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Association between hemoglobin-to-red blood cell distribution width ratio and chronic kidney disease

A cross sectional study

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Abstract

The hemoglobin-to-red blood cell distribution width ratio (HRR) is recognized as a novel prognostic biomarker; however, studies exploring its relationship with chronic kidney disease (CKD) are scarce. This study used data from the National Health and National Health and Nutrition Examination Survey database from 2005 to 2018. The analysis included individuals aged ≥ 20 years who had complete HRR and CKD data. Weighted univariate and multivariate logistic regression analyses were used to assess the association between the HRR and CKD prevalence. Additionally, restricted cubic spline and subgroup analyses were conducted for further validation. Ultimately, 19,426 participants were included in this study. After adjusting for confounders, multivariate logistic regression analysis revealed a negative association between HRR and CKD (OR = 0.35, 95% CI = 0.22–0.56). In addition, restricted cubic spline regression analysis revealed a negative linear association between HRR and CKD, with higher levels of HRR associated with a lower prevalence of CKD. The subgroup analysis revealed that the negative association between HRR and CKD was stronger in the male population. HRR is negatively associated with the prevalence of CKD in the adult population of the US. HRR is a potential indicator for assessing the prevalence of CKD and provides a rationale for personalized management.

Abbreviations: CBC = complete blood count, CKD = chronic kidney disease, CVD = cardiovascular disease, HGB = hemoglobin, HRR = hemoglobin-to-red blood cell distribution width ratio, NHANES = National Health and Nutrition Examination Survey, RDW = red cell distribution width.

Keyword: chronic kidney disease, hemoglobin, hemoglobin-to-red blood cell distribution width ratio, NHANES, red blood cell distribution width

1. Introduction

Chronic kidney disease (CKD) is defined as persistent kidney damage or a decline in renal function lasting 3 months or more, impairing the body's ability to effectively clear waste and excess fluid from the blood.[1,2] With an aging population, the prevalence of CKD is increasing, posing a significant challenge to global public health. CKD progresses through various stages, with nonspecific early symptoms.[3,4] However, as the disease progresses, significant renal impairment can lead to multisystem complications, including cardiovascular and hematological diseases.[5–7] Therefore, exploring the factors associated with CKD can help to better understand management strategies for CKD.

The complete blood count (CBC) is an essential fundamental test crucial for the assessment and diagnosis of diseases.[8] It reflects an individual's blood health status, with hemoglobin (HGB) and red cell distribution width (RDW) serving as the key indicators. HGB, which is responsible for oxygen transport, is often associated with low levels of oxygen in anemia, a common condition across various diseases, notably CKD, where renal impairment influences red blood cell production.[9,10] RDW signifies variations in red blood cell volume and is correlated with systemic inflammation.[11] As a prognostic marker, RDW is linked to increased mortality risk and prevalence of sepsis-induced acute kidney injury.[12,13] Therefore, CBC and its critical markers are indispensable for the diagnosis and treatment of various diseases.

LN and JT contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are publicly available.

The National Center for Health Statistics and the Centers for Disease Control and Prevention conducted NHANES. The National Center for Health Statistics Research Ethics Review Board was established after reviewing and approving the National Health and NHANES study protocols. All participants provided written informed consent. The NHANES database is a de-identified database, so no additional ethics approval was required.

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The hemoglobin-to-red blood cell distribution width ratio (HRR) is recognized as an innovative evaluation marker.[14] It is prized for its ease of acquisition, reliability, and cost-effectiveness and shows significant potential for disease surveillance and management. HRR is closely correlated with the prognosis and survival rates of patients with various diseases, including cancer, cardiovascular disease, and cerebrovascular disease, indicating that HRR has superior correlation and predictive value over single measurements of HGB or RDW.[15–18] However, the relationship between HRR and CKD still lacks sufficient evidence. Therefore, the primary objective of this study was to investigate the relationship between the HRR and the prevalence of CKD in the US adult population. It was hypothesized that higher levels of HRR would be associated with a lower prevalence of CKD.

