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The interaction and joint effects of the hemoglobin-to-red cell distribution width ratio and the triglyceride-glucose index (TyG) on depressive symptoms among residents of Nanjing City, along with the mediating role of TyG: a population-based study of 181,752 participants

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To investigate the mediating role of the triglyceride-glucose (TyG) in the association between the hemoglobin-to-red cell distribution width ratio (HRR) and depressive symptoms (DS), and to analyze the interaction and joint effects of HRR and TyG on DS. Based on cross-sectional data from 181,752 adult residents in Nanjing City (2020–2024), multivariable logistic regression, restricted cubic spline, and mediation analysis were used to assess the relationships of HRR and TyG with DS. HRR showed a nonlinear negative correlation with DS (Q4 vs. Q1: OR = 0.01, 95% CI 0.01–0.02), while TyG exhibited a nonlinear positive correlation (Q4 vs. Q1: OR = 6.22, 95% CI 5.64–7.15). Mediation analysis revealed heterogeneity in the proportion of the HRR - DS association mediated by TyG (Q1: 11.81%; Q3: −42.37%). A significant additive interaction between HRR and TyG on DS was observed (RERI = −7.59, 95% CI −8.18 to −7.00), but no significant multiplicative interaction. Joint analysis indicated that the HRR_Q1 + TyG_Q4 group had the highest DS risk (OR = 8.00, 95% CI 7.80–8.10), while the HRR_Q4 + TyG_Q1/Q3 groups showed the strongest protective effects (OR ≈ 0.04). The combined HRR + TyG model demonstrated significantly superior predictive performance compared to individual biomarkers (AUC = 0.861). TyG partially mediates the HRR-DS association, and HRR and TyG jointly influence DS risk through antagonistic effects. The combined model (HRR + TyG) may serve as an efficient biomarker panel for screening high-risk DS populations. Targeting improvements in iron metabolism and insulin resistance may provide novel strategies for DS prevention and management.

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INTRODUCTION

Depressive symptoms (DS) pose a growing global public health challenge, with the disease burden escalating persistently [1]. According to the World Health Organization (WHO), over 300 million people worldwide are affected by DS, which not only severely impairs patients' quality of life but also imposes substantial socioeconomic burdens [2, 3]. Elucidating the risk factors for DS has become crucial for achieving effective prevention and management.

Insulin resistance (IR), as a core feature of metabolic disorders, has received significant attention in the research of DS in recent years [4]. Substantial evidence indicates a significant association between IR and DS. The underlying mechanisms are complex, involving the spread of peripheral inflammation to the central nervous system (CNS), which subsequently impairs neuroplasticity and the synthesis of monoamine neurotransmitters [5]. The triglyceride-glucose (TyG), a novel surrogate marker for assessing IR, integrates triglyceride and fasting glucose levels to sensitively reflect peripheral IR status [6]. Large-scale cohort studies have confirmed that elevated TyG levels are independently associated with DS [7, 8].

Simultaneously, the hemoglobin-to-red cell distribution width ratio (HRR), an emerging integrated biomarker of inflammation and oxidative stress, has demonstrated unique value for the assessment of cardiovascular disease and cancer prognosis [9, 10]. Mechanistic studies suggest that disordered iron metabolism and oxidative stress may contribute to DS by altering blood-brain barrier permeability and suppressing monoamine neurotransmitter synthesis [11]. However, currently, the epidemiological evidence of HRR in the field of mental diseases is only supported by scattered cross-sectional studies, and more in-depth research is urgently needed [12].

Notably, chronic inflammation may suppress insulin signaling transduction via the TNF-α/NF-κB pathway, driving IR (manifested

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as elevated TyG) and promoting neuroinflammation, thereby establishing a cascade of 'inflammation → metabolic dysregulation → brain dysfunction [13, 14]. Elucidating the mediating role of TyG could provide valuable insights into the mechanisms linking HRR to DS. This understanding may reveal novel therapeutic targets and new intervention pathways, offering approaches to alleviate DS by addressing IR and ultimately strengthening prevention strategies and patient care.

Against this backdrop, we investigate two primary questions using data from 181,752 adults participating in health screenings in Nanjing City: (1) Does TyG mediate the association between HRR and depressive symptoms? (2) Do TyG and HRR exert joint effects on depressive symptom risk? By directly investigating these questions, we seek to clarify the complex interplay between inflammation, metabolic dysregulation, and brain dysfunction in depression, potentially identifying novel intervention targets.

METHODS

Study participants

This study enrolled 258,013 adults who underwent health screenings at Gaochun People's Hospital of Nanjing between January 2020 and May 2024. Inclusion criteria encompassed individuals aged 18–80 years with complete data for calculating the TyG and HRR. Exclusion criteria included a history of hematological diseases, major surgery or severe trauma within the past 3 months, malignancy, and end-stage renal disease. After applying exclusion criteria, 76,261 individuals were excluded, resulting in a final analytical cohort of 181,752 participants (see Figure S1). All participants underwent standardized DS assessments, structured physical examinations, and centralized laboratory testing. The study protocol was approved by the Ethics Review Committee of Gaochun People's Hospital (Approval No.: 2024-038-01) and was conducted in strict adherence to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants after full disclosure of the study's purpose and procedures.

