



OPEN Correlation of red cell distribution width with depression among adults with and without self-reported history of cancer

Yanming Li^{1,5}, Hongliang Hu^{2,5}, Ziming Liu^{3,5}, Shumin Zhu¹, Lisha Wang¹, Zining Liu¹, Xintong Pang¹ & Yulan Geng⁴✉

Red blood cell distribution width (RDW), recognized as a biomarker for systemic inflammation and oxidative stress, has been associated with various health outcomes, including depression. However, the precise relationship between RDW and depression, particularly in individuals with differing cancer statuses, remains ambiguous. In this cross-sectional study, data from 32,467 adults aged 18 and older from the NHANES 2005–2018 cohort were analyzed. Depressive symptoms were evaluated using the Patient Health Questionnaire-9 (PHQ-9), where a score of 10 or above indicated moderate-to-severe depression. Multivariate logistic regression models assessed the association between RDW and depression, accounting for demographic, lifestyle, clinical, and laboratory covariates. Subgroup analyses considered cancer status, revealing that a higher RDW was associated with depression in the general population [adjusted odds ratio (OR), 1.04; 95% confidence interval (CI), 1.01–1.07]. This link persisted for individuals without cancer (adjusted OR, 1.05; 95% CI, 1.02–1.08) but not for those with self-reported cancer history (adjusted OR, 0.97; 95% CI, 0.89–1.06), indicating significant interaction differences (P for interaction = 0.012). These results suggest RDW may serve as a cost-effective marker associated with depression, particularly in individuals without cancer, and highlight the need for further exploration of its implications and mechanisms across various clinical contexts.

Keywords Red blood cell distribution width (RDW), Depression, Systemic inflammation, NHANES, Cancer status, Patient health questionnaire-9 (PHQ-9)

Abbreviations

OR	odds ratio
CI	confidence interval
PIR	the ratio of family income to poverty
BMI	body mass index
WBC	white blood cells
RBC	red blood cell count
RDW	red cell distribution width
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
TC	total cholesterol
CRP	C-reactive protein

Red cell distribution width (RDW), a measure of the variability in red blood cell size, has traditionally been used in diagnosing hematological disorders. However, recent studies have highlighted its broader role as a marker of systemic inflammation and oxidative stress^{1,2}. Elevated RDW levels have been linked to poor outcomes

¹Department of Laboratory Medicine, The First Hospital of Hebei Medical University, Shijiazhuang 050031, China.

²Department of Radiology and Nuclear Medicine, The First Hospital of Hebei Medical University, Shijiazhuang 050031, China. ³Computer Network Information Center of Chinese Academy of Sciences, Haidian District, Beijing, China. ⁴Central Laboratory, The First Hospital of Hebei Medical University, Shijiazhuang 050031, China. ⁵Yanming Li, Hongliang Hu and Ziming Liu: These authors contributed equally to this work. ✉email: Ylgeng123@163.com

in chronic diseases such as cardiovascular conditions, diabetes, and cancer^{3–6}. Despite growing interest, the relationship between RDW and mental health, particularly depressive symptoms, remains underexplored⁷.

Depression, a prevalent mental health disorder, is a leading cause of global disability. Its pathogenesis involves complex interactions between genetic, environmental, and biological factors, with systemic inflammation emerging as a key contributor^{8,9}. Elevated RDW, as a surrogate marker for inflammatory states, has been hypothesized to be associated with depression. Mechanistically, systemic inflammation and oxidative stress may disrupt erythropoiesis and impair red blood cell homeostasis, thereby increasing RDW levels. These processes have also been implicated in the etiology of depressive disorders, suggesting a possible link between elevated RDW and depression^{10,11}.

Moreover, RDW has demonstrated significant associations with other inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), which are known to play roles in depressive pathophysiology^{12,13}. These findings underscore the potential utility of RDW as a cost-effective and accessible biomarker associated with depression. However, studies investigating this association have primarily focused on general populations, with limited attention to specific subgroups, such as individuals with cancer.

