

Red cell distribution width-to-albumin ratio and serum neurofilament light chain: A population-based study

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ABSTRACT

Introduction: Neurofilament light chain (NfL) is a blood biomarker of neuronal injury in inflammatory and neurodegenerative disorders. The red cell distribution width-to-albumin ratio (RAR) reflects systemic inflammation and nutritional status. This study investigated whether higher RAR is associated with higher serum NfL (sNfL) in a general adult population.

Methods: Data from 1750 adults who participated in the 2013–2014 National Health and Nutrition Examination Survey were analysed. RAR was calculated as red cell distribution width (%) divided by serum albumin (g/dL). sNfL was measured using an automated Atellica chemiluminescent immunoassay. Participants were grouped into RAR quartiles. Survey-weighted multivariable linear regression and restricted cubic spline (RCS) models assessed associations between RAR and log-transformed sNfL, adjusting for demographic, socioeconomic, lifestyle and clinical factors.

Results: Each unit increase in RAR was associated with higher sNfL in unadjusted analysis, and this association remained significant in partially and fully adjusted models. Compared with participants in the lowest quartile, those in the highest RAR quartile had higher sNfL, with a significant trend across quartiles. RCS analysis showed a non-linear but monotonic increase in log-transformed sNfL with higher RAR (P for non-linearity = 0.020). Associations varied by race/ethnicity, body mass index and diabetes status.

Conclusion: Higher RAR is associated with higher sNfL in US adults. This epidemiological association suggests that inflammation/nutritional status may relate to neuroaxonal injury. Longitudinal studies are needed to establish temporality and assess prognostic value before any clinical application.

Keywords: neurofilament light chain, neurology, neuronal injury, NHANES, RAR

CLINICAL IMPACT

What is New

- Analysis of 1750 US adults shows that higher red cell distribution width-to-albumin ratio (RAR) is associated with higher serum neurofilament light chain (sNfL).
- RAR–sNfL associations persist after adjustment for demographic and clinical factors, with variation by race/ethnicity, body mass index and diabetes status.

Clinical Implications

- RAR is calculated from routine full blood count and albumin tests and may help identify individuals with higher sNfL levels. These data support further prospective evaluation of RAR as a simple adjunctive marker of neuronal injury in diverse clinical populations.

INTRODUCTION

Neurofilament light chain (NfL), a member of the neurofilament protein family, is highly expressed in the axons of mature neurons, where it forms a fibrous network that constitutes a key component of the neuronal cytoskeleton.¹ When neurons die or are injured, NfL is released in large amounts into the extracellular space and subsequently reaches the cerebrospinal fluid and peripheral blood.² Owing to its high solubility and abundant expression, NfL has become a reliable subunit for neurofilament detection in body fluids.

In recent years, NfL has been established as an early biomarker for various neurological diseases, including

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Alzheimer's disease,³ frontotemporal dementia,⁴ Parkinson's disease,⁵ amyotrophic lateral sclerosis,⁶ multiple sclerosis⁷ and traumatic brain injury.⁸ Under optimal conditions, NfL is also used to monitor treatment responses. Currently, Quanterix's single-molecule array technology (Simoa; Quanterix Corporation, Lexington, MA, US) is regarded as the gold standard for measuring serum NfL (sNfL) levels.⁹ Accurate and flexible monitoring of blood NfL levels plays a crucial role in disease staging, subtyping and differential diagnosis.

The red cell distribution width-to-albumin ratio (RAR) has emerged as a novel composite biomarker reflecting both inflammatory and nutritional status. Red cell distribution width (RDW), an indicator of heterogeneity in red blood cell volume, is a readily available laboratory parameter, with higher values indicating greater variability in red blood cell size.¹⁰ Previous studies have shown that RDW is closely associated with various chronic inflammatory conditions and oxidative stress.¹¹ Albumin, the most abundant plasma protein, exerts multiple physiological functions, including anti-inflammatory, anticoagulant and antioxidant activities, as well as the maintenance of osmotic pressure.¹² Abnormalities in RDW and albumin levels may partially reflect alterations in nutritional status, inflammation and oxidative stress.¹³ As an integrated index, RAR has shown prognostic relevance or strong associations with several inflammation- and ageing-related conditions; however, its relationship with biomarkers of neuronal injury remains unclear.

