International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Nonlinear Association Between Oxidative Balance Score and Premature Menopause: A Cross-Sectional Analysis of NHANES 2007-2018 Data

Cai Xian Qiu*, Meng Qiu*, Ke Xu*, Xi Yu Li, Xin Yu Wang, Xue Cen Wu, Yun Shi

Department of Gynecology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yun Shi, Department of Gynecology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, People's Republic of China, Email zysyun@163.com

Background: Oxidative stress is a critical mediator in ovarian aging, a key process leading to premature menopause (PM), which is defined as menopause before age 40. While the Oxidative Balance Score (OBS), a composite measure of dietary and lifestyle pro- and anti-oxidant exposures, provides valuable insight, its association with PM remains unclear. This study aimed to investigate the association between OBS and PM in a nationally representative US population.

Methods: This cross-sectional study utilized data from 4,128 participants in the National Health and Nutrition Examination Survey (NHANES) 2007–2018. The OBS was calculated from 16 dietary and 4 lifestyle components. Multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), with all analyses accounting for the complex survey design using appropriate NHANES sample weights. The potential nonlinear relationship was explored using restricted cubic splines (RCS).

Results: A higher total OBS was significantly associated with a lower risk of PM (Adjusted OR for the highest compared to the lowest quartile, 0.51; 95% CI, 0.31 to 0.83). The dietary OBS component showed a consistent inverse association. Subgroup analysis suggested potential ethnic variations, although the interaction did not reach statistical significance (P for interaction = 0.054). RCS analysis confirmed a nonlinear inverse association. Further threshold effect analysis identified a turning point at an OBS of 28; the association was significant below this threshold (OR per unit increase, 0.95; 95% CI, 0.93 to 0.97), but this was not observed above it (OR, 1.09; 95% CI, 1.00 to 1.18).

Conclusion: In this nationally representative sample of US women, a higher OBS was associated with a lower risk of PM, particularly below a score of 28. These findings suggest that dietary and lifestyle factors contributing to antioxidant balance may play a role in preserving ovarian function, although prospective studies are required to confirm causality.

Keywords: oxidative balance score, premature menopause, oxidative stress, primary ovarian insufficiency, reproductive aging, NHANES

Introduction

Premature menopause (PM), defined as the cessation of ovarian function before age 40, affects approximately 1% of women globally, with variations linked to genetic and environmental factors.[1] While assisted reproductive technologies have expanded fertility options for affected women, PM remains associated with increased risks of cardiovascular diseases, osteoporosis, type 2 diabetes, mental health disorders, and other health concerns.[2–5] Oxidative stress (OS), an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, is widely recognized as a key factor in ovarian aging and primary ovarian insufficiency (POI), a major precursor to PM.[6] Persistent OS damages

Received: 22 May 2025
Accepted: 10 November 2025
Published: 25 November 2025

ovarian granulosa cells, accelerates follicular atresia, and disrupts hormonal homeostasis, ultimately contributing to ovarian reserve depletion.[7] Specifically, oxidative stress induces apoptosis in ovarian granulosa cells, impairs oocyte quality, and exacerbates the ovarian inflammatory microenvironment through pathways such as the NLRP3 inflammasome, further accelerating follicular atresia.[8–10] Additionally, OS induces chronic inflammatory responses, further exacerbating ovarian dysfunction.[11] Women with PM frequently exhibit reduced antioxidant capacity, including lower glutathione (GSH) levels and decreased superoxide dismutase (SOD) activity, suggesting a potential role of oxidative balance in maintaining ovarian health.[12]

Despite accumulating evidence linking OS to PM, the impact of oxidative balance on ovarian function remains unclear. The Oxidative Balance Score (OBS) is a validated composite measure integrating dietary and lifestyle factors to assess overall oxidative stress burden. Higher OBS has been associated with a lower risk of chronic diseases, including diabetes and cardiovascular disease, but its relationship with PM has not been well established.[13–16] Especially among young women, whether the OBS can serve as a potential early indicator for predicting ovarian function decline remains insufficiently explored in systematic epidemiological studies. This study uses the nationally representative NHANES dataset to examine the association between OBS and PM. NHANES provides rich multi-domain data, including dietary information, lifestyle factors, health assessments, and clinical biomarkers; in this study, we specifically utilized its detailed dietary recall and reproductive health questionnaire data. Such database studies offer advantages including large sample sizes, strong population representativeness, and improved ability to control for confounding factors.[17] By investigating this relationship, we aim to elucidate how oxidative balance influences ovarian aging and provide scientific evidence for targeted public health interventions.

Methods

Research Question and Hypothesis

The objective of this study is to examine the potential relationship between OBS and the risk of PM among adult women in the United States. We hypothesize that a higher OBS is significantly associated with a lower risk of PM. This hypothesis is based on the premise that the balance between antioxidants and pro-oxidants, as reflected by OBS, may play a protective role in ovarian function, thereby contributing to the delayed onset of menopause.

Data Source

The National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics (NCHS), uses a complex multistage probability sampling design to obtain nationally representative data on the US population. The survey, which has been approved by the NCHS Institutional Review Board, with all participants providing informed consent, covers multiple domains including demographics, dietary behaviors, and reproductive health history. For this study, we utilized publicly available data from six consecutive NHANES cycles spanning from 2007 to 2018.

Study Participants

This study utilized data from 6 consecutive NHANES cycles (2007–2018). These specific cycles were selected due to the consistent measurement of key variables, particularly the Physical Activity Questionnaire (PAQ), and the need for a complete dataset. From the initially extracted 59,842 participants, the following exclusion criteria were applied: (1) male participants (n = 29,629); (2) participants younger than 20 years (n = 12,306); (3) missing responses to the "age at menopause" question (n = 10,036); (4) participants who reported regular menstruation in the past 12 months (ie, having at least one menstrual cycle within the last year) (n = 22); (5) participants with other causes of amenorrhea (eg, pregnancy, lactation, or surgical interventions) (n = 2,723); (6) participants with incomplete OBS data (ie, fewer than 20 recorded components) (n = 540); (7) participants with extreme total energy intake (<800 kcal/day or >4,200 kcal/day for men; <500 kcal/day or >3,500 kcal/day for women) (n = 65);[18] (8) participants with missing dietary two-day sample weights (n = 393). After applying these exclusion criteria, a final sample of 4,128 participants was included in the study (Figure 1).

