▪ Headache Medicine 2026, v. 17, n. 2 ▪ p. 139-149 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2026.17

Original

The platelet-to-HDL ratio as a novel integrative biomarker for migraine: insights from NHANES and CHARLS

Qi-Wei Lin[1], Yun-Dong-Xu Xiao[2], Yu-Ying Jing[3], Wen-Bin Lu[1]

[1]Integrated Traditional Chinese and Western Medicine Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China
[2]Peking University Health Science Center, Haidian, Beijing, China
[3]North Anhui Health Vocational College, Suzhou, Anhui, China

Wen-Bin Lu
wenbin526@163.com
Edited by:
Marcelo Moraes Valença

Abstract

Background
Systemic inflammation is widely recognized as a driver of migraine pathophysiology, yet the integrative role of coagulation and lipid metabolism remains poorly defined. We evaluated the Platelet-to-High-Density Lipoprotein Ratio (PHR), a novel biomarker representing the balance between pro-thrombotic activity and vascular protection, to determine its association with migraine prevalence in two large national cohorts.

Methods
We conducted cross-sectional analyses using data from the National Health and Nutrition Examination Survey (NHANES 1999–2004, n=4,764) and the China Health and Retirement Longitudinal Study (CHARLS 2015, n=10,790). Migraine status was identified through validated self-report modules in both databases. Multivariable logistic regression and restricted cubic spline (RCS) models were applied to assess both linear and non-linear dose–response patterns after adjusting for potential socio-demographic and metabolic confounders.

Results
In the NHANES cohort, higher PHR was independently associated with increased odds of migraine, exhibiting a consistent linear trend (adjusted OR = 1.001 per 1-unit increase, 95% CI: 1.000–1.002; P = 0.014). Although the linear association was not statistically significant in the CHARLS cohort (P = 0.074), RCS analysis revealed a robust U-shaped relationship (Wald χ^2 for non-linearity = 13.95, P = 0.0009). This suggests that both low and high extremes of the PHR index are linked to elevated migraine prevalence in the Chinese population.

Conclusion
PHR is significantly associated with migraine status in both US and Chinese populations, though the specific dose–response morphology appears to be sensitive to population characteristics. These findings highlight the importance of considering non-linear modeling when evaluating inflammatory biomarkers and suggest that PHR may serve as a cost-effective tool for risk stratification in diverse clinical settings.

Keywords
Migraine disorders
Platelet-to-HDL ratio
Inflammation
Cross-sectional studies
Dose-response relationship

Received: March 26, 2026
Revised: April 13, 2026
Accepted: June 17, 2026

© Copyright 2026

Introduction

Migraine is no longer viewed as a mere episodic headache disorder but is increasingly recognized as a leading cause of global disability, affecting over one billion individuals worldwide (1,2). While the classic pathophysiology centers on trigeminovascular activation and the release of vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP) (3,4), emerging evidence suggests that migraine is a complex systemic condition rooted in chronic low-grade inflammation and endothelial perturbation (5). These systemic processes are not only pivotal during the ictus of an attack but also contribute to the long-term risk of cardiovascular and cerebrovascular complications, particularly in individuals with migraine with aura (6).

The search for reliable, accessible biomarkers has led to the exploration of several composite inflammatory indices derived from routine hematological parameters. Markers such as the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune-inflammation index (SII) have been widely investigated for their ability to reflect cellular immune activation in various neurological conditions (7–9). However, these indices primarily capture the leukocytic response and often overlook the intricate interplay between thrombotic activity, lipid metabolism, and vascular homeostasis—a triadic relationship that is increasingly defined as the "metabolic face" of migraine (10,11). Recent research indicates that migraineurs frequently exhibit platelet hyperreactivity and abnormal lipid profiles, characterized by altered levels of high-density lipoprotein cholesterol (HDL-C), which possesses potent antioxidant and anti-inflammatory properties (12–14).

The Platelet-to-HDL Ratio (PHR) has recently emerged as a novel, integrative biomarker that bridges these pathological pathways. By combining the absolute platelet count—a surrogate for pro-thrombotic and pro-inflammatory signaling—with HDL-C levels, PHR reflects the systemic balance between vascular injury and protection. Platelets are central to neurogenic inflammation, acting as primary reservoirs for serotonin (5-HT) and a diverse array of cytokines that can sensitize the trigeminal nerves (15). Conversely, HDL-C promotes endothelial health by facilitating cholesterol efflux and inhibiting the oxidation of low-density lipoproteins (LDL) (16). Although PHR has demonstrated significant prognostic value in coronary artery disease and ischemic stroke, its potential utility in the context of migraine has remained virtually unexplored (17,18).

Furthermore, existing neuro-epidemiological studies often rely on linear modeling, which may fail to capture the biological complexity inherent in metabolic-inflammatory transitions. Given that the underlying physiological landscape of migraine may vary significantly across different life stages and ethnic backgrounds, it is unclear whether the association between PHR and migraine exhibits population-specific heterogeneity or non-linear dose–response patterns (19–21). To address these critical knowledge gaps, we utilized data from two large-scale, nationally representative cohorts: the National Health and Nutrition Examination Survey (NHANES) in the United States and the China Health and Retirement Longitudinal Study (CHARLS) in China. By comparing a young-to-middle-aged Western population with an older Eastern population, this study aims to clarify the association between PHR and migraine prevalence while specifically investigating the necessity of non-linear modeling in characterizing these diverse clinical phenotypes (22,23).