This study aimed to investigate the association between RAR and sNfL levels. Clinically, the measure-

ment of blood NfL often requires specialised platforms such as Simoa, which is expensive and not yet widely incorporated into routine laboratory testing. While NfL is a potent marker of injury, understanding how it relates to routine physiological indices remains limited. Exploring correlations between routinely available blood biomarkers and sNfL may therefore help elucidate the biological relationship between systemic physiological states and subclinical neuronal injury. Using data from the National Health and Nutrition Examination Survey (NHANES), this study conducted a cross-sectional analysis to evaluate the association between RAR and sNfL in US adults.

METHODS

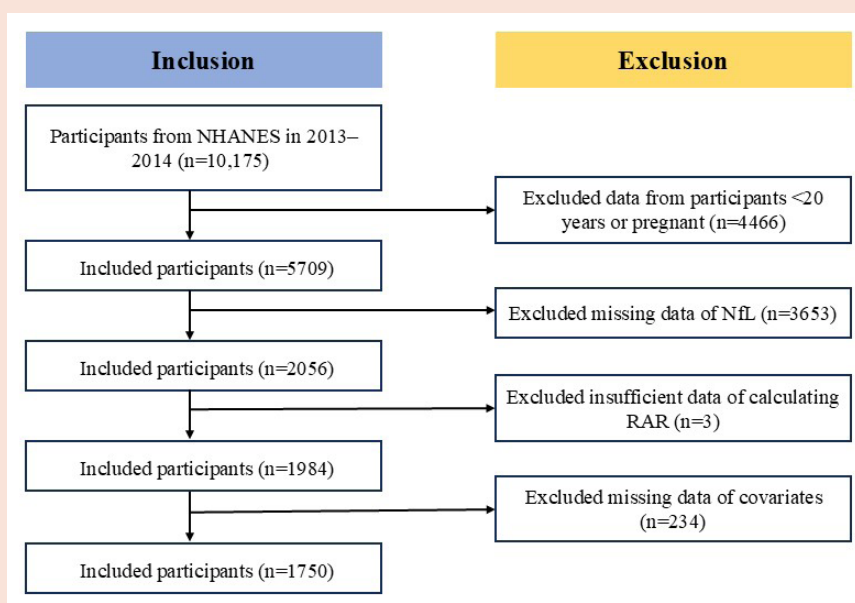
Study population

This study focused on data from the 2013–2014 NHANES cycle, as it contains complete information on sNfL. Fig. 1 shows that 10,175 individuals were initially included. Participants were excluded based on the following criteria: (1) age under 20 years ($n=4466$), (2) missing sNfL data ($n=3653$), (3) missing RAR data ($n=3$) and (4) incomplete or missing covariate information ($n=234$).

The final analyses included relevant covariates such as age, sex, body mass index (BMI), poverty income ratio (PIR), education level, race/ethnicity, smoking status, alcohol consumption and the presence of diabetes or hypertension.

Serum albumin concentrations were determined based on the formation of a coloured complex with

Fig. 1. Flowchart of participant selection.



NHANES: National Health and Nutrition Examination Survey; NfL: neurofilament light chain; RAR: red cell distribution width-to-albumin ratio

bromocresol purple, where the colour intensity is directly proportional to the albumin level. The bichromatic digital endpoint method (DcX 800) was then used to measure absorbance and convert it into albumin concentration (g/dL).

Participants were divided into quartiles based on RAR values: Q1 (<2.95), Q2 (2.95–3.16), Q3 (3.16–3.44) and Q4 (>3.44), with Q1 defined as the reference group.

Measurement of NfL

In the 2013–2014 NHANES cycle, sNfL levels were measured using a highly sensitive chemiluminescent immunoassay developed by Siemens Healthineers. Serum samples were first incubated with acridinium ester (AE)-labelled antibodies specifically targeting NfL. Subsequently, paramagnetic microparticles (PMPs) were added to form a stable NfL–AE-labelled antibody–PMP complex.

