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Baseline and Cumulative Exposure to the Hemoglobin A1c–Systolic Blood Pressure Index × Waist-to-Height Ratio and Risk of New-Onset Cardiometabolic Multimorbidity in Middle-Aged and Older Chinese Adults: A Nationwide Prospective Cohort Study

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Article

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Abstract

Background

Cardiometabolic multimorbidity (CMM), the coexistence of at least two cardiometabolic diseases in the same individual, is a growing public health challenge in aging populations, yet simple composite indicators simultaneously capturing glycemic status, blood pressure, and central obesity remain scarce. We investigated the associations of baseline and cumulative exposure to the hemoglobin A1c–systolic blood pressure index (HSI) combined with waist-to-height ratio (WHtR) with new-onset CMM among middle-aged and older Chinese adults.

Methods

This prospective cohort study included 6,279 participants free of CMM at baseline from the China Health and Retirement Longitudinal Study (2011–2020). HSI×WHtR was calculated, and cumulative exposure (cuHSI×WHtR) was derived from repeated measurements weighted by time intervals. K-means clustering identified longitudinal trajectories of HSI×WHtR. Cox proportional hazards models, restricted cubic spline (RCS) analyses, subgroup analyses, and Fine-Gray competing risk models were applied.

Results

During a median follow-up of approximately 9 years, 410 incident CMM cases occurred. Each 1-SD increment in baseline HSI×WHtR was associated with a 57% higher risk (HR 1.57, 95% CI 1.43–1.72), and the corresponding HR for cuHSI×WHtR was 1.83 (95% CI 1.67–2.00). Three trajectory patterns were identified (low-stable, moderate, and high-increasing); the high-increasing group had an approximately 4-fold higher risk (HR 4.00, 95% CI 2.88–5.56). RCS analyses indicated nonlinear dose–response associations (P for nonlinearity < 0.001).

Conclusions

Higher baseline and cumulative HSI×WHtR were independently associated with increased risk of new-onset CMM, with the strongest risk observed among individuals with high-increasing trajectories. Joint monitoring of glucose–blood pressure status and central obesity may facilitate early CMM risk stratification.

Background

Cardiometabolic multimorbidity (CMM), commonly defined as the coexistence of at least two cardiometabolic diseases such as hypertension, diabetes, heart disease, and stroke in the same individual, has emerged as a global health crisis that disproportionately affects aging populations [1],[2].

The burden of CMM is substantial: individuals with multiple cardiometabolic conditions face markedly elevated all-cause mortality in large general-practice cohorts [3],[4], and the coexistence of cardiometabolic diseases imposes a heavier economic and functional burden than the sum of its individual components. In China, multimorbidity patterns involving cardiometabolic diseases are highly prevalent among middle-aged and older adults and are associated with considerably elevated mortality risk [4]. Meanwhile, the prevalence of diabetes and hypertension continues to rise in China; the International Diabetes Federation estimated that more than 140 million adults in China were living with diabetes, the largest national burden worldwide [5],[6], and recent national surveys have documented a persistently high prevalence of hypertension among Chinese adults [7]. These converging trends underscore the urgent need for simple, reliable, and scalable tools for the early identification of individuals at high risk of CMM, particularly in primary care settings where sophisticated risk-stratification algorithms are often unavailable. Given the rapid aging of the Chinese population and the projected increase in the absolute number of older adults living with multiple cardiometabolic conditions, the identification of pragmatic risk markers suitable for routine measurement is a public health priority.

The American Heart Association recently proposed the cardiovascular-kidney-metabolic (CKM) syndrome framework, which emphasizes the synergistic interactions among metabolic risk factors, chronic kidney disease, and cardiovascular disease, and advocates integrated rather than organ-specific risk assessment [8]. This paradigm shift recognizes that metabolic disturbances, including dysglycemia, elevated blood pressure, and adiposity, do not operate in isolation but jointly drive cardiovascular and kidney disease through shared pathophysiological pathways. In line with this paradigm, composite indicators that simultaneously integrate multiple metabolic dimensions may outperform single biomarkers in capturing the shared pathophysiology underlying CMM, offering a pragmatic approach to integrated risk assessment in clinical and population settings.

The hemoglobin A1c–systolic blood pressure index (HSI), calculated as HbA1c (%) × systolic blood pressure (SBP, mmHg)/100, is a novel composite index that jointly reflects long-term glycemic status and blood pressure load. Previous evidence has shown that a higher hemoglobin glycation index, a related measure integrating HbA1c with glucose, predicts adverse cardiovascular outcomes in both general and diabetic populations [9]–[10]–[11]. More recently, HSI was established as a robust predictor of incident cardiovascular disease across three international prospective cohorts, with predictive performance superior to that of HbA1c or SBP alone [11]. However, whether HSI, which captures only two of the major cardiometabolic domains, is associated with the development of CMM—a condition that also heavily involves obesity—remains unexplored.

Central obesity, commonly assessed by waist-to-height ratio (WHtR), is an independent risk factor for hypertension, diabetes, and cardiovascular disease [12],[13]. WHtR captures abdominal adiposity more sensitively than body mass index (BMI) and has been consistently associated with hypertension and other cardiometabolic outcomes [12],[13]. A large multicohort study demonstrated that higher BMI, particularly abdominal adiposity, increases the risk of developing obesity-related complex multimorbidity

[13],[14]. Moreover, metabolic syndrome, a cluster of interrelated cardiometabolic risk factors, remains highly prevalent among Chinese middle-aged and older adults [15]; several composite metabolic indices combining glucose, lipid, and obesity parameters, such as the triglyceride-glucose (TyG) index and the cardiometabolic index, have been associated with CMM in Chinese cohorts [16],[17],[18]. Nevertheless, the independent and joint contributions of glucose–blood pressure load and central obesity to CMM risk have rarely been examined simultaneously, and no single composite index has yet combined these two complementary domains in a simple, clinically accessible form.

