Mediation roles of oxidative stress, inflammation, and insulin resistance biomarkers in the sitting time-depression association among U.S. adults

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Highlights

- Sitting time positively associated with depression among U.S. adults.
- Oxidative stress partially mediates sitting time–depression association.
- Inflammatory biomarkers significantly mediate sedentary effects on depression.
- Insulin resistance acts as a biological pathway linking sitting time to depression.
- Findings highlight biomarker-based targets for sedentary behavior interventions.

Abstract

Objective

This study aimed to investigate the mediating roles of biomarkers of oxidative stress, inflammation, and insulin resistance in the association between sitting time and depression, and to determine the threshold value of sitting time linked to elevated depression rate.

Methods

Nationally representative data from the United States were analyzed, including 22,410 adults. Sitting time was self-reported using a Global Physical Activity Questionnaire (GPAQ) based interview item. Depression was assessed with the Patient Health Questionnaire-9 (PHQ-9), with a score of ≥10 indicating depression. Mediators included biomarkers of oxidative stress (GGT, UA, HDL, UHR), inflammation (NLR, MLR, NMLR, HRR, RAR, SIRI, SII), and insulin resistance (TYG, TYG_BMI, TYG_WHTR, HOMA_IR, METS_IR). Associations and mediation effects were examined using logistic regression, linear regression, restricted cubic spline (RCS) analyzes, and Bayesian mediation models, adjusted for demographic and comorbidity confounders.

Results

Sitting time ≥ 8 h per day was significantly associated with increased rate of depression (OR = 1.39, 95% CI: 1.17–1.66). RCS analysis revealed a nonlinear J-shaped relationship between sitting time and depression (P for nonlinear =0.010), with the curve nadir located around 3.3 h (P = 0.004). Insulin resistance biomarkers showed the strongest mediation effects, with TYG_WHTR accounting for the largest proportion (11.45%), followed by METS_IR (9.25%), TYG_BMI (9.17%), and HOMA_IR (1.53%). Among inflammatory markers, RAR (5.03%) had the highest mediating effect, followed by SIRI (2.36%), NLR (1.26%), NMLR (1.22%), and SII (1.08%). For oxidative stress, HDL and UHR mediated 3.45% and 2.22% of the sitting time–depression association, respectively.

Conclusion

Sitting time is associated with depression rate partly mediated by biomarkers of oxidative stress, inflammation, and, most notably, insulin resistance. These findings suggest that reducing sitting time is associated with a lower depression risk, and this association may be accompanied by improvements in related biological pathways such as insulin resistance.

Keywords: Depression, Inflammation. Insulin resistance; Mediation analysis; Oxidative stress; Sitting time

1. Background

Sedentary behavior has become a prominent feature of modern lifestyles, and its high prevalence is closely linked to increased risks for various chronic diseases. Epidemiological evidence indicates that prolonged sitting time is an independent risk factor for numerous adverse health outcomes, including cardiovascular diseases, metabolic syndrome, type 2 diabetes mellitus (T2DM), and certain cancers (Pinto et al., 2023; Wu et al., 2022; Zheng et al., 2018; Hermelink et al., 2022). In recent years, there has been growing attention to the impact of sedentary behavior on mental health, particularly regarding depressive symptoms and depression. Multiple large-scale population-based studies have demonstrated a significant positive association between self-reported daily sedentary time and both elevated depressive symptom scores and increased risk of depression (Wang et al., 2019; Guo et al., 2024).

Although the association between sedentary behavior and depression has been preliminarily established, its underlying biological mechanisms remain incompletely understood. Elucidating the pathophysiological pathways linking these phenomena is critical for advancing disease understanding, identifying high-risk populations, and formulating precise intervention strategies (Chen et al., 2025). Currently, oxidative stress, chronic low-grade inflammation, and insulin resistance are considered key pathophysiological links that connect unhealthy lifestyles with a wide range of chronic conditions, including mental disorders (Jomova et al., 2023; Leuti et al., 2020; Mattson et al., 2017). Previous studies have proposed the following explanations for these factors:

1) Oxidative Stress: Prolonged sedentary time can lead to reduced energy expenditure,

impaired mitochondrial function, and weakened antioxidant defenses, thereby intensifying the production and accumulation of reactive oxygen species (ROS) and causing oxidative stress (Apel and Hirt, 2004). Excessive oxidative stress may damage neurons, disrupt neurotransmitter metabolism and signaling, and contribute to neuroinflammatory processes, all of which have been implicated in the pathogenesis of depression (Zheng et al., 2025; Jindal et al., 2013).

2) Inflammatory Markers: Sedentary behavior has been shown to promote the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), resulting in a state of chronic low-grade systemic inflammation (Liu et al., 2021; Illán-Gómez et al., 2012). These inflammatory mediators can cross the blood-brain barrier and directly affect the central nervous system, interfering with neuroplasticity, monoamine neurotransmitter function, and the hypothalamic-pituitary-adrenal (HPA) axis (Dudesek et al., 2014; Chrousos, 1995). Such processes are recognized as important biological underpinnings for the development and progression of depression.

3) Insulin Resistance: Extended periods of sedentary behavior markedly reduce skeletal muscle glucose uptake and utilization, serving as a major contributor to systemic insulin resistance (Garthwaite et al., 2023). Notably, insulin signaling pathways also exist in the central nervous system, insulin resistance may impact brain energy metabolism and, through mechanisms involving neurotransmitter dysfunction, augmented neuroinflammation, and increased oxidative stress, be associated with a heightened risk of depression (Duarte, 2023; Masenga et al., 2023). Increasing evidence suggests that insulin resistance may represent a potential pathophysiological feature of mood disorders, particularly depression (Fernandes et al., 2022; Wang et al., 2023).

Collectively, these findings suggest that oxidative stress, inflammatory markers, and insulin resistance may play key mediating roles in the relationship between sedentary behavior and increased depression risk. However, there remains a paucity of studies

that simultaneously examine the combined mediating effects of these three critical biological markers in the sitting time–depression association, especially within nationally representative large-scale populations. Furthermore, identifying the optimal "sitting time" cutoff associated with significant health risks is crucial for the development of public health guidelines and the design of individualized behavioral interventions. Considerable heterogeneity exists in the definitions and thresholds of sedentary behavior across existing studies (Wu et al., 2023), highlighting the urgent need for investigation and validation of meaningful cutoff values for sedentary time using large samples and hard endpoints.

