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The effect of serum calcium on the association of depression with infertility among U.S. women

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ABSTRACT

This study aimed to explored the association between depressive symptoms and infertility among U.S. women, and the effect of serum calcium on this association. We used data from the National Health and Nutrition Examination Survey (2013–2018), relating to women aged 20–45 years. Depressive symptoms were determined using the nine-item Patient Health Questionnaire (PHQ-9 scores ≥10), and interview data were used to identify self-reported infertility. Of 2708 women (mean age: 32.7 ± 7.5 years), 274 were depressed and 12.0 % self-reported being "ever-infertile." Depressive symptoms were associated with infertility in multivariable logistic regression (OR, 1.62; 95 % CI, 1.11–2.38). Depressive symptoms were associated with infertility among participants who were obese (OR, 1.68; 95 % CI, 1.03–2.74), had not received psychological counseling (OR, 1.60; 95 % CI, 1.03–2.50), were antidepressant users (OR 3.22; 95 % CI, 1.15–9.00), and had high serum calcium levels (OR, 2.05; 95 % CI, 1.25–3.35). A significant interaction between serum calcium and depression was observed for infertility (P = .038, interaction likelihood ratio test). In sensitivity analyses, the association between depressive symptoms and infertility remained after excluding women aged ≥35 years (OR, 1.87; 95 % CI, 1.08–3.23), lowering the cut-off for PHQ-9 scores (≥5) (OR, 1.48; 95 % CI, 1.12–1.96), excluding women with some gynecological diseases (OR, 1.63; 95 % CI, 1.07–2.49), and using inverse probability of treatment weighting (OR, 1.64; 95 % CI, 1.17–2.31).

Conclusion: Our findings indicate that depression is associated with infertility among U.S. women and serum calcium may have an effect on the association. Interventions such as serum calcium reduction, weight management and psychosocial counseling for infertility treatment in individuals with depression may be integrated into routine clinical practice. Additionally, more caution could be exercised when using antidepressants.

1. Introduction

Depression affects about 8 % of the U.S. population [1]. In 2009, the estimated cost of treatment for depression in the United States

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was $22.8 billion, with an additional cost of approximately $23 billion in lost productivity [2]. The definition of depression is based on symptoms forming a syndrome and causing functional impairment. Diagnostic and Statistical Manual of Mental Disorders(DSM) and International Classification of Diseases (ICD) are two main classificatory diagnostic systems, which are widely used in hospital [3]. There are several depression screening methods reported in studies, such as "NIH Patient Reported Outcome Measurement Information System (PROMIS) screening tool","Self-Rating Depression Scale", and the nine-item Patient Health Questionnaire (PHQ-9). PHQ-9 is widely used in large sample epidemiological investigation and its sensitivity and specificity of definition for depression were both reported to be 88 % [4].

Depression is closely related to many diseases such as type 2 diabetes mellitus [5], dementia [6], irritable bowel syndrome [7], osteoporosis [8], Parkinson's disease [9], and cancer [10]. Women are more likely than men to experience depression [11]. Nonetheless, whether mental illnesses, including depression, cause infertility remains debatable. Depression was associated with a reduced live birth rate in a cohort of 42,880 women undergoing assisted reproductive technologies (ARTs) [12]. Similarly, Nillni et al. found that depressive symptoms were negatively associated with incidence of pregnancy [13]. However, previous studies disagreed with the conclusion. A study of 202 women treated with *in vitro* fertilization found no difference in the live birth rate in individuals with depression [14]. Casilla-Lennon et al. found that depressive symptoms in female participants had no negative impact on infertility treatment outcomes [15], and a meta-analysis found that pre-ART depression was not associated with clinical pregnancy rates [16]. However, previous research has largely focused on participants visiting hospitals for treatment, and the generalizability of these findings about the association of depression and infertility may be approached cautiously. Besides, the contradictory result also could be attributed to the failure to account for other potential covariates, such as nutrients.

Previous animal and human studies have suggested a link between nutrition and female fertility [17]. Nutrition is important for the success of ART in women [18]. Diet is recommended to treat infertility caused by polycystic ovary syndrome [19]. Furthermore, the recommendations of the International Federation of Gynecology and Obstetrics on pre-pregnancy and maternal nutrition suggest some nutrients including calcium should be considered [20]. Calcium is considered an important macro element in female reproduction because it plays an essential role in estrogen synthesis, meiotic cell cycles of oocytes, and ovarian ovulation [21]. Additionally, calcium has been reported to correlate with depression in female adults [22]. However, to the best of our knowledge, no studies have reported the role of calcium in the relationship between depression and infertility.

Therefore, this study aimed to (1) explore the association between depression and infertility among U.S. women; and (2) investigate how serum calcium may influence this association.