Cancer patients represent a unique population characterized by chronic inflammation, anemia of chronic disease, and high psychological distress. These factors might collectively elevate RDW levels and contribute to an increased prevalence of depressive symptoms^{3,14,15}. Additionally, cancer-related systemic inflammation and comorbidities may amplify the complex interplay between RDW and depression, necessitating further investigation^{16,17}.

The National Health and Nutrition Examination Survey (NHANES), a comprehensive and nationally representative dataset, offers an ideal framework for exploring these associations. By integrating demographic, clinical, and laboratory data, NHANES enables robust evaluations of health determinants across diverse populations¹⁸. Utilizing NHANES data from 2005 to 2018, this study aims to clarify the relationship between RDW and depressive symptoms, with a specific focus on differences between cancer and non-cancer populations.

Specifically, this study has two objectives: (1) to assess the independent association between RDW and depression in the general population after adjusting for confounders, and (2) to evaluate the effect modification by cancer status on the RDW-depression relationship. By addressing these objectives, this research seeks to enhance the understanding of RDW as a potential biomarker for depression and provide insights into tailored intervention strategies for vulnerable populations.

Materials and methods

Study design and population

This was a cross-sectional study based on continuous public data from NHANES, with all data details taken from the official NHANES website (https://www.cdc.gov/nchs/nhanes/about_nhanes.htm). It conducted extensive household interviews and collected population baseline information and health questionnaire data. Physical examination and collection of blood samples was done through a mobile examination center (MEC). Serum specimens were stored in appropriate frozen (−30 °C) conditions until transported to the Laboratory Sciences Division of the National Center for Environmental Health at the Centers for Disease Control and Prevention for testing. Detailed specimen collection and handling procedures are documented in the NHANES Laboratory/Medical Technician Procedures Manual (LPM). Our study population was adults (≥18 years old) from the 2005–2018 NHANES, all of whom completed interviews and assessments at the MEC. Data on depressive status, RDW, and cancer status were excluded if missing. At the same time, we exclude women who are pregnant. The final study population of 32,467 (16,300 female and 16,167 male) participated in the retrospective study. The NHANES survey protocol was approved by the National Center for Health Statistics Research Ethics Review Committee. All participants provided written informed consent, and all methods were carried out in accordance with relevant guidelines and regulations.

RDW

RDW was measured from EDTA-anticoagulated whole blood using automated hematology analyzers (Coulter DxH series) in NHANES-certified laboratories following standardized protocols. Blood samples were processed within 24–48 h of collection under refrigerated conditions (4 °C) to ensure stability, with rigorous quality control measures including daily calibration. RDW was analyzed both as a continuous variable (per 1% increment) and categorically (T1 < 12.6%, T2: 12.7–13.4%, T3 > 13.5%) to assess its association with depression.

Depressive symptoms and cancer

In NHANES, the Patient Health Questionnaire (PHQ-9), a 9-item screening instrument that measures the frequency of various depressive symptoms in the past 2 weeks, was used to assess participants' depressive status¹⁹. Each of the 9 items consists of a 4-point scale, with 0 meaning “not at all,” 1 meaning “a few days,” 2 meaning “more than half the time,” and 3 meaning “almost every day,” with a total score of 0 to 27. Based on the PHQ-9 score, a score of 10 was used as the cut-off point for inclusion in the depression group, indicating moderate to severe depressive symptoms. 88% sensitivity and 88% specificity of the PHQ-9 for suggesting moderate to severe depressive symptoms were obtained²⁰.

Cancer status was defined based on self-reported responses to the NHANES questionnaire item: ‘Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?’ Participants answering ‘Yes’ were classified as having cancer. This definition included both primary and recurrent cases but did not distinguish between active treatment, remission, or time since diagnosis due to data limitations.

