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Association of Red Cell Distribution Width and Red-Cell-Distribution-Width-to-Albumin Ratio with Cardiovascular Diseases in Postmenopausal Women: A Cross-Sectional Study based on the National Health and Nutrition Examination Survey 2003-2016

ABSTRACT

Background: Cardiovascular disease (CVD) significantly increases in postmenopausal women. This study aims to investigate the potential association between red cell distribution width (RDW), the RDW-to-albumin ratio (RAR), and the prevalence of CVD in postmenopausal women.

Methods: This study analyzed data extracted from the National Health and Nutrition Examination Survey (NHANES) database spanning the years 2003-2016. Weighted multiple logistic regression models were used to evaluate the associations between RDW, RAR, and CVD. Smoothing curve fitting and generalized additive models were applied to explore potential nonlinear relationships. Subgroup analyses and interaction tests were conducted to investigate whether the associations between RDW, RAR, and CVD varied across different subpopulations. Sensitivity analyses were performed to assess the robustness of the findings.

Results: This study included a total of 7619 postmenopausal women, of whom 1181 had CVD. Logistic regression models revealed that for each unit increase in RDW and RAR, the risk of total CVD in postmenopausal women increased by 11% and 42%, respectively. When RDW and RAR were categorized into groups, the risk of CVD significantly increased with higher levels of RDW and RAR. Smoothing curve fitting demonstrated a nonlinear relationship between RDW, RAR, and total CVD. Subgroup analyses revealed that the positive associations between RDW, RAR, and CVD were particularly significant in individuals aged ≥60 years and with a body mass index (BMI) ≥25 kg/m^2.

Conclusion: Higher RDW and RAR in postmenopausal women are positively associated with an increased risk of CVD, supporting the potential use of RDW and RAR as risk biomarkers for CVD in this population.

Keywords: Red cell distribution width, ratio of red cell distribution width to albumin, postmenopausal women, cardiovascular disease

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of the global disease burden and a major contributor to mortality worldwide. According to the 2019 Global Burden of Disease study, the total number of CVD cases increased from 271 million in 1990 to 523 million in 2019, accompanied by a continuous rise in mortality.[1] The 2011 American Heart Association guidelines for CVD prevention in women highlighted common and sex-specific risk factors, significantly enhancing awareness of gender differences in CVD.[2] Menopause marks the decline or complete cessation of ovarian function, cessation of menstruation, and termination of natural reproductive capacity. Natural menopause is defined as the absence of menstruation for ≥12 consecutive months, signaling the end of a woman's reproductive cycle. Menopause is a critical bio-psycho-social transition point linked to increased CVD risk.[3,4] Women typically experience atherosclerotic cardiovascular

ORIGINAL INVESTIGATION

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diseases about 10 years later than men, which may be associated with the decline in ovarian hormone concentrations during and after the menopausal transition.[5] Estrogen and testosterone are involved in the development of female CVD, influencing endothelial function, vascular tone, and cardiac function.[6] Studies indicate that menopause is a risk factor for CVD due to the adverse effects of estrogen withdrawal on cardiovascular function and metabolism. Menopause also increases traditional CVD risk factors, including altered fat distribution, impaired glucose tolerance, dyslipidemia, hypertension, vascular inflammation, and endothelial dysfunction.[7] Cardiovascular disease is the leading cause of death among middle-aged and elderly women.[8] Therefore, understanding the physiological changes in postmenopausal women and evaluating biomarkers associated with CVD are essential for identifying and preventing CVD.

The red cell distribution width (RDW), a parameter derived from routine complete blood count (CBC) tests, measures the variation in red blood cell (RBC) size and serves as an indicator of RBC size heterogeneity.[9] Elevated RDW indicates greater variation in RBC volume in peripheral blood and is commonly used alongside other blood cell parameters to differentiate hematological diseases.[10] Recently, RDW has been strongly and independently associated with various inflammatory markers,[11,12] suggesting that it could serve as a surrogate marker of inflammation with predictive value. A post-hoc analysis by Tonelli et al[13] on 4111 myocardial infarction patients revealed a significant association between RDW levels and both all-cause mortality and cardiovascular events during a nearly 5-year follow-up period.[13] Albumin, a vital plasma protein, is widely used to assess nutritional status and systemic health. It plays biological roles in regulating inflammatory responses, maintaining colloid osmotic pressure, binding endogenous and exogenous substances, and exhibiting antithrombotic properties.[14,15] Studies have reported a negative correlation between albumin levels and C-reactive protein,[16] and low albumin levels have been linked to an increased risk of cardiovascular events.[17,18] The ratio of RDW to albumin (RAR) combines these 2 classic clinical parameters and can be quickly obtained in laboratory testing. Red-cell-distribution-width-to-albumin ratio has been reported to be associated with mortality in heart failure patients[19] and has also been linked to diabetes,[20] metabolic syndrome,[21] and end-stage renal disease.[22]

To elucidate the clinical significance of RDW and RAR in postmenopausal women and identify valuable CVD risk biomarkers, the authors analyzed data from the NHANES 2003-2016 cycles to investigate the associations of RDW and RAR with CVD.

HIGHLIGHTS

- We found that higher RDW and RAR in postmenopausal women were positively associated with an increased risk of CVD.
- Red cell distribution width and RAR may serve as risk biomarkers for CVD in this population.
- Red cell distribution width and RAR are readily accessible biomarkers that can be utilized to predict the risk of CVD in postmenopausal women.

METHODS

Data Source

The NHANES is conducted by the National Center for Health Statistics (NCHS), a division of the U.S. Centers for Disease Control and Prevention (CDC). It is designed to assess the health and nutritional status of adults and children in the United States through a combination of interviews, physical assessments, and laboratory analyses. The survey protocol is reviewed and approved by the NCHS Research Ethics Review Board, and all participants provide written informed consent prior to participation. Detailed information about the NHANES protocol and procedures has been described elsewhere.[23]

Study Population

We extracted data from 7 NHANES cycles (2003-2016), which included 71 058 participants in total.

The exclusion criteria were as follows: (1) male participants (n = 35 122); (2) premenopausal women or women with missing menopausal status information (n = 27 334); (3) participants with missing RDW or RAR data (n = 490); (4) participants with missing CVD questionnaire data (n = 106), including congestive heart failure (n = 28), coronary heart disease (n = 29), angina pectoris (n = 22), heart attack (n = 14), stroke (n = 13); (5) participants with missing data on necessary covariates (n = 387). Ultimately, 7619 postmenopausal women were included in the analysis. The screening process is illustrated in Figure 1.

Menopausal Status Definitions

Menopausal status was defined based on responses to reproductive health-related questions in the NHANES questionnaire. Women who answered "No" to the first question, "Have you had at least 1 menstrual period in the past 12 months? (Please do not include bleeding caused by medical conditions, hormone therapy, or surgeries)," and "Hysterectomy or menopause/lifestyle changes" to the second question, "What is the reason that you have not had a period in the past 12 months?" were considered postmenopausal.[24,25]

Exposure Variables and Outcome Variables

Red cell distribution width (%) was obtained from the CBC section of the laboratory data, while serum albumin (g/dL) was sourced from the standard biochemical profile section.

$$RAR = \frac{RDW\,(\%)}{Albumin\,(g/dl)}$$

Cardiovascular disease was derived from the questionnaire, based on self-reported diagnoses from a doctor or other healthcare professional of congestive heart failure, coronary heart disease, angina pectoris, heart attack, or stroke. A "Yes" answer to any of these 5 questions was used to define CVD.[26]