2. Methods

2.1. Study population

The data for this research were sourced from the National Health and Nutrition Examination Survey (NHANES), a project of the National Center for Health Statistics that received Institutional Review Board approval. Consent was obtained from all subjects. This study employed the National Health and NHANES database for cross-sectional analysis. This study included data from 2005 to 2018, involving a total of 70,190 participants. During the selection process, we established the following exclusion criteria: individuals younger than 20 years; participants with incomplete kidney disease-related data, specifically missing serum creatinine, urine creatinine, and urine albumin data; and those with incomplete CBC data, including missing HGB and RDW data. After the screening, 19,426 participants met the study criteria and were included in the final analysis.

2.2. Evaluation of chronic kidney disease

In this study, serum and urine creatinine levels were assessed using the Jaffe method, whereas urine albumin content was determined using a solid-phase fluorescence immunoassay. The eGFR was calculated based on the serum creatinine concentration using the CKD-EPI equation.[19] Urinary albumin-to-creatinine ratio was calculated as the ratio of urine albumin-to-creatinine. CKD in this study was characterized by an eGFR <60 mL/min/1.73 m² or a urinary albumin-to-creatinine ratio ≥ 30 mg/g.[20]

2.3. HRR calculations

CBC parameters were obtained using Beckman Coulter counting and classification technology, complemented by automated diluting and mixing equipment. Furthermore, the calculation of HRR was simplified to the ratio of the HGB value to the red cell distribution width.

2.4. Selection of covariates

In this study, a range of covariates was included to control for potential confounding factors, thereby enhancing the accuracy of the analysis. These confounding factors included age, sex, race, education level, poverty income ratio (PIR), body mass index, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, smoking status, hypertension, hypercholesterolemia, diabetes, and cardiovascular disease (CVD), among other key variables. Individuals who smoked fewer than 100 cigarettes in their lifetime were classified as nonsmokers. The PIR was calculated by comparing household income to the poverty line, and further categorized into 3 groups (<1, 1–3, and >3) to assess the potential impact of economic status on health. CVD was determined based on a diagnosis of congestive heart failure, coronary artery disease, angina, heart attack, or stroke. Hypertension was defined as a diagnosis by a medical professional, an average blood pressure ≥ 130/80 mm Hg, or use of hypertension medication. Diabetes mellitus was defined as a diagnosis by a physician or other healthcare professional, glycohemoglobin (%) >6.5, random serum glucose (mmol/L) ≥ 11.1, or use of diabetes medications or insulin.

2.5. Statistical analysis

This study analyzed data from 7 NHANES survey cycles, adhering to official NHANES documentation, to ensure the accurate application of weights. Descriptive statistics were calculated for participants, with continuous variables expressed as means (standard deviations) and compared using independent samples *t* tests and categorical variables expressed as percentages and using chi-square tests. To investigate the relationship between HRR and CKD prevalence, weighted univariate and multivariate logistic regression analyses were employed, including Model 1 without any covariate adjustments; Model 2 adjusted for age, sex, and race; and Model 3 incorporating additional covariate impacts. Restricted cubic spline regressions were used to further examine the relationship between HRR and CKD. Three knots were selected, with node positions set at the 5th, 50th, and 95th percentiles of the HRR distribution. HRR was converted into quartile variables (Q1: <0.96, Q2: 0.96–1.07, Q3: 1.07–1.17, and Q4: >1.17) in order to explore the effect of different HRR levels on CKD, and a trend test was used to detect the trend relationship between HRR quartiles and to ensure that the associations found were significant across groups. Subgroup analyses were also conducted to explore variations in the association between the HRR and CKD across different demographics and health backgrounds. All statistical analyses were performed using R software (version 4.2.2), with $P < .05$ considered to indicate statistical significance.

3. Results

3.1. Participant selection and baseline characteristics

The selection and inclusion process of the participants is detailed in Figure 1, with 19,426 participants included in this study. Of these, 15,696 were non-CKD patients, and 3730 were CKD patients. Observations indicate that CKD may occur in elderly individuals, obese individuals, individuals with an average income, individuals with a low educational level, and smokers. These patients also exhibited increased levels of blood urea nitrogen and uric acid along with an increased risk of hypertension, hypercholesterolemia, and diabetes. Notably, the HRR of patients without CKD was significantly greater than that of patients with CKD. Baseline characteristics of the study participants are presented in Table 1.

