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Association of hemoglobin-to-red blood cell distribution width ratio and bone mineral density in older adults

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Abstract

Background Hemoglobin-to-Red Cell Distribution Width Ratio (HRR) represents novel prognostic markers for diseases. However, there remains a lack of systematic research into the relationship between HRR and Bone Mineral Density (BMD) or osteoporosis in older adults.

Methods This study utilized information from the NHANES database, selecting individuals over 50 years of age with complete femoral DXA scans and full blood counts. The relationship between HRR and femoral BMD was investigated using weighted linear models and restricted cubic spline (RCS) models. Moreover, the association between HRR and osteoporosis was further explored using logistic regression models and RCS models, with subgroup analysis conducted to test the robustness of the results.

Results This study included a total of 7,149 participants, and the BMD of the group with higher HRR was significantly greater than that of the group with lower HRR. Weighted linear regression analysis found a linear positive correlation between HRR and femoral BMD. When HRR was converted from a continuous variable to a categorical variable, this relationship remained stable. In addition, multivariate logistic regression analysis showed that for each 1-unit increase in HRR, the prevalence of osteoporosis significantly decreased (OR = 0.25, 95% CI: 0.12–0.51), further confirming the findings of this study. Subgroup analysis showed that this association was not significantly affected by confounding factors across different populations.

Conclusion HRR may serve as one of the potential indicators for evaluating BMD and assessing the prevalence of osteoporosis in the elderly. Elevating HRR levels may play a crucial role in the prevention and slowing of osteoporosis progression.

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Keywords Hemoglobin-to-red cell distribution width ratio, Hemoglobin, Red cell distribution width, Bone Mineral Density, Osteoporosis

Introduction

Osteoporosis, characterized by reduced bone mass, deterioration of bone tissue microarchitecture, and diminished skeletal strength, is a systemic bone disease caused by various factors [1]. With the increasing aging of the population, the prevalence of osteoporosis continues to rise, imposing a significant economic burden globally [2–4]. A 2010 survey in the United States revealed that approximately 53.6 million individuals aged 50 and above were suffering from osteoporosis or low bone mass, a number that is expected to grow [5]. However, osteoporosis is often detected only after a fracture occurs. Therefore, assessing factors associated with the incidence of osteoporosis is of significant importance in the fields of clinical medicine and public health.

In the evaluation and diagnosis of diseases, complete blood counts (CBC) play a pivotal role in revealing an individual's blood health status [6]. Specifically, hemoglobin (HGB) and red cell distribution width (RDW) are crucial for assessing blood health. HGB is primarily responsible for carrying and transporting oxygen throughout the body, and its level directly reflects the oxygen-carrying capacity of the blood[7]. However, the link between HGB and BMD remains contentious, with their biological mechanisms not fully elucidated. One study indicated that variations in HGB were not associated with BMD and could not serve as an indicator of low BMD in the elderly [8]. Conversely, other research has shown a positive correlation between serum HGB levels and BMD in the elderly, suggesting that lower HGB levels might increase the prevalence of osteoporosis [9, 10]. RDW is a quantitative measure of the variability in circulating red blood cell sizes, with higher values indicating greater cell size heterogeneity [11]. Studies have reported a significant correlation between RDW values and the risk of hip fractures in the elderly [12], evaluating it as a potential screening marker for chronic liver diseases and a prognostic marker for heart failure and coronary artery disease [13–15]. While RDW has shown potential clinical utility in assessing the health of the elderly in various aspects, its relationship with BMD remains unclear.

The hemoglobin to red cell distribution width ratio (HRR) was first proposed as a novel prognostic marker and has been validated in esophageal squamous cell carcinoma [16]. The uniqueness of HRR lies in its ability to reflect subtle changes in blood parameters that may not be easily detected when analyzing HGB or RDW independently. By combining HGB and RDW into a ratio, HRR assesses the severity of the disease and the prognosis of patients. It has been proven to be associated with various diseases, adverse outcomes, and poor prognosis, such as tumors, cardiovascular diseases, and kidney diseases [17–19]. However, current research on the relationship between HRR and bone health in the elderly is lacking, thereby, this paper explores the relationship between HRR and bone density in the elderly.

