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Red blood cell distribution width to albumin ratio (RAR) is associated with low cognitive performance in American older adults: NHANES 2011–2014

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Abstract

Background The red blood cell distribution width to albumin ratio (RAR) is a novel comprehensive biomarker of inflammation and nutrition, which has emerged as a reliable prognostic indicator for adverse outcomes and mortality in patients with various diseases. However, the association between RAR and low cognitive performance in older adults remains unclear. This study aims to investigate the relationship between RAR and low cognitive performance among older adults in the United States.

Methods This study, a retrospective analysis, included 2,765 participants aged 60 years and older from the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2014. Low cognitive performance was assessed using word learning subset from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), the Digit Symbol Substitution Test (DSST), and the Animal Fluency Test (AFT). Low cognitive performance was defined as scores below the lowest quartile in each cognitive test. The association between RAR and low cognitive performance was evaluated using weighted multivariable logistic regression, restricted cubic splines (RCS), and subgroup analyses.

Results After adjusting for all potential confounders, RAR was independently and linearly positively associated with both low DSST performance and low AFT performance. Specifically, compared to participants in the first quartile of RAR, those in the fourth quartile had adjusted ORs (95% CIs) of 1.81 (1.03, 3.20) for low DSST performance and 1.68 (1.05, 2.67) for low AFT performance. Subgroup analysis did not reveal significant interactions between stratification variables.

Conclusion RAR is significantly linearly positively associated with low cognitive performance. Maintaining a lower RAR may be a crucial strategy for mitigating the risk of cognitive decline in the elderly population.

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Keywords The red blood cell distribution width to albumin ratio (RAR), Low cognitive performance, Dementia, Older adults, NHANES

Introduction

Cognitive impairment (CI) is a common and concerning aspect of the aging process, characterized by declines in learning, memory, attention, and executive function, leading to impairment of function [1, 2]. Research indicates that declines in CI are closely associated with an increased risk of developing dementia [3], and over 50% of individuals with CI are expected to progress to dementia within 5 years [4]. In individuals with mild cognitive impairment (MCI), functional independence is generally preserved, whereas in dementia, patients experience progressive deterioration in memory and other cognitive functions, severely impairing quality of life and the ability to live independently [5]. With the increasing population aging, dementia has become a significant global public health challenge, posing serious difficulties for individuals, families, and society [6]. According to the 2022 World Alzheimer Report, it is estimated that there are currently approximately 50 million people with dementia worldwide, with this number projected to reach 152 million by 2050 [7]. In 2020, over 6 million individuals aged 65 and older in the United States were diagnosed with Alzheimer's disease, and this number is estimated to rise to 13.85 million by 2060 [8].

The etiology of dementia remains unclear, and its pathogenesis is complex [8]. There are currently no effective treatments to completely reverse dementia, and up to 60% of dementia patients remain undiagnosed, so early detection of dementia symptoms and modifiable risk factors is essential [9, 10]. Notably, chronic inflammation is considered a significant component in the pathogenesis of dementia [11]. Research indicates that neuroinflammation caused by excessive activation of microglia in the central nervous system is a critical mechanism leading to neuronal structural and functional damage, which in turn results in CI [12–15]. In addition to central nervous system inflammation [16], a growing body of research has confirmed the association between peripheral inflammation and dementia [17–20]. A study from the UK has shown that peripheral inflammatory cytokines are significantly elevated in patients with early-stage dementia compared to healthy controls [20]. Several studies [21–24] have confirmed the association between various inflammatory markers and CI. Additionally, a large cohort study from the UK Biobank involving 84,342 older adults, utilized a population-based measure of the dietary inflammatory index (DII). This index assessed 31 inflammation-related dietary parameters, such as macronutrients, micronutrients, bioactive components, and specific foods. The study demonstrated that an anti-inflammatory diet can significantly suppress systemic inflammation, particularly in individuals with cardiometabolic diseases, thereby slowing the progression of dementia [25].

The red blood cell distribution width (RDW) to albumin ratio (RAR) is a novel comprehensive biomarker of inflammation and nutrition, used to evaluate immune status and immune response. Specifically, RDW serves as a biomarker that reflects the heterogeneity in red blood cell (RBC) volume [26]. Multiple large-scale cohort studies and Mendelian randomization analyses have demonstrated a causal relationship between RDW and CI, as well as Alzheimer's disease [27, 28]. Serum albumin stands as a pivotal biomarker for assessing nutritional status and inflammation. Numerous studies have demonstrated a correlation between serum albumin levels and both neurodegenerative diseases and blood-brain barrier permeability [29–31]. Previous studies have identified that RDW and serum albumin levels serve as biomarkers for multidimensional dysfunctions related to inflammation, oxidative stress, and nutrition [32, 33], but they represent these pathological aspects from different perspectives. It is noteworthy that the RAR, which combines RDW and serum albumin, has demonstrated significant predictive value in the prognosis of stroke [34] and acute respiratory distress syndrome (ARDS) [35]. Recent studies have found that RAR can accurately predict the prognosis of patients with community-acquired bacteremia [36], acute pancreatitis [37], and rheumatic diseases [38]. However, the relationship between RAR and low cognitive performance in older adults remains unclear. Therefore, this study aims to investigate the association between RAR and low cognitive ability in the elderly, with the hope of contributing to the understanding of the pathogenesis of low cognitive ability and early identification.

Methods

Study population

The NHANES is a continuous, publicly accessible, nationwide research program conducted by the Centers for Disease Control and Prevention (CDC), from which researchers worldwide can freely access the data. It employs a complex, multistage probability sampling design to evaluate the nutritional status and overall health of both adults and children in the United States. The research protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (https://www.cdc.gov/nchs/nhanes/irba98.htm) and informed consent was obtained from all participants. We selected data from NHANES 2011–2014 (https://ww

w.cdc.gov/nchs/nhanes/index.htm), ultimately including 2,765 participants (Fig. 1).

Assessment of RAR

In the NHANES survey, highly trained medical personnel measured participants' peripheral blood RDW (%) using a Coulter analyzer at the Mobile Examination Center (MEC). The concentration of albumin was measured using the DcX 800 method, a bichromatic digital endpoint method. In this process, albumin forms a complex with bromocresol purple (BCP) reagent, and the system monitors changes in absorbance at 600 nm. This absorbance is directly proportional to the concentration of albumin in the blood sample, reflecting serum albumin levels (g/dL). The RAR is calculated using the following formula: [RDW (%) / serum albumin (g/dL)]. Based on the quartile of RAR, participants were categorized into four groups (Q1, Q2, Q3, and Q4) as follows: Q1 (< 2.95), Q2 (2.95–3.16), Q3 (3.16–3.40), and Q4 (> 3.40), with Q1 serving as the reference group.