Assessment of HRR and TyG

Morning fasting venous blood samples were collected. Complete blood count analysis was performed using a Beckman Coulter automated hematology analyzer (Beckman Coulter, Inc., Fullerton, CA, USA) to measure red cell distribution width (RDW) and hemoglobin (HGB). Biochemical parameters [triglycerides (TG) and fasting plasma glucose (FPG)] were quantified using a Hitachi 7600 automated biochemical analyzer via enzymatic spectrophotometry. HRR was calculated as HGB (g/dl) / RDW (%) [10], and TyG was calculated as ln [TG (mg/dl) × FPG (mg/dl)/2] [8].

Assessment of DS

DS were assessed using the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10), a widely validated instrument with excellent reliability and validity in population-based studies [15]. Participants rated the frequency of depressive symptoms over the past week across 10 items: (1) bothered by little things, (2) had trouble concentrating, (3) felt depressed, (4) everything was an effort, (5) felt hopeless, (6) felt fearful, (7) sleep was restless, (8) felt unhappy, (9) felt lonely, and (10) could not get going. Items 5 and 8 required reverse scoring. Each item was scored as follows: 0 (rarely or none of the time, <1 day), 1 (some or a little of the time, 1–2 days), 2 (occasionally or a moderate amount of time, 3–4 days), 3 (most or all the time, 5–7 days). The total CESD-10 score ranged from 0–30. In this study, a CESD-10 score ≥10 was defined as DS, while scores below 10 were classified as Non-DS [16].

Statistical analysis

All analyses were conducted using R software (version 4.3.1). Continuous variables are presented as mean ± standard deviation, while categorical variables are summarized as frequencies and percentages. Chi-square tests and analysis of variance (ANOVA) were employed to compare characteristics across groups. Missing covariate data (approximately 0.1% of total entries, 141 out of 181,752) were handled using Multiple Imputation by Chained Equations (MICE), with the mice package utilized to generate a single imputed dataset. Logistic regression models were employed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between HRR (categorized into quartiles) and TyG (categorized into quartiles) with DS. Three models were constructed: Model 1 (unadjusted), Model 2 (adjusted for gender, age, marital status, smoking, drinking, and body mass index), Model 3 (adjusted for all variables in Model 2 plus hypertension, diabetes, and dyslipidemia). Additionally, restricted cubic spline (RCS) regression with three knots (placed at the 25th, 50th, and 75th percentiles) was implemented using the mgcv package in R to explore potential nonlinear relationships. Mediation effects (TyG-mediated indirect associations) and non-mediated direct associations were assessed using the mets package. A regression-based approach was applied to decompose the total effect of HRR (categorized into quartiles) on DS into natural indirect effects (NIE) and natural direct effects (NDE). Two models were constructed: A multivariate regression model for TyG (mediator variable) conditional on HRR (exposure factor) and confounders; A multivariate regression model for DS (outcome variable) conditional on HRR, TyG, and confounders. The NDE represents the effect of HRR on DS independent of TyG, while the NIE quantifies the proportion of the HRR-DS association mediated through TyG. The proportion mediated was calculated as NIE / (NDE + NIE) (see Figure S2). Notably, negative proportion occurs when the NIE and NDE act in opposite directions, thereby attenuating the total effect. Positive proportion occurs when the NIE and NDE act in the same direction, thereby amplifying the total effect. Stratified analyses by HRR quartiles were performed to examine TyG-DS associations across HRR subgroups. To quantify interaction effects, product terms between HRR (quartiles) and TyG (quartiles) were included in the models. Multiplicative interaction, which examines whether the combined effect of HRR and TyG differs from the product of their individual effects and is often interpreted biologically, was evaluated using ORs and 95% CIs. Additive interaction, which examines whether the combined effect exceeds the sum of their individual effects and is often interpreted for public health impact regarding joint exposures, was assessed via the relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (SI). These indicators reflect the interaction from different aspects, including the part of the effect attributable to the interaction, the proportion of the combined effect generated by the interaction, and the ratio between the combined effect and the individual effects. Specifically, RERI = 0, AP = 0, and SI = 1 indicate that there is no interaction between HRR and TyG in terms of DS. Conversely, when RERI > 0, AP > 0, and SI > 1, it indicates that the combined effect of HRR and TyG on DS exceeds the sum of their individual effects, suggesting a synergistic effect. On the contrary, if RERI < 0, AP < 0, and SI < 1, it indicates that the combined effect is less than the sum of the individual effects of HRR and TyG, suggesting an antagonistic effect [17]. Participants were stratified into 16 groups based on HRR and TyG quartiles. Using the CMAverse package, a four-way decomposition method was applied to evaluate joint effects, with the reference group defined as individuals in the first quartiles of both HRR and TyG [18]. The discriminatory ability of HRR, TyG, HRR_TyG, and the combined HRR+TyG was evaluated using receiver operating characteristic (ROC) curves. Subsequently, the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indices were calculated to quantify the incremental predictive value of HRR+TyG compared to HRR or TyG alone. Decision curve analysis (DCA) was performed to compare clinical utility by plotting net benefit against varying threshold probabilities [19]. Additionally, the incremental predictive value of HRR and TyG over traditional risk factors was assessed. To test robustness and potential heterogeneity across subgroups, all analyses were repeated with stratification by gender, age, and marital status. Data and code will be made available upon reasonable request.