Methods

Data sources and study population

This comparative cross-sectional study utilized data from two large-scale, nationally representative databases: the NHANES in the United States and the CHARLS in China. NHANES, conducted by the National Center for Health Statistics (NCHS), employs a complex, multistage, probability sampling design to assess the health and nutritional status of the non-institutionalized U.S. population. To ensure sufficient statistical power and a stable migraine prevalence estimate, we pooled data from three consecutive NHANES cycles (1999–2000, 2001–2002, and 2003–2004). For the Chinese cohort, we utilized Wave 3 (2015) of the CHARLS database, a longitudinal survey of individuals aged 45 and older (and their spouses) across 150 counties and 450 villages in China, managed by Peking University. Both surveys received approval from their respective institutional ethics review boards, and written informed consent was obtained from all participants prior to data collection.

Participant selection and exclusion criteria

The initial sampling frames consisted of 31,126 individuals from NHANES and 21,095 from CHARLS. To focus on the adult population and minimize developmental physiological noise, we excluded participants aged under 20 years (n=15,794 for NHANES; n=3 for CHARLS). Further exclusion criteria were applied to ensure data integrity: (1) individuals with missing or incomplete migraine status information (n=11 for NHANES; n=1,403 for CHARLS); and (2) participants lacking data for the primary exposure (platelet count and HDL-C) or essential covariates (n=10,557 for NHANES; n=8,899 for CHARLS). After these stringent filters, the final analytic sample comprised 4,764 participants in the NHANES cohort and 10,790 in the CHARLS cohort. The detailed selection process is visualized in the study flow diagram (Figure 1).

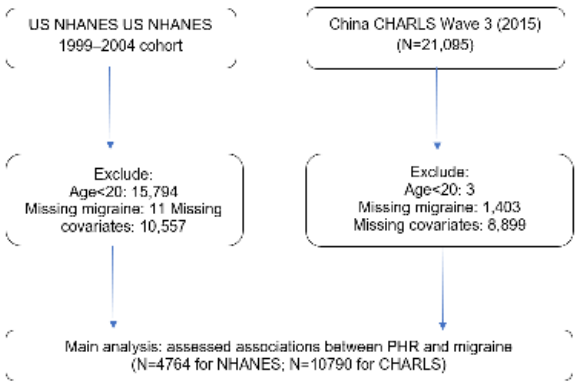


Figure 1. Flow diagram of participant inclusion and exclusion for NHANES (1999–2004) and CHARLS (2015). Flow diagram illustrating the inclusion and exclusion criteria for study participants. From the initial 31,126 individuals in NHANES (1999–2004) and 21,095 in CHARLS Wave 3 (2015), participants were excluded if they were under 20 years of age, had missing migraine status, or lacked essential data for primary covariates. The final analysis included a total of 4,764 participants from NHANES and 10,790 from CHARLS. NHANES, National Health and Nutrition Examination Survey; CHARLS, China Health and Retirement Longitudinal Study.

Assessment of migraine and inflammatory indices

Migraine status was determined through standardized, validated survey modules unique to each database. In NHANES, participants were classified as having migraine if they responded "yes" to the Miscellaneous Pain Questionnaire item (MPQ090), which specifically asks whether the respondent had experienced "severe headaches or migraines" during the preceding three months. In the CHARLS cohort, migraine-related pain was identified through the physical health and pain module. Respondents were asked to identify specific body regions affected by pain; those who explicitly reported headache pain were categorized as the migraine group.

The primary exposure, the PHR, was calculated as the absolute platelet count divided by the HDL-C concentration. Platelet counts were measured using automated hematology analyzers, and HDL-C levels were determined via direct enzymatic methods in standardized laboratories. To contextualize the performance of PHR, we also calculated a suite of auxiliary inflammatory indices, including the SII, systemic inflammation response index (SIRI), NLR, and platelet-to-lymphocyte ratio (PLR), based on standard leukocyte differential counts.

Selection of covariates

Potential confounders were selected a priori based on their documented associations with both systemic inflammation and migraine pathophysiology. Demographic variables included age, sex, ethnicity (in NHANES), and marital status. Physiological and lifestyle metrics comprised body mass index (BMI), smoking status, and alcohol consumption. Clinical comorbidities, specifically hypertension and diabetes, were defined using a stringent combination of self-reported physician diagnoses, the use of anti-hypertensive or hypoglycemic medications, and laboratory confirmation (e.g., blood pressure measurements or HbA1c levels). Laboratory-based covariates further included C-reactive protein (CRP), white blood cell (WBC) counts, and a full lipid panel (triglycerides, total cholesterol, and LDL-C) to adjust for baseline metabolic status.

Statistical analysis

All statistical analyses were conducted using R software (Version 4.3.2), with full consideration of the complex survey designs. For the NHANES cohort, we integrated specialized sampling weights (WTMEC2YR), strata (SDMVSTRA), and primary sampling units (SDMVPSU) to ensure the findings were generalizable to the U.S. population. Similarly, CHARLS weights were applied to the Chinese cohort to account for non-response and the multi-stage sampling approach.

Baseline characteristics were compared using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical data. We constructed multivariable logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals (CIs). To explore potential non-linear dynamics, restricted cubic spline (RCS) models were implemented in the CHARLS cohort, with four knots strategically positioned at the 5th, 35th, 65th, and 95th percentiles of the PHR distribution. This approach allows for the visualization of dose-response relationships and the detection of non-linearity through Wald χ^2 statistics. A two-sided P-value < 0.05 was considered statistically significant for all tests.