Beyond single-time-point assessments, cumulative exposure and longitudinal trajectories of metabolic risk factors may capture the duration and intensity of risk burden more accurately than baseline values alone. Cumulative measures derived from repeated measurements have been shown to be superior to baseline measures in predicting cardiometabolic outcomes [19]–[20]–[21], and trajectory-based analyses have revealed heterogeneous patterns of metabolic change with distinct prognostic implications [22],[23]. These dynamic approaches recognize that cardiometabolic risk is not static but evolves over time, and that the cumulative burden and the direction of change may carry prognostic information beyond that contained in a single baseline measurement. However, no study has yet evaluated the associations of baseline and cumulative HSI×WHtR, together with its longitudinal trajectories, with new-onset CMM.

Therefore, using data from a large nationally representative prospective cohort of middle-aged and older Chinese adults, we aimed to (1) investigate the association of baseline HSI×WHtR with incident CMM; (2) examine the dose–response relationship using RCS analyses; (3) identify longitudinal trajectories of HSI×WHtR by K-means clustering and evaluate their associations with CMM; and (4) explore subgroup differences and the robustness of associations in competing risk analyses.

Methods

Study design and population

This prospective cohort study used data from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative, population-based survey of community-dwelling adults aged 45 years and older in China [24]. CHARLS was initiated in 2011 (Wave 1) and has been followed up biennially; the present analysis used data from Wave 1 (2011) through Wave 5 (2020). The CHARLS study protocol was approved by the Biomedical Ethics Review Committee of Peking University, and all participants provided written informed consent at each wave. We used the publicly available de-identified data; therefore, no additional ethical approval was required for this secondary analysis.

From 17,708 participants in Wave 1, we sequentially excluded those aged < 45 years, those with CMM or missing outcome data at baseline, those with missing HSI or WHtR data at baseline, and those lost to follow-up. A total of 6,279 participants were ultimately included in the primary analysis (Fig. 1). Details of the participant selection process are presented in the flow diagram.

Exposure assessment

HSI was calculated as HbA1c (%) × SBP (mmHg)/100 at each wave [11]. WHtR was calculated as waist circumference (cm) divided by height (cm). The primary exposure of interest was the product of HSI and WHtR (HSI×WHtR), a composite index simultaneously integrating long-term glycemic status, blood pressure load, and central adiposity. Cumulative exposure (cuHSI×WHtR) was calculated as the sum of the average HSI×WHtR values between two consecutive visits multiplied by the corresponding time interval, divided by the total follow-up duration [19],[20]. This approach weights the duration of exposure and has been widely used in cumulative burden analyses [20],[21]; it assumes that the exposure level between two visits is reasonably approximated by the average of the two measurements and that longer exposure to an elevated level confers greater cumulative risk.

Trajectory analysis

To characterize the dynamic changes of HSI×WHtR over time, we applied K-means clustering based on the standardized HSI×WHtR values at Waves 1, 2, and 3, following previously established methods for metabolic trajectory identification [22],[23]. Standardization was performed before clustering to ensure that the three time points contributed comparably to the distance metric, thereby avoiding a disproportionate influence of any single wave on cluster assignment. The optimal number of clusters was determined by the elbow criterion and the interpretability of the resulting patterns (Supplementary Figure S2), balancing within-cluster homogeneity against parsimony. Three distinct trajectory groups were identified: low-stable (n = 3,093), moderate (n = 2,543), and high-increasing (n = 643).

Outcome ascertainment

The primary outcome was new-onset CMM, defined as the first occurrence of at least two of the following cardiometabolic diseases during follow-up: hypertension, diabetes, heart disease, and stroke [17],[19]. All outcomes were ascertained from self-reported physician diagnoses, a validated approach in CHARLS. Follow-up was calculated from the baseline interview to the date of CMM onset, death, loss to follow-up, or the end of follow-up (Wave 5), whichever occurred first. For participants who developed two or more component diseases, the date of CMM onset was defined as the date on which the second component disease was first reported.

Covariates

Covariates were selected based on clinical relevance and prior literature [11],[17],[19], including age (years), sex (male/female), education level, marital status, residence (rural/urban), smoking status, alcohol consumption, physical activity, BMI (kg/m²), self-reported comorbidities, and medication use for hypertension or diabetes. Models were progressively adjusted as follows: Model 1 adjusted for age and sex; Model 2 further adjusted for education, marital status, residence, smoking, alcohol consumption, and physical activity; Model 3 additionally adjusted for BMI, history of dyslipidemia, and medication use.

This hierarchical adjustment strategy allowed us to evaluate the extent to which the observed associations were explained by sociodemographic, lifestyle, and metabolic factors.

Statistical analysis

Baseline characteristics were summarized as means (SD) for continuous variables and frequencies (percentages) for categorical variables, and compared across trajectory groups using analysis of variance or chi-squared tests as appropriate. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of baseline HSI×WHtR (per 1-SD increment and by quartiles) and cuHSI×WHtR (per 1-SD increment) with incident CMM. Follow-up time was used as the underlying time scale, and participants were censored at the time of CMM onset, death, loss to follow-up, or the end of the study period. For the quartile-based analysis, quartiles of baseline HSI×WHtR were derived from the baseline distribution, and the lowest quartile served as the reference category; tests for linear trend across quartiles were performed by entering the quartile medians as a continuous variable in the models. The proportional hazards assumption was checked using Schoenfeld residuals, and no material violations were detected. Restricted cubic spline (RCS) analyses with three knots (placed at the 10th, 50th, and 90th percentiles) were used to examine potential nonlinear dose–response relationships between HSI×WHtR and CMM risk [25]; the null hypothesis of linearity was tested by comparing the model with the spline terms against the linear model, and P for nonlinearity was reported.