2. Materials and methods

2.1. Data sources

This study used the dataset from the National Health and Nutrition Examination Survey (NHANES) and considering the effect of the coronavirus disease pandemic, this analysis included continuous public data from cycles (2013–2018). NHANES includes adults and children, ranging in age from 0 to 80 years. Briefly, Centers for Disease Control and Prevention (CDC) and National Center for Health Statistics (NCHS) used complex, multistage, stratified methods to obtain nationally representative sample for the United States population. NHANES covers a wide variety of variables, which mainly related to demographic, laboratory, dietary, examination as well as important questionnaire data. These questionnaire variables were conducted by trained professionals during the process of both in-home and mobile examination center (MEC) interview. The NCHS research ethics review board approved the NHANES study protocol. The original protocol is provided, along with further details, at https://www.cdc.gov/nchs/nhanes/irba98.htm. Participants in this study provided written informed consent when enrolled. Data were analyzed between April and October 2022.

2.2. Study design and population

Three 2-year NHANES cycles were used to determine the study population (2013–2014, 2015–2016, and 2017–2018). We included only women aged 20–45 years in this cross-sectional study to limit our analysis to infertile participants [23]. Participants were excluded from the analysis if any of the following data were missing: infertility (no, yes), depression (non-depressed, depressed), serum calcium, psychological counseling (no, yes), antidepressant use (no, yes), age, race/ethnicity (non-Hispanic white, Mexican–American, non-Hispanic black, other Hispanics, other races), marital status (married or lives with partner, lives alone), family income, educational status (college graduate or above, high school graduate, did not graduate from high school), body mass index (BMI), work activity (light, moderate, vigorous), smoking status (current smokers, former smokers, never smokers), alcohol consumption, and dietary intake. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

2.3. Diagnosis of depression and infertility

PHQ-9 was used to assess depression, which included items related to depressive symptoms [24]. Each of these nine items was divided into four categories, with the score for each item ranging from 0 to 3, and the final score was between 0 and 27 [24]. Participants with an overall PHQ-9 score of $\geq$10 were defined as depressed [4]. In mobile examination centers, the PHQ-9 scale was used as part of a computer-assisted personal interview (NCHS, 2009). Infertility was defined according to participant response to the question in the questionnaire (Have you ever tried and failed to become pregnant for at least 1 year?). After excluding the missing responses, the response was a dichotomous variable (yes = ever-infertile, no = fertile) [25].

Table 1
Baseline characteristics of the study sample.