Covariates

The NHANES database contains lifestyle information and personal medical history based on standardized questionnaires. Age, gender, race, education level, marital status, household income to poverty ratio (PIR), body mass index (BMI), smoking status, drinking status, and laboratory results including white blood cells (WBC), red blood cell count (RBC), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, total cholesterol (TC) and comorbid diabetes, hypertension and coronary heart disease. Race was categorized as Mexican-American, non-Hispanic white, non-Hispanic black, other Hispanic, or other. Educational level was categorized as less than high school, high school or equivalent, and above high school. According to standardized protocols, BMI was calculated as weight in kilograms divided by height in meters squared and was categorized as < 25.0 , $25.0\text{--}30.0$, and ≥ 30.0 kg/m². Smoking status was categorized as never smokers, former smokers, and current smokers. Participants who had never smoked a cigarette in their lives were labeled as “never smokers.” Those who had previously smoked ≥ 100 cigarettes but were no longer smoking were considered as “former smokers.” Participants who had previously smoked ≥ 100 cigarettes and were currently smoking at the time of the interview were classified as “current smokers.” Never drinkers, former drinkers, and current drinkers were all separated into three categories participants who had had < 12 drinks in their lives were labeled as “never drinkers.” Participants who had had ≥ 12 drinks in 1 year and did not drink last year were considered to be “former drinkers.” Individuals who have consumed more than 12 drinks and continued drinking in the past year are referred to as “current drinkers.” Medication use was categorized as “no” for individuals not taking any medication, “antidepressants drugs” for those taking antidepressants, and “other drugs” for those taking medications other than antidepressants. Cases of diabetes were defined based on self-reported questionnaires and the American Diabetes Association’s criteria²¹. The criteria were as follows: FPG ≥ 126 mg/dL, glycosylated hemoglobin (HbA1c) $\geq 6.5\%$, 2-hour plasma glucose from an oral glucose tolerance test (OGTT) ≥ 200 mg/dL, current use of insulin or diabetes pills to lower blood glucose, and self-reported questionnaire data indicating a physician diagnosis of diabetes. In addition, self-reported current use of antihypertensive medication or physician diagnosis was used to define hypertension. Coronary heart disease is based on the “Ever told you had coronary heart disease” question, and the answer is yes.

Statistical analysis

Multivariate logistic regression analyses were adopted to assess the independent association between RDW and the prevalence of depression between all participants, with and without cancer participants. An extended logistic model approach was used for different covariates adjusted models. In multivariate logistic regression, RDW was analyzed as a continuous and categorical variable, with model 1 adjusting for age and gender and model 2 adjusting for variables from model 1 as well as clinical indications including BMI, race, education level, smoking status, drinking status and PIR, model 3 was adjusted for model 2 plus WBC, RBC, Albumin, ALT, AST, BUN, creatinine, TC and diabetes, hypertension, coronary heart disease and medication use. Multiple imputation was applied for covariates with missing values ($< 10\%$). All the variables have no multicollinearity (Supplementary Table 1). More importantly, the relationship between participants’ RDW and depression was compared between the non-cancer and cancer group. Interaction among subgroups was inspected by the likelihood ratio test. Descriptive analyses were used for all participants, based on cancer status. Categorical variables are expressed as frequencies (%). For continuous data, normal distributions were expressed as mean \pm standard deviation (SD) or skewed data were expressed using median and interquartile range (IQR), as applicable. Variables were compared using independent samples t-test (normal distribution) and Mann-Whitney U test (skewed distribution) and chi-square test (categorical variables), respectively. All analyses were performed using the free statistical software version 2.1²² and the statistical software packages R4.2.2 (The R Foundation, <http://www.R-project.org>). $P < 0.05$ was considered statistically significant (two-tailed test).

Results

Study population

This study extracted data from NHANES 2005–2018 in which 70,190 potential participants completed interviews and underwent MEC screening were included in our study. Participants younger than 18 years of age and missing PHQ-9 scores ($n = 33,731$) were excluded. After excluding participants with missing data for RDW ($n = 1,464$), cancer status ($n = 2,001$) and pregnant women ($n = 527$), the remaining 32,467 participants were included in our analysis and were classified into two categories based on cancer status. The flowchart of the study population selection is presented in Fig. 1.

