly caffeine intake (estimated from coffee, tea, energy drinks,

Table 3
Logistic regression analyses of association between caffeine intake and depressive symptoms.

Models	Caffeine intake Quartile 1 Reference	Quartile 2 OR (95% CI)	Quartile 3 OR (95% CI)	Quartile 4 OR (95% CI)	*P* for trend
Crude	1	0.65 (0.31–1.39)	0.86 (0.44–1.69)	0.69 (0.38–1.27)	0.26
Model 1	1	0.66 (0.28–1.53)	0.87 (0.44–1.71)	0.78 (0.40–1.52)	0.65
Model 2	1	0.41 (0.19–0.90)	0.49 (0.25–0.95)	0.25 (0.09–0.72)	0.04
Model 3	1	0.37 (0.14–0.97)	0.41 (0.19–0.88)	0.23 (0.06–0.80)	0.07

Model 1: Adjusted for age, sex, family PIR, education, and marital status.
Model 2: Adjusted for Model 1 plus history of disease, sleep disorders, thyroid problems, physical activity, social support, and smoking.
Model 3: Adjusted for Model 2 plus total energy, cholesterol, retinol, vitamin A, beta-caroten, betacriptoxanthin, vitamin B1, iron, and phosphorus.
-Sampling design complexity is taken into account in all analyses.

Table 4
Multiple linear regression analyses of association between caffeine intake and PHQ-9 scores stratified by selected factors.

Variable		Coefficient (Beta)	*P*-value	*P* interaction
Gender	male	0.00	0.75	0.25
	female	−0.002	0.17	
Race/Ethnicity	Mexican American	0.00	0.88	0.76
	Other Race - Including Multi-Racial + Other Hispanic	0.001	0.64	
	Non-Hispanic White	0.00	0.72	
	Non-Hispanic Black	−0.001	0.59	
Marital Status	Married	−0.001	0.21	0.05
	Widowed	−0.004	<0.001	
	Divorced	−0.001	0.46	
	Separated	0.019	0.002	
	Never married	0.00	0.91	
	Living with partner	0.001	0.67	
History of disease	Yes	−0.001	0.31	0.70
	No	0.00	0.87	
education	Less than 9th grade	0.001	0.45	0.16
	9–11th grade	−0.001	0.67	
	High School grad/GED or equivalent	0.002	0.10	
	Some college or AA degree	−0.001	0.16	
	College graduate or above	−0.001	0.55	
Sleep disorders	Yes	−0.002	0.03	0.36
	No	0.000	0.80	
thyroid problems	Yes	−0.004	0.05	0.04
	No	0.000	0.71	
Anyone to help with emotional support	Yes	−0.001	0.29	0.002
	No	−0.004	0.02	
Average level of physical activity each day	Sits during the day and does not walk about very much	−0.003	0.26	0.68
	Stands or walks about a lot during the day, but does not have to carry or lift things very often	0.00	0.56	
	Lift(s) light load or to climb stairs or hills often.	0.00	0.49	
	Heavy work or {carry/carries} heavy loads	0.006	0.01	
Home status	Owned or being bought	−0.001	0.11	0.75
	Rented + Other arrangement	0.00	0.76	
Smoking status	Every day	−0.001	0.41	0.31
	Some days	−0.015	0.003	
	Not at all	−0.001	0.33	
Age	18–44	0.001	0.42	0.03
	45–69	−0.001	0.15	
	≥70	−0.002	0.04	
Family PIR	<100%)	0.003	0.02	0.53
	between 101% and 200%	−0.002	0.13	
	above 201%	−0.001	0.15	
BMI (kg/m**2)	<20	−0.001	0.69	0.81
	20 to < 25	−0.001	0.17	
	25 to < 30	−0.001	0.44	
	≥30	−0.001	0.47	
Hemoglobin (g/dL)	<12	0.032	<0.001	0.15
	≥12	−0.001	0.21	

Each analysis adjusted for age, sex, family PIR, education, marital status, history of disease, sleep disorders, thyroid problems, physical activity, social support, smoking, total energy, cholesterol, retinol, vitamin A, beta-caroten, betacriptoxanthin, vitamin B1, iron, phosphorus.
-Sampling design complexity is taken into account in all analyses.

and cola) and depression in both males and females (Richards and Smith, 2015). Depression in such study was ascertained by inquiring participants about their frequency of experiencing depressive moods over the previous 6 months on a five-point scale (1 = not at all, 2 = rarely, 3 = sometimes, 4 = frequently, 5 = very frequently).