Characteristic	Total (n = 2708)	No Depression (n = 2434)	Depression[a] (n = 274)	P value
Demographic Variables				
Age, (years), Mean ± SD	32.7 ± 7.5	32.7 ± 7.5	33.0 ± 7.8	0.568
Race, n (%)				0.002
Non-Hispanic White	952 (35.2)	835 (34.3)	117 (42.7)	
Non-Hispanic Black	568 (21.0)	500 (20.5)	68 (24.8)	
Mexican American	450 (16.6)	416 (17.1)	34 (12.4)	
Other Hispanic	268 (9.9)	244 (10)	24 (8.8)	
Other Race	470 (17.4)	439 (18)	31 (11.3)	
Education_level, n (%)				<0.001
Did not graduate from high school	405 (15.0)	344 (14.1)	61 (22.3)	
Graduated from high school	517 (19.1)	453 (18.6)	64 (23.4)	
College education or above	1786 (66.0)	1637 (67.3)	149 (54.4)	
Marital-status, n (%)[b]				<0.001
Married or live with partner	1591 (58.8)	1467 (60.3)	124 (45.3)	
Live alone	1117 (41.2)	967 (39.7)	150 (54.7)	
BMI, (kg/m2), n (%)				0.009
Underweight–normal	907 (33.5)	837 (34.4)	70 (25.5)	
Overweight	651 (24.0)	583 (24)	68 (24.8)	
Obese	1150 (42.5)	1014 (41.7)	136 (49.6)	
Poverty income ratio, Median (IQR)	1.9 (1.0, 3.7)	2.0 (1.0, 3.7)	1.2 (0.7, 2.5)	<0.001
Dietary Variables[c]				
Magnesium, (mg) Median (IQR)	247.0 (178.0, 332.0)	250.0 (182.0, 335.0)	221.0 (149.2, 312.8)	<0.001
Energy, (kcal) Median (IQR)	1853.0 (1384.0, 2368.0)	1862.0 (1388.0, 2366.0)	1790.0 (1264.0, 2382.0)	0.213
Protein, (gm) Median (IQR)	67.6 (49.2, 91.9)	68.2 (50.5, 92.2)	60.2 (41.4, 87.5)	<0.001
Folat, (mcg) Median (IQR)	308.0 (205.0, 446.0)	312.0 (213.0, 448.0)	268.5 (159.2, 419.5)	<0.001
Fiber, (gm) Median (IQR)	13.4 (8.7, 19.7)	13.7 (8.9, 19.9)	11.2 (6.1, 18.0)	<0.001
Calcium, (mg) Median (IQR)	787.0 (510.0, 1117.0)	792.0 (517.0, 1121.0)	701.0 (450.2, 1054.0)	0.006
Vitamin D, (mcg) Median (IQR)	2.6 (0.9, 5.2)	2.7 (0.9, 5.3)	2.0 (0.6, 4.4)	0.005
Vitamin A, (mcg) Median (IQR)	435.0 (233.8, 721.0)	446.5 (238.5, 724.8)	340.5 (180.0, 613.0)	<0.001
Vitamin C, (mg) Median (IQR)	45.2 (18.8, 104.7)	47.0 (19.6, 107.2)	28.4 (11.2, 75.4)	<0.001
Vitamin E, (mg) Median (IQR)	6.9 (4.5, 10.5)	7.0 (4.7, 10.6)	6.1 (3.3, 9.4)	<0.001
Lycopene, (mcg) Median (IQR)	1747.0 (14.8, 5206.0)	1754.0 (26.0, 5307.0)	1590.0 (0.0, 4567.0)	0.076
Selenium, (mcg) Median (IQR)	94.8 (67.9, 129.7)	96.1 (69.1, 129.9)	84.8 (52.7, 128.2)	<0.001
Zinc, (mg) Median (IQR)	8.7 (6.0, 12.0)	8.8 (6.1, 12.0)	7.7 (4.8, 11.4)	<0.001
Caffeine, (mg) Median (IQR)	71.0 (5.0, 151.0)	72.0 (5.0, 150.0)	67.0 (3.0, 161.0)	0.769
Copper, (mg) Median (IQR)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)	0.8 (0.6, 1.2)	<0.001
Iron, (mg) Median (IQR)	11.1 (7.8, 15.3)	11.3 (8.0, 15.4)	9.5 (6.2, 14.6)	<0.001
Beta-carotene, (mcg) Median (IQR)	700.5 (262.8, 2183.0)	728.5 (276.0, 2272.0)	456.5 (184.2, 1666.0)	<0.001
Vitamin K, (mcg) Median (IQR)	67.7 (37.1, 133.8)	69.9 (38.3, 138.2)	50.6 (25.9, 103.6)	<0.001
Niacin, (mg) Median (IQR)	20.4 (14.2, 27.9)	20.5 (14.3, 27.8)	19.0 (11.9, 28.6)	0.016
Beta-cryptoxanthin, (mcg) Median (IQR)	25.0 (7.0, 80.0)	26.0 (7.0, 83.0)	17.5 (3.2, 55.5)	<0.001
Lutein-zeaxanthin, (mcg) Median (IQR)	687.5 (315.0, 1436.0)	708.5 (330.2, 1465.0)	520.0 (200.5, 1070.0)	<0.001
Sodium, (mg) Median (IQR)	3020.0 (2154.0, 3980.0)	3056.0 (2208.0, 3982.0)	2650.0 (1752.0, 3946.0)	<0.001
Potassium, (mg) Median (IQR)	2137.0 (1526.0, 2839.0)	2166.0 (1552.0, 2853.0)	1893.0 (1229.0, 2718.0)	<0.001
Phosphorus, (mg) Median (IQR)	1160.0 (838.8, 1539.0)	1172.0 (857.0, 1545.0)	1066.0 (702.5, 1479.0)	0.001
Use_multivitamin, n (%)				0.104
No	2681 (99.0)	2407 (98.9)	274 (100)	
Yes	27 (1.0)	27 (1.1)	0 (0)	
Alcohol consumption, (gm) Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.073
Lifestyle Variables				
Smoke, n (%)				<0.001
Never	1896 (70.0)	1770 (72.7)	126 (46)	
Former	305 (11.3)	274 (11.3)	31 (11.3)	
Current	507 (18.7)	390 (16)	117 (42.7)	
Work.activity, n (%)				<0.001
Light	1505 (55.6)	1366 (56.1)	139 (50.7)	
Moderate	709 (26.2)	653 (26.8)	56 (20.4)	
Vigorous	494 (18.2)	415 (17.1)	79 (28.8)	
Antidepressant use, n (%)[d]				<0.001
No	2442 (90.2)	2247 (92.3)	195 (71.2)	
Yes	266 (9.8)	187 (7.7)	79 (28.8)	
Psychological counseling, n (%)[e]				<0.001
No	2398 (88.6)	2215 (91)	183 (66.8)	
Yes	310 (11.4)	219 (9)	91 (33.2)	
Other Variables				
Serum calcium, (mg/dL) Mean ± SD	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	0.768
Infertile, n (%)[f]				0.006
Fertile	2383 (88.0)	2156 (88.6)	227 (82.8)	
Ever infertile	325 (12.0)	278 (11.4)	47 (17.2)	

Abbreviation: interquartile range (IQR), standard deviations (SD), body mass index (BMI).