Baseline characteristics

The age of all participants was 50.1 ± 17.7 years and 50.2% were female. Mean baseline RDW was $13.3 \pm 1.4\%$. Detailed characteristics of the population as determined by cancer status are shown in Table 1. Individuals who are older, have a relatively high PIR, have a higher BMI, and have a high school education or less appear to have a higher cancer prevalence. The prevalence of depression in cancer and non-cancer patients was 10.5% and 8.7%, respectively. Notably, the cancer group demonstrated a significantly higher RDW ($13.6 \pm 1.5\%$) compared to the non-cancer group ($13.3 \pm 1.4\%$) ($P < 0.001$). The prevalence of diabetes, hypertension and coronary heart disease among the participants were all higher in the cancer patients. Interestingly, current rates of smoking and drinking appear to be lower among cancer patients, which may be the reason for abstinence due to cancer.

Univariate and multivariate analyses of RDW and depression

Gender, race, education level, marital, PIR, BMI, smoking status, drinking status, RBC, RDW, albumin, WBC, ALT, AST, BUN, TC, medication use, comorbid diabetes, hypertension and coronary heart disease were significantly associated with prevalence of depression, as shown in Supplementary Table 2. Table 2 showed that

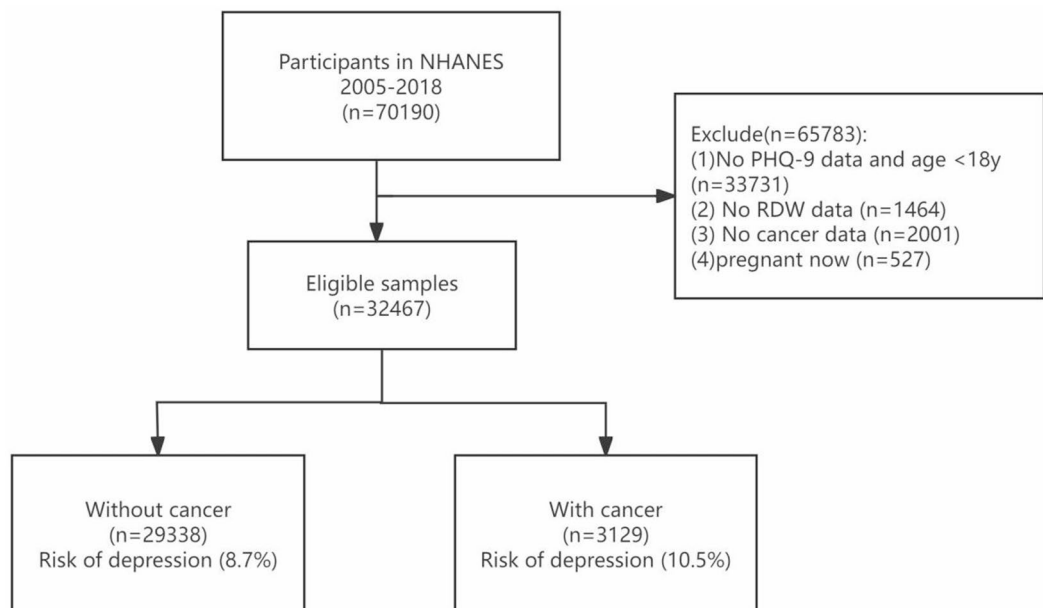


Fig. 1. The flowchart of the study.

after adjusting for different confounders, such as age, gender, race, education level, PIR, marital, BMI, smoking status, drinking status, WBC, RBC, Albumin, ALT, AST, BUN, creatinine, TC, medication use, diabetes, hypertension and coronary heart disease, RDW was positively associated with depression in all four models. The odds ratio (OR) for RDW was consistently significant in all different models, regardless of whether RDW was analyzed as a continuous variable or as three tertiles.

When RDW was assessed as a continuous variable, after adjusting for all covariates in Table 1, it was observed that the prevalence of depressive group (OR, 1.04, 95% CI: 1.01–1.07) increased by 4% with higher RDW (per 1-unit increment) (Model 3, Table 2). When RDW was analyzed as three tertiles, the adjusted OR for depressive group was 1.01 (95% CI: 0.91–1.13) and 1.16 (95% CI: 1.04–1.29) for T2 and T3 in model 3 with T1 as reference. In the same models and analyses, the adjusted OR for participants without cancer in T2 and T3 was 1.04 (95% CI: 0.93–1.16) and 1.20 (95% CI: 1.07–1.34) respectively, with T1 as reference. Accordingly, RDW was positively associated with depression in all models for the overall population and for participants without self-reported cancer (P for trend < 0.05). However, this association was not significant among individuals with self-reported cancer.