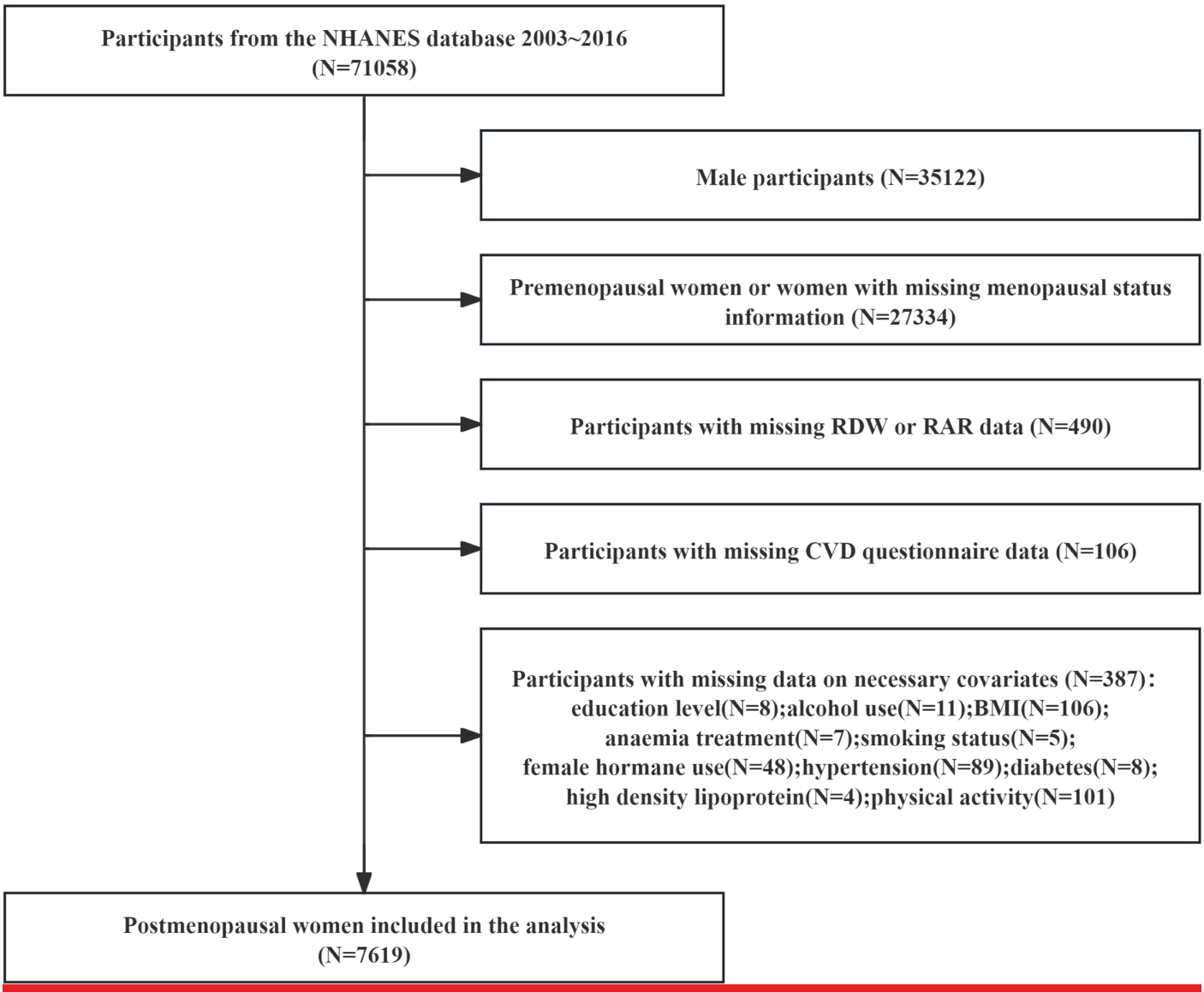

Figure 1. Flowchart of participant selection.

Covariates

This study, based on relevant literature,[27,28] considered potential covariates that may influence the association between RDW, RAR, and CVD in postmenopausal women. The covariates included age, race, education level, family poverty-to-income ratio (PIR), smoking, alcohol use, physical activity, history of anemia treatment, family history of heart attack, cancer history, female hormone use history, body mass index (BMI), hypertension, diabetes, serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and estimated glomerular filtration rate (eGFR). Detailed definitions and descriptions of these covariates are provided in Supplementary Table 1.

Statistical Analysis

To reduce the variability in the dataset, the authors applied weighting adjustments according to the CDC guidelines.[29] The statistical analyses incorporated sample weights, clustering, and stratification. Continuous variables are presented as means with 95% CI, while categorical variables are reported as percentages with 95% CI. Weighted linear regression or weighted chi-square tests were used to assess differences between participants with and without CVD. The primary outcome of this study was the presence of CVD, defined as a self-reported history of any of the following conditions: heart failure, coronary heart disease, angina, myocardial infarction, or stroke. Participants reporting at least one of these conditions were classified as having CVD (yes/no). In addition, each of the 5 CVD subtypes was analyzed separately as a binary outcome in subtype-specific analyses. The primary independent variables were RDW and RAR, which were first entered into weighted binary logistic regression models as continuous variables to evaluate their associations with overall CVD and its subtypes. To further assess the robustness of the findings, RDW and RAR were also categorized into quartiles and included in the models as categorical variables. Three multiple models were constructed with progressive adjustment for covariates: Model 1

(adjusted for age, race, education level and PIR); Model 2 (further adjusted for BMI, smoking, alcohol consumption, physical activity, family history of heart disease, history of female hormone use, and history of anemia treatment, in addition to the variables in Model 1); Model 3 (Additionally adjusted for hypertension, diabetes, self-reported cancer history, TC, HDL-C, and eGFR, building upon the adjustments in Model 2 (page 7, line 129-145)). Smoothed curve fitting and generalized additive models were used to assess potential nonlinear relationships between RDW, RAR, and CVD. Subgroup analyses and interaction tests were conducted to explore potential differences in the association of RDW and RAR with CVD across various populations of postmenopausal women. Finally, to test the robustness of the results, a sensitivity analysis was performed excluding participants with a history of cancer. All analyses were performed using the R software and EmpowerStats. Statistical significance was set at $P<.05$.

Baseline Characteristics

This study included a total of 7619 postmenopausal women, of whom 1181 were diagnosed with CVD. Table 1 highlights the baseline differences between postmenopausal women with and without CVD. Women diagnosed with CVD were more likely to be older, obese, non-Hispanic, less educated, and have lower income levels. Additionally, these women were more likely to consume alcohol, have hypertension, diabetes, cancer, lack physical activity, have a family history of heart attack, smoke, and have a history of anemia treatment. Furthermore, postmenopausal women with CVD had lower levels of TC, high-density HDL-C, serum albumin, and eGFR, while their RDW and RAR levels were significantly higher (all $P < .05$).

Association between Red Cell Distribution Width (RDW), Red Cell Distribution Width-to-Albumin Ratio, and Total Cardiovascular Disease

Table 2 presents the associations between RDW, RAR, and total CVD among postmenopausal women. Across all 3 models, a positive association between RDW, RAR, and total CVD was consistently observed. In the fully adjusted model (Model 3), each unit increase in RDW was associated with an 11% higher risk of CVD (OR = 1.11, 95% CI: 1.04~1.19). Similarly, each unit increase in RAR was associated with a 42% higher risk of CVD (OR = 1.42, 95% CI: 1.17~1.73). When RDW was categorized into quartiles, women in the Q4 had an 82% higher risk of CVD compared to those in the Q1 (OR = 1.83, 95% CI: 1.40~2.37). Similarly, for RAR, women in Q4 had a 67% higher risk of CVD compared to those in Q1 (OR = 1.67, 95% CI: 1.28~2.20), with all *P* for trend values <.05.

Across the 3 models, the association between RDW, RAR, and CVD gradually attenuated as more covariates were adjusted for, suggesting that some covariates may have a confounding effect on this relationship. Detailed parameter estimates, including OR, 95% CI, and *P*-values for all covariates, are presented in Tables 3 and 4.

In the analysis of CVD subtypes (Supplementary Table 2), Model 3 revealed significant positive associations between higher RDW levels and the risks of congestive heart failure (*P* for trend <.001), coronary heart disease (*P* for trend = .004), heart attack (*P* for trend = .004), and stroke (*P* for trend = .002). No association was observed between RDW and angina pectoris (*P* for trend = .658). Similarly, higher RAR levels were significantly associated with congestive heart failure (*P* for trend <.001), coronary heart disease (*P* for trend = .025), heart attack (*P* for trend = .028), and stroke (*P* for trend = .022), but not with angina pectoris (*P* for trend = .317).