RESULTS

Population characteristics

Table 1 shows that this study included 181,752 adult residents, with the majority aged 45–59 years (43.53%), followed by <45 years (35.21%) and ≥60 years (21.26%). Females accounted for a slightly higher proportion than males (56.10% vs. 43.90%), and 8.40% of participants were unmarried. The mean TyG was 8.66 ± 0.62, showing a significant increasing trend with higher HRR levels (Q1: 8.52 ± 0.63; Q4: 8.83 ± 0.63). The prevalence of DS was 6.94%, with the lowest HRR quartile (Q1) having the highest prevalence (12.27%). Additionally, the highest HRR quartile (Q4) exhibited significantly higher proportions of smoking (Q4: 46.77% vs. Q1: 8.83%) and drinking (Q4: 58.20% vs. Q1: 11.31%). Table S1 presents the comparison of characteristics between included and excluded participants.

Table 1. Characteristics participants according to HRR.

Characteristic	Overall ($n = 181,752$)	HRR_Q1 ($n = 45,233$)	HRR_Q2 ($n = 45,538$)	HRR_Q3 ($n = 45,685$)	HRR_Q4 ($n = 45,296$)	t/χ2	*p*
Age (*n*, %)						3579.90	< 0.001
< 45 (years)	64,007 (35.21)	13,836 (30.59)	14,463 (31.76)	15,590 (34.12)	20,118 (44.41)		
≥ 45 and < 60 (years)	79,109 (43.53)	19,693 (43.54)	19,704 (43.27)	20,735 (45.39)	18,977 (41.90)		
≥ 60 (years)	38,636 (21.26)	11,704 (25.87)	11,371 (24.97)	9360 (20.49)	6201 (13.69)		
Gender (*n*, %)						2435.42	< 0.001
Male	79,788 (43.90)	36,675 (81.08)	27,824 (61.10)	12,672 (27.74)	2617 (5.78)		
Female	101,964 (56.10)	8558 (18.92)	17,714 (38.90)	33,013 (72.26)	42,679 (94.22)		
Marital status (*n*, %)						1266.82	< 0.001
Married	166,487 (91.60)	42,586 (94.15)	42,308 (92.91)	41,752 (91.39)	39,841 (87.96)		
Unmarried	15,265 (8.40)	2647 (5.85)	3230 (7.09)	3933 (8.61)	5455 (12.04)		
Area (*n*, %)						2.75	0.431
Rural	162,978 (89.67)	40,570 (89.69)	40,918 (89.85)	40,928 (89.59)	40,562 (89.55)		
Urban	18,774 (10.33)	4663 (10.31)	4620 (10.15)	4757 (10.41)	4734 (10.45)		
Education level (*n*, %)						11.45	0.491
Below primary school	81,911 (45.07)	20,479 (45.27)	20,374 (44.74)	20,598 (45.09)	20,460 (45.17)		
Primary school	39,381 (21.67)	9655 (21.35)	10,005 (21.97)	9865 (21.59)	9856 (21.76)		
Middle school	37,440 (20.60)	9319 (20.60)	9478 (20.81)	9420 (20.62)	9223 (20.36)		
High school	14,242 (7.84)	3595 (7.95)	3480 (7.64)	3591 (7.86)	3576 (7.89)		
Above high school	8778 (4.83)	2185 (4.83)	2201 (4.83)	2211 (4.84)	2181 (4.81)		
Smoking (*n*, %)						162.67	< 0.001
Yes	49,504 (27.24)	3992 (8.83)	8061 (17.70)	16,264 (35.60)	21,187 (46.77)		
No	132,248 (72.76)	41,241 (91.17)	37,477 (82.30)	29,421 (64.40)	24,109 (53.23)		
Drinking (*n*, %)						687.51	< 0.001
Yes	61,902 (34.06)	5115 (11.31)	10,446 (22.94)	19,980 (43.73)	26,361 (58.20)		
No	119,850 (65.94)	40,118 (88.69)	35,092 (77.06)	25,705 (56.27)	18,935 (41.80)		
Dyslipidemia (*n*, %)						101.40	< 0.001
Yes	33,963 (18.69)	9127 (20.18)	8331 (18.29)	8498 (18.60)	8007 (17.68)		
No	147,789 (81.31)	36,106 (79.82)	37,207 (81.71)	37,187 (81.40)	37,289 (82.32)		
Diabetes (*n*, %)						309.31	< 0.001
Yes	9330 (5.13)	1834 (4.05)	2041 (4.48)	2581 (5.65)	2874 (6.34)		
No	172,422 (94.87)	43,399 (95.95)	43,497 (95.52)	43,104 (94.35)	42,422 (93.66)		
Coronary heart disease (*n*, %)						2.99	0.393
Yes	18,099 (9.96)	4426 (9.78)	4603 (10.11)	4580 (10.03)	4490 (9.91)		
No	163,653 (90.04)	40,807 (90.22)	40,935 (89.89)	41,105 (89.97)	40,806 (90.09)		
Hypertension (*n*, %)						1351.28	< 0.001
Yes	50,523 (27.80)	10,352 (22.89)	11,806 (25.93)	13,263 (29.03)	15,102 (33.34)		
No	131,229 (72.20)	34,881 (77.11)	33,732 (74.07)	32,422 (70.97)	30,194 (66.66)		
TyG	8.66 ± 0.62	8.52 ± 0.63	8.57 ± 0.62	8.71 ± 0.62	8.83 ± 0.63	741.16	< 0.001
BMI (kg/m2)	23.97 ± 3.14	23.28 ± 3.21	23.57 ± 3.19	24.20 ± 3.11	24.85 ± 3.03	587.21	< 0.001
Depression Symptom (*n*, %)						4145.79	< 0.001
Yes	12,615 (6.94)	5549 (12.27)	3651 (8.02)	2689 (5.89)	726 (1.60)		
No	169,137 (93.06)	39,684 (87.73)	41,887 (91.98)	42,996 (94.11)	4457 (98.40)		

HRR_Q1 = [1.17, 9.55]; HRR_Q2 = (9.55, 10.51]; HRR_Q3 = (10.51, 11.48]; HRR_Q4 = (11.48, 15.50];
HRR hemoglobin-to-red cell distribution width ratio, *TyG* triglyceride-glucose, *BMI* body mass index.