Subgroup analyses by different cancer status

After adjusting for age, gender, race, education level, PIR, marital, BMI, smoking status, drinking status, WBC, RBC, Albumin, ALT, AST, BUN, creatinine, TC, medication use, diabetes, hypertension and coronary heart disease, higher RDW levels were significantly associated with a higher prevalence of depression in the group without cancer (OR, 1.05; 95% CI, 1.02–1.08), but not in the cancer group (OR, 0.97; 95% CI, 0.89–1.06). There was an interaction between RDW and depression in patients with cancer and those without cancer when RDW was transformed into a categorical variable (P -value for the likelihood ratio test for the interaction was $P = 0.026$) (Table 3). Furthermore, to account for the potential influence of inflammatory markers, we further included CRP as an additional covariate. The results remained consistent with the main findings (Supplementary Table 3).

Discussion

In this study, we investigated the association between RDW and depressive symptoms using data from the NHANES 2005–2018 cohort. Our findings demonstrated a significant positive relationship between RDW and depression in the general population, consistent across multiple adjustment models. Notably, this association was pronounced in participants without cancer but not in those with cancer, suggesting that cancer status may modify the relationship between RDW and depression.

Elevated RDW has been previously identified as a marker of systemic inflammation and oxidative stress², both of which play crucial roles in the pathogenesis of depression^{10,23}. Mechanistically, systemic inflammation disrupts erythropoiesis by impairing iron metabolism and erythrocyte maturation, leading to increased RDW. This inflammatory state, characterized by elevated pro-inflammatory cytokines (e.g., IL-6, TNF- α), is implicated in depression through direct effects on the brain, including neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and reduced neurogenesis^{8,12,24}. Inflammation-induced disruptions in erythropoiesis may lead to increased RDW, reflecting the inflammatory burden underlying depressive symptoms¹². Additionally, RDW has been associated with other biomarkers of inflammation, such as CRP and IL-6, which promote blood-brain barrier permeability and microglial activation, exacerbating depressive phenotypes^{12,13,24}. Our findings align with this biological framework, further supporting the potential role of RDW as a surrogate marker for