3.2. Association of HRR with CKD

This study utilized weighted logistic regression analysis, as shown in Table 2. In Model 1, a negative association emerged between HRR and CKD (OR = 0.07, 95% CI = 0.05–0.10). After adjusting for multiple covariates, this relationship continued to be robust (OR = 0.35, 95% CI = 0.22–0.56). Converting the HRR to a quartile variable adjusted for full covariates, each unit increase in high HRR was associated with a 32% reduction in CKD prevalence compared to a decrease in HRR. As shown in Figure 2, restricted cubic spline analysis revealed that HRR was linearly negatively correlated with CKD. The above results indicate a strong negative correlation between the HRR and CKD prevalence.

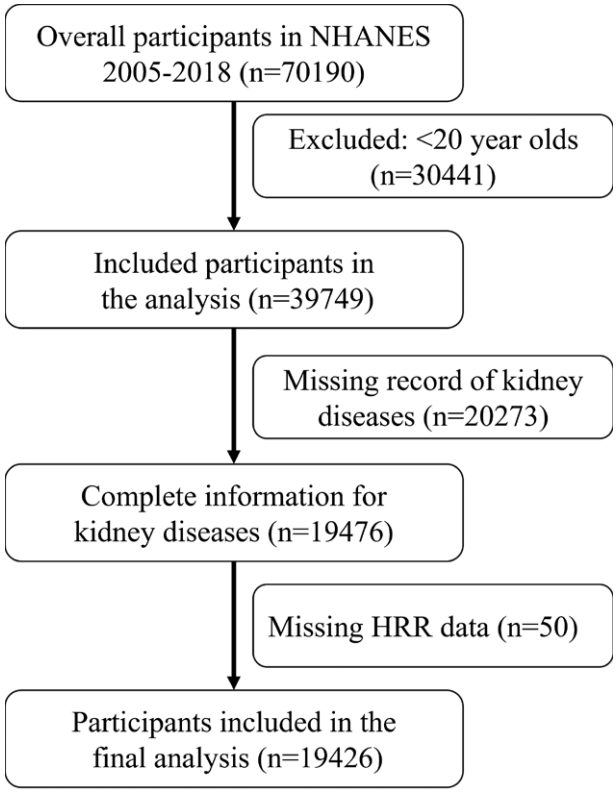

Figure 1. Participant inclusion process.

3.3. Subgroup analysis of the HRR in patients with CKD

In order to gain insight into the influence of various factors on the relationship between HRR and CKD, subgroup analyses were conducted for age, gender, body mass index, smoking status, diabetes, hypertension and CVD. As shown in Table 3, after adjusting for all covariates, the results showed that HRR was negatively associated with CKD in different populations. Notably, the interaction test showed significant interactions with gender (P value = 0.004) and CVD (P value = 0.049), with stronger negative associations between HRR and CKD in the male and CVD populations.

3.4. Sensitivity analysis of HRR and CKD

To strengthen the reliability of the findings of this study, we excluded covariates with missing values. A final total of 17,614 participants remained, including 15,696 non-CKD patients and 3730 CKD patients. Table S1, Supplemental Digital Content, http://links.lww.com/MD/N848 reveals the results of the sensitivity analysis between HRR and CKD prevalence. The negative association between HRR and CKD prevalence was found to remain stable, consistent with the results of this study.

4. Discussion

This study used data from the NHANES database to explore the correlation between the HRR and the prevalence of CKD. The results clearly showed a significant negative correlation between HRR and CKD after accounting for multiple confounders, and this relationship has been consistently confirmed across different models and populations. Notably, subgroup analyses showed that the negative correlation between HRR and CKD was stronger in males and CVD populations. Due to differences in blood parameters between males and females, hemoglobin levels are usually greater in males,[21] which may be due to the influence of testosterone and other erythropoiesis-promoting sex hormones, making the relationship between HRR and CKD more pronounced in males.[22] In the female population, significant fluctuations in sex hormones such as estrogen may have different effects on erythropoiesis and iron metabolism, thus attenuating the correlation between HRR and CKD.[21,23] Previous studies have demonstrated a more significant positive correlation between RDW and CVD in women, and patients with CVD are usually accompanied by higher RDW and chronic inflammatory status, which is consistent with the results of the present study.[24] In conclusion, HRR has an important clinical application as a potential indicator for assessing the risk of developing CKD, especially in high-risk groups, and provides a scientific basis for individualized management of CKD.