Results

Baseline characteristics of the study populations

The study flowchart (Figure 1) delineates the selection process, resulting in a final analytical sample of 4,764 participants from the NHANES (1999–2004) and 10,790 from the CHARLS (2015). These two cohorts represent distinct demographic landscapes: a young-to-middle-aged Western population and an older Eastern population, providing a robust basis for cross-cultural comparison. To further characterize demographic differences between cohorts, age distributions were visualized using cohort-specific histograms (Figure 2). The NHANES analytic sample showed a broader adult age distribution, whereas the CHARLS sample was concentrated among middle-aged and older adults, consistent with the original CHARLS sampling framework.

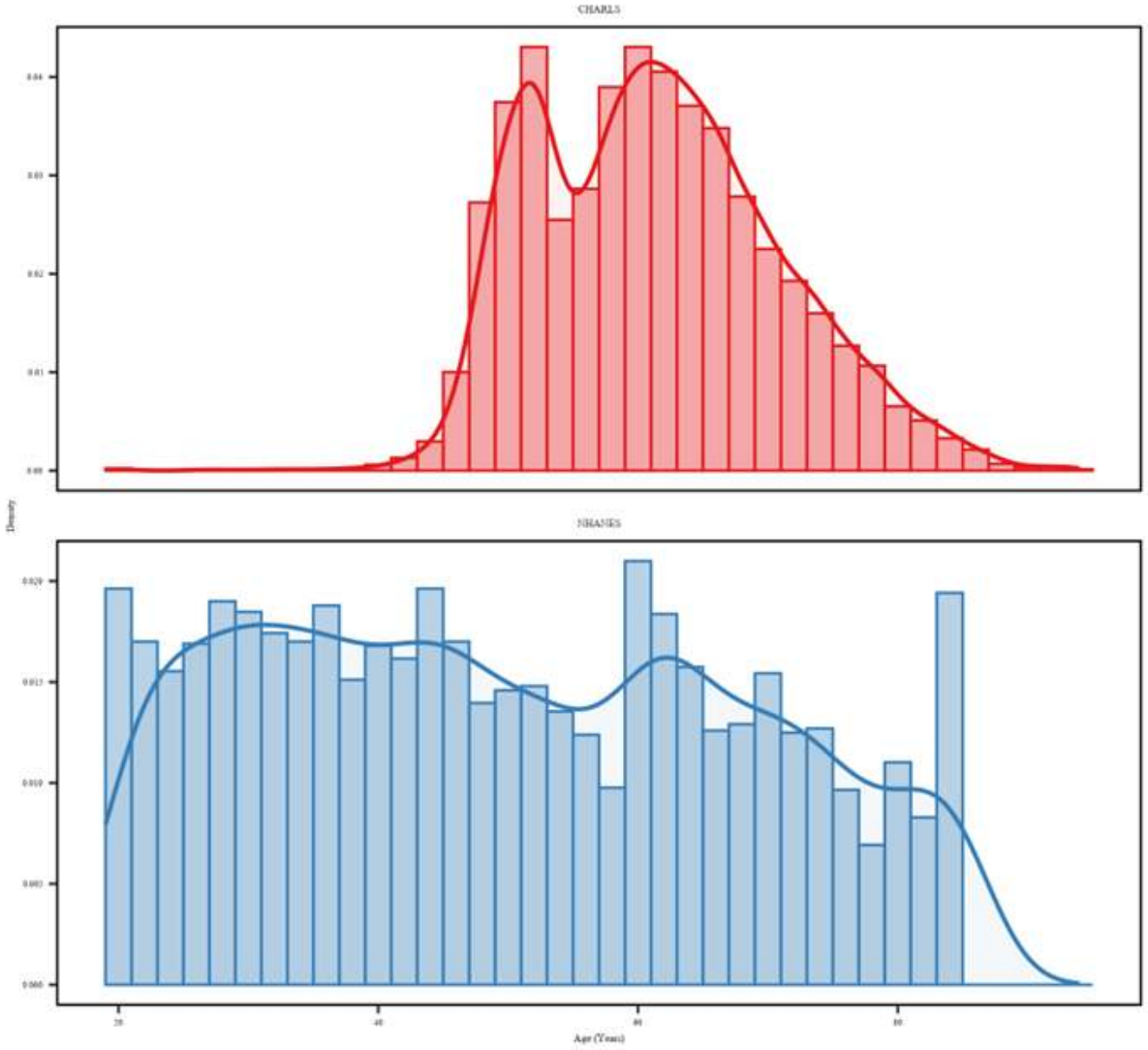


Figure 2. Age distributions of participants in the NHANES and CHARLS cohorts. The upper panel presents the age distribution of the CHARLS Wave 3 analytic sample, and the lower panel presents the age distribution of the pooled NHANES 1999–2004 analytic sample. Histograms were constructed using 2-year age bins and overlaid with kernel density curves. CHARLS participants were concentrated among middle-aged and older adults, whereas NHANES participants showed a broader adult age distribution. CHARLS, China Health and Retirement Longitudinal Study; NHANES, National Health and Nutrition Examination Survey.

Table 1 details the baseline characteristics of the NHANES cohort. In the U.S. population, individuals with migraine (n=934) were significantly younger than their non-migraine counterparts, with a median age of 42.0 vs. 51.0 years (P < 0.001). Female predominance was starkly evident, with women accounting for 74.7% of the migraine group compared to 50.6% in the non-migraine group (P < 0.001). Socioeconomic disparities were also observed; migraineurs tended to have lower poverty-income ratios (PIR) [median 1.87 vs. 2.62, P < 0.001] and lower education levels (P < 0.001). Regarding laboratory profiles, the migraine group demonstrated a heightened systemic inflammatory tone, characterized by significantly elevated CRP (0.26 vs. 0.23 mg/dl, P = 0.003), neutrophil counts (3.90 vs. 3.80 *10^3/μL, P = 0.008), and platelet counts (262.00 vs. 253.00 *10^3/μL, P < 0.001). Interestingly, while total cholesterol and HDL-C levels did not differ significantly, LDL-C was nominally lower in the migraine group (3.00 vs. 3.08 mmol/L, P = 0.043).

