Research Square

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Behavioral–Physiological Risk Discordance and Incident Cardiometabolic Multimorbidity in Middle-Aged and Ol der Chinese Adults: A Longitudinal Analysis Based on CHARLS

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Research Article

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Abstract

Background

The behavioral–physiological risk discordance index (BPRDI) was constructed as an integrated indicator of behavioral risk and physiological burden. However, research on the relationship between behavioral–physiological risk discordance and incident cardiometabolic multimorbidity (CMM) is limited. This study aimed to investigate the associations of BPRDI and BRS4–PLS phenotypes with incident CMM risk.

Methods

Participants were drawn from the China Health and Retirement Longitudinal Study (CHARLS). Incident CMM was defined as the occurrence of cardiometabolic multimorbidity during follow-up among participants free of CMM at baseline. BRS4–PLS phenotypes were used to classify behavioral–physiological risk patterns, and BPRDI was calculated to quantify discordance between behavioral risk and physiological load. To assess the associations of BPRDI and BRS4–PLS phenotypes with incident CMM risk, Cox regression and restricted cubic spline (RCS) regression models were applied.

Results

A total of 7,454 participants were included in the study, among whom 690 (9.3%) developed incident CMM. The risk of CMM increased with higher levels of BPRDI. In the multivariable-adjusted model, Cox regression analysis showed that each 1-unit increase in BPRDI was associated with a significantly increased risk of incident CMM (HR = 1.21, 95% CI: 1.13–1.31, P < 0.001). RCS analysis demonstrated an approximately linear association between BPRDI and CMM risk (P for nonlinearity = 0.965). BRS4–PLS phenotype classification identified four distinct behavioral–physiological risk patterns: Low-Low, High-Low, Low-High, and High-High. Compared with the Low-Low phenotype, participants in the Low-High and High-High phenotypes had significantly higher risks of incident CMM, whereas the High-Low phenotype showed weaker and mostly nonsignificant associations. Furthermore, the model incorporating both BPRDI and BRS4–PLS phenotypes showed the highest predictive performance for 5-year incident CMM risk (AUC = 0.839), with a modest but significant improvement compared with the base model (AUC = 0.827, P = 0.042).

Conclusion

This study demonstrates that both BPRDI and BRS4–PLS phenotypes are associated with incident CMM risk in middle-aged and older adults. Participants with physiological-load-dominant and dual-high-risk phenotypes may have a significantly increased risk of incident CMM, suggesting that behavioral–physiological risk discordance may provide additional value for cardiometabolic risk stratification.

Research insights

What is currently known about this topic?

Current understanding suggests that adverse behavioral profiles and elevated physiological load are both associated with an increased risk of cardiometabolic multimorbidity. However, existing evidence has primarily examined behavioral risk and physiological burden separately, with limited attention to behavioral–physiological discordance and its role in identifying high-risk phenotypes.

What is the key research question?

What is the association between behavioral–physiological risk discordance, as reflected by BPRDI and BRS4–PLS phenotypes, and the incidence of cardiometabolic multimorbidity among middle-aged and older adults?

What is new?

This study provides evidence that behavioral–physiological risk discordance is associated with incident cardiometabolic multimorbidity. Higher BPRDI levels were associated with increased CMM risk, with an approximately linear risk pattern. In phenotype-based analyses, participants in the Low-High and High-High BRS4–PLS groups showed a higher risk of incident CMM compared with those in the Low-Low group, whereas the High-Low group showed weaker and mostly nonsignificant associations. The combined model incorporating BPRDI and BRS4–PLS phenotype also showed modest incremental predictive value for 5-year incident CMM risk.

How might this study influence clinical practice?

In summary, this study provides new evidence supporting the use of integrated behavioral–physiological risk assessment for identifying individuals at high risk of cardiometabolic multimorbidity. Clinically, BPRDI and BRS4–PLS phenotypes may serve as low-cost and accessible risk stratification tools, helping to identify individuals with elevated physiological burden even when behavioral risk appears relatively low, and informing targeted prevention and early management strategies.

Introduction

Cardiometabolic multimorbidity is a chronic systemic disorder caused by metabolic dysregulation and vascular injury, and it has become an increasingly serious public health challenge among middle-aged and older adults[1]. According to the China Health and Retirement Longitudinal Study (CHARLS), cardiometabolic multimorbidity (CMM) increased substantially among middle-aged and older Chinese adults from 2011 to 2020, and it has become an important contributor to disability and health-care burden[2]. Although cardiometabolic disease prevention has improved since 2011, the burden of cardiometabolic multimorbidity in China remains substantial[3]. Therefore, there is an urgent need to

develop cost-effective and reproducible risk stratification measures to more effectively identify high-risk populations.

Behavioral risk and physiological burden represent two interrelated but non-equivalent dimensions of cardiometabolic risk[4]. Behavioral risk, reflected by smoking, alcohol consumption, sleep duration, and physical activity, may contribute to long-term metabolic and vascular injury, whereas physiological load captures accumulated biological dysregulation involving adiposity, blood pressure, glucose metabolism, lipid metabolism, inflammation, and renal function[5, 6]. Discordance between behavioral risk and physiological load may therefore represent a potentially informative risk pattern for CMM, particularly when elevated physiological burden is present despite apparently low behavioral risk[7, 8]. In the present study, BPRDI was constructed to quantify the relative discordance between behavioral risk and physiological load, and BRS4–PLS phenotypes were used to classify distinct behavioral–physiological risk patterns.

Physiological load score (PLS) is a composite biological burden indicator closely associated with cardiometabolic disease risk[9]. Research has shown a significant interaction between behavioral risk and physiological load, suggesting that relying on a single risk dimension may underestimate the true risk[10].

Previous evidence indicates that integrating lifestyle-related risk factors with cumulative physiological burden may provide a more informative framework for cardiometabolic risk stratification [11, 12]. Given the synergistic role of behavioral risk and physiological load in CMM development, BPRDI was constructed as a dual-domain index integrating behavioral and physiological indicators, providing a more comprehensive reflection of cardiometabolic risk [13]. Integrated behavioral–physiological risk frameworks have shown potential value in evaluating the risk of cardiometabolic diseases, including diabetes, ischemic heart disease, stroke, cardiovascular disease, and CMM [14–18]. However, although lifestyle-related risk factors and cumulative physiological burden have been linked to cardiometabolic multimorbidity, systematic evidence remains limited regarding the association between behavioral–physiological discordance phenotypes and incident CMM risk in the general population [19, 20]. Most existing studies rely on single time-point measurements, which fail to capture the dynamic evolution of behavioral physiological burden and lack longitudinal analysis of BPRDI phenotypes. Multi-time-point cumulative indicators and discordance patterns may offer a more accurate reflection of the synergistic effects between lifestyle risk and physiological burden.

Therefore, this study utilizes data from the China Health and Retirement Longitudinal Study (CHARLS), a national longitudinal cohort, to evaluate the role of BPRDI and behavioral physiological discordance phenotypes in CMM risk stratification among middle-aged and elderly populations. This will provide evidence for the early identification of high-risk CMM populations and the development of individualized prevention strategies.

Methods

Study design and participants

This study utilized data from the China Health and Retirement Longitudinal Study (CHARLS). CHARLS is an ongoing national cohort study designed to collect high-quality microdata representing households and individuals aged 45 and above in China. The primary aim of the study is to analyze issues related to population aging and promote interdisciplinary research on aging. The CHARLS questionnaire covers various aspects, including personal demographic information, family structure and economic support, health status, physical measurements, healthcare utilization and insurance, employment, retirement and pensions, income, consumption, assets, and community characteristics. The baseline national survey was conducted in 2011 (Wave 1), covering a random sample of over 10,000 households from 150 counties and 450 villages across China. Follow-up surveys were conducted in 2013 (Wave 2), 2015 (Wave 3), 2018 (Wave 4), and 2020 (Wave 5). Blood samples were collected during the Wave 1 and Wave 3 surveys. The design of the CHARLS study has been previously described[21]. This study, based on the CHARLS research, is a secondary analysis of a time-limited longitudinal survey, using the first wave with complete BPRDI assessment as the exposure baseline, with follow-up extending through Wave 5. Exclusion criteria for this study were as follows: (1) absence of a complete BPRDI exposure wave; (2) age < 45 years at the exposure baseline; (3) prevalent CMM at the exposure baseline; (4) missing follow-up after the exposure baseline (Fig. 1).