Assessment of low cognitive performance

The NHANES assesses cognitive function in participants aged 60 and older, utilizing three components: the word learning and recall modules from the Consortium to Establish a Registry for Alzheimer's disease (CERAD), the Digit Symbol Substitution Test (DSST), and the Animal Fluency Test (AFT). Notably, the selection of cognitive assessment tools for the NHANES was based on the criteria that these tools should be concise, easily understood by diverse populations, and both simple to administer and to score [39]. Higher scores on these tests indicate better cognitive function. The CERAD Word Learning subtest (CERAD-WL) includes three consecutive immediate recall learning trials (CERAD-IR) and one delayed recall test (CERAD-DR), to assess an individual's immediate and delayed learning abilities for new verbal information (memory sub-domain). The scores for the three CERAD-IR tests range from 0 to 10 points each, while the CERAD-DR test score ranges from 0 to 10 points [40]. The CERAD-WL score is the sum of the

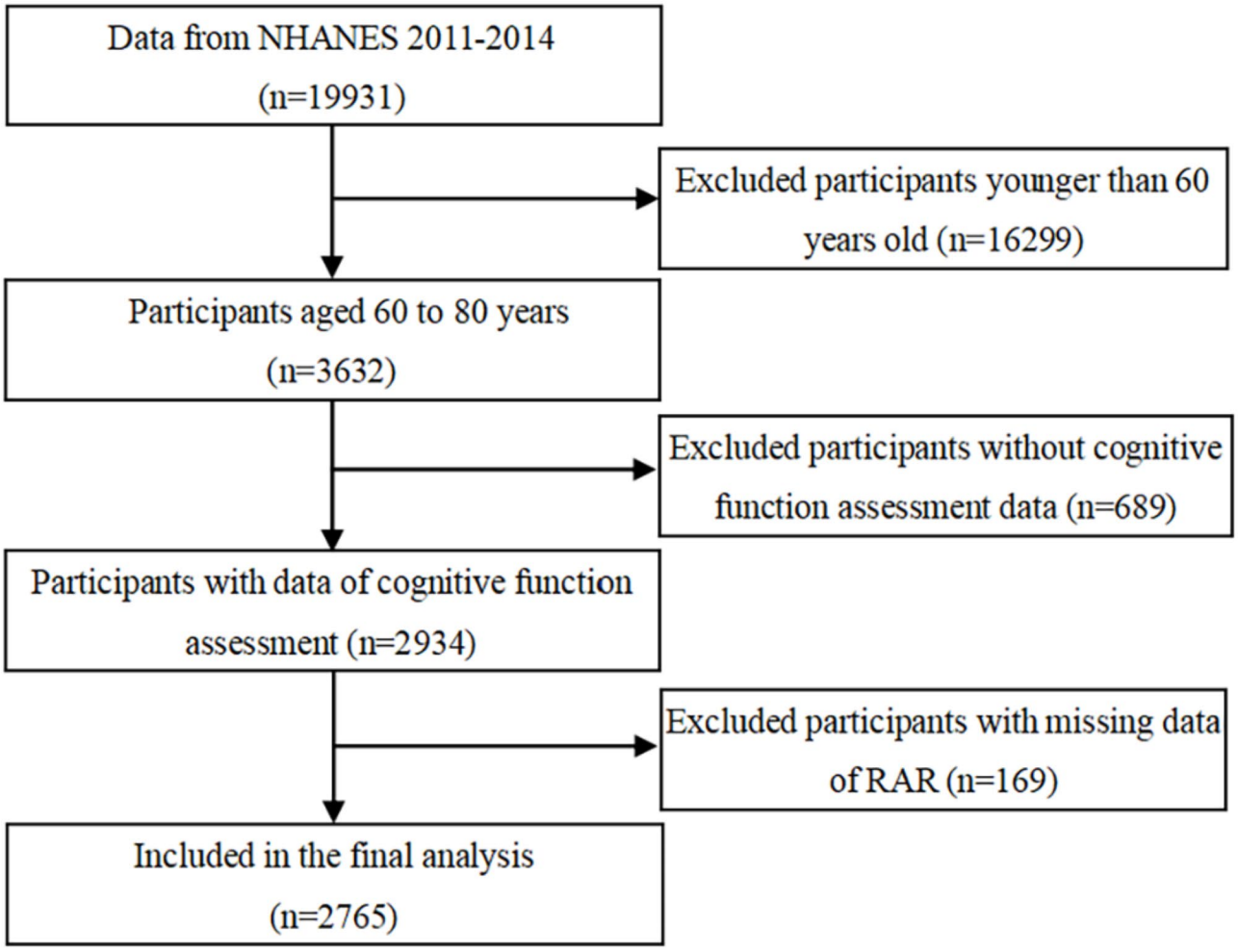

Fig. 1 Flow chart of the study participants

CERAD-IR and CERAD-DR scores [41]. The DSST is used to assess an individual's processing speed, sustained attention, and working memory. The test involves a paper form with a keyboard containing nine digits and symbols. Participants are required to fill in 133 boxes with the corresponding symbols within a 2-minute time frame to match the digits. The total number of correct matches constitutes the DSST score [42]. The AFT primarily evaluates participants' verbal fluency [43]. Participants are asked to name as many animals as possible within one minute. The AFT score is determined by the number of animal names provided. This study uses the scores from the three cognitive tests as outcome variables. Since NHANES does not specify a particular threshold for low cognitive performance in each cognitive test, we have defined low cognitive performance as the lowest quartile for each cognitive assessment within the full sample. The lowest quartile may be a preferable choice for selecting participants with low cognitive performance. This approach is consistent with multiple previously published studies and is widely recognized [39, 44].