Table 1. Baseline characteristics of NHANES participants

Variable	Category	No Migraine	Migraine	P-value
N		3830	934	
Age		51.00 (35.00–67.00)	42.00 (31.00–54.00)	**<0.001**
Gender	Female	1816 (47.4%)	614 (65.7%)	**<0.001**
	Male	2014 (52.6%)	320 (34.3%)	
BMI, kg/m²		26.99 (23.91–30.95)	27.74 (23.93–31.88)	**0.006**
Ethnicity	Mexican American	820 (21.4%)	234 (25.1%)	**0.014**
	Non-Hispanic Black	670 (17.5%)	172 (18.4%)	
	Non-Hispanic White	2108 (55.0%)	458 (49.0%)	
	Other Hispanic	145 (3.8%)	42 (4.5%)	
	Other Race - Including Multi-Racial	87 (2.3%)	28 (3.0%)	
Education	High school	1422 (37.1%)	419 (44.9%)	**<0.001**
	Less than high school	546 (14.3%)	143 (15.3%)	
	More than high school	1862 (48.6%)	372 (39.8%)	
Marriage	Married/living with partner	2465 (64.4%)	620 (66.4%)	**0.041**
	Never married	547 (14.3%)	148 (15.8%)	
	Widowed/divorced/separated	818 (21.4%)	166 (17.8%)	
Hypertension	No	2888 (75.4%)	764 (81.8%)	**<0.001**
	Yes	942 (24.6%)	170 (18.2%)	
Diabetes	No	3508 (91.6%)	863 (92.4%)	0.462
	Yes	322 (8.4%)	71 (7.6%)	
Smoke	No	1932 (50.4%)	485 (51.9%)	0.437
	Yes	1898 (49.6%)	449 (48.1%)	
Alcohol	No	1110 (29.0%)	317 (33.9%)	**0.003**
	Yes	2720 (71.0%)	617 (66.1%)	
PIR		2.62 (1.34–4.52)	1.87 (1.07–3.63)	**<0.001**
CRP, mg/dl		0.23 (0.09–0.50)	0.26 (0.11–0.62)	**0.003**
NEU, *10³/μL		3.80 (3.00–4.80)	3.90 (3.00–5.10)	**0.008**
LYM, *10³/μL		1.80 (1.50–2.30)	1.90 (1.60–2.30)	**<0.001**
MONO, *10³/μL		0.50 (0.40–0.60)	0.50 (0.40–0.60)	**0.027**
PLT, *10³/μL		253.00 (214.00–295.00)	262.00 (225.00–313.00)	**<0.001**
TRIGLY, mmol/L		1.34 (0.95–1.93)	1.35 (0.95–2.02)	0.391
TC, mmol/L		5.15 (4.50–5.84)	5.07 (4.50–5.79)	0.128
HDL, mmol/L		1.29 (1.09–1.60)	1.29 (1.09–1.60)	0.878
LDL, mmol/L		3.08 (2.51–3.70)	3.00 (2.48–3.61)	**0.043**

Continuous variables are presented as mean (standard deviation) or median (interquartile range), as appropriate. Categorical variables are presented as n (%), with percentages calculated within each migraine-status group. P-values were calculated using Student's t-test, Mann–Whitney U test, or chi-square test, as appropriate. Bold values indicate statistical significance ($P < 0.05$).

The CHARLS cohort presented a contrasting physiological profile (Table 2). Unlike the NHANES findings, there was no significant age difference between migraineurs and non-migraineurs in this older Chinese population (median age 61.0 years for both, P = 0.78). However, the female predominance remained consistent, with 70.0% of migraineurs being female (P < 0.001). Migraine status in this cohort was associated with a higher burden of metabolic comorbidities, including significantly higher rates of hypertension (32.2% vs. 23.9%) and diabetes (8.2% vs. 6.0%) [all P ≤ 0.001]. Notably, the lipid profile of Chinese migraineurs showed a different pattern from the U.S. cohort, with significantly higher levels of triglycerides (119.47 vs. 114.16 mg/dL, P = 0.02), total cholesterol (183.78 vs. 181.08 mg/dL, P = 0.008), and HDL-C (50.58 vs. 49.81 mg/dL, P = 0.005).