Methods

Study Population

Data pertaining to all participants were sourced from the National Health and Nutrition Examination Survey (NHANES), which seeks to evaluate the nutritional and health status of the general US populace through a cross-sectional methodology. The study was approved by the Ethics Review Board and all participants signed a written informed consent form.

This study extracted data from the NHANES for the years 2007–2018, the NHANES 2011–2012 and NHANES 2015–2016 cycles were not included in the analysis due to the lack of femoral BMD data. The inclusion criteria were as follows: (1) elderly patients aged > 50 years; (2) participants with complete BMD and blood indicator data; (3) participants with complete covariate data.

Measurement of BMD and definition of osteoporosis

Dual-energy X-ray Absorptiometry (DXA) is the most widely accepted method for measuring BMD, partly due to its speed, ease of use, and low radiation exposure. DXA scanning of the proximal femur was conducted at the NHANES Mobile Examination Center (MEC) during the years 2007 to 2010, 2013–2014, and 2017–2018. DXA exams are performed using a Hologic densitometer and are performed by trained and certified radiologic technicians.

NHANES classifies participants into osteoporotic and non-osteoporotic groups based on different criteria for femoral BMD. Participants with a T-score of less than −2.5 standard deviations for total femur BMD, femoral neck BMD, trochanter BMD, and intertrochanteric BMD are defined as having osteoporosis. The T-score of participants was calculated using a reference group of non-Hispanic white women aged 20 to 29 years, as recommended by the World Health Organization [20]. The T-score calculation formula is T-Score = (Individual BMD - Average normal BMD) / Standard deviation. (Details are provided in Supplementary Table 1)

HRR calculations

HRR is derived from the complete blood count test by dividing HGB by RDW. As a ratio of these two hematologic parameters, HRR is dimensionless, meaning it lacks any specific physical unit. In this study, HRR was analyzed both as a continuous and categorical variable. For the continuous analysis, the effect of each 1-unit increase in HRR was evaluated to determine its impact on the prevalence of osteoporosis and BMD. Additionally, HRR was categorized into quartiles: Q1 (0.308 to 0.969), Q2 (0.969 to 1.064), Q3 (1.064 to 1.159), and Q4 (1.159 to 1.642), with Q1 serving as the reference group. This approach was employed to comprehensively explore the association between HRR and skeletal health indicators, offering both linear and categorical insights into its potential predictive value.

Covariates

When considering the impact of various factors on bone metabolism, this study conducted a comprehensive analysis incorporating multiple covariates. Data collected and analyzed included age, sex, race, body mass index (BMI), educational level, marital status, poverty income ratio (PIR), smoking, serum calcium levels, physical activity, diabetes, and hypertension. Regarding smoking status, individuals with a total lifetime smoking quantity of less than 100 cigarettes were classified as nonsmokers. Physical activity assessment was based on the International Physical Activity Questionnaire, which includes leisure time, work, and travel activities, aiming to comprehensively assess an individual's level of physical activity. The metabolic equivalent (MET) value was calculated using the formula: MET value (minutes/week)=MET intensity of each activity × frequency per week × duration of each activity. Individuals with a MET value lower than 600 min/week were defined as having insufficient physical activity [21].

Statistical methods

This study compiled data from four NHANES survey cycles, focusing on participants over the age of 50 with complete data; thus, individuals with missing covariate data were excluded from the final analysis. Weighted univariate and multivariate linear regression models were used to evaluate the association between HRR and femoral BMD, adjusting models for different covariates included. Additionally, restricted cubic spline (RCS) analysis was utilized to further characterize the relationship between HRR and femoral BMD. Moreover, the association between HRR and osteoporosis was assessed using weighted univariate and logistic regression, with RCS regression exploring the relationship between HRR and osteoporosis. Finally, subgroup analysis was conducted using stratification factors for validation, including age, sex, BMI, smoking status, hypertension, and diabetes. All analyses were performed using R software (version 4.2.3), with statistical significance set at $P<0.05$.