K-means clustering was applied to identify trajectory patterns as described above, and Cox models were used to estimate HRs for each trajectory group relative to the low-stable group. Subgroup analyses were performed by age, sex, BMI, smoking, alcohol consumption, and physical activity, and interactions were tested using likelihood ratio tests comparing models with and without the multiplicative interaction terms. Sensitivity analyses included (1) Fine-Gray competing risk models treating death as a competing event [26],[27], which account for the possibility that death prevents the observation of the outcome of interest and thereby reduce the bias inherent in conventional cause-specific approaches; (2) excluding participants with events occurring within the first year of follow-up to address potential reverse causation; and (3) complete-case analyses restricted to participants with complete data on all covariates. All statistical analyses were performed using R software (version 4.4.1). A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Among 6,279 participants, the mean age was 58.60 (SD 8.89) years, and 45.1% were male. The mean HSI, WHtR, and HSI×WHtR were 6.75 (SD 1.46), 0.54 (SD 0.08), and 3.65 (SD 1.08), respectively. Participants in the high-increasing trajectory group were more likely to be older, male, and to have higher

baseline HSI, WHtR, and HSI×WHtR values, as well as a higher prevalence of cardiometabolic risk factors (Table 1 and Supplementary Table S1).

Table 1
Baseline characteristics of participants according to CMM status

Variables	Total (n = 6279)	CMM (Cardiometabolic multimorbidity)		*P*
		No (n = 5869)	Yes(n = 410)	
Demographics Data				
Age (years)	58.60 ± 8.89	58.41 ± 8.89	61.31 ± 8.42	< 0.001
Male, n (%)	2832 (45.1)	2661 (45.3)	171 (41.7)	0.168
Married, n (%)	5370 (85.5)	5030 (85.7)	340 (82.9)	0.141
Iliteracy, n (%)	3171 (50.5)	2970 (50.6)	201 (49.0)	0.767
Middle school below, n (%)	1418 (22.6)	1320 (22.5)	98 (23.9)	0.767
Middle school and above, n (%)	1690 (26.9)	1579 (26.9)	111 (27.1)	0.767
Rural residence, n (%)	5340 (85.0)	5034 (85.8)	306 (74.6)	< 0.001
Current smoker, n (%)	1854 (29.5)	1753 (29.9)	101 (24.6)	< 0.001
Current drinker, n (%)	2029 (32.3)	1942 (33.1)	87 (21.2)	< 0.001
Laboratory inspection				
SBP (mmHg)	128.51 ± 20.71	127.98 ± 20.51	136.01 ± 21.97	< 0.001
DBP (mmHg)	75.05 ± 11.81	74.84 ± 11.76	78.06 ± 12.24	< 0.001
HbA1c (%)	5.25 ± 0.68	5.21 ± 0.65	5.72 ± 0.99	< 0.001
TC (mg/dL)	192.92 ± 36.68	192.56 ± 36.58	198.08 ± 37.77	0.004
HDL-C (mg/dL)	50.96 ± 14.75	51.29 ± 14.76	46.23 ± 13.76	< 0.001
LDL-C (mg/dL)	115.91 ± 33.61	115.65 ± 33.46	119.73 ± 35.41	0.024
TG (mg/dL)	130.77 ± 85.64	128.95 ± 84.55	156.79 ± 96.45	< 0.001
CRP (mg/L)	2.30 ± 4.62	2.25 ± 4.53	3.04 ± 5.71	0.006

Variables	Total (n = 6279)	CMM (Cardiometabolic multimorbidity)		*P*
		No (n = 5869)	Yes(n = 410)	
Scr (mg/dL)	0.77 ± 0.17	0.77 ± 0.17	0.79 ± 0.19	0.004
UA (mg/dL)	4.37 ± 1.19	4.35 ± 1.18	4.63 ± 1.31	< 0.001
Composite indicator				
BMI (kg/m²)	23.60 ± 3.58	23.46 ± 3.52	25.61 ± 3.82	< 0.001
WC (cm)	84.45 ± 12.22	84.00 ± 12.10	90.79 ± 12.27	< 0.001
HSI	6.75 ± 1.46	6.68 ± 1.40	7.78 ± 1.85	< 0.001
WHtR	0.54 ± 0.08	0.53 ± 0.08	0.58 ± 0.08	< 0.001
HSI×WHtR	3.65 ± 1.08	3.59 ± 1.04	4.52 ± 1.35	< 0.001
Death, n (%)	475 (7.6)	429 (7.3)	46 (11.2)	0.005

Data are presented as mean (SD) for continuous variables and n (%) for categorical variables, unless otherwise stated.

Education level was categorized into three groups: no formal education (illiteracy), middle school or below, and middle school or above.P values were calculated using analysis of variance, the Kruskal–Wallis test, or the chi-squared test, as appropriate.

CMM, cardiometabolic multimorbidity; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; CRP, C-reactive protein; Scr, serum creatinine; UA, uric acid; HSI, hepatic steatosis index; WHtR, waist-to-height ratio.

Association of baseline HSI×WHtR with incident CMM

During a median follow-up of approximately 9 years, 410 participants (6.5%) developed new-onset CMM. In the fully adjusted model (Model 3), each 1-SD increment in baseline HSI×WHtR was associated with a 57% higher risk of CMM (HR 1.57, 95% CI 1.43–1.72) (Table 2). When HSI×WHtR was modeled as quartiles, a graded increase in risk was observed across quartiles (P for trend < 0.001). Notably, the association was stronger for cumulative exposure: each 1-SD increment in cuHSI×WHtR was associated

with an 83% higher risk of CMM (HR 1.83, 95% CI 1.67–2.00) (Table 2), indicating that the cumulative burden of the composite exposure over time captured additional risk beyond the baseline snapshot.

Table 2
Associations of HSI, WHtR, HSI×WHtR, and cumulative HSI×WHtR (per SD and in quartiles) with the risk of new-onset CMM.

