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Association Between Red Blood Cell Distribution Width-to-Albumin Ratio and Stroke Among Adults in the United States

ORIGINAL INVESTIGATION

ABSTRACT

Background: The red blood cell distribution width-to-albumin ratio (RAR) has emerged as a novel indicator of inflammation and nutrition. However, the association between RAR and the risk of stroke remains unclear. This study aims to evaluate the association between RAR and stroke among adults in the United States.

Methods: The study data was acquired from the National Health and Nutrition Examination Survey (NHANES) 2007-2018. Multivariate logistic regression was utilized to analyze the association between RAR and stroke. Restricted cubic spline (RCS) was used to investigate the non-linear relationship between RAR and stroke. Subgroup analysis was conducted to explore the potential interaction. Finally, receiver-operating characteristic (ROC) curve with area under curve (AUC) was used to evaluate the predictive ability of RAR for stroke risk.

Results: A total of 24 658 adult participants was included in the study. The RAR exhibited an independently positive correlation with stroke [OR (95% CI), 1.45 (1.26, 1.66)], and the correlation was confirmed to be linear by RCS analysis (*P* for non-linear = .160). Compared to the participants in the lowest quartile of RAR, those in the highest quartile of RAR showed an increased risk of stroke [OR (95% CI), 1.39 (1.06, 1.83)]. Subgroup analysis revealed no significant interactions between stratification variables. Receiver-operating characteristic curve showed an excellent predictive efficacy of RAR for stroke (AUC = 0.829).

Conclusion: There is an independent and positive linear relationship between RAR and stroke among US adults. Further longitudinal research is needed to establish the causality and evaluate clinical relevance of RAR.

Keywords: Cross-section study, National Health and Nutrition Examination Survey, RAR, stroke

INTRODUCTION

Stroke remains a leading cause of death and disability worldwide, posing a massive global public health challenge. In 2019, there were 12.2 million new stroke cases, 101 million prevalent cases of stroke, and 6.55 million deaths from stroke globally.[1] The 5 leading risk factors for stroke were high systolic blood pressure, high body mass index (BMI), high fasting plasma glucose, ambient particulate matter pollution, and smoking.[1,2] Therefore, in the context of an aging population and the prevalence of unhealthy lifestyles, prevention through management of risk factors, public awareness of stroke signs, and rapid access to specialized treatment are of critical importance.

Red blood cell distribution width (RDW), a routine parameter derived from hematology analyzer tests, reflects the degree of heterogeneity in erythrocyte volume. The role of RDW in cardiovascular and thrombotic disorders has been reviewed.[3] Clinical studies confirmed RDW to be a potential predictor of cardiovascular disease risk and mortality, especially heart failure[4-7] and coronary heart disease.[8] Red blood cell distribution width was also related to other diseases, such as gastrointestinal disorders[9] and thyroid dysfunction.[10] Serum albumin, the most abundant protein in plasma, performs various physiological functions, including the

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maintenance of colloid osmotic pressure, substance transport, antioxidation, endothelial stabilization, and vascular health.[11] Clinically, albumin is used as a biochemical indicator of nutritional status and inflammatory response,[12] and its dysfunction is closely associated with many pathological conditions.[13-16] The RAR is an emerging index that integrates RDW and albumin. It serves as a robust composite predictive tool by combining information from both RDW and albumin, thereby providing a more comprehensive, stable, and accurate assessment of disease risk and prognosis. The RAR effectively amplifies the predictive signals of each individual biomarker, demonstrating significant advantages in predicting disease severity and mortality.[17] Recent studies confirmed RAR to be associated with multiple disease risks and prognosis, such as cardiovascular diseases,[18,19] diabetes,[20] depression,[21] acute respiratory failure,[22] chronic kidney disease,[23] sepsis,[24] and atrial fibrillation.[25] Red blood cell distribution width-to-albumin ratio even had a promising predictive value for the all-cause and cause-specific mortality of the general population, suggesting that RAR may be an accessible and reliable laboratory indicator for identifying clinical individuals at high risk of mortality.[26] However, the association between RAR and stroke remains unclear. This study aims to explore the potential of RAR as a regular index for predicting stroke risk.