We then adjusted for the covariates in model 3 and used smoothing curve fitting to describe the nonlinear association between RDW, RAR, and total CVD in postmenopausal women (Figures 2 and 3).

Subgroup Analyses

To account for the influence of different population characteristics on total CVD risk, the authors performed subgroup analyses to determine whether the associations of RDW and RAR with CVD were consistent. As shown in Table 5, in the subgroups stratified by smoking, alcohol use, physical activity, hypertension, and eGFR, RDW was significantly positively associated with total CVD (all $P < .05$). However, in subgroups stratified by age, BMI, diabetes, and HDL-C, RDW was significantly positively associated with total CVD only in the subgroups of age ≥ 60 years, BMI 25-30 kg/m^2, non-diabetic individuals, and HDL-C ≥ 50 mg/dL. Similarly, in the subgroups of age <60 years and BMI <25 kg/m^2, the association between RAR and CVD was not statistically significant ($P > .05$). On the other hand, in subgroups stratified by smoking, alcohol use, physical activity, hypertension, diabetes, eGFR, TC, and HDL-C, RAR showed a significant positive association with total CVD (all $P < .05$). Interaction tests indicated that the stratified variables had no significant effect on the positive associations between RDW, RAR, and total CVD in postmenopausal women (all *P* for interaction >.05).

Sensitivity analysis

To verify the robustness of the authors' results, they conducted a logistic regression model analysis excluding participants with cancer. The sensitivity analysis results indicated that the associations between RDW, RAR, and total CVD, as well as its subtypes, remained consistent with the above findings (Supplementary Table 3).

DISCUSSION

This cross-sectional study found a significant positive association between RDW, RAR, and total CVD risk in postmenopausal women. Higher levels of RDW and RAR were also associated with an increased risk of congestive heart failure, coronary artery disease, myocardial infarction, and stroke. Subgroup analyses and interaction results indicated that the positive association between RDW, RAR, and CVD was consistent across different populations, suggesting that RDW and RAR could serve as biomarkers for assessing CVD risk in postmenopausal women.

Previous studies have reported associations between certain biomarkers and CVD risk in postmenopausal women. For example, serum transferrin levels have been linked

Table 1. Baseline Characteristics of Participants, Weighted

Variables	Non-CVD (n = 6438)	CVD (n = 1181)	*P*
Age (years)	61.54 (61.15, 61.93)	68.29 (67.38, 69.20)	<.001
BMI (kg/m^2)	29.33 (29.08, 29.58)	30.57 (29.94, 31.21)	<.001
TC (mg/dL)	211.89 (210.34, 213.44)	195.26 (191.74, 198.78)	<.001
HDL-C (mg/dL)	61.17 (60.37, 61.97)	55.74 (54.58, 56.90)	<.001
Albumin (g/dL)	4.21 (4.20, 4.23)	4.11 (4.09, 4.13)	<.001
eGFR (mL/min/1.73 m^2)	81.33 (80.54, 82.11)	68.77 (67.03, 70.51)	<.001
RDW (%)	13.11 (13.06, 13.15)	13.64 (13.55, 13.73)	<.001
RAR	3.13 (3.12, 3.14)	3.35 (3.31, 3.38)	<.001
Race (%)			.004
Mexican American	4.80 (3.74, 6.15)	3.64 (2.55, 5.18)	
Other Hispanic	3.60 (2.86, 4.51)	3.24 (2.43, 4.32)	
Non-Hispanic White	77.26 (74.61, 79.71)	74.47 (70.86, 77.77)	
Non-Hispanic Black	9.48 (8.11, 11.05)	12.48 (10.58, 14.67)	
Other race	4.86 (4.13, 5.70)	6.16 (4.40, 8.57)	
Education (%)			<.001
Less than 9th grade	6.37 (5.59, 7.25)	9.76 (7.95, 11.93)	
9th-11th grade	10.17 (9.12, 11.32)	17.82 (15.12, 20.88)	
High school grad/GED or equivalent	25.56 (24.11, 27.07)	30.82 (27.87, 33.94)	
Some college or AA degree	31.96 (30.36, 33.61)	30.79 (27.28, 34.53)	
College graduate or above	25.94 (23.96, 28.04)	10.81 (8.44, 13.75)	
PIR (%)			<.001
≤1	9.37 (8.35, 10.50)	18.42 (15.88, 21.26)	
1~4	34.45 (32.64, 36.31)	49.58 (45.71, 53.45)	
>4	49.40 (47.05, 51.76)	25.64 (21.82, 29.88)	
Drink (%)			<.001
Yes	63.41 (61.09, 65.67)	51.98 (47.63, 56.29)	
No	36.59 (34.33, 38.91)	48.02 (43.71, 52.37)	
Hypertension (%)			<.001
Yes	57.35 (55.96, 58.72)	85.76 (83.25, 87.95)	
No	42.65 (41.28, 44.04)	14.24 (12.05, 16.75)	
Diabetes (%)			<.001
Yes	14.97 (13.82, 16.21)	36.40 (33.00, 39.94)	
No	85.03 (83.79,86.18)	63.60 (60.06, 67.00)	
Cancer (%)			<.001
Yes	13.81 (12.64,15.07)	20.48 (17.67, 23.60)	
No	69.04 (66.63, 71.35)	62.57 (58.85, 66.15)	
A family history of heart attack			<.001
Yes	14.31 (13.04, 15.67)	22.74 (19.74, 26.05)	
No	72.44 (70.31, 74.47)	60.12 (55.74, 64.34)	
Physical activity (%)			<.001
Yes	50.85 (48.52, 53.17)	35.39 (31.08, 39.94)	
No	49.15 (46.83, 51.48)	64.61 (60.06, 68.92)	
Female hormone use (%)			.194
Yes	45.37 (43.74, 47.01)	42.79 (39.02, 46.65)	
No	54.63 (52.99, 56.26)	57.21 (53.35, 60.98)	
Smoke status (%)			<.001
Yes	43.05 (41.31, 44.80)	52.80 (49.17, 56.39)	
No	56.95 (55.20, 58.69)	47.20 (43.61, 50.83)	
Anemia treatment (%)			<.001
Yes	4.20 (3.56, 4.96)	9.76 (7.95, 11.93)	
No	95.80 (95.04, 96.44)	90.24 (88.07, 92.05)	

BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; RAR, red cell distribution width-to-albumin ratio; RDW, red cell distribution width; TC, total cholesterol.

Table 2. The Association between Red Cell Distribution Width, Red-Cell-Distribution-Width-to-Albumin Ratio, and Total Cardiovascular Disease and Total CVD

	Model 1 OR (95%CI) *P*	Model 2 OR (95%CI) *P*	Model 3 OR (95%CI) *P*
RDW	1.22 (1.14,1.30) <.001	1.16 (1.08, 1.24) <.001	1.11 (1.04, 1.19) .002
RAR	2.02(1.66,2.47) <.001	1.66 (1.37, 2.03) <.001	1.42 (1.17, 1.73) .001
RDW quartile			
Q1 (10.8~12.4)	Ref	Ref	Ref
Q2 (12.5~13.0)	1.26 (0.991, 1.59) .062	1.23 (0.96, 1.56) .104	1.29 (1.00, 1.66) .051
Q3 (13.1~13.7)	1.56 (1.24, 2.06) <.001	1.51 (1.16, 1.95) .003	1.50 (1.15, 1.97) .004
Q4 (13.8~37.8)	2.28 (1.82, 2.85) <0.001	1.97 (1.58, 2.46) <.001	1.82 (1.40, 2.37) <.001
P for trend	<.001	<.001	<.001
RAR quartile			
Q1 (2.28~2.93)	Ref	Ref	Ref
Q2 (2.94~3.14)	1.44(1.10, 1.89) .010	1.34 (1.02,1.76) .040	1.31 (0.99, 1.72) .062
Q3 (3.15~3.41)	1.69(1.28, 2.23) <.001	1.45 (1.10, 1.91) .011	1.31 (0.99, 1.74) .064
Q4 (3.42~10.22)	2.56 (1.98, 3.31) <.001	2.03 (1.58, 2.61) <.001	1.67 (1.28, 2.20) <.001
P for trend	<.001	<.001	<.001

