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ORIGINAL RESEARCH

Association of Depression with Age at Natural Menopause: A Cross-Sectional Analysis with NHANES Data

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Purpose: To evaluate the association between depression and age of natural menopause in American women.

Patients and Methods: This cross-sectional study utilized eight cycles of the National Health and Nutrition Examination Survey (NHANES) conducted from 2005 to 2023. We assessed depression using the Patient Health Questionnaire-9 (PHQ-9). We obtained ANM information from the Reproductive Health questionnaire. We screened menopausal women between the ages of 40 and 70 years, excluding those with surgical menopause. We used multivariable logistic regression models to investigate the association between depression and ANM. Additionally, we conducted subgroup analyses and interaction tests.

Results: A total of 4732 women were included, and the mean age of natural menopause was 47.9 ± 6.8 years. Of these, 1123 (23.7%) were classified as early menopause, 2971 (62.8%) as normal menopause, and 638 (13.5%) as late menopause. Preliminary analysis showed a positive association between PHQ-9 score and the risk of early menopause (OR = 1.11, 95% CI = 1.06–1.16). After full adjustment in multivariate logistic regression, it was estimated that each one-unit increase in the PHQ-9 score was associated with a 7% increased risk of early menopause (OR = 1.07, 95% CI = 1.02–1.12). After classifying depression into three grades: no, mild, and severe, it was found that, compared with American women without depression, the risk of early menopause increased significantly. American women with major depression had an increased risk of early menopause (OR = 2.49, 95% CI = 1.10–5.63). In College or above (OR = 1.10, 95% CI = 1.02–1.19), PIR≤1 (OR = 1.10, 95% CI = 1.04–1.16), Current smoker (OR = 1.12, 95% CI = 1.00–1.24), the positive association between depression and early menopause was more significant.

Conclusion: In this cross-sectional study, the severity of depression in American women was positively correlated with the risk of early menopause. This suggests that women should pay more attention to their mental health and actively manage depression. For women with depression, early intervention and treatment may help improve their reproductive health and delay menopause.

Keywords: depression, ANM, early menopause, National Health and Nutrition Examination Survey.

Introduction

Natural menopause is defined as 12 consecutive months of amenorrhea without an apparent cause, characterized by the natural cessation of menstruation unrelated to pharmacological treatments or surgical procedures.[1] Natural menopause is the end of a woman's reproductive life when ovarian function is lost, reproductive hormones stop secretion, and fertility is irreversibly lost.[2] The age at natural menopause (ANM) generally ranges from 45 to 55 years, with menopause occurring before the age of 45 referred to as early menopause.[3] Women experiencing early menopause may face risks comparable to those associated with premature ovarian insufficiency,[4] including an increased risk of dementia,[5] osteoporosis,[6] type 2 diabetes,[7] and cardiovascular disease.[8] Furthermore, women of childbearing age generally tend to postpone their intentions to bear children.[9] Consequently, ANM serves as a crucial determinant of women's future health status. Predicting ANM, particularly earlier menopause, allows women to take proactive steps in managing their

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long-term health. While factors such as genetics, environmental conditions, and lifestyle play a critical role in determining ANM, emerging evidence suggests that mental health, particularly depression, may also exert a significant influence.

Depression is a prevalent mental disorder characterized by a persistent negative mood, diminished interest and attention, and is accompanied by somatic symptoms and cognitive function changes.[10] According to the World Health Organization, depression affects over 300 million individuals globally, accounting for 4.4% of the total population, and is the leading cause of disability and suicide worldwide.[11] Depression is associated with transitions in the female reproductive aging cycle and fluctuations in ovarian hormone levels.[12] Recent research has advanced our understanding of the complex interplay between depression and female reproductive health. For instance, a prospective cohort study of North American pregnancy planners found that women with a history of major depressive symptoms were 80% more likely to experience irregular menstrual cycles during follow-up.[13] In a cross-sectional study examining depression and infertility, moderate-to-severe depressive states were independently associated with an increased risk of infertility, with this association partially mediated through lipoprotein cholesterol levels.[14] During assisted reproductive technology treatment, scores of depression and anxiety among pregnant women were negatively correlated with treatment outcomes.[15] In a prospective cohort study of women with breast cancer, incident breast cancer patients with a history of depression were at significantly increased risk for all-cause death and late-stage breast cancer death.[16] However, its specific effects on the age at menopause remain inadequately studied. Given the increasing prevalence of depression, understanding its relationship to age at natural menopause is essential for mitigating potential risks associated with women's health.