Variables	Total (n = 32467)	Without cancer (n = 29338)	With cancer (n = 3129)	P
Age (years)	50.1 ± 17.7	48.5 ± 17.3	65.6 ± 13.9	< 0.001
Gender				0.001
Female	16,300 (50.2)	14,643 (49.9)	1657 (53)	
Male	16,167 (49.8)	14,695 (50.1)	1472 (47)	
Race				< 0.001
Mexican American	5079 (15.6)	4871 (16.6)	208 (6.6)	
Non-Hispanic white	14,065 (43.3)	11,910 (40.6)	2155 (68.9)	
Non-Hispanic black	6807 (21.0)	6380 (21.7)	427 (13.6)	
Other Hispanic	3104 (9.6)	2921 (10)	183 (5.8)	
Other races	3412 (10.5)	3256 (11.1)	156 (5)	
Education level				< 0.001
Less than high school	7862 (24.2)	7234 (24.7)	628 (20.1)	
High school or equivalent	7497 (23.1)	6787 (23.2)	710 (22.7)	
Above high school	17,085 (52.7)	15,295 (52.2)	1790 (57.2)	
Marital status				< 0.001
Married	16,744 (51.6)	14,958 (51)	1786 (57.1)	
Never married	5758 (17.7)	5563 (19)	195 (6.2)	
Living with partner	2614 (8.1)	2515 (8.6)	99 (3.2)	
Other	7336 (22.6)	6289 (21.4)	1047 (33.5)	
PIR	2.5 ± 1.6	2.5 ± 1.6	2.8 ± 1.6	< 0.001
BMI (kg/m²)	29.3 ± 7.0	29.3 ± 7.0	29.2 ± 6.6	0.506
Smoking status				< 0.001
Never smoker	17,732 (54.6)	16,310 (55.6)	1422 (45.4)	
Former smoker	8021 (24.7)	6803 (23.2)	1218 (38.9)	
Current smoker	6714 (20.7)	6225 (21.2)	489 (15.6)	
Drinking status				< 0.001
Never drinker	4639 (14.3)	4217 (14.4)	422 (13.5)	
Former drinker	5312 (16.4)	4613 (15.7)	699 (22.3)	
Current drinker	22,516 (69.4)	20,508 (69.9)	2008 (64.2)	
Laboratory results				
RBC, (million cells/uL)	4.7 ± 0.5	4.7 ± 0.5	4.5 ± 0.5	< 0.001
RDW, (%)	13.3 ± 1.4	13.3 ± 1.4	13.6 ± 1.5	< 0.001
Albumin, (g/L)	42.2 ± 3.4	42.3 ± 3.4	41.5 ± 3.4	< 0.001
WBC, (1000 cells/uL)	6.9 (5.7, 8.4)	6.9 (5.7, 8.4)	6.9 (5.6, 8.3)	0.112
ALT, (U/L)	21.0 (16.0, 28.0)	21.0 (16.0, 28.0)	20.0 (16.0, 26.0)	< 0.001
AST, (U/L)	23.0 (19.0, 27.0)	23.0 (19.0, 27.0)	23.0 (19.0, 27.0)	0.055
BUN, (mmol/L)	4.9 ± 2.2	4.8 ± 2.1	5.9 ± 2.7	< 0.001
Creatinine, (umol/L)	76.0 (63.6, 89.3)	75.1 (63.6, 88.4)	81.3 (67.2, 97.2)	< 0.001
TC, (mmol/L)	5.0 ± 1.1	5.0 ± 1.1	5.0 ± 1.1	0.287
Medical condition				
Depression, n (%)				< 0.001
no	29,574 (91.1)	26,775 (91.3)	2799 (89.5)	
yes	2893 (8.9)	2563 (8.7)	330 (10.5)	
Medication use, n (%)				< 0.001
no	13,440 (41.4)	13,030 (44.4)	410 (13.1)	
antidepressants drugs	3598 (11.1)	3042 (10.4)	556 (17.8)	
other drugs	15,429 (47.5)	13,266 (45.2)	2163 (69.1)	
Hypertension, n (%)				< 0.001
no	18,779 (57.8)	17,641 (60.1)	1138 (36.4)	
yes	13,688 (42.2)	11,697 (39.9)	1991 (63.6)	
Diabetes, n (%)				< 0.001
Continued				

Variables	Total (n = 32467)	Without cancer (n = 29338)	With cancer (n = 3129)	P
no	26,164 (80.6)	23,926 (81.6)	2238 (71.5)	
yes	6303 (19.4)	5412 (18.4)	891 (28.5)	
Coronary heart disease, n (%)				<0.001
no	31,107 (95.8)	28,273 (96.4)	2834 (90.6)	
yes	1360 (4.2)	1065 (3.6)	295 (9.4)	

Table 1. Characteristics of the study participants. Notes: Data were mean \pm SD or median (IQR) for skewed variables or numbers (proportions) for categorical variables. Independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normal continuous variables, Chi-square test for categorical variables. Abbreviations: PIR, the ratio of family income to poverty; BMI, body mass index; RDW, red cell distribution width; WBC, white blood cells; RBC, red blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TC, total cholesterol.