Results

Participant selection and baseline characteristics

The participant selection flowchart is depicted in Fig. 1. Ultimately, 7419 individuals aged≥50 years were included in the final analysis. Baseline characteristics of the participants, according to the quartiles of HRR, are presented in Supplementary Table 2 and the weighted baseline information is available in Supplementary Table 3. The results indicated that higher levels of HRR were associated with higher femoral BMD and a lower proportion of osteoporosis in the higher HRR level group.

Association between HRR and BMD

The association between HRR and femoral BMD is presented in Table 1. Weighted linear regression analysis demonstrated a positive correlation between HRR and femoral BMD in the univariate regression analysis of Model 1. After adjusting for various covariates, Models 2 and 3 demonstrated that this positive correlation remained stable. Moreover, when HRR was categorized into four levels from a continuous variable, higher levels of HRR showed a more significant association with femoral BMD compared to lower levels. RCS analysis revealed a linear positive relationship between HRR and femoral BMD (Fig. 2), enhancing our understanding of HRR as a potential marker for assessing skeletal health in the elderly.

Adjusted for age, sex, BMI, race, educational level, PIR, marital status, smoking status, activity status, hypertension, calcium, diabetes.

Association between HRR and osteoporosis

To further strengthen the link between HRR and skeletal indicators, this study employed weighted univariate and multivariate logistic regression analysis to assess the association between HRR and osteoporosis (Table 2). The results demonstrated a negative correlation between HRR and osteoporosis across all models. In Model 1, each 1-unit increase in HRR was associated with a significantly reduced prevalence of osteoporosis (OR=0.07, 95% CI: 0.04–0.11). This negative association persisted after adjusting for covariates in Model 2 (OR=0.18, 95% CI: 0.10–0.32) and Model 3 (OR=0.25, 95% CI: 0.12–0.51). The analysis of HRR as a categorical variable (Q1-Q4) was consistent with the main analysis results. RCS analysis evaluated the relationship between HRR and osteoporosis and found a linear negative correlation between HRR and osteoporosis (Fig. 3).