Existing literature offers preliminary insights into the relationship between depression and menopause. Most studies have focused on depression as a concomitant symptom of menopause rather than investigating its role as a contributing factor to an earlier age at natural menopause. Therefore, the primary aim of this study was to investigate the relationship between depression and ANM in a large sample of US women. By uncovering this potential association, the findings aim to support healthcare professionals in more effectively managing the mental and physical health of female patients.

Materials and Methods

Study Design and Participants

The National Health and Nutrition Examination Survey (NHANES) is a series of nationally representative, cross-sectional surveys aimed at assessing the health and nutritional status of individuals in the United States. Participants are systematically selected from various regions to ensure diverse demographic representation. The survey results were used to determine the prevalence of major diseases and disease risk factors to aid in epidemiological studies and health science research. Participants underwent an initial home interview to provide socio-demographic, medical, and family history information. Subsequently, they visited mobile examination centers for comprehensive health assessments, including anthropometric measurements, blood pressure evaluation, and laboratory testing. Previous publications detailed the sampling methods and data collection procedures.[17] Ethical approval for NHANES is granted by the National Center for Health Statistics and Research Ethics Review Committee, adhering strictly to ethical guidelines. Informed consent is obtained from all participants prior to their inclusion in the survey.

In our investigation of the link between depression and ANM, we utilized NHANES survey data spanning eight cycles from 2005 to 2020 and from 2021 to 2023. According to previous studies,[18] our study focused on menopausal women aged 40 to 70. Excluding those without Patient Health Questionnaire-9 (PHQ-9) score, those without age at menopause data, and those who had undergone surgical menopause (eg, hysterectomy and bilateral oophorectomy). We collected participants' information on demographics, health-related lifestyle, and medical history. Missing covariate data were addressed using multiple imputations. Ultimately, our study included 4732 participants. We illustrated the selection process for study participants in Figure 1. Our analyses exclusively relied on publicly accessible data, and ethical approval was not required for this investigation.