Previous research has primarily concentrated on the association between the HRR and diseases such as cancer and cardiovascular disorders.[15,25–27] A retrospective analysis revealed that low HRR is an independent risk factor for acute kidney injury, and the link between HRR and CKD remains underexplored.[28] To the best of our knowledge, this is the first study to examine the relationship between HRR and CKD prevalence, demonstrating a linear negative correlation, in which a low HRR is associated with a greater prevalence of CKD. This association may be attributed to low levels of HRR, a novel inflammatory marker, as inflammation may lead to changes in whole blood cell counts. Previous studies have shown that RDW is an important marker for assessing inflammation, can serve as a prognostic indicator for heart failure and diabetes, and has been validated in various diseases.[29–31] Compared to traditional markers such as Hb or RDW, low levels of HRR have been identified as a novel inflammatory index that exhibits superior predictive capabilities for assessing disease states.[14] Multiple studies have demonstrated that various inflammatory biomarkers are closely linked to CKD,[32–34] and the levels of inflammatory markers are positively correlated with the risk of CKD, a finding that is corroborated by our findings.

Many pathophysiological processes can influence the progression of CKD, indicating complex links between HRR and CKD. A fundamental issue in CKD is the gradual decline in kidney function, which affects the ability of the kidney to produce erythropoietin (EPO).[10] Patients with CKD often experience disturbances in iron metabolism, such as reduced iron absorption and utilization, which further exacerbates anemia.[35,36] As kidney failure progresses, toxins that are not effectively excreted accumulate in the body, directly damaging red blood cells and reducing their lifespan, thus lowering hemoglobin levels.[37,38] Additionally, an increase in RDW among patients with CKD reflects greater variability in red blood cell size, which is closely associated with various pathophysiological mechanisms related to CKD. As renal function deteriorates, chronic inflammation, malnutrition, and toxin accumulation in patients with CKD further disrupt the normal production and maturation of blood cells, leading to increased size disparities between new and old blood cells.[34,39,40] These pathological conditions can also accelerate the destruction of red blood cells, thereby further increasing the heterogeneity of red blood cell sizes. Thus, a decrease in HRR is not only a marker of anemia associated with CKD but also reflects multiple pathological processes, including poor nutritional status and shortened red blood cell lifespan.

In summary, HRR, the ratio of hemoglobin-to-RDW, comprehensively reflects the multifaceted changes in the blood status of patients with CKD. When anemia caused by CKD coexists with inconsistencies in red blood cell production, the HRR may more sensitively reflect the pathological state of patients, potentially indicating more extensive hematological changes and metabolic disorders. Notably, HRR is not intended to replace the traditional eGFR marker for early prediction of CKD. The HRR offers additional insights, particularly when eGFR alone may not fully capture a patient's health status, thereby enhancing the overall diagnostic accuracy and management of CKD.

Table 1

Basic characteristics of the study population in NHANES 2005 to 2018.