After washing to remove unbound antibodies, a trigger solution was applied to initiate the chemiluminescent reaction of the AE label. The resulting light emission, which is directly proportional to the concentration of sNfL in the sample, was detected and quantified. All measurements were conducted using the Atellica IM analyzer platform (Siemens Healthineers, Tarrytown, NY, US), ensuring high-throughput processing and analytical consistency.

Covariates

Several covariates were included to account for demographic, lifestyle and clinical characteristics. Age was grouped as 20–39, 40–59 and ≥60 years; sex as male or female; and race/ethnicity as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black and other races. Educational attainment was categorised as less than high school, high school graduate or equivalent, and above high school. PIR was grouped as ≤1.3, 1.3–3.5 and >3.5. Marital status was classified as married or living with a partner, widowed/divorced/separated, or never married. Smoking status was defined according to whether participants had smoked at least 100 cigarettes in their lifetime. Alcohol consumption was defined as intake of more than 100 alcoholic drinks per year. Diabetes was identified by a clinical diagnosis or by any of the following: glycated haemoglobin ≥6.5%, fasting plasma glucose ≥7.0 mmol/L, random plasma glucose ≥11.1 mmol/L, 2-hour oral glucose tolerance test glucose ≥11.1 mmol/L, or use of glucose-lowering medication or insulin. Hypertension was defined as a clinical diagnosis or use of antihypertensive medication, or measured systolic/diastolic blood pressure ≥140/90 mmHg on 3 separate occasions by trained personnel. Laboratory covariates included total cholesterol (TC), uric acid (UA) and serum creatinine (Scr).

Statistical analyses

To better represent the US population, sample weights and stratified analyses were applied. As sNfL showed a non-normal distribution, its natural logarithm (ln) was used for analyses. Continuous variables are presented as mean ± standard deviation, and categorical variables as frequencies (percentages). The association between RAR and ln-transformed sNfL (ln-sNfL) was assessed using multivariable linear regression with 3 models: Model 1 (unadjusted), Model 2 (adjusted for age, sex, race/ethnicity, education, PIR and marital status) and Model 3 (further adjusted for smoking, alcohol use, diabetes, hyper-tension, TC, UA and Scr). A *P*-trend test evaluated potential trends. Restricted cubic spline (RCS) regression based on Model 2 examined possible non-linear associations. Subgroup and interaction analyses explored the relationship between RAR and ln-sNfL across categories of age, sex, race/ethnicity, education, PIR, marital status, BMI, smoking, alcohol use, diabetes and hypertension. All analyses were performed in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), with 2-sided *P*<0.05 considered statistically significant.

RESULTS

Characteristics of the study population

Table 1 presents the baseline characteristics of 1750 eligible participants stratified by quartiles of RAR. Among them, 850 were male and 900 were female. Participants were categorised into 3 age groups in ascending order, and the proportion of individuals aged over 40 years gradually increased from the lowest (Q1) to the highest (Q4) RAR quartile. Compared with those in the low RAR group, participants with higher RAR were more likely to be female, non-Hispanic black and have lower income levels (*P*<0.05). Moreover, elevated RAR was more frequently observed in participants with obesity (BMI ≥30 kg/m²); smoking; alcohol consumption; hypertension; diabetes and higher levels of TC, UA and Scr, indicating that these unfavourable lifestyle factors and metabolic abnormalities tended to cluster in the higher RAR quartiles.

Association between RAR and sNfL

Survey-weighted multivariable linear regression was conducted to examine the association between RAR and sNfL. Table 2 shows that higher RAR levels were significantly associated with increased ln-sNfL ($\beta=0.23$; 95% confidence interval [CI], 0.17–0.29; *P*<0.001). This association remained statistically significant after additional adjustment for demographic, socioeconomic, lifestyle and clinical factors in the fully adjusted model ($\beta=0.14$; 95% CI, 0.08–0.20;

Table 1. Baseline characteristics of study participants in NHANES 2013–2014.