Assessment of covariates

This study considered various covariates including demographic and health-related information, as follows: age; sex, categorized as male or female; race, classified as Mexican American, non-Hispanic White, non-Hispanic Black, or other; education, divided into less than high school, high school or equivalent, or college and above; marital status, categorized as married/ living with partner, widowed/divorced/separated, or never married. The poverty income ratio (PIR) was divided into low income (< 1.3), moderate income (1.3–3.5), and high income (> 3.5). Body mass index (BMI) was calculated as weight (kg)/height (m^2), and categorized as normal/underweight (< 25), overweight (25–30), or obese (> 30). Smoking status was classified as never (lifetime consumption of fewer than 100 cigarettes), former (lifetime consumption of more than 100 cigarettes but currently not smoking), or current (lifetime consumption of more than 100 cigarettes and currently smoking daily). Drinking status was categorized as yes or no based on whether the individual drank more than 12 drinks per year. Physical activity (PA) was assessed using the Global Physical Activity Questionnaire (GPAQ) and classified according to the Metabolic Equivalent of Task (MET) adult guidelines (≥ 600 MET minutes/week, equivalent to 150 min/week of moderate-intensity or 75 min/week of high-intensity physical activity) [45, 46]. Hypertension was defined based on self-reported history of high blood pressure, use of antihypertensive medications, or systolic blood pressure (SBP) > 130 mmHg or diastolic blood pressure (DBP) > 80 mmHg [47]. Hyperlipidemia was defined as self-reported high cholesterol levels, use of cholesterol-lowering medications, or laboratory results showing triglycerides ≥ 150 mg/dl, low density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dl, high density lipoprotein cholesterol (HDL-C) < 40 mg/dl (male) or < 50 mg/dl (female), and total cholesterol (TC) ≥ 200 mg/dl. Diabetes was defined based on self-reported history of diabetes, use of insulin or antidiabetic medications, or laboratory results indicating hemoglobin A1c (HbA1c) ≥ 6.5%, fasting blood glucose (FBG) ≥ 7.0 mmol/L, or 2-hour postprandial glucose (2hPG) ≥ 11.1 mmol/L [48].

Statistical analyses

To ensure that the research findings accurately represent the U.S. civilian non-institutionalized population, our study incorporated sample weights, stratification, and clustering in the analysis. Participants were divided into four groups (Q1-Q4) based on RAR quartiles. Continuous variables were reported as means and standard deviations (SDs), while categorical variables were presented as frequencies and percentages in the baseline characteristics. Differences of continuous variables were assessed using one-way ANOVA, and differences of categorical variables were evaluated using Pearson chi-square ($\chi 2$) tests. To mitigate the reduction in sample size due to missing covariate data, we employed multiple imputation by chained equations (MICE) to address the missing values. The proportion of missing covariates and the imputation methods used are detailed in Additional file: Table S1 and Fig. S1. We conducted tests for multicollinearity on all variables, and the variance inflation factors (VIFs) for each variable were below 2, indicating that no significant multicollinearity issues were detected (Additional file: Table S2). We employed weighted multivariable logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (95%CIs) to estimate the independent associations between RAR quartiles and scores of three cognitive tests. Model 1 did not adjust for any covariates. Model 2 adjusted for age, sex, race, education, marital status, PIR, and BMI. Model 3 further adjusted for smoking status, drinking status, physical activity, hypertension, hyperlipidemia, and diabetes mellitus (DM). We employed restricted cubic spline (RCS) fitting logistic regression model to investigate the dose-response relationship between RAR and low cognitive performance. We further stratified the study population into two subgroups based on gender and conducted separate dose-response analyses to examine the association between RAR and low cognitive performance within each gender. Additionally, exploratory subgroup analyses were conducted stratified by age, sex, education, BMI, drinking status, smoking status, hypertension, and DM to evaluate the relationship between RAR and low cognitive performance across different population characteristics. Likelihood ratio tests were utilized to assess interactions

between grouping variables and RAR. We also conducted a further analysis using the Receiver Operating Characteristic (ROC) curve to assess the diagnostic capability of RAR in detecting low cognitive performance. Finally, we conducted several sensitivity analyses to assess the stability of the association between RAR and low cognitive performance. First, we excluded missing values for any covariates to mitigate the potential impact of data missingness on the primary results. Second, we removed all extreme values of RAR (defined as mean ± 3SD) to minimize their influence on the significance and stability of the results. Third, to account for the potential impact of cancer on cognitive function, we excluded participants who self-reported a malignant tumor at baseline. Bonferroni correction was applied to adjust for multiple comparisons, setting the threshold for statistical significance for subgroup interaction tests at $\alpha = 0.05/8 = 0.006$. All analyses were performed using R software (version 4.1.2), with P-values < 0.05 (two-sided) considered statistically significant.

Results

Characteristics of the study participants

This study included 2,765 participants with a mean age of 69.19 ± 6.64 years, and 46.2% of them were male. The mean RAR of the participants was 3.22 ± 0.40. Table 1 presents the baseline characteristics of the participants. They were divided into four groups based on RAR quartiles. Compared to participants in the first quartile, those in the fourth quartile of RAR were generally older, more likely to be female, non-Hispanic Black, and exhibited higher levels of waist circumference (WC), creatinine (Cr), and HbA1c, as well as lower levels of HDL-C and hemoglobin. Additionally, participants with higher RAR levels generally demonstrated lower cognitive performance, as evidenced by low scores on the AFT, DSST, and CERAD-WL. Moreover, a higher quartile of RAR was associated with increased numbers of participants who exhibited obesity, drinking, lack of physical activity, and diabetes. This suggests a potential association between unhealthy lifestyle habits and elevated RAR levels.

Association between RAR and low cognitive performance

We employed weighted multivariable logistic regression analysis to estimate the independent association between RAR quartiles and low cognitive performance. The relationship between RAR and low cognitive performance is illustrated in Table 2. After adjusting for multiple variables (Model 3), no significant association was found between RAR quartiles and low CERAD-WL performance ($P > 0.05$). For low DSST performance, the ORs (95% CIs) were 1.00 (reference), 0.97 (0.56, 1.70), 1.03 (0.60, 1.78), and 1.81 (1.03, 3.20). For low AFT performance, the ORs (95% CIs) were 1.00 (reference), 1.38 (0.81, 2.34), 1.27 (0.76, 2.11), and 1.68 (1.05, 2.67). The results indicate that higher levels of RAR (Q4 vs. Q1) are associated with an 81% increased risk of low DSST performance and a 68% increased risk of low AFT performance.