Against this backdrop, the present study aims to leverage data from the National Health and Nutrition Examination Survey (NHANES), a large and nationally representative database enriched with comprehensive biomarker and questionnaire data. The primary objective is to systematically evaluate the mediating roles of oxidative stress markers, inflammatory factors, and insulin resistance indices in the association between self-reported sitting time and depression, and to elucidate the potential biological pathways through which sedentary behavior may impact depression risk. A secondary objective is to employ statistical methods to identify and determine the optimal cutoff value of sitting time associated with significantly increased depression rate, thereby providing more targeted scientific evidence for future public health recommendations aimed at reducing sedentary behavior and preventing depression. The findings of this study are expected to advance our understanding of the biological mechanisms underlying the detrimental impact of sedentary behavior on mental health and to inform the identification of intervention targets, individual risk assessment, and development of precision strategies for depression prevention.

2. Materials and methods

2.1. Participants

The participants in this study were drawn from the U.S. NHANES. NHANES is a nationally representative cross-sectional survey conducted by the National Center for Health Statistics (NCHS), part of the Centers for Disease Control and Prevention (CDC). Initiated in the 1960s, NHANES has operated as a continuous program since 1999. Each year, a stratified, multistage probability sampling design is used to select approximately 5000 participants from the U.S. civilian, non-institutionalized population, with each individual representing a specific segment of the national population through sampling weights. The survey combines in-home interviews to collect demographic, socioeconomic, dietary, and health behavior data, with physical examinations and laboratory measurements (blood, urine, etc.) conducted at Mobile Examination Centers (MECs) to comprehensively assess health and nutritional status (Mo et al., 2023). NHANES data are released in two-year cycles and are freely accessible, serving as a key resource for epidemiological research and public health policy development. The survey adheres to the Declaration of Helsinki, and its protocols, including secondary data analyzes, are approved by the CDC Institutional Review Board (IRB). Written informed consent is obtained from all participants.

For this analysis, the data were based on a previously collated and standardized NHANES 1988–2018 dataset, initially including 101,316 participants. This dataset harmonizes variables across cycles and is designed to support high-throughput exposome-health research. Using this standardized dataset helps ensure consistency in variable definitions when merging data across cycles and provides a reliable foundation for handling survey weights (Nguyen et al., 2023). For the purposes of this analysis, we excluded participants with missing data on depression, sitting time, or demographic variables. The final analytic sample consisted of 22,410 participants. Details of the participant exclusion process are depicted in Supplementary Fig. S1.

2.2. Assessment of depression

Depression was the outcome variable in this study and was assessed by trained interviewers using the Patient Health Questionnaire-9 (PHQ-9) during face-to-face or

computer-assisted interviews at the MECs. The PHQ-9 comprises nine items which correspond to the core diagnostic criteria for major depressive disorder: loss of interest, depressed mood, sleep disturbance, fatigue, changes in appetite, feelings of guilt or worthlessness, concentration difficulties, psychomotor retardation or agitation, and suicidal ideation. Respondents rated the frequency of each symptom over the past two weeks on a 4-point Likert scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total PHQ-9 score ranges from 0 to 27, with higher scores indicative of more severe depressive symptoms (Levis et al., 2019). Severity was classified as follows: 0–4, none or minimal; 5–9, mild; 10–14, moderate; 15–19, moderately severe; and 20–27, severe depression. In this study, a PHQ-9 score of ≥10 was used to define clinically significant depression (Costantini et al., 2021; Levis et al., 2020).

2.3. Assessment of sitting time

Sitting time was the primary exposure variable and was similarly assessed by trained interviewers at the MECs during face-to-face or computer-assisted interviews. The Global Physical Activity Questionnaire (GPAQ) was utilized to capture physical activity behaviors in various domains and sedentary time. Sitting time was ascertained using a single item: “The following question is about sitting at school, at home, getting to and from places, or with friends, including time spent sitting at a desk, traveling in a car or bus, reading, playing cards, watching television, or using a computer. Do not include time spent sleeping. How much time do you usually spend sitting on a typical day?” Responses were recorded in minutes per day (Yang et al., 2019). The self-reported sitting time data were derived from the harmonized NHANES 1988–2018 dataset (Nguyen et al., 2023), which ensures consistency in the question wording and units (minutes per day) across survey cycles, including the alignment of comparable items from earlier cycles (1999–2006).

2.4. Assessment of biomarkers of oxidative stress, inflammation, and insulin resistance

Biomarkers related to oxidative stress, inflammation, and insulin resistance were examined as potential mediators in this study. The primary laboratory and physical examination variables included gamma-glutamyl transferase (GGT), uric acid (UA), high-density lipoprotein (HDL), neutrophil count, monocyte count, lymphocyte count, mean cell volume, red cell distribution width, albumin, platelet count, triglycerides (TG), fasting blood glucose (FBG), height, weight, body mass index (BMI = weight/height^2), waist circumference (WC), fasting insulin, glycemia, and high-density lipoprotein cholesterol (HDL-C). These laboratory measures and physical examinations were obtained through rigorous protocols by trained personnel at the MECs, with detailed procedures available on the NHANES website.

The composite biomarkers evaluated were as follows: 1) Oxidative Stress: GGT, UA, HDL, uric acid to HDL ratio (UHR) (Liu et al., 2025a). 2) Inflammatory Markers: neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-monocyte-to-lymphocyte ratio (NMLR), hemoglobin-to-red blood cell distribution width ratio (HRR), red cell distribution width-to-albumin ratio (RAR), systemic inflammation response index (SIRI), systemic immune-inflammation index (SII) (Liu et al., 2025b; You et al., 2023). 3) Insulin Resistance: triglyceride-glucose index (TYG), TYG adjusted for BMI (TYG_BMI), TYG adjusted for waist-to-height ratio (TYG_WHTR), homeostatic model assessment for insulin resistance (HOMA-IR), metabolic score for insulin resistance (METS-IR) (Zhang et al., 2025; Peng et al., 2024). Detailed computation methods for these composite indices are provided in Supplementary Table S1.

2.5. Confounding variables

Potential confounding variables were included in the analyzes. Sociodemographic covariates included age, gender (male/female), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race), education level (below high school, high school graduate, college or above), poverty income ratio (PIR), smoking (yes/no), alcohol (yes/no), and physical activity level (low/high). Additionally,

medical comorbidities potentially related to both sedentary behavior and depression were adjusted for, including hypertension, diabetes, and stroke (Warburton et al., 2006; Katzmarzyk et al., 2022), each classified as yes/no.

2.6. Statistical analysis

All statistical analyzes in this study were performed using R software version 4.2. We followed the guidelines of the NCHS to account for the complex sampling design of NHANES. To combine data across the ten survey cycles from 1999 to 2018, a 20-year integrated sample weight was created. In all subsequent analyzes, the survey design was explicitly specified using the "svydesign()" function from the survey package, incorporating the stratum, primary sampling unit, and the integrated weight to ensure accurate estimation of standard errors.