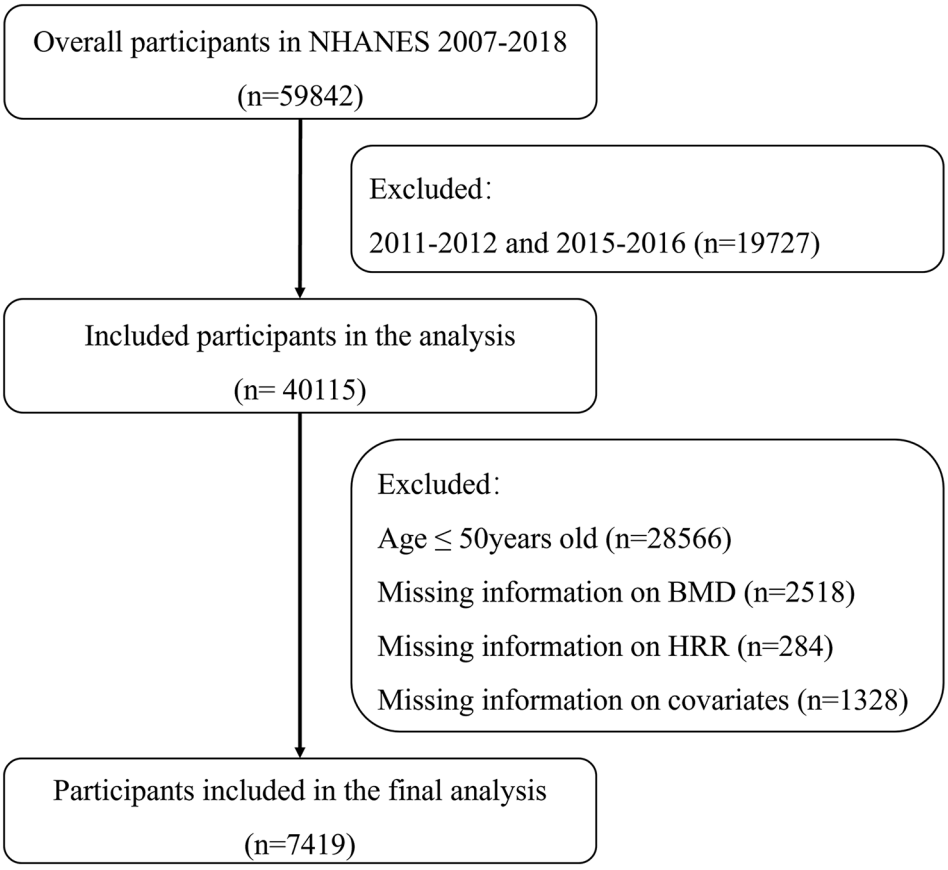

Fig. 1 Participant inclusion process

Model 3: Adjusted for age, sex, BMI, race, educational level, PIR, marital status, smoking, activity status, hypertension, calcium, diabetes.

Adjusted for age, sex, BMI, race, educational level, PIR, marital status, smoking, activity status, hypertension, calcium, diabetes.

Subgroup Analysis of HRR with osteoporosis

Subgroup analysis was performed to assess the potential effects of the relationship between HRR and the prevalence of osteoporosis (Fig. 4). Stratifying factors such as age, sex, BMI, smoking status, hypertension, and diabetes, the analysis showed an independent negative correlation between HRR and the prevalence of osteoporosis across different subgroups after adjusting for all covariates, with no significant interaction between subgroup characteristics. These results further strengthen the value of HRR as an important marker for assessing skeletal health.

Additivity analysis

To further enhance the reliability of the research findings, this study conducted additional analyses to explore the relationship of HGB and RDW with BMD. The results, as shown in Supplementary Table 4, indicate that HGB is positively correlated with BMD, while RDW is negatively correlated with BMD, with effect sizes lower than those of HRR. Additionally, Supplementary Fig. 1 presents the ROC analysis results for HRR, with an AUC value of 0.6040, indicating that HRR offers valuable supplementary insights into blood health status in osteoporosis. Finally, the association between HRR and population mortality was further examined. The results of Supplementary Table 5 indicate that high levels of HRR are associated with low mortality rates, further supporting HRR as an important indicator of health status.

Discussion

This study utilizes NHANES data to investigate the link between HRR and skeletal health in the elderly. To our knowledge, this is the first study to explore the connection between HRR and BMD. The results of this study found a significant positive linear correlation between HRR and femoral BMD in older adults over the age of 50 in the United States. Concurrently, lower levels of HRR are associated with an increased prevalence of osteoporosis, underscoring HRR as a vital marker for assessing bone health. Compared to traditional full-blood indices

Table 1 The relationship between HRR and femur BMD (g/cm^2)