Another study with a correlational nature of the data conducted on 51 children, aged 9–12 years, also found a unfavorable association between caffeine intake and depressive symptoms, measured using the Children's Depression Inventory (CDI) (Benko et al., 2011). Moreover, a small study comprising participants aged from7–17 years with 30 major depressive disorder (MDD) cases and 23 healthy controls found depressed children consumed more caffeine than their healthy counterparts at baseline (Whalen et al., 2008). MDD in that study was determined using the Schedule for Affective Disorders and Schizophrenia in School-Age Children-Present and Lifetime version through an interview.

The discrepancy between our study and previous ones (Richards and Smith, 2015; Benko et al., 2011; Whalen et al., 2008) regarding the association between habitual caffeine intake and depressive symptoms is not clear, but may partly be related to the age difference between the populations. Indeed, we noted a significant qualitative interaction between caffeine intake and age for depressive symptoms. For each 1 mg increment in caffeine intake, the multivariable beta for depressive symptoms was 0.001 for those aged 18–44 years, −0.001 for those 45–69 years and −0.002 for those ≥ 70 years. However, because of very small effect sizes observed between the age groups as well as presence or absence of thyroid problems and social support, further studies are required to clarify this issue before possible explanations for statistical or biological interaction can be made. Another possibility for discrepancy is difference in measurement tools and definition of outcome (depression), as well as dose of caffeine intake and characteristics of study population.

One possible mechanism is antagonist action of caffeine on the adenosine receptor (Fredholm et al., 1999), which occurs at levels of caffeine that normally consumed in the diet (Fredholm, 1995). This function leads to very important secondary effects on neurotransmitters, including serotonin, noradrenaline, acetylcholine, dopamine, glutamate, and GABA (Fredholm et al., 1999). In addition, experimental studies demonstrated that caffeine increased the release of serotonin (Okada et al., 1999; Yokogoshi et al., 1987) and dopamine (Borycz et al., 2007; Okada et al., 1997), suggesting that caffeine can enhance the serotonergic system. Meanwhile, reduced activity of serotonergic system plays a central role in depression, and antidepressant drugs increases the serotonergic activity (Willner, 1985).

4.1. Strength

A major strength of our study is a large sample size that represents the general U.S adult population. In addition, a wide range of potential confounders including nutrients were adequately adjusted to ensure an independent association between caffeine intake and depressive symptoms.

4.2. Limitations

Results of our study should be interpreted with caution due to some limitations. First, a cross-sectional study does not necessarily indicate causality. Therefore, the possibility of reverse-causation or bidirectionality cannot be disregarded. Second, random measurement errors may not be avoidable because we used the first day of dietary recall only, in which intra individual variation was not taken into account. However, when dietary intake is assessed from a large sample, random errors normally negate each other (National Center for Health Statistics, 2018).

Third, we used a PHQ-9 score of 10 or greater as the threshold to define depression. Although the PHQ-9 is an established and validated tool for assessing depression (sensitivity and specificity of 88% (Kroenke and Spitzer, 2002), some people may receive a different diagnosis as compared to examination by a mental health professional. Fourth, Instead of using concentrations of caffeine in the blood obtained from laboratory methods, we estimated the amount of caffeine based on nutrient files. This may not have captured actual intakes of caffeine precisely, though dietary data obtained from non-laboratory methods are well suited to large-scale epidemiological surveys.

5. Conclusions

There was a significant inverse association between caffeine intake and depressive symptoms. The caffeine's psychostimulant properties appear to protect against depressive symptoms; however, further prospective studies are required to elucidate whether or not increasing caffeine intake can reduce the risk of depression.

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Competing interests

The authors declare that they have no competing interests.

Author disclosures

The authors have nothing to disclose.

Conflict of interest

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Supplementary material

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