First, participants were categorized into four groups based on daily sitting time (4 h, 4–6 h, 6–8 h, ≥8 h). Group comparisons were conducted using survey-weighted analysis of variance (ANOVA) for continuous variables and survey-weighted chi-square tests for categorical variables to describe the sample characteristics, presenting the distribution differences in demographics, lifestyle, and health outcomes across different sitting level groups.

Subsequently, we built a series of survey-weighted regression models. All models employed a three-level adjustment strategy to control for covariates sequentially: Model 1 was an unadjusted crude model; Model 2 adjusted for demographic, socioeconomic, and lifestyle factors, including age, sex, race, education level, PIR, smoking status, alcohol consumption, and physical activity level; Model 3 further adjusted for clinical comorbidities potentially related to both sedentary behavior and depression, including hypertension, diabetes, and stroke. Results from the fully adjusted Model 3 were considered primary. The statistical significance level was set at $\alpha = 0.05$.

To explore potential non-linear associations between sitting time and depression, we used the "rms" package. Within the survey-weighted logistic regression framework,

sitting time was flexibly modeled using restricted cubic splines (RCS) via the "rcs()" function. The number of knots was automatically selected based on the Akaike Information Criterion. The significance of the non-linear association was assessed by testing the *P*-value for the overall and nonlinear term, with results presented as a curve. Further threshold analysis was conducted using the "segmented" package. Based on the indication of a non-linear relationship from the spline analysis, this algorithm iteratively searches for the optimal inflection point that maximizes model fit and estimates the linear slopes on either side of the point.

Finally, to evaluate the mediating roles of biomarkers, we employed Bayesian mediation analysis based on the counterfactual framework, implemented through the "brms" package, which provides an interface for Bayesian generalized linear models via Stan. For each biomarker tested, two models were established: the first was a mediator model with the continuous biomarker as the dependent variable and sitting time as the independent variable; the second was an outcome model with depression status (binary) as the dependent variable, simultaneously including sitting time and the biomarker as independent variables. Both models were adjusted for all covariates specified in Model 3, and the results were presented in a schematic diagram. The mediation models were fitted using default weakly informative prior distributions. Parameter estimation was performed via Markov Chain Monte Carlo MCMC sampling, running 4 independent chains with 4000 iterations each (including 2000 warm-up iterations). Convergence was ensured by monitoring the R-hat statistic (all <1.01) and trace plots. From the posterior distributions, we calculated the average direct effect (ADE), average causal mediation effect (ACME), total effect (TE), and the proportion mediated (PE, %; indirect effect/total effect) (Cao et al., 2025). It should be noted that this study aimed to exploratively evaluate the independent mediating pathways of multiple biomarkers. Therefore, all biomarkers were entered individually into the mediation model framework for separate estimation and interpretation, rather than being competitively compared within a single model. Biomarker values were entered into regression models in their original scale without transformation.

As standard Bayesian mediation R packages cannot directly incorporate complex survey design variables, we forced the adjustment of the full set of demographic covariates closely related to the sampling design into the mediation models. Furthermore, all foundational "sitting time-biomarker-depression" associations included in the mediation analysis had been validated in the preceding survey-weighted regressions that strictly accounted for the complex design, aiming to minimize potential estimation bias. All survey-weighted linear and logistic regression models were checked for multicollinearity by calculating the variance inflation factor (VIF), confirming that all VIFs were below 5. For the Bayesian models, besides convergence diagnostics, posterior predictive checks were performed to verify the overall goodness-of-fit of the models to the data.

3. Results

3.1. Sociodemographic characteristics of participants

A total of 22,410 participants were included in the final analysis, with a mean age of 47.19 ± 0.27 years. Of these, 11,055 (48.80%) were male and 11,355 (51.20%) were female. Participants were categorized into four groups based on daily sitting time: "<4" hours (n = 5984), "4 to <6" hours (n = 5261), "6 to <8" hours (n = 3560), and "≥8" hours (n = 7605). Comparisons of potential confounders and outcome variables across these four groups revealed significant differences in race, education level, PIR, smoking, alcohol, physical activity, hypertension, diabetes, and stroke (all $P < 0.05$). There was no statistically significant difference in gender distribution across the groups ($P > 0.05$). Notably, the rate of depression differed significantly across the groups ($P = 0.003$). Importantly, all potential confounders with statistically significant group differences were confirmed to have no strong correlation with sitting time ($r < 0.7$). Even if certain variables show no significant differences between groups, they were still included as covariates in the models to control for potential confounding. (see Table 1).

Table 1
Characteristics of participants by categories of sitting time per day, weighted.