METHODS

Study Population

The US National Health and Nutrition Examination Survey (NHANES) is a nationwide cross-sectional survey program conducted by the National Center for Health Statistics and is designed to assess the health and nutritional status of adults and children through a combination of interviews and physical examinations. The data used in this study were obtained from NHANES, which involves publicly available, de-identified data and does not require additional ethical approval. The NHANES protocol was approved by the Institutional Review Board of the National Center for Health Statistics, Centers for Disease Control and Prevention. The data was selected from NHANES 2007-2018, which encompasses a total of 59 842 participants. The study excluded participants: 1) younger than 20 years; 2) missing data on stroke, RDW, and albumin; and 3) missing data on covariates, including age, sex, race, education level, marital status, PIR, BMI, smoking, drinking, diabetes, and hypertension. Ultimately, a total of 24 658 participants with complete data were included in the study (Figure 1).

HIGHLIGHTS

- This study firstly investigates the association between red blood cell distribution width to albumin ratio (RAR) and stroke among a large scale of US populations based on National Health and Nutrition Examination Survey.
- A positive, linear dose-response relationship exists between RAR and stroke.
- The RAR exhibits a strong capacity for predicting stroke risk.

Measure of RAR Index

In NHANES, the serum albumin concentration was measured by the bromocresol purple method, while peripheral blood RDW was determined using a Coulter analyzer. The RAR index was calculated as RDW (%)/albumin (g/dL).

Assessment of Stroke

In the questionnaire data from NHANES, participants were asked a self-reported question, "Has a doctor or other health professional ever told you that you had a stroke?" Those who responded "Yes" were considered to have a history of stroke. It should be noted that this method relies on participants' memory and physicians' accurate diagnosis, which may introduce recall bias or misreporting.

Covariates

To control and reduce confounding bias, multiple covariates were included. Demographic characteristics included age, sex, race, education level, marital status, poverty income ratio (PIR). The PIR was divided into 3 levels (<1.3, 1.3-3.5, >3.5). Lifestyle behaviors included smoking and drinking. Smoking status was categorized as "yes" or "no" based on whether lifetime consumption was more than 100 cigarettes. Drinking status was classified into "yes" or "no" based on whether an individual drank more than 12 times within 1 year. Clinical information included BMI, diabetes, and hypertension. Body mass index was calculated as weight (kg)/height (m^2) and used to divide participants into normal weight (<25), overweight (25-30), and obese (>30). Demographic and lifestyle information, as well as the history of diabetes and hypertension, were obtained from a self-reported questionnaire.

Statistical Analysis

We incorporated weighting, stratification, and clustering to ensure that the research results could represent the entire American population. Participants' characteristics were shown based on RAR quartiles. Continuous variables are presented as medians (quartile 1, quartile 3), while categorical variables are presented as frequencies (percentages). Intergroup differences for continuous variables were assessed using the Kruskal–Wallis rank-sum test, while differences for categorical variables were analyzed using the chi-squared test. Multicollinearity was assessed for all variables, and the variance inflation factor for each variable was below 2, indicating no significant multicollinearity issues. Weighted multivariate logistic regression models were employed to calculate OR and 95% CI to evaluate the association between RAR and stroke. Model 1 was unadjusted; Model 2 was adjusted for age, sex, and race; Model 3 was further adjusted for educational level, marital status, PIR, BMI, smoking, drinking, diabetes, and hypertension based on Model 2. Restricted cubic spline with 4 knots was applied to explore the potential non-linear relationship between RAR and stroke. Additionally, subgroups were created according to age, sex, race, educational level, marital status, PIR, BMI, smoking, drinking, diabetes, and hypertension. Subsequently, stratified analysis was conducted to evaluate the consistency of the association between RAR and stroke across different characteristic populations. Interactions