Table 2. Baseline characteristics of CHARLS participants

Variable	Category	No Migraine	Migraine	P-value
N		9138	1652	
Age		61.00 (54.00–68.00)	61.00 (53.00–67.00)	0.780
Gender	Female	4626 (50.6%)	1156 (70.0%)	**<0.001**
	Male	4512 (49.4%)	496 (30.0%)	
BMI, kg/m²		23.68 (21.32–26.22)	23.46 (21.11–26.19)	0.158
Marriage	Married/living with partner	7930 (86.8%)	1378 (83.4%)	**0.001**
	Never married	61 (0.7%)	16 (1.0%)	
	Widowed/divorced/ separated	1147 (12.6%)	258 (15.6%)	
Hypertension	No	6951 (76.1%)	1120 (67.8%)	**<0.001**
	Yes	2187 (23.9%)	532 (32.2%)	
Diabetes	No	8586 (94.0%)	1517 (91.8%)	**0.001**
	Yes	552 (6.0%)	135 (8.2%)	
Smoke	No	5160 (56.5%)	1161 (70.3%)	**<0.001**
	Yes	3978 (43.5%)	491 (29.7%)	
Alcohol	No	2522 (27.6%)	285 (17.3%)	**<0.001**
	Yes	6616 (72.4%)	1367 (82.7%)	
CRP, mg/l		1.40 (0.80–2.60)	1.60 (0.80–2.90)	**<0.001**
WBC, *10³/μL		5.71 (4.80–6.90)	5.64 (4.61–6.93)	0.101
PLT, *10⁹/L		200.00 (159.00–243.00)	201.00 (155.00–246.00)	0.945
TRIGLY, mg/dL		114.16 (82.30–169.03)	119.47 (84.96–172.57)	**0.020**
TC, mg/dL		181.08 (159.46–205.79)	183.78 (162.07–208.59)	**0.008**
HDL, mg/dL		49.81 (42.86–57.53)	50.58 (43.63–58.69)	**0.005**
LDL, mg/dL		100.77 (82.63–119.31)	101.93 (83.01–120.56)	0.258

Continuous variables are expressed as mean (standard deviation) or median (interquartile range), as appropriate. Categorical variables are presented as n (%), with percentages calculated within each migraine-status group. P-values were determined using Student's t-test, Mann–Whitney U test, or chi-square test, as appropriate. Bold values indicate statistical significance (P < 0.05).

Association between inflammatory indices and migraine in NHANES

We conducted a comprehensive evaluation of ten composite inflammatory and lipid-based indices in the NHANES cohort (Table 3). In the univariate analysis, several markers including NHR, PHR, and NMR demonstrated significant associations with migraine prevalence (all $P < 0.05$).

Table 3. Odds ratios for the associations between systemic inflammatory indices and migraine risk in NHANES

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
SII	1.000 (1.000–1.000)	0.186	1.000 (1.000–1.000)	0.782
SIRI	0.949 (0.878–1.026)	0.187	0.982 (0.907–1.063)	0.657
NLR	0.987 (0.931–1.048)	0.674	0.994 (0.934–1.058)	0.845
PLR	1.000 (0.999–1.001)	0.821	1.000 (0.999–1.001)	0.928
PNR	1.001 (0.999–1.003)	0.543	1.000 (0.998–1.002)	0.974
NHR	1.053 (1.010–1.097)	**0.014**	1.040 (0.995–1.087)	0.085
MHR	0.788 (0.557–1.114)	0.178	1.228 (0.854–1.764)	0.267
PHR	1.002 (1.001–1.002)	**<0.001**	1.001 (1.000–1.002)	**0.014**
LHR	1.021 (0.967–1.077)	0.457	1.024 (0.962–1.089)	0.456
NMR	1.045 (1.025–1.065)	**<0.001**	1.008 (0.987–1.030)	0.433

Data are presented as ORs with 95% CIs. Multivariable analysis was adjusted for age, sex, BMI, hypertension, and alcohol consumption.

Table 4. Association between PHR and migraine risk in the China CHARLS cohort

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
PHR	0.990 (0.962–1.019)	0.513	0.973 (0.944–1.003)	0.074

Data are presented as ORs with 95% CIs. Multivariable analysis was adjusted for age, sex, BMI, hypertension, and alcohol consumption

To control for potential confounding factors, we employed multivariable logistic regression models adjusted for age, gender, BMI, hypertension, and alcohol consumption. Following this rigorous adjustment, the PHR emerged as the only index maintaining a stable and independent positive association with migraine (Adjusted OR = 1.001 per 1-unit increase, 95% CI: 1.000–1.002; P = 0.014). Other widely studied immune-inflammatory indices, such as the SII, the SIRI, and the NLR, failed to reach statistical significance in the adjusted models (all $P > 0.05$). This finding highlights the unique utility of PHR in integrating thrombotic activity and lipid-mediated protection within the Western population.

Dose-response relationship and non-linearity in CHARLS

In the CHARLS cohort, the linear association between PHR and migraine status was not statistically significant in either the univariate or the multivariable-adjusted models (Adjusted OR = 0.973, 95% CI: 0.944–1.003; P = 0.074), indicating that a simple linear model might fail to capture the complexity of the biomarker's relationship with the disease in an older demographic (Table 4).

To further explore this potential complexity, we utilized RCS models. As illustrated in Figure 3, the RCS analysis uncovered a robust U-shaped dose-response relationship between PHR and migraine prevalence. The overall association was highly significant (Wald $\chi^2 = 16.76$, df = 3, P = 0.001). Crucially, the non-linear component of the model demonstrated strong statistical significance (Wald $\chi^2 = 13.95$, df = 2, P = 0.001), confirming that the odds of migraine do not change at a constant rate with PHR levels. The spline curve revealed that migraine risk reached a nadir at moderate PHR levels, but increased substantially at both the lower and higher extremes of the PHR spectrum.

This U-shaped pattern remained significant after adjusting for gender, hypertension, smoking, diabetes, and alcohol consumption, emphasizing the necessity of considering non-linear dynamics when evaluating PHR in the Chinese elderly population.