Variable	Total $N = 22,410$	Sitting time/day (h)				Statistic	*P*
		<4 n = 5984	4 to <6 n = 5261	6 to <8 n = 3560	≥8 n = 7605		
Age (years), Mean (SE)	47.19 (0.27)	45.25 (0.30)	47.56 (0.44)	48.58 (0.46)	47.54 (0.34)	F = 23.47	<0.001
Gender, n(%)						$\chi^2 = 1.16$	0.853
Male	11,055 (48.80)	2905 (48.14)	2666 (48.94)	1783 (49.03)	3701 (49.02)		
Female	11,355 (51.20)	3079 (51.86)	2595 (51.06)	1777 (50.97)	3904 (50.98)		
Race, n(%)						$\chi^2 = 611.15$	<0.001
Mexican American	3297 (8.03)	1447 (14.56)	755 (8.00)	406 (6.22)	689 (4.84)		
Other Hispanic	2278 (5.29)	833 (8.11)	562 (5.59)	306 (4.47)	577 (3.73)		
Non-Hispanic White	9928 (69.09)	2131 (60.09)	2372 (69.52)	1720 (71.97)	3705 (73.08)		
Non-Hispanic Black	4649 (10.72)	1117 (11.07)	1080 (10.43)	738 (10.45)	1714 (10.81)		
Other Race	2258 (6.87)	456 (6.17)	492 (6.47)	390 (6.90)	920 (7.54)		
Education level, n(%)						$\chi^2 = 849.24$	<0.001
Below high school	5314 (15.60)	2068 (24.42)	1323 (17.06)	731 (13.80)	1192 (10.09)		
High school graduate	5109 (22.04)	1488 (26.35)	1290 (23.94)	833 (23.45)	1498 (17.62)		
College or above	11,987 (62.36)	2428 (49.22)	2648 (58.99)	1996 (62.74)	4915 (72.29)		
PIR, Mean (SE)	2.99 (0.04)	2.55 (0.05)	2.90 (0.05)	2.96 (0.06)	3.33 (0.05)	F = 261.41	<0.001
Smoking, n(%)						$\chi^2 = 19.59$	0.019
No	12,278 (55.12)	3414 (55.06)	2790 (53.44)	1868 (53.62)	4206 (56.86)		
Yes	10,132 (44.88)	2570 (44.94)	2471 (46.56)	1692 (46.38)	3399 (43.14)		
Alcohol, n(%)						$\chi^2 = 65.79$	<0.001
No	6209 (22.31)	1914 (26.31)	1415 (21.49)	953 (22.10)	1927 (20.48)		
Yes	16,201 (77.69)	4070 (73.69)	3846 (78.51)	2607 (77.90)	5678 (79.52)		
Physical activity, n(%)						$\chi^2 = 628.16$	<0.001
Low physical activity	8680 (34.05)	1862 (25.06)	1726 (27.81)	1390 (33.33)	3702 (43.73)		
High physical activity	13,730 (65.95)	4122 (74.94)	3535 (72.19)	2170 (66.67)	3903 (56.27)		
Hypertension, n(%)						$\chi^2 = 90.88$	<0.001
No	12,901 (62.52)	3718 (68.06)	3015 (61.97)	1955 (60.43)	4213 (60.39)		
Yes	9509 (37.48)	2266 (31.94)	2246 (38.03)	1605 (39.57)	3392 (39.61)		
Diabetes, n(%)						$\chi^2 = 50.77$	<0.001
No	18,133 (85.53)	4947 (87.79)	4281 (86.76)	2866 (84.66)	6039 (83.77)		
Yes	4277 (14.47)	1037 (12.21)	980 (13.24)	694 (15.34)	1566 (16.23)		
Stroke, n(%)						$\chi^2 = 27.91$	<0.001
No	21,600 (97.27)	5837 (98.09)	5090 (97.64)	3396 (96.56)	7277 (96.86)		
Yes	810 (2.73)	147 (1.91)	171 (2.36)	164 (3.44)	328 (3.14)		
Depression, n(%)						$\chi^2 = 20.34$	0.003
No	20,364 (92.13)	5451 (92.34)	4830 (93.09)	3244 (92.74)	6839 (91.14)		
Yes	2046 (7.87)	533 (7.66)	431 (6.91)	316 (7.26)	766 (8.86)		

SE: Standard Error; F: ANOVA, χ^2: Chi-square test.

3.2. Associations between sitting time and depression

To further elucidate the complex association between sitting time and depression, we conducted progressive logistic regression analyzes, RCS modeling, and cutoff value analysis. The fully adjusted logistic regression model (Model 3) indicated that, when sitting time was treated as a continuous variable, there was a significant association with depression (OR per hour [95% CI]: 1.05 [1.03–1.07], $P < 0.001$). When categorized, with "<4" hours/day as the reference group, sitting "4 to <6" or "6 to <8" hours/day was not significantly associated with depression ($P = 0.641$, 0.915, respectively). However, sitting "≥8" hours/day was significantly associated with increased depression rate (OR [95% CI]: 1.39 [1.17–1.66], $P < 0.001$), with a significant interaction between models observed (P for interaction <0.001). This significant interaction suggests that the strength of the association was meaningfully modified by the sets of covariates adjusted for in the models, with the association becoming stronger and more precise after full adjustment. (see Table 2).

Table 2
Logistic regression analysis of associations between sitting time and depression, weighted.

Variables	Model1		Model2		Model3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Sitting time (h)	1.03 (1.01–1.05)	0.010	1.06 (1.04–1.08)	<0.001	1.05 (1.03–1.07)	<0.001
Sitting time (h)						
<4	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
4 to <6	0.89 (0.76–1.05)	0.183	0.98 (0.83–1.15)	0.799	0.96 (0.81–1.14)	0.641
6 to <8	0.94 (0.77–1.16)	0.586	1.02 (0.83–1.26)	0.840	0.99 (0.80–1.22)	0.915
≥8	1.17 (0.99–1.39)	0.068	1.47 (1.23–1.74)	<0.001	1.39 (1.17–1.66)	<0.001
P for interaction	0.020		<0.001		<0.001	

Model 1: Crude.

Model 2: Adjusted for covariates: age, gender, race, education level, smoking, drinking, PIR, physical activity.

Model 3: Adjusted for covariates: age, gender, race, education level, smoking, drinking, PIR, physical activity, hypertension, diabetes, and stroke.

P for interaction tests whether the association between sitting time (categorical) and depression differs across models with increasing levels of covariate adjustment.

RCS analysis revealed a nonlinear J-shaped relationship between sitting time (as a continuous variable) and depression after adjustment for all confounders, with the lowest depression risk observed at approximately 3.3 h of daily sitting time. The longer the sitting time, the higher the odds ratio for depression. The overall association and nonlinearity were statistically significant (P for overall <0.001; P for nonlinear =0.010; see Fig. 1).

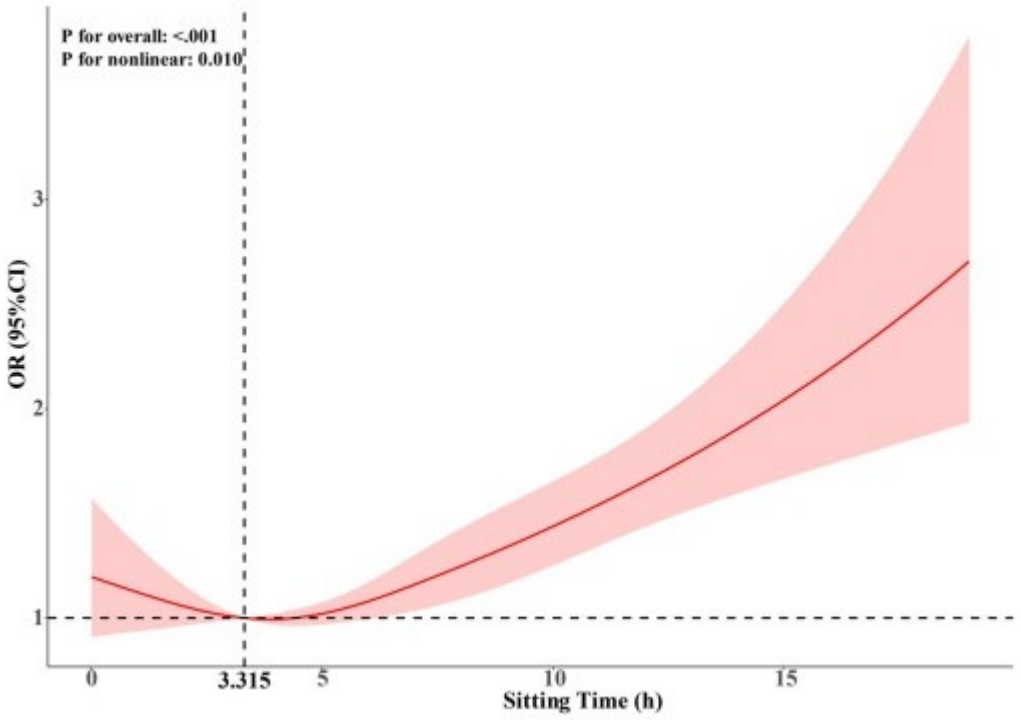

Fig. 1. RCS curve of association between sitting time and depression.