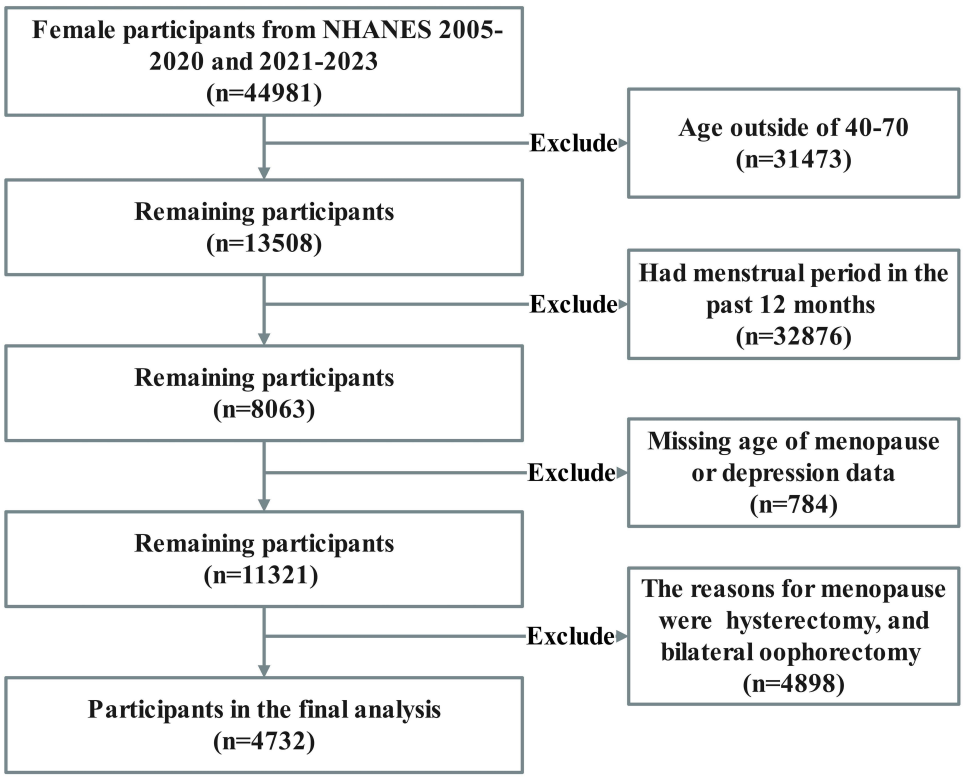

Figure 1 Flowchart of the participant selection from NHANES 2007–2020 and 2021–2023.

Measurement of ANM

The age of natural menopause was assessed based on responses in the reproductive health questionnaire. To answer the question "Had regular periods in past 12 months" (variable named RHQ031), Participants who answered "No" and "Menopause" in the "Reason not having regular periods" (variable name RHD043) were identified as menopausal women. According to the question "Had a hysterectomy?" (Variable name is RHD280), "Had both ovaries removed?" Responses (variable named RHQ305) divided participants into either natural or surgical menopause. The Age of natural menopause was determined based on the answer to the question "Age at last menstrual period" (variable named RHQ060). Participants were divided into Early menopause (< 45 years), Normal menopause (45 to 54 years), and Late menopause (≥55 years) according to ANM.[19]

Measurement of Depression

The PHQ-9 depression scale assessed depression. This validated self-report instrument assesses nine questions about depressive symptoms in the past two weeks and encompasses psychiatric issues such as sadness, difficulty sleeping, fatigue, and difficulty concentrating.[20] Scores on the nine items of the PHQ-9 Depression scale range from 0 (not at all) to 3 (almost every day), with total scores ranging from 0 to 27. We defined a total score of ≥10 as indicative of depression.[21] The severity of depressive symptoms was classified as follows: no depression (< 10 points), moderate depression (10–15 points), and severe depression (> 15 points).

Covariates

Based on previous studies, our study considered variables that may confound the association between depression and ANM. Data included demographic characteristics (age, race/ethnicity, education, marital status, and family poverty to income ratio (PIR)), lifestyle factors (smoking, alcohol drinking, and body mass index (BMI)), clinical features (hypertension, hypercholesterolemia, and diabetes), and reproductive factors (age at menarche and parity). Race was categorized as non-Hispanic white, non-Hispanic black, Mexican American, and other races. The level of education was

classified as less than high school, high school graduate, and college or above. Marital status was divided into unmarried, married/cohabitating, separated/divorced/widowed. PIR assesses income levels by dividing household (or individual) income by the poverty line. The PIR was divided into ≤1 and > 1. Smoking status was categorized as never, former, or current. The drinking status was divided into "1-5 times/year" and "5+ times/year" groups. BMI was divided into 3 categories: normal (< 25), overweight (25–30), and obese (≥30). Clinical features of hypertension, hypercholesterolemia, and diabetes were determined from questionnaire data and physical examination. According to the question "Ever told you had high blood pressure" (variable named BPQ020) "Now taking prescribed medicine" Hypertension was determined by the response (variable named BPQ050A) and the mean of three measurements of systolic/diastolic blood pressure from the physical examination data (systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 80 mm Hg indicates hypertension). According to the questions "Doctor told you - high cholesterol level" (variable named BPQ080) and "Now taking prescribed. "medicine" (variable BPQ100D) answers and physical examination data on low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) (LDL-C ≥ 160 mg/dL; TC ≥ 240 mg/dL indicates hypercholesterolemia) to determine hypercholesterolemia. Diabetes was determined based on the response to the question, "Doctor told you have diabetes" (variable named DIQ010). The age of menarche was calculated from her responses to the reproductive health questionnaire (the variable was named RHQ010). Based on the question "Age when first menstrual period occurred" The answer determines the age of menarche. Related variables can be defined to the corresponding module by the variable name.