Model 1: Adjusted for age, race, education level, and PIR; Model 2: Further adjusted for BMI, smoking, alcohol consumption, physical activity, family history of heart disease, history of female hormone use, and history of anemia treatment, in addition to the variables in Model 1; Model 3: Additionally adjusted for hypertension, diabetes, self-reported cancer history, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and estimated glomerular filtration rate (eGFR), building upon the adjustments in Model 2.
RAR, red cell distribution width-to-albumin ratio; RDW, red cell distribution width.

to traditional cardiovascular risk factors.[30] A prospective cohort study demonstrated a significant association between the triglyceride-glucose (TyG) index and total CVD in postmenopausal women.[31] Another study, which included postmenopausal women without a history of CVD or cancer, showed that elevated homocysteine levels increased the risk of CVD after a 3-year follow-up, potentially due to hyperhomocysteinemia-induced endothelial dysfunction and dysregulation of circulating endothelial progenitor cells.[32,33] Moreover, lipid accumulation product and visceral adiposity index were significantly associated with increased CVD risk in postmenopausal women.[34] The dietary inflammation index (DII) was positively correlated with coronary heart disease and stroke, while an anti-inflammatory diet reduced CVD mortality in this population.[35,36] The auhtors' findings support the potential use of RDW and RAR as predictive biomarkers for CVD in postmenopausal women. Subgroup analyses revealed that the positive associations between RDW, RAR, and CVD risk were not influenced by smoking, alcohol consumption, physical activity, hypertension, eGFR, or serum TC. Comparatively, RAR may have a broader applicability as its association with CVD was not affected by diabetes or HDL-C, whereas RDW showed a positive association with CVD only in non-diabetic individuals and those with lower HDL-C levels. It is worth noting that in postmenopausal women under 60 years old or with a BMI < 25 kg/m^2, no significant associations were observed between RDW, RAR, and CVD.

This study reveals a significant positive correlation between RDW and CVD events in postmenopausal women. After menopause, significant changes in hormone levels may disrupt the normal regulation of erythropoiesis. An increase in RDW indicates greater heterogeneity in red blood cell production, suggesting abnormal development of some red blood cells. This imbalance in erythropoiesis may affect the production and function of erythropoietin, leading to the formation of red blood cells of varying sizes, which in turn impairs the effective delivery of oxygen.[37] To compensate for inadequate oxygen delivery, the heart must increase its pumping workload, which, over time, may lead to myocardial hypertrophy and impaired function, thereby increasing the risk of CVD.[38] In addition, postmenopausal women are often in a state of chronic low-grade inflammation, with elevated levels of inflammatory markers such as tumor necrosis factor-α and interleukin-6.[39] These inflammatory markers may not only disrupt the stability of red blood cell membranes, making them more prone to damage, but they can also directly injure the vascular endothelium, impairing the vessels' anticoagulant, antithrombotic, and vascular tone-regulating functions, thereby promoting thrombosis and the development of atherosclerosis.[40,41]

Table 3. Associations between Red Cell Distribution Width and Cardiovascular Disease Risk Across 3 Multiple Logistic Regression Models

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
RDW	1.22 (1.14, 1.30) <.001	1.16 (1.08, 1.24) <.001	1.11 (1.04, 1.19) .002
Age (years)	1.05 (1.04, 1.06) <.001	1.06 (1.05, 1.07) <.001	1.03 (1.02, 1.04) <.001
Race			
Mexican American	Ref	Ref	Ref
Other Hispanic	1.18 (0.82, 1.67) .379	1.21 (1.85, 1.72) .279	1.27 (0.88, 1.82) .200
Non-Hispanic White	1.44 (1.06, 1.96) .021	1.28 (0.94, 1.74) .114	1.28 (0.94, 1.72) .119
Non-Hispanic Black	1.63 (1.19, 2.21) 0.003	1.49 (1.08, 2.05) .134	1.41 (1.03, 1.92) .035
Other Race	2.18 (1.36, 3.49) .002	2.26 (1.44, 3.55) <.001	2.05 (1.31, 3.20) .002
Education			
Less than 9th grade	Ref	Ref	Ref
9-11th grade	1.38 (1.05, 1.81) 0.022	1.33 (1.00, 1.76) 0.052	1.46 (1.08, 1.96) 0.015
High school grad/GED or equivalent	1.13 (0.88, 1.46) 0.33	1.17 (0.91, 1.52) 0.22	1.28 (0.98, 1.68) 0.071
Some college or AA degree	1.05 (0.78, 1.42) .728	1.11 (0.82, 1.52) .49	1.26 (0.93, 1.74) .143
College graduate or above	0.56 (0.40, 0.79) .001	0.68 (0.48, 0.97) .032	0.82 (0.56, 1.18) .284
PIR			
≤1	Ref	Ref	Ref
1~4	0.63 (0.50, 0.78) <.001	0.66 (0.52, 0.83) <.001	0.67 (0.54, 0.84) .001
>4	0.36 (0.28, 0.46) <.001	0.40 (0.31, 0.52) <.001	0.42 (0.32, 0.55) <.001
BMI (kg/m^2)		1.02 (1.01, 1.04) <.001	1.00 (0.99, 1.01) .898
Drink			
No		Ref	Ref
Yes		0.81 (0.66, 0.98) .034	0.88 (0.72, 1.08) .227
A family history of heart attack			
No		Ref	Ref
Yes		1.94 (1.57, 2.39) <.001	1.84 (1.48, 2.28) <.001
Physical activity			
No		Ref	Ref
Yes		0.81 (0.66, 0.99) .044	0.86 (0.69, 1.06) .173
Female hormone use			
No		Ref	Ref
Yes		1.08(0.90,1.29) .429	1.04 (0.87, 1.25) .653

(*Continued*)

Table 3. Associations between Red Cell Distribution Width and Cardiovascular Disease Risk Across 3 Multiple Logistic Regression Models (*Continued*)

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
Smoke status			
No		Ref	Ref
Yes		1.71 (1.42, 2.06) <.001	1.66 (1.39, 2.00) <.001
Anemia treatment			
No		Ref	Ref
Yes		1.64 (1.21, 2.21) .002	1.38 (1.00, 1.90) .048
TC (mg/dL)			0.99 (0.99, 1.00) <.001
HDL-C (mg/dL)			0.99 (0.99, 1.00) .007
eGFR (mL/min/1.73 m^2)			0.99 (0.98, 0.99) <.001
Hypertension			
No			Ref
Yes			2.25 (1.82, 2.79) <.007
Diabetes			
No			Ref
Yes			1.78 (1.44, 2.19) <.001
Cancer			
No			Ref
Yes			1.42 (1.12, 1.80) .004

eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; RAR, red cell distribution width-to-albumin ratio; RDW, red cell distribution width; PIR, poverty-to-income ratio; TC, total cholesterol.