Dose-response analysis of RAR with low cognitive performance

We employed RCS fitted for logistic regression models to further investigate the relationship between RAR and low cognitive performance. The results revealed a significant linear relationship between RAR and low CERAD-WL performance. (Fig. 2A), low DSST performance (Fig. 2B), and low AFT performance (Fig. 2C) (P for nonlinear > 0.05). After adjusting for all confounding factors, we observed a generally linear positive association between RAR and both low DSST performance and low AFT performance, with an increased risk of low cognitive performance as RAR levels rise. Furthermore, we estimated the relationship between RAR and low cognitive performance across different genders. The results showed that RAR was linearly associated with low cognitive performance in both genders, with an increased risk of low DSST performance (Fig. 2E) and low AFT performance (Fig. 2F) as RAR levels increased across different gender groups.

Subgroup analyses

To further elucidate whether the association between RAR and low cognitive performance is consistent across different populations, we conducted a series of subgroup analyses. In these analyses (Fig. 3), we stratified by age, gender, education, BMI, drinking status, smoking status, hypertension, and DM. After applying the Bonferroni correction for statistical significance, the results demonstrated that the associations between RAR and low performance on the CERAD-WL, DSST, and AFT were consistent across all subgroups, with no significant interaction observed between RAR and the stratification variables (P for interaction > 0.006).

Receiver operating characteristic (ROC) curve analysis

The results demonstrated that RAR exhibited the optimal independent predictive ability for low DSST performance. The area under the ROC curve (AUC) and its 95% CI were 0.845 (95% CI: 0.829–0.860), indicating a strong predictive power. The AUC and 95% CI for the RAR in relation to low CERAD-WL performance and low AFT performance were 0.730 (95% CI: 0.710–0.750) and 0.750 (95% CI: 0.731–0.770), respectively. These values indicate that the model demonstrates a certain level of discriminative ability (Fig. 4).

Table 1 Baseline characteristics according to RAR quartiles

Characteristics	Quartiles of RAR					*P*-value
	Overall	Q1(< 2.95)	Q2(2.95–3.16)	Q3(3.16–3.40)	Q4(> 3.40)	
N (%)	2765	605	654	696	810	
Age, years, mean (SD)	69.19(6.64)	67.70(6.11)	68.90(6.64)	69.80(6.63)	70.36(6.87)	< 0.001
Gender, n (%)						0.018
Male	1357(46.2)	310(46.0)	347(52.4)	335(43.8)	365(42.2)	
Female	1408(53.8)	295(54.0)	307(47.6)	361(56.2)	445(57.8)	
Race, n (%)						< 0.001
Mexican American	244(3.4)	64(3.5)	73(4.0)	46(2.5)	61(3.3)	
Non-Hispanic White	1351(80.3)	293(82.5)	335(82.5)	359(81.8)	364(74.2)	
Non-Hispanic Black	628(7.9)	79(3.4)	113(5.2)	165(8.4)	271(14.8)	
Other	542(8.4)	169(10.6)	133(8.2)	126(7.3)	114(7.7)	
Education, n (%)						0.005
Less than high school	689(15.7)	130(10.8)	163(15.3)	169(16.6)	227(20.0)	
High school grad or equivalent	658(22.3)	134(23.5)	146(19.3)	165(20.8)	213(25.8)	
Some college or above	1418(62.0)	341(65.8)	345(65.3)	362(62.6)	370(54.2)	
Marital, n (%)						< 0.001
Married/Living with partner	1604(65.0)	382(70.4)	419(69.9)	399(64.2)	404(55.3)	
Widowed/Divorced/Separated	1001(30.6)	182(24.9)	203(26.5)	261(31.8)	355(39.3)	
Never married	160(4.4)	41(4.7)	32(3.6)	36(4.0)	51(5.4)	
PIR, n (%)						< 0.001
Low	841(18.1)	167(15.5)	186(13.9)	206(18.1)	282(25.2)	
Moderate	1043(37.4)	192(31.0)	251(37.8)	278(39.9)	322(40.9)	
High	881(44.4)	246(53.6)	217(48.3)	212(42.0)	206(33.8)	
BMI (kg/m^2), n (%)						< 0.001
Normal/Underweight	758(26.8)	206(34.5)	197(27.3)	180(24.6)	175(20.8)	
Overweight	978(36.3)	255(41.9)	247(40.0)	247(34.9)	229(28.4)	
Obese	1029(36.9)	144(23.7)	210(32.7)	269(40.6)	406(50.7)	
WC, (cm), mean (SD)	102.50(14.71)	97.91(13.00)	101.42(13.00)	103.51(14.87)	107.17(16.23)	< 0.001
HDL-C, mmol/L, mean (SD)	55.57(16.74)	58.83(18.53)	55.92(16.35)	54.10(15.59)	53.41(15.84)	0.001
Cr, mg/dL, mean (SD)	0.99(0.58)	0.91(0.23)	0.97(0.31)	0.97(0.33)	1.14(1.04)	< 0.001
UA, mg/dL, mean (SD)	5.61(1.43)	5.50(1.38)	5.65(1.42)	5.57(1.38)	5.73(1.53)	0.281
GGT, U/L, mean (SD)	25.56(30.50)	24.57(24.16)	24.48(25.53)	24.27(19.92)	28.93(45.61)	0.219
Hemoglobin, g/dL, mean (SD)	13.97(1.37)	14.27(1.24)	14.26(1.16)	14.02(1.28)	13.30(1.56)	< 0.001
HbA1c, %, mean (SD)	5.94(0.96)	5.74(0.74)	5.87(0.89)	5.97(0.91)	6.18(1.18)	< 0.001
Smoking status, n (%)						0.400
Never	1364(49.9)	310(49.9)	329(52.0)	339(50.2)	386(47.5)	
Former	1042(38.9)	240(40.2)	236(36.4)	271(40.3)	295(38.6)	
Current	359(11.2)	55(10.0)	89(11.6)	86(9.4)	129(13.9)	
Drinking status, n (%)						0.008
Yes	1893(72.9)	444(78.3)	458(75.4)	478(71.2)	513(66.6)	
No	872(27.1)	161(21.7)	196(24.6)	218(28.8)	297(33.4)	
Physical activity, n (%)						< 0.001
Yes	1332(51.3)	348(62.6)	355(56.3)	324(47.0)	305(39.2)	
No	1433(48.7)	257(37.4)	299(43.7)	372(53.0)	505(60.8)	
Hypertension, n (%)						0.068
Yes	2210(77.0)	460(74.4)	515(75.5)	548(75.9)	687(82.3)	
No	555(23.0)	145(25.6)	139(24.5)	148(24.1)	123(17.7)	
Hyperlipidemia, n (%)						0.232
Yes	2345(85.8)	528(87.1)	556(86.1)	596(87.6)	665(82.3)	
No	420(14.2)	77(12.9)	98(13.9)	100(12.4)	145(17.7)	
DM, n (%)						< 0.001
Yes	903(26.5)	150(17.2)	200(24.8)	234(30.0)	319(33.9)	
No	1862(73.5)	455(82.8)	454(75.2)	462(70.0)	491(66.1)	