Mediation analyses of HRR of TyG with DS

Figure S3 shows that after adjusting for potential confounders (in Model 3), the adjusted OR for DS in HRR_Q4 versus HRR_Q1 was 0.01 (95% CI 0.01–0.02), while the adjusted OR for DS in TyG_Q4 versus TyG_Q1 was 6.22 (95% CI 5.64–7.15). RCS regression revealed a nonlinear negative association between HRR and DS and a nonlinear positive association between TyG and DS, with consistent trends across all three models (Fig. 1). Figure S4 and Table S2 demonstrate a nonlinear relationship between HRR and TyG. Mediation analysis (in Model 3)

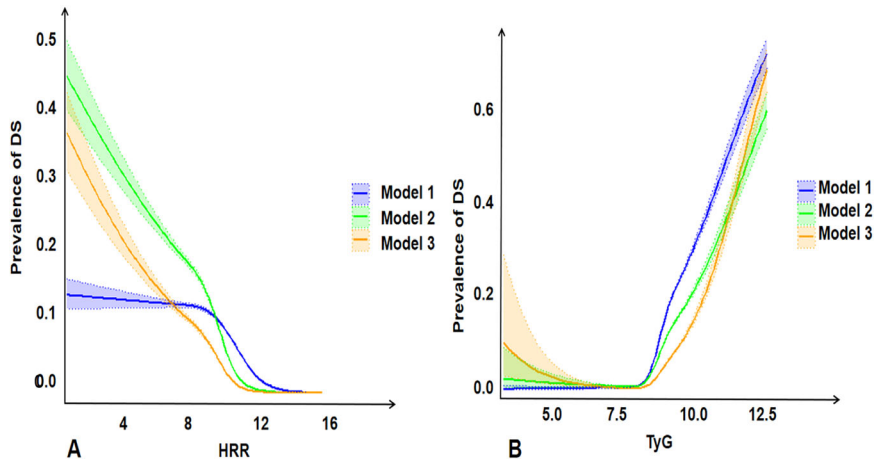

Fig. 1 Nonlinear associations of TyG and HRR with DS. Model 1: Crude. Model 2: Adjusted for gender, age, marital status, smoking, drinking, body mass index. Model 3: Adjusted for hypertension, diabetes, dyslipidemia, plus variable in model 2. HRR hemoglobin-to-red cell distribution width ratio, TyG triglyceride-glucose, DS depression symptom. Solid lines indicate ORs, and shadow shapes indicate 95% CIs. **A** Nonlinear associations of HRR with DS; **B** Nonlinear associations of TyG with DS.

Table 2. Decomposition of the total association between HRR and the risk of DS into direct and indirect associations mediated by the TyG.

Model	Association		Proportion mediated
	Indirect OR (95% CI)	Direct OR (95% CI)	
Model 1			
HHR_Q1	1 [Reference]		
HHR_Q2	1.12 (1.10, 1.14)	0.50 (0.48, 0.53)	−19.55%
HHR_Q3	1.49 (1.46, 1.51)	0.26 (0.24, 0.27)	−42.05%
HHR_Q4	1.94 (1.90, 1.98)	0.04 (0.03, 0.04)	−25.92%
Model 2			
HHR_Q1	1 [Reference]		
HHR_Q2	0.98 (0.97, 0.99)	0.76 (0.54, 0.77)	6.86%
HHR_Q3	1.21 (1.10, 1.23)	0.49 (0.48, 0.59)	−36.46
HHR_Q4	1.10 (1.08, 1.12)	0.46 (0.41, 0.51)	−13.99%
Model 3			
HHR_Q1	1 [Reference]		
HHR_Q2	0.98 (0.96, 0.99)	0.86 (0.84, 0.88)	11.81%
HHR_Q3	1.17 (0.98, 1.21)	0.59 (0.58, 0.61)	−42.37%
HHR_Q4	1.07 (1.05, 1.09)	0.51 (0.48, 0.53)	−11.18%

Model 1: Crude.
Model 2: Adjusted for gender, age, marital status, smoking, drinking, body mass index.
Model 3: Adjusted for hypertension, diabetes, dyslipidemia, plus variable in model 2.
HRR_Q1 = [1.17, 9.55]; HRR_Q2 = (9.55, 10.51]; HRR_Q3 = (10.51, 11.48]; HRR_Q4 = (11.48, 15.50];
HRR hemoglobin-to-red cell distribution width ratio, *TyG* triglyceride-glucose, *DS* depression symptom, *CI* confidence interval, *OR* odds ratio.

indicated an indirect association OR of 0.98 (95% CI 0.96–0.99) for HRR_Q2 versus HRR_Q1, while the indirect association OR for HRR_Q3 was 1.17 (95% CI 0.98–1.21). The mediation proportion was 11.81% for HRR_Q1 and −42.37% for HRR_Q3 (details in Table 2).