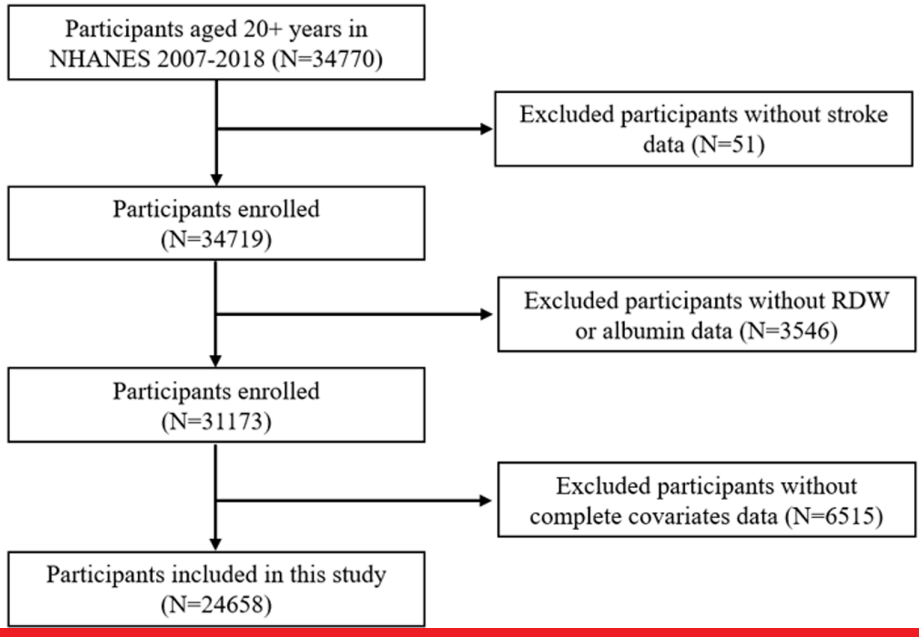

Figure 1. Flow chart of the study participants. RDW, red blood cell distribution width.

between grouping variables and RAR were evaluated using likelihood ratio tests. The ROC curve was used to assess the predictive capability of RAR for stroke. All analyses were conducted using R software (version 4.2.1), and 2-sided *P* values < .05 were considered statistically significant.

RESULTS

Weighted Characteristics of the Study Population

Table 1 shows the characteristics of the 24 658 participants categorized by RAR quartiles. The median age of the population is 47 years, and 50.96% were female. Compared to participants in the Q1 group, individuals with higher RAR were more likely to be older, female, Non-Hispanic Black, less educated, divorced, and have lower income, higher BMI, non-drinking, smoking, diabetes, hypertension, and stroke.

Association Between RAR and Stroke

Table 2 presents the weighted multivariate logistic regression analysis results of the association between RAR and stroke. In all models, elevated RAR levels were significantly associated with increased risk of stroke, and the ORs (95% CIs) were respectively 2.17 (1.95, 2.41), 1.76 (1.54, 2.00), and 1.45 (1.26, 1.66). When converting RAR into a categorical variable, the positive relationship between RAR quartiles and stroke was still observed. In unadjusted Model 1, compared to the Q1 group (reference), those participants in Q3 [1.97 (1.49, 2.62)] and Q4 [4.07 (3.16, 5.26)] groups exhibited increased risk of stroke. The effect size decreased with additional covariate adjustments in Models 2 and 3 but remained statistically significant in Q4 groups [1.75 (1.35, 2.27) in Model 2, 1.39 (1.06, 1.83) in Model 3]. A significant positive trend was observed across all models ($P < .001$ in Models 1 and 2, $P = .018$ in Model 3), indicating that higher RAR quartiles were generally associated with increased risk of stroke. Furthermore, RCS analysis was performed using an absolutely adjusted logistic regression model to explore the potential non-linear relationship between RAR and stroke (Figure 2). The result further confirmed the significantly linear association between RAR and stroke (*P* for non-linear = .160).

Subgroup Analysis

Stratified analysis was conducted to estimate the potential interactions between RAR and grouping variables (Figure 3). No significant interactions between all stratification variables were observed (All *P* for interaction > .05), suggesting that the association between RAR and stroke was consistent across different populations.

Predictive Efficacy of RAR for Stroke

The ROC curve was utilized to assess the predictive efficacy of RAR for stroke (Figure 4). The result revealed an excellent prediction capability of RAR for stroke, and the AUC (95% CI) was 0.829 (0.818-0.841).

DISCUSSION

This is the first study to investigate the association between RAR and stroke risk utilizing a large-scale population database based on NHANES 2007-2018. The study revealed that RAR was independently and positively linearly associated with stroke, suggesting the potential of RAR serving as an auxiliary indicator for predicting the risk and prognosis of stroke. However, further longitudinal research is still needed to establish the causality and evaluate clinical relevance of RAR.