Statistical Analysis

Integrating the study data from 2005 to 2023, according to the sampling method of NHANES, 19-year sampling weights were formulated for the subsequent analysis. Baseline characteristics were analyzed with the use of mean and standard deviation (SD) describing continuous variables. Meanwhile, categorical variables are reported as sample counts and weighted percentages. Differences between the three categories of ANM were compared using the Wilcoxon rank-sum test for continuous variables and the Rao-Scott chi-square test for categorical variables. Weighted logistic regression analysis was performed to examine the relationship between depression and ANM, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated. Three models were developed: Model 1 (unadjusted), Model 2 (adjusted for demographic factors including age, race, education level, marital status, poverty-to-income ratio (PIR), and BMI), and Model 3 (fully adjusted for additional lifestyle and clinical variables such as smoking, alcohol consumption, hypertension, hypercholesterolemia, age of menarche with diabetes, and number of parity). Subgroup analyses stratified by education level, PIR, cigarette smoking, and alcohol drinking were performed under the fully adjusted model. In addition, interaction analyses were performed to assess potential interactions between each subgroup and early menopause. All statistical analyses were performed with the use of R software, version 4.3.3. A two-sided *P* value of less than 0.05 indicated statistical significance.

Results

NHANES Participant Characteristics

A total of 4732 participants were included in the analysis spanning 2005–2023. Among them, 1123 (23.7%) experienced early menopause, 2971 (62.8%) underwent normal menopause, and 638 (13.5%) had late menopause. Table 1 lists the baseline characteristics of participants stratified by ANM. The mean age of natural menopause of the included participants was 47.9 ± 6.8 years, and the mean PHQ-9 score was 3.4 ± 4.3. For the early, normal, and late menopause groups, the mean ANM was 38.0 ± 5.3 years, 49.8 ± 2.6 years, and 56.2 ± 1.5 years, respectively. Most participants identified as Non-Hispanic White (71.6%), had the highest education level of college or above (62.2%) and reported a poverty-to-income ratio (PIR) greater than 1 (87.7%). Significant differences in education level and poverty-to-income ratio (PIR) were observed among the three menopausal groups ($P < 0.001$). Women in the early menopausal group were more likely to be smokers (25.0%) and heavy drinkers (6.1%) and report severe depressive symptoms (5.4%) compared to their normal or late menopausal counterparts (all $P < 0.001$). Women with late menopause were more likely to have never smoked (59.7%) and to drink less alcohol (98.6%) (both $P < 0.001$). Significant differences in race, education level, PIR, smoking, drinking, and depression were found among

Table 1 Characteristics of Participants in Three Age at Natural Menopause Categories