[a] Depression was assessed using the 9-item Patient Health Questionnaire (PHQ-9), and participants with an overall PHQ-9 score of ≥10 were defined as depressed.

[b] Live alone included widowed, separated, never married, and divorced.

[c] Data on dietary intake and alcohol consumption were collected from dietary questionnaires in mobile examination centers.

[d] Antidepressants included monoamine oxidase inhibitors, phenylpiperazine, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, and miscellaneous antidepressants.

[e] Psychological counseling was defined based on the following questionnaire item in the NHANES: "During the past 12 months, have you seen or talked to a mental health professional such as a psychologist, psychiatrist, psychiatric nurse, or clinical social worker about your health?"

[f] Infertility was defined according to the participants' response to the following item in the questionnaire: "Have you ever tried and failed to become pregnant for at least 1 year?"

2.4. Covariates

Based on previous literature [26,27], the following variables were considered as covariates: serum calcium, psychological counseling, antidepressant use, age, marital status, race/ethnicity, family income, educational status, BMI, work activity, smoking status, alcohol consumption, and dietary factors (Table 1). The family income-to-poverty ratio (PIR) was used to define family income. "Lives alone" in marital status included widowed, separated, never married, and divorced. BMI was calculated from examination data as weight in kilograms divided by height in meters squared. BMI was divided three groups: underweight/normal weight (<25), overweight (25–29.9), and obese (≥30). Participants smoked ≥100 cigarettes are "current smokers"; Participants who smoked ≥100 cigarettes but quit smoking are "former smokers"; Participants who smoked <100 cigarettes are "never smokers" [28]. Briefly, vigorous work activity was defined as activity that significantly raised breathing or heart rate, while moderate work activity was defined as activity that only slightly raised breathing rate; light work activity included those who did not engage in vigorous or moderate work activity. In the mobile examination center, dietary questionnaires were used to collect information on dietary intake and alcohol consumption [29]. Antidepressants, including monoamine oxidase inhibitors, phenylpiperazine, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, and miscellaneous antidepressants, were identified based on the Lexicon Plus treatment classification (category I: "psychotherapeutic agents"; category II: "antidepressants") [29]. The NHANES question "Have you seen or talked to a mental health professional such as a psychologist, psychiatrist, psychiatric nurse, or clinical social worker about your health during the past 12 months?" served as the basis for the definition of psychological counseling [30]. Laboratory tests were used to collect the data on serum calcium; the method is detailed in the NHANES (https://www.cdc.gov/nchs/nhanes). Serum calcium levels were categorized as low or high based on a mean value of 2.3 mg/dL.

2.5. Statistical analysis

All analyses were performed using the R statistical software package (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.4. Categorical and continuous variables were presented as numbers (*n*) with percentages (%) and as means with standard deviations. Two-tailed Student's t-test, logistic regression, and chi-squared test were used as statistical methods. A two-sided *P*-value of <.05 was considered statistically significant.

A logistic regression model was used to assess the association between depression and infertility. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated. Model 1 was a crude model without any variable adjustments. Model 2 was adjusted for age and race/ethnicity in the multivariable analysis. Model 3 was adjusted for all covariates, except for nutrient factors. Model 4 was adjusted for all covariates, including nutrient factors. A subgroup analysis was performed based on serum calcium, obesity (BMI ≥30 kg/m^2), psychological counseling, and antidepressant use. To explore these interactions between subgroups, the likelihood ratio test was used.

Several sensitivity analyses were conducted to assess the reliability of our findings. First, considering the effect of advanced age on attempts to conceive by women, we performed a sensitivity analysis that excluded women aged ≥35 years at the time of the interview. Second, the study shown that PHQ-9 scores of 20, 15, 10, and 5 indicated severe, moderately severe, moderate, and mild depression respectively [24], we performed another sensitivity analysis to validate our findings by redefining depression (PHQ-9 scores ≥5). Third, we excluded women who had a hysterectomy and ever treated for a pelvic infection/PID, Fourth, we used the inverse probability of treatment weighting (IPTW) method to address other potential confounders and more detailed formation about method can be found the previous studies [31]. The variables included in the model were age, race/ethnicity, PIR, educational level, marital status, BMI, serum calcium, psychological counseling, and antidepressant use.