Threshold analysis indicated that the inflection point occurs at 3.315 h. For sitting time < 3.315 h, its association with depression was not statistically significant (*P* = 0.094). For sitting time ≥ 3.315 h, there was a significant positive linear association with depression rate (β [95% CI]: 1.06 [1.04–1.08], *P* < 0.001; P for likelihood test = 0.004; see Table 3).

Table 3. Threshold effect of the association between sitting time and depression.

Table 3
Threshold effect of the association between sitting time and depression.

Outcome	Effect	*P*
Model 1 Fitting model by standard linear regression	1.05 (1.03–1.06)	<0.001
Model 2 Fitting model by two-piecewise linear regression		
Inflection point (h)	3.315	
<3.315	0.91 (0.82–1.02)	0.094
≥3.315	1.06 (1.04–1.08)	<0.001
P for likelihood test		0.004

3.3. Associations between sitting time and biomarkers of oxidative stress, inflammation, and insulin resistance

Linear regression analyzes were performed to examine associations between sitting time and potential mediator biomarkers. For oxidative stress predictors, sitting time was significantly associated with UA (β [95% CI]: 0.02 [0.01–0.02], $P < 0.001$), HDL (β [95% CI]: −0.24 [−0.32 to −0.16], $P < 0.001$), and UHR (β [95% CI]: 0.01 [0.01–0.01], $P < 0.001$), but not with GGT ($P = 0.452$). Among inflammation predictors, sitting time was significantly associated with SIRI, HRR, NLR, NMLR, RAR, and SII (all $P < 0.01$), with corresponding β (95% CI): SIRI 0.01 (0.01–0.02), HRR –0.01 (−0.99 to −0.01), NLR 0.01 (0.01–0.02), NMLR 0.01 (0.01–0.02), RAR 0.01 (0.01–0.01), and SII 2.42 (0.78–4.06). No significant association was found with MLR ($P = 0.062$). For insulin resistance predictors, sitting time showed significant associations with TYG_BMI (β [95% CI]: 1.78 [1.19–2.36], $P < 0.001$), TYG_WHTR (0.03 [0.02–0.03], $P < 0.001$), HOMA_IR (0.08 [0.04–0.12], $P < 0.001$), and METS_IR (0.34 [0.24–0.45], $P < 0.001$), but not with TYG ($P = 0.091$). All results reflect full adjustment in Model 3 (see Table 4).

Table 4
The Associations Between Sitting Time and Oxidative Stress, Inflammation, and Insulin Resistance Biomarkers, weighted.

Variables	Model1		Model2		Model3	
	β (95%CI)	*P*	β (95%CI)	*P*	β (95%CI)	*P*
Oxidative stress index						
GGT	−0.04 (−0.18–0.10)	0.600	0.04 (−0.12–0.21)	0.603	−0.06 (−0.23–0.10)	0.452
UA	0.02 (0.02–0.03)	<0.001	0.02 (0.02–0.03)	<0.001	0.02 (0.01–0.02)	<0.001
HDL	0.02 (0.02–0.03)	<0.001	−0.32 (−0.40 – −0.24)	<0.001	−0.24 (−0.32 – −0.16)	<0.001
UHR	0.01 (0.01–0.01)	<0.001	0.01 (0.01–0.01)	<0.001	0.01 (0.01–0.01)	<0.001
Inflammatory index						
SIRI	0.01 (0.01–0.02)	<0.001	0.02 (0.01–0.02)	<0.001	0.01 (0.01–0.02)	<0.001
HRR	0.01 (0.01–0.02)	<0.001	−0.01 (−0.99 – −0.01)	<0.001	−0.01 (−0.99 – −0.01)	<0.001
MLR	0.01 (0.01–0.02)	<0.001	0.01 (0.01–0.01)	0.024	0.00 (−0.00–0.00)	0.062
NLR	0.01 (0.01–0.02)	<0.001	0.01 (0.01–0.02)	<0.001	0.01 (0.01–0.02)	<0.001
NMLR	0.01 (0.01–0.02)	<0.001	0.01 (0.01–0.02)	<0.001	0.01 (0.01–0.02)	<0.001
RAR	0.01 (0.01–0.01)	<0.001	0.01 (0.01–0.01)	<0.001	0.01 (0.01–0.01)	<0.001
SII	0.01 (0.01–0.02)	<0.001	3.51 (1.85–5.16)	<0.001	2.42 (0.78–4.06)	0.005
Insulin resistance index						
TYG	0.01 (0.01–0.01)	0.003	0.01 (0.01–0.02)	0.001	0.00 (−0.00–0.01)	0.091
TYG_BMI	2.05 (1.43–2.67)	<0.001	2.43 (1.74–3.12)	<0.001	1.78 (1.19–2.36)	<0.001
TYG_WHTR	0.03 (0.02–0.04)	<0.001	0.04 (0.03–0.05)	<0.001	0.03 (0.02–0.03)	<0.001
HOMA_IR	0.39 (0.27–0.50)	<0.001	0.14 (0.09–0.18)	<0.001	0.08 (0.04–0.12)	<0.001
METS_IR	0.39 (0.27–0.50)	<0.001	0.47 (0.34–0.60)	<0.001	0.34 (0.24–0.45)	<0.001

Model 1: Crude.

Model 2: Adjusted for covariates: age, gender, race, education level, smoking, drinking, PIR, physical activity.

Model 3: Adjusted for covariates: age, gender, race, education level, smoking, drinking, PIR, physical activity, hypertension, diabetes, and stroke.

CI: Confidence Interval, GGT: Gamma-Glutamyl Transferase, UA: Uric Acid, HDL: High-Density Lipoprotein, UHR: Uric Acid to High-Density Lipoprotein Ratio, NLR: Neutrophil-to-Lymphocyte Ratio, MLR: Monocyte-to-Lymphocyte Ratio, NMLR: Neutrophil-to-Monocyte-to-Lymphocyte Ratio, HRR: Heart Rate Recovery, RAR: Red Cell Distribution Width-to-Albumin Ratio, SIRI: Systemic Inflammation Response Index, SII: Systemic Immune-Inflammation Index, TYG: Triglyceride-Glucose Index, TYG_BMI: Triglyceride-Glucose Index Adjusted for Body Mass Index, TYG_WHTR: Triglyceride-Glucose Index Adjusted for Waist-To-Height Ratio, HOMA_IR: Homeostasis Model Assessment for Insulin Resistance, METS_IR: Metabolic Score for Insulin Resistance.