CHARLS has received approval from the Institutional Review Board of Peking University (IRB00001052-11015 for the household survey and IRB00001052-11014 for blood samples), and all participants provided written informed consent before participation.

Assessment of BPRDI phenotypes

The primary exposures in this study were baseline BPRDI, BPRDI quartiles, and BRS4–PLS phenotypes assessed at the first complete exposure wave from the 2011 or 2015 CHARLS surveys[13]. BPRDI was calculated using the formula: (PLS − mean PLS)/SD PLS − (BRS4 − mean BRS4)/SD BRS4. The cumulative BPRDI was calculated using a linear model, as shown in the following formula: cumulative BPRDI = (BPRDI at the index baseline + BPRDI at the next complete follow up)/2 × time interval between the index baseline and the next complete follow up. Here, BPRDIindex and BPRDInext represent the BPRDI values measured at the index baseline and the next complete follow up survey, with the time interval defined as the number of years between the two measurements. The average of these two BPRDI measurements was calculated to reflect the mean discordance level, and then multiplied by the duration to estimate long term cumulative BPRDI exposure. This method follows the approach for calculating cumulative exposure indicators in CHARLS-based longitudinal analyses, which is consistent with the methods described by Wu et al. and Ma et al. [22, 23]. K-means clustering based on BPRDI values at the index baseline and the next follow-up survey was used only as a descriptive exploratory analysis to

visualize longitudinal BPRDI change patterns and was not included as a primary exposure in the main Cox regression models (Fig. 2).

Determination of incident CMM events

CMM events were identified using the following standardized doctor diagnosis questions for diabetes, heart disease, and stroke: “Have you been diagnosed with this condition by a doctor?” Participants who provided positive responses for two or more of these conditions during follow-up were classified as having incident CMM. Additionally, if participants reported diabetes, heart disease, or stroke in a prior follow up, confirmation of the disease occurrence was sought in the subsequent visit. In cases where participants denied a previously self reported diagnosis of diabetes, heart disease, or stroke, inconsistencies were retrospectively corrected. Participants were assessed in subsequent CHARLS follow-up surveys in 2013, 2015, 2018, and 2020, depending on their index baseline. If a participant developed CMM during any follow-up before 2020, no further event assessments were conducted. Otherwise, participants were monitored until 2020. The occurrence time of incident CMM is defined as the difference between the follow up time point and the index baseline year[24].

Data collection

Baseline data for participants were carefully collected by trained interviewers using structured questionnaires. The data collected included the following categories: (1) Demographic and Lifestyle Data: This section included information on gender, age, residence, education level, marital status, smoking status, alcohol consumption, sleep duration, and physical activity. (2) Physical Measurements: Recorded measurements included height, weight, waist circumference, body mass index (BMI), and both systolic blood pressure (SBP) and diastolic blood pressure (DBP). (3) Medical History and Disease Status: This section included information on existing conditions such as heart disease, hypertension, diabetes, stroke, and kidney disease. (4) Laboratory Test Data: Laboratory data collected included fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), HbA1c, and creatinine. Hypertension was defined by meeting at least one of the following criteria: (1) Systolic blood pressure ≥ 140 mmHg, (2) Diastolic blood pressure ≥ 90 mmHg, (3) Self-reported physician-diagnosed hypertension.

Statistical analysis

Participants were grouped based on BRS4–PLS phenotypes and quartiles of BPRDI, while longitudinal BPRDI change patterns were visualized descriptively. Continuous variables following a normal distribution were expressed as mean ± standard deviation (SD), and those not normally distributed were presented as median (interquartile range, IQR). Categorical variables were reported as frequencies and percentages. For group comparisons, chi-square (x2) tests were used for categorical variables, analysis

of variance (ANOVA) for normally distributed continuous variables, and the Kruskal–Wallis test for non-normally distributed data.

This study utilized BPRDI data from the index baseline and the next follow up survey to classify subjects into subgroups with different behavioral physiological discordance patterns using the K means clustering algorithm. K-means is an unsupervised learning method that optimizes intra-cluster homogeneity and inter-cluster heterogeneity by minimizing the within-cluster sum of squares (WCSS). We employed the elbow method to determine the optimal number of clusters. In this approach, we plotted the relationship between the WCSS and the number of clusters, identifying the point where the reduction in the sum of squared distances began to slow down, commonly referred to as the elbow.

Based on this analysis, we selected three clusters, as this point represents where the curve flattens, indicating that three clusters best balance model simplicity and explanatory accuracy while avoiding overfitting (Fig. 2A). Three Cox proportional hazards models were constructed to evaluate the associations of baseline BPRDI, BPRDI quartiles, and BRS4–PLS phenotypes with incident CMM risk. The specific models were: Model 1 (unadjusted), Model 2 (adjusted for age, gender, residence, marital status, education level, and index baseline wave), and Model 3 (further adjusted for baseline CMD count, hypertension, kidney disease, health insurance, and household wealth based on Model 2). In Model 3, we employed the Benjamini–Hochberg procedure to adjust for the false discovery rate (FDR), thereby reducing the likelihood of type I errors arising from multiple testing. Additionally, restricted cubic spline (RCS) regression analysis was used to explore potential nonlinear relationships between BPRDI, PLS, and incident CMM. We calculated the 5-year time-dependent area under the receiver operating characteristic curve (AUC) to evaluate the predictive performance of models incorporating BPRDI, BRS4, PLS, and BRS4–PLS phenotypes for incident CMM risk. Finally, subgroup analyses were conducted, stratified by age, gender, residence, smoking status, alcohol consumption, hypertension, diabetes, and heart disease, to examine the relationship between BPRDI phenotypes and incident CMM risk across various populations, with all models adjusted as per Model 3.

All statistical analyses were performed using Python version 3.9. Two-sided P values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

In accordance with the inclusion and exclusion criteria of this study, 25,873 participants with valid longitudinal records were initially identified from the CHARLS cohort. Of these, 16,772 participants were excluded due to absence of a complete BPRDI exposure wave. An additional 1,647 participants were excluded due to age < 45 years at the index baseline, prevalent CMM at the index baseline, or lack of valid follow up after the index baseline (Fig. 1). Ultimately, 7,454 participants were included in this analysis, comprising 3,432 males (46%), with an average age of 59.76 ± 9.08 years. During a median

follow up period of 5 years, 690 participants (9.3%) developed incident CMM. The median BPRDI, BRS4, and PLS at the index baseline were 0.14, 2.00, and 2.00, respectively.

Table 1
Baseline characteristics of the study population based on BRS4–PLS phenotypes

Characteristic	Overall n = 7,454	Low-Low n = 1,206	High-Low n = 1,003	Low-High n = 2,424	High-High n = 2,821	p-value
Age, Mean (SD)	59.76 (9.08)	57.02 (8.62)	59.31 (8.90)	59.58 (8.80)	61.25 (9.26)	< 0.001
Gender, n (%)						< 0.001
Male	3,432 (46)	236 (20)	589 (59)	792 (33)	1,815 (64)	
Female	4,022 (54)	970 (80)	414 (41)	1,632 (67)	1,006 (36)	
Education, n (%)						< 0.001
No formal education	3,626 (49)	639 (53)	483 (48)	1,240 (51)	1,264 (45)	
Primary school	1,635 (22)	244 (20)	204 (20)	527 (22)	660 (23)	
Middle school	1,459 (20)	220 (18)	207 (21)	453 (19)	579 (21)	
High school or above	734 (9.8)	103 (8.5)	109 (11)	204 (8.4)	318 (11)	
Marital status, n (%)						0.391
Other	1,180 (16)	191 (16)	169 (17)	360 (15)	460 (16)	
Married	6,274 (84)	1,015 (84)	834 (83)	2,064 (85)	2,361 (84)	
Residence, n (%)						< 0.001
Urban	4,829 (65)	850 (70)	708 (71)	1,558 (64)	1,713 (61)	
Rural	2,625 (35)	356 (30)	295 (29)	866 (36)	1,108 (39)	
Hypertension, n (%)	2,078 (28)	160 (13)	114 (11)	834 (35)	970 (35)	< 0.001
Diabetes, n (%)	393 (5.3)	20 (1.7)	25 (2.5)	182 (7.6)	166 (5.9)	< 0.001
Heart disease, n (%)	915 (12)	105 (8.7)	98 (9.9)	325 (14)	387 (14)	< 0.001
Stroke, n (%)	128 (1.7)	13 (1.1)	11 (1.1)	49 (2.0)	55 (2.0)	0.057
Kidney disease, n (%)	526 (7.1)	75 (6.3)	67 (6.7)	173 (7.2)	211 (7.6)	0.492