3. Results

3.1. Characteristics of the study population

Out of 29,400 participants, 14,452 male individuals and 4995 female individuals aged <20 years and ≥45 years were excluded (Fig. 1). Individuals with missing data on PHQ-9 scores, infertility, serum calcium, psychological counseling, antidepressant use, dietary intake, and other covariates were also excluded during data processing. In total, 2708 adult women (mean age: 32.71 ± 7.50 years) were included in the final analysis. Overall, 274 and 2434 participants were depressed and nondepressed, respectively, based on

their PHQ-9 scores. At baseline, there were many differences in dietary characteristics between the depressed and nondepressed groups, except for energy, lycopene, and coffee. Depression was more common in women from low-income families (median PIR, 1.20 [0.71, 2.51]), and the median of the comparison group is 2.00 [1.00, 3.70]. In total, 12.00 % of participants self-reported as being infertile. The prevalence of infertility was higher among participants with depression (n = 47 [17.21 %]) than among those without depression (n = 278 [11.40 %]). (Table 1).

3.2. Multivariable regression analyses

In crude Mode, participants who were depressed exhibited a higher infertility than those who were non-depressed (OR, 1.61; 95 % CI, 1.15–2.25; P = .006) (Table 2). Model 1 retained the association, which was adjusted for age and race/ethnicity (OR, 1.56; 95 % CI, 1.10–2.19; P = .011). Similarly, when considering more covariates, the association between depression and infertility was observed in Model 2 (OR, 1.65; 95 % CI, 1.13–2.40; P = .009), and Model 3 (OR, 1.62; 95 % CI, 1.11–2.38; P = .013).

3.3. Subgroup analysis

Table 3 depicts the results of the subgroup analysis. Depression was positively associated with an increased risk of infertility among participants who were obese (OR, 1.68; 95 % CI, 1.03–2.74), those who had not received psychological counseling (OR, 1.60; 95 % CI, 1.03–2.50), were antidepressant users (OR, 3.22; 95 % CI, 1.15–9.00), and those with high serum calcium levels (OR, 2.05; 95 % CI, 1.25–3.35). The association between depression and infertility was insignificant in participants with low serum calcium levels (OR,