Characteristic	Total	Age at Natural Menopause			*P* value
		Early (< 45 years old)	Normal (45–54 years old)	Late (≥ 55 years old)	
Overall	4732 (100.0%)	1123 (23.7%)	2971 (62.8%)	638 (13.5%)	
Age (years)	58.9 ± 6.6	56.1 ± 8.1	59.0 ± 5.8	63.1 ± 4.1	<0.001
Race/ethnicity, n (%)					<0.001
Non-Hispanic White	1989 (71.6%)	464 (69.9%)	1204 (70.7%)	321 (78.2%)	
Non-Hispanic Black	1000 (10.5%)	288 (13.9%)	578 (9.6%)	134 (8.6%)	
Mexican American	649 (5.4%)	157 (5.4%)	428 (5.9%)	64 (3.2%)	
Other	1094 (12.6%)	214 (10.8%)	761 (13.8%)	119 (10.0%)	
Education level, n (%)					<0.001
Less than high school	1092 (13.3%)	340 (20.5%)	651 (11.9%)	101 (7.6%)	
High school or equivalent	1085 (24.5%)	288 (28.4%)	657 (23.6%)	141 (22.4%)	
College or above	2555 (62.2%)	495 (51.1%)	1663 (64.5%)	397 (70.0%)	
Marital status, n (%)					0.6
Never married	436 (6.5%)	107 (6.5%)	279 (7.0%)	50 (4.2%)	
Married/Living with partner	2644 (65.3%)	609 (66.8%)	1482 (67.3%)	313 (66.3%)	
Widowed/Divorced/Separated	4652 (28.3%)	407 (26.7%)	328 (10.1%)	73 (9.5%)	
PIR, n (%)					<0.001
≤1	976 (12.3%)	281 (16.7%)	603 (11.8%)	92 (7.6%)	
>1	3756 (87.7%)	842 (83.3%)	2368 (88.2%)	546 (92.4%)	
BMI (kg/m^2), n (%)					0.10
Normal (<25)	1187 (28.4%)	250 (25.2%)	793 (30.3%)	144 (25.4%)	
Overweight (25–30)	1367 (29.1%)	319 (28.4%)	861 (29.4%)	187 (29.2%)	
Obese (≥30)	2178 (42.5%)	554 (46.5%)	1317 (40.3%)	307 (45.4%)	
Cigarette smoking, n (%)					<0.001
Never smoker	2796 (56.4%)	595 (48.6%)	1798 (58.6%)	403 (59.7%)	
Former smoker	1121 (27.3%)	250 (26.4%)	701 (26.8%)	170 (31.3%)	
Current smoker	815 (16.3%)	278 (25.0%)	472 (14.6%)	65 (9.1%)	
Alcohol drinking, n (%)					<0.001
1–5 drinks/year	4505 (96.3%)	1047 (93.9%)	2837 (96.6%)	621 (98.6%)	
5+ drinks/year	227 (3.7%)	76 (6.1%)	134 (3.4%)	17 (1.4%)	
Hypertension, n (%)					0.2
No	2432 (56.6%)	574 (57.8%)	1545 (57.3%)	313 (51.9%)	
Yes	2300 (43.4%)	549 (42.2%)	1426 (42.7%)	325 (48.1%)	
Hypercholesterolemia, n (%)					>0.9
No	2343 (50.9%)	540 (50.7%)	1497 (51.2%)	306 (49.9%)	
Yes	2389 (49.1%)	583 (49.3%)	1474 (48.8%)	332 (50.1%)	
Diabetes, n (%)					0.6
No	3738 (83.5%)	862 (82.2%)	2370 (83.8%)	506 (83.8%)	
Yes	994 (16.5%)	261 (17.8%)	601 (16.2%)	132 (16.2%)	
Age at menarche (years)	12.8 ± 1.7	12.7 ± 1.8	12.8 ± 1.7	13.0 ± 1.7	0.058
Parity	3.1 ±1.7	3.2 ±1.8	3.1 ±1.7	3.0 ± 1.6	0.4
Age at natural menopause (years)	47.9 ± 6.8	38.0 ± 5.3	49.8 ± 2.6	56.2 ± 1.5	<0.001
PHQ-9 score	3.4 ± 4.3	4.4 ± 4.9	3.2 ± 4.2	2.7 ± 3.4	<0.001
Depression, n (%)					<0.001
No	4186 (91.2%)	951 (87.9%)	2645 (91.6%)	590 (94.7%)	
Moderate	309 (5.6%)	88 (6.7%)	190 (5.7%)	31 (3.9%)	
Severe	237 (3.2%)	84 (5.4%)	136 (2.7%)	17 (1.4%)	

Abbreviations: PIR, ratio of family income to poverty; BMI, body mass index; PHQ-9, Patient Health Questionnaire-9.