The physiological mechanisms underlying the association between RAR and cardiovascular events may involve the synergistic effects of nutritional metabolic imbalance, chronic inflammation, and oxidative stress. Serum albumin is a key indicator of nutritional status, and postmenopausal women often experience malnutrition due to physiological decline and changes in dietary habits.[42] The combined effect of low albumin levels and elevated RDW, resulting in a higher RAR value, suggests that the body may be in a state of malnutrition and metabolic disturbance. Hypoalbuminemia leads to a decrease in plasma colloid osmotic pressure, causing tissue edema and increasing the heart's preload.[43] Nutritional deficiency may also affect myocardial energy metabolism and the integrity of cellular structures, further leading to a decline in cardiac function.[44] An elevated RAR not only reflects a state of malnutrition but is also closely associated with chronic inflammation and oxidative stress. In a chronic inflammatory environment, the body's antioxidant defense system becomes imbalanced, exacerbating oxidative stress. High levels of reactive oxygen species can oxidatively modify serum albumin, reducing its anti-inflammatory effects and further exacerbating damage to red blood cell membranes.[45] Additionally, inflammation and oxidative stress activate a series of cellular signaling pathways that promote the proliferation and migration of vascular smooth muscle cells, accelerating the formation of atherosclerotic plaques and ultimately increasing the risk of cardiovascular disease.[46]

In conclusion, this study found a positive association between RDW, RAR levels, and CVD risk in postmenopausal women. For women with elevated RDW and RAR levels, early individualized interventions are recommended. These may include adopting a healthy diet, engaging in regular exercise, and consulting with a healthcare provider to determine whether hormone replacement therapy is appropriate.

Strengths and Limitations

This study has several strengths. It is the first extensive cross-sectional investigation to explore the association between RDW, RAR, and CVD in postmenopausal women. By considering the complex sampling design of NHANES, the study population has strong national representativeness. Additionally, the large sample size and adjustment for confounding variables contribute to the robustness and reliability of the findings. Lastly, sensitivity analyses further confirmed the consistency of the results. However, this study also has limitations. First, the cross-sectional design

Table 4. Associations Between Red-Cell-Distribution-Width-to-Albumin Ratio, and Total Cardiovascular Disease Risk Across 3 Multiple Logistic Regression Models

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
RAR	2.02 (1.66, 2.47) <.001	1.66 (1.37, 2.03) <.001	1.42 (1.17, 1.73) .001
Age (years)	1.05 (1.04, 1.06) <.001	1.06 (1.05, 1.07) <.001	1.03 (1.02, 1.05) <.001
Race			
Mexican American	Ref	Ref	Ref
Other Hispanic	1.20 (0.84, 1.71) .313	1.23 (0.87, 1.73) .252	1.28 (0.88, 1.86) .190
Non-Hispanic White	1.47 (1.08, 2.00) .015	1.30 (0.96, 1.76) .099	1.29 (0.95, 1.76) .106
Non-Hispanic Black	1.57 (1.16, 2.14) .004	1.47 (1.08, 2.01) .018	1.39 (1.01, 1.92) .042
Other race	2.27 (1.41, 3.64) .001	2.31 (1.48, 3.61) <.001	2.08 (1.32, 3.27) .002
Education			
Less than 9th grade	Ref	Ref	Ref
9-11th Grade	1.38 (1.05, 1.81) .020	1.33 (1.00, 1.76) .050	1.46 (1.08, 1.97) .014
High school grad/GED or equivalent	1.16 (0.90, 1.48) .260	1.19 (0.92, 1.53) .188	1.29 (0.99, 1.69) .061
Some college or AA degree	1.07 (0.80, 1.45) .642	1.12 (0.83, 1.52) .449	1.27 (0.92, 1.75) .137
College graduate or above	0.59 (0.42, 0.82) .002	0.69 (0.49, 0.97) .037	0.82 (0.57, 1.19) .294
PIR			
≤1	Ref	Ref	Ref
1~4	0.64 (0.51, 0.80) <.001	0.67 (0.53, 0.84) .001	0.68 (0.54, 0.86) 001
>4	0.36 (0.28, 0.47) <.001	0.40 (0.31, 0.52) <.001	0.42 (0.32, 0.56) <.001
BMI (kg/m^2)		1.02 (1.01, 1.03) <.001	1.00 (0.98, 1.01) .686
Drink			
No		Ref	Ref
Yes		0.82 (0.67, 0.99) .046	0.89 (0.73, 1.09) .258
A family history of heart attack			
No		Ref	Ref
Yes		1.93 (1.56, 2.37) <.001	1.83 (1.47, 2.28) <.001
Physical activity			
No		Ref	Ref
Yes		0.82 (0.67, 1.01) .07	0.87 (0.70, 1.08) .206
Female hormone use			
No		Ref	Ref
Yes		1.08 (0.90, 1.29) .432	1.05 (0.87, 1.26) .634

(*Continued*)

Table 4. Associations Between Red-Cell-Distribution-Width-to-Albumin Ratio, and Total Cardiovascular Disease Risk Across 3 Multiple Logistic Regression Models (*Continued*)

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
Smoke status			
No		Ref	Ref
Yes		1.69 (1.41,2.02) <0.001	1.65 (1.37,1.99) <0.001
Anemia treatment			
No		Ref	Ref
Yes		1.62 (1.20, 2.17) .002	1.38 (1.00, 1.91) .051
TC (mg/dL)			1.00 (0.99, 1.00) <.001
HDL-C (mg/dL)			0.99 (0.99, 1.00) .010
eGFR (mL/min/1.73 m^2)			0.99(0.98,0.99) <.001
Hypertension			
No			Ref
Yes			2.27 (1.83, 2.81) <.001
Diabetes			
No			Ref
Yes			1.78 (1.44, 2.21) <.001
Cancer			
No			Ref
Yes			1.42 (1.12, 1.80) .005

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; PIR, poverty-to-income ratio; RAR, red-cell-distribution-width-to-albumin ratio; TC, total cholesterol.

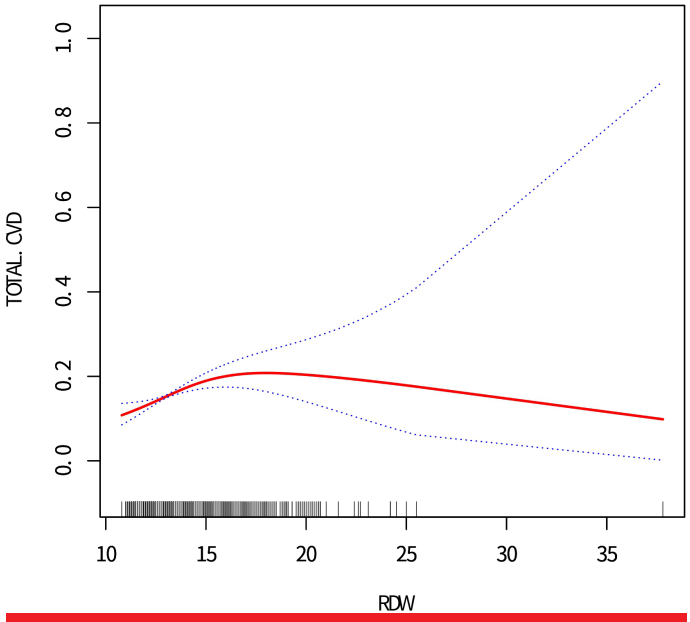

Figure 2. The association between red cell distribution width and total cardiovascular disease.

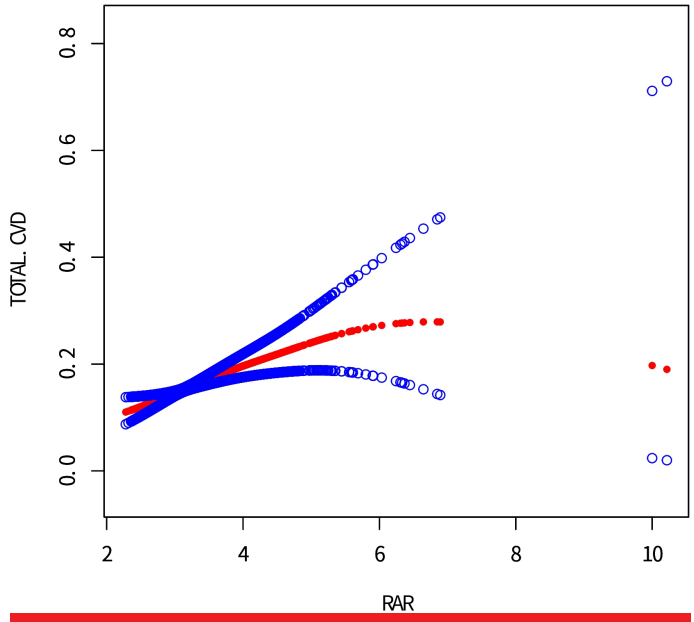

Figure 3. The association between red-cell-distribution-width-to-albumin ratioand total cardiovascular disease.