		Model 1 β (95%CI) *P*-value	Model 2 β (95%CI) *P*-value	Model 3 β (95%CI) *P*-value
Total femur BMD	HRR	0.21 (0.17, 0.24) < 0.001	0.05 (0.02, 0.08) 0.003	0.06 (0.03, 0.09) < 0.001
	Q1	[Reference]	[Reference]	[Reference]
	Q2	0.01 (0.00, 0.03) 0.082	0.00 (-0.01, 0.02) 0.700	0.01 (-0.01, 0.02) 0.400
	Q3	0.04 (0.03, 0.06) < 0.001	0.01 (0.00, 0.02) 0.067	0.02 (0.00, 0.03) 0.013
	Q4	0.08 (0.07, 0.10) < 0.001	0.02 (0.00, 0.03) 0.021	0.02 (0.01, 0.04) 0.002
	P for trend	< 0.001	0.008	< 0.001
Femoral neck BMD	HRR	0.13 (0.10, 0.15) < 0.001	0.03 (0.01, 0.06) 0.007	0.04 (0.01, 0.06) 0.003
	Q1	[Reference]	[Reference]	[Reference]
	Q2	0.00 (-0.01, 0.02) 0.600	-0.01 (-0.02, 0.00) 0.200	0.00 (-0.01, 0.01) > 0.900
	Q3	0.02 (0.01, 0.04) < 0.001	-0.01 (-0.02, 0.00) 0.600	0.01 (0.00, 0.03) 0.070
	Q4	0.05 (0.04, 0.06) < 0.001	0.00 (-0.02, 0.01) 0.600	0.02 (0.00, 0.03) 0.017
	P for trend	< 0.001	0.800	0.005
Trochanter BMD	HRR	0.17 (0.14, 0.20) < 0.001	0.04 (0.02, 0.07) 0.002	0.04 (0.02, 0.07) 0.001
	Q1	[Reference]	[Reference]	[Reference]
	Q2	0.01 (0.00, 0.02) 0.032	0.01 (-0.01, 0.02) 0.400	0.01 (0.00, 0.02) 0.200
	Q3	0.03 (0.02, 0.05) < 0.001	0.01 (0.00, 0.03) 0.061	0.01 (0.00, 0.03) 0.039
	Q4	0.07 (0.06, 0.08) < 0.001	0.02 (0.00, 0.03) 0.013	0.02 (0.01, 0.03) 0.005
	P for trend	< 0.001	0.005	0.002
Intertrochanter BMD	HRR	0.24 (0.19, 0.28) < 0.001	0.05 (0.01, 0.09) 0.022	0.07 (0.03, 0.10) < 0.001
	Q1	[Reference]	[Reference]	[Reference]
	Q2	0.01 (0.00, 0.03) 0.011	0.00 (-0.02, 0.02) 0.800	0.01 (-0.01, 0.02) 0.400
	Q3	0.04 (0.03, 0.06) < 0.001	0.01 (0.01, 0.03) 0.200	0.02 (0.00, 0.03) 0.025
	Q4	0.09 (0.08, 0.11) < 0.001	0.02 (0.00, 0.04) 0.052	0.03 (0.01, 0.05) 0.002
	P for trend	< 0.001	0.027	< 0.001

HRR: Hemoglobin to Red cell distribution width Ratio; OR: Odds Ratio; CI: Confidence Interval;

Model 1: No covariates adjusted

Model 2: Adjusted for age, sex, and race

Model 3: Adjusted for age, sex, BMI, race, educational level, PIR, marital status, smoking status, activity status, hypertension, calcium, diabetes

such as HGB or RDW, HRR offers a more comprehensive perspective, demonstrating greater predictive value.

HRR is highlighted as a novel inflammatory marker, known for its non-invasiveness, ease of acquisition, and cost-effectiveness, offering broad prospects for clinical implementation. The positive correlation between HRR and femoral BMD could be attributed to several factors. Previous studies have shown that higher levels of HGB have a protective effect on bone quality in the elderly [10]. Additionally, individuals with higher HGB levels may exhibit better physical capability and endurance, as their muscles receive more oxygen and nutrients. Regular weight training and other forms of physical activity have been proven to increase BMD [22, 23]. Furthermore, an increase in HRR could relate to an overall improvement in nutritional status, essential for maintaining BMD [24]. Improved blood circulation enhances the nutritional supply to the bones, such as calcium, phosphorus, and vitamin D, vital for bone health [25, 26].

The association between lower levels of HRR and an increased prevalence of osteoporosis further strengthens the argument for a positive correlation between HRR and BMD. As another critical component of HRR, RDW has been closely linked to various adverse health conditions, including chronic inflammation, oxidative stress, and malnutrition [27–29]. Chronic inflammation is widely regarded as a key factor leading to osteoporosis, where inflammation promotes bone tissue resorption and inhibits new bone formation, resulting in reduced BMD [30, 31]. On the other hand, the pathogenesis of osteoporosis is multifaceted, involving aging, oxidative stress, inflammation, and other factors that collectively impact bones, leading to decreased density and increased fragility, thereby elevating fracture risk. Lower levels of HRR may also reflect the presence of chronic diseases or systemic inflammation, which could further increase the prevalence of osteoporosis. Based on our findings, effectively raising HGB levels or reducing RDW could