Recently, RAR has emerged as a novel composite marker for the assessment of risk and mortality of various diseases. It was confirmed that elevated RAR was strongly and independently associated with increased risks of all-cause and cause-specific mortality in 2 large-scale general populations based on NHANES and the UK Biobank.[26] Similarly, higher RAR was associated with increased risk of cardiovascular diseases in postmenopausal women.[18] Elevated

Table 1. Weighted Characteristics of the Study Population According to RAR Quartiles

Characteristic	Overall (n = 24 658)	Q1 (<2.84)	Q2 (2.84-3.05)	Q3 (3.05-3.32)	Q4 (>3.32)	*P*
Age, median (Q1, Q3) (years)	47 (33, 60)	38 (28, 51)	46 (33, 58)	50 (36, 63)	53 (39, 67)	<.001
Sex (%)						<.001
Male	12 226 (49.04)	3411 (64.02)	3241 (54.20)	2849 (44.94)	2725 (32.95)	
Female	12 432 (50.96)	1819 (35.98)	2595 (45.80)	3311 (55.06)	4707 (67.05)	
Race (%)	2473 (5.42)	456 (4.47)	621 (5.50)	693 (5.95)	703 (5.77)	<.001
Mexican American	3643 (8.18)	831 (8.00)	948 (8.66)	916 (8.08)	948 (7.97)	
Non-Hispanic White	10 866 (68.98)	2730 (75.02)	2705 (71.26)	2683 (69.11)	2748 (60.54)	
Non-Hispanic Black	4967 (10.14)	489 (4.18)	845 (7.03)	1251 (10.42)	2382 (18.92)	
Other Hispanic	2473 (5.42)	456 (4.47)	621 (5.50)	693 (5.95)	703 (5.77)	
Other race	2709 (7.28)	724 (8.32)	717 (7.54)	617 (6.44)	651 (6.80)	
Education level (%)						<.001
Less than high school	5627 (14.62)	1018 (12.14)	1270 (13.63)	1442 (14.78)	1897 (17.94)	
High school or equivalent	5678 (22.90)	1124 (20.64)	1309 (22.44)	1431 (22.70)	1814 (25.81)	
More than high school	13 353 (62.48)	3088 (67.22)	3257 (63.93)	3287 (62.52)	3721 (56.25)	
Marital status (%)						<.001
Married/living with partner	14 700 (63.65)	3222 (63.73)	3756 (67.14)	3679 (64.05)	4043 (59.66)	
Widowed/divorced/separated	5476 (18.30)	678 (11.18)	1078 (16.02)	1514 (20.44)	2206 (25.58)	
Never married	4482 (18.05)	1330 (25.08)	1002 (16.84)	967 (15.50)	1183 (14.76)	
PIR, median (Q1, Q3)	3.03 (1.49, 5.00)	3.43 (1.72, 5.00)	3.33 (1.65, 5.00)	2.97 (1.48, 5.00)	2.40 (1.24, 4.48)	<.001
BMI, median (Q1, Q3) (kg/m^2)	27.99 (24.30, 32.60)	25.90 (22.96, 29.26)	27.50 (24.16, 31.30)	28.70 (24.80, 33.42)	30.90 (26.10, 36.80)	<.001
Smoking (%)						.007
No	13 487 (55.05)	2967 (56.89)	3279 (56.25)	3322 (53.75)	3919 (53.27)	
Yes	11 171 (44.95)	2263 (43.11)	2557 (43.75)	2838 (46.25)	3513 (46.73)	
Drinking (%)						<.001
No	7612 (25.67)	1064 (15.74)	1552 (21.48)	1947 (27.16)	3049 (38.32)	
Yes	17 046 (74.33)	4166 (84.26)	4284 (78.52)	4213 (72.84)	4383 (61.68)	
Diabetes (%)						<.001
No	21 342 (90.08)	4922 (95.97)	5285 (92.96)	5289 (88.81)	5846 (82.56)	
Yes	3316 (9.92)	308 (4.03)	551 (7.04)	871 (11.19)	1586 (17.44)	
Hypertension (%)						<.001
No	15 799 (68.33)	4031 (78.49)	4052 (71.76)	3812 (66.53)	3904 (56.53)	
Yes	8859 (31.67)	1199 (21.51)	1784 (28.24)	2348 (33.47)	3528 (43.47)	
Stroke (%)						<.001
No	23 732 (97.23)	5147 (98.65)	5690 (98.20)	5936 (97.37)	6959 (94.71)	
Yes	926 (2.77)	83 (1.35)	146 (1.80)	224 (2.63)	473 (5.29)	

Continuous variables are presented as median (quartile 1, quartile 3). Categorical variables are presented as unweighted number (weighted percentage). BMI, body mass index; PIR, poverty income ratio; RAR, red blood cell distribution-to-albumin ratio.