Table 5. Subgroup Analysis for the Association Between Red Cell Distribution Width, Red-cell-distribution-width-to-albumin Ratio, and Total Cardiovascular Disease

	RDW		RAR	
	OR (95% CI) *P*	*P* for interaction	OR (95% CI) *P*	*P* for interaction
Age (years)		.363		.252
<60	1.09 (0.99, 1.19) .090		1.29 (0.98, 1.71) .070	
≥60	1.14 (1.05, 1.24) .002		1.57 (1.24, 1.98) <.001	
BMI (kg/m^2)		.550		.854
<25	1.10 (1.00, 1.20) .053		1.33 (0.97, 1.81) .081	
25~30	1.18 (1.04, 1.35) .016		1.51 (1.07, 2.14) .020	
≥30	1.08 (0.96, 1.22) .184		1.40 (1.04, 1.88) .032	
Smoke		.379		.179
Yes	1.09 (1.02, 1.17) .018		1.31 (1.04, 1.64) .022	
No	1.14 (1.03, 1.27) .012		1.60 (1.24, 2.06) .001	
Alcohol use		.618		.716
Yes	1.10 (1.01, 1.19) .030		1.38 (1.11, 1.72) .005	
No	1.13 (1.02, 1.25) .017		1.47 (1.10, 1.98) .012	
Physical activity		.442		.453
Yes	1.16 (1.03, 1.29) .015		1.57 (1.17, 2.10) .004	
No	1.10 (1.02, 1.19) .018		1.37 (1.10, 1.71) .006	
Hypertension		.538		.808
Yes	1.10 (1.02, 1.19) .018		1.41 (1.12, 1.77) .004	
No	1.15 (1.01, 1.31) .035		1.48 (1.05, 2.09) .027	
Diabetes		.903		.370
Yes	1.11 (0.97, 1.26) .128		1.62 (1.16, 2.27) .006	
No	1.12 (1.03, 1.22) .013		1.35 (1.08, 1.69) .011	
eGFR (mL/min/1.73 m^2)		.140		.898
<60	1.19 (1.06, 1.32) .003		1.46 (1.07, 1.98) .019	
≥60	1.09 (1.01, 1.17) .037		1.42 (1.14, 1.77) .003	
TC (mg/dL)		.330		.275
<200	1.09 (1.01, 1.18) .039		1.33 (1.05, 1.69) .020	
≥200	1.17 (1.04, 1.31) .012		1.68 (1.20, 2.35) .004	
HDL-C (mg/dL)		.614		.723
<50	1.09 (1.00, 1.20) .062		1.38 (1.09, 1.75) .010	
≥50	1.12 (1.04, 1.21) .004		1.45 (1.15, 1.83) .002	

BMI, body mass index; hypertension, diabetes; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; RAR, red-cell-distribution-width-to-albumin ratio; RDW, red cell distribution width; TC, total cholesterol.

prevents the determination of causal relationships between RDW, RAR, and CVD. Second, the outcome variables were derived from self-reported questionnaires, which may introduce recall bias or misclassification in the diagnosis of CVD. Although self-reported data are commonly used in large-scale epidemiological studies like NHANES, they are inherently less accurate than clinically confirmed diagnoses. Nevertheless, the large sample size and population-based nature of the NHANES dataset help mitigate this limitation to some extent. Future studies should incorporate clinically verified diagnostic data to improve validity. Lastly, although extensive adjustments were made for potential confounders that could influence the association between RDW, RAR, and CVD, unmeasured factors may still affect the results. Future prospective cohort studies are needed to clarify the specific relationship between RDW, RAR, and CVD in postmenopausal women.

CONCLUSION

Red cell distribution width and RAR are readily accessible biomarkers that can be utilized to predict the risk of CVD in postmenopausal women. When RDW and RAR levels are abnormally elevated, postmenopausal women should be aware of the potential risk of CVD and take proactive measures for prevention. However, due to the limitations of this study, further prospective research is needed to explore the causal relationship between RDW, RAR, and CVD in postmenopausal women.

Availability of Data and Materials: The data and materials in the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: Not applicable.

Peer-review: Externally peer reviewed.

Author Contributions: L.C., YHQ., and C.Y. analyzed the association between RDW, RAR and the prevalence of CVD and its subtypes in postmenopausal women. C.Y. and S.X.S. conducted the literature search. L.C. was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Supplementary Table 1. Description of Covariates

Covariates	Description
Age (years)	Age was categorized into two groups: <60 and≥60 years
Race	Race was reported as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race.
Education level	Education level was categorized into five groups: Less than 9th Grade, 9-11th Grade (includes 12^{th} grade with no diploma), High School Grad/GED or Equivalent, Some College or AA degree, College Graduate or above
Ratio of family income to poverty (PIR)	PIR was categorized into three groups: ≤1, 1~4, >4
The body mass index (BMI)	The body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. It was categorized into four groups: normal weight (<25 kg/m^2), overweight (25~29.9 kg/m^2), obesity (≥30 kg/m^2).
Alcohol use	Alcohol use was defined as consuming at least 12 drinks of any type of alcoholic beverage in any one year
Smoking status	Smoking status were based on whether participants had smoked at least 100 cigarettes in their lifetime.
Physical activity	The Physical Activity questionnaire recorded whether participants engaged in moderate or vigorous recreational activities. Responses were categorized as "yes" or "no".
Hypertension	Hypertension was defined according to the following criteria: ① self-reported history of hypertension; ② currently taking antihypertensive medication; ③ average systolic blood pressure (SBP) ≥140 mmHg; ④ average diastolic blood pressure (DBP) ≥90 mmHg.
Diabetes	Diabetes was defined according to the following criteria: ① self-reported history of diabetes; ② currently using insulin; ③ currently using oral hypoglycemic agents; ④ glycated hemoglobin (HbA1c) ≥6.5%; ⑤ fasting blood glucose (FBG) ≥126 mg/dL.
A family history of heart	A family history of heart attack was defined as a self reported "yes" response to the question "Have any of your close biological relatives, including father, mother, sisters or brothers, been told by a health professional that they had a heart attack or angina before the age of 50?".
Cancer	Cancer was defined as a self reported "yes" response to the question "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?"
Anaemia treatment	Anaemia treatment was defined as a self reported "yes" response to the question "During the past 3 months, have you been on treatment for anemia, sometimes called "tired blood" or "low blood"? [Include diet, iron pills, iron shots, transfusions as treatment.]
Female hormone use	Female hormone use was defined as a self reported "yes" response to the question "Have you ever used female hormones such as estrogen and progesterone? Please include any forms of female hormones, such as pills, cream, patch, and injectables, but do not include birth control methods or use for infertility."
Estimated glomerular filtration rate (eGFR)	Data about gender, race, age, and SCr were used to calculate estimated glomerular filtration rate (eGFR) according to the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation for each participants.
Total cholesterol (TC)	TC was categorized into two groups: <200 mg/dl and ≥200 mg/dl
High-density lipoprotein cholesterol (HDL-C)	HDL-C was categorized into two groups: <50 mg/dl and ≥50 mg/dl