Variables	Total	RAR				P
		Q1 (≤2.95)	Q2 (2.95–3.16)	Q3 (3.16–3.44)	Q4 (>3.44)	
n	1750	439	442	433	436	
Age, no. (%)						
20–39	609 (34.8)	231 (52.6)	158 (35.7)	122 (28.2)	98 (22.5)	<0.001
40–59	674 (38.5)	145 (33.0)	169 (38.2)	173 (40.0)	187 (42.9)	
≥60	467 (26.7)	63 (14.4)	115 (26.0)	138 (31.9)	151 (34.6)	
Sex, no. (%)						
Male	850 (48.6)	285 (64.9)	233 (52.7)	188 (43.4)	144 (33.0)	<0.001
Female	900 (51.4)	154 (35.1)	209 (47.3)	245 (56.6)	292 (67.0)	
Race, no. (%)						
Mexican American	239 (13.7)	59 (13.4)	75 (17.0)	50 (11.5)	55 (12.6)	<0.001
Other Hispanic	154 (8.8)	33 (7.5)	45 (10.2)	46 (10.6)	30 (6.9)	
Non-Hispanic white	811 (46.3)	245 (55.8)	210 (47.5)	195 (45.0)	161 (36.9)	
Non-Hispanic black	309 (17.7)	26 (5.9)	41 (9.3)	90 (20.8)	152 (34.9)	
Other races (including multiracial)	237 (13.5)	76 (17.3)	71 (16.1)	52 (12.0)	38 (8.7)	
Education, no. (%)						
Lower than high school	348 (19.9)	75 (17.1)	76 (17.2)	88 (20.3)	109 (25.0)	0.005
High school graduate/GED or equivalent	367 (21.0)	83 (18.9)	87 (19.7)	97 (22.4)	100 (22.9)	
Higher than high school	1035 (59.1)	281 (64.0)	279 (63.1)	248 (57.3)	227 (52.1)	
PIR, no. (%)						
≤1.3	597 (34.1)	127 (28.9)	138 (31.2)	154 (35.6)	178 (40.8)	<0.001
1.3–3.5	589 (33.7)	114 (26.0)	164 (37.1)	152 (35.1)	159 (36.5)	
>3.5	564 (32.2)	198 (45.1)	140 (31.7)	127 (29.3)	99 (22.7)	
Marital status, no. (%)						
Married/living with partner	1077 (61.5)	275 (62.6)	295 (66.7)	255 (58.9)	252 (57.8)	<0.001
Widowed/divorced/separated	333 (19.0)	56 (12.8)	68 (15.4)	100 (23.1)	109 (25.0)	
Never married	340 (19.4)	108 (24.6)	79 (17.9)	78 (18.0)	75 (17.2)	
BMI, no. (%)						
<25 kg/m ²	522 (29.8)	185 (42.1)	138 (31.2)	127 (29.3)	72 (16.5)	<0.001
25–30 kg/m ²	566 (32.3)	160 (36.4)	166 (37.6)	137 (31.6)	103 (23.6)	
≥30 kg/m ²	662 (37.8)	94 (21.4)	138 (31.2)	169 (39.0)	261 (59.9)	
Smoking status, no. (%)						
Smokers	778 (44.5)	173 (39.4)	199 (45.0)	191 (44.1)	215 (49.3)	0.032
Non-smokers	972 (55.5)	266 (60.6)	243 (55.0)	242 (55.9)	221 (50.7)	

Table 1. Baseline characteristics of study participants in NHANES 2013–2014. (Cont'd)

Variables	Total		RAR			P
Drinking status, no. (%)						
Drinkers	1312 (75.0)	356 (81.1)	346 (78.3)	316 (73.0)	294 (67.4)	<0.001
Non-drinkers	438 (25.0)	83 (18.9)	96 (21.7)	117 (27.0)	142 (32.6)	
Diabetes, no. (%)						
Yes	194 (11.1)	21 (4.8)	41 (9.3)	48 (11.1)	84 (19.3)	<0.001
No	1556 (88.9)	418 (95.2)	401 (90.7)	385 (88.9)	352 (80.7)	
Hypertension, no. (%)						
Yes	621 (35.5)	101 (23.0)	132 (29.9)	155 (35.8)	233 (53.4)	<0.001
No	1129 (64.5)	338 (77.0)	310 (70.1)	278 (64.2)	203 (46.6)	
TC (mmol/L), mean (SD)	189.02 (39.56)	189.67 (39.81)	193.10 (40.13)	189.52 (38.27)	183.75 (39.56)	0.005
UA (mg/dL), mean (SD)	5.47 (1.39)	5.65 (1.37)	5.39 (1.40)	5.38 (1.37)	5.46 (1.42)	0.011
Scr (mg/dL), mean (SD)	0.90 (0.63)	0.88 (0.19)	0.85 (0.19)	0.86 (0.21)	0.99 (1.21)	0.002
NfL (pg/ml), mean (SD)	2.56 (0.66)	2.39 (0.57)	2.53 (0.65)	2.62 (0.63)	2.70 (0.75)	<0.001