Variables	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*	Model 3 HR (95% CI)	*P*
HSI (per SD)	1.69 (1.58–1.82)	< 0.001	1.65 (1.53–1.77)	< 0.001	1.49 (1.38–1.61)	< 0.001
Q1	Reference	—	Reference	—	Reference	—
Q2	0.96 (0.65–1.42)	0.838	0.93 (0.63–1.37)	0.719	0.82 (0.56–1.22)	0.331
Q3	2.08 (1.49–2.89)	< 0.001	1.94 (1.39–2.71)	< 0.001	1.50 (1.07–2.11)	0.018
Q4	4.09 (3.02–5.55)	< 0.001	3.62 (2.65–4.95)	< 0.001	2.49 (1.80–3.43)	< 0.001
P for trend	< 0.001	—	< 0.001	—	< 0.001	—
WHtR (per SD)	1.91 (1.71–2.14)	< 0.001	1.93 (1.71–2.17)	< 0.001	1.21 (1.03–1.42)	0.017
Q1	Reference	—	Reference	—	Reference	—
Q2	1.77 (1.21–2.60)	0.003	1.83 (1.24–2.68)	0.002	1.45 (0.98–2.14)	0.061
Q3	2.64 (1.84–3.79)	< 0.001	2.79 (1.94–4.01)	< 0.001	1.62 (1.10–2.38)	0.015
Q4	4.90 (3.50–6.86)	< 0.001	5.10 (3.59–7.24)	< 0.001	1.91 (1.23–2.97)	0.004
P for trend	< 0.001	—	< 0.001	—	0.005	—
HSI×WHtR (per SD)	1.86 (1.73–1.99)	< 0.001	1.82 (1.69–1.96)	< 0.001	1.57 (1.43–1.72)	< 0.001
Q1	Reference	—	Reference	—	Reference	—
Q2	1.20 (0.79–1.81)	0.393	1.17 (0.77–1.76)	0.470	1.02 (0.67–1.54)	0.939
Q3	2.36 (1.64–3.40)	< 0.001	2.25 (1.56–3.25)	< 0.001	1.63 (1.11–2.38)	0.012
Q4	5.84 (4.19–8.15)	< 0.001	5.35 (3.81–7.51)	< 0.001	3.08 (2.11–4.49)	< 0.001
P for trend	< 0.001	—	< 0.001	—	< 0.001	—
CuHSI×WHtR (per SD)	2.02 (1.89–2.17)	< 0.001	2.01 (1.87–2.16)	< 0.001	1.83 (1.67–2.00)	< 0.001

Variables	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*	Model 3 HR (95% CI)	*P*
Q1	Reference	—	Reference	—	Reference	—
Q2	2.10 (1.30–3.38)	0.002	2.07 (1.29–3.34)	0.003	1.86 (1.15–3.00)	0.011
Q3	3.55 (2.28–5.55)	< 0.001	3.42 (2.19–5.34)	< 0.001	2.64 (1.67–4.17)	< 0.001
Q4	10.61 (7.03–16.00)	< 0.001	10.09 (6.65–15.30)	< 0.001	6.61 (4.21–10.39)	< 0.001
P for trend	< 0.001	—	< 0.001	—	< 0.001	—
Trajectory grouping						
Class 1 (Low-Stable)	Reference	—	Reference	—	Reference	—
Class 2 (Moderate)	2.84 (2.21–3.66)	< 0.001	2.71 (2.10–3.50)	< 0.001	1.98 (1.51–2.59)	< 0.001
Class 3 (High-Increasing)	7.56 (5.75–9.94)	< 0.001	6.91 (5.21–9.16)	< 0.001	4.00 (2.88–5.56)	< 0.001
P for trend	< 0.001	—	< 0.001	—	< 0.001	—

Exposures were entered per 1-SD increment; quartile analyses used the lowest quartile (Q1) as the reference, and P for trend was derived by modelling the median value of each quartile as a continuous variable.

Model 1: unadjusted. Model 2: adjusted for demographic and lifestyle factors (age, sex, education, residence, marital status, smoking, and drinking). Model 3: fully adjusted for age, sex, marital status, education, residence, smoking, drinking, and body mass index.

CMM, cardiometabolic multimorbidity; HSI, hepatic steatosis index; WHtR, waist-to-height ratio; HSI×WHtR, the product of HSI and WHtR; cuHSI×WHtR, cumulative HSI×WHtR; HR, hazard ratio; CI, confidence interval; SD, standard deviation; BMI, body mass index.All tests were two-sided, and P < 0.05 was considered statistically significant.

Dose–response relationship

RCS analyses revealed a significant nonlinear association between HSI×WHtR and CMM risk (overall P < 0.001; P for nonlinearity < 0.001), with the risk increasing steeply at higher values (Fig. 2). When stratified by trajectory groups, the association was nonlinear in the moderate and high-increasing groups, whereas

no evidence of nonlinearity was observed in the low-stable group (P for nonlinearity = 0.570), suggesting that the dose–response shape differs according to the underlying risk trajectory.

Trajectory patterns and CMM risk

Kaplan–Meier curves showed significantly different cumulative incidence of CMM across the three trajectory groups (log-rank P < 0.001) (Fig. 3). Compared with the low-stable group, the high-increasing group had a substantially elevated risk of CMM (Model 3 HR 4.00, 95% CI 2.88–5.56), and the moderate group also showed a significantly elevated risk (Table 2). The graded risk pattern across trajectory groups remained consistent after additional adjustment and in sensitivity analyses.

Subgroup and interaction analyses

In subgroup analyses, the positive association between HSI×WHtR and CMM risk was generally consistent across strata of age, sex, smoking, alcohol consumption, and physical activity (Fig. 4 and Supplementary Table S2). A significant interaction was observed with BMI for both baseline (P for interaction = 0.028) and trajectory-based analyses (P for interaction = 0.031, Supplementary Figure S1), with stronger associations among participants with higher BMI.

Sensitivity and competing risk analyses

In Fine-Gray competing risk models treating death as a competing event, the association of cuHSI×WHtR with CMM remained significant (HR 1.76, 95% CI 1.54–2.00, P < 0.001) (Supplementary Table S3), whereas the association of baseline HSI×WHtR was attenuated, indicating that cumulative exposure is a more robust predictor when competing mortality is accounted for. Excluding events occurring within the first year of follow-up and complete-case analyses yielded similar results (data not shown).