Supplementary Table 2. The association between RDW, RAR and CVD subtypes

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
Congestive heart failure			
RDW	1.33(1.21,1.46) <0.001	1.22(1.11,1.35) <0.001	1.16(1.07,1.26) 0.001
RAR	2.54(1.96,3.30) <0.001	1.88(1.41,2.49) <0.001	1.54(1.21,1.97) <0.001
RDW quartile			
Q1	Ref	Ref	Ref
Q2	1.26(0.80,2.00) 0.321	1.17(0.73,1.88) 0.510	1.20 (0.74,1.94) 0.470
Q3	2.10(1.29,3.41) 0.004	1.84(1.11,3.05) 0.020	1.76(1.06,2.95) 0.034
Q4	4.79(3.13,7.31) <0.001	3.49(2.21,5.51) <0.001	3.06(1.87,5.00) <0.001
P for trend	<0.001	<0.001	<0.001
RAR quartile			
Q1	Ref	Ref	Ref
Q2	1.67(1.01,2.76) 0.048	1.44(0.87,2.38) 0.154	1.36(0.83,2.24) 0.233
Q3	2.31(1.51,3.54) <0.001	1.73(1.12,2.67) 0.016	1.49(0.96,2.33) 0.082
Q4	4.80(3.26,7.07) <0.001	3.06(1.20,4.68) <0.001	2.30(1.48,3.59) <0.001
P for trend	<0.001	<0.001	<0.001
Coronary heart disease			
RDW	1.17(1.08,1.26) <0.001	1.13(1.04,1.23) 0.006	1.07(0.98,1.17) 0.120
RAR	1.67(1.31,2.13) <0.001	1.48(1.12,1.95) 0.006	1.23(0.93,1.63) 0.160
RDW quartile			
Q1	Ref	Ref	Ref
Q2	1.19(0.75,1.90) 0.466	1.19(0.74,1.90) 0.475	1.28(0.78,2.09) 0.335
Q3	1.87(1.21,2.90) 0.006	1.81(1.17,2.81) 0.009	1.74(1.11,2.74) 0.019
Q4	2.38(1.56,3.63) <0.001	2.20(1.42,3.41) <0.001	1.87(1.17,3.00) 0.011
P for trend	<0.001	0.0001	0.004
RAR quartile			
Q1	Ref	Ref.	Ref
Q2	1.65(1.03,2.66) 0.042	1.61(1.01,2.55) 0.049	1.52(0.95,2.45) 0.087
Q3	1.85(1.15,2.99) 0.013	1.71(1.07,2.73) 0.029	1.50(0.94,2.41) 0.095
Q4	2.59(1.65,4.07) 0.0001	2.34(1.48,3.70) 0.0005	1.79(1.13,2.85) 0.016
P for trend	<0.001	0.0007	0.025
Angina pectoris			
RDW	1.08(1.00,1.17) 0.059	1.04(0.95,1.14) 0.389	1.00(0.90, 1.11) 0.964
RAR	1.45(1.15,1.83) 0.002	1.26(0.97,1.64) 0.083	1.12(0.86, 1.47) 0.402

(*Continued*)

Supplementary Table 2. The association between RDW, RAR and CVD subtypes (*Continued*)

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
RDW quartile			
Q1	Ref	Ref.	Ref
Q2	0.99(0.65,1.49) 0.942	0.98(0.64,1.51) 0.926	1.00(0.65,1.53) 0.987
Q3	1.27(0.81,1.98) 0.295	1.24(0.79,1.94) 0.358	1.18(0.75,1.86) 0.483
Q4	1.36(0.93,2.00) 0.117	1.23(0.78,1.92) 0.375	1.06(0.66,1.70) 0.803
P for trend	0.049	0.212	0.658
RAR quartile			
Q1	Ref	Ref	Ref
Q2	1.69(1.00,2.85) 0.053	1.59(0.94,2.69) 0.088	1.57(0.92,2.69) 0.103
Q3	1.52(0.89,2.62) 0.131	1.35(0.79,2.31) 0.267	1.25(0.72,2.15) 0.428
Q4	2.05(1.29,3.26) 0.003	1.72(1.06,2.80) 0.030	1.44(0.88,2.37) 0.153
P for trend	0.007	0.070	0.327
Heart attack			
RDW	1.22(1.12,1.32) <0.001	1.18(1.07,1.30) <0.001	1.12(1.04,1.20) 0.003
RAR	1.79(1.46,2.20) <0.001	1.57(1.26,1.95) <0.001	1.28(1.05,1.55) 0.014
RDW quartile			
Q1	Ref	Ref	Ref
Q2	1.54(1.03,2.30) 0.038	1.53(1.03,2.28) 0.038	1.63(1.08,2.45) 0.021
Q3	1.68(1.09,2.58) 0.020	1.61(1.05,2.47) 0.030	1.58(1.01,2.46) 0.049
Q4	2.40(1.72,3.41) <0.001	2.23(1.57,3.17) <0.001	1.93(1.32,2.83) 0.001
P for trend	<0.001	<0.001	0.004
RAR quartile			
Q1	Ref	Ref	Ref
Q2	1.10(0.71,1.70) 0.684	1.06(0.69,1.64) 0.792	0.99(0.64,1.55) 0.982
Q3	1.80(1.27,2.55) 0.001	1.66(1.18,2.35) 0.005	1.45(1.02,2.07) 0.043
Q4	2.09(1.45,3.01) <0.001	1.87(1.29,2.71) 0.001	1.39(0.94,2.04) 0.104
P for trend	<0.001	<0.001	0.028
Stroke			
RDW	1.18(1.10,1.27) <0.001	1.14(1.04,1.24) 0.004	1.11 (1.03,1.19) 0.008
RAR	1.75(1.41,2.18) <0.001	1.53(1.20,1.95) 0.001	1.38(1.09,1.76) 0.010
RDW quartile			
Q1	Ref	Ref	Ref
Q2	1.39(0.91,2.12) 0.127	1.37(0.90,2.08) 0.151	1.42(0.94,2.15) 0.104
Q3	1.85(1.26,2.73) 0.002	1.74(1.16,2.62) 0.009	1.76(1.16,2.66) 0.009
Q4	2.37(1.61,3.48) <0.001	2.11(1.40,3.19) <0.001	1.98(1.30,3.04) 0.002
P for trend	<0.001	<0.001	0.002

(*Continued*)

Supplementary Table 2. The association between RDW, RAR and CVD subtypes (*Continued*)

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
RAR quartile			
Q1	Ref	Ref	Ref
Q2	1.61(1.07,2.42) 0.025	1.53(1.01,2.32) 0.049	1.52(1.00,2.32) 0.054
Q3	1.63(1.11,2.41) 0.015	1.46(0.98,2.17) 0.063	1.37(0.92,2.03) 0.128
Q4	2.41(1.64,3.56) <0.001	2.08(1.36,3.17) 0.001	1.81(1.17,2.80) 0.009
P for trend	<0.001	0.002	0.022

RDW: Q1(10.8~12.4); Q2(12.5~13.0); Q3(13.1~13.7); Q4(13.8~37.8)
RAR: Q1(2.28~2.93); Q2(2.94~3.14); Q3(3.15~3.41); Q4(3.42~10.22)
Model 1: Adjusted for age, race, education level and PIR; Model 2: Further adjusted for BMI, smoking, alcohol consumption, physical activity, family history of heart attack, history of female hormone use, and history of anemia treatment, in addition to the variables in Model 1; Model 3: Additionally adjusted for hypertension, diabetes, self-reported cancer history, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and estimated glomerular filtration rate (eGFR), building upon the adjustments in Model 2.