Characteristic	Overall n = 7,454	Low-Low n = 1,206	High-Low n = 1,003	Low-High n = 2,424	High-High n = 2,821	p-value
Smoker, n (%)	2,152 (29)	79 (6.6)	510 (51)	168 (6.9)	1,395 (49)	< 0.001
Drinking, n (%)	2,535 (34)	116 (9.6)	564 (56)	243 (10)	1,612 (57)	< 0.001
Abnormal sleep, n (%)	2,602 (35)	192 (16)	564 (56)	297 (12)	1,549 (55)	< 0.001
Low physical activity, n (%)	4,673 (63)	525 (44)	713 (71)	1,226 (51)	2,209 (78)	< 0.001
Waist, Mean (SD)	86.00 (10.10)	80.42 (7.76)	80.18 (7.13)	88.79 (9.95)	88.04 (10.21)	< 0.001
BMI, Mean (SD)	23.76 (3.80)	22.07 (2.70)	21.54 (2.54)	25.03 (3.88)	24.18 (3.90)	< 0.001
SBP, Mean (SD)	128.31 (20.37)	118.75 (15.47)	118.41 (15.65)	132.09 (21.14)	132.66 (20.44)	< 0.001
DBP, Mean (SD)	75.25 (11.72)	69.71 (9.07)	69.52 (9.40)	77.21 (11.92)	77.97 (11.79)	< 0.001
HDL, Mean (SD)	51.32 (13.52)	55.33 (11.48)	55.68 (12.84)	49.20 (12.60)	49.89 (14.58)	< 0.001
LDL, Mean (SD)	109.61 (32.15)	104.18 (25.52)	101.15 (25.03)	115.02 (34.73)	110.31 (33.63)	< 0.001
TC, Mean (SD)	188.90 (37.17)	178.51 (28.85)	175.87 (27.81)	195.49 (39.25)	192.32 (39.26)	< 0.001
TG, Mean (SD)	136.37 (90.29)	98.15 (44.85)	94.28 (44.29)	151.53 (92.36)	154.68 (104.29)	< 0.001
Glu, Mean (SD)	105.11 (30.85)	96.81 (16.24)	96.08 (17.18)	109.25 (34.77)	108.32 (34.28)	< 0.001
HbA1c, Mean (SD)	5.59 (0.93)	5.23 (0.57)	5.24 (0.56)	5.76 (1.00)	5.72 (1.02)	< 0.001
CRP, Mean (SD)	2.56 (6.09)	1.05 (1.75)	1.25 (2.54)	3.15 (6.17)	3.16 (7.71)	< 0.001
Crea, Mean (SD)	0.79 (0.26)	0.69 (0.13)	0.74 (0.14)	0.79 (0.29)	0.84 (0.30)	< 0.001
BRS4, Mean (SD)	1.60 (0.95)	0.76 (0.43)	2.34 (0.57)	0.80 (0.40)	2.40 (0.60)	< 0.001
PLS, Mean (SD)	2.39 (1.45)	0.70 (0.46)	0.73 (0.45)	3.08 (1.09)	3.12 (1.10)	< 0.001

Characteristic	Overall n = 7,454	Low-Low n = 1,206	High-Low n = 1,003	Low-High n = 2,424	High-High n = 2,821	p-value
BPRDI, Mean (SD)	0.13 (1.35)	-0.16 (0.54)	-1.80 (0.66)	1.45 (0.84)	-0.20 (0.99)	< 0.001
Incident CMM, n (%)	690 (9.3)	45 (3.7)	46 (4.6)	295 (12)	304 (11)	< 0.001

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; Glu: fasting blood glucose; HbA1c: glycated hemoglobin; CRP: C-reactive protein; Crea: creatinine; BRS4: behavioral risk score; PLS: physiological load score; BPRDI: behavioral–physiological risk discordance index; CMM: cardiometabolic multimorbidity; SD: standard deviation.

Table 1 summarizes the baseline characteristics of participants categorized into four groups based on BRS4 and PLS phenotypes: (1) the Low-Low group (n = 1,206), characterized by low behavioral risk and low physiological load; (2) the High-Low group (n = 1,003), characterized by high behavioral risk and low physiological load; (3) the Low-High group (n = 2,424), characterized by low behavioral risk and high physiological load; (4) the High-High group (n = 2,821), characterized by high behavioral risk and high physiological load. Compared with the Low-Low group, participants in the two high physiological load groups were older and had higher BMI, waist circumference, systolic and diastolic blood pressure, fasting glucose, HbA1c, total cholesterol, triglycerides, LDL cholesterol, C-reactive protein, and creatinine, as well as lower HDL cholesterol. They also had higher prevalences of hypertension and baseline cardiometabolic disease components, particularly diabetes and heart disease, whereas stroke showed only a borderline between-group difference. Participants in the two high behavioral risk groups were more likely to be male, current smokers, current drinkers, have abnormal sleep duration, and have low physical activity. During a median follow-up period of 5 years, 690 participants (9.3%) developed incident CMM. The incidence of CMM was higher in the Low-High group (12.0%) and High-High group (11.0%) than in the Low-Low group (3.7%) and High-Low group (4.6%). The supplementary table presents similar baseline characteristics of participants grouped by BPRDI quartiles.

Table 2
Multivariate Cox regression of the relationships between BPRDI, BRS4–PLS phenotypes and the risk of new-onset CMM

	Model 1		Model 2		Model 3		P value^{FDR}
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	
BPRDI	1.38 (1.30, 1.46)	< 0.001	1.37 (1.29, 1.45)	< 0.001	1.21 (1.13, 1.31)	< 0.001	< 0.001
Quartiles of BPRDI							
Q1	Reference		Reference		Reference		
Q2	1.44 (1.15, 1.81)	0.002	1.44 (1.14, 1.82)	0.002	1.26 (0.94, 1.68)	0.128	0.149
Q3	1.90 (1.52, 2.36)	< 0.001	1.89 (1.50, 2.37)	< 0.001	1.47 (1.09, 1.98)	0.012	0.017
Q4	2.96 (2.40, 3.65)	< 0.001	2.88 (2.32, 3.57)	< 0.001	1.92 (1.44, 2.56)	< 0.001	< 0.001
P for trend		< 0.001		< 0.001		< 0.001	
BRS4–PLS phenotypes							
Low-Low	Reference		Reference		Reference		
High-Low	1.17 (0.83, 1.64)	0.381	1.22 (0.86, 1.73)	0.271	1.16 (0.78, 1.72)	0.470	0.470
Low-High	3.70 (2.86, 4.80)	< 0.001	3.57 (2.74, 4.64)	< 0.001	2.47 (1.87, 3.25)	< 0.001	< 0.001
High-High	3.46 (2.68, 4.48)	< 0.001	3.53 (2.68, 4.64)	< 0.001	2.51 (1.90, 3.33)	< 0.001	< 0.001
Model 1 was unadjusted							

Model 2 was adjusted for age, sex, residence, marital status, education level, and index baseline wave

Model 3 was adjusted for age, sex, residence, marital status, education level, index baseline wave, baseline CMD count, hypertension, kidney disease, health insurance, and household wealth