Interaction and joint analyses of HRR and TyG with DS

Table 3 and Fig. 2A demonstrate a significant additive interaction between HRR and TyG on DS (RERI = −7.59, 95% CI − 8.18 to −7.00), but no significant multiplicative interaction (OR = 0.91, 95% CI 0.70–1.19). Figure 2B illustrates the joint association of HRR and TyG with DS. After adjusting for confounders, compared to HRR_Q1 and TyG_Q1, the highest risk was observed for HRR_Q1 and TyG_Q4 (OR = 8.00, 95% CI 7.80–8.10), while HRR_Q4 and TyG_Q1 (OR = 0.04, 95% CI 0.02–0.07) and HRR_Q4 and TyG_Q3 (OR = 0.04, 95% CI 0.03–0.06) exhibited strong protective effects.

Predictive value of HRR and TyG in DS

Figure 3 demonstrates that the combined HRR+TyG index achieved an area under the curve (AUC) of 0.861 (Fig. 3A), with DCA further confirming its clinical relevance (Fig. 3B). Notably, the HRR+TyG composite index showed statistically significant differences compared to using HRR or TyG alone (Fig. 3C). Table S3 reveals that incorporating both HRR and TyG indices into the traditional model substantially improved predictive performance, increasing the AUC from 0.75–0.89. This enhanced model also exhibited superior discriminative ability and risk reclassification, with an IDI of 0.01 (95% CI 0.01–0.02; $p = 0.003$) and NRI of 0.21 (95% CI 0.10–0.27; $p < 0.001$).

Subgroup analyses

Tables S4–S12 reveal that the mediating effect of TyG on the association between HRR and DS is more complex in women

Table 3. Interactive effects of TyG and HRR on DS.

Interactive items	Interactive effects (95% CI)		
	Model 1	Model 2	Model 3
Additive effects			
RERI	−2.06 (−2.18, −1.93)	−7.52 (−7.99, −7.05)	−7.59 (−8.18, −7.00)
AP	−13.96 (−16.41, −11.52)	−8.50 (−10.06, −6.94)	−6.18 (−7.42, −4.94)
SI	−0.71 (−0.79, −0.63)	−0.02 (−0.04, 0.01)	0.03 (0.01, 0.06)
Multiplicative effect	0.94 (0.73, 1.21)	0.86 (0.67, 1.11)	0.91 (0.70, 1.19)

Model 1: Crude.
Model 2: Adjusted for gender, age, marital status, smoking, drinking, body mass index.
Model 3: Adjusted for hypertension, diabetes, dyslipidemia, plus variable in model 2.
HRR hemoglobin-to-red cell distribution width ratio, *TyG* triglyceride-glucose, *DS* depression symptom, *AP* proportion attributable to interaction, *CI* confidence interval, *RERI* relative excess risk due to interaction, *SI* synergy index.

compared to men. Among participants aged <45 years and ≥60 years, TyG exhibited a higher proportion of mediating effects between HRR and DS. Furthermore, compared to unmarried individuals, married participants predominantly showed antagonistic interactions and clear protective combinations.

DISCUSSION

This study systematically investigated the mediating, interactive, and joint effects of HRR and TyG on DS using cross-sectional data from 181,752 adult residents in Nanjing. The findings reveal a nuanced perspective on how these factors intertwine to influence DS assessment, carrying significant implications for clinical practice and public health strategies.

Our study reaffirmed the association between reduced HRR and elevated DS risk (Q1 group OR = 12.27, 95% CI 11.89–12.66), corroborating previous findings that low HRR—reflecting iron dysregulation or elevated oxidative stress—may impair monoamine neurotransmitter synthesis via reduced tryptophan hydroxylase cofactor availability [20] and could promote neuroinflammation through microglial activation [21]. In contrast to the protective effect of HRR, elevated TyG (Q4 group OR = 6.22) showed a positive association with DS, further confirming the central role of IR in mental disorders [22, 23]. A meta-analysis, which analyzed 7 studies involving 58,981 participants, found that a high TyG index is associated with depression and can serve as a predictive indicator for depression-related events [24]. Another meta-analysis revealed that age, participants' sex, TyG index cut-off values, and depression diagnostic methods did not significantly influence the association between the TyG index and the prevalence of depression in the adult population [25]. Notably, the association between TyG and DS remained significant even after adjusting for the diabetic status, suggesting that IR may drive the pathological process of DS directly, independent of glucose metabolism disorders, a finding consistent with the hypothesis of the 'metabolic-inflammation vicious cycle' related to obesity - associated DS [26].

As a robust surrogate marker of IR, TyG demonstrated a partial mediation effect (11.81%), indicating that metabolic dysregulation served as an important pathway through which HRR influenced DS. However, in the HRR_Q3 group, the mediation proportion reversed to −42.37%. This observed heterogeneity suggests that two potential underlying mechanisms are operative. First, a threshold effect might exist. When HRR levels are low, TH may lack its essential iron cofactor, impairing serotonin synthesis and contributing to disruption of neurotransmitter-mediated mood regulation [27]. Concurrently, enhanced oxidative stress could activate microglia to release proinflammatory cytokines, which might compromise the blood-brain barrier and create cerebral microenvironment imbalance, thereby increasing DS risk [28]. Conversely, at higher HRR levels, its inherent antioxidant properties and role in maintaining iron homeostasis might effectively suppress inflammatory responses [29], which could thereby indirectly mitigate TyG-associated metabolic damage and limit the translocation of inflammatory cytokines across the blood-brain barrier. These potential changes collectively might help preserve hippocampal neuroplasticity and BDNF expression, ultimately contributing to reduced DS susceptibility [30].