Characteristic	Level	Overall	Non-CKD	CKD	*P*-value
n		19,426	15,696	3730	
Age (%)	<50	10,146 (52.2)	9340 (59.5)	806 (21.6)	<.001
	>50	9280 (47.8)	6356 (40.5)	2924 (78.4)	
Sex (%)	Female	9969 (51.3)	8054 (51.3)	1915 (51.3)	.990
	Male	9457 (48.7)	7642 (48.7)	1815 (48.7)	
Race (%)	Mexican American	3083 (15.9)	2595 (16.5)	488 (13.1)	<.001
	Non-Hispanic black	4085 (21.0)	3102 (19.8)	983 (26.4)	
	Non-Hispanic white	7805 (40.2)	6205 (39.5)	1600 (42.9)	
	Others	4453 (22.9)	3794 (24.2)	659 (17.7)	
BMI (%)	Normal	5465 (28.4)	4599 (29.5)	866 (23.7)	<.001
	Overweight	6352 (33.0)	5208 (33.4)	1144 (31.3)	
	Obese	7418 (38.6)	5777 (37.1)	1641 (44.9)	
Education level (%)	Under high school	4697 (24.2)	3560 (22.7)	1137 (30.5)	<.001
	High school	4476 (23.0)	3566 (22.7)	910 (24.4)	
	Above high school	10,235 (52.7)	8557 (54.5)	1678 (45.0)	
	No record	18 (0.1)	13 (0.1)	5 (0.1)	
PIR (%)	<1	3678 (21.0)	2920 (20.6)	758 (22.7)	<.001
	1–3	7494 (42.9)	5885 (41.6)	1609 (48.2)	
	>3	6310 (36.1)	5340 (37.8)	970 (29.1)	
Smoke (%)	No	10,566 (54.4)	8737 (55.7)	1829 (49.0)	<.001
	Yes	8849 (45.6)	6951 (44.3)	1898 (50.9)	
	No record	11 (0.1)	8 (0.1)	3 (0.1)	
Hypertension (%)	No	7868 (43.8)	7227 (50.1)	641 (18.1)	<.001
	Yes	10,075 (56.2)	7184 (49.9)	2891 (81.9)	
CVD (%)	No	17,278 (88.9)	14,557 (92.7)	2721 (72.9)	<.001
	Yes	2148 (11.1)	1139 (7.3)	1009 (27.1)	
Hypercholesterolemia (%)	No	11,119 (62.9)	9413 (66.5)	1706 (48.5)	<.001
	Yes	6439 (36.4)	4667 (33.0)	1772 (50.4)	
	No record	111 (0.6)	72 (0.5)	39 (1.1)	
Diabetes (%)	No	16,122 (83.1)	13,777 (87.9)	2345 (62.9)	<.001
	Yes	3280 (16.9)	1896 (12.1)	1384 (37.1)	
SCR (mean (SD)) (mg/dL)		0.89 (0.37)	0.83 (0.18)	1.16 (0.70)	<.001
UCR (mean (SD)) (mg/dL)		124.60 (81.44)	126.19 (82.36)	117.92 (77.07)	<.001
UA (mean (SD)) (mg/L)		49.94 (330.29)	10.05 (10.06)	217.80 (730.05)	<.001
eGFR (mean (SD))		91.46 (23.43)	96.88 (18.51)	68.65 (27.81)	<.001
UACR (mean (SD))		49.12 (358.28)	8.28 (5.66)	220.94 (794.97)	<.001
BUN (mean (SD)) (mmol/L)		2.34 (0.09)	2.34 (0.09)	2.35 (0.10)	<.001
ALT (mean (SD)) (U/L)		4.98 (2.14)	4.59 (1.52)	6.59 (3.30)	<.001
AST (mean (SD)) (U/L)		24.60 (17.64)	24.98 (17.96)	23.02 (16.15)	<.001
Glycohemoglobin (mean (SD)) (%)		5.79 (1.11)	5.64 (0.90)	6.39 (1.59)	<.001
Glucose (mean (SD)) (mmol/L)		6.16 (2.08)	5.93 (1.66)	7.14 (3.14)	<.001
HGB (mean (SD)) (g/dL)		14.04 (1.56)	14.13 (1.51)	13.64 (1.69)	<.001
RDW (mean (SD)) (%)		13.49 (1.37)	13.39 (1.30)	13.93 (1.57)	<.001
HRR (mean (SD))		1.05 (0.17)	1.07 (0.16)	0.99 (0.17)	<.001

Mean (SD) for continuous variables, % for categorical variables. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, CKD = chronic kidney disease, CVD = cardiovascular disease, eGFR = estimated Glomerular filtration rate, HGB = hemoglobin, HRR = hemoglobin-to-red cell distribution width ratio, NHANES = National Health and Nutrition Examination Survey, PIR = poverty income ratio, RDW = red cell distribution width, SCR = serum creatinine, UA = urinary albumin, UACR = urinary albumin-to-creatinine ratio; UCR: urinary creatinine.

Table 2

The relationship between the HRR and CKD prevalence.

	Model 1 OR (95% CI) *P*-value	Model 2 OR (95% CI) *P*-value	Model 3 OR (95% CI) *P*-value
HRR	0.07 (0.05, 0.10) <.001	0.08 (0.06, 0.12) <.001	0.35 (0.22, 0.56) <.001
Q1	[Reference]	[Reference]	[Reference]
Q2	0.56 (0.51, 0.62) <.001	0.56 (0.49, 0.62) <.001	0.81 (0.69, 0.96) .014
Q3	0.42 (0.37, 0.48) <.001	0.44 (0.39, 0.50) <.001	0.76 (0.64, 0.91) .003
Q4	0.29 (0.25, 0.34) < 0.001	0.34 (0.28, 0.41) < 0.001	0.68 (0.54, 0.85) < 0.001
P for trend	<.001	<.001	<.001

Model 1: no covariates adjusted; Model 2: adjusted for age, sex, and race; Model 3: adjusted for age, sex, BMI, race, educational level, PIR, smoking, hypertension, hypercholesterolemia, CVD, diabetes, BUN, ALT, AST.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, CI = confidence interval, CKD = chronic kidney disease, HRR, hemoglobin-to-red cell distribution width ratio, OR = odds ratio, PIR = poverty income ratio, Q = quartile.