BPRDI: behavioral–physiological risk discordance index; BRS4: behavioral risk score; PLS: physiological load score; CMM: cardiometabolic multimorbidity; CMD: cardiometabolic disease

*P value adjusted using the False Discovery Rate (FDR) correction

Association between BPRDI/BRS4–PLS phenotypes and incident CMM risk

Three Cox proportional hazards models were developed to assess the association between BPRDI/BRS4–PLS phenotypes and incident CMM risk (Table 2). In the unadjusted Model 1, each 1-unit increase in BPRDI was significantly associated with a 38% higher incident CMM risk (HR = 1.38, 95% CI: 1.30–1.46, P < 0.001). After adjusting for demographic and socioeconomic factors (Model 2), the hazard ratio remained significant (HR = 1.37, 95% CI: 1.29–1.45, P < 0.001). Further adjustment for baseline CMD count, hypertension, and kidney disease still showed a significant association, with each 1-unit increase in BPRDI linked to a 21% increase in incident CMM risk (HR = 1.21, 95% CI: 1.13–1.31, P < 0.001, FDR-adjusted P < 0.001). Compared to the lowest BPRDI quartile group (Q1), the highest quartile group (Q4) showed a 92% increased risk of incident CMM (HR = 1.92, 95% CI: 1.44–2.56, P < 0.001, FDR-adjusted P < 0.001), with the risk incrementally rising across BPRDI quartiles (P for trend < 0.001). In terms of BRS4–PLS phenotypes, compared to the Low-Low group, the Low-High group had a 147% higher risk (HR = 2.47, 95% CI: 1.87–3.25, P < 0.001, FDR-adjusted P < 0.001), and the High-High group had a 151% higher risk (HR = 2.51, 95% CI: 1.90–3.33, P < 0.001, FDR-adjusted P < 0.001). By contrast, the High-Low group was not significantly associated with incident CMM risk after full adjustment (HR = 1.16, 95% CI: 0.78–1.72, P = 0.470, FDR-adjusted P = 0.470). A restricted cubic spline regression model adjusting variables from Model 3 indicated an approximately linear increase in incident CMM risk with increasing BPRDI (P for overall < 0.001; P for nonlinearity = 0.965) (Fig. 3).

Figure 4 shows that the model incorporating both BPRDI and BRS4–PLS phenotype achieved the highest 5-year time-dependent AUC for predicting incident CMM risk (AUC = 0.839), with a modest but significant improvement over the base model (AUC = 0.827, P = 0.042). The model adding BRS4–PLS phenotype also showed a slightly higher AUC than the base model (AUC = 0.837 vs. 0.827), with a borderline difference (P = 0.050). In contrast, adding BRS4 alone (AUC = 0.827, P = 0.533), BPRDI alone (AUC = 0.827, P = 0.987), or PLS alone (AUC = 0.835, P = 0.099) did not significantly improve predictive performance compared with the base model. In the single-marker analysis shown in Supplementary Fig. 1, PLS demonstrated the highest discriminatory ability for 5-year incident CMM risk (AUC = 0.670), followed by BPRDI (AUC = 0.615), BRS4–PLS phenotype (AUC = 0.607), and BRS4 (AUC = 0.512). While BPRDI-related dimensions showed limited predictive performance when used alone, the combined phenotype-based model demonstrated a modest incremental value beyond conventional clinical predictors.

Supplementary Fig. 1 Receiver operating characteristic curves for single-marker discrimination predicting 5-year incident CMM risk. BRS4, behavioral risk score; PLS, physiological load score; BPRDI, behavioral physiological risk discordance index; CMM, cardiometabolic multimorbidity; AUC, area under the receiver operating characteristic curve.

Subgroup analysis

A further analysis was conducted across selected subgroups of enrolled participants to evaluate the risk stratification value of BPRDI and BRS4–PLS phenotypes for incident CMM, including age, sex, residence, baseline CMD count, hypertension, diabetes, heart disease, and kidney disease. Figure 5 shows that higher BPRDI was associated with an increased risk of incident CMM across most subgroups, with no significant interactions detected among the selected strata. Similarly, BRS4–PLS phenotype-based analyses showed consistent risk patterns across subgroups. Compared with the Low-Low group, the Low-High and High-High groups were generally associated with higher incident CMM risk, whereas the High-Low group showed weaker and mostly nonsignificant associations. No significant interactions were detected across the selected subgroups in the phenotype-based analysis (Fig. 6).

Discussion

In this secondary analysis based on nationwide longitudinal cohort data, we investigated the potential impact of behavioral–physiological risk discordance and its phenotype-based patterns on the risk of incident cardiometabolic multimorbidity among middle-aged and older adults. Our primary findings are as follows: (1) Compared to individuals with low behavioral risk and low physiological load, those with low behavioral risk but high physiological load and those with high behavioral risk and high physiological load exhibited a higher risk of incident cardiometabolic multimorbidity. However, no significant interactions were detected across age, sex, residence, baseline CMD count, hypertension, diabetes, heart disease, or kidney disease, suggesting that this association was not materially modified by the selected subgroup factors. (2) Behavioral–physiological risk discordance, as reflected by BPRDI, was associated with incident cardiometabolic multimorbidity in middle-aged and older adults. Notably, there was an approximately linear trend in the association between BPRDI and CMM occurrence. These results provide support for the potential application of behavioral–physiological risk discordance as a clinical risk stratification indicator, suggesting that it may help identify phenotypes associated with the risk of incident cardiometabolic multimorbidity in middle-aged and older populations.

Previous studies have extensively explored the positive associations between individual behavioral risk factors, physiological burden indicators, and the risk of cardiometabolic multimorbidity[25]. Various cohort studies indicate that unfavorable lifestyle profiles, clinical risk factors, and elevated physiological burden are closely linked to an increased risk and progression of cardiometabolic multimorbidity [26–29]. Furthermore, Forrester et al. found that health behaviors, including smoking, diet, physical activity, and alcohol use, were associated with distinct allostatic-load profiles characterized by metabolic, cholesterol, and blood-pressure dysregulation, while Guan et al. reported in the SWAN cohort that unfavorable lifestyle factors were longitudinally associated with increased allostatic load [30, 31]. These findings suggest that unhealthy behaviors often coexist with elevated blood pressure, adiposity, dyslipidemia, glucose dysregulation, inflammation, and renal dysfunction, which are key components in the development of cardiometabolic multimorbidity. Adverse behavioral risk, as reflected by BRS4, may contribute to CMM risk through smoking, alcohol consumption, abnormal sleep duration, and physical inactivity, whereas elevated physiological load, as reflected by PLS, may further amplify this risk through

adiposity, hypertension, dysglycemia, dyslipidemia, systemic inflammation, and renal–metabolic dysfunction[32–35]. Concurrently, PLS, a composite indicator of physiological burden, is increasingly significant in cardiometabolic risk screening and risk assessment. Elevated PLS levels can reflect increased adiposity, blood pressure elevation, glucose and lipid dysregulation, systemic inflammation, and renal–metabolic impairment. These processes contribute to the development and progression of cardiometabolic dysfunction, which can ultimately lead to incident cardiometabolic multimorbidity[36–40]. Xu et al. analyzed data from 205,504 UK Biobank participants without cardiovascular disease at baseline and found that higher allostatic load, a composite indicator of multisystem physiological dysregulation, was associated with progressively increased cardiovascular disease risk [41]. Additionally, the Diabetes Prevention Program Research Group demonstrated that intensive lifestyle intervention targeting weight reduction, dietary modification, and physical activity significantly reduced the incidence of diabetes among individuals at high metabolic risk, supporting the value of targeted primary prevention for unfavorable behavioral and physiological risk profiles [42]. Similarly, Estruch et al. demonstrated in the PREDIMED trial that, among individuals at high cardiovascular risk but without cardiovascular disease at enrollment, a Mediterranean diet supplemented with extra-virgin olive oil or nuts significantly reduced the incidence of major cardiovascular events, supporting the role of targeted lifestyle intervention in primary prevention [43].