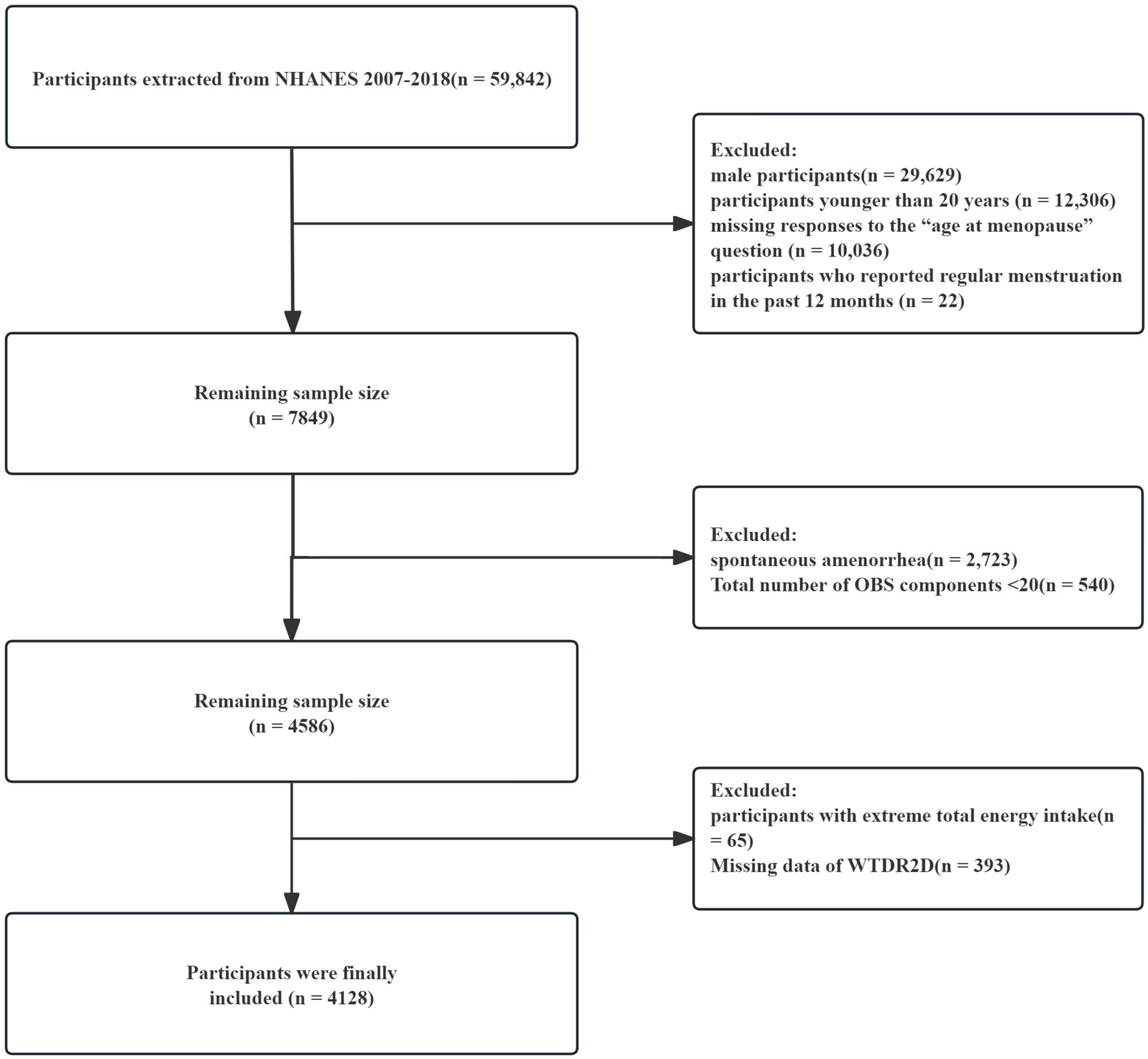

Figure 1 Flowchart of participant selection in the study.

Oxidative Balance Score

The Oxidative Balance Score (OBS) was determined by integrating 16 dietary components and 4 lifestyle factors, including 5 pro-oxidants and 15 antioxidants.[19] The dietary OBS comprises dietary fiber, total fat, total folate, vitamins (B6, B12, C, and E), niacin, carotene, riboflavin, calcium, iron, selenium, copper, magnesium, and zinc, all of which were obtained from dietary recall data. The lifestyle OBS includes four factors: smoking, alcohol consumption, physical activity, and body mass index (BMI). Dietary OBS components were categorized into tertiles, with antioxidant scores assigned as 0, 1, and 2 for the first, second, and third tertiles, respectively, while pro-oxidant scores were assigned in the opposite order. Lifestyle OBS was classified according to specific criteria. Serum cotinine levels were used to assess smoking exposure, accounting for both direct smoking and secondhand smoke exposure. Given that more than one-third of the collected samples had serum cotinine levels ≤0.011, the highest tertile in this study was manually defined as ≤0.011. Alcohol consumption was categorized according to female-specific standards: heavy drinkers (≥15 g/day), non-heavy drinkers (0–15 g/day), and non-drinkers. Physical activity levels were quantified using metabolic equivalents of task (MET), based on the cumulative weekly duration of transportation and moderate-intensity activities.[20] Considering that the study population primarily ranged from 40 to 80 years old, MET was classified into low, moderate, and high levels, with thresholds set at 600 MET-min/week and 3000 MET-min/week.[21]

Total OBS was calculated by summing the scores assigned to each component. Lifestyle OBS was derived by summing the scores for smoking, alcohol consumption, physical activity, and BMI, while dietary OBS was calculated by summing the scores of the 16 dietary components. A higher OBS score indicates greater antioxidant potential and increased antioxidant exposure. The specific calculation methods for OBS are provided in Supplementary Table S1. (Ingredients that make up the oxidative balance score). In our study population, the total OBS ranged from 4 to 36. For categorical analysis, OBS was categorized into quartiles. This approach makes no assumptions about the linearity of the relationship, allows for the assessment of a potential dose-response trend, and provides results that are more readily interpretable in a clinical and public health context.