Group	RDW Category	Crude model ^a	Model 1 ^b	Model 2 ^c	Model 3 ^d
All participants					
	Continuous (per 1%)	1.14 (1.11–1.16)	1.12 (1.10–1.15)	1.06 (1.04–1.09)	1.04 (1.01–1.07)
	T1 (<12.6%)	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
	T2 (12.7%–13.4%)	1.12 (1.01–1.24)	1.14 (1.03–1.26)	1.03 (0.92–1.14)	1.01 (0.91–1.13)
	T3 (>13.5%)	1.59 (1.45–1.74)	1.57 (1.43–1.73)	1.24 (1.12–1.37)	1.16 (1.04–1.29)
	P for trend	<0.001	<0.001	<0.001	0.005
Without cancer					
	Continuous (per 1%)	1.15 (1.12–1.18)	1.13 (1.10–1.16)	1.07 (1.04–1.10)	1.05 (1.02–1.08)
	T1 (<12.6%)	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
	T2 (12.7%–13.4%)	1.15 (1.03–1.28)	1.16 (1.04–1.29)	1.05 (0.94–1.17)	1.04 (0.93–1.16)
	T3 (>13.5%)	1.65 (1.50–1.83)	1.61 (1.45–1.78)	1.27 (1.14–1.42)	1.20 (1.07–1.34)
	P for trend	<0.001	<0.001	<0.001	0.002
With cancer					
	Continuous (per 1%)	1.05 (0.97–1.13)	1.10 (1.02–1.18)	1.02 (0.94–1.10)	0.97 (0.89–1.06)
	T1 (<12.6%)	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
	T2 (12.7%–13.4%)	0.82 (0.60–1.13)	1.01 (0.73–1.40)	0.87 (0.62–1.23)	0.81 (0.57–1.16)
	T3 (>13.5%)	1.03 (0.78–1.36)	1.40 (1.04–1.88)	1.01 (0.73–1.40)	0.87 (0.62–1.22)
	P for trend	0.628	0.015	0.794	0.522

Table 2. OR (95% CIs) for prevalence of depression according to RDW concentrations among all participants with and without cancer in NHANES 2005–2018. Notes: ^a Crude model: no adjusted. ^b Model 1: adjusted for age, gender. ^c Model 2: adjusted for age, gender, race, education level, PIR, marital, BMI, smoking status, drinking status. ^d Model 3: adjusted for model 2 plus WBC, RBC, Albumin, ALT, AST, BUN, creatinine, TC, diabetes, hypertension, coronary heart disease and medication use. Abbreviations: OR, odds ratio; CI, confidence interval; PIR, the ratio of family income to poverty; BMI, body mass index; WBC, white blood cells; RBC, red blood cell count; RDW, red cell distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TC, total cholesterol.

depression and highlighting its utility in reflecting shared pathways between hematologic dysregulation and mood disorders^{7,10,23}.

The subgroup analysis revealed a nuanced relationship between RDW and depression based on cancer status. While RDW was significantly associated with depression in the non-cancer group, this relationship was not observed in participants with cancer. Cancer patients typically exhibit elevated RDW due to anemia of chronic disease, chemotherapy-induced hematological changes, and chronic systemic inflammation^{25,26}. These factors may obscure the specific contribution of RDW to depressive symptoms in this population. Furthermore, psychological stress and other unique aspects of cancer-related depression may involve distinct mechanisms, such as neuroendocrine dysregulation and cytokine release^{16,24}. The lack of association between RDW and depression in cancer patients may reflect heterogeneity in cancer types, stages, or treatment status, which NHANES data do not capture. For example, active treatment or advanced disease could disproportionately elevate RDW due to anemia of chronic disease, obscuring its relationship with depression. Future studies should stratify cancer patients by treatment and remission status to clarify these mechanisms.

Interestingly, the higher prevalence of depression in cancer patients (10.5%) compared to non-cancer participants (8.7%) underscores the importance of addressing mental health in this vulnerable group. While

Variable	Without cancer (n = 29338)		With cancer (n = 3129)		P for interaction
	OR_95CI%	P value	OR_95CI%	P value	
RDW (continuous)	1.05 (1.02–1.08)	0.001	0.97 (0.89–1.06)	0.508	0.012
Subgroups					
T1 (< 12.6%)	1(Ref)		1(Ref)		0.026
T2 (12.7%–13.4%)	1.04 (0.93–1.16)	0.520	0.81 (0.57–1.16)	0.246	
T3 (> 13.5%)	1.20 (1.07–1.34)	0.002	0.87 (0.62–1.22)	0.427	
Trend test		0.002		0.522	

Table 3. Interactive effect of RDW and depression in patients with or without cancer. Adjusted for age, gender, race, education level, PIR, marital, BMI, smoking status, drinking status, WBC, RBC, Albumin, ALT, AST, BUN, creatinine, TC, diabetes, hypertension, Coronary heart disease and medication use. Abbreviations: OR, odds ratio; CI, confidence interval; PIR, the ratio of family income to poverty; BMI, body mass index; WBC, white blood cells; RBC, red blood cell count; RDW, red cell distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TC, total cholesterol.