Supplementary Table 3. The association of RDW, RAR with total CVD and its subtypes

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
Total CVD			
RDW	1.23 (1.15,1.32) <0.001	1.17 (1.09,1.25) <0.001	1.13 (1.06,1.20) <0.001
RAR	2.12 (1.72,2.63) <0.001	1.72 (1.40,2.12) <0.001	1.51 (1.24,1.83) <0.001
RDW quartile			
Q1	Ref	Ref	Ref
Q2	1.15 (0.89,1.50) 0.291	1.13 (0.87,1.47) 0.373	1.21 (0.91,1.59) 0.187
Q3	1.61 (1.23,2.11) <0.001	1.53 (1.16,2.01) 0.003	1.51 (1.14,1.99) 0.005
Q4	2.27 (1.77,2.91) <0.001	1.95 (1.53,2.49) <0.001	1.81 (1.40,2.36) <0.001
P for trend	<0.001	<0.001	<0.001
RAR quartile			
Q1	Ref.	Ref.	Ref.
Q2	1.32 (1.00,1.74) 0.053	1.24 (0.94,1.63) 0.125	1.22 (0.93,1.61) 0.148
Q3	1.65 (1.23,2.22) 0.001	1.42 (1.05,1.91) 0.024	1.29 (0.95,1.74) 0.110
Q4	2.66 (2.01,3.52) <0.001	2.08 (1.60,2.71) <0.001	1.77 (1.35,2.30) <0.001
P for trend	<0.001	<0.001	<0.001
Congestive heart failure			
RDW	1.33 (1.21,1.47) <0.001	1.20 (1.09,1.32) <0.001	1.15 (1.07,1.25) <0.001
RAR	2.51 (1.93, 3.27) <0.001	1.76 (1.35,2.29) <0.001	1.52 (1.21,1.92) <0.001
RDW quartile			
Q1	Ref.	Ref.	Ref.
Q2	1.24 (0.71,2.16) 0.455	1.12 (0.64,1.98) 0.695	1.16 (0.64,2.09) 0.631
Q3	1.98 (1.13,3.45) 0.019	1.69 (0.96,2.99) 0.071	1.59 (0.89,2.83) 0.118
Q4	4.51 (2.78,7.32) <0.001	3.07 (1.87,5.03) <0.001	2.69 (1.59,4.54) <0.001
P for trend	<0.001	<0.001	<0.001

(*Continued*)

Supplementary Table 3. The association of RDW, RAR with total CVD and its subtypes (*Continued*)

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
RAR quartile			
Q1	Ref.	Ref.	Ref.
Q2	1.29 (0.71,2.36) 0.401	1.12 (0.61,2.05) 0.720	1.09 (0.59,2.01) 0.794
Q3	2.17 (1.34,3.53) 0.002	1.61 (0.99,2.63) 0.059	1.42 (0.86,2.35) 0.175
Q4	4.60 (3.04,6.96) <0.001	2.80 (1.81,4.34) <0.001	2.24 (1.41,3.54) <0.001
P for trend	<0.001	<0.001	<0.001
Coronary heart disease			
RDW	1.19 (1.09,1.29) <0.001	1.14 (1.04,1.26) 0.009	1.10 (0.99,1.21) 0.067
RAR	1.80 (1.38,2.34) <0.001	1.56 (1.16,2.12) 0.005	1.32 (0.98,1.79) 0.075
RDW quartile			
Q1	Ref	Ref	Ref
Q2	1.15 (0.70,1.90) 0.573	1.17 (0.70,1.93) 0.552	1.28 (0.75,2.18) 0.366
Q3	1.98 (1.25,3.14) 0.005	1.93 (1.20,3.10) 0.008	1.86 (1.14,3.03) 0.016
Q4	2.60 (1.64,4.13) <0.001	2.40 (1.46,3.95) <0.001	2.12 (1.27,3.52) 0.005
P for trend	<0.001	<0.001	0.002
RAR quartile			
Q1	Ref	Ref	Ref
Q2	1.62 (0.98,2.68) 0.061	1.60 (0.98,2.60) 0.061	1.53 (0.92,2.54) 0.102
Q3	1.74 (1.07,2.82) 0.028	1.59 (1.00,2.54) 0.054	1.39 (0.86,2.24) 0.178
Q4	2.74 (1.74,4.32) <0.001	2.43 (1.55,3.83) <0.001	1.90 (1.21,2.98) 0.006
P for trend	<0.001	<0.001	0.011
Angina pectoris			
RDW	1.09 (1.00,1.18) 0.051	1.05 (0.95,1.16) 0.352	1.02 (0.92,1.13) 0.774
RAR	1.57 (1.21,2.04) <0.001	1.38 (1.03,1.85) 0.033	1.26 (0.93,1.71) 0.133
RDW quartile			
Q1	Ref	Ref	Ref
Q2	0.93 (0.56,1.55) 0.781	0.94 (0.55,1.60) 0.816	0.99 (0.59,1.66) 0.965
Q3	1.20 (0.70,2.04) 0.511	1.19 (0.69,2.07) 0.529	1.16 (0.67,2.01) 0.604
Q4	1.33 (0.87,2.03) 0.193	1.21 (0.73,2.01) 0.469	1.10 (0.67,1.80) 0.701
P for trend	0.090	0.288	0.563
RAR quartile			
Q1	Ref.	Ref.	Ref.
Q2	1.33 (0.77,2.30) 0.305	1.29 (0.75,2.23) 0.359	1.30 (0.75,2.26) 0.349
Q3	1.32 (0.74,2.35) 0.353	1.20 (0.67,2.12) 0.543	1.11 (0.61,2.01) 0.734
Q4	1.97 (1.22,3.18) 0.007	1.69 (1.01,2.81) 0.048	1.46 (0.88,2.41) 0.148
P for trend	0.010	0.069	0.225
Heart attack			
RDW	1.22 (1.12,1.32) <0.001	1.16 (1.05,1.29) 0.004	1.11 (1.03,1.20) 0.008
RAR	1.82 (1.45,2.30) <0.001	1.54 (1.19,2.00) 0.001	1.27 (1.02,1.59) 0.036

(*Continued*)

Supplementary Table 3. The association of RDW, RAR with total CVD and its subtypes (*Continued*)

	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*
RDW quartile			
Q1	Ref	Ref	Ref
Q2	1.44 (0.90,2.31) 0.129	1.42 (0.89,2.26) 0.141	1.54 (0.96,2.47) 0.079
Q3	1.89 (1.15,3.11) 0.014	1.79 (1.09,2.95) 0.024	1.70 (1.02,2.85) 0.047
Q4	2.35 (1.57,3.52) <0.001	2.08 (1.38,3.14) <0.001	1.79 (1.18,2.71) 0.008
P for trend	<0.001	<0.001	0.009
RAR quartile			
Q1	Ref	Ref	Ref
Q2	0.96 (0.56,1.64) 0.870	0.92 (0.54,1.59) 0.771	0.87 (0.50,1.49) 0.613
Q3	1.65 (1.10,2.48) 0.018	1.49 (1.00,2.21) 0.052	1.27 (0.85,1.90) 0.246
Q4	2.27 (1.49,3.44) <0.001	1.96 (1.28,3.01) 0.003	1.49 (0.99,2.23) 0.057
P for trend	<0.001	<0.001	0.010
Stroke			
RDW	1.22 (1.12,1.32) <0.001	1.17 (1.06,1.28) 0.003	1.14 (1.05,1.23) 0.002
RAR	1.95 (1.54,2.46) <0.001	1.68 (1.28,2.20) <0.001	1.55 (1.21,1.99) <0.001
RDW quartile			
Q1	Ref	Ref	Ref
Q2	1.43 (0.91,2.24) 0.123	1.42 (0.91,2.21) 0.129	1.48 (0.95,2.29) 0.084
Q3	1.90 (1.25,2.88) 0.003	1.79 (1.17,2.76) 0.009	1.76 (1.15,2.70) 0.011
Q4	2.55 (1.64,3.95) <0.001	2.28 (1.43,3.62) <0.001	2.08 (1.32,3.27) 0.002
P for trend	<0.001	<0.001	0.002
RAR quartile			
Q1	Ref	Ref	Ref
Q2	1.48 (0.95,2.30) 0.089	1.41 (0.90,2.22) 0.135	1.43 (0.91,2.24) 0.125
Q3	1.82 (1.16,2.83) 0.010	1.62 (1.02,2.57) 0.042	1.52 (0.96,2.42) 0.080
Q4	2.63 (1.70,4.07) <0.001	2.25 (1.42,3.56) 0.001	2.00 (1.27,3.16) 0.004
P for trend	<0.001	<0.001	0.004

Model 1: Adjusted for age, race, education level and PIR; Model 2: Further adjusted for BMI, smoking, alcohol consumption, physical activity, family history of heart attack, history of female hormone use, and history of anemia treatment, in addition to the variables in Model 1; Model 3: Additionally adjusted for hypertension, diabetes, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and estimated glomerular filtration rate (eGFR), building upon the adjustments in Model 2.