Second, HRR may influence DS through two potential pathways. The first could be a direct anti-inflammatory pathway independent of TyG [31]. Specifically, elevated HRR levels might improve iron homeostasis, regulate redox balance, and suppress inflammatory signaling pathways – potentially reducing proinflammatory cytokine production and neuroinflammation risk [32]. The second potential pathway may involve indirect metabolic regulation mediated by TyG [33]. Here, HRR-driven changes in iron metabolism could alter energy/lipid metabolism processes linked to TyG [34]. These findings challenged the assumptions of traditional linear mediation models and highlighted the need for future studies to incorporate nonlinear analytical approaches to accurately decipher the complex roles of biomarkers.

Further analysis revealed a significant antagonistic effect between HRR and TyG on DS (RERI = −7.59). This antagonism may stem from competing biological pathways: Elevated TyG levels reflect IR, which prior studies link to chronic inflammation via FFA mediated macrophage activation and inflammatory cascades (e.g., TNF-α/NF-κB) [8, 35]. Such processes can establish a self-perpetuating cycle where inflammation exacerbates IR. Conversely, higher HRR levels—indicating improved iron homeostasis and reduced oxidative stress—may disrupt this cycle through antioxidant effects [36]. Preclinical evidence suggests that iron homeostasis regulates inflammatory responses and that enhanced antioxidant activity mitigates oxidative damage [37, 38]. Supporting this, animal studies show iron chelation alleviates inflammation-associated behaviors [39]. While these pathways provide biological plausibility for the observed antagonism, our cross-sectional design cannot establish causality. The precise molecular mechanisms require validation through longitudinal studies with direct assessment of inflammatory/iron biomarkers.

Joint-effect analysis demonstrated that the HRR_Q1+TyG_Q4 group exhibited the highest DS risk (OR = 8.00), while the HRR_Q4+TyG_Q1/Q3 groups showed the strongest protective effects (OR ≈ 0.04). These findings suggest that the "dual hit" of metabolic dysfunction combined with iron homeostasis imbalance may substantially increase DS risk, whereas elevated HRR levels might partially attenuate TyG-related detrimental effects [40]. This pattern provides a rationale for developing interventions targeting metabolic-inflammatory interactions [41].

Although this study did not reveal a synergistic effect between HRR and TyG, it underscored the importance of jointly considering these factors in DS risk assessment. Our findings demonstrated