RDW was not independently associated with depression in cancer patients, it remains a valuable biomarker for assessing overall disease burden and inflammation in this population. Further studies are warranted to explore alternative biomarkers or mechanisms driving depression in cancer patients.

Our study has several strengths. The use of a large, nationally representative cohort enhances the generalizability of our findings. The availability of comprehensive covariate data from NHANES allowed for robust adjustments to minimize confounding bias. Additionally, this study is one of the few to examine the interaction between cancer status and the RDW-depression relationship, contributing to the growing understanding of RDW as a biomarker in different clinical contexts.

However, several limitations should be noted. First, the cross-sectional design precludes causal inference. Longitudinal studies are needed to establish whether elevated RDW precedes depressive symptoms or vice versa. Second, despite adjusting for a comprehensive set of covariates, residual confounding from unmeasured factors (e.g., dietary habits, inflammatory disease or nutritional factors) may persist. For instance, certain medications (e.g., iron supplements or chemotherapy agents) could influence RDW independently of depression, potentially biasing our results. Third, while NHANES employs standardized protocols, measurement errors in RDW or PHQ-9 scores are possible. RDW variability may arise from pre-analytical factors (e.g., sample handling delays), though NHANES mitigates this through strict laboratory procedures. Similarly, depression was assessed via self-reported PHQ-9, which, despite its validated sensitivity (88%), may misclassify cases due to subjective reporting or comorbid conditions (e.g., anxiety). Fourth, the classification of medication use was necessarily simplified. The 'other' category encompassed a heterogeneous group of individuals taking various non-antidepressant medications. These simplifications highlight the need for future research to further investigate the effects of medications. Finally, cancer status was self-reported and lacked details on stage, treatment, or remission, which could mask heterogeneity in the RDW-depression relationship among cancer subtypes. Future studies should incorporate clinical records to refine cancer classifications and explore mediation by treatment-related anemia or inflammation.

Conclusions

This study provides evidence for a positive association between RDW and depressive symptoms, particularly in individuals without cancer. The findings highlight the potential of RDW as a cost-effective and accessible marker associated with depression. Future research should explore the longitudinal relationship between RDW and depression, investigate alternative markers in cancer populations, and elucidate the biological mechanisms underlying these associations.

Data availability

The datasets generated and analyzed during the current study are available on the NHANES website: <https://www.cdc.gov/nchs/nhanes/Default.aspx>.

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Author contributions

Yulan Geng and Ziming Liu conceived and designed the study. Yanming Li, Hongliang Hu., and Shumin Zhu drafted the manuscript. Yanming Li, Hongliang Hu., Lisha Wang., Zining Liu., and Xintong Pang collected and organized data. Ziming Liu and Yanming Li performed the statistical analysis and interpreted the data. All authors read and approved the final version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The survey protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics (<https://www.cdc.gov/nchs/nhanes/irba98.htm>). The NCHS Research Ethics Review Board reviewed and approved NHANES, and all survey participants provided written informed consent. Therefore, no further ethical approval and informed consent were required.

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NHANES 2015–2016	Continuation of Protocol #2011-17
NHANES 2013–2014	Continuation of Protocol #2011-17
NHANES 2011–2012	Protocol #2011-17
NHANES 2009–2010	Continuation of Protocol #2005-06
NHANES 2007–2008	Continuation of Protocol #2005-06
NHANES 2005–2006	Protocol #2005-06

Consent for publication

Since all NHANES data were de-identified, the study did not require the approval of the institutional board review committee or the informed consent of participants.

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-025-25383-9>.

Correspondence and requests for materials should be addressed to Y.G.

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