Table 1 (continued)

Characteristics	Quartiles of RAR					*P*-value
	Overall	Q1(< 2.95)	Q2(2.95–3.16)	Q3(3.16–3.40)	Q4(> 3.40)	
CERAD-WL, (mean (SD)	25.99(6.39)	26.41(6.26)	26.46(6.49)	26.04(6.00)	25.04(6.70)	0.018
DSST, (mean (SD)	52.21(16.73)	57.06(16.60)	53.32(16.07)	51.64(15.88)	46.80(16.78)	< 0.001
AFT, (mean (SD)	18.08(5.64)	18.97(5.45)	18.71(5.79)	18.04(5.52)	16.61(5.48)	< 0.001

The data are presented as the mean (SD) or n (%). All estimates were obtained from complex survey designs, analysis of variance or χ2 tests where appropriate. *PIR* poverty income ratio, *BMI* body mass index, *WC* waist circumference, *HDL-C* high density lipoprotein cholesterol, *Cr* creatinine, *UA* uric acid, *GGT* gamma-glutamyl transferase, *HbA1c* hemoglobin A1c, *DM* diabetes mellitus, *RAR* The red blood cell distribution width to albumin ratio, *CERAD* Consortium to Establish a Registry for Alzheimer's Disease-Word Learning subtest, *DSST* Digit Symbol Substitution Test, *AFT* Animal Fluency Test, *SD* standard deviation

Table 2 ORs (95% CIs) for low cognitive performance according to RAR quartiles

	Quartiles of RAR			
	Q1(< 2.95)	Q2(2.95–3.16)	Q3(3.16–3.40)	Q4(> 3.40)
Low CERAD-WL performance				
Model 1 OR (95%CI) P value	1	1.04(0.74,1.47)0.794	1.05(0.75,1.45)0.785	1.60(1.19,2.15)0.003
Model 2 OR (95%CI) P value	1	0.86(0.56,1.32)0.466	0.80(0.52,1.16)0.204	1.07(0.72,1.61)0.711
Model 3 OR (95%CI) P value	1	0.85(0.54,1.32)0.419	0.76(0.50,1.16)0.183	1.03(0.66,1.61)0.888
Low DSST performance				
Model 1 OR (95%CI) P value	1	1.25(0.77,2.02)0.346	1.55(0.99,2.42)0.056	3.10(1.99,4.83)0.001
Model 2 OR (95%CI) P value	1	0.98(0.58,1.66)0.936	1.05(0.62,1.76)0.859	1.86(1.06,3.24)0.032
Model 3 OR (95%CI) P value	1	0.97(0.56,1.70)0.915	1.03(0.60,1.78)0.901	1.81(1.03,3.20)0.041
Low AFT performance				
Model 1 OR (95%CI) P value	1	1.51(1.04,2.20)0.032	1.60(1.09,2.37)0.019	2.54(1.79,3.60)0.001
Model 2 OR (95%CI) P value	1	1.41(0.89,2.25)0.132	1.32(0.85,2.06)0.196	1.82(1.21,2.74)0.007
Model 3 OR (95%CI) P value	1	1.38(0.81,2.34)0.200	1.27(0.76,2.11)0.318	1.68(1.05,2.67)0.034

Model 1 was unadjusted

Model 2 was adjusted for sex, age, race, education, marital status, PIR, and BMI

Model 3 was further adjusted for smoking status, drinking status, physical activity, hypertension, hyperlipidemia, and DM, based on model2

Results are presented as ORs and 95% CIs. *OR* odds ratio, *CI* confidence interval, *PIR* poverty income ratio, *BMI* body mass index, *DM* diabetes mellitus, *RAR* The red blood cell distribution width to albumin ratio, *CERAD-WL* Consortium to Establish a Registry for Alzheimer's Disease Word Learning test, *DSST* Digit Symbol Substitution Test, *AFT* Animal Fluency Test

Sensitivity analysis

To assess the stability of our results, we conducted several sensitivity analyses. After excluding participants with missing values for covariates, 2,265 participants were included in the study. Adjusting for a range of confounding factors, the association between RAR and low cognitive performance remained relatively stable (Additional file: Table S3). Following the removal of extreme RAR values, 2,707 participants were included, and after adjusting for various covariates, the results were consistent with the preliminary analysis (Additional file: Table S4). Finally, excluding participants who self-reported having cancers at baseline, 2,226 participants were included, and after adjusting for all confounding factors, the relationship between RAR and low cognitive performance remained robust (Additional file: Table S5).

Discussion

To the best of our knowledge, this study is the first cross-sectional research revealing the association between RAR and low cognitive performance. The results indicate that the RAR levels are independently and linearly positively associated with low DSST performance and low AFT performance among older adults in the United States. As RAR levels increase, the risk of low cognitive performance rises. Our findings underscore the importance of RAR as a novel comprehensive biomarker of inflammation and nutrition, providing some evidence of the role of inflammation and nutritional status in the development of low cognitive performance.

Recent studies have shown that RAR is closely associated with the prognosis of cardiovascular and