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early menopausal, normal menopausal, and late menopausal women (all $P < 0.001$). No significant differences in marital status, BMI, hypertension, hypercholesterolemia, diabetes, age at menarche, or parity were observed among the three groups.

Association Between Depression and ANM

Table 2 presents the association between depression and ANM. Multivariate logistic regression analysis showed that higher PHQ-9 scores were linked to an elevated risk of early natural menopause. In Model 1 (unadjusted), each standard deviation increase in PHQ-9 score was associated with an 11% higher likelihood of early menopause (OR = 1.11, 95% CI = 1.06–1.16, $P < 0.001$). In Model 2 (adjusted for age, race, education level, marital status, PIR, and BMI), each standard deviation increase in PHQ-9 score was associated with an 8% increase in premature menopause risk (OR = 1.08, 95% CI = 1.03–1.13, $P = 0.002$). In Model 3, which fully adjusted for demographic, lifestyle, and clinical variables (eg, smoking, alcohol consumption, hypertension, and diabetes), each standard deviation increase in PHQ-9 score corresponded to an 8% greater risk of early menopause (OR = 1.07, 95% CI = 1.02–1.12, $P = 0.014$). The degree of depression was categorized into no depression (reference group), moderate depression, and severe depression. In all three models, severe depression significantly increased the risk of premature menopause, whereas moderate depression exhibited a nonsignificant effect. Specifically, in Model 1, compared to the no depression group, an increase of one standard deviation in major depression was associated with a 310% increased risk of premature menopause (OR = 4.10, 95% CI = 1.99–8.41, $P < 0.001$). In Model 2, after adjusting for certain covariates, the risk of premature menopause increased by 187% (OR = 2.87, 95% CI = 1.36–6.07, $P = 0.006$) for each standard deviation increase in major depression. In Model 3, following full adjustment for covariates, the risk of premature menopause increased by 149% (OR = 2.49, 95% CI = 1.10–5.63, $P = 0.029$) for each standard deviation increase in major depression. Trend tests for Model 1 and Model 2 indicated significant differences (Model 1: $P < 0.001$, Model 2: $P = 0.018$, Model 3: $P = 0.078$), suggesting that the risk of premature menopause increases with the degree of depression.

Subgroup

Table 3 displays the results of the subgroup analyses. In Model 3, with all variables adjusted, subgroup analysis demonstrated that various characteristics, including education level and cigarette smoking, significantly influenced the association between depression and early menopause, indicating that these characteristics may moderate the effect of depression on early menopause (both $P \leq 0.001$).

Table 2 Weighted Multivariate Logistic Regression Models of Depression with the Age at Natural Menopause (Early Versus Late)

Characteristic	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
PHQ-9 score	1.11 (1.06, 1.16)	<0.001	1.08 (1.03, 1.13)	0.002	1.07 (1.02, 1.12)	0.014
Depression						
No	Reference		Reference		Reference	
Moderate	1.85 (0.90, 3.81)	0.092	1.59 (0.65,3.91)	0.310	1.42 (0.58, 3.43)	0.438
Severe	4.10 (1.99, 8.41)	<0.001	2.87 (1.36, 6.07)	0.006	2.49 (1.10, 5.63)	0.029
P for trend	<0.001		0.018		0.078	

Notes: Model 1: no covariates were adjusted. Model 2: age, race, education level, marital status, PIR and BMI were adjusted. Model 3: age, race, education level, marital status, PIR, BMI, cigarette smoking, alcohol drinking, hypertension, high cholesterol levels, diabetes, age at menarche and number of pregnancies were adjusted.
Abbreviations: OR, Odds Ratio, 95% CI, 95% confidence interval, PHQ-9, Patient Health Questionnaire-9.