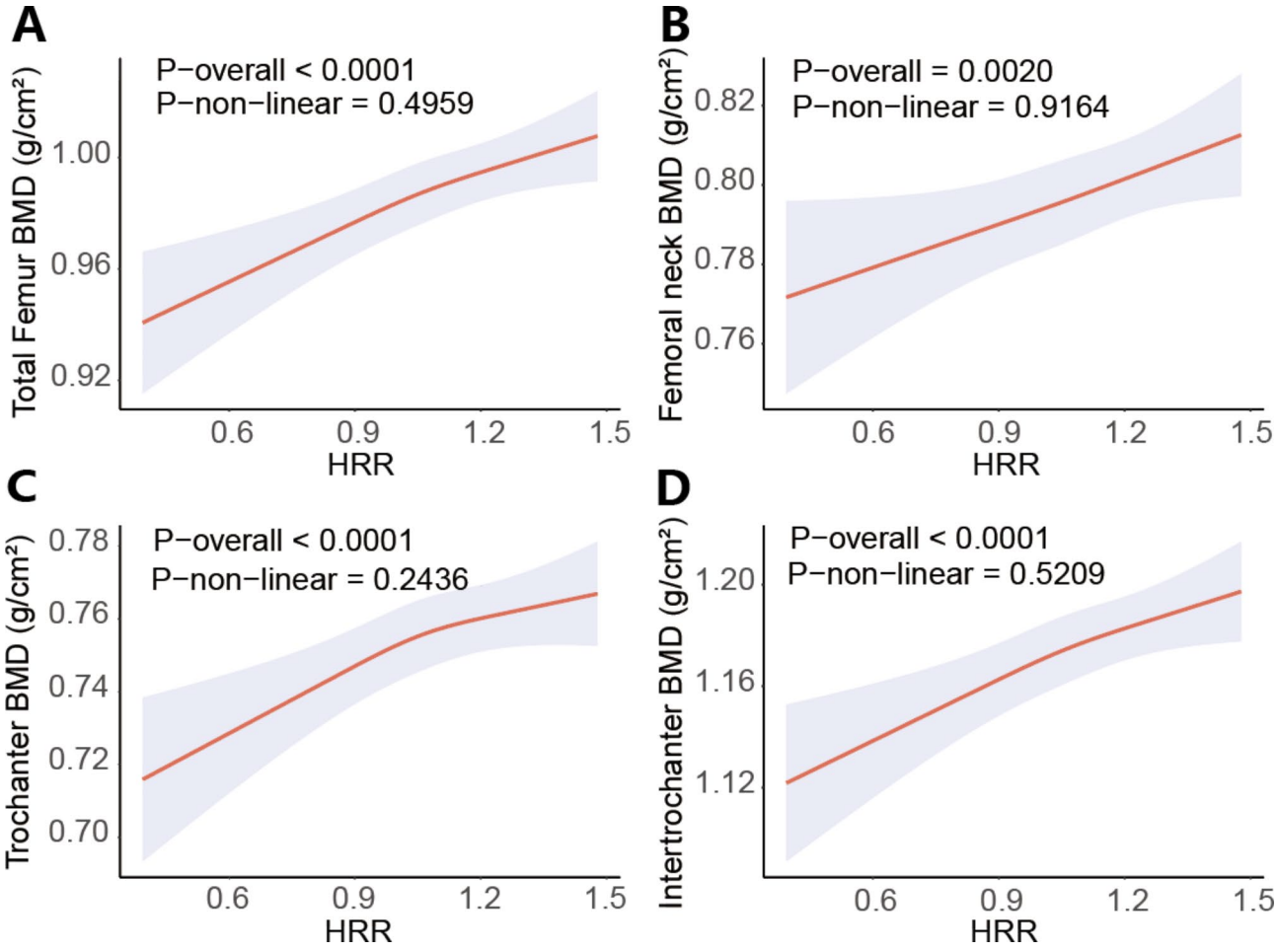

Fig. 2 RCS regression analysis of HRR with BMD

Table 2 The relationship between HRR and osteoporosis

	Model 1 OR (95%CI) *P*-value	Model 2 OR (95%CI) *P*-value	Model 3 OR (95%CI) *P*-value
HRR	0.07 (0.04, 0.11) < 0.001	0.18 (0.10, 0.32) < 0.001	0.25 (0.12, 0.51) < 0.001
Q1	[Reference]	[Reference]	[Reference]
Q2	0.72 (0.55, 0.95) 0.021	0.82 (0.62, 1.08) 0.200	0.88 (0.66, 1.18) 0.400
Q3	0.50 (0.38, 0.66) < 0.001	0.64 (0.48, 0.85) 0.002	0.71 (0.52, 0.97) 0.032
Q4	0.27 (0.20, 0.38) < 0.001	0.49 (0.35, 0.70) < 0.001	0.54 (0.38, 0.77) < 0.001
P for trend	< 0.001	< 0.001	< 0.001