RAR was also related to higher all-cause and cardiovascular mortality in patients with concomitant cardiovascular disease and diabetes.[27] There were also many studies recognizing RAR as a risk predictor for other diseases, such as depression[21] and chronic kidney disease.[23] Due to the extensive association of RAR with various diseases, some studies have been performed to investigate the correlation between RAR and stroke. In a South Korean cohort study of 988 patients with acute minor ischemic stroke, the results revealed an association between elevated RAR and poor 3-month prognosis.[28] Similar results were shown in another clinical cohort study including 1906 individuals.[29] The study suggested that the RAR index was independently and positively linearly associated with stroke risk, and the association was stable in different subgroup populations. Compared to previous studies, the study is the first to assess the association between RAR and stroke in the US population based on NHANES.

The precise biological mechanism underlying the association between RAR and stroke remains unclear. Currently, inflammation and nutritional deficiency are widely recognized as pathological states reflected by RAR. Because of the derivation of RAR from RDW and albumin, elevated RAR is attributed to either increased RDW, or decreased albumin, or the combinative effect of both. Increased RDW

Table 2. Weighted Multivariate Logistic Regression Analysis for the Association Between RAR and Stroke

	Model 1		Model 2		Model 3	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
RAR	2.17 (1.95, 2.41)	<.001	1.76 (1.54, 2.00)	<.001	1.45 (1.26, 1.66)	<.001
RAR group						
Q1	Reference		Reference		Reference	
Q2	1.34 (0.98, 1.82)	.066	0.89 (0.65, 1.02)	.438	0.87 (0.63, 1.19)	.374
Q3	1.97 (1.49, 2.62)	<.001	1.04 (0.78, 1.38)	.783	0.93 (0.69, 1.26)	.653
Q4	4.07 (3.16, 5.26)	<.001	1.75 (1.35, 2.27)	<.001	1.39 (1.06, 1.83)	.020
P for trend		<.001		<.001		.018

Model 1, unadjusted model.
Model 2, adjusted for age, sex, race.
Model 3, adjusted for age, sex, race, education level, marital status, PIR, BMI, smoking, drinking, diabetes, and hypertension.
BMI, body mass index; PIR, poverty income ratio; RAR, red blood cell distribution to albumin ratio.

reflects impaired erythropoiesis and abnormal red blood cell survival, which may contribute to systemic endothelial dysfunction.[30] Mechanically, high RDW resulted in increased interactions between the vascular wall and circulating morphotic elements, further inducing vascular pathology.[31] The RAR was also significantly related to carotid plaque formation in patients with coronary heart disease.[32] These results hinted at a possibility that increased RDW may induce cerebrovascular dysfunction by damaging the vascular wall and endothelium, further accelerating plaque formation and ischemia, ultimately leading to stroke. Additionally, abnormal RDW possibly impaired oxygen delivery and caused cellular hypoxia, thus influencing critical illness outcomes.[33] Similar to RDW, serum albumin can also reflect inflammation and nutritional status.[34] Thus, the RAR, a composite index combining RDW and albumin, exhibited more predictive value for mortality.[17] Consistently, the ROC result also suggested that RAR had an excellent predictive ability for stroke with an AUC of 0.829.

In conclusion, the study found that RAR was independently and positively linearly associated with stroke. Red blood cell distribution width-to-albumin ratio, a novel, accessible, and cost-effective marker, provides more comprehensive and precise information about systemic inflammation and nutritional status, thereby exhibiting greater potential for the prediction of stroke risk. In the future, RAR could be incorporated into regular health assessment to identify individuals at high risk of stroke and prompt necessary monitoring or intervention.