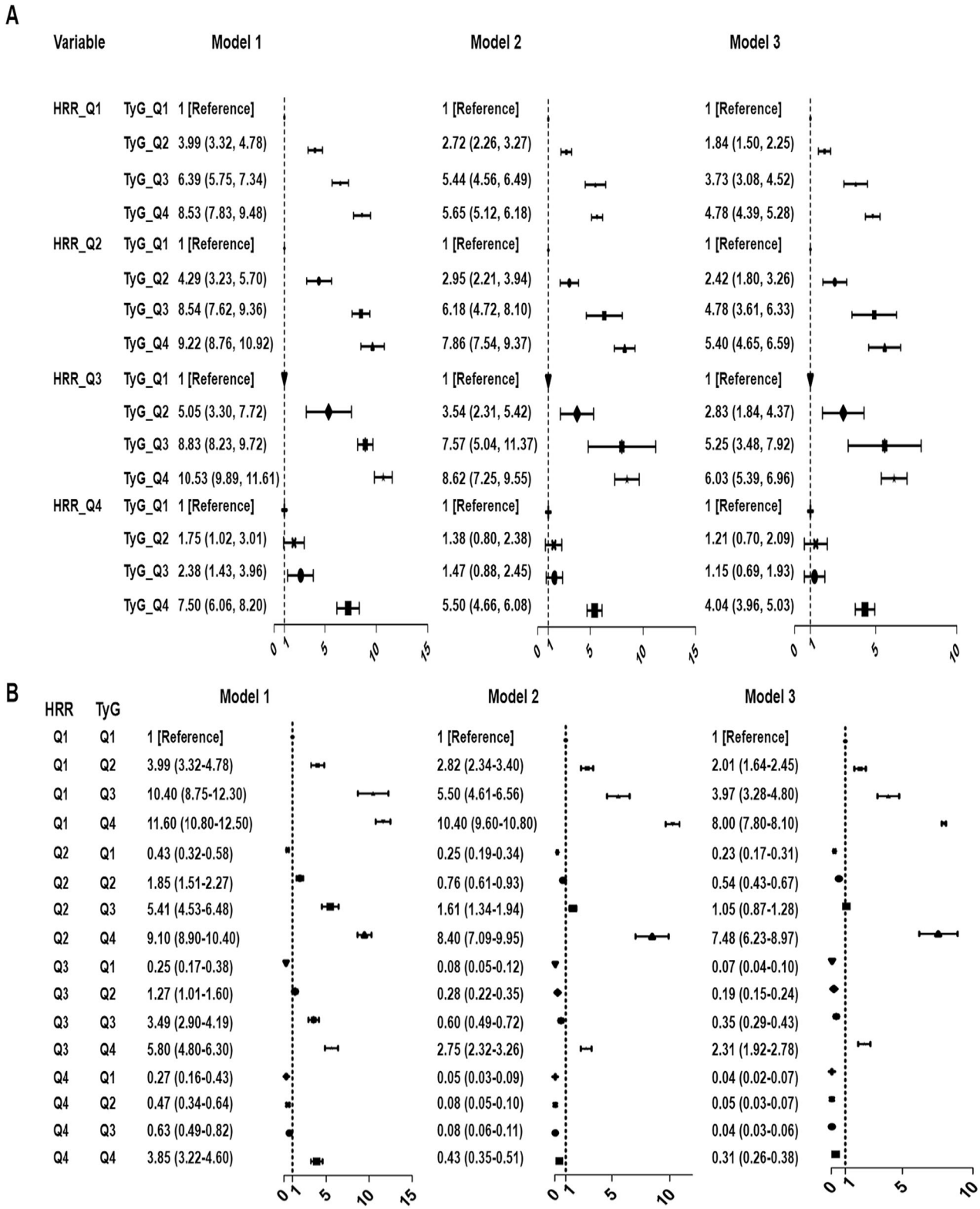

Fig. 2 Interacting and joint effects of TyG and HRR on DS. A Associations of TyG with DS by HRR; **B** Joint associations of TyG and HRR with DS. Model 1: Crude. Model 2: Adjusted for gender, age, marital status, smoking, drinking, body mass index. Model 3: Adjusted for hypertension, diabetes, dyslipidemia, plus variable in model 2. HRR_Q1 = [1.17, 9.55]; HRR_Q2 = (9.55, 10.51]; HRR_Q3 = (10.51, 11.48]; HRR_Q4 = (11.48, 15.50]; TyG_Q1 = [3.69, 8.21]; TyG_Q2 = (8.21, 8.61]; TyG_Q3 = (8.61, 9.04]; TyG_Q4 = (9.04, 12.72]; HRR hemoglobin-to-red cell distribution width ratio, TyG triglyceride-glucose, DS depression symptom, CI confidence interval, OR odds ratio.