BMI: body mass index; GED: general education development; NfL: neurofilament light chain; PIR: poverty income ratio; RAR: red cell distribution width-to-albumin ratio; Scr: serum creatinine; SD: standard deviation; TC: total cholesterol; UA: uric acid

The *P* value was calculated by weighted linear regression model. Percentage for categorical variables: the *P* value was calculated by a weighted chi-square test.

$P < 0.001$). In sensitivity analyses, RAR was categorised into quartiles and treated as a categorical variable; the association persisted. Compared with individuals in the lowest quartile (Q1), those in the highest quartile (Q4) showed an adjusted β of 0.16 (95% CI, 0.08–0.25; $P < 0.001$). Similar findings were observed in Models 1 and 2. Thus, higher RAR values were significantly associated with increased sNfL levels (P for trend < 0.001). Additionally, RCS regression was used to assess the potential non-linear relationship between RAR and ln-sNfL. Fig. 2 illustrates that the test for non-linearity was statistically significant ($P = 0.02$).

Stratified analyses

To further investigate how the association between RAR and sNfL varied across subgroups, stratified analyses were performed according to age, sex, race, education level, PIR, marital status and BMI (Table 3). The results indicated that the association between RAR and sNfL was significantly different across categories of race (P for interaction = 0.016), BMI (P for interaction < 0.001) and diabetes status (P for interaction = 0.008), whereas no significant interactions were observed with other covariates. Across subgroups defined by age, sex, smoking status, alcohol consumption, diabetes and hypertension, RAR remained significantly positively associated with sNfL levels.

DISCUSSION

To the authors' knowledge, this study is the first cross-sectional analysis based on data from the nationally representative NHANES 2013–2014 cohort. Data from 1750 participants were analysed to investigate the association between RAR and sNfL. Results from multivariable linear regression (Model 3), which adjusted for multiple covariates, demonstrated a significant positive relationship between RAR and sNfL (both raw and log-transformed values, ln-sNfL), showing that higher RAR levels are associated with higher levels of a blood biomarker of neuronal injury. The findings, supported by stratified linear models and RCS analyses, suggested a monotonic increasing association without an obvious threshold. Interaction analyses revealed that race, BMI and diabetes status were significant effect modifiers of the association between RAR and sNfL. Overall, these results provide epidemiological evidence linking a composite marker of systemic inflammation and nutritional status with a blood biomarker of neuroaxonal injury.

sNfL is recognised as a sensitive biomarker of axonal damage and has shown considerable clinical and research utility in various neurological disorders. Recent studies have demonstrated that sNfL levels are elevated in patients with multiple sclerosis,¹⁴ depression,¹⁵ cognitive impairment¹⁶ and cerebrovascular diseases.¹⁷ Accordingly, sNfL is widely utilised

Table 2. Association of RAR with serum neurofilament light chain levels.