HRR: Hemoglobin to Red cell distribution width Ratio; OR: Odds Ratio; CI: Confidence Interval;

Model 1: No covariates adjusted;

Model 2: Adjusted for age, sex, and race;

significantly enhance HRR levels, a strategy of substantial importance for preventing and delaying the progression of osteoporosis.

In summary, HRR reflects inflammation, oxidative stress and nutritional status, which play key roles in bone metabolism and osteoporosis. Higher HRR may suggest healthier blood status and promote balanced bone metabolism, while lower HRR may be associated with chronic inflammation and malnutrition, increasing the prevalence of osteoporosis. The findings of this study provide a new perspective on the use of HRR in bone health assessment, and further validation of these associations and in-depth exploration of the specific biological mechanisms are needed.

This study offers several key advantages. First, the sample size, derived from the NHANES database, is sufficiently large and representative, due to the appropriate use of weights. Second, the correlation between HRR

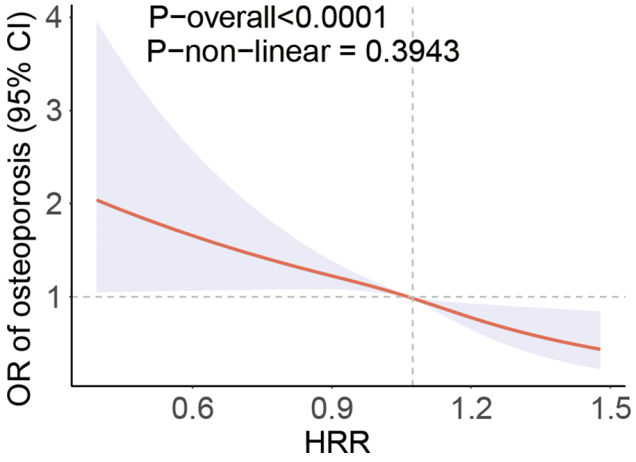

Fig. 3 RCS regression analysis of HRR with osteoporosis

and the prevalence of osteoporosis was consistently confirmed through subgroup and sensitivity analyses. However, the primary limitation of this study is its observational design, which limits our ability to establish causality. Only participants with a complete dataset were included in this study, which may have led to selective bias, as individuals with missing data may have differed from the included sample in areas such as health status. Additionally, because the study population included individuals over the age of 50, the findings are only applicable to this specific age group. Although we adjusted for multiple confounders, there may still be unmeasured confounders, and future studies should utilize a prospective design and more comprehensive data collection to further explore the relationship between HRR, BMD, and osteoporosis and to validate our findings.

Conclusion

HRR may serve as one of the potential indicators for evaluating BMD and assessing the prevalence of osteoporosis in the elderly. Elevating HRR levels may play a crucial role in the prevention and slowing of osteoporosis progression.

Abbreviations

BMD	Bone Mineral Density
BMI	Body Mass Index
CBC	Complete Blood Cell Count
CI	Confidence Interval
HGB	Hemoglobin
HRR	Hemoglobin-to-Red Cell Distribution Width Ratio
MET	Metabolic Equivalent
OR	Odds Ratio
PIR	Poverty Income Ratio
RDW	Red Cell Distribution Width

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-024-07984-z.