Discussion

In this nationwide prospective cohort study of 6,279 middle-aged and older Chinese adults, we found that higher baseline HSI×WHtR was independently associated with an increased risk of new-onset CMM, and the association was stronger for cumulative exposure (cuHSI×WHtR). Three distinct longitudinal trajectories of HSI×WHtR were identified, among which the high-increasing pattern conferred the greatest risk, with an approximately 4-fold elevation compared with the low-stable pattern. The associations were nonlinear, consistent across most subgroups, and robust in competing risk and sensitivity analyses.

Our findings extend the emerging literature on composite cardiometabolic indices in several ways. First, we demonstrated that a simple product of HSI and WHtR—two routinely available clinical measures—is a strong predictor of CMM, complementing previous studies of HSI with cardiovascular disease [11] and of the TyG index with CMM [17]. The magnitude of the association (HR 1.57 per SD for baseline and 1.83 per SD for cumulative exposure) is comparable to those reported for other composite metabolic indices in

Chinese cohorts, such as the cardiometabolic index [16] and the TyG index [17], supporting the clinical utility of HSI×WHtR as a parsimonious risk marker. Importantly, because HbA1c, blood pressure, and waist and height measurements are already collected in routine clinical practice and large-scale health surveys, HSI×WHtR can be calculated without additional testing or cost, a property that is particularly valuable for primary care and community-based screening programs where resource constraints limit the use of more complex biomarker panels.

Second, our results underscore the importance of cumulative exposure and trajectory patterns in CMM risk assessment. Consistent with previous studies of cumulative exposure to composite metabolic indices in CHARLS [18]–[19]–[20]–[21], cumulative HSI×WHtR outperformed the baseline measure. The trajectory analysis further revealed that individuals whose HSI×WHtR increased over time, even if their baseline values were not extreme, faced the highest risk, echoing findings from other Chinese cohorts on the prognostic value of metabolic trajectories [22],[23]. These observations support the notion that the duration and longitudinal dynamics of risk-factor burden, rather than a single snapshot, are central to the development of multimorbidity. From a preventive perspective, they also imply that repeated monitoring of the composite index may identify individuals with rising risk trajectories who could benefit from intensified lifestyle and pharmacological interventions before clinical disease onset.

Third, the observed nonlinear dose–response relationship suggests that the risk of CMM accelerates beyond a certain threshold of HSI×WHtR. Similar nonlinear patterns have been reported for TyG-based indices [28],[29] and for cumulative metabolic risk factors [25],[30], supporting the biological plausibility of a threshold effect. The differential nonlinearity across trajectory groups further implies that interventions may yield the greatest benefit in individuals whose composite risk burden is already elevated and rising, whereas in low-stable individuals the exposure–outcome relationship may be more modest and gradual.

Several biological mechanisms may explain our findings. HSI integrates HbA1c and SBP, both of which reflect chronic hyperglycemia and hemodynamic load, two core drivers of vascular injury, endothelial dysfunction, and target-organ damage [11]. Chronic hyperglycemia promotes advanced glycation end-product accumulation, oxidative stress, and inflammation, while elevated blood pressure imposes mechanical stress on the vasculature; together, these processes accelerate atherosclerosis and impair microvascular function across multiple organs. WHtR captures abdominal adiposity, which promotes systemic inflammation, insulin resistance, and ectopic fat deposition, thereby linking obesity to the development of diabetes, hypertension, and atherosclerosis [13],[14]. Visceral adipose tissue acts as an active endocrine organ, secreting pro-inflammatory adipokines and free fatty acids that contribute to the metabolic dysregulation underlying each of the component diseases of CMM. The synergistic combination of these domains in a single product may better approximate the shared cardiometabolic pathophysiology that underpins CMM [8],[16]. The stronger association of cumulative exposure is consistent with the cumulative damage hypothesis, whereby prolonged exposure to elevated cardiometabolic risk accelerates the transition from single-disease states to multimorbidity [18]–[19]–[20]–[21].

The significant interaction with BMI deserves comment. The stronger association among participants with higher BMI may reflect the combined burden of general and central obesity, which act through partly overlapping but additive pathways [14],[16]. It is plausible that in individuals with excess overall adiposity, the metabolic consequences of elevated glucose–blood pressure load and abdominal fat accumulation are amplified, rendering the composite exposure particularly informative for risk stratification. From a clinical perspective, our results suggest that simultaneous attention to glycemic control, blood pressure management, and abdominal obesity—rather than any single domain—may be required for effective CMM prevention, in line with the integrative CKM framework [8]. The CKM framework explicitly recognizes the interconnectedness of metabolic risk factors, kidney function, and cardiovascular disease, and our composite exposure operationalizes this integrative principle using three routinely measured parameters. Future work should examine whether HSI×WHtR-guided monitoring, particularly the repeated assessment of cumulative exposure and trajectory patterns, improves risk prediction and clinical decision-making beyond conventional single-risk-factor management in real-world settings.

Strengths and limitations

This study has several strengths, including the use of a large, nationally representative prospective cohort with up to 9 years of follow-up; the simultaneous evaluation of baseline, cumulative, and trajectory-based exposures; comprehensive adjustment for confounders; and the use of competing risk models to account for the high mortality in this population. To our knowledge, this is the first study to jointly examine baseline and cumulative HSI×WHtR together with its longitudinal trajectories in relation to new-onset CMM, thereby providing a more complete picture of the dynamic risk burden than single-time-point analyses. In addition, the exposure combines three parameters that are inexpensive and routinely measured in clinical practice, which enhances the translational potential of the findings for resource-limited settings. However, several limitations should be acknowledged. First, CMM was ascertained from self-reported physician diagnoses, which may be subject to misclassification, although this approach has been widely used and validated in CHARLS-based studies [17],[19],[20]. Second, HbA1c and anthropometric measurements were not available at every wave for all participants, and cumulative exposure was based on available repeated measurements, which may introduce measurement error; moreover, the trajectory analysis was based on the first three waves, and longer-term dynamics beyond this window could not be characterized. Third, residual confounding by unmeasured factors, such as dietary intake, socioeconomic status dynamics, and medication adherence, cannot be fully excluded. Fourth, our study was conducted exclusively in Chinese adults aged 45 years and older, and the generalizability of our findings to other populations warrants further investigation. Finally, the observational design precludes causal inference, and the optimal threshold of HSI×WHtR for clinical use requires external validation in independent cohorts.