While behavioral risk factors and physiological burden indicators are established predictors of cardiometabolic disease, previous research has primarily focused on their independent relationships with cardiometabolic multimorbidity. The connection between behavioral risk and physiological load is complex. Rodriquez et al. showed that unhealthy behaviors, including smoking, excessive or binge drinking, insufficient physical activity, and poor diet, are closely examined in relation to allostatic load, a biomarker-based measure of cumulative physiological burden [44]. It significantly affects cardiometabolic homeostasis, altering glucose and lipid metabolism, increasing vascular burden, and worsening systemic physiological dysregulation[45]. Given the close relationship between behavioral risk and physiological burden, BPRDI, which reflects the discordance between these two domains, has recently gained increasing relevance in cardiometabolic risk stratification. For instance, Zhang et al. showed that higher Life's Essential 8 scores were associated with lower risks of cardiovascular outcomes and mortality, while Liu et al. reported that Life's Essential 8, insulin resistance, and CRP were jointly associated with CMM risk, supporting an integrated behavioral–physiological approach to cardiometabolic risk stratification [46, 47]. Yang et al. demonstrated that shift-work exposure was associated with an increased risk of cardiometabolic multimorbidity among patients with hypertension, while Zhu et al. reported that elevated allostatic load, as an indicator of cumulative physiological dysregulation, was associated with the progression of cardio-renal multimorbidity in a large UK Biobank cohort [48, 49]. These studies generally benefit from large sample sizes, high-quality cohort data, and robust multivariable adjustments. Recent evidence has further incorporated composite metabolic risk indices, subgroup analyses, and nonlinear dose–response modeling, thereby improving the characterization of behavioral risk, physiological burden, and cardiometabolic multimorbidity [50, 51].

However, much of the previous research has focused on single-domain measurements of behavioral risk or physiological load, overlooking their discordant patterns[52]. This lack of integrated evaluation of behavioral–physiological discordance could obscure risk heterogeneity, potentially compromising the accuracy of cardiometabolic risk stratification. Moreover, only a few studies have explored the joint impact of behavioral risk and physiological load on cardiometabolic outcomes, and evidence remains limited regarding the association between behavioral–physiological discordance and incident cardiometabolic multimorbidity[53]. Given that cardiometabolic multimorbidity encompasses the coexistence of multiple cardiometabolic diseases as a composite outcome, the specific contribution of behavioral–physiological discordance to disease clustering may be obscured when individual cardiometabolic conditions are examined separately.

Compared with previous studies, this research not only assesses behavioral–physiological risk discordance through BPRDI but also captures its phenotype-based patterns using BRS4–PLS classification, thereby enhancing the understanding of incident cardiometabolic multimorbidity risk. Our findings demonstrate that BPRDI, as an indicator of behavioral–physiological risk discordance, was significantly associated with incident cardiometabolic multimorbidity, with this association remaining robust after multivariable adjustment. Compared to individuals in the lowest BPRDI quartile, those in the highest quartile exhibited a substantially higher risk of incident cardiometabolic multimorbidity, with the incidence increasing from 5.5% to 14.1% across the two extreme quartiles. Furthermore, we performed a phenotype-based classification by jointly considering BRS4 and PLS, which identified four distinct groups: Low-Low, High-Low, Low-High, and High-High phenotypes. Notably, these four phenotypes showed distinct risk patterns: the Low-High and High-High groups were consistently associated with higher incident CMM risk, whereas the High-Low group showed weaker associations, suggesting that elevated physiological load may be more closely related to CMM development than behavioral risk alone. Consequently, caution is warranted in interpreting these phenotype-based results as reflecting behavioral risk alone. From a clinical perspective, the significance of behavioral risk may differ across physiological load levels, and elevated physiological burden appears to identify individuals at higher CMM risk even when behavioral risk is relatively low. For example, even among individuals with relatively low behavioral risk, elevated physiological load may reflect accumulated metabolic, inflammatory, renal, and vascular dysregulation, which was associated with higher incident CMM risk. This finding is consistent with recent evidence suggesting that lifestyle-related risk exposures and cumulative physiological dysregulation are both relevant to cardiometabolic disease clustering. Liu et al. reported that depression combined with insufficient vigorous physical activity was associated with a higher risk of incident cardiometabolic multimorbidity, whereas Memiah et al. showed that elevated allostatic load was associated with dual chronic conditions involving cardiovascular disease and diabetes [54, 55].

Our study also reveals that the predictive performance of the combined BPRDI and BRS4–PLS phenotype model for 5-year incident CMM risk was modestly superior to that of the base clinical model. While BPRDI and BRS4–PLS phenotypes demonstrated different overall predictive capabilities, the independent association of BPRDI with incident CMM suggests that relying on a single-domain

assessment may overlook latent high-risk groups with behavioral–physiological discordance, such as individuals with relatively low behavioral risk but elevated physiological load. This further emphasizes the clinical importance of jointly assessing behavioral risk and physiological load. Although the incremental gain in AUC was relatively small, it is important to note that these indicators are part of a larger predictive model, and their performance may improve when combined with other clinical, behavioral, and biomarker data. In clinical practice, even small improvements in predictive performance are meaningful, especially in complex cardiometabolic settings where multiple behavioral and physiological factors jointly influence disease progression[55]. Overall, this study provides new evidence for understanding the relationship between behavioral–physiological discordance, phenotype-based risk patterns, and incident cardiometabolic multimorbidity. Although the added predictive value of BPRDI alone was limited, our results support considering both behavioral–physiological discordance and phenotype-based risk patterns in cardiometabolic risk stratification. Particularly in settings with limited healthcare resources, BPRDI and BRS4–PLS phenotypes, as low-cost and easily accessible indicators, could help identify high-risk individuals and inform early intervention and clinical management.

This study has several limitations. First, incident cardiometabolic multimorbidity was identified based on self-reported physician-diagnosed cardiometabolic conditions, and the CHARLS dataset lacks complete medical record verification, making it difficult to fully validate the occurrence and timing of CMM events. However, previous research has shown that self-reported physician-diagnosed chronic diseases are generally consistent with clinical records and can be used in large-scale epidemiological studies[56, 57]. Furthermore, this study did not differentiate between different patterns of cardiometabolic multimorbidity, such as diabetes–heart disease, diabetes–stroke, or heart disease–stroke combinations, which may reduce the clinical specificity of the results. Second, BPRDI was assessed based on baseline behavioral and physiological profiles, which may not accurately reflect the true cumulative burden of behavioral–physiological discordance over time. The single-baseline assessment may not capture the full dynamic changes in behavioral–physiological discordance, and the relationship between BPRDI and incident CMM risk could be influenced by subclinical cardiometabolic disease, with potential reverse causality in the short term. Although subgroup analyses found no significant interactions between the selected stratifying factors and BPRDI or BRS4–PLS phenotypes, the possibility of residual confounding cannot be entirely excluded. Third, we were unable to obtain information on several factors that could influence BPRDI and BRS4–PLS phenotypes, such as medication use, dietary patterns, psychosocial stress, environmental exposures, or other chronic diseases. Additionally, there may be measurement variability or batch differences in physiological indicators, potentially affecting the calculation of PLS and the classification of BRS4–PLS phenotypes. Fourth, due to the lack of precise onset times for individual cardiometabolic diseases, the Cox proportional hazards regression model could only estimate incident CMM risk based on available follow-up intervals, potentially affecting the accuracy of the results. Fifth, this study was limited to middle-aged and older adults from a Chinese longitudinal cohort, which may restrict the external generalizability of the findings to other populations. Future studies should validate these results in other populations. Moreover, to further assess the robustness and clinical applicability of BPRDI and BRS4–PLS phenotype classification, sensitivity analyses based on alternative thresholds and

external validation cohorts could be considered. Finally, as an observational study, this research is subject to loss to follow-up and selection bias. Additionally, the observational design can only demonstrate associations, not causality. Although this study highlights the epidemiological association of BPRDI and BRS4–PLS phenotypes with incident CMM, more detailed longitudinal mechanisms need to be further validated in future research through repeated-measure cohorts, external validation, and mechanistic studies.