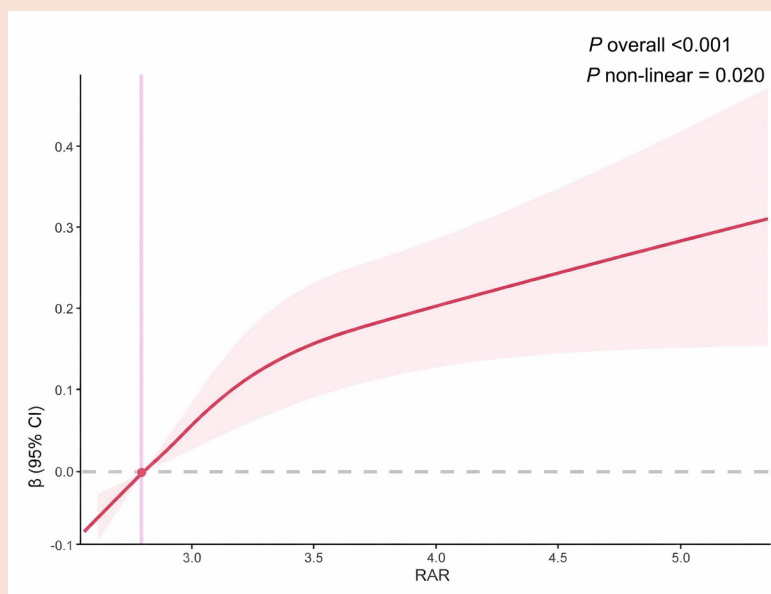
	Model 1		Model 2		Model 3	
	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>
Continuous	0.23 (0.17–0.29)	<0.001	0.17 (0.11–0.23)	<0.001	0.14 (0.08–0.20)	<0.001
Q1	Reference		Reference		Reference	
Q2	0.14 (0.05–0.23)	0.001	0.07 (–0.01–0.14)	0.087	0.07 (0.00–0.15)	0.05
Q3	0.23 (0.15–0.32)	<0.001	0.12 (0.04–0.20)	0.003	0.13 (0.05–0.20)	0.001
Q4	0.32 (0.23–0.40)	<0.001	0.2 (0.12–0.28)	<0.001	0.16 (0.08–0.25)	<0.001
<i>P</i> for trend	<0.001		<0.001		<0.001	

CI: confidence interval; RAR: red cell distribution width-to-albumin ratio

Model 2 was adjusted for age, sex, race, education, poverty income ratio and marital status.

Model 3 was adjusted for age, sex, race, education, poverty income ratio, marital status, smoking status, drinking status, diabetes, hypertension, total cholesterol, uric acid and serum creatinine.

Fig. 2. RCS curve of the association between RAR and NfL.



CI: confidence interval; NfL: neurofilament light chain; RAR: red cell distribution width-to-albumin ratio; RCS: restricted cubic spline

in research and clinical settings to reflect the burden of neuro-axonal damage, as well as for prognostic evaluation and monitoring disease progression in these conditions.¹⁸ However, sNfL is not disease-specific and may reflect neuroaxonal injury arising from multiple neurological and systemic processes. Thus, these findings should be interpreted as an epidemiological association rather than evidence supporting a specific clinical diagnostic or screening application.

The ratio of RAR has recently been proposed as a comprehensive indicator reflecting inflammation and

nutritional metabolism.¹⁹ Calculated from RDW and serum albumin, RAR combines these 2 parameters to more comprehensively reflect inflammatory status, oxidative stress and nutritional imbalance, and may provide more prognostic information than RDW or albumin alone.¹³ Elevated RAR is associated with adverse systemic inflammatory and wasting diseases, such as sepsis, cancer and heart failure.^{20–23} Moreover, recent research has revealed a positive correlation between high RAR levels and the prevalence of kidney stones in adults.²⁴ Increased RAR has also been linked to higher mortality risk in the general population,¹³ and

Table 3. Stratification analysis of the relationship between RAR and NfL based on Model 3.