Conclusions

In this nationwide prospective cohort of middle-aged and older Chinese adults, higher baseline and cumulative HSI×WHtR were independently associated with an increased risk of new-onset CMM, with a

particularly strong risk among individuals with high-increasing trajectories. HSI×WHtR, a simple composite of three routinely available clinical measures, may serve as a pragmatic tool for early CMM risk stratification and prevention, and its cumulative and trajectory-based versions offer additional insight into the dynamic nature of cardiometabolic risk. Given the increasing burden of cardiometabolic multimorbidity in aging populations, scalable screening tools are urgently needed, particularly in primary-care and community settings where comprehensive risk stratification is often unavailable. This composite exposure captures key modifiable components along the cardiometabolic–kidney–cardiovascular continuum and could be integrated into routine health examinations with minimal additional cost or participant burden. Future studies are warranted to validate the optimal threshold and to evaluate the clinical utility of trajectory-based monitoring in cardiometabolic risk management.

Declarations

Ethics approval and consent to participate

The China Health and Retirement Longitudinal Study (CHARLS) was approved by the Biomedical Ethics Review Committee of Peking University, and all participants provided written informed consent at each wave. The present study used publicly available de-identified data; therefore, no additional ethical approval was required for this secondary analysis.

Consent for publication

Not applicable.

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Author Contribution

ZiHao Huang: Conceptualization, Methodology, Formal analysis, Writing – original draft. Changjiang Li: Methodology, Data curation, Visualization. Yangcheng Cao: Investigation, Software. Jianfeng Chen: Investigation, Validation. Shiqiang Yang: Formal analysis, Visualization. Sen Tan: Data curation, Writing – review & editing. Jianhao Tan: Investigation, Resources. AnQiang Yang: Supervision, Writing – review & editing. All authors read and approved the final manuscript.

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Data Availability

The CHARLS data are publicly available at http://charls.pku.edu.cn after free registration, and the 2011 baseline data are also deposited at the Peking University Open Research Data Platform (https://doi.org/10.18170/DVN/IZU8OF). No new data were generated for this study; the present analysis is a secondary analysis of publicly available de-identified CHARLS data (Wave 1-5). The analytic code is available from the corresponding author upon reasonable request.