Covariates

Demographic characteristics, including age, race, marital status, education level, and the poverty-income ratio (PIR), were obtained through standardized household interviews. Age was categorized into four groups, each covering a 20-year range. Race was classified as non-Hispanic White, Mexican American, non-Hispanic Black, and other racial groups. Education level was categorized as less than high school, high school, and more than high school. Poverty status was classified into three groups based on PIR (≤1.3, (1.3, 3.5], and ≥3.5).

In addition, we included common health conditions associated with menopause, including cardiovascular disease (CVD), diabetes, hypertension, and hyperlipidemia. The definitions of these conditions are detailed in the supplementary materials (Table S2). Furthermore, female-specific factors such as age at menarche and live birth count were considered. Age at menarche was classified into early menarche (≤11 years), normal menarche (12–14 years), and late menarche (≥14 years). Live birth count was categorized as 0, 1, 2, or ≥3. For categorical covariates with missing values, the missing data were treated as a separate category in the analyses.

Statistical Analysis

Following the NHANES database usage guidelines, WTDR2D was selected as the study weight, as it is specifically designed for two-day dietary recall data. This choice ensures appropriate bias adjustments, enhances national representativeness, and aligns with the study's objective of investigating the relationship between OBS and PM. Baseline characteristics were analyzed using medians and interquartile ranges (IQRs) for continuous variables with a non-normal distribution, while categorical variables were presented as sample counts and weighted percentages. Group differences across OBS quartiles were assessed using the Wilcoxon rank-sum test for continuous variables and the Rao-Scott chi-square test for categorical variables, providing a comprehensive characterization of the study population. To examine the association between OBS and PM, weighted logistic regression models were applied. Model 1 was an unadjusted crude model, Model 2 adjusted for marital status, education level, poverty status, and race, while Model 3 further incorporated adjustments for hypertension, diabetes, cardiovascular disease, hyperlipidemia, total energy intake, age at menarche, and the number of live births. All regression models accounted for dietary weights to ensure precise estimations. Additionally, OBS was further categorized into dietary and lifestyle components to explore their distinct contributions to PM risk. Interaction analyses were conducted to assess potential effect modifications across subgroups. To investigate potential nonlinear relationships between OBS and PM, we used weighted restricted cubic spline (RCS) analysis with three knots placed at fixed OBS values of 10, 20, and 30. Threshold effect analysis was also performed to identify inflection points where the exposure-outcome relationship may shift. Sensitivity analyses were conducted by sequentially removing each OBS component from Model 3 to evaluate the robustness of the findings. All statistical analyses were performed using R software (version 4.3.3) and DecisionLinn 1.0 (https://analysis.statsape.com), utilizing packages such as *gtsummary, survey, rms, segmented, and ggplot2*. Statistical significance was set at $P < 0.05$ for all two-sided tests.

Statistical Model Validation

To assess the performance of the final multivariable logistic regression model, we conducted a comprehensive validation analysis. We evaluated the model's overall performance using the weighted Brier score. Discrimination, the ability of the model to distinguish between individuals with and without PM, was assessed using the Area Under the Curve (AUC). Calibration, the agreement between predicted probabilities and observed frequencies, was evaluated by calculating the calibration intercept and slope, and by examining the coverage of observed rates within the 95% confidence intervals of predicted probabilities across deciles of risk.

Results

Baseline Characteristics Associated with PM

Table 1 presents the weighted baseline characteristics of participants stratified by OBS quartiles, accounting for complex sampling weights. Compared to individuals in the lowest OBS quartile (Q1), those in the highest quartile (Q4) were more

Table 1 Baseline Characteristics and Socioeconomic Disparities Across OBS Quartiles, NHANES 2007–2018

Characteristic	Total OBS Score					*p* value
	Overall, N = 33,238,928[1]	**Q1Weighted N = 6,015,141 Unweighted n = 925[1]**	**Q2Weighted N = 7,287,533 Unweighted n = 992[1]**	**Q3Weighted N = 8,798,372 Unweighted n = 1,041[1]**	**Q4Weighted N = 11,137,883 Unweighted n = 1,170[1]**	
OBS interquartile range		4≤Total OBS<14	14≤Total OBS<20	20≤Total OBS<26	26≤Total OBS<36	
Menopausal Age	50 (45, 53)	48 (42, 52)	50 (44, 53)	50 (45, 52)	50 (45, 53)	<0.001[1]
Energy intake(kcal)	1,663 (1,328, 2,049)	1,168 (943, 1,393)	1,502 (1,271, 1,768)	1,731 (1,441, 2,081)	2,016 (1,696, 2,376)	<0.001[1]
Race						<0.001[2]
Non-Hispanic White	1,896 (74.0%)	365 (65.0%)	402 (71.3%)	495 (75.7%)	634 (79.4%)	
Mexican American	585 (5.7%)	138 (6.9%)	165 (7.0%)	141 (5.8%)	141 (4.1%)	
Non-Hispanic Black	781 (8.7%)	263 (17.2%)	206 (10.4%)	163 (6.7%)	149 (4.7%)	
Other Race	866 (11.6%)	159 (10.9%)	219 (11.4%)	242 (11.9%)	246 (11.8%)	
Marital Status						<0.001[2]
Married or living with partner	2,102 (60.6%)	394 (49.7%)	503 (59.6%)	538 (62.5%)	667 (65.5%)	
Widowed or Divorced or Separated	1,650 (32.9%)	412 (39.9%)	426 (35.4%)	406 (31.8%)	406 (28.4%)	
Never married	374 (6.5%)	119 (10.4%)	63 (5.0%)	96 (5.7%)	96 (6.0%)	
Missing	2 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)	
Education						<0.001[2]
Below high school	1,044 (15.2%)	321 (23.2%)	313 (20.8%)	232 (13.7%)	178 (8.2%)	
High school	995 (25.9%)	259 (31.5%)	244 (30.1%)	247 (26.5%)	245 (19.6%)	
Above high school	2,085 (58.9%)	345 (45.3%)	435 (49.1%)	558 (59.7%)	747 (72.2%)	
Missing	4 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.1%)	0 (0.0%)	
Poverty Ratio						<0.001[2]
≤ 1.3	1,157 (17.9%)	373 (31.4%)	292 (21.2%)	251 (14.2%)	241 (11.3%)	
(1.3, 3.5]	1,386 (31.4%)	307 (33.5%)	344 (30.2%)	378 (34.9%)	357 (28.2%)	
>3.5	1,175 (43.3%)	151 (26.1%)	248 (39.9%)	305 (44.4%)	471 (54.0%)	
Missing	410 (7.4%)	94 (9.0%)	108 (8.7%)	107 (6.4%)	101 (6.5%)	
Diabetes						<0.001[2]
Yes	1,005 (17.8%)	291 (24.8%)	272 (22.2%)	253 (18.1%)	189 (11.0%)	
No	3,123 (82.2%)	634 (75.2%)	720 (77.8%)	788 (81.9%)	981 (89.0%)	
Hypertension						0.108[2]
Yes	1,085 (22.1%)	258 (24.2%)	281 (25.2%)	272 (20.8%)	274 (20.0%)	
No	3,043 (77.9%)	667 (75.8%)	711 (74.8%)	769 (79.2%)	896 (80.0%)	
Hyperlipidemia						0.151[2]
Yes	3,009 (73.1%)	687 (78.4%)	716 (71.1%)	766 (73.9%)	840 (71.0%)	
No	1,106 (26.7%)	232 (21.4%)	274 (28.8%)	272 (26.0%)	328 (28.8%)	
Missing	13 (0.2%)	6 (0.2%)	2 (0.2%)	3 (0.2%)	2 (0.2%)	
CVD						<0.001[2]
Yes	542 (11.1%)	183 (16.7%)	135 (11.6%)	119 (10.4%)	105 (8.2%)	
No	3,586 (88.9%)	742 (83.3%)	857 (88.4%)	922 (89.6%)	1,065 (91.8%)	

(*Continued*)

Table 1 (Continued).

Characteristic	Total OBS Score					p value
	Overall, N = 33,238,928[1]	Q1Weighted N = 6,015,141 Unweighted n = 925[1]	Q2Weighted N = 7,287,533 Unweighted n = 992[1]	Q3Weighted N = 8,798,372 Unweighted n = 1,041[1]	Q4Weighted N = 11,137,883 Unweighted n = 1,170[1]	
Live Birth Count						0.527[2]
0	134 (4.0%)	26 (4.8%)	33 (2.9%)	40 (4.6%)	35 (3.8%)	
1	566 (16.4%)	120 (15.7%)	132 (16.4%)	148 (17.8%)	166 (15.8%)	
2	1,086 (31.1%)	217 (26.8%)	247 (31.0%)	277 (30.8%)	345 (33.7%)	
≥3	1,969 (38.5%)	494 (44.7%)	502 (39.1%)	469 (36.5%)	504 (36.2%)	
Missing	373 (10.0%)	68 (8.0%)	78 (10.6%)	107 (10.3%)	120 (10.5%)	
Menarche						0.549[2]
Normal Menarche	2,590 (64.8%)	558 (61.4%)	611 (63.9%)	666 (65.3%)	755 (66.8%)	
Early Menarche	822 (19.6%)	190 (20.8%)	205 (21.3%)	214 (21.5%)	213 (16.3%)	
Late Menarche	686 (14.6%)	167 (16.8%)	172 (14.0%)	157 (12.5%)	190 (15.6%)	
Missing	30 (1.0%)	10 (1.0%)	4 (0.9%)	4 (0.8%)	12 (1.3%)	

Note: [1] Kruskal–Wallis rank-sum test for complex survey samples [2] Chi-square test with Rao & Scott's second-order correction.
Abbreviations: OBS, Oxidative Balance Score, a composite index of pro-oxidant and antioxidant exposures from diet and lifestyle; PM, Premature Menopause, defined as cessation of ovarian function before age 40; NHANES, National Health and Nutrition Examination Survey, a nationally representative survey of the US population.

likely to be non-Hispanic White and married or cohabiting. Higher OBS scores were associated with greater educational attainment, higher socioeconomic status, and increased total dietary energy intake, while the prevalence of diabetes, hypertension, and cardiovascular disease significantly declined across quartiles (all $P < 0.05$). Additional subgroup analysis stratified by PM status is provided in Supplementary Table S3.

Association Between OBS and PM Risk

Table 2 presents findings from three logistic regression models using complex sampling weights to examine the association between OBS and PM risk. Model 1 is unadjusted, Model 2 adjusts for marital status, education level, poverty, and race, while Model 3 includes full adjustments for all covariates to ensure a comprehensive analysis.