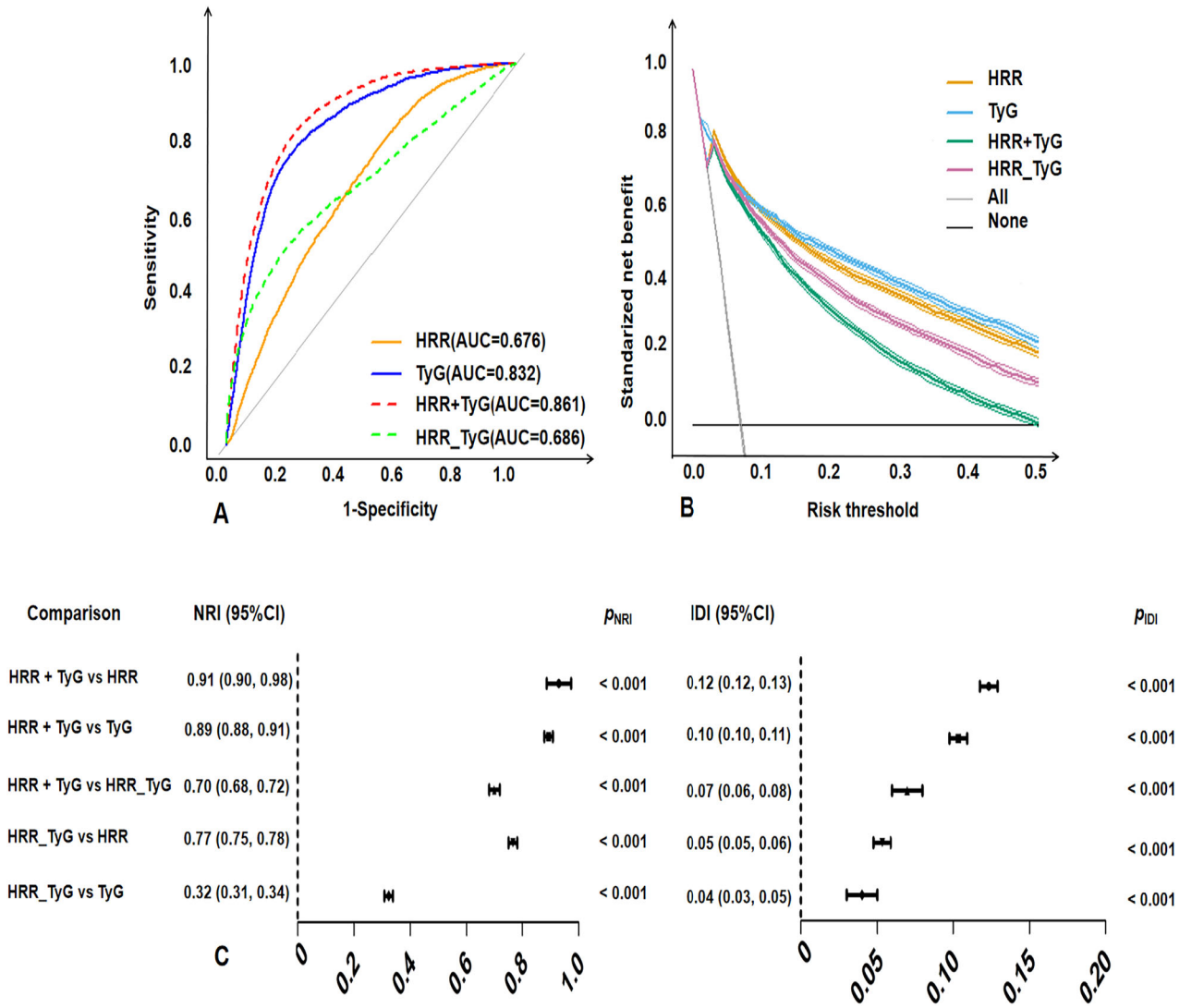

Fig. 3 Predictive performance of the combined TyG and HRR for DS. A The receiver operating characteristic (ROC) curve evaluating the discriminative capabilities by calculating the AUC; **B** Decision curve analysis to compare the clinical utility, the y-axis represents net benefits, calculated by subtracting the relative harm (false positives) from the benefits (true positives). The x-axis calculates the threshold probability; **C** NRI and IDI index for TyG combined with HRR. HRR, hemoglobin-to-red cell distribution width ratio; TyG, triglyceride-glucose; DS, depression symptom. HRR_TyG was calculated from normalized HRR×TyG. HRR+TyG represents the combined effect of normalized HRR and TyG.

that the HRR + TyG model (AUC = 0.861) offered significant advantages in DS risk prediction, with clinical translation potential for high-risk population screening and personalized intervention strategies. By incorporating both HRR and TyG indicators into routine health examinations, low-cost identification of high-risk individuals (HRR_Q1 + TyG_Q4) becomes feasible. For populations with elevated TyG, lifestyle interventions or pharmacological treatments could be implemented to modulate insulin sensitivity, while those with low HRR would require correction of iron metabolism imbalances. DCA further confirmed the model's clinical net benefit within the 10–30% threshold probability range, highlighting its utility as a stratification tool.

The complex mediating effects of TyG in women may originate from estrogen's dynamic regulation of hepcidin, with cyclical iron loss exacerbating monoamine neurotransmitter synthesis impairment associated with low HRR [42, 43]. Meanwhile, subcutaneous fat distribution patterns amplify IR-driven inflammatory cascades through adiponectin/leptin imbalance. In younger populations (<45 years), heightened metabolic activity promotes ectopic lipid deposition, activating M1 polarization of adipose tissue macrophages and intensifying TyG-mediated neuroinflammation [44]. In contrast, older adults (≥60 years) exhibit diminished HRR protection due to age-related chronic low-grade inflammation and iron accumulation-induced oxidative damage, allowing TyG's metabolic pathology to dominate [45]. Married individuals demonstrated significant antagonistic effects, likely attributable to social support's buffering effect on HPA axis reactivity [46]. This mechanism reduces cortisol peaks, improves insulin sensitivity, and enhances high HRR's compensatory capacity against metabolic damage. Unmarried individuals, lacking such protective buffering, proved more vulnerable to HRR/TyG imbalance. It should be noted that multiple comparisons may increase the risk of false positive results. To mitigate this risk, we employed a sequential covariate adjustment strategy during model construction. However, given the exploratory nature of subgroup analyses, future studies should validate these findings using larger sample sizes or more stringent statistical corrections (e.g., the Bonferroni method). These results may provide preliminary directions for personalized interventions but they should be interpreted with caution.

This study has several limitations. First, the cross-sectional design precludes definitive conclusions about causal relationships between HRR/TyG and DS, necessitating further investigation through prospective cohort studies or randomized controlled trials. Second, the study did not adjust for important psychosocial confounders such as socioeconomic status, sleep, diet, or chronic stress, which may influence both TyG/HRR levels and depressive symptoms. The absence of these data limits our ability to fully disentangle the observed associations. However, the robustness across multiple adjusted models and subgroup analyses suggests that the antagonistic interaction between HRR and TyG is unlikely to be entirely driven by unmeasured psychosocial factors. Future prospective studies should prioritize integrating comprehensive psychosocial assessments. Additionally, the lack of neuroimaging data limits mechanistic interpretation depth. Finally, and importantly, as the data were collected exclusively from a single city in China, the results may be influenced by regional characteristics, lifestyle factors, and healthcare practices specific to the study population, limiting the generalizability of our findings. Future validation across diverse geographic regions and populations is essential.

CONCLUSIONS

This study for the first time reveals the antagonistic effects of HRR and TyG on the risk of DS, and proposes a novel mechanism of the inflammation-metabolism interaction. The combined model of HRR and TyG provides a biomarker panel featuring low cost and high efficiency for screening high risk populations of DS. In the future, intervention strategies targeting iron metabolism and IR could be implemented to reduce the risk of DS.

DATA AVAILABILITY

Due to privacy or ethical restrictions, the data supporting this study are not publicly available. Researchers interested in accessing the data should contact Prof. Lu directly.

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AUTHOR CONTRIBUTIONS

Mingfei Jiang: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. Xiaoran Li: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. Yong Lu: Methodology, Investigation, Supervision, Data curation, Writing – review & editing, Resources. Co-first author, Mingfei Jiang and Xiaoran Li contributed equally to this work.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS

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