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Figures

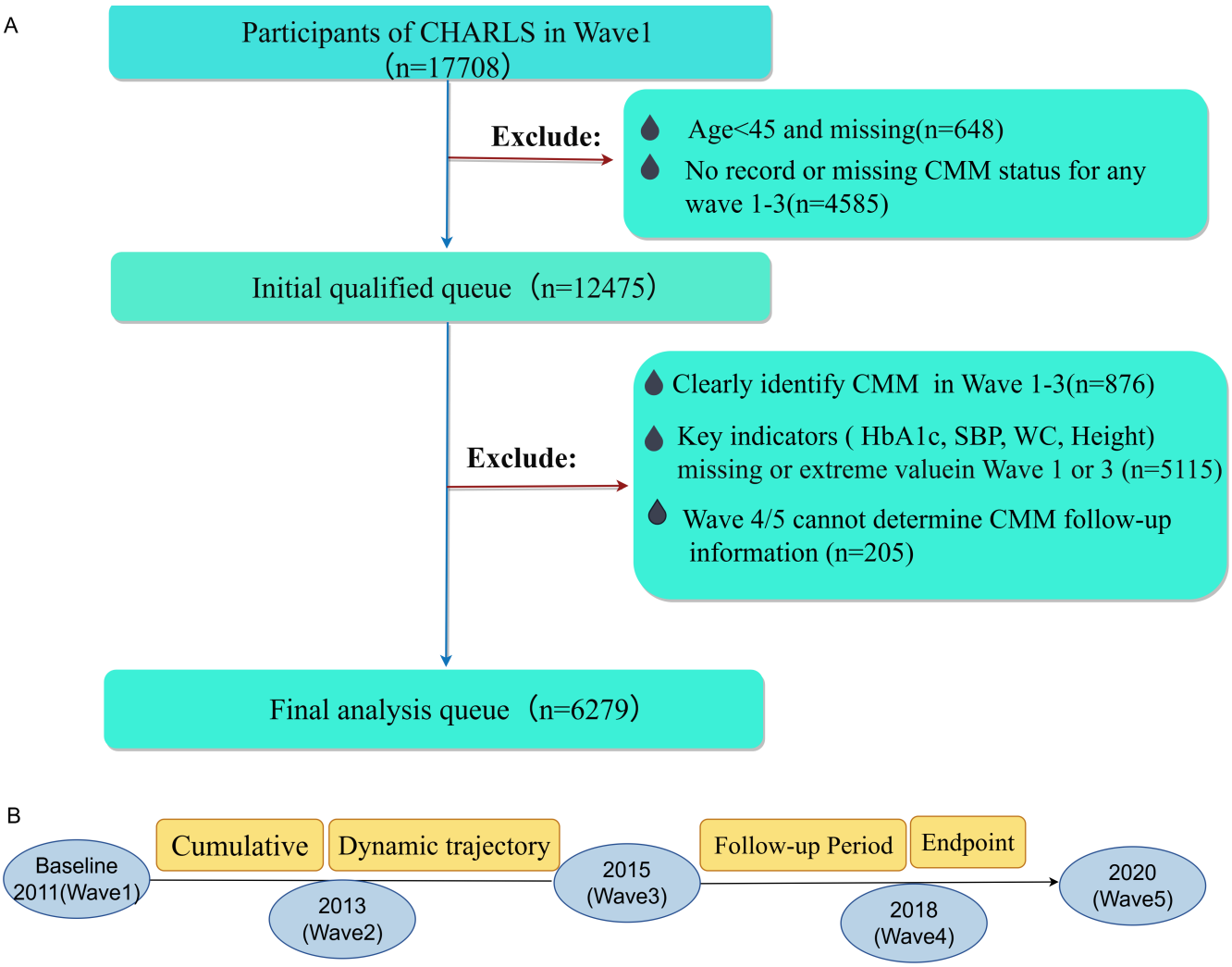


Figure 1

Flow diagram of participant selection. From 17,708 participants in Wave 1, we sequentially excluded those aged <45 years, those with CMM or missing outcome data at baseline, those with missing HSI or WHtR data at baseline, and those lost to follow-up. A total of 6,279 participants were ultimately included in the primary analysis.

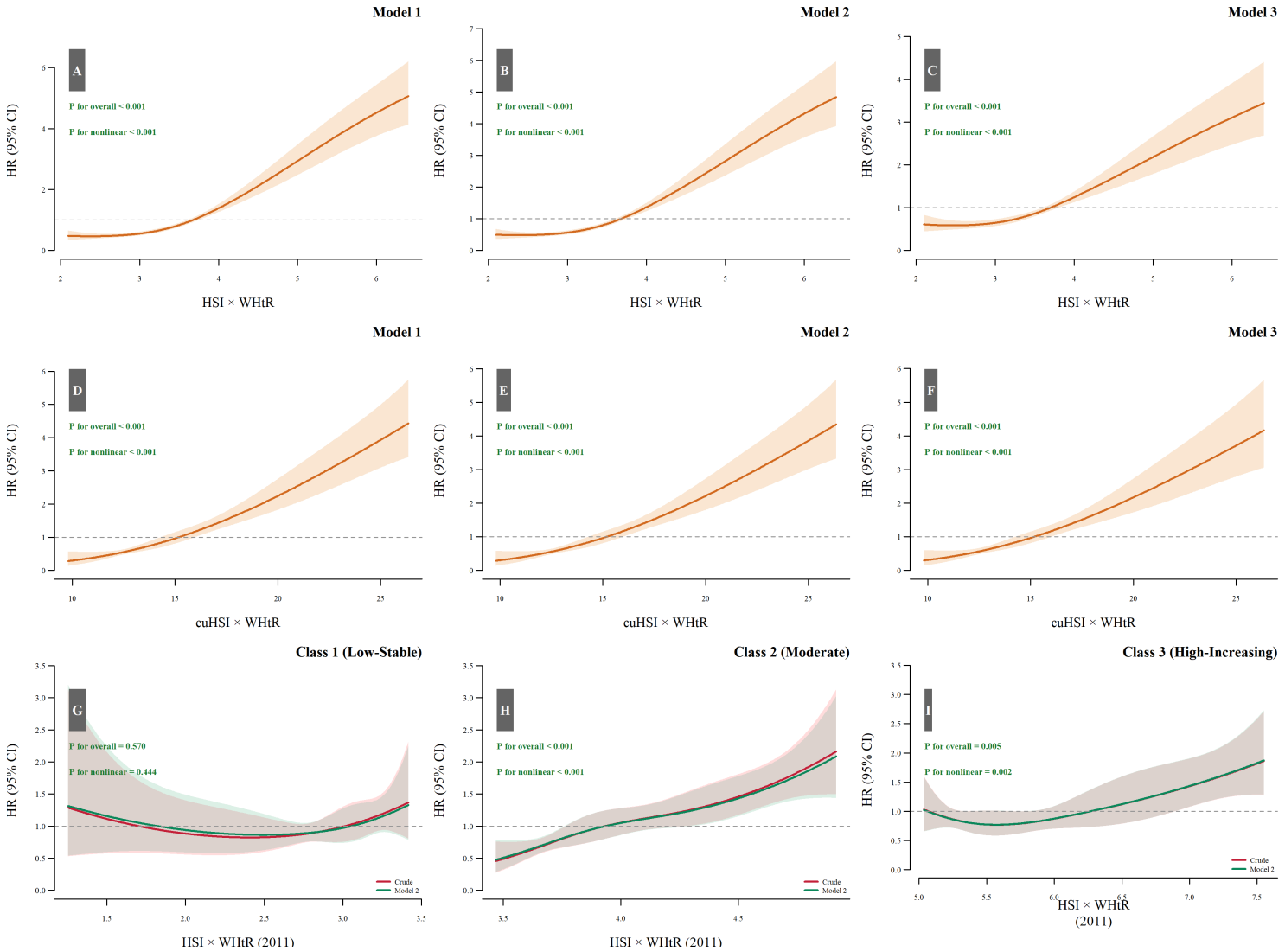


Figure 2

Dose–response relationship between HSI×WHtR and CMM risk. Restricted cubic spline analysis showed a significant nonlinear association (overall P < 0.001; P for nonlinearity < 0.001), with risk increasing steeply at higher HSI×WHtR values. The solid line represents the estimated hazard ratio and the shaded area represents the 95% confidence interval, adjusted for Model 3 covariates.