3.4. Associations between biomarkers and depression

Logistic regression analyzes were conducted to assess the associations between potential mediator biomarkers and depression. For oxidative stress predictors, significant associations with depression were observed for GGT (OR [95% CI]: 1.01 [1.01–1.01], $P < 0.01$), HDL (0.99 [0.99–0.99], $P < 0.01$), and UHR (4.75 [1.64–13.75], $P < 0.01$). UA was not significantly associated with depression ($P = 0.917$). Among inflammatory predictors, NLR, NMLR, RAR, SIRI, and SII were all significantly associated with depression (NLR OR: 1.05 [1.01–1.09], NMLR OR: 1.05 [1.01–1.09], RAR OR: 1.27 [1.14–1.42], SIRI OR: 1.08 [1.02–1.15], SII OR: 1.01 [1.01–1.01]; all $P < 0.05$), while MLR and HRR were not ($P = 0.701$ and 0.087, respectively). All five insulin resistance indices were significantly associated with depression: TYG_BMI (OR: 1.30 [1.14–1.49]), TYG_WHTR (1.01 [1.01–1.01]), HOMA_IR (1.23 [1.13–1.33]), METS_IR (1.01 [1.01–1.02]), and TYG (1.01 [1.01–1.02]) (all $P < 0.01$; see Table 5).

Table 5
Associations between biomarkers of oxidative stress, inflammation, and insulin resistance with depression, weighted.

Variables	Model1		Model2		Model3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Oxidative stress index						
GGT	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001
UA	0.95 (0.91–0.99)	0.015	1.04 (0.99–1.09)	0.151	1.00 (0.95–1.05)	0.917
HDL	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	0.001
UHR	2.18 (0.86–5.56)	0.106	15.18 (5.21–44.20)	<0.001	4.75 (1.64–13.75)	0.006
Inflammatory index						
NLR	1.07 (1.03–1.12)	0.001	1.07 (1.03–1.11)	0.002	1.05 (1.01–1.09)	0.013
MLR	0.60 (0.32–1.12)	0.114	1.19 (0.65–2.17)	0.578	1.13 (0.61–2.08)	0.701
NMLR	1.06 (1.02–1.10)	0.005	1.06 (1.02–1.10)	0.003	1.05 (1.01–1.09)	0.021
HRR	0.22 (0.16–0.32)	<0.001	0.57 (0.35–0.92)	0.025	0.65 (0.40–1.06)	0.087
RAR	1.71 (1.53–1.92)	<0.001	1.34 (1.19–1.51)	<0.001	1.27 (1.14–1.42)	<0.001
SIRI	1.11 (1.05–1.17)	<0.001	1.11 (1.05–1.17)	<0.001	1.08 (1.02–1.15)	0.008
SII	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	0.003
Insulin resistance index						
TYG	1.43 (1.27–1.60)	<0.001	1.39 (1.22–1.59)	<0.001	1.30 (1.14–1.49)	<0.001
TYG_BMI	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001
TYG_WHTR	1.37 (1.27–1.48)	<0.001	1.28 (1.19–1.38)	<0.001	1.23 (1.13–1.33)	<0.001
HOMA_IR	1.02 (1.01–1.03)	<0.001	1.01 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	0.007
METS_IR	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	<0.001

Model 1: Crude.

Model 2: Adjusted for covariates: age, gender, race, education level, smoking, drinking, PIR, physical activity.

Model 3: Adjusted for covariates: age, gender, race, education level, smoking, drinking, PIR, physical activity, hypertension, diabetes, and stroke.

OR: Odds Ratio, CI: Confidence Interval, GGT: Gamma-Glutamyl Transferase, UA: Uric Acid, HDL: High-Density Lipoprotein, UHR: Uric Acid to High-Density Lipoprotein Ratio, NLR: Neutrophil-to-Lymphocyte Ratio, MLR: Monocyte-to-Lymphocyte Ratio, NMLR: Neutrophil-to-Monocyte-to-Lymphocyte Ratio, HRR: Heart Rate Recovery, RAR: Red Cell Distribution Width-to-Albumin Ratio, SIRI: Systemic Inflammation Response Index, SII: Systemic Immune-Inflammation Index, TYG: Triglyceride-Glucose Index, TYG_BMI: Triglyceride-Glucose Index Adjusted for Body Mass Index, TYG_WHTR: Triglyceride-Glucose Index Adjusted for Waist-To-Height Ratio, HOMA_IR: Homeostasis Model Assessment for Insulin Resistance, METS_IR: Metabolic Score for Insulin Resistance.

These results are based on Model 3. RCS analyses of the associations between all 16 potential mediator biomarkers and depression are presented in Fig. 2.

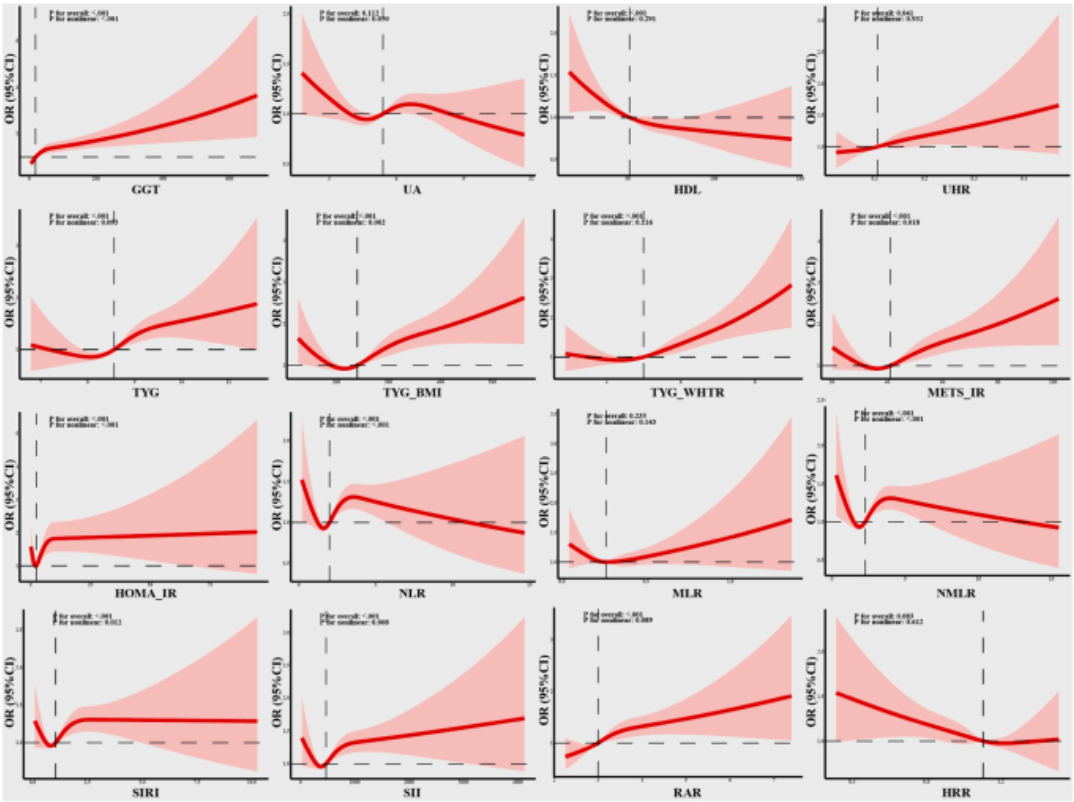

Fig. 2. RCS curves of association between oxidative stress, inflammation, and insulin resistance biomarkers with depression.

Fig. 2. RCS curves of association between oxidative stress, inflammation, and insulin resistance biomarkers with depression.

3.5. Mediation effects of oxidative stress, inflammation, and insulin resistance biomarkers in the association between sitting time and depression

Based on prior findings, we included mediator variables with confirmed associations in a Bayesian mediation analysis using logistic regression (Model 3). Among oxidative stress predictors, HDL accounted for 3.45% and UHR for 2.22% of the mediation effect. For inflammation predictors, mediation proportions were as follows: NLR, 1.26%; NMLR, 1.22%; RAR, 5.03%; SIRI, 2.36%; and SII, 1.08%. For insulin resistance predictors, TYG_BMI accounted for 9.17%, TYG_WHTR for 11.45%, HOMA_IR for 1.53%, and METS_IR for 9.25% of the mediation effect (see Fig. 3).

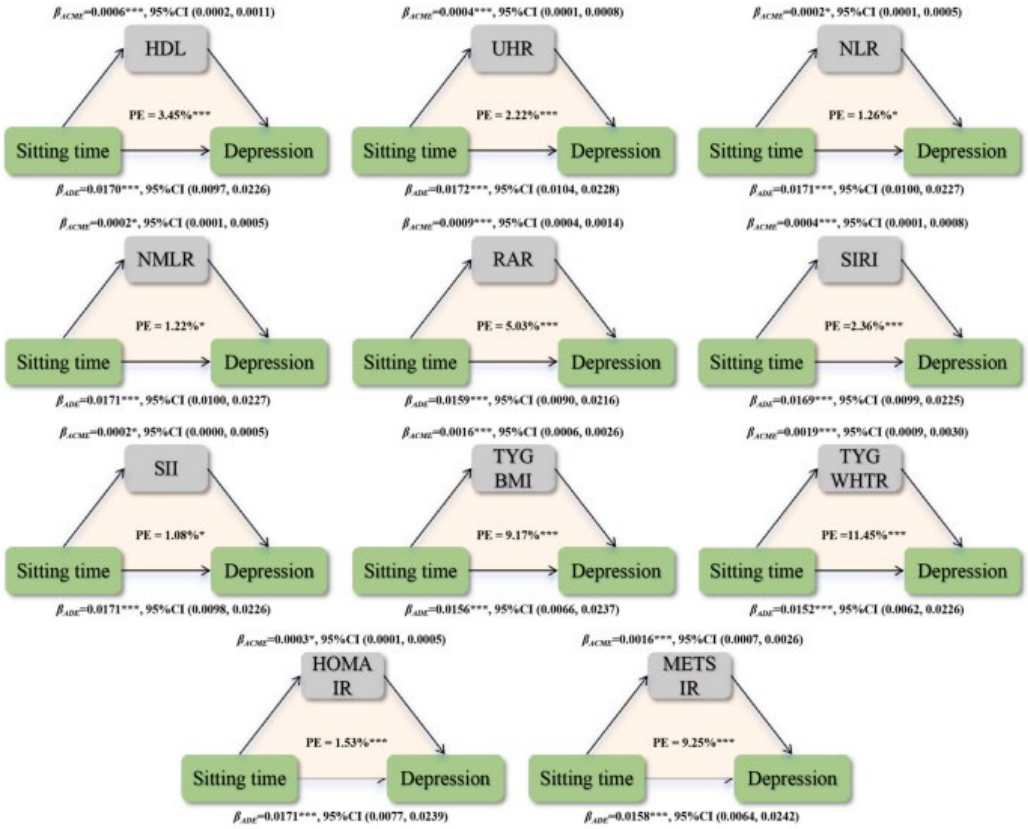

Fig. 3. Mediation effects of oxidative stress, inflammation, and insulin resistance biomarkers on the relationship between sitting time and depression.

Detailed results for all 11 mediator variables in the association between sitting time and depression, including estimates for ACME, ADE, TE, PE, and *p*-values, are summarized in Supplementary Table S2.

4. Discussion

Using large-scale data from the U.S. NHANES, this study systematically elucidated the biological pathways linking sitting time and depression, yielding three interesting findings. First, there is a dose–response relationship: sitting time is associated with depression in a J-shaped manner, with a threshold of 3.315 h/day. Compared with individuals with sitting time < 4 h, those sitting ≥8 h/day had an increased depression

rate (OR = 1.39, 95% CI: 1.17–1.66). Second, we identified key mediating pathways: insulin resistance (particularly TYG_WHTR, with a mediation proportion of 11.45%), the inflammatory marker RAR (5.03%), and the oxidative stress marker UHR (2.22%). Third, there were notable differences in the predictive value of biomarkers: the mediation effects of insulin resistance markers TYG_WHTR and METS_IR substantially exceeded that of the conventional HOMA-IR (only 1.53%). The following sections elaborate and interpret these findings in detail.