Analyzing total OBS as a continuous variable showed a consistent association with lower PM risk across all models. In the unadjusted model, each one-unit increase in OBS was linked to a 5% reduction in PM risk (OR=0.95, 95% CI: 0.93–0.98, P<0.001). After adjusting for demographic factors (Model 2), the association remained significant, with a 4%

Table 2 Association Between Oxidative Balance Score (OBS) and Premature Menopause (PM)

Characteristic	Model 1			Model 2			Model 3		
	OR[1]	95% CI[1]	p value	OR[1]	95% CI[1]	p value	OR[1]	95% CI[1]	p value
Total OBS (Continuous)	0.95	0.93–0.98	<0.001	0.96	0.94–0.99	<0.003	0.96	0.93–0.99	0.006
Total OBS (Quartiles)									
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	0.73	0.45–1.17	0.189	0.84	0.50–1.41	0.509	0.85	0.52–1.41	0.535
Q3	0.51	0.33–0.79	0.003	0.62	0.39–0.97	0.037	0.59	0.36–0.98	0.040
Q4	0.42	0.27–0.65	<0.001	0.52	0.33–0.81	0.004	0.51	0.31–0.83	0.007
P for trend			<0.001			<0.001			<0.001

Notes: Total OBS quartiles were defined as: Q1 (4≤OBS<14), Q2 (14≤OBS<20), Q3 (20≤OBS<26), and Q4 (26≤OBS≤36).Model 1: Unadjusted. Model 2: Adjusted for marital status, education status, poverty status, and ethnicity.Model 3: Adjusted for all covariates in Model 2 plus diabetes, hypertension, CVD, live birth count, hyperlipidemia, and age at menarche.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; OBS, Oxidative Balance Score; PM, Premature Menopause.

risk reduction per unit increase (OR=0.96, 95% CI: 0.94–0.99, *P*=0.003). Even in the fully adjusted model (Model 3), the protective effect persisted (OR=0.96, 95% CI: 0.93–0.99, *P*=0.006).

When categorized into quartiles (Q1–Q4), higher total OBS levels were linked to a lower risk of PM, with a clear dose-response trend (*P* for trend < 0.001). Compared to the lowest quartile (Q1), women in the highest quartile (Q4) had a 58% lower PM risk in the unadjusted model (OR=0.42, 95% CI: 0.27–0.65, *P*<0.001). After adjusting for demographic factors, the risk reduction was 48% (OR=0.52, 95% CI: 0.33–0.81, *P*=0.004), and in the fully adjusted model, it remained at 49% (OR=0.51, 95% CI: 0.31–0.83, *P*=0.007).

These results indicate a strong and consistent protective effect of higher total OBS against PM, regardless of whether it was analyzed as a continuous or categorical variable. Trend analysis further supports the gradient protective effect of total OBS (*P* for trend < 0.001).

Subgroup Analysis

Table 3 illustrates the relationship between total OBS and PM. A fully adjusted multivariable logistic regression analysis revealed that, in the majority of subgroups, total OBS exhibited a significant negative association with the incidence of PM. For example, the protective effect of total OBS was particularly pronounced in non-Hispanic White individuals,

Table 3 Subgroup Analysis of the Association Between Total OBS and Premature Menopause (PM)

Subgroup	N	Adjusted OR (95% CI)[1]	*p* value	*P* for Interaction
Overall	27,252,821 (100%)	0.94 (0.91–0.98)	0.001	
Race				0.054
Mexican American	1,527,806 (5.6%)	0.95 (0.88–1.03)	0.218	
Non-Hispanic White	20,383,662 (75%)	0.95 (0.91–0.99)	0.015	
Non-Hispanic Black	2,277,870 (8.4%)	1.02 (0.98–1.06)	0.462	
Other Race	3,063,482 (11%)	0.88 (0.82–0.95)	0.001	
Education Status				0.698
Below high school	4,219,896 (15%)	0.94 (0.87–1.02)	0.132	
High school	7,068,708 (26%)	0.93 (0.89–0.98)	0.004	
Above high school	15,964,217 (59%)	0.96 (0.92–1.01)	0.152	
Poverty Status				0.733
≤ 1.3	5,248,799 (19%)	0.95 (0.91–1.00)	0.035	
(1.3, 3.5]	9,267,394 (34%)	0.90 (0.86–0.94)	<0.001	
>3.5	12,736,629 (47%)	0.99 (0.93–1.05)	0.804	
Marital Status				0.077
Married or living with partner	16,888,453 (62%)	0.94 (0.90–0.99)	0.017	
Widowed or Divorced or Separated	9,335,888 (34%)	0.95 (0.91–0.99)	0.031	
Never married	1,028,480 (3.8%)	1.00 (0.89–1.12)	0.968	
Diabetes				0.219
No	22,182,710 (81%)	0.94 (0.91–0.98)	0.003	
Yes	5,070,111 (19%)	0.94 (0.87–1.01)	0.1	
Hypertension				0.961
No	21,037,264 (77%)	0.94 (0.91–0.98)	0.003	
Yes	6,215,557 (23%)	0.93 (0.89–0.98)	0.01	
Hyperlipidemia				0.945
No	7,090,900 (26%)	0.95 (0.89–1.00)	0.05	
Yes	20,161,921 (74%)	0.94 (0.91–0.98)	0.006	
CVD				0.115
No	24,033,764 (88%)	0.95 (0.91–0.98)	0.006	
Yes	3,219,057 (12%)	0.92 (0.86–0.99)	0.034	

(*Continued*)

Table 3 (Continued).

Subgroup	N	Adjusted OR (95% CI)[1]	*p* value	*P* for Interaction
Menarche				0.86
Normal Menarche	17,918,047 (66%)	0.93 (0.89–0.98)	0.009	
Early Menarche	5,428,106 (20%)	0.99 (0.92–1.05)	0.675	
Late Menarche	3,906,668 (14%)	0.94 (0.87–1.00)	0.07	
Live Birth Count				0.094
0	1,248,033 (4.6%)	1.10 (0.89–1.35)	0.389	
1	4,967,717 (18%)	0.93 (0.86–0.99)	0.033	
2	9,455,339 (35%)	0.95 (0.88–1.02)	0.176	
≥3	11,581,732 (42%)	0.94 (0.90–0.98)	0.009	

Note: N represents the weighted population count for each subgroup.
Abbreviations: CI, Confidence Interval; OBS, Oxidative Balance Score; OR, Odds Ratio; PM, Premature Menopause.

those with a high school education, individuals with a poverty-income ratio of 1.3–3.5, and those with normal menarche ($P < 0.001$). This suggests that total OBS may delay menopause through multiple mechanisms.

In a few specific subgroups, such as Mexican Americans, individuals with low education levels, and unmarried individuals, no significant association was observed. Interaction analysis indicated that the interaction effect of racial subgroups approached significance ($P = 0.054$), while interactions with other variables did not show statistical significance. Overall, total OBS significantly reduced PM risk in most populations, further emphasizing its potential protective effect.

RCS Analysis

After adjusting for all confounding factors, we utilized RCS curves to investigate the association between OBS (total OBS, Dietary OBS, and Lifestyle OBS) and PM. The analysis revealed a significant nonlinear negative relationship between total OBS and PM ($P = 0.025$, Figure 2. A). In contrast, a significant linear relationship was observed between Dietary OBS and PM (P for nonlinearity = 0.109, Figure 2. B), while no evidence of nonlinearity was found between Lifestyle OBS and PM ($P > 0.05$).

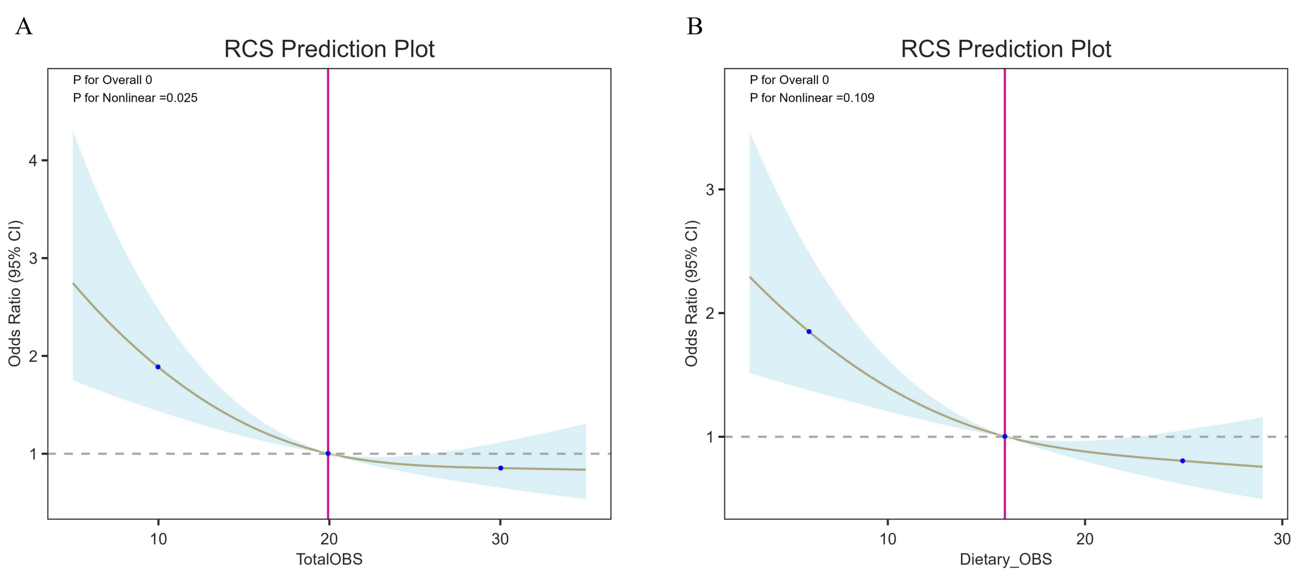

Figure 2 Restricted cubic spline (RCS) analysis of the association between Oxidative Balance Score (OBS) and the risk of premature menopause (PM): (**A**) Total OBS; (**B**) Dietary OBS.

Table 4 Threshold Effect Analysis of the Association Between Total OBS and PM

Variable	Odds Ratio (OR)	95% CI	*P* value
Linear Model	0.96	0.94–0.98	<0.001
Two-piecewise Model (Threshold at OBS = 28)			
Association below threshold (OBS ≤ 28)	0.95	0.93–0.97	<0.001
Association above threshold (OBS > 28)	1.09	1.00–1.18	0.044
Log-likelihood ratio test			0.007

Abbreviations: CI, Confidence Interval; OBS, Oxidative Balance Score; OR, Odds Ratio; PM, Premature Menopause.

Furthermore, we identified a threshold within the nonlinear relationship between total OBS and PM, specifically at a value of 28. Based on this threshold, we conducted a threshold effect analysis. On the left side of the threshold (OBS ≤ 28), the effect size was 0.95 (95% CI: 0.93–0.97), indicating that higher OBS levels were associated with a reduced risk of PM. However, on the right side of the threshold (OBS > 28), the effect size increased to 1.09 (95% CI: 1.00–1.18), suggesting that higher OBS levels may no longer confer a significant protective effect. The results of the threshold effect analysis are presented in Table 4. Additionally, sensitivity analysis showed that excluding individual OBS components did not significantly affect its association with PM risk, confirming the robustness of our findings (Supplementary Table S4).

Model Performance and Validation

The final adjusted model underwent a comprehensive validation analysis. While the model's discrimination was modest (AUC = 0.661; 95% CI, 0.627–0.695), its calibration performance was excellent. The weighted Brier score was low at 0.0974, and the model was well-calibrated with a calibration slope of 1.00 (95% CI, 0.87–1.13) and an intercept of 0.00 (95% CI, −0.25–0.25). Furthermore, across deciles of predicted risk, 70% of the observed PM rates fell within their corresponding 95% confidence intervals. Detailed results of the validation analyses are presented in Supplementary Table S5.

Discussion

In this large, nationally representative sample of US women, we found that a higher total OBS was significantly associated with a lower risk of PM, with a clear dose-response trend across quartiles. This inverse relationship remained robust after adjusting for multiple covariates and was confirmed by sensitivity analyses. A key finding of our study is the nonlinear nature of this association. Threshold effect analysis identified a turning point at an OBS of 28, a value that falls within the highest quartile of our study population. This suggests that while increasing OBS is protective, the benefits may plateau at higher levels of antioxidant balance, a finding with important clinical implications for public health interventions. As the OBS provides a comprehensive assessment of various pro- and anti-oxidant factors, this nonlinear inverse association strongly reflects the underlying relationship between the body's overall oxidative state and the risk of PM.

Our findings, which directly address the risk of PM, have significant implications for the broader clinical spectrum of POI. PM is recognized as the definitive endpoint of the progressive loss of ovarian function that characterizes POI.[22] Therefore, by identifying factors associated with PM, our study provides critical insights into the terminal stages of this condition and offers potential avenues for early intervention strategies aimed at mitigating the overall decline in ovarian function. This is biologically plausible, as previous studies have firmly established that OS is a key driver of ovarian aging.[23] Specifically, excessive ROS can damage DNA and mitochondria in ovarian granulosa cells, induce their apoptosis, accelerate follicular atresia, and exacerbate the ovarian inflammatory microenvironment through pathways such as the NLRP3 inflammasome, ultimately leading to the depletion of the ovarian reserve.[24,25]

Dietary antioxidants have demonstrated significant potential in mitigating such oxidative stress-induced damage, a concept supported by high-level evidence. For instance, dietary patterns rich in antioxidants, such as the Mediterranean diet, are thought to improve ovarian reserve by enhancing endogenous antioxidant enzyme activity and protecting the ovarian microenvironment.[26] Our findings reinforce this evidence, suggesting that a holistic assessment of both dietary and lifestyle factors, as captured by the OBS, is crucial. Indeed, a higher OBS has been linked to a lower risk of other reproductive conditions like female infertility and endometriosis, further underscoring the importance of oxidative homeostasis in female reproductive health.[27–29]

A key strength of our study is the rigorous validation of the statistical model. The findings of good calibration, as reflected by a low weighted Brier score of 0.097 and near-ideal calibration slope and intercept (1.00 and 0.00, respectively), support that the observed nonlinear association is robust. At the same time, we acknowledge the model's modest discrimination (AUC = 0.661), which indicates that OBS alone is not sufficient as an individual-level predictive tool for premature menopause. However, for an etiological investigation such as ours, calibration is of greater importance than discrimination. Good calibration ensures that the model provides unbiased and reliable risk estimates at the population level, thereby reinforcing the validity of the associations we report.

Beyond its methodological rigor, a major contribution of our study is that, to our knowledge, this is the first to specifically investigate the association between the comprehensive OBS and PM risk using a large, nationally representative dataset. The robust methodology and large sample size lend credibility to our findings and enhance their generalizability to the broader US population. This provides a strong evidence base for the public health implications of promoting an antioxidant-rich lifestyle.

Limitation

However, some limitations should be acknowledged. First, the cross-sectional design limits our ability to establish causal relationships. Second, the reliance on self-reported dietary and lifestyle data introduces the potential for recall bias. This could lead to non-differential misclassification of exposures, which would typically bias the results towards the null, suggesting our reported association might be an underestimation. Third, our study lacked direct oxidative stress biomarkers, which restricts mechanistic interpretation. Additionally, PM diagnosis was based on self-reported menstrual history rather than clinical hormone assays, which may affect diagnostic precision. Lastly, as NHANES primarily represents non-institutionalized civilian individuals from the United States, further studies in diverse ethnic groups are needed to assess the generalizability of these findings.

Conclusion

In conclusion, this large, nationally representative cross-sectional study demonstrates a significant inverse association between the Oxidative Balance Score and the risk of premature menopause. The identification of a nonlinear relationship with a clear threshold effect provides novel insights, suggesting that the protective benefits of a pro-antioxidant balance may plateau at higher levels. In addition, the robustness of our findings is supported by comprehensive validation analyses, which further reinforces the reliability of the reported associations. These findings underscore the critical role of dietary and lifestyle interventions in preserving ovarian function and provide a strong rationale for future prospective studies to confirm causality and refine public health recommendations.

Future Directions

To strengthen causal inference and mechanistic understanding, future research should incorporate prospective cohort studies to validate the long-term effects of a high OBS on ovarian aging. Randomized controlled trials assessing the impact of antioxidant-rich diets on PM risk are also needed, along with biomarker-driven studies integrating oxidative stress markers and reproductive hormone levels.

Data Sharing Statement

The datasets analyzed for this study can be found in the National Health and Nutrition Examination Survey (NHANES) database https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics Statement

This study is a secondary analysis of the publicly available, fully anonymized National Health and Nutrition Examination Survey (NHANES) dataset. The original NHANES protocols were approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and all participants provided written informed consent. According to the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (National Health Commission of China, 2023, Article 32, Items 1 and 2), studies using anonymized, publicly available databases are exempt from institutional ethical review. Therefore, this research was exempt from further approval.

Acknowledgments

We sincerely thank Diya Xie from the Department of General Surgery, Fuzhou First General Hospital Affiliated with Fujian Medical University, Fuzhou, Fujian, China, for providing additional data that contributed to the validation process of this study.

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.