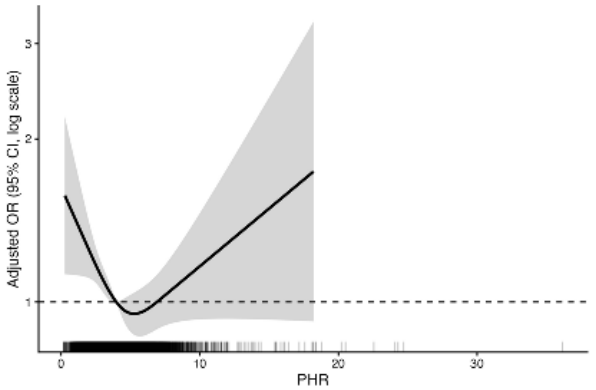


Figure 3. Dose–response relationship between PHR and migraine/headache-related status in CHARLS assessed using RCS. RCS analysis illustrating the dose–response relationship between PHR and migraine/headache-related status in CHARLS. The solid black line represents multivariable-adjusted ORs, while the shaded gray area indicates 95% CIs. The model was adjusted for sex, hypertension, smoking status, diabetes, and alcohol consumption. Four knots were positioned at the 5th, 35th, 65th, and 95th percentiles of the PHR distribution. The results revealed a significant U-shaped association (overall association: χ^2 = 16.76, P = 0.001; non-linearity: χ^2 = 13.95, P = 0.001), with the lowest risk observed at moderate PHR levels. The rug plot along the x-axis illustrates the density of the PHR distribution.

Discussion

In this large-scale, cross-sectional comparative study involving two nationally representative cohorts, we identified a significant but heterogeneous association between the PHR and migraine prevalence. Our findings reveal that the association was approximately linear in NHANES, whereas the relationship in CHARLS manifested as a robust U-shaped dose-response pattern. To our knowledge, this is the first investigation to characterize the non-linear dynamics of this integrative biomarker in the context of migraine, highlighting that population-specific factors—particularly age-related metabolic shifts—fundamentally modulate the systemic manifestation of neurogenic inflammation (19,24).

The biological plausibility of PHR as a clinical correlate of migraine lies in its unique capacity to reflect the dual pathways of pro-thrombotic activity and vascular protection. Migraine is no longer viewed as a localized sensory event but as a systemic condition involving chronic endothelial perturbation and neurogenic inflammation (25). Platelets play a central role in this cascade, acting as primary reservoirs for serotonin (5-HT) and a variety of proinflammatory cytokines (26).

Upon activation—potentially triggered by cortical spreading depression—platelets release these vasoactive mediators, which directly sensitize the trigeminovascular system and increase blood-brain barrier permeability. Conversely, HDL-C serves as a potent endogenous defense against vascular injury, exerting antioxidant, anti-inflammatory, and anti-apoptotic properties that support endothelial homeostasis (27). By facilitating cholesterol efflux and neutralizing reactive oxygen species (ROS), HDL-C helps mitigate the inflammatory signaling that perpetuates migraine attacks (28). Therefore, an elevated PHR represents a critical shift toward a pro-inflammatory and pro-coagulant environment, directly contributing to the susceptibility and persistence of migraine phenotypes.

A significant strength of our study is the comparative evaluation of multiple composite inflammatory indices. While cellular-based markers such as the NLR and the SII have gained popularity, our multivariable models demonstrated that PHR was the only index to maintain independent significance in the NHANES cohort. This superiority likely stems from the fact that NLR and SII primarily reflect cellular immune activation, whereas PHR integrates both coagulation and lipid metabolism (29). Given that migraine frequently exhibits a "metabolic face," characterized by dyslipidemia and altered vascular reactivity, the inclusion of HDL-C in the denominator allows PHR to capture a more multidimensional picture of the patient's systemic health than leukocyte-based markers alone.

Crucially, the most striking finding of our study is the divergence in dose-response morphology between the two cohorts, which may be partly related to their distinct age structures. As shown in the newly added age-distribution figure, the NHANES analytic sample covered a broader adult age range, whereas the CHARLS sample was concentrated among middle-aged and older adults. These age-structure differences indicate that the two cohorts should not be interpreted as demographically interchangeable populations. Therefore, the divergent dose-response patterns observed between NHANES and CHARLS should be interpreted with consideration of age-structure heterogeneity, rather than as purely country- or ethnicity-specific effects. In younger individuals, systemic inflammation and disease susceptibility may follow a more linear trajectory. However, in older populations, the physiological landscape is complicated by "inflammaging"—a state of chronic, sterile, low-grade inflammation that intertwines with age-related metabolic dysfunction.

The U-shaped relationship identified in the CHARLS cohort suggests that both extremes of the PHR spectrum are detrimental. While high PHR aligns with the classic inflammatory hypothesis, the risk associated with low PHR

presents a more nuanced insight. In an aging Chinese population, exceptionally low PHR levels may reflect either subclinical thrombocytopenia—indicating a fragile vascular state—or excessively high HDL levels. Intriguingly, in the context of systemic stress or aging, HDL particles can become "dysfunctional" or "pro-inflammatory," losing their protective capacity (30). This transition underscores the necessity of maintaining an optimal "inflammatory-metabolic tone," where both extremes represent homeostatic failure and increased migraine risk.

From a clinical standpoint, PHR offers a cost-effective and readily available tool for migraine risk stratification in diverse settings. Unlike specialized neuropeptide assays, PHR is derived from routine blood work, making it highly feasible for large-scale screenings. However, our findings caution against a "one-size-fits-all" interpretation of inflammatory markers. For older patients, clinicians must consider non-linear dynamics to avoid overlooking high-risk individuals at the lower end of the biomarker spectrum.