Conclusion

Overall, our findings suggest a significant association between behavioral–physiological risk discordance, its phenotype-based patterns, and the risk of incident cardiometabolic multimorbidity. Specifically, individuals with elevated BPRDI levels and those with high physiological load phenotypes, particularly the Low-High and High-High groups, showed a notably higher risk of incident cardiometabolic multimorbidity. While these results provide preliminary insights into behavioral–physiological risk stratification for cardiometabolic multimorbidity prevention, further studies in other cohorts are needed to validate and extend our findings.

Declarations

Ethics approval and consent to participate

CHARLS was approved by the Institutional Review Board of Peking University (approval numbers: IRB00001052-11015 for the household survey and IRB00001052-11014 for blood samples), and all participants provided written informed consent. The present study was conducted in accordance with the Declaration of Helsinki.

Competing interests

The authors declare no competing interests.

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Author Contribution

CQ: Writing – original draft, Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. WW: Writing – original draft, Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. QD: Writing – review & editing, Methodology, Formal analysis, Data curation, Visualization, Software. LK: Writing – review & editing, Validation, Resources,

Project administration. GL: Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. CQ and WW contributed equally to this work and share first authorship.

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Data Availability

The data supporting the findings of this study are available from the China Health and Retirement Longitudinal Study database. Researchers can apply for access to the CHARLS data through the official CHARLS platform.

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Figures

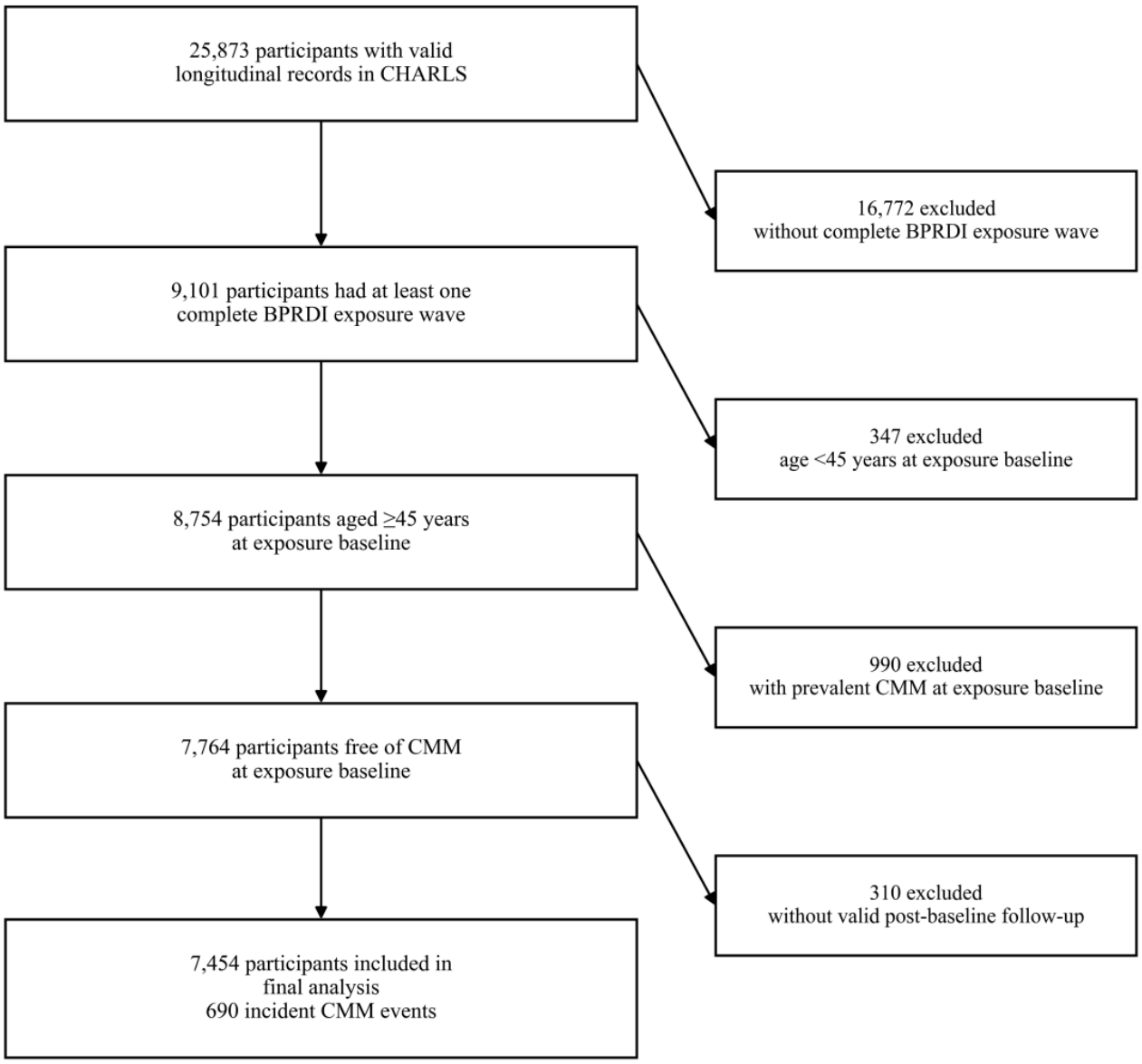


Figure 1

Flowchart of the study population

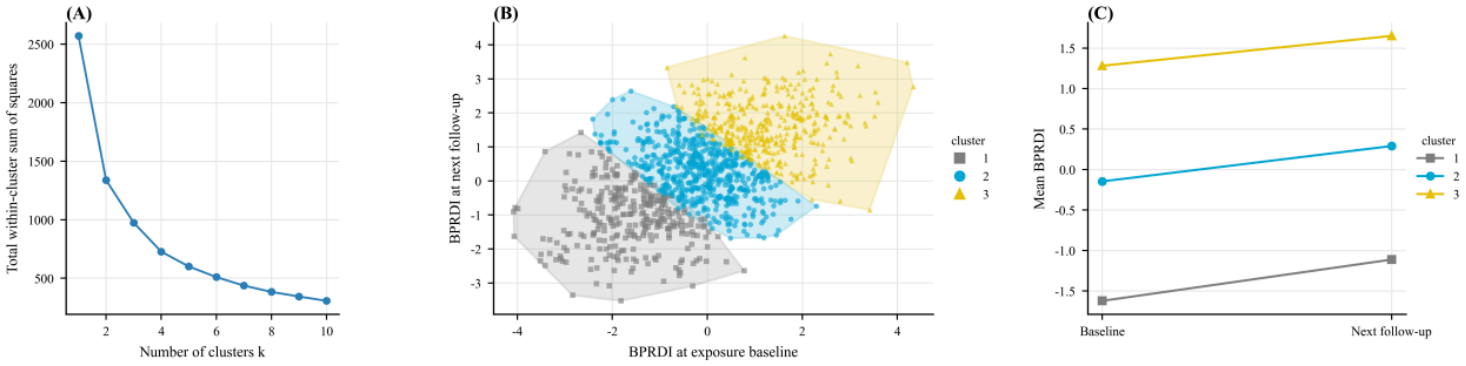


Figure 2

Clustering of the change in BPRDI from the index baseline to the next follow up survey. **A** K value determined according to the elbow method. **B** Three clusters were found via the K means method with Euclidean distance. **C** Change in BPRDI from the index baseline to the next follow up survey.