The limitations of the study are apparent. First, NHANES is a cross-sectional survey program and the causality of the

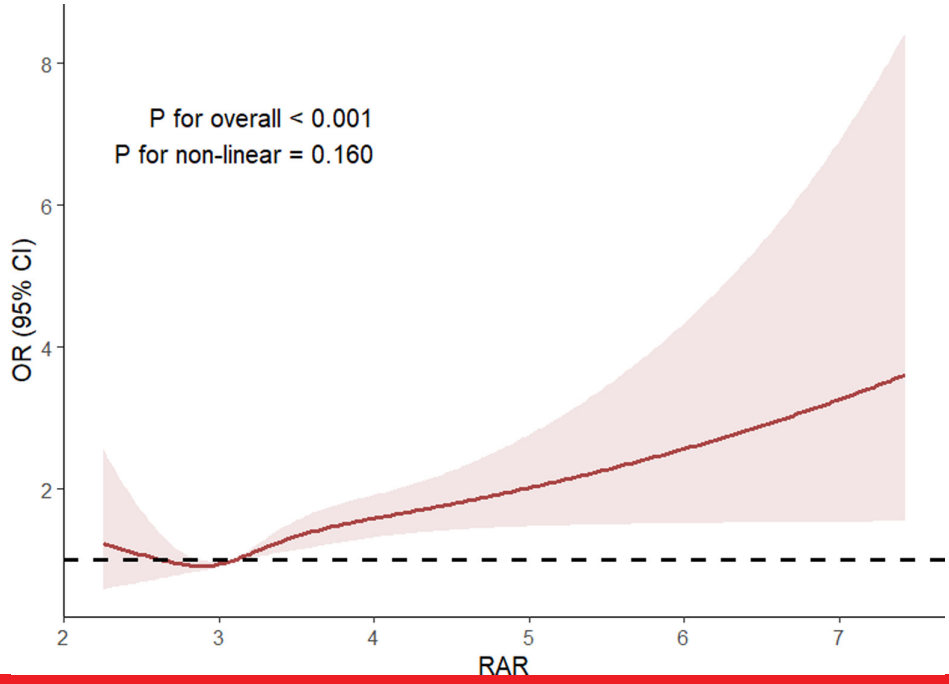

Figure 2. Restricted cubic spline model of the association between RAR and stroke. The model was adjusted for age, sex, race, education level, marital status, PIR, BMI, smoking, drinking, diabetes and hypertension. RAR, red blood cell distribution width to albumin ratio; PIR, poverty income ratio; BMI, body mass index.

Subgroup	OR (95% CI)	P value	P for interaction
Age			0.795
<60	1.32 (1.06, 1.63)	0.015	
>=60	1.60 (1.34, 1.92)	<0.001	
Sex			0.923
Male	1.42 (1.14, 1.77)	0.003	
Female	1.56 (1.27, 1.91)	<0.001	
Race			0.216
Mexican American	1.07 (0.54, 2.12)	0.856	
Non-Hispanic White	1.64 (1.37, 1.98)	<0.001	
Non-Hispanic Black	1.25 (1.03, 1.51)	0.029	
Other Hispanic	1.39 (0.95, 2.02)	0.094	
Other Race	1.55 (0.72, 3.34)	0.265	
Education level			0.63
Less than high school	1.46 (1.16, 1.85)	0.002	
High school or equivalent	1.52 (1.14, 2.03)	0.006	
More than high school	1.49 (1.17, 1.88)	0.001	
Marital status			0.481
Married/living with partner	1.57 (1.28, 1.92)	<0.001	
Widowed/divorced/separated	1.54 (1.27, 1.89)	<0.001	
Never married	0.84 (0.55, 1.29)	0.433	
PIR			0.082
<=1.3	1.29 (1.08, 1.54)	0.006	
1.3-3.5	1.64 (1.33, 2.01)	<0.001	
>=3.5	1.71 (1.15, 2.54)	0.009	
BMI			0.376
<=25	1.45 (1.09, 1.92)	0.012	
25-30	1.77 (1.34, 2.34)	<0.001	
>=30	1.37 (1.07, 1.76)	0.016	
Smoking			0.782
No	1.42 (1.10, 1.84)	0.01	
Yes	1.56 (1.30, 1.86)	<0.001	
Drinking			0.68
No	1.54 (1.25, 1.89)	<0.001	
Yes	1.52 (1.25, 1.84)	<0.001	
Diabetes			0.364
No	1.52 (1.27, 1.81)	<0.001	
Yes	1.47 (1.16, 1.85)	0.002	
Hypertension			0.87
No	1.29 (0.95, 1.74)	0.102	
Yes	1.58 (1.35, 1.84)	<0.001	