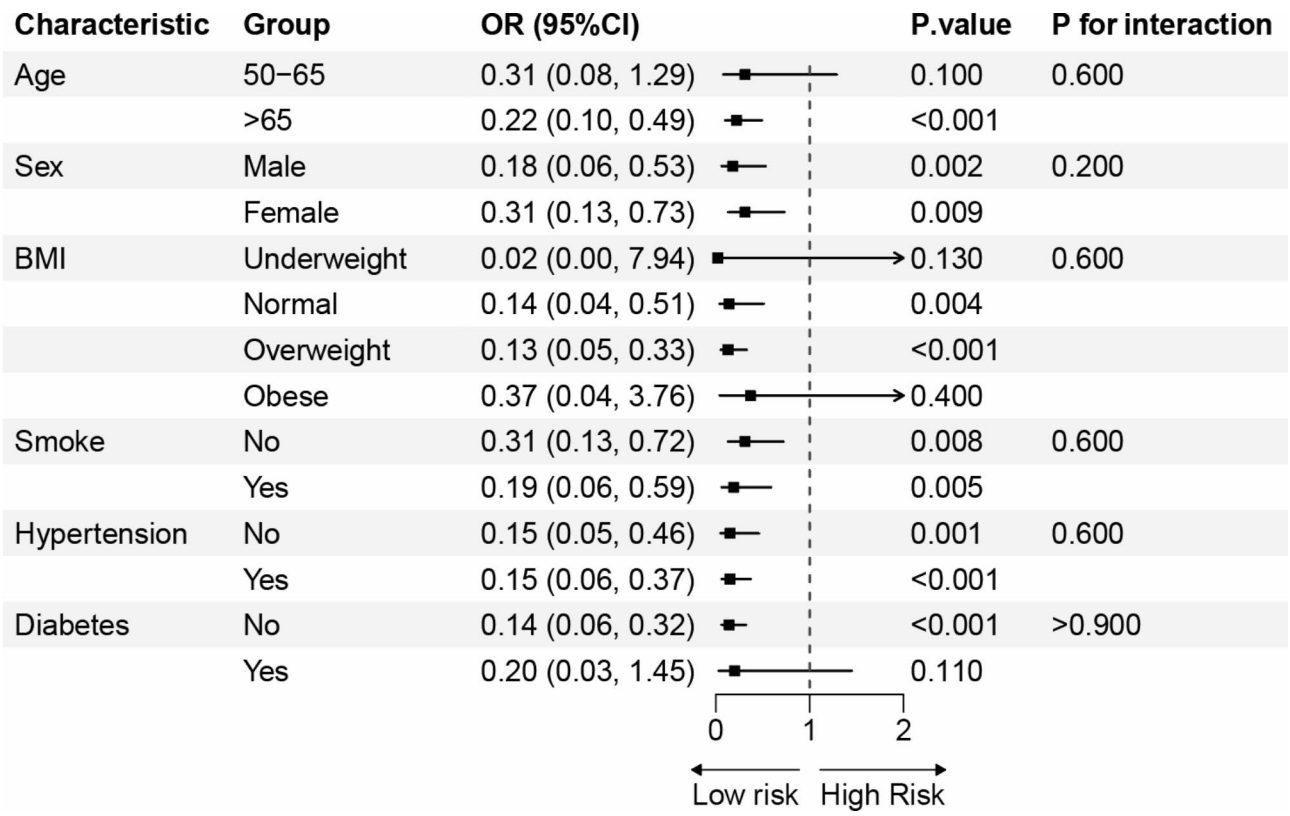

Fig. 4 Subgroup analysis of the association between HRR and the prevalence of osteoporosis

Supplementary Material 1

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Author contributions
ZJ, HL and JL conceived the idea and planned the study. YX, HP and RH analyzed the data. YX and HP performed the literature search. YX and RH wrote the paper. PW, CP, JL, JW and ZW made the critical revision of the paper. All authors have contributed significantly to the manuscript to be published.

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Data availability
The National Health and Nutrition Examination Survey dataset is publicly available at the National Center for Health Statistics of the Center for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/nhanes_products.htm).

Declarations

Ethics approval and consent to participate
NHANES is conducted by the Centers for Disease Control and Prevention and the National Center for Health Statistics. The National Center for Health Statistics Research Ethics Review Committee reviewed and approved the NHANES study protocol. All participants signed written informed consent. NAHNES is a de-identified database, and this study used publicly available secondary data analyses; therefore, it did not involve a direct request for ethical approval.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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