Characteristics	β (95% CI)	P value	P for interaction
Age, no. (%)			0.921
20–39	0.16 (0.04–0.27)	0.008	
40–59	0.14 (0.06–0.22)	<0.001	
≥60	0.12 (0.02–0.23)	0.025	
Sex, no. (%)			0.146
Male	0.20 (0.10–0.30)	<0.001	
Female	0.11 (0.04–0.18)	0.002	
Race, no. (%)			0.016 ^a
Mexican American	0.10 (–0.05–0.25)	0.175	
Other Hispanic	0.03 (–0.17–0.23)	0.762	
Non-Hispanic white	0.20 (0.11–0.29)	<0.001	
Non-Hispanic black	0.04 (–0.07–0.14)	0.495	
Other races (including multiracial)	0.34 (0.16–0.53)	<0.001	
Education, no. (%)			0.478
Lower than high school	0.10 (–0.01–0.21)	0.068	
High school graduate/GED or equivalent	0.12 (0.00–0.24)	0.046	
Higher than high school	0.17 (0.09–0.25)	<0.001	
PIR, no. (%)			0.096
≤1.3	0.20 (0.12–0.29)	<0.001	
1.3–3.5	0.10 (–0.00–0.20)	0.056	
>3.5	0.07 (–0.04–0.18)	0.231	
Marital status, no. (%)			0.26
Married/living with partner	0.11 (0.03–0.19)	0.006	
Widowed/divorced/separated	0.21 (0.11–0.32)	<0.001	
Never married	0.11 (–0.02–0.25)	0.095	
BMI, no. (%)			<0.001 ^a
<25 kg/m ²	0.16 (0.05–0.28)	0.005	
25–30 kg/m ²	0.30 (0.19–0.41)	<0.001	
≥30 kg/m ²	0.04 (–0.04–0.13)	0.298	
Smoking status, no. (%)			0.371
Smokers	0.16 (0.08–0.25)	<0.001	
Non-smokers	0.12 (0.03–0.20)	0.005	
Drinking status, no. (%)			0.197
Drinkers	0.12 (0.05–0.19)	<0.001	
Non-drinkers	0.20 (0.09–0.31)	<0.001	

Table 3. Stratification analysis of the relationship between RAR and NfL based on Model 3. (Cont'd)

Characteristics	β (95% CI)	P value	P for interaction
Diabetes, no. (%)			0.008 ^a
Yes	0.34 (0.18–0.49)	<0.001	
No	0.11 (0.05–0.18)	<0.001	
Hypertension, no. (%)			0.389
Yes	0.12 (0.04–0.20)	0.005	
No	0.17 (0.08–0.25)	<0.001	

BMI: body mass index; CI: confidence interval; GED: general education development; NfL: neurofilament light chain; PIR: poverty income ratio; RAR: red cell distribution width-to-albumin ratio

^a statistically significant

rising RAR levels may serve as a potential predictive marker for depression.²⁵

While these findings support the positive association between RAR and sNfL, the underlying mechanisms remain speculative. RDW, the main component of RAR, reflects variability in red blood cell volume (anisocytosis) and is often associated with nutritional deficiencies, chronic inflammation and other pathological conditions.²⁶ Prior studies suggest that changes in RDW and related haematological parameters may be linked to neural vulnerability, although the biological pathways connecting RDW, albumin and neuroaxonal injury remain unclear. Albumin, a major extracellular protein, contributes to plasma oncotic pressure, transport functions, microcirculatory regulation and antioxidant/anti-inflammatory capacity,^{12,27} which may be relevant to systemic and vascular homeostasis. Epidemiological studies have reported associations between lower albumin levels and higher risk of neural injury; however, direct experimental evidence supporting a causal role of albumin deficiency in neurodegeneration remains limited. This study does not directly address these mechanisms. Further research is needed to clarify how RAR may relate to neuroaxonal damage, particularly in the context of inflammatory and nutritional imbalances.

Overall, our findings highlight the potential clinical utility of RAR as a readily accessible indicator for evaluating the risk of neuronal injury. Determining its specific prognostic and risk-stratification value will be an important direction for future clinical research.

CONCLUSION

This cross-sectional study, based on data from NHANES, demonstrated a significant positive association between RAR and sNfL in US adults. These findings suggest a potential link between systemic inflammation, nutritional status and blood biomarkers

of neuronal injury. However, given the nature of the study, further large-scale, multicentre prospective studies are necessary to validate these associations, establish temporal relationships and explore the underlying biological mechanisms linking RAR, systemic inflammation, nutritional status and neural injury.

Ethics statement

The data used in this study were obtained from the publicly available NHANES database (<https://www.cdc.gov/nchs/nhanes/index.htm>). All NHANES protocols were approved by the National Center for Health Statistics Ethics Review Board, and written informed consent was obtained from all participants.

Declaration

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