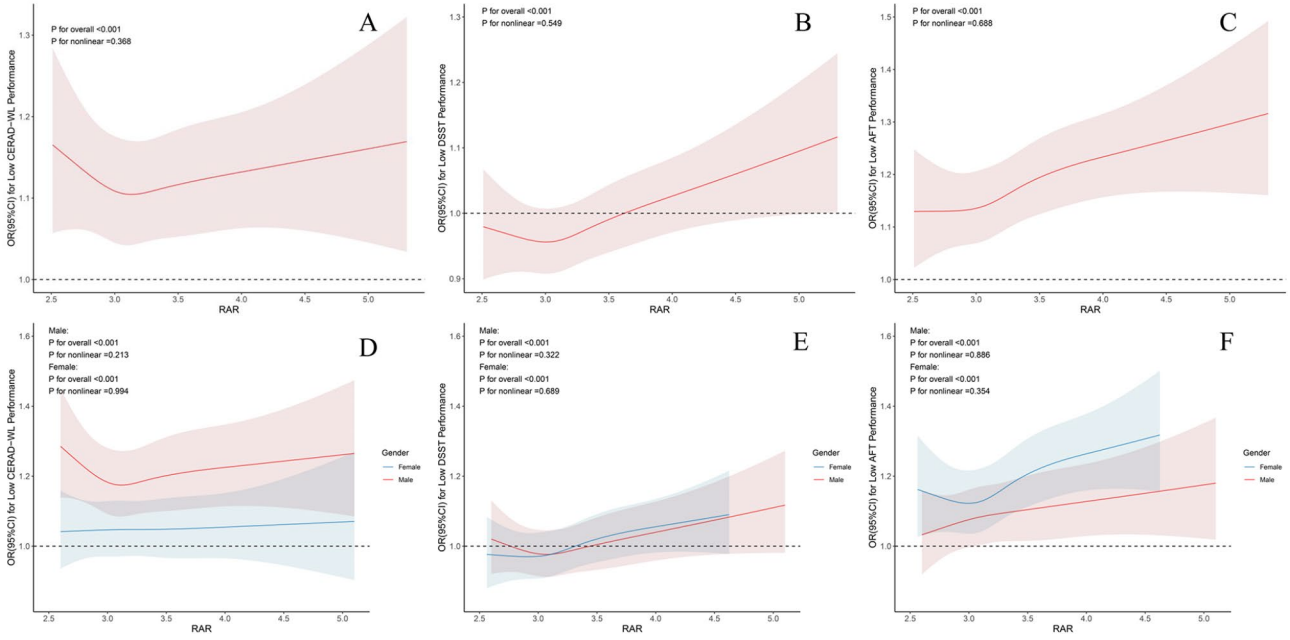

Fig. 2 Restricted cubic splines were used to test the associations between RAR and low cognitive performance among all participants and different genders. low CERAD-WL performance (**A**), low DSST performance (**B**), low AFT performance (**C**), low CERAD-WL performance between different genders (**D**), low DSST performance between different genders (**E**), low AFT performance between different genders (**F**). The analysis was adjusted for sex, age, race, education, marital status, PIR, BMI, smoking status, drinking status, physical activity, hypertension, hyperlipidemia, and DM. *PIR* poverty income ratio, *BMI* body mass index, *DM* diabetes mellitus, *RAR* red blood cell distribution width to albumin ratio, *CERAD-WL* consortium to establish a registry for Alzheimer's disease word learning test, *DSST* digit symbol substitution test, *AFT* animal fluency test

cerebrovascular diseases, such as coronary artery disease, myocardial infarction, and stroke, and lower RAR level is linked to higher short-term and long-term survival rates in patients [34, 49, 50]. As a novel biomarker, RAR combines two classical clinical parameters, RDW and albumin, and demonstrates a superior predictive ability for adverse disease outcomes and all-cause mortality compared to either RDW or albumin alone [49]. Our study also suggests that RAR may serve as an important predictive factor for the risk of low cognitive performance.

The specific biological mechanisms about association between higher RAR and increased risk of low cognitive performance have not yet been fully elucidated, but may be related to chronic inflammation and poor nutritional status [51, 52]. RAR is a composite indicator integrating RDW and albumin, with increases in RDW and decreases in albumin both contributing to elevated RAR levels. Several studies have indicated that elevated RDW is associated with cognitive decline [53, 54]. A cross-sectional study [55]indicated a "J-shaped" relationship between elevated RDW levels and the likelihood of dementia in older adults. Additionally, a prospective cohort study highlighted a causal impact of RDW on the risk of Alzheimer's disease [27]. Elevated RDW is commonly associated with systemic inflammatory states, which can affect erythropoiesis, red blood cell lifespan, and red blood cell deformability, leading to increased cell anisotropy and subsequently raising RDW levels [56]. Chronic inflammation is considered one of the key mechanisms underlying low cognitive performance. Abnormal deposition of amyloid proteins can lead to excessive activation of microglia and astrocytes in the central nervous system, triggering neuroinflammatory responses. Prolonged inflammatory conditions result in structural and functional damage to neurons, further contributing to cognitive decline [28]. Additionally, RDW is used in the differential diagnosis of anemia, which is considered a contributing factor to CI and Alzheimer's disease [28]. In the condition of anemia, pathological changes in red blood cells, including alterations in quantity, volume, distribution, and overall mass, can reduce the blood's oxygen-carrying capacity. Hypoxic changes in cerebral blood vessels may be a crucial mechanism in the pathogenesis of neurodegenerative diseases, leading to low cognitive performance and dementia [57]. Our study also found that participants with higher RAR often had lower hemoglobin levels and a higher risk of low cognitive performance.

Albumin is an essential protein in human plasma. Hypoalbuminemia, often caused by inflammatory conditions, reflects the presence of inflammation and is associated with increased mortality rates in various diseases and among healthy individuals [58]. Research indicates that albumin can predict cognitive decline, and