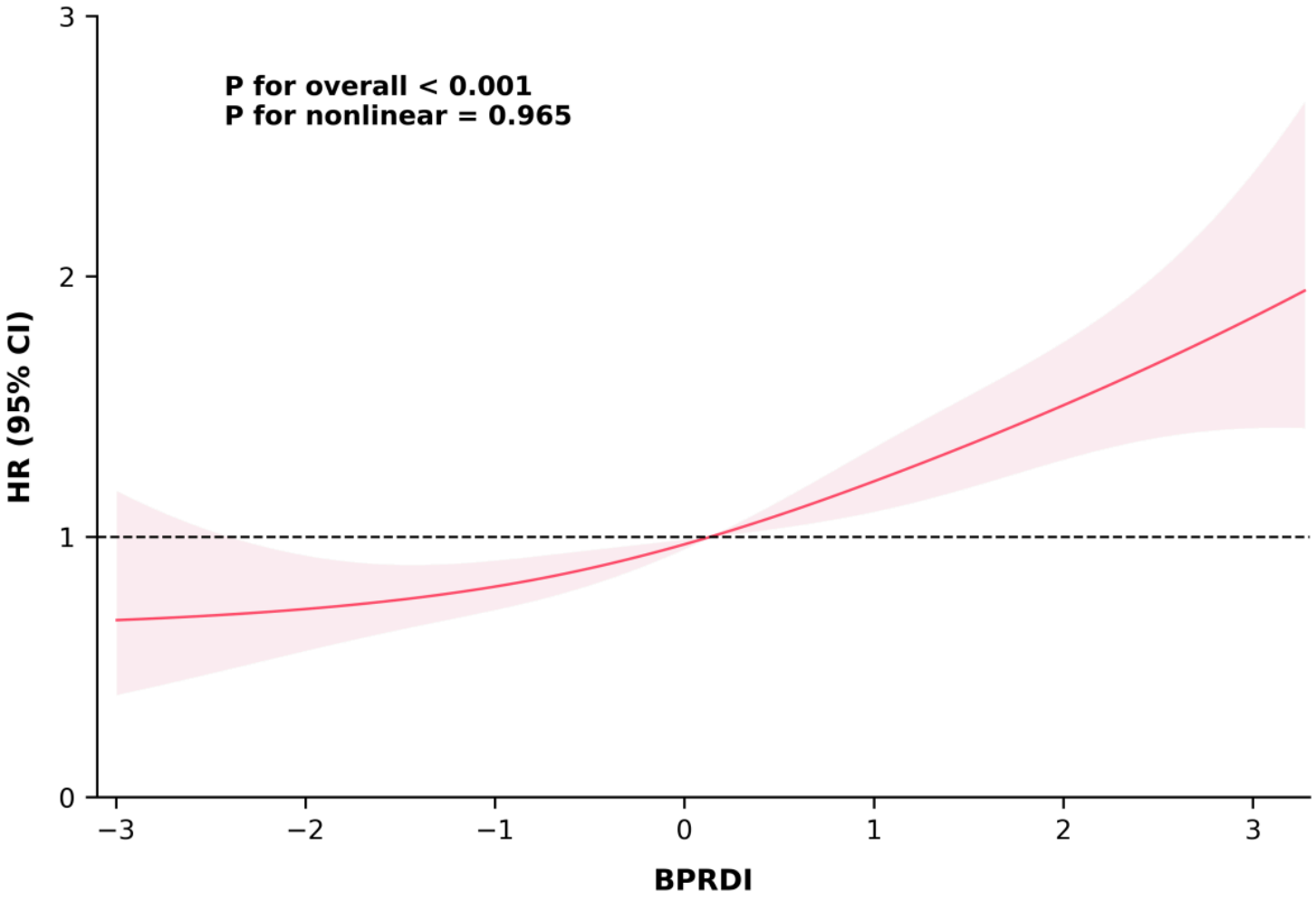


Figure 3

RCS curve between BPRDI and incident CMM risk. HR: Hazard Ratio; CI: Confidence Interval; BPRDI, behavioral physiological risk discordance index; CMM, cardiometabolic multimorbidity.

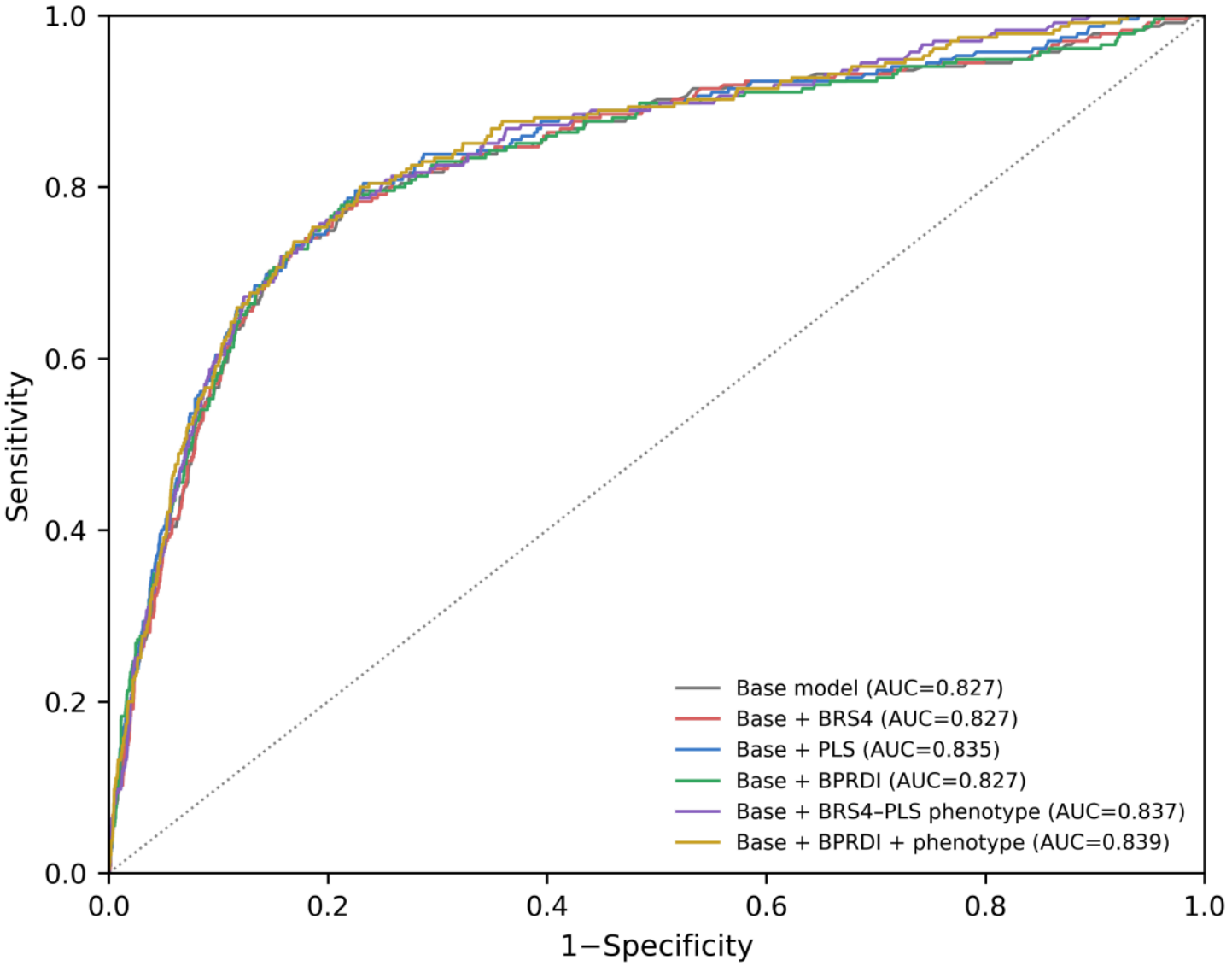


Figure 4

Time-dependent receiver operating characteristic curves for incremental models predicting 5-year incident CMM risk. BRS4, behavioral risk score; PLS, physiological load score; BPRDI, behavioral physiological risk discordance index; CMM, cardiometabolic multimorbidity; AUC, area under the receiver operating characteristic curve.