Despite the robustness of our analysis, several limitations must be acknowledged. First, the cross-sectional design precludes the establishment of causal relationships, and it remains unclear whether an altered PHR precedes migraine onset or is a systemic consequence of recurring attacks. Second, migraine status was defined using self-reported questionnaire items rather than physician-confirmed diagnoses based on formal diagnostic criteria. More importantly, the outcome definitions were not fully harmonized across the two cohorts. In NHANES, migraine was inferred from a self-reported item referring to severe headache or migraine, whereas CHARLS assessed headache-related pain rather than migraine specifically. Because headache is a nonspecific symptom that may arise from many primary and secondary etiologies, the CHARLS definition may have captured a broader headache phenotype rather than strictly defined migraine. This discrepancy may introduce outcome misclassification and, more importantly, differential outcome definition bias across cohorts. Therefore, the observed between-cohort differences in the shape of the PHR–migraine association should be interpreted cautiously, as they may reflect not only true population-specific biological differences but also differences in symptom ascertainment. Nevertheless, given the lack of physician-adjudicated migraine diagnoses in these large-scale population-based datasets, our findings should be viewed as hypothesis-generating evidence regarding the relationship between PHR and migraine/headache-related symptoms. Future studies using harmonized migraine definitions based on standardized diagnostic criteria are needed to validate these findings and clarify whether the observed nonlinear association persists in clinically confirmed migraine populations.

In conclusion, PHR is a significant correlate of migraine status, but its manifestation is population-dependent. The discovery of a U-shaped relationship in the Chinese cohort emphasizes the necessity of flexible modeling in neuro-epidemiology and supports the role of systemic inflammation-lipid interactions in the pathophysiology of migraine.

Conclusion

This study identifies the PHR as a significant correlate of migraine across both US and Chinese populations. Notably, the dose-response relationship is population-dependent, manifesting as a linear trend in the NHANES cohort and a robust U-shaped pattern in the CHARLS cohort. These findings suggest that systemic inflammation and lipid metabolism interact differently across age groups and ethnicities. Beyond providing a cost-effective biomarker for risk stratification, our results advocate for the integration of non-linear modeling in neuro-epidemiological research to capture complex metabolic-inflammatory transitions.

References

1. Ashina M, Katsarava Z, Do TP, Buse DC, Pozo-Rosich P, Özge A, et al. Migraine: epidemiology and systems of care. The Lancet 2021;397:1485–95. Doi:10.1016/S0140-6736(20)32160-7.
2. Chen Z, Kong X, Yang C, Li X, Guo H, Wang Z. Global, regional, and national burden and trends of migraine among youths and young adults aged 15–39 years from 1990 to 2021: findings from the global burden of disease study 2021. J Headache Pain 2024;25. Doi:10.1186/s10194-024-01832-0.
3. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA. Migraine and the trigeminovascular system—40 years and counting. Lancet Neurol 2019;18:795–804. Doi:10.1016/S1474-4422(19)30185-1.
4. Wattiez A-S, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. Expert Opin Ther Targets 2020;24:91–100. Doi:10.1080/14728222.2020.1724285.
5. Dağıdır HG, Topa E, Vuralli D, Bolay H. Medication overuse headache is associated with elevated lipopolysaccharide binding protein and pro-inflammatory molecules in the bloodstream. J Headache Pain 2023;24. Doi:10.1186/s10194-023-01672-4.
6. Kurth T, Rist PM, Ridker PM, Kotler G, Bubes V, Buring JE. Association of Migraine With Aura and Other Risk Factors With Incident Cardiovascular Disease in Women. JAMA 2020;323. Doi:10.1001/jama.2020.7172.
7. Fernández-Garza LE, González-Aquines A, Botello-Hernández E, Pérez-Vázquez G, Cristobal-Niño M, Góngora-Rivera F. Segmented neutrophil-to-monocyte ratio and systemic immune-inflammation index associated with the severity and functional prognosis of acute ischemic stroke. International Journal of Neuroscience 2025;135:228–36. Doi:10.1080/0020

7454.2023.2294705.
8. Hu B, Yang X-R, Xu Y, Sun Y-F, Sun C, Guo W, et al. Systemic Immune-Inflammation Index Predicts Prognosis of Patients after Curative Resection for Hepatocellular Carcinoma. Clinical Cancer Research 2014;20:6212–22. Doi:10.1158/1078-0432.CCR-14-0442.
9. Wijeratne T, Murphy MJ, Wijeratne C, Martelletti P, Karimi L, Apostolopoulos V, et al. Serial systemic immune inflammation indices: markers of acute migraine events or indicators of persistent inflammatory status? J Headache Pain 2025;26. Doi:10.1186/s10194-024-01929-6.
10. Wang K, Mao Y, Lu M, Ding Y, Li Z, Li Y, et al. Association between migraine and cardiovascular disease: A cross-sectional study. Front Cardiovasc Med 2022;9. Doi:10.3389/fcvm.2022.1044465.
11. Winsvold BS, Sandven I, Hagen K, Linde M, Midthjell K, Zwart J-A. Migraine, headache and development of metabolic syndrome: An 11-year follow-up in the Nord-Trøndelag Health Study (HUNT). Pain 2013;154:1305–11. Doi:10.1016/j.pain.2013.04.007.
12. Danese E, Montagnana M, Lippi G. Platelets and migraine. Thromb Res 2014;134:17–22. Doi:10.1016/j.thromres.2014.03.055.
13. Liampas I, Mylonas KS, Brotis A, Dervenis P, Siokas V, Mentis AA, et al. Serum lipid abnormalities in migraine: A meta–analysis of observational studies. Headache: The Journal of Head and Face Pain 2021;61:44–59. Doi:10.1111/head.14039.
14. Onderwater GLJ, Ligthart L, Bot M, Demirkan A, Fu J, van der Kallen CJH, et al. Large-scale plasma metabolome analysis reveals alterations in HDL metabolism in migraine. Neurology 2019;92. Doi:10.1212/WNL.0000000000007313.
15. Gasparini CF, Smith RA, Griffiths LR. Genetic and biochemical changes of the serotonergic system in migraine pathobiology. J Headache Pain 2017;18. Doi:10.1186/s10194-016-0711-0.
16. Barter PJ, Nicholls S, Rye K-A, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory Properties of HDL. Circ Res 2004;95:764–72. Doi:10.1161/01.RES.0000146094.59640.13.
17. Jin X, Jia W, Liu Y, Cui M, Zhang H, Wu H, et al. Association of platelet to high density lipoprotein cholesterol ratio with coronary lesion severity in middle aged and elderly adults. Sci Rep 2025;15. Doi:10.1038/s41598-025-12981-w.
18. Zhang Z, Lin Y, Liu Y, Wang Y. Prognostic Value of PHR and FHR for Outcomes in Acute Ischemic Stroke Patients with Large Artery Occlusion Undergoing Endovascular Treatment. Curr Neurovasc Res 2025;22:307–18. Doi:10.2174/0115672026416428251201133449.
19. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343–9. Doi:10.1212/01.wnl.0000252808.97649.21.
20. Wang M-H, Pan L-J, Zhang Y-H, Zhu H-Q, Zhu X-B, Wang X-Q. Prevalence and risk factors of headache in Chinese with stroke: a cross-sectional study based on CHARLS. J Headache Pain 2024;25. Doi:10.1186/s10194-024-01930-z.
21. Yu L, Bian L, Ren L, Wei W, Zhang H, Miao M. Nonlinear dose–response relationship between dietary inflammatory index and risk of depression: a systematic review and meta-analysis. Front Nutr 2025;12. Doi:10.3389/fnut.2025.1645789.
22. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 2010;29:1037–57. Doi:10.1002/sim.3841.
23. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. J Headache Pain 2022;23. Doi:10.1186/s10194-022-01402-2.
24. Lipton RB, Bigal ME. Migraine and cardiovascular disease: is there a link? Nat Clin Pract Neurol 2007;3:74–5. Doi:10.1038/ncpneuro0396.
25. Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles A, et al. Migraine. Nat Rev Dis Primers 2022;8. Doi:10.1038/s41572-021-00328-4.
26. Tietjen GE, Collins SA. Hypercoagulability and Migraine. Headache: The Journal of Head and Face Pain 2018;58:173–83. Doi:10.1111/head.13044.
27. Lotfollahi Z, Dawson J, Fitridge R, Bursill C. The Anti-inflammatory and Proangiogenic Properties of High-Density Lipoproteins: An Emerging Role in Diabetic Wound Healing. Adv Wound Care (New Rochelle) 2021;10:370–80. Doi:10.1089/wound.2020.1308.
28. Xepapadaki E, Zvintzou E, Kalogeropoulou C, Filou S, Kypreos KE. The Antioxidant Function of HDL in Atherosclerosis. Angiology 2020;71:112–21. Doi:10.1177/0003319719854609.
29. Zhang H, Xu Y, Xu Y. The association of the platelet/high-density lipoprotein cholesterol ratio with self-reported stroke and cardiovascular mortality: a population-based observational study. Lipids Health Dis 2024;23. Doi:10.1186/s12944-024-02115-y.
30. Endo Y, Sasaki K, Ikewaki K. Bridging the Gap Between the Bench and Bedside: Clinical Applications of High-density Lipoprotein Function. J Atheroscler Thromb 2024;31. Doi:10.5551/jat.RV22020.

Qi-Wei Lin
https://orcid.org/0009-0004-6976-9915
Yun-Dong-Xu Xiao
https://orcid.org/0009-0002-9767-0803
Yu-Ying Jing
https://orcid.org/0009-0009-8895-1743
Wen-Bin Lu
https://orcid.org/0009-0001-2962-9537

Authors Contribution: WBL: Conceptualization, Methodology, Formal analysis (NHANES and CHARLS data), Drafted the original manuscript, Supervision; QWL, YYJ: Data curation, Literature investigation; YDXX: Visualization of results, Revision. All authors read and approved the final manuscript.
Conflict of interest: There are no conflicts of interest.
Funding: The authors received no financial support for the research, authorship, and/or publication of this article.
Data Availability: The datasets supporting the conclusions of this article are available in the following public repositories: NHANES data are publicly available through the NCHS website at: https://www.cdc.gov/nchs/nhanes/index.htm. CHARLS data are available to registered users through the China Health and Retirement Longitudinal Study portal at: https://charls.ch.pku.edu.cn/. The harmonized datasets and statistical codes used for the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: The protocols for NHANES were approved by the NCHS Research Ethics Review Board. For the CHARLS cohort, the study was approved by the Ethical Review Committee of Peking University (IRB00001052-11015). All participants in both databases provided written informed consent prior to data collection. All methods in this study were conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines.

Acknowledgments: We would like to express our gratitude to the NCHS of the Centers for Disease Control and Prevention (CDC) for conducting the NHANES and making the data available. We also thank the National School of Development at Peking University for providing the CHARLS data. Most importantly, we are deeply grateful to all the participants in both the NHANES and CHARLS cohorts for their contribution to scientific research. Additionally, we thank our colleagues at Integrated Traditional Chinese and Western Medicine Hospital of Wenzhou Medical University for their administrative support and helpful discussions during the preparation of this manuscript.