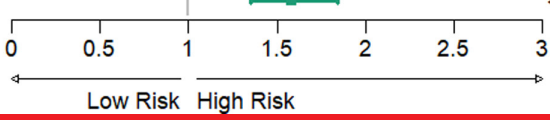

Figure 3. Stratified analysis of the association between RAR and stroke. The model was adjusted for age, sex, race, education level, marital status, PIR, BMI, smoking, drinking, diabetes, and hypertension. RAR, red blood cell distribution width-to-albumin ratio; PIR, poverty income ratio; BMI, body mass index.

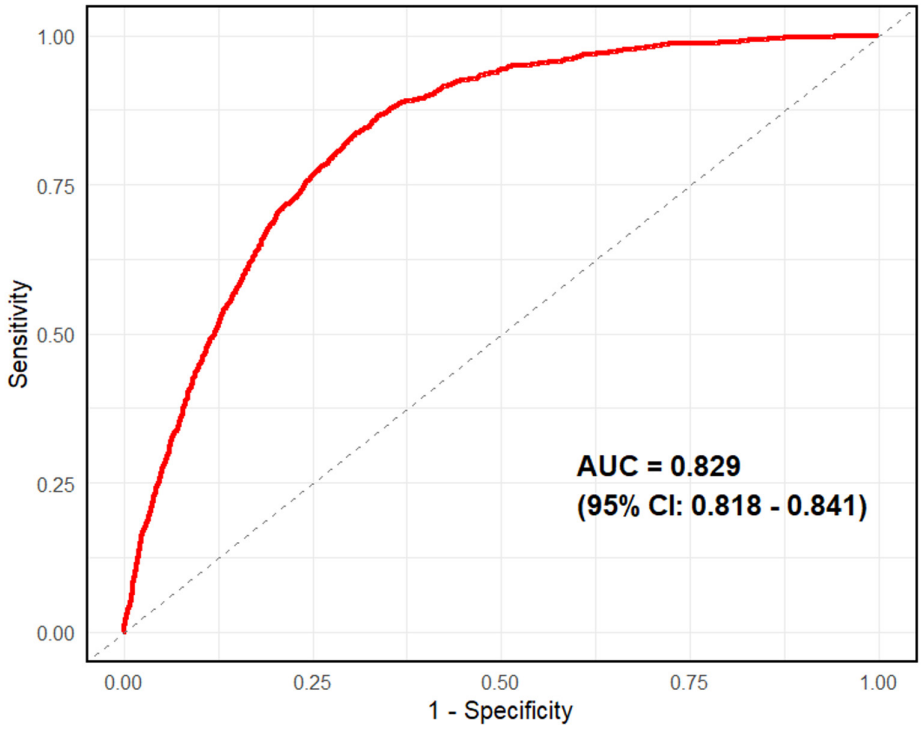

Figure 4. Receiver-operating characteristic curve of RAR for the prediction of stroke. The model was adjusted for age, sex, race, education level, marital status, PIR, BMI, smoking, drinking, diabetes, and hypertension. RAR, red blood cell distribution width to albumin ratio; PIR, poverty income ratio; BMI, body mass index; AUC, area under curve.

association between RAR and stroke is unclear, which needs to be addressed in further longitudinal studies. Second, although many covariates were incorporated to control for the influence of confounders, all potential residual confounders cannot be ruled out. Finally, the confirmation of stroke was based on a self-reported questionnaire, which may result in recall bias or misreporting.

Ethics Committee Approval: The NHANES study protocol was approved by the Ethics Review Board of National Center for Health Statistics. This study used de-identified, publicly available NHANES data and was exempt from additional ethical review.

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept – K.W.; Design – K.W.; Supervision – K.W.; Resources – K.W.; Materials – C.X.; Data Collection and/or Processing – C.X.; Analysis and/or Interpretation – C.X., K.W.; Literature Search – K.W.; Writing – C.X., K.W.; Critical Review – K.W.

Declaration of Interests: The authors have no conflicts of interest to declare. None of the authors are members of the journal's editorial board or advisory board, and no potential conflicts of interest exist.

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