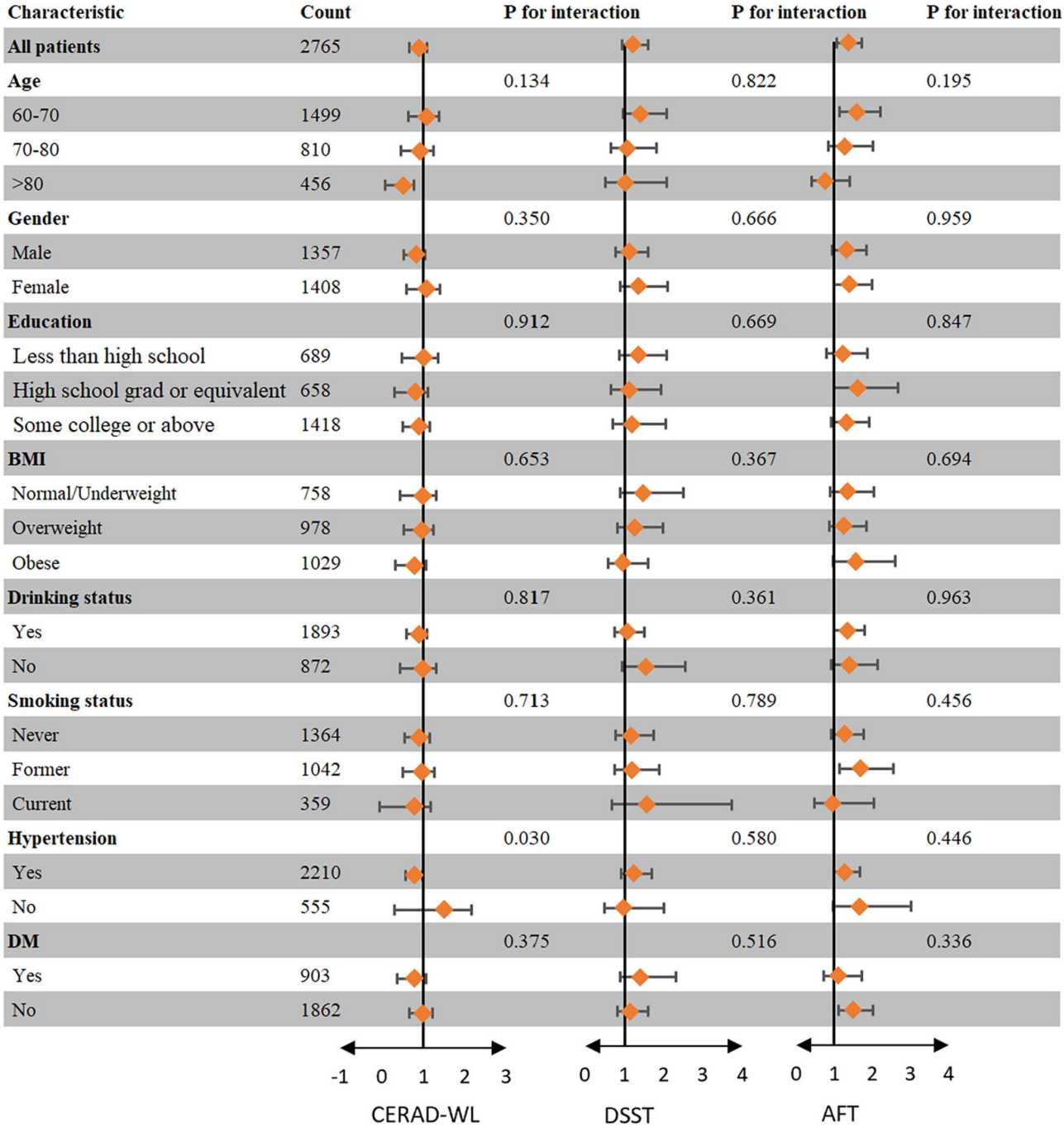

Fig. 3 Subgroup analysis of the associations between RAR and low cognitive performance. The analysis was adjusted for age, gender, education, BMI, smoking status, drinking status, smoking status, hypertension, and DM. *BMI* body mass index, *DM* diabetes mellitus, *RAR* The red blood cell distribution width to albumin ratio, *CERAD-WL* consortium to establish a registry for alzheimer's disease word learning test, *DSST* digit symbol substitution test, *AFT* animal fluency test

increasing albumin levels may improve Alzheimer's disease-related pathology and CI [59, 60]. Albumin plays a crucial role in regulating inflammatory responses, and a decrease in its levels may lead to uncontrolled inflammation, which can subsequently impact cognitive function [50]. Additionally, albumin has antioxidant properties and is capable of neutralizing free radicals and peroxides in the body. When albumin levels decrease, the body's antioxidant capacity is reduced, leading to increased oxidative stress and contributing to cognitive decline [61]. Furthermore, low albumin levels reflect malnutrition or inadequate protein intake. Such nutritional deficiencies can lead to damage to brain structure and function, thereby affecting cognitive abilities [62]. In summary,

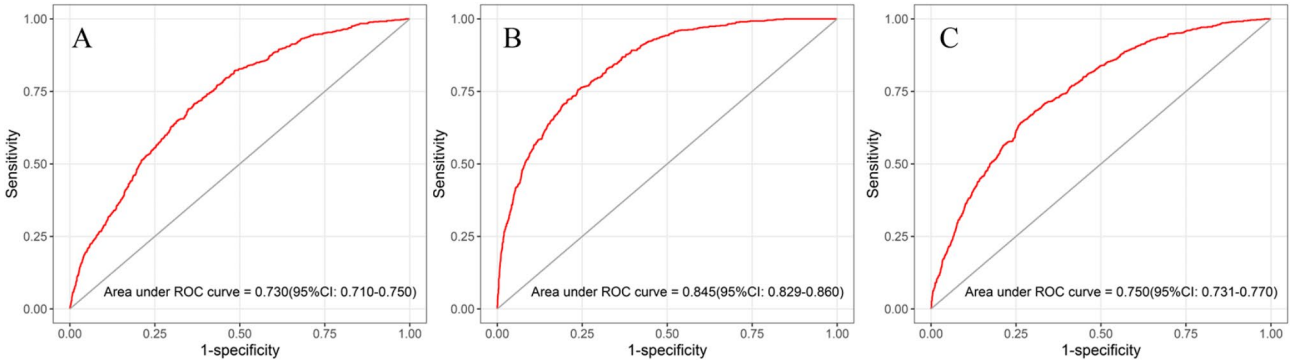

Fig. 4 ROC curve analysis for low cognitive performance. low CERAD-WL performance (**A**), low DSST performance (**B**), low AFT performance (**C**). The analysis was adjusted for sex, age, race, education, marital status, PIR, BMI, smoking status, drinking status, physical activity, hypertension, hyperlipidemia, and DM. *PIR* poverty income ratio, *BMI* body mass index, *DM* diabetes mellitus, *RAR* The red blood cell distribution width to albumin ratio, *CERAD-WL* consortium to establish a registry for Alzheimer's disease word learning test, *DSST* digit symbol substitution test, *AFT* animal fluency test

previous studies have highlighted the significant independent associations of RDW and albumin with CI. Our research demonstrates that RAR can serve as a valuable biomarker for identifying the risk of low cognitive performance more comprehensively and intuitively than RDW and albumin alone. Elevated RAR may reflect underlying chronic inflammation, oxidative stress, and poor nutritional status, with these combined factors potentially leading to central nervous system damage and cognitive decline.