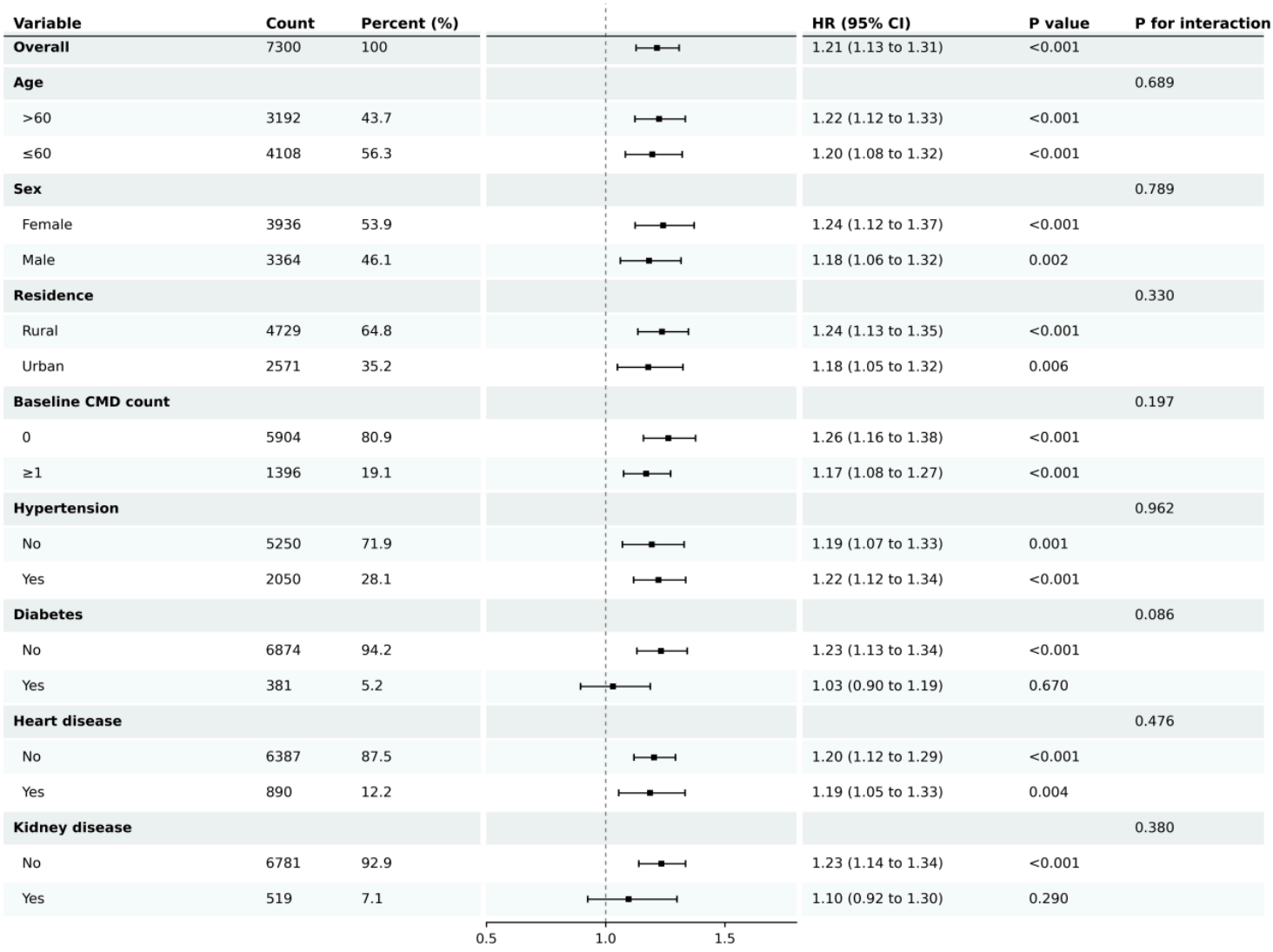


Figure 5

Subgroup and interaction analyses of the association between BPRDI and incident CMM risk. Adjusted for age, sex, residence, marital status, education level, baseline CMD count, hypertension, diabetes, heart disease, and kidney disease, except for the corresponding stratifying variable. HR: Hazard Ratio; CI: Confidence Interval; BPRDI, behavioral physiological risk discordance index; CMM, cardiometabolic multimorbidity.

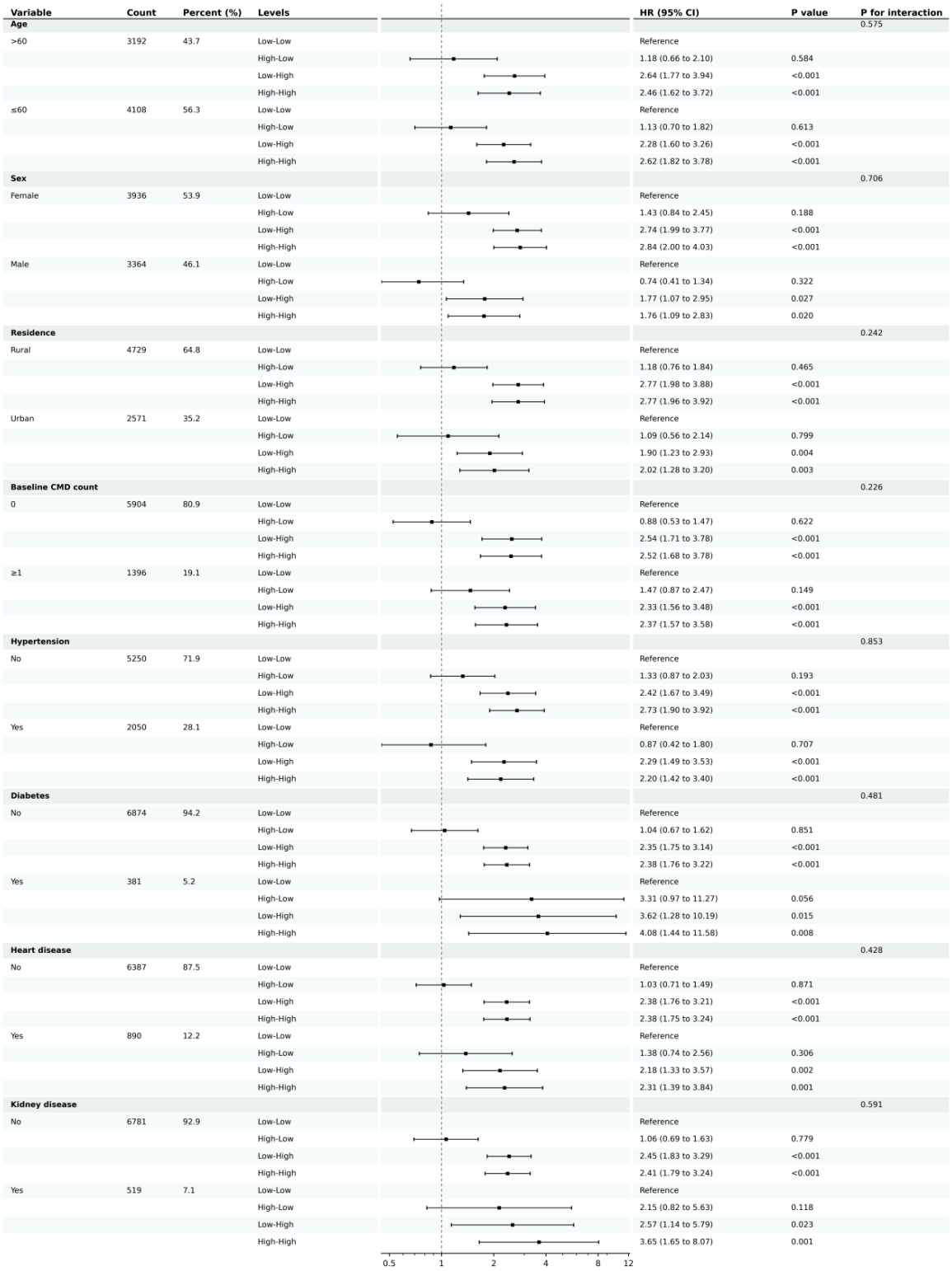


Figure 6

Subgroup and interaction analyses of the associations between BRS4–PLS phenotypes and incident CMM risk. Adjusted for age, sex, residence, marital status, education level, baseline CMD count, hypertension, and kidney disease, except for the corresponding stratifying variable. HR: Hazard Ratio; CI: Confidence Interval; BRS4, behavioral risk score; PLS, physiological load score; CMM, cardiometabolic multimorbidity.

Supplementary Files

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- SupplementaryFig.docx