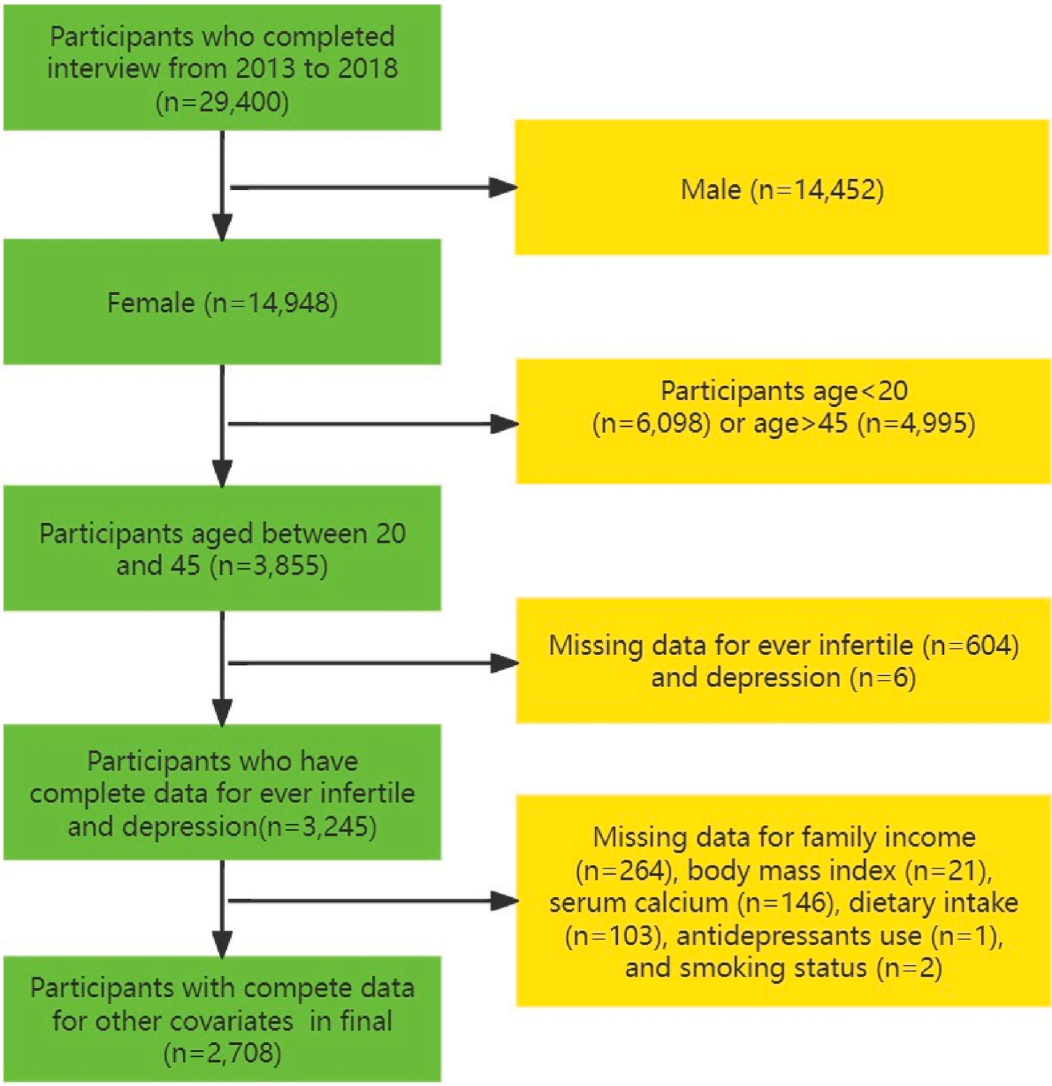

Fig. 1. Flowchart of the participant selection.

Table 2
Association between depression and infertility.

Depression	Event (%)	Crude Model		Model 1		Model 2		Model 3	
		OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value
Non-depressed	2434 (11.4)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Depressed	274 (17.2)	1.61(1.15–2.25)	0.006	1.56 (1.1–2.19)	0.011	1.65 (1.13–2.40)	0.009	1.62(1.11–2.38)	0.013

Abbreviations: OR, odds ratio; CI, confidence intervals; Ref, reference.
Crude Model: unadjusted.
Model 1: adjusted for age and race/ethnicity.
Model 2: adjusted for age, race/ethnicity, family income, smoking status, alcohol consumption, educational level, marital status, work activity, BMI, psychological counseling, and antidepressiants use.
Model 3: adjusted for age, race/ethnicity, family income, smoking status, alcohol consumption, educational level, marital status, work activity, BMI, psychological counseling, antidepressiants use, serum calcium, and dietary intake such as energy, protein, fibre, caffeine, zinc, selenium, sodium, potassium, phosphorus, calcium, magnesium, copper, iron, lycopene, folate, beta-cryptoxanthin, beta-carotene, vitamin E, vitamin C, vitamin A, vitamin D, vitamin K, lutein-zeaxanthin, niacin, and use of multivitamins.

1.10; 95 % CI, 0.56–2.14). Moreover, a significant interaction between serum calcium and depression was observed for infertility (P = .038, interaction likelihood ratio test), which suggested that serum calcium may have an effect on the association between depression and infertility. No association between depression and infertility was observed among subgroups of participants who were not obese, received psychological counseling, and were not being administered antidepressants.

3.4. Sensitivity analyses

Table 4 summarizes the results of sensitivity analyses. Following adjustment for all covariates, the association between depression and infertility remained statistically significant. The study shown that PHQ-9 scores of 20, 15, 10, and 5 indicated severe, moderately severe, moderate, and mild depression respectively [24]. When the cut-off for PHQ-9 scores was lowered to ≥5 to redefine depression, the effect value (OR, 1.48; 95 % CI, 1.12–1.96) is slightly low when compared with the primary analyses (OR, 1.62; 95 % CI, 1.11–2.38; P = .013), which may imply the severity of depression was positively associated with infertility. Considering the effect of advanced age on attempts to conceive by women, women aged ≥35 years were excluded (n = 1082). The results shown the association between depression and infertility still existed. When also compared with the primary analyses, the effect value (OR, 1.87; 95 % CI, 1.08–3.23) was slightly high, which can indicated that in women of prime reproductive age, depression is more likely to be associated with infertility. When those who had a hysterectomy (n = 140) and ever treated for a pelvic infection/PID (n = 166) were excluded, the effect value(OR, 1.63; 95 % CI, 1.07–2.49) was almost constant with the primary analyses. Using IPTW (n = 2708), the OR was 1.64 (95 % CI, 1.17–2.31).

4. Discussion

We explored the association between depression and infertility in a nationally representative sample of U.S. women. The

Table 3
Subgroup analysis.

Subgroup[a]	Non-depressed N(%)[b]	Depressed N(%)[b]	Adjusted OR (95%Cl)	P for interaction
Serum calcium[c]				0.038
Low	113 (12.1)	15 (13.4)	1.1 (0.56–2.14)	
High	165 (11)	32 (19.8)	2.05 (1.25–3.35)	
Psychosocial counseling				0.938
No	253 (11.4)	32 (17.5)	1.60 (1.03–2.50)	
Yes	25 (11.4)	15 (16.5)	1.81 (0.71–4.64)	
Antidepressants use				0.466
No	258 (11.5)	32 (16.4)	1.47 (0.95–2.30)	
Yes	20 (10.7)	15 (19)	3.22(1.15–9.00)	
Obesity				0.663
No	123 (8.7)	17 (12.3)	1.5 (0.82–2.74)	
Yes	155 (15.3)	30 (22.1)	1.68 (1.03–2.74)	