In addition to central nervous system inflammation, peripheral inflammation also plays an indirect role in the development of CI. Research indicates that increased peripheral inflammation is a driving factor for the onset of dementia and Alzheimer's disease [63, 64], higher rates of CI have been observed in patients with rheumatoid arthritis and skin inflammation [24, 65]. Furthermore, systemic inflammatory response syndrome (SIRS) is associated with acute CI [66], and persistent systemic inflammation remains a key characteristic of long-term CI [67]. This may be related to increased peripheral inflammation, which elevates the circulating levels of pro-inflammatory cytokines, damages the blood-brain barrier, and subsequently induces central nervous system inflammation, thereby contributing to the development of CI [24]. It is noteworthy that research indicates a dynamic relationship between central and peripheral inflammation during the progression of dementia. Early in the disease, activation of microglia in the central nervous system leads to increased central inflammation. In later stages, as cognitive function declines, central inflammation may diminish while T-cell-related peripheral inflammation intensifies [68]. Thus, the type and level of inflammation can vary across different stages of CI, yet chronic inflammation remains a crucial factor in its onset and progression. Additionally, various inflammatory markers, such as the dietary inflammatory index [69], blood inflammatory index [70], systemic immune-inflammation index [71], and periodontal disease [72] are all considered to significantly impact cognitive function. This further supports the role of RAR as a novel and comprehensive inflammatory marker associated with low cognitive performance.

It is noteworthy that our study found RAR to be more strongly associated with low AFT performance and low DSST performance, while no significant correlation was observed with low CERAD-WL performance. The influence of RAR on cognitive function may be more closely related to language production assessed by AFT, as well as attention and working memory capacity evaluated by DSST, rather than immediate learning and delayed recall abilities assessed by CERAD-WL. Similar studies [73, 74] have indicated that the dietary inflammatory index is positively correlated with aspects of low cognitive performance reflected by AFT and DSST, while showing no correlation with low CERAD-WL performance. These findings are consistent with our study's conclusions. It is important to emphasize that our study shows that, compared to the lowest RAR quartile, the highest RAR quartile is associated with an 81% increased risk of low DSST performance and a 68% increased risk of low AFT performance. This finding partially confirms that elevated RAR may be a significant risk factor for low cognitive performance, underscoring its importance.

Through gender stratification, our study also found that the risk of low AFT performance and low DSST performance increases with higher RAR levels in both male and female. This finding is consistent with conclusions from most studies on CI [43, 75, 76]. In the subgroup analyses, we did not observe significant interactions between RAR and the stratification variables. Sensitivity analysis results indicate that the relationship between RAR and low cognitive performance remains relatively stable.

Strengths and limitations

This study has several notable strengths. First, we evaluate the association between RAR and the risk of low

cognitive performance. RAR, as a novel comprehensive indicator of inflammation and nutrition, is simple, reliable, practical, and easily obtainable, providing significant predictive value for low cognitive performance in the older adults. Second, the NHANES database employs a complex multistage probability sampling design, and weighting of the analyses allows for generalization of the findings to the U.S. non-institutionalized civilian population. To enhance the reliability of our analysis, we constructed and adjusted multiple confounding factor models and conducted stratified analyses to explore the relationship between RAR and different cognitive performance tests. However, this study has several limitations. First, as a cross-sectional study, it cannot establish a causal relationship between RAR and low cognitive performance, necessitating further large-scale cohort studies to assess the predictive capability of RAR for low cognitive performance. Second, despite adjusting for numerous confounding factors, we cannot completely rule out the influence of unknown or unmeasurable confounders on the results. Third, while we conducted exploratory subgroup analyses and adjusted p-values to control for the risk of false positives due to multiple comparisons, these results require validation in future clinical studies. Finally, we did not adjust the cognitive function assessment results based on age, gender, and education level, which may have a certain impact on the research results.

Conclusions

We conducted a cross-sectional study based on the NHANES database and found a significant linear positive association between RAR and low cognitive performance in older adults. As RAR levels increase, the risk of low DSST performance and low AFT performance also rises. Our study highlights that maintaining lower RAR could be an important strategy for reducing the risk of low cognitive performance. In the future, large-scale, multicenter prospective studies are warranted to assess the predictive value of RAR for cognitive function in the elderly and to further explore the specific mechanisms by which low RAR levels lead to low cognitive performance.

Abbreviations

AFT	Animal Fluency Test
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
BCP	Bromocresol purple
CI	Cognitive impairment
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CERAD-WL	Consortium to Establish a Registry for Alzheimer's Disease-Word Learning subtest
CERAD-IR	Consortium to Establish a Registry for Alzheimer's Disease-Immediate Recall Test
CERAD-DR	Consortium to Establish a Registry for Alzheimer's Disease-Delayed Recall Test
CIs	Confidence intervals
Cr	Creatinine
DSST	Digit Symbol Substitution Test
DBP	Diastolic blood pressure
DM	Diabetes mellitus
FBG	Fasting blood glucose
GGT	Gamma-glutamyl transferase
GPAQ	Global physical activity questionnaire
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein- cholesterol
LDL-C	Low density lipoprotein- cholesterol
MCI	Mild cognitive impairment
MEC	Mobile Examination Center
MICE	Multiple imputation by chained equations
MET	Metabolic equivalent of task
NHANES	National Health and Nutrition Examination Survey
ORs	Odds ratios
PIR	Poverty income ratio
PA	Physical activity
RAR	Red blood cell distribution width to albumin ratio
RCS	Restricted cubic spline
RDW	Red blood cell distribution width
RBC	Red blood cell
SBP	Systolic blood pressure
SD	Standard deviations
SIRS	Systemic inflammatory response syndrome
TC	Total cholesterol
UA	Uric acid
VIF	Variance inflation factor
WC	Waist circumference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05800-4 .

Additional file: Table S1: The proportion of missing covariates and imputation methods; Table S2: Assessment of multicollinearity among independent variables; Table S3: ORs (95% CIs) for low cognitive performance according to RAR quartiles after excluding participants with any missing covariate values; Table S4: ORs (95% CIs) for low cognitive performance according to RAR quartiles after excluding extreme values (mean ± 3 standard deviations) of RAR; Table S5: ORs (95% CIs) for low cognitive performance according to RAR quartiles after excluding participants with self-reported cancer; Figure S1: Specific distribution of missing covariate values.

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Author contributions

The study was conceived by BY, ML, and RG3, who were responsible for performing the data analysis and manuscript writing. ZY and HZ extracted the data from the official NHANES website. RG2 contributed to the revision and review of the manuscript. XF and AG conducted a repeat analysis of the data and verified the results. All authors have reviewed and approved the final version of the manuscript.

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Data availability

The dataset used for this study analysis can be found on the official website of the National Health and Nutrition Examination Survey (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethics approval and consent to participate
The NHANES protocol was approved by the National Center for Health Statistics and the Institutional Review Board. All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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