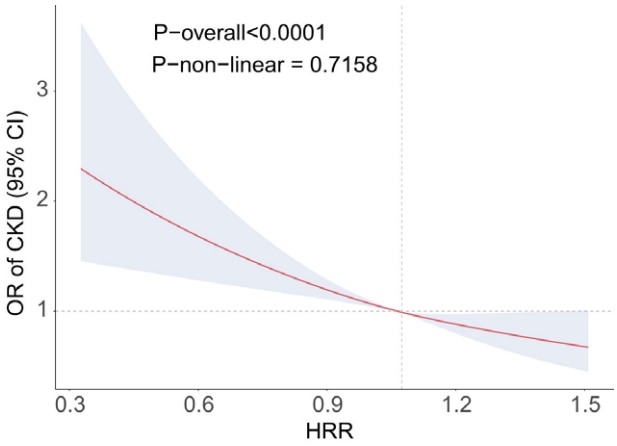

Figure 2. RCS analysis of HRR and CKD. Adjusted for age, sex, BMI, race, educational level, PIR, smoking status, hypertension status, hypercholesterolemia status, CVD status, diabetes status, BUN, ALT, AST. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, CKD = chronic kidney disease, CVD = cardiovascular disease, HRR = hemoglobin-to-red cell distribution width ratio, PIR = poverty income ratio.

Additionally, HRR measurements are relatively simple and cost-effective, making them highly accessible and potentially valuable in resource-limited settings. Therefore, HRR can provide supplementary information to traditional detection metrics, thereby improving the early detection and comprehensive assessment of CKD.

The present study has several strengths. First, the sample size from the NHANES database was large and representative, which was attributed to the appropriate weighting. Second, the inclusion of various covariates to adjust for potential confounding factors affecting CKD onset enhanced the reliability of the results. Furthermore, subgroup analysis revealed a stable association between the HRR and CKD in the male population. However, this study has several limitations. Given the cross-sectional nature of this study, causality could not be established. Moreover, despite controlling for confounding factors, other factors may have also affected the study results. Our research was based on an adult population in the United States; therefore, additional data collected from diverse populations are required to further explore the relationship between HRR and CKD.

5. Conclusions

HRR is negatively associated with the prevalence of CKD in the adult population of the US. HRR is a potential indicator for assessing the prevalence of CKD and provides a rationale for personalized management.

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Author contributions

Conceptualization: Lin Ning, Min He.
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Investigation: Junping Tang, Zhiqiang Chen, Quan Liu.
Methodology: Junping Tang, Zhiqiang Chen.

Table 3

Subgroup analysis between the HRR and CKD patients.

Characteristic	Group	OR (95% CI) *P* value	*P* for interaction
Age	<50	0.57 (0.27, 1.22) .15	>.9
	>50	0.41 (0.23, 0.73) .003	
Sex	Male	0.21 (0.10, 0.42) <.001	.004
	Female	0.58 (0.33, 1.04) .067	
BMI	Normal	0.39 (0.16, 0.99) .047	.088
	Overweight	0.24 (0.11, 0.52) <.001	
	Obese	0.46 (0.23, 0.91) .025	
Smoke	No	0.52 (0.29, 0.95) .033	.300
	Yes	0.25 (0.14, 0.45) <0.001	
Hypertension	No	0.37 (0.16, 0.85) .020	.500
	Yes	0.36 (0.21, 0.60) <.001	
Diabetes	No	0.38 (0.22, 0.66) <.001	0.051
	Yes	0.27 (0.12, 0.60) .001	
CVD	No	0.45 (0.28, 0.74) .002	.049
	Yes	0.13 (0.05, 0.33) <.001	

BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, CVD = cardiovascular disease, OR = odds ratio.

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Resources: Lin Ning, Junping Tang, Zhiqiang Chen, Xiaolin Zeng.
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Validation: Lin Ning.
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Writing – original draft: Lin Ning.
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