Abbreviations: OR: odds ratio, CI: confidence interval.
[a] Covariates in subgroup analysis included age, race/ethnicity, family income, smoking status, alcohol consumption, educational level, marital status, work activity, BMI, psychological counseling, antidepressiants use, serum calcium, and dietary intake such as energy, protein, fibre, caffeine, zinc, selenium, sodium, potassium, phosphorus, calcium, magnesium, copper, iron, lycopene, folate, beta-cryptoxanthin, beta-carotene, vitamin E, vitamin C, vitamin A, vitamin D, vitamin K, lutein-zeaxanthin, niacin, and use of multivitamins.
[b] N (%): "N" is the total number of Non-depressed or Depressed. "%" means the ratio of infertility.
[c] Serum calcium levels were categorized as low or high based on a mean value of 2.3 mg/dL.

Table 4
Sensitivity analyses.

Analysis	N (%)[c]	OR	95 % CI	*P*-value
PHQ-9 score of ≥ 5 to define depression[a]				
Non-depressed	1953 (10.9)	Reference		
Depressed	755 (14.8)	1.48	1.12–1.96	0.005
Excluding women who were aged 35 years or older[a]				
Non-depressed	1476 (8.5)	Reference		
Depressed	150 (14.7)	1.87	1.08–3.23	0.025
Excluding women with some gynecological diseases[a]				
Non-depressed	247 (11)	Reference		
Depressed	35 (16.4)	1.63	1.07–2.49	0.023
Inverse probability treatment weighted analyses[b]				
Non-depressed	2434 (11.4)	Reference		
Depressed	274 (17.2)	1.64	1.17–2.31	0.004

Abbreviations: OR, odds ratio; CI, confidence intervals; PHQ-9, the 9-item Patient Health Questionnaire.

[a] Adjusted for age, race/ethnicity, family income, smoking status, alcohol consumption, educational level, marital status, work activity, BMI, psychological counseling, antidepressiants use, serum calcium, and dietary intake such as energy, protein, fibre, caffeine, zinc, selenium, sodium, potassium, phosphorus, calcium, magnesium, copper, iron, lycopene, folate, beta-cryptoxanthin, beta-carotene, vitamin E, vitamin C, vitamin A, vitamin D, vitamin K, lutein-zeaxanthin, niacin, and use of multivitamins.

[b] The variables included in the model were age, race/ethnicity, PIR, educational level, marital status, BMI, serum calcium, psychological counseling, and antidepressant use.

[c] N (%): "N" is the total number of Non-depressed or Depressed. "%" means the ratio of infertility.

association between depression and infertility remained statistically significant even after excluding women aged ≥35 years, lowering the PHQ-9 scores to redefine depression, excluding women with some gynecological diseases, and conducting a sensitivity analysis with IPTW to account for potential residual confounding. The subgroup analysis revealed that depression was not significantly associated with infertility among the participants who had a low BMI, received psychological counseling, were not taking antidepressants, and had low serum calcium levels. Moreover, we found for the first time an interaction between serum calcium and depression concerning infertility, suggesting that serum calcium may have an effect on the association between depression and infertility.

Numerous previous studies have investigated the association between depression and infertility among participants visiting hospitals for treatment. Women with depression have been reported to be less likely to seek fertility treatment than those without depression (OR, 0.55; 95 % CI, 0.31–0.95) [32]. Enrollment in a fertility treatment study may reduce the effect of depression on infertility from a psychological standpoint. Our findings, which are based on a nationally representative sample of U.S. women from the NHANES conducted by the NCHS and CDC, appear more credible. Depression may exacerbate other diseases due to its chronic and debilitating nature [33]. Increasing attention has focused on the effect of psychological stress on depression; however, the underlying mechanism of depression remains poorly understood [34]. Currently, there seem to be more psychologically stressful events than ever before. Psychological stress triggers various physiological responses, including immune, neurological, and endocrine system responses [35], which may harm the reproductive system [36]. Additionally, previous studies have suggested that the hypothalamic–pituitary–adrenal (HPA) axis may have an inhibitory effect on the female reproductive system [37,38]. Psychological stress causes unexplained infertility and miscarriage, which may be related to HPA axis dysfunction [39]. Approximately 70 % of individuals with depression exhibit HPA axis dysfunction [40], and HPA axis hyperactivity is a common neurobiological change in depression [41].