4.1. Public health implications of the sitting time threshold for depression

This study identified 3.315 h/day as a critical threshold for significantly increased depression rate, a value lower than most current guideline recommendations of 8–10 h/day, including WHO guidelines (Bull et al., 2020; Raichlen et al., 2023; Sagelv et al., 2023). Although we also confirmed the established finding that ≥8 h/day of sitting time substantially increases depression rate, it is important to note that the linear increase in depression begins at 3.315 h/day. This discrepancy may be explained by several methodological strengths of our study: the use of RCS modeling allowed for the detection of non-linear associations, reducing bias introduced by conventional and inconsistent categorization schemes, e.g., thresholds at 3, 7, 8, or 10 h in prior studies (Guo et al., 2024; Colley et al., 2022); additionally, the nationally representative and multi-ethnic NHANES sample enhances the generalizability of our results. Our findings provide new evidence regarding the dose-response relationship between sitting time and depression. This could inform the ongoing discussion and future refinement of public health guidelines on sedentary behavior, also highlight the potential value of strategies aimed at breaking up prolonged sitting, such as intermittent activity interventions.

4.2. Central mediating role of insulin resistance

Our results demonstrate that TYG_WHTR exhibited the strongest mediation effect (11.45%), providing a robust indicator for future intervention strategies. Several mechanisms may underlie this observation. Disruption of cerebral energy metabolism,

as mentioned earlier, may play a role: evidence had shown that prolonged sitting reduces skeletal muscle glucose uptake, induces systemic insulin resistance, impairs brain insulin signaling, and diminishes hippocampal glucose utilization. Other predictors in our model likely contribute to this pathway, particularly through enhanced neuroinflammatory cascades. Peripheral insulin resistance has been shown to activate microglia, promote the release of pro-inflammatory cytokines (TNF-α, IL-1β), and inhibit the synthesis of brain-derived neurotrophic factor (BDNF), all of which impact emotional regulation via central nervous system pathways (de Baat et al., 2023; Rozanska et al., 2020). Furthermore, previous research has found a significant positive correlation between insulin resistance and inflammatory markers, supporting the notion of a synergistic insulin resistance–inflammation axis (Korkmazer and Solak, 2015).

4.3. Roles of inflammation and oxidative stress pathways

RAR, a novel inflammatory marker, had a higher mediation proportion (5.03%) than traditional inflammation markers, supporting its potential as a clinically relevant biomarker. This may be attributable to RAR's ability to reflect both chronic inflammation (increased red cell distribution width) and nutritional status (decreased albumin), thereby more sensitively predicting changes in blood–brain barrier permeability (Zhu et al., 2025; Liu et al., 2025c). On the other hand, UHR displayed a moderate mediation effect (2.22%), lower than that of HDL alone, yet its composite nature remains informative. Its significance underscores the possibility that sedentary behavior contributes to oxidative damage via at least two mechanisms: reducing antioxidant capacity, decreased HDL, and increasing oxidative products (elevated uric acid), ultimately leading to neuronal DNA damage (Kuo et al., 2015; Hamurcu et al., 2010; Zoppini et al., 2006). The joint mediation effect of HDL and uric acid was slightly less than that of HDL alone, possibly due to their inter-correlation.

4.4. Comparison with prior studies and novelty of findings

Some of our results align with previous studies. The observed OR for the association

between sitting time and depression (1.39 [1.17–1.66]) is highly consistent with data from the UK Biobank (HR =1.19, *n* = 71,556) (Yu et al., 2025; Zhu et al., 2024), supporting the generalizability of our findings. The strong mediation effect of TYG_WHTR corroborates the central role of insulin resistance in central nervous system disorders, while the effectiveness of RAR represents a novel finding.

Compared with existing literature, our study addresses contentious areas and makes innovative contributions. Published thresholds for depressive risk due to sedentary behavior have varied widely (3–10 h/day), yet our use of RCS modeling allowed us to pinpoint 3.315 h/day as an evidence-based intervention target. In terms of biomarker selection, the lack of traditional inflammatory markers (e.g., C-reactive protein, CRP) in NHANES is noted. Nonetheless, the novel composite indices employed in our study (e.g., RAR, SIRI) outperformed conventional markers and offer compelling justification for their clinical adoption.

Our study combines theoretical innovation with practical value. At the theoretical level, we establish a multi-pathway mediation model for the association between sitting time and depression, identifying insulin resistance as the core pathway and proposing TYG_WHTR as a promising biomarker for depression risk screening. These findings highlight insulin resistance, indexed by TYG_WHTR, as a potential target for future research on depression prevention. Future studies could explore whether interventions that reduce sitting time and improve metabolic health yield mental health benefits. Our study also supports the consideration of both behavioral (e.g., sitting time) and metabolic factors in a comprehensive assessment of depression risk.

4.5. Limitations and future directions

Several limitations of this study should be acknowledged. First, the cross-sectional design precludes causal inference, and reverse causality or bidirectional relationships between depression, sedentary behavior, and the biomarkers cannot be ruled out. The mediation analysis within this framework is also limited in verifying the assumption of sequential ignorability. Second, exposure and covariate measurements have inherent

constraints. Sitting time was self-reported and may be subject to recall bias, and several important potential confounders (e.g., sleep quality, chronic pain, medication use, social support) were not designed for adjustment, which may lead to residual confounding. Third, regarding analytical methods, the proportion mediated was calculated based on ORs, which are non-collapsible; thus, this metric should be interpreted as an exploratory comparison of relative pathway importance rather than a precise effect estimate. Additionally, multiple comparisons were conducted without alpha-level adjustment. Fourth, several biomarkers with skewed distributions were analyzed in their original scale without transformation, which may affect the precision of some linear regression estimates.

Future research should address these limitations and build upon our findings. Prospective cohort or intervention studies are needed to establish temporal sequence and causality. Specifically, longitudinal studies could validate the sitting time threshold and incorporate objective measures (e.g., accelerometers) and advanced imaging (e.g., to assess central insulin sensitivity) to elucidate mechanisms. Randomized controlled trials are warranted to test whether interventions reducing sedentary behavior or targeting identified pathways (e.g., insulin resistance) lower depression risk. Furthermore, research should expand to diverse populations, such as Asian cohorts, to examine the generalizability of these associations. Finally, subsequent studies focusing on prediction could select the most promising biomarkers identified here to evaluate their added clinical value using standardized effect sizes and model validation metrics like decision curve analysis or area under the receiver operating characteristic curve (AUC).

5. Conclusion

Based on data from a large cohort of U.S. adults across multiple survey cycles of the NHANES database, this study demonstrates that prolonged daily sitting time is significantly associated with an increased risk of depression. RCS modeling revealed a nonlinear J-shaped relationship between sitting time and depression, with an optimal

threshold identified. Depression rate increased linearly beyond this threshold. Mediation analysis identified oxidative stress, inflammatory markers, and insulin resistance as key mechanistic pathways. These findings suggest that reducing sitting time and implementing targeted interventions on these biological pathways may effectively lower the risk of depression. Future intervention studies are needed to confirm whether reducing sitting time causally lowers depression risk through these pathways.

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