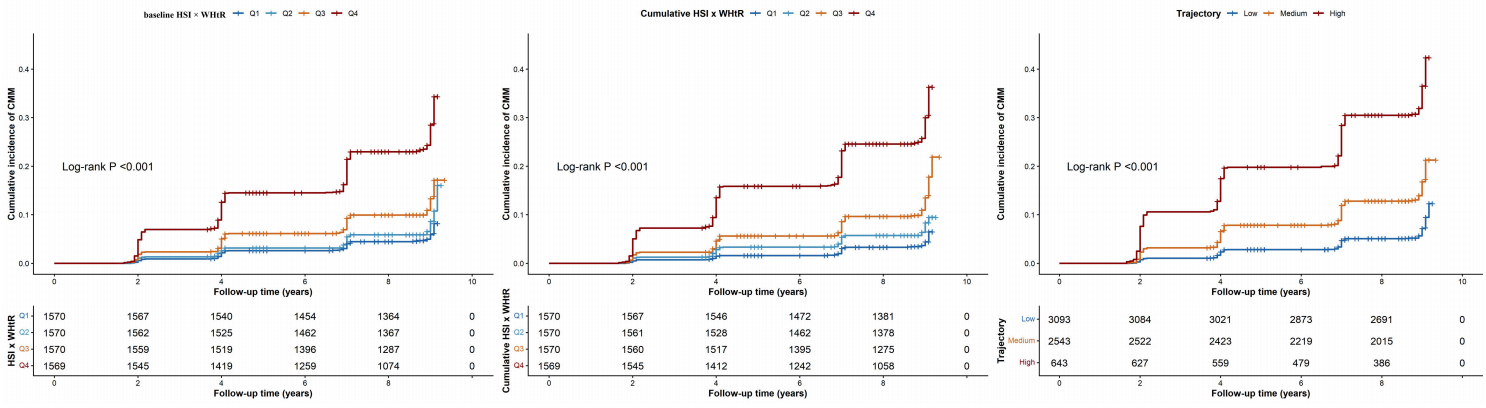


Figure 3

Kaplan–Meier curves for cumulative incidence of CMM according to HSI×WHtR trajectory groups (low-stable, moderate, and high-increasing). Log-rank P < 0.001.

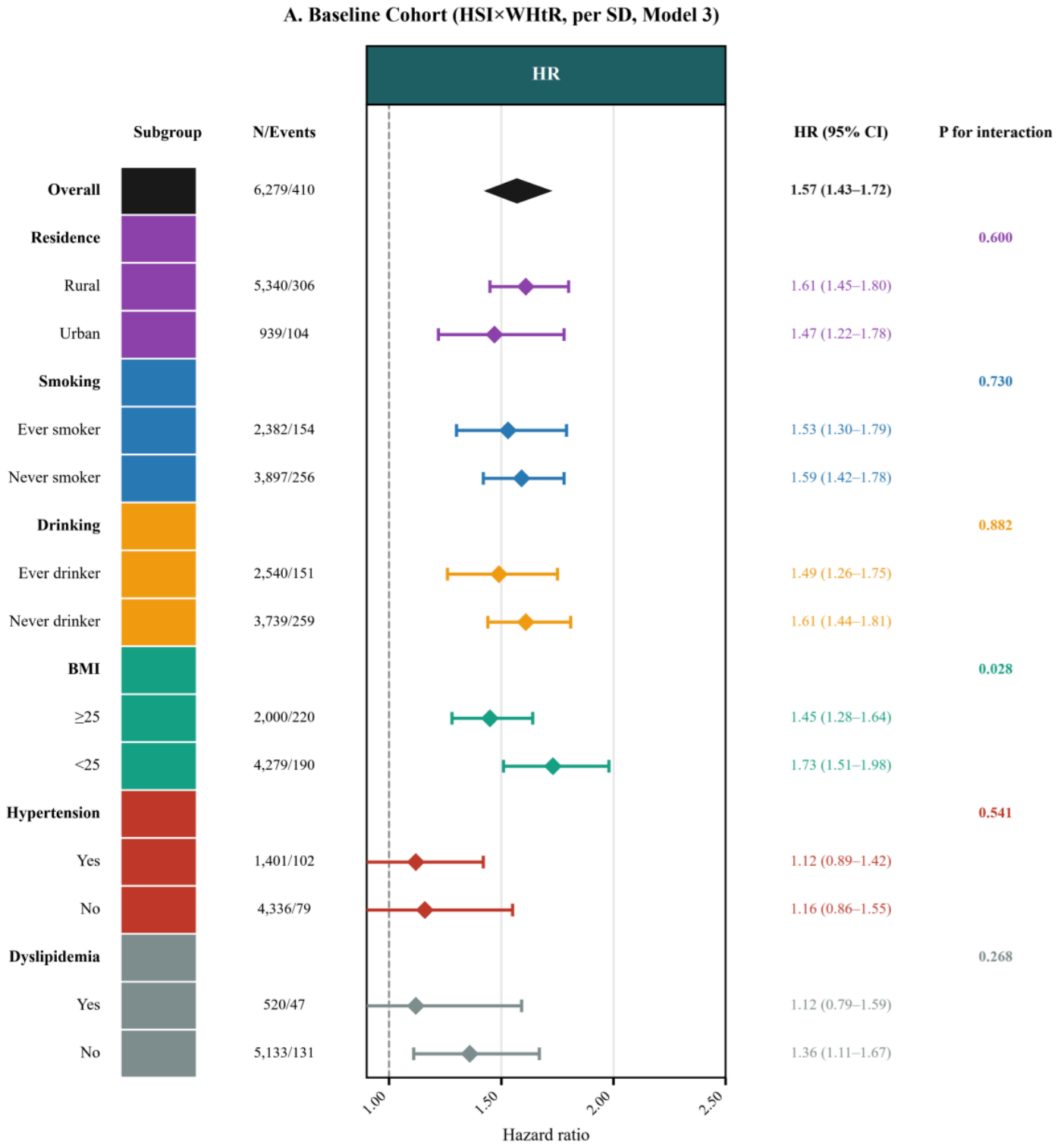


Figure 4

Subgroup analysis of the association between HSI×WHtR and CMM risk. Forest plot showing adjusted hazard ratios (95% CIs) of new-onset CMM per 1-SD increment in baseline HSI×WHtR across strata of age, sex, smoking, alcohol consumption, and physical activity. The model was adjusted for Model 3 covariates.

Supplementary Files

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