Dietary factors have been identified as potentially modifiable factors in the treatment of depression [42], and there is a growing body of evidence suggesting an association between dietary factors and female fertility [43]. However, to the best of our knowledge, previous studies examining the association between depression and infertility have not considered dietary factors. Calcium is important for the preconception health of women, and it regulates blood vessel function, nerve transmission, and gland hormone secretion [44]. Calcium plays an important role in activating several neurophysiological pathways, including the influx of extracellular calcium for neurotransmitter release [45]. Calcium exists in the blood in ionized form or in combination with anions or plasma proteins [46]. In contrast, cerebrospinal fluid (CSF) calcium mainly depends on serum calcium concentration and blood-brain barrier permeability [47]. Therefore, serum calcium may affect neuronal and cognitive functions [45]. The normal cognitive function requires calcium homeostasis [48,49]. Cognitive dysfunction is a key feature of depression, and abnormal serum calcium levels are associated with cognitive impairment and depressive symptoms [50,51]. In depression, a calcium metabolism disorder can manifest as elevated serum and CSF calcium levels as well as intracellular calcium changes [52–54]. Jimerson et al. indicated that high serum calcium was significantly associated with brain white matter lesions in participants with depression [53], which is consistent with our findings. The association between calcium consumption and brain lesions was also observed in participants with depression [55,56]. Women are more likely than men to take calcium supplements daily. It is worth noting that an increase in estrogen levels in women undergoing ART due to ovarian overstimulation has been suggested to affect serum calcium levels [44], which may explain the inconsistent findings regarding the relationship between depression and infertility.

In our subgroup analysis, depression was found to be positively associated with infertility in participants with obesity; in contrast, this association was not observed in participants without obesity. Frank et al. found that obesity was significantly associated with an

increased risk of depressive symptoms [57]. We further explored the relationship between depression and infertility in antidepressant users. Interestingly, we found that depression was associated with infertility in antidepressant users; however, no such association was found in non-antidepressant users. Previous studies reported that antidepressant use in women was associated with early pregnancy loss or cause infertility, which is consistent with our findings [27,58]. The effect of antidepressant use on fertility may be a side effect of the drugs, as these decrease libido and affect neurosteroid levels, resulting in decreased ovulation [59,60]. Clinical and animal studies suggest that antidepressant use may negatively impact fertility by altering isopregnenolone and neurosteroid levels [15]. We found no association between depression and infertility in participants who had psychosocial counseling when considering nonpharmacologic treatments such as psychosocial interventions to reduce depression scores. Moreover, a meta-analysis by Frederiksen et al. concluded that psychosocial interventions for infertile couples could improve clinical pregnancy rates [61].

Despite the strengths above, this study also has some limitations. First, due to the cross-sectional study, we could not establish a temporal connection or causality between depression and infertility events. The directionality isn't also determined. We assume that depression and infertility are bidirectional, and their pathogenesis and basis may be caused by the increase of serum calcium, which needs to be proved by further studies. Second, Serum Vitamin D was unavailable in NHANES. It was reported that Vitamin D was associated with infertility [62]. However, as a part of the sensitivity analysis, we considered the influence of dietary intakes such as vitamin D and calcium, adjusted these factors in the model 3 in Table 2, and the results remained largely unchanged. Third, residual confounding influencing infertility may still exist; however, we included as many variables as possible based on previous studies, used the IPTW method to address potential confounders. Fourth, although we performed a sensitivity analysis to reduce the effect of advanced age and some gynecological diseases in women, there were still other gynecological factors that NHANES had not documented. Fifth, recall bias may have been introduced by using self-reported data. We also performed a sensitivity analysis by lowering the PHQ-9 scores to redefine depression and conducted a subgroup analysis of participants who received psychological counseling and were antidepressant users, considering possible depression interventions. Sixth, male factor was not taken into account in our study, because there was no information on male factors contributing to infertility in the NHANES database. However, the overall rate of self-reported infertility was comparable to the Framingham Heart Study (12.0 % vs 14.0 %) (https://www.framinghamheartstudy.org/). Seventh, our findings are primarily based on U.S. citizens; genetic factors and geography also need to be considered.

5. Conclusions

There appears to be a positive association between depression and infertility among U.S. women and serum calcium may change the association. Further prospective studies are needed to determine the etiological relationship.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author. Research data associated with our study also can be available at https://www.cdc.gov/nchs/nhanes.

Ethical statement

Participants came from National Health and Nutrition Examination Survey (NHANES), which is is a public database. The NHANES study was approved by the NCHS research ethics review board (protocols 98-12, 2005–06, 2011–17, and 2018–01) (http://www.cdc.gov/nchs/nhanes/irba98.htm). Patients aged ≥18 years who provided written informed consent upon enrollment were included in the study. NHANES is a publicly available datasets and is free for all readers and researchers at https://www.cdc.gov/nchs/nhanes/index.htm. Ethical review and approval was not required for this secondary analysis in accordance with the national legislation and the institutional requirements.

CRediT authorship contribution statement

Jungao Huang: Writing – original draft. **Xuan Xiao:** Formal analysis, Data curation. **Linyu Zhang:** Software, Data curation. **Shanfeng Gao:** Resources, Data curation. **Xia Wang:** Software, Data curation. **Juan Yang:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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