Table 3 Subgroup Analysis for the Associations Between Depression and the Age at Natural Menopause (Early Versus Late)

Subgroup	OR (95% CI)	*P* value	*P* for Interaction
Education level			<0.001
Less than high school	1.01 (0.95, 1.08)	0.8	
High school or equivalent	1.06 (0.98, 1.15)	0.12	
College or above	1.10 (1.02, 1.19)	0.017	
PIR			0.071
≤1	1.10 (1.04, 1.16)	0.001	
>1	1.06 (1.00, 1.12)	0.045	
Cigarette smoking			0.001
Never smoker	1.05 (0.99, 1.11)	0.13	
Former smoker	1.07 (1.00, 1.16)	0.060	
Current smoker	1.12 (1.00, 1.24)	0.043	
Alcohol drinking			-*
1–5 drinks/year	1.07 (1.01, 1.12)	0.017	
5+ drinks/year	-*	-*	

Notes: Adjusted for age, race, education level, marital status, PIR, BMI, cigarette smoking, alcohol drinking, hypertension, high cholesterol levels, diabetes, age at menarche and number of pregnancies.
*The model failed because of the small sample size.
Abbreviations: OR, Odds Ratio; 95% CI, 95% confidence interval; PIR, ratio of family income to poverty; BMI, body mass index; PHQ-9, Patient Health Questionnaire-9.

Discussion

This large cross-sectional study identified a significant association between depression and an increased risk of early menopause compared to late menopause. Additionally, the relationship appeared to be influenced by factors such as education level, PIR, smoking status, and cigarette smoking.

The most common endocrine abnormality in depressed patients is overactivity of the hypothalamic-pituitary-adrenal (HPA) axis.[22] The HPA axis is significantly activated in depressed states, resulting in increased release of Adrenocorticotropin, resulting in elevated glucocorticoid levels in the body. Glucocorticoids inhibit the function of the hypothalamic-pituitary-ovarian (HPO) axis and interfere with the normal secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). After being treated with glucocorticoids, primary rat granulosa cells regulate the mechanism of steroid production through BMP-Smad signaling, leading to a decrease in the secretion of estradiol induced by FSH in the cell.[23] A drop in estrogen levels can lead to follicular dysplasia, decreased sensitivity of the ovaries to gonadotropins, and an overall decline in ovarian function. Depression is often accompanied by increased levels of pro-inflammatory factors such as IL-6, TNF-α, and CRP, leaving the body in a chronic, low-grade state of systemic inflammation. Long-term chronic inflammation can adversely affect tissues and organs and may lead to decreased ovarian reserve and the development of ovarian fibrosis.[24,25] It was found that TNF-α -/- mice had increased granulosa cell proliferation and decreased oocyte apoptosis, and had higher follicular reserve than WT mice.[26] Similarly, IL-1α and IL-1β-KO mice exhibited higher serum anti-Mullerian hormone than WT mice, accompanied by decreased apoptosis signaling in the mouse ovaries.[27] In addition, hormonal changes in a depressed state may further amplify the negative effects of the HPA axis and inflammation, creating a vicious cycle that leads to accelerated decline in ovarian function and early menopause.

Our findings confirm that women with depression face a significantly higher risk of early menopause, aligning with results from prior studies. In a study of 2232 menopausal women, the prevalence of suicidal ideation was found to vary with age at menopause (30.0% for POI, 12.7% for early menopause, and 8.0% for natural menopause).[28] These results support the possibility that depression may affect a woman's age of menopause through multiple pathways, while also revealing the possibility that women with POI are at higher risk for mental health. The association between medicated depression and early menopause was greatest among women who experienced natural menopause before age 40 (OR = 6.6, 95% CI 0.7–58.9), and among women who reported a history of medicated depression for more than 3 years (OR =

4.0, 95% CI = 1.3–12.0). This is the first study to show a link between self-reported history of medicated depression and early menopause.[29] Exposure to chronic psychosocial stress, such as lower income, higher perceived stress and negative attitudes towards menopause, is associated with increased psychological and physical symptoms and earlier onset of menopause (before age 45).[30]

Moreover, our results suggest an association between lower educational attainment, lower PIR, and early menopause, aligning with findings from previous studies.[31–34] Women with higher levels of education had higher scores on the menopausal quality of life assessment. Low socioeconomic status and inadequate living conditions can disrupt an individual's psychological homeostasis and health management, thereby increasing the risk of chronic diseases.[35]

We also found that smoking was strongly associated with a higher risk of early menopause, corroborating previous studies.[36] Tobacco smoke has been shown to impair follicular growth, induce apoptosis, and accelerate ovarian follicle depletion, ultimately reducing ovarian reserve and advancing menopause onset. Cigarette smoke contains about 4000 substances that fall into a variety of chemical categories, including polycyclic aromatic hydrocarbons, heavy metals and alkaloids, which are all compounds with reproductive toxicity.[37] The toxic substances in cigarette smoke can significantly reduce the level of estrogen in the blood by affecting estrogen metabolism and inhibiting aromatase activity. Oxidative stress caused by smoking can cause damage to ovarian tissue through the production of free radicals. There were indications of persistent oxidative stress in ovarian tissue and undamaged oocytes exposed to tobacco smoke, with significant increases in mitochondrial ROS and lipid peroxidation levels, as well as CYP2E1 detoxes, leading to follicle depletion and oocyte dysfunction.[38]

In contrast, we found no effect of age at menarche or parity on the association with premature menopause. An observational study pooling data from postmenopausal women in the UK, Scandinavia, Australia, and Japan suggested that early menarche and nulliparity are risk factors for premature menopause.[39] Additionally, a study utilizing data from the UK Biobank indicated that early age at menarche is a risk factor for early menopause.[40] The discrepancies between our findings and previous results may be attributed to differences in sample sizes as well as variations in the populations studied.

The results of this study provide important implications for clinical practice and public health policy. In women's health management, mental health should be the focus of early intervention. Interventions that target these high-risk groups, such as mental health support and mood management, may help delay ovarian decline and reduce the risk of early menopause.

However, this study has several limitations. First, the study population was derived from a specific cohort of women in the United States, which may limit the generalizability of the findings to other populations. Second, due to the cross-sectional design of this study, we could not determine whether the self-reported conditions were diagnosed before or after menopause; further research should employ prospective designs to explore the association between depression and ANM. Third, the lack of data on reproductive hormone levels such as FSH and AMH in this study prevented an objective assessment of ovarian function. Additionally, the reliance on self-reported data introduces potential recall bias and inaccuracies. Future longitudinal studies will help better to reveal the long-term effects of depression on ovarian function and provide stronger evidence for causal inference. In addition, the geographical scope of the study population can be expanded to improve the extrapolation of the study results. It is also possible to explore in depth whether other possible interventions, such as mental health interventions, can be effective in delaying the onset of early menopause.

Conclusion

In this cross-sectional study, the severity of depression in American women was positively correlated with the risk of early menopause. This suggests that women should pay more attention to their mental health and actively manage depression. For women with depression, early intervention and treatment may help improve their reproductive health and delay menopause.

Abbreviations

ANM, age at natural menopause; NHANES, National Health and Nutrition Examination Survey; PHQ-9, Patient Health Questionnaire-9; PIR, ratio of poverty income; BMI, body mass index; SD, standard deviation; OR, odds ratio; CI, confidence interval; HPA, hypothalamic-pituitary-adrenal; HPO, hypothalamic-pituitary-ovarian; FSH, follicle-stimulating hormone; LH, luteinizing hormone; POI, premature ovarian insufficiency.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author, [ZCMU], upon reasonable request.

Ethics Approval and Informed Consent

The National Health and Nutrition Examination Survey was approved by the National Center for Health Statistics Research Ethics Review Board (https://www.cdc.gov/nchs/nhanes/irba98.htm). The patients/participants provided their written informed consent to participate in this study. The Ethics Committee of the Third Affiliated Hospital of Zhejiang Chinese Medicine University abandoned the ethical approval of this study because NHANES is a publicly accessible database.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

No potential conflict of interest was reported by the authors.

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