Funding

This study was supported by the Beijing Natural Science Foundation (Grant No. 7232292) and the "Revealing the Leader" Project of Beijing University of Chinese Medicine (Grant No. 2025 JYB JBGS 002).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Leone T, Brown L, Gemmill A. Secular trends in premature and early menopause in low-income and middle-income countries. *BMJ Glob Health*. 2023;8(6):e012312. doi:10.1136/bmjgh-2023-012312
2. Honigberg MC, Zekavat SM, Aragam K, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA*. 2019;322(24):2411. doi:10.1001/jama.2019.19191
3. Jones AR, Enticott J, Ebeling PR, Mishra GD, Teede HT, Vincent AJ. Bone health in women with premature ovarian insufficiency/early menopause: a 23-year longitudinal analysis. *Hum Reprod*. 2024;39(5):1013–1022. doi:10.1093/humrep/deae037
4. Lambrinoudaki I, Paschou SA, Armeni E, Goulis DG. The interplay between diabetes mellitus and menopause: clinical implications. *Nat Rev Endocrinol*. 2022;18(10):608–622. doi:10.1038/s41574-022-00708-0
5. Xu M, Yin X, Gong Y. Association of premature natural and surgical menopause with incidence of depression requiring hospitalization: a prospective cohort study. *Am J Obstet Gynecol*. doi:10.1016/j.ajog.2024.11.002
6. Stuenkel CA, Gompel A. Primary ovarian insufficiency. *N Engl J Med*. 2023;388(2):154–163. doi:10.1056/NEJMcp2116488
7. Liang J, Gao Y, Feng Z, Zhang B, Na Z, Li D. Reactive oxygen species and ovarian diseases: antioxidant strategies. *Redox Biol*. 2023;62:102659. doi:10.1016/j.redox.2023.102659
8. Liu S, Jia Y, Meng S, Luo Y, Yang Q, Pan Z. Mechanisms of and potential medications for oxidative stress in ovarian granulosa cells: a review. *Int J Mol Sci*. 2023;24(11):9205. doi:10.3390/ijms24119205
9. Moustakli E, Stavros S, Katopodis P, et al. Oxidative stress and the NLRP3 inflammasome: focus on female fertility and reproductive health. *Cells*. 2025;14(1):36. doi:10.3390/cells14010036
10. Yan F, Zhao Q, Li Y, et al. The role of oxidative stress in ovarian aging: a review. *Jovarian Res*. 2022;15(1):100. doi:10.1186/s13048-022-01032-x
11. Zeng Y, Wang C, Yang C, Shan X, Meng XQ, Zhang M. Unveiling the role of chronic inflammation in ovarian aging: insights into mechanisms and clinical implications. *Hum Reprod*. 2024;39(8):1599–1607. doi:10.1093/humrep/deae132
12. Xu H, Mao X, Nie Z, Li Y. Oxr1a prevents the premature ovarian failure by regulating oxidative stress and mitochondrial function in zebrafish. *Free Radic Biol Med*. 2023;203:102–113. doi:10.1016/j.freeradbiomed.2023.04.002
13. Li Y. Adherence to an antioxidant diet and lifestyle is associated with reduced risk of cardiovascular disease and mortality among adults with nonalcoholic fatty liver disease: evidence from NHANES 1999–2018. *Front Nutr*. 2024;11. doi:10.3389/fnut.2024.1361567
14. Qu H. The association between oxidative balance score and periodontitis in adults: a population-based study. *Front Nutr*. 2023;10. doi:10.3389/fnut.2023.1138488
15. Xu Z, Xue Y, Wen H, Chen C. Association of oxidative balance score and lung health from the national health and nutrition examination survey 2007–2012. *Front Nutr*. 2023;9. doi:10.3389/fnut.2022.961950

16. Hernández-Ruiz Á, García-Villanova B, Guerra-Hernández E, Amiano P, Ruiz-Canela M, Molina-Montes E. A review of a priori defined oxidative balance scores relative to their components and impact on health outcomes. *Nutrients*. 2019;11(4):774. doi:10.3390/nu11040774
17. Zhao Y, Fang M, Fang M. Research trends of rheumatoid arthritis and depression from 2019 to 2023: a bibliometric analysis. *J Multidisciplinary Healthcare*. 2024;17:4465–4474. doi:10.2147/JMDH.S478748
18. Delanaye P, Schaeffner E, Cozzolino M, et al. The new, race-free, chronic kidney disease epidemiology consortium (CKD-EPI) equation to estimate glomerular filtration rate: is it applicable in Europe? A position statement by the european federation of clinical chemistry and laboratory medicine (EFLM). *Clin Chem Lab Med CCLM*. 2023;61(1):44–47. doi:10.1515/cclm-2022-0928
19. Zhang W, Peng SF, Chen L, Chen HM, Cheng XE, Tang YH. Association between the oxidative balance score and telomere length from the national health and nutrition examination survey 1999-2002. *Oxid Med Cell Longevity*. 2022;2022(1):1345071. doi:10.1155/2022/1345071
20. Tian X, Xue B, Wang B, et al. Physical activity reduces the role of blood cadmium on depression: a cross-sectional analysis with NHANES data. *Environ Pollut*. 2022;304:119211. doi:10.1016/j.envpol.2022.119211
21. Chen L, Cai M, Li H, et al. Risk/benefit tradeoff of habitual physical activity and air pollution on chronic pulmonary obstructive disease: findings from a large prospective cohort study. *BMC Med*. 2022;20(1):70. doi:10.1186/s12916-022-02274-8
22. Laven JSE, Louwers YV. Can we predict menopause and premature ovarian insufficiency? *Fertil Sterility*. 2024;121(5):737–741. doi:10.1016/j.fertnstert.2024.02.029
23. Smits MA, Schomakers BV, van WM, et al. Human ovarian aging is characterized by oxidative damage and mitochondrial dysfunction. *Hum Reprod Oxf Eng*. 2023;38:2208–2220. doi:10.1093/humrep/dead177
24. Shi Y, Zhu XT, Zhang S, et al. Premature ovarian insufficiency: a review on the role of oxidative stress and the application of antioxidants. *Front Endocrinol*. 2023:14. doi:10.3389/fendo.2023.1172481.
25. Immediata V, Ronchetti C, Spadaro D, Cirillo F, Levi-Setti PE. Oxidative stress and human ovarian response—from somatic ovarian cells to oocytes damage: a clinical comprehensive narrative review. *Antioxidants*. 2022;11(7):1335. doi:10.3390/antiox11071335
26. Shelling AN, Ahmed Nasef N. The role of lifestyle and dietary factors in the development of premature ovarian insufficiency. *Antioxidants*. 2023;12(8):1601. doi:10.3390/antiox12081601
27. Su Z, Ding P, Su W, et al. Association between oxidative balance score and female infertility from the national health and nutrition examination survey 2013–2018. *Front Endocrinol*. 2024:15. doi:10.3389/fendo.2024.1386021.
28. Zhou X, Shen W, Zhu J, Chen Y, Zhang J. Association between the oxidative balance score and endometriosis: a population-based study. *Int J Womens Health*. 2024;16:1293–1301. doi:10.2147/IJWH.S466189
29. Lei X, Liu X, Yu C, et al. Higher oxidative balance score is associated with lower female infertility: a cross-sectional study. *Front Nutr*. 2024:11. doi:10.3389/fnut.2024.1484756.