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Yibo Lin
Dongguan Key Laboratory of Chronic Disease Prevention and Control,The First Dongguan Affiliated Hospital,School of Public Health Guangdong Medical University

Haimei Zhong
Dongguan Key Laboratory of Chronic Disease Prevention and Control,The First Dongguan Affiliated Hospital,School of Public Health Guangdong Medical University

Qintong Ruan
Dongguan Key Laboratory of Chronic Disease Prevention and Control,The First Dongguan Affiliated Hospital,School of Public Health Guangdong Medical University

Yingen Feng
Dongguan Key Laboratory of Chronic Disease Prevention and Control,The First Dongguan Affiliated Hospital,School of Public Health Guangdong Medical University

Yupeng Huang
Dongguan Key Laboratory of Chronic Disease Prevention and Control,The First Dongguan Affiliated Hospital,School of Public Health Guangdong Medical University

Zhuguo Wu
Dongguan Key Laboratory of Chronic Disease Prevention and Control,The First Dongguan Affiliated Hospital,School of Public Health Guangdong Medical University

Yu Zhao
Affiliated Hospital Group of Guangdong Medical University Shenzhen Baoan Central Hospital

Zilong Wen
Affiliated Hospital Group of Guangdong Medical University Shenzhen Baoan Central Hospital

Haibing Yu
hby616688@gdmu.edu.cn

Dongguan Key Laboratory of Chronic Disease Prevention and Control,The First Dongguan Affiliated Hospital,School of Public Health Guangdong Medical University

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Research Article

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Long-term maintenance of healthy adiposity and risk of cardiometabolic multimorbidity: from three prospective cohorts

Yibo Lin[1], Haimei Zhong[1], Qintong Ruan[1], Yingen Feng[1],Yupeng Huang[1],Zhuguo Wu[1,4],Yu Zhao[3] ,Zilong Wen[3#], Haibing Yu[1,2#]

1.Dongguan Key Laboratory of Chronic Disease Prevention and Control,The First Dongguan Affiliated Hospital,School of Public Health，Guangdong Medical University. Dongguan, Guangdong, 523710, China

2.Qinghai Province Haidong City Center for Disease Control and Prevention, Haidong, Qingha, 810699, China

3.Affiliated Hospital Group of Guangdong Medical University Shenzhen Baoan Central Hospital, Shenzhen, Guangdong, 518100, China

Corresponding Author:

Haibing Yu, School of Public Health, The First Affiliated Hospital of Dongguan, Dongguan Key Laboratory of Chronic Disease Prevention and Control,State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia, Guangdong Medical University, Dongguan, Guangdong, China.

E-mail:hby616688@gdmu.edu.cn Tel:15913825522 ORCID : https://orcid.org/0000-0002-1877-3074

Zilong Wen,Affiliated Hospital Group of Guangdong Medical University Shenzhen Baoan Central Hospital (Baoan Central Hospital of Shenzhen), Shenzhen, Guangdong, China 516003, China.

mail: zxyytjzx0812@163.com.

Abstract

Objective: To investigate associations of BMI-TTR, WC-TTR, and WHtR-TTR with incident cardiometabolic multimorbidity (CMM) risk.

Methods: 4,954 participants from the China Health and Retirement Longitudinal Study (CHARLS) were included. Cox proportional hazards regression, restricted cubic spline, subgroup, and time-dependent ROC curve analyses were performed. External validation was conducted using the Health and Retirement Study (HRS) and English Longitudinal Study of Ageing (ELSA). Sensitivity analyses assessed findings robustness.

Results: During follow-up, 459 participants developed CMM. In fully adjusted models, higher BMI-TTR, WC-TTR, and WHtR-TTR were associated with lower CMM risk. Compared with 0% TTR, 100% TTR yielded HRs of 0.657 (BMI-TTR), 0.545 (WC-TTR), and 0.555 (WHtR-TTR). All three indices showed near-linear inverse associations with CMM risk. Significant associations were mainly observed in women, not men. WC-TTR had the best discriminatory ability for 3- and 5-year CMM risk and most consistent results across HRS and ELSA.

Conclusions: Long-term maintenance of healthy overall and central adiposity is associated with lower cardiometabolic multimorbidity risk. Maintaining waist circumference within recommended ranges may effectively reduce CMM risk in middle-aged and older women.

Keywords:BMI-TTR; WC-TTR; WHtR-TTR; cardiometabolic multimorbidity; older adults; risk prediction

1.Background

Cardiometabolic multimorbidity (CMM) refers to the coexistence of two or more cardiometabolic diseases (CMDs) within the same individual, including diabetes, myocardial infarction, and stroke. Compared with the presence of a single cardiometabolic condition, CMM is associated with substantially higher risks of mortality and adverse health outcomes[1]. With the accelerated aging of populations worldwide, the prevalence of CMM has increased progressively. A previous Chinese study reported that nearly 3% of adults aged ⩾18 years had CMM, with prevalence increasing markedly with age, reaching 5.2% among individuals aged ⩾40 years and 11.6% among those aged ⩾60 years[2]. Individuals with CMM experience higher risks of all-cause mortality, functional decline, impaired quality of life, and increased healthcare expenditure, with life expectancy reduced by more than 10 years by the age of 60 years[3–5]. Given the substantial disease burden and rapidly increasing prevalence of CMM, early identification based on comprehensive risk assessment is essential for timely intervention and prevention.

Excess adiposity and weight gain are well-established modifiable risk factors for cardiovascular disease and diabetes. Anthropometric indices, owing to their simplicity, non-invasive nature, and cost-effectiveness, are widely used for cardiometabolic risk screening[6]. A large-scale Chinese study involving 101,973 adults demonstrated that adiposity-related measures, including body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR), were associated with CMM risk[7]. However, previous studies have predominantly focused on single-time-point measurements of obesity-related indicators, which may not adequately capture long-term exposure patterns, Furthermore, few studies have performed external validation to determine whether these associations are consistent across populations[8].Time in therapeutic range (TTR) is a longitudinal indicator that reflects the proportion of time an indicator remains within a predefined target range. It has been widely used to assess long-term patterns of glycemic and blood pressure control and to predict disease outcomes[9–12]. However, whether the long-term TTR levels of different anthropometric indices are associated with the risk of incident CMM remains unclear.

In the present study, we used data from the China Health and Retirement Longitudinal Study (CHARLS), which initially recruited middle-aged and older adults aged ⩾45 years and followed them longitudinally. External validation was further performed using the Health and Retirement Study (HRS) and the English Longitudinal Study of Ageing (ELSA). We aimed to investigate the associations of BMI-TTR, WC-TTR, and WHtR-TTR with the risk of incident cardiometabolic multimorbidity among middle-aged and older adults.

2.METHODS

2.1. Study design and population

The China Health and Retirement Longitudinal Study (CHARLS) is an ongoing longitudinal cohort study that collects high-quality micro-level data on households and individuals aged ⩾45 years in China. Detailed information regarding the study design and data collection procedures has been described previously and is available from the official CHARLS website[13]. All waves of CHARLS were approved by the Institutional Review Board of Peking University, and written informed consent was obtained from all participants before participation.

The first wave of CHARLS was used as the baseline, and participants were subsequently followed through 2020. A complete-case analysis was performed. After applying the eligibility criteria, 4,954 participants were included in the final study population (Figure 1).

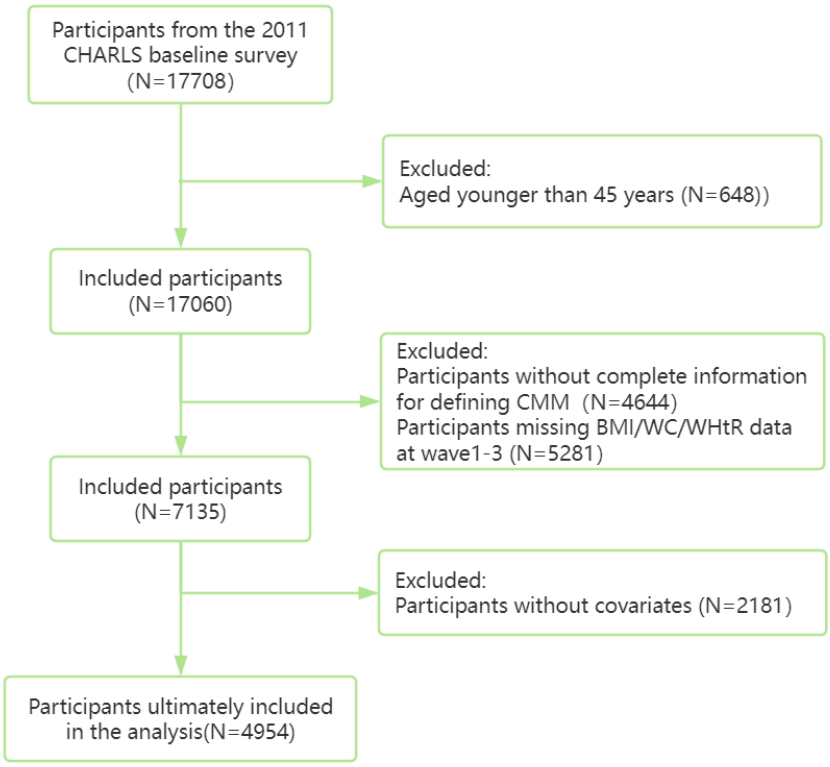


Figure 1 Flowchart of the research population selection process

2.2 Exposure assessment

BMI was calculated as body weight in kilograms divided by height in meters squared. WHtR was calculated as waist circumference divided by height. TTR was defined as the proportion of follow-up time during which an anthropometric indicator remained within the predefined target range. TTR was calculated using linear interpolation according to the Rosendaal method[14].Specifically, for each interval between two consecutive measurements, the amount of time during which the anthropometric indicator remained within the target range was estimated by linear interpolation and multiplied by the duration of that interval. The estimated time within the target range across all intervals was then summed and divided by the total follow-up duration to obtain the TTR.

BMI-TTR was defined as the proportion of follow-up time during which BMI remained within the normal range for Chinese adults ($18.5 \leqslant BMI < 24.0$ kg/m^2). Based on the diagnostic criteria for central obesity in Chinese populations, WC-TTR was defined as the proportion of follow-up time during which WC remained below 90 cm in men and below 85 cm in women. WHtR-TTR was defined as the proportion of follow-up time during which WHtR remained below the generally accepted optimal cutoff of 0.5[15–17].Because a relatively large proportion of participants had TTR values of 0% or 100%, participants with TTR values of 0% and 100% were classified into separate categories, while the remaining participants were divided at 50%. Accordingly, TTR was categorized into

four groups: 0%, >0% to ≤50%, >50% to <100%, and 100%.CHARLS used objective measurement data from waves 1, 2, and 3 (2011, 2013, 2015); HRS selected nurse-measured anthropometric data from waves 8, 9, and 10 (2006, 2008, 2010); ELSA only did nurse exams in even waves, so we used measurement data from waves 2, 4, and 6 (2004/05, 2008/09, 2012/13). We kept participants who had valid measurements all three times.

2.3 Outcome

The primary outcome was the occurrence of incident CMM, defined as the coexistence of two or more of the following conditions: diabetes, heart disease, and stroke.Diabetes was defined according to the following criteria: fasting plasma glucose (FPG) ≥7.0 mmol/L, glycated hemoglobin (HbA1c) ≥6.5%, current use of antidiabetic medication, or self-reported physician diagnosis of diabetes or high blood glucose [21].Information on heart disease and stroke was collected using standardized questions. Participants were asked, "Have you ever been diagnosed by a doctor with coronary heart disease, angina, congestive heart failure, or other heart problems?" and "Have you ever been diagnosed by a doctor with a stroke?" respectively.For participants who developed CMM during follow-up, the event time was defined as the interval between the previous interview and the interview at which a new CMM diagnosis was reported. For participants who did not report CMM during follow-up, follow-up time was determined as the interval between the baseline assessment and the date of the final survey [22].

2.4 Covariate selection

Covariates were selected based on clinical relevance and a combination of univariable logistic regression analysis and least absolute shrinkage and selection operator (LASSO) regression analysis. The final covariates included age, sex, hypertension, dyslipidemia, chronic lung disease, chronic kidney disease, arthritis, fasting glucose (GLU), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) (Figure S1).

2.5 Statistical analysis

For descriptive analyses, continuous variables were expressed as the mean±standard deviation (SD) or median with interquartile range (IQR), as appropriate, while categorical variables were presented as frequencies and percentages. Differences in baseline characteristics between groups were assessed using one-way analysis of variance or the Kruskal–Wallis test for continuous variables, depending on the distribution of the data, and the chi-square test for categorical variables. A two-sided *P* value <0.05 was considered statistically significant.

Multivariable Cox proportional hazards regression models and restricted cubic spline (RCS) analyses were used to investigate the associations of BMI-TTR, WC-TTR, and WHtR-TTR with the risk of incident CMM. Results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs).The TTR indices were analyzed both as continuous variables and as four-category variables to assess linear trends. RCS models were further used to explore potential dose‐response relationships, with four knots selected for the spline functions.

Sex-stratified Cox regression analyses were subsequently performed to examine whether the associations differed between women and men. Receiver operating characteristic (ROC) curves were used to evaluate the predictive performance of BMI-TTR, WC-TTR, and WHtR-TTR for incident CMM. The area under the curve (AUC) was calculated to compare the discriminatory ability of the three indices for identifying individuals at risk of CMM.Subgroup analyses were also conducted to evaluate the consistency of the associations across different baseline characteristics. Potential effect modification was assessed by including interaction terms in the regression models.All statistical analyses were performed using R software version 4.4.3.

2.6 External validation and sensitivity analyses

Two independent cohorts, the Health and Retirement Study (HRS; n = 3,275) and the English Longitudinal Study of Ageing (ELSA; n = 2,597), were used for external validation.Because the proportions of missing data for fasting glucose and low-density lipoprotein cholesterol exceeded 50% in the ELSA cohort, these two covariates were excluded from the external validation analyses.Three additional sensitivity analyses were conducted to assess the robustness of the findings.

3.RESULTS

3.1.Characteristics of study participant

A total of 4,954 participants were included in the present study, among whom 459 developed incident cardiometabolic multimorbidity (CMM) during follow-up. Compared with participants without CMM, those who developed CMM were older (median age, 61.00 vs. 59.00 years, $P < 0.001$), had a higher proportion of men and rural residents, and had lower proportions of current smokers and drinkers ($P < 0.01$).Participants who developed CMM also had significantly higher systolic blood pressure, diastolic blood pressure, fasting glucose, lipid levels, and C-reactive protein (CRP) levels, as well as lower high-density lipoprotein cholesterol (HDL) levels ($P < 0.001$). In addition, BMI-TTR, WC-TTR, and WHtR-TTR were all significantly lower in the CMM group than in the non-CMM group, indicating poorer long-term maintenance of anthropometric indicators within the target

ranges ($P < 0.001$).Furthermore, the prevalence of comorbidities was significantly higher among participants with CMM than among those without CMM ($P < 0.05$). No statistically significant differences were observed between the two groups in educational attainment, marital status, asthma, or cancer prevalence ($P > 0.05$) (Table 1).

Table 1 Characteristics of the Charls participants

Variables	Total (n = 4954)	Without CMM (n = 4495)	CMM (n = 459)	Statistic	*P*
Age, M (Q_1, Q_3)	59.00 (53.00, 65.00)	59.00 (53.00, 65.00)	61.00 (55.00, 66.00)	Z=-3.33	**<0.001**
Systo, M (Q_1, Q_3)	129.00 (116.00, 146.00)	129.00 (116.00, 145.00)	136.00 (123.00, 152.50)	Z=-6.77	**<0.001**
Diasto, M (Q_1, Q_3)	75.00 (68.00, 84.00)	75.00 (68.00, 84.00)	79.00 (70.00, 87.00)	Z=-5.44	**<0.001**
GLU, M (Q_1, Q_3)	102.24 (94.50, 112.68)	101.88 (94.14, 111.42)	111.06 (99.36, 125.82)	Z=-10.17	**<0.001**
TG, M (Q_1, Q_3)	103.55 (74.34, 150.45)	101.78 (72.57, 148.68)	124.78 (89.83, 182.31)	Z=-7.51	**<0.001**
CHO, M (Q_1, Q_3)	191.37 (167.78, 215.72)	190.98 (167.40, 214.56)	198.71 (174.94, 226.55)	Z=-4.89	**<0.001**
HDL, M (Q_1, Q_3)	50.26 (40.98, 60.70)	50.64 (41.37, 61.08)	45.62 (37.50, 54.51)	Z=-6.96	**<0.001**
LDL, M (Q_1, Q_3)	114.43 (94.04, 137.63)	113.66 (93.94, 136.08)	121.78 (96.84, 148.07)	Z=-4.57	**<0.001**
CRP, M (Q_1, Q_3)	0.97 (0.54, 2.05)	0.94 (0.53, 1.99)	1.30 (0.71, 2.50)	Z=-5.71	**<0.001**
BMI-TTR, M (Q_1, Q_3)	58.05 (0.00, 100.00)	65.06 (0.00, 100.00)	0.00 (0.00, 97.93)	Z=-8.63	**<0.001**
WC-TTR, M (Q_1, Q_3)	70.92 (0.00, 100.00)	79.17 (0.00, 100.00)	0.00 (0.00, 91.82)	Z=-10.80	**<0.001**
WHtR-TTR, M (Q_1, Q_3)	0.00 (0.00, 47.30)	0.00 (0.00, 52.40)	0.00 (0.00, 0.16)	Z=-7.90	**<0.001**
Ragender, n(%)				χ^2=16.59	**<0.001**
Female	2782 (56.16)	2483 (55.24)	299 (65.14)		
Male	2172 (43.84)	2012 (44.76)	160 (34.86)		
Rural, n(%)				χ^2=8.91	**0.003**
No	4349 (87.79)	3966 (88.23)	383 (83.44)		
Yes	605 (12.21)	529 (11.77)	76 (16.56)		
Raeducl, n(%)				χ^2=1.77	0.184
No	4911 (99.13)	4459 (99.20)	452 (98.47)		
Yes	43 (0.87)	36 (0.80)	7 (1.53)		
Marry, n(%)				χ^2=0.08	0.773
No	552 (11.14)	499 (11.10)	53 (11.55)		
Yes	4402 (88.86)	3996 (88.90)	406 (88.45)		

Smoke, n(%)				χ^2=7.75	**0.005**
No	3092 (62.41)	2778 (61.80)	314 (68.41)		
Yes	1862 (37.59)	1717 (38.20)	145 (31.59)		
Drinke, n(%)				χ^2=8.39	**0.004**
No	3113 (62.84)	2796 (62.20)	317 (69.06)		
Yes	1841 (37.16)	1699 (37.80)	142 (30.94)		
Hibpe, n(%)				χ^2=153.64	**<0.001**
No	3726 (75.21)	3490 (77.64)	236 (51.42)		
Yes	1228 (24.79)	1005 (22.36)	223 (48.58)		
Dyslipe, n(%)				χ^2=137.91	**<0.001**
No	4532 (91.48)	4179 (92.97)	353 (76.91)		
Yes	422 (8.52)	316 (7.03)	106 (23.09)		
Lunge, n(%)				χ^2=9.98	**0.002**
No	4488 (90.59)	4091 (91.01)	397 (86.49)		
Yes	466 (9.41)	404 (8.99)	62 (13.51)		
Livere, n(%)				χ^2=4.71	**0.030**
No	4791 (96.71)	4355 (96.89)	436 (94.99)		
Yes	163 (3.29)	140 (3.11)	23 (5.01)		
Kidneye, n(%)				χ^2=21.40	**<0.001**
No	4672 (94.31)	4261 (94.79)	411 (89.54)		
Yes	282 (5.69)	234 (5.21)	48 (10.46)		
Digeste, n(%)				χ^2=7.28	**0.007**
No	3802 (76.75)	3473 (77.26)	329 (71.68)		
Yes	1152 (23.25)	1022 (22.74)	130 (28.32)		
Arthre, n(%)				χ^2=16.42	**<0.001**
No	3221 (65.02)	2962 (65.90)	259 (56.43)		
Yes	1733 (34.98)	1533 (34.10)	200 (43.57)		
Asthmae, n(%)				χ^2=3.60	0.058
No	4719 (95.26)	4290 (95.44)	429 (93.46)		
Yes	235 (4.74)	205 (4.56)	30 (6.54)		
Cancre, n(%)				χ^2=2.80	0.094
No	4916 (99.23)	4464 (99.31)	452 (98.47)		
Yes	38 (0.77)	31 (0.69)	7 (1.53)		

Z: Mann-Whitney test, χ^2: Chi-square test, M: Median, Q_1: 1st Quartile, Q_3: 3st Quartile

3.2 Associations between BMI-TTR, WC-TTR, WHtR-TTR and incident CMM

The proportional hazards assumption was assessed using Schoenfeld residuals, and no significant evidence of violation of the Cox proportional hazards assumption was observed.Multivariable Cox regression analyses showed that higher levels of BMI-TTR, WC-TTR, and WHtR-TTR were significantly associated with a lower risk of incident CMM (Table 2). In the fully adjusted model (Model 3), BMI-TTR, WC-TTR, and WHtR-TTR, when analyzed as continuous variables, were all inversely associated with the risk of CMM, with HRs of 0.996 (95% CI, 0.994 – 0.998; $P < 0.001$), 0.995 (95% CI, 0.992 – 0.997; P < 0.001), and 0.995 (95% CI, 0.991 – 0.998; $P = 0.001$), respectively.

Further analyses using four TTR categories showed that, compared with participants in the lowest TTR category (Q1, 0%), those with higher BMI-TTR levels had significantly lower risks of incident CMM. Participants in the highest BMI-TTR category (Q4, 100%) had a 34.3% lower risk of CMM (HR, 0.657; 95% CI, 0.527 – 0.821; $P < 0.001$), with a significant dose – response trend (P for trend < 0.001).Similarly, WC-TTR and WHtR-TTR were both inversely associated with CMM risk. Participants with a WC-TTR of 100% had the lowest risk of incident CMM (HR, 0.545; 95% CI, 0.427 – 0.695; $P < 0.001$), while those with a WHtR-TTR of 100% had a 44.5% lower risk of CMM (HR, 0.555; 95% CI, 0.376 – 0.820; $P = 0.003$). Significant linear trends were observed between all three TTR indices and CMM risk (P for trend < 0.05).

Sex-stratified Cox regression analyses were further performed to explore sex-specific associations. The inverse associations between the three TTR indices and incident CMM were statistically significant in women but not in men(Table 3).

Table 2 Associations between BMI-TTR, WC-TTR, WHtR-TTR and incident CMM in overall population

Categories	Model 1			Model 2			Model 3		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
BMI-TTR									
Continuous	0.991	0.990, 0.993	<0.001	0.994	0.992, 0.996	<0.001	0.996	0.994, 0.998	<0.001
Q1 (0%)	Ref.	—	—	Ref.	—	—	Ref.	—	—
Q2 (>0% to ≤50%)	0.642	0.495, 0.833	<0.001	0.761	0.585, 0.989	0.041	0.789	0.580, 1.074	0.132
Q3 (>50% to <100%)	0.471	0.363,	<0.001	0.583	0.446,	<0.001	0.676	0.503,	0.010

		0.613			0.761			0.910	
Q4 (100%)	0.416	0.344, 0.502	<0.001	0.548	0.450, 0.668	<0.001	0.657	0.527, 0.821	<0.001
P for trend	—	—	<0.001	—	—	<0.001	—	—	<0.001
WC-TTR									
Continuous	0.989	0.987, 0.991	<0.001	0.993	0.991, 0.995	<0.001	0.995	0.992, 0.997	<0.001
Q1 (0%)	Ref.	—	—	Ref.	—	—	Ref.	—	—
Q2 (>0% to ≤50%)	0.518	0.399, 0.673	<0.001	0.609	0.469, 0.792	<0.001	0.688	0.513, 0.923	0.013
Q3 (>50% to <100%)	0.477	0.372, 0.613	<0.001	0.630	0.488, 0.814	<0.001	0.790	0.598, 1.043	0.096
Q4 (100%)	0.315	0.260, 0.381	<0.001	0.446	0.363, 0.548	<0.001	0.545	0.427, 0.695	<0.001
P for trend	—	—	<0.001	—	—	<0.001	—	—	<0.001
WHtR-TTR									
Continuous	0.988	0.986, 0.991	<0.001	0.992	0.990, 0.995	<0.001	0.995	0.991, 0.998	0.001
Q1 (0%)	Ref.	—	—	Ref.	—	—	Ref.	—	—
Q2 (>0% to ≤50%)	0.546	0.422, 0.706	<0.001	0.652	0.502, 0.847	0.001	0.848	0.643, 1.118	0.242
Q3 (>50% to <100%)	0.453	0.334, 0.615	<0.001	0.615	0.451, 0.840	0.002	0.790	0.555, 1.124	0.189
Q4 (100%)	0.320	0.231, 0.441	<0.001	0.472	0.337, 0.661	<0.001	0.555	0.376, 0.820	0.003
P for trend	—	—	<0.001	—	—	<0.001	—	—	0.002

Model one: Uncorrected for covariates.

Model two: Adjusted for age, gender, hypertension, dyslipidemia, chronic lung disease, chronic kidney disease, arthritis.

Model three: Adjusted for age, gender, hypertension, dyslipidemia, chronic lung disease, chronic kidney disease, arthritis, GLU, HDL and LDL.

Table 3 Sex-stratified associations between BMI-TTR, WC-TTR, WHtR-TTR and incident CMM (Model 3)

Categories	Female			Male		
	HR	95% CI	*P* value	HR	95% CI	*P* value
BMI-TTR						
Continuous	0.994	0.992, 0.997	<0.001	1.000	0.996, 1.003	0.833
Q1 (0%)	Ref.	—	—	Ref.	—	—
Q2 (>0% to ≤50%)	0.785	0.539, 1.143	0.206	0.836	0.486, 1.438	0.517
Q3 (>50% to <100%)	0.541	0.363, 0.804	0.002	1.093	0.689, 1.733	0.707
Q4 (100%)	0.580	0.436, 0.773	<0.001	0.924	0.641, 1.333	0.672
P for trend	—	—	<0.001	—	—	0.779
WC-TTR						
Continuous	0.993	0.990, 0.996	<0.001	0.999	0.995, 1.002	0.433
Q1 (0%)	Ref.	—	—	Ref.	—	—
Q2 (>0% to ≤50%)	0.708	0.503, 0.997	0.048	0.634	0.357, 1.128	0.121
Q3 (>50% to <100%)	0.542	0.369, 0.796	0.002	1.359	0.893, 2.068	0.152
Q4 (100%)	0.511	0.369, 0.708	<0.001	0.723	0.496, 1.053	0.091
P for trend	—	—	<0.001	—	—	0.235
WHtR-TTR						
Continuous	0.992	0.987, 0.998	0.005	0.998	0.993, 1.002	0.296

Q1 (0%)	Ref.	—	—	Ref.	—	—
Q2 (>0% to ≤50%)	0.696	0.472, 1.027	0.068	1.223	0.813, 1.838	0.334
Q3 (>50% to <100%)	0.720	0.434, 1.193	0.202	1.034	0.627, 1.706	0.896
Q4 (100%)	0.427	0.209, 0.872	0.019	0.817	0.499, 1.338	0.422
P for trend	—	—	0.004	—	—	0.559

RCS analyses showed that, in the overall population, BMI-TTR, WC-TTR, and WHtR-TTR were all significantly inversely associated with the risk of incident CMM, with no evidence of significant nonlinearity (*P*-overall < 0.001; *P*-nonlinear > 0.05).Among women, BMI-TTR, WC-TTR, and WHtR-TTR were all significantly inversely associated with CMM risk. BMI-TTR showed a significant overall association with CMM risk (P-overall < 0.001), with no evidence of a significant nonlinear relationship (*P*-nonlinear = 0.094). Similarly, WC-TTR (*P*-overall < 0.001; *P*-nonlinear = 0.668) and WHtR-TTR (*P*-overall = 0.025; *P*-nonlinear = 0.936) demonstrated approximately linear decreasing associations with CMM risk.In contrast, no significant associations between BMI-TTR, WC-TTR, or WHtR-TTR and incident CMM were observed among men, and no significant nonlinear relationships were detected (*P*-nonlinear > 0.05) (Figure 3).

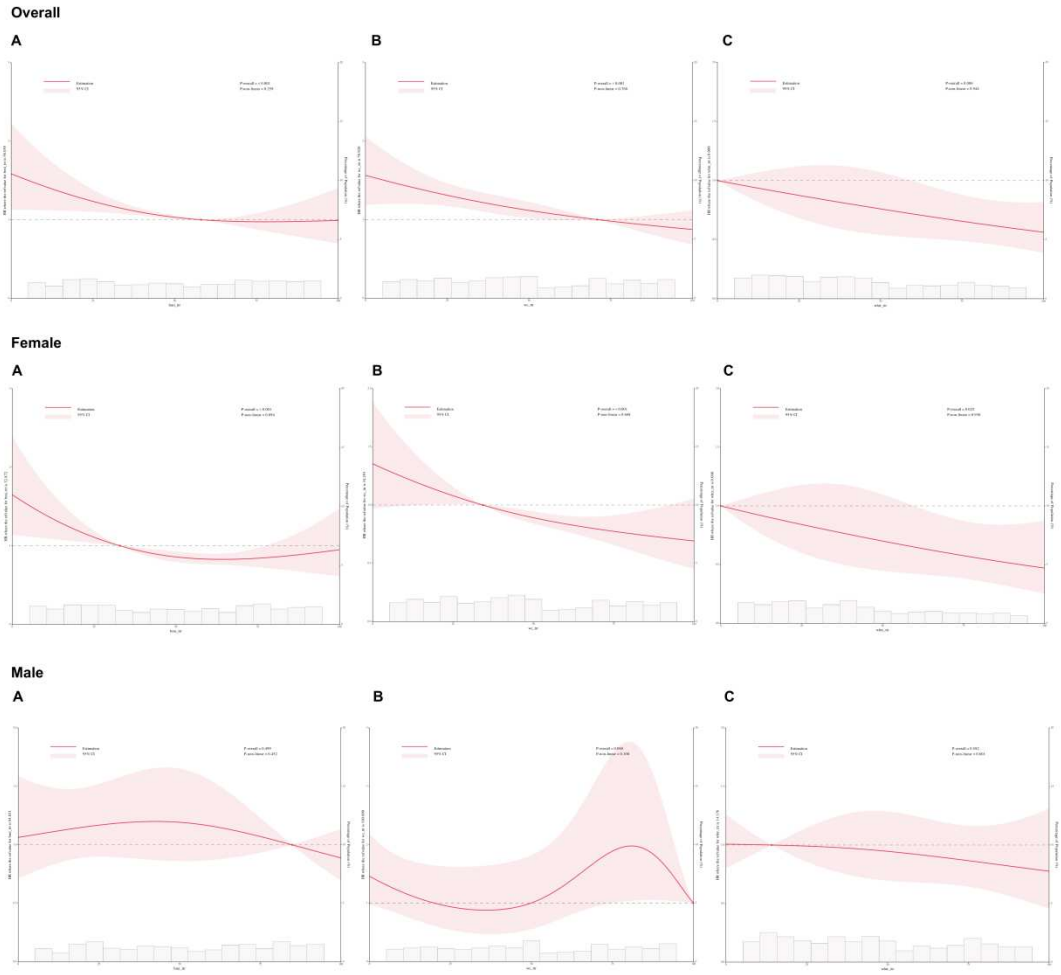


Figure 3 RCS of the associations between BMI-TTR, WC-TTR, WHtR-TTR and incident CMM

(A) Association between BMI-TTR and incident CMM. (B) Association between WC-TTR and incident CMM.

(C) Association between WHtR-TTR and incident CMM.

3.3 Subgroup analyses

Subgroup analyses further evaluated the robustness of the associations between BMI-TTR, WC-TTR, WHtR-TTR, and the risk of incident CMM. Overall, BMI-TTR, WC-TTR, and WHtR-TTR consistently showed inverse associations with CMM risk, and these associations were generally maintained across subgroups defined by age, sex, hypertension, dyslipidemia, chronic lung disease, chronic kidney disease, and arthritis.In most subgroups, the effect estimates were below 1, with the 95% confidence intervals generally showing directions consistent with those observed in the overall analyses, suggesting that higher TTR levels were associated with a lower risk of CMM. Interaction analyses showed that most stratifying factors did not significantly modify the associations between TTR indices and CMM risk (*P* for interaction > 0.05), indicating that age, sex, and major

chronic disease status did not substantially alter these associations.Overall, the associations between BMI-TTR, WC-TTR, WHtR-TTR, and lower CMM risk appeared relatively robust and consistent across different population subgroups.

Notably, significant interactions were observed in a small number of subgroups. For WHtR-TTR, age and chronic lung disease status showed potential effect modification (*P* for interaction < 0.05), suggesting that the association between WHtR-TTR and CMM risk may vary according to age or certain disease conditions. However, because the vast majority of interaction tests were not statistically significant, the overall findings continued to support the stability of the associations between TTR indices and CMM risk (Figure 4).

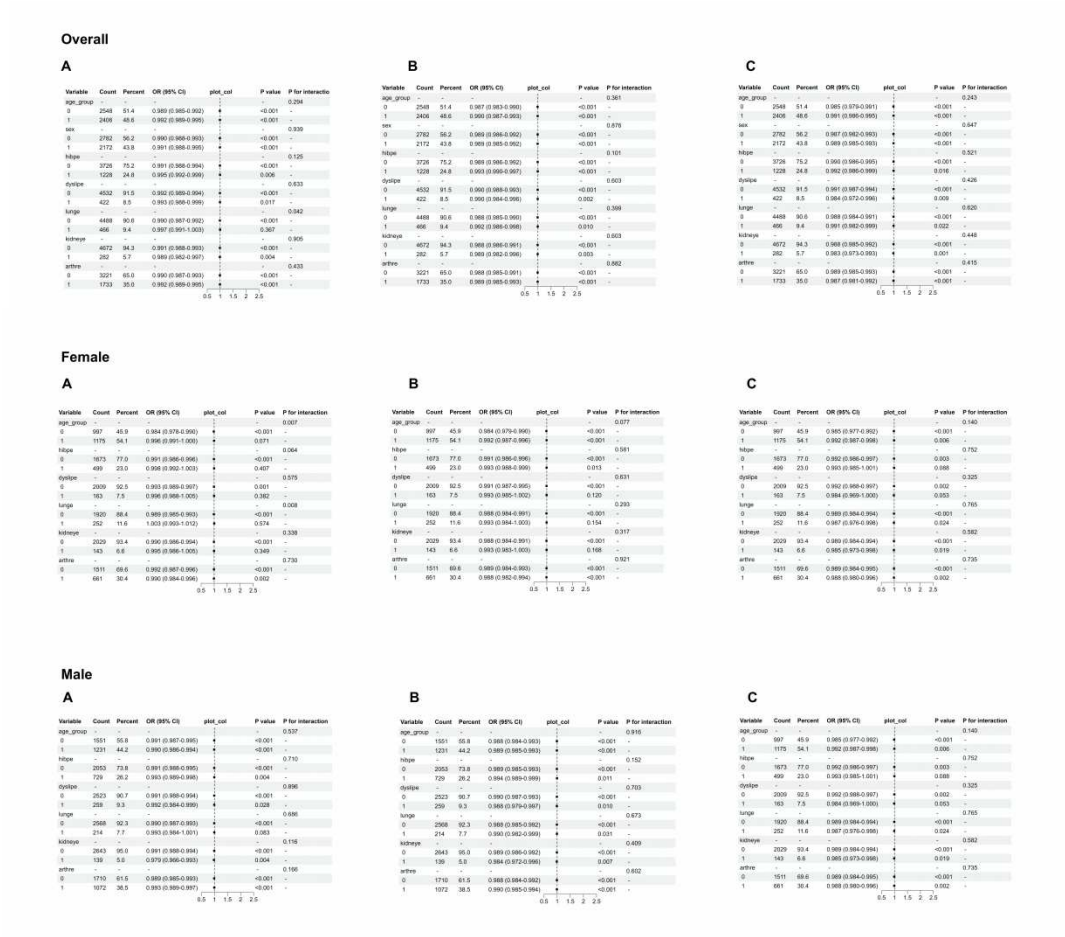


Figure 4 Subgroup analyses of the associations between TTR indices and incident CMM

(A) Association between BMI-TTR and incident CMM. (B) Association between WC-TTR and incident CMM.

(C) Association between WHtR-TTR and incident CMM.

3.4 Predictive performance analyses using time-dependent ROC curves

Time-dependent receiver operating characteristic (ROC) curve analyses were performed to evaluate the

discriminatory ability of BMI-TTR, WC-TTR, and WHtR-TTR for incident CMM.All three TTR indices demonstrated a certain degree of discriminatory ability for CMM risk during 3- and 5-year follow-up periods. At 3 years, WC-TTR had the highest area under the curve (AUC) of 0.721, followed by BMI-TTR (AUC = 0.674) and WHtR-TTR (AUC = 0.627), suggesting that WC-TTR had relatively better discriminatory performance for short-term CMM risk identification.Overall, WC-TTR consistently showed the highest AUC across the different follow-up time points, suggesting that it may have better discriminatory performance for CMM risk than BMI-TTR and WHtR-TTR.(Figure 5)

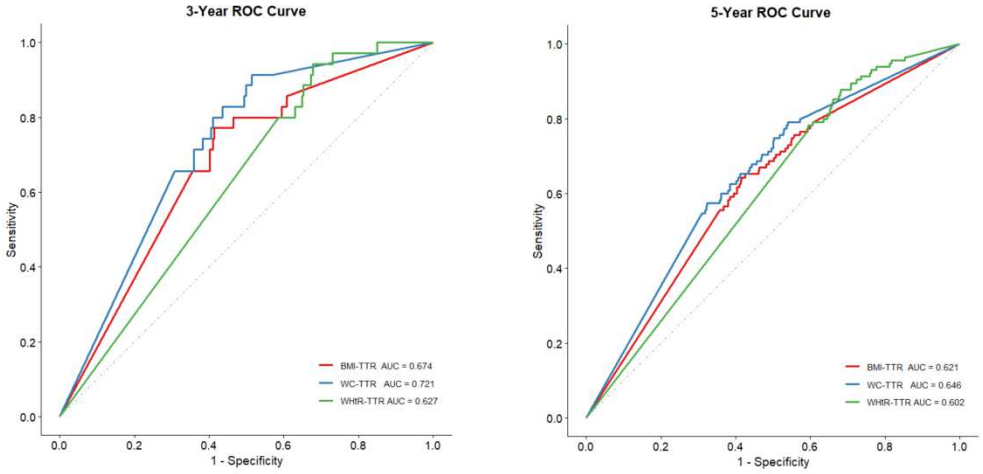


Figure 5 ROC curves of BMI-TTR, WC-TTR and WHtR-TTR for predicting 3-year and 5-year endpoints

3.5 External validation in the HRS and ELSA cohorts

External validation was performed in two independent cohorts, the Health and Retirement Study (HRS) and the English Longitudinal Study of Ageing (ELSA).In the HRS cohort, higher WC-TTR was significantly associated with a lower risk of incident CMM (HR = 0.994, 95% CI: 0.989 – 1.000; *P* = 0.046), and the risk of CMM showed a significant decreasing trend with increasing WC-TTR levels (*P* for trend = 0.031). In contrast, although BMI-TTR and WHtR-TTR remained inversely associated with CMM risk after full adjustment, these associations did not reach statistical significance.In the ELSA cohort, the inverse associations of WC-TTR and WHtR-TTR with CMM risk were further validated. Compared with participants in the lowest TTR category, those with a WC-TTR of 100% had a 51.5% lower risk of incident CMM, while those with a WHtR-TTR of 100% had a 55.7% lower risk. Significant trends across TTR categories were observed for both indices.

Sex-stratified analyses showed that the significant associations were primarily observed among women. WC-TTR demonstrated a relatively consistent inverse association in women in both the HRS and ELSA cohorts,

whereas no clear association was observed among men. Overall, the two external validation cohorts further supported the inverse associations between anthropometric TTR indices and CMM risk, with WC-TTR demonstrating the most consistent cross-cohort reproducibility (Tables S1 – S4).

3.6 Sensitivity analyses

The sensitivity analyses demonstrated the robustness of the study findings. After multiple imputation of missing covariates, the associations of BMI-TTR, WC-TTR, and WHtR-TTR with incident CMM remained essentially unchanged (Table S5).Further adjustment for the corresponding baseline anthropometric measurements did not substantially alter the results, suggesting that TTR captures the long-term maintenance of adiposity status beyond a single baseline measurement (Table S6).E-value analyses indicated that relatively strong unmeasured confounding would be required to fully explain the observed associations, further supporting the robustness of the findings (Table S7).

4. DISCUSSION

This study was based on the CHARLS cohort to systematically evaluate the associations of BMI-TTR, WC-TTR, and WHtR-TTR with the risk of incident cardiometabolic multimorbidity (CMM), and further performed external validation in two independent cohorts, the HRS and ELSA. The main findings of this study were as follows: First, higher levels of BMI-TTR, WC-TTR, and WHtR-TTR were significantly associated with a lower risk of incident CMM, and these associations showed an approximately linear dose – response relationship. Second, compared with individuals with the lowest TTR levels, those who maintained anthropometric measurements within the target ranges over time had a substantially lower risk of CMM. Third, WC-TTR demonstrated the best discriminatory ability for risk prediction in time-dependent ROC analyses and showed the most consistent reproducibility across the HRS and ELSA cohorts. Fourth, sex-stratified analyses indicated that the inverse associations between TTR and CMM risk were primarily observed among women. Overall, these findings suggest that long-term maintenance of healthy anthropometric status, rather than focusing solely on single-time-point measurements, may represent an important strategy for reducing the risk of CMM among middle-aged and older adults.

Obesity and abnormal fat distribution are important risk factors for the development of CMM, mainly through increasing cardiometabolic burden by promoting insulin resistance, chronic low-grade inflammation, oxidative stress, and endothelial dysfunction[18]. BMI, as a classic indicator for assessing obesity, has long been widely used to predict the risks of diabetes, cardiovascular disease, and multimorbidity. However, BMI mainly reflects overall

body weight status, cannot distinguish between fat mass and lean mass, and cannot accurately characterize fat distribution[19]. In contrast, WC and WHtR more directly reflect abdominal fat accumulation, and central obesity is considered a key driver of metabolic abnormalities[20]. Therefore, increasing attention has been paid to the value of central obesity indicators in predicting CMM.

Previous studies have mainly focused on the associations between single-time-point anthropometric measurements and disease risk. However, anthropometric indices undergo substantial dynamic changes during long-term follow-up, and weight fluctuations may indicate underlying metabolic dysfunction[21–23]. In this study, we innovatively introduced the concept of TTR and used the proportion of time that anthropometric indices remained within the target ranges as indicators of long-term exposure. Similar approaches have been widely applied in blood pressure and glucose management. Previous studies have shown that higher systolic blood pressure TTR is associated with lower risks of cardiovascular events and adverse renal outcomes; even among individuals with similar average blood pressure levels, maintaining stable blood pressure over time provides additional benefits[24,25]. In addition, glucose and glycated hemoglobin TTR have been demonstrated to predict the risks of diabetes incidence and mortality independently of baseline BMI[26–28]. However, evidence regarding the association between anthropometric TTR indices and CMM risk remains limited. This study further extends the application of the TTR concept in population health management and suggests that long-term maintenance of BMI, WC, and WHtR within appropriate ranges may provide important metabolic benefits.

Our findings showed that BMI-TTR, WC-TTR, and WHtR-TTR were all associated with a reduced risk of CMM, with WC-TTR demonstrating the strongest and most consistent association. This finding is biologically plausible. One of the key mechanisms underlying the development of CMM is excessive visceral fat accumulation, which promotes the release of free fatty acids and the expression of inflammatory factors, subsequently inducing insulin resistance, lipid metabolism disorders, and vascular damage[18]. WC is an important indicator of abdominal fat accumulation, and more than 70% of abdominal fat consists of visceral fat, which is strongly correlated with visceral adiposity levels[29]. Therefore, long-term maintenance of a lower WC level may reflect a lower metabolic inflammatory burden. In contrast, although BMI reflects overall obesity status, it has limited ability to distinguish differences in fat distribution[30]. Thus, the superior performance of WC-TTR in risk prediction and external validation in this study may reflect the important role of long-term exposure to central adiposity in the development of CMM.

The findings of this study are consistent with several previous investigations. Zhang et al. reported that WC showed better predictive performance for CMM compared with other obesity-related indicators[8]. Lu et al., in a

nationwide longitudinal cohort study involving 10,521 Chinese adults, reported that WC and other central obesity indicators performed better than BMI in predicting CMM[31]. Most previous studies were based on cross-sectional designs or single measurements, whereas the present study focused on long-term dynamic changes. Because TTR integrates both the level and duration of exposure, it may provide a more accurate reflection of cumulative metabolic burden.

Stratified analyses revealed that the association between TTR and reduced CMM risk was mainly observed among women. In the female subgroup, BMI-TTR, WC-TTR, and WHtR-TTR all demonstrated relatively consistent protective associations, whereas these associations were weaker among men. This finding is consistent with previous research. Chao et al. reported that maintaining BMI within the target range over time was associated with a reduced risk of incident diabetes among women. These sex differences may be related to differences in fat distribution, hormonal status, and metabolic characteristics. After menopause, declining estrogen levels in women may promote a shift in fat distribution from subcutaneous fat to abdominal visceral fat, thereby increasing the risk of metabolic diseases[32]. In addition, women generally have a higher proportion of body fat, whereas men may maintain better glucose metabolism through greater muscle mass[33]. Therefore, long-term maintenance of healthy anthropometric status may provide greater metabolic protection among women. However, it should be noted that the interaction test for sex did not demonstrate statistically significant differences; therefore, these findings require further validation in larger-scale studies.

This study has several strengths. First, it is the first to systematically compare the relationships between multiple anthropometric TTR indices and CMM risk, providing new evidence for the evaluation of dynamic anthropometric indicators. Second, multiple statistical approaches, including Cox regression, restricted cubic spline analyses, subgroup analyses, and time-dependent ROC curve analyses, were applied to assess the robustness of the findings from different perspectives. Third, external validation using the HRS and ELSA cohorts enhanced the reliability and generalizability of the results. Multiple sensitivity analyses further supported the robustness of the findings.

An important strength of this study was the external validation. The HRS and ELSA cohorts, representing populations from different countries and healthcare backgrounds, further supported the association between WC-TTR and reduced CMM risk. In both external cohorts, WC-TTR demonstrated good reproducibility, whereas the associations of BMI-TTR and WHtR-TTR were attenuated in some analyses. These findings suggest that WC-TTR may have greater cross-population stability than BMI-based control alone. Given that WC measurement is simple, inexpensive, and widely applicable, WC-TTR may have potential clinical value as an indicator for

long-term health management.

This study has several strengths. First, it is the first to systematically compare the relationships between multiple anthropometric TTR indices and CMM risk, providing new evidence for the evaluation of dynamic anthropometric indicators. Second, multiple statistical approaches, including Cox regression, restricted cubic spline analyses, subgroup analyses, and time-dependent ROC curve analyses, were applied to assess the robustness of the findings from different perspectives. Third, external validation using the HRS and ELSA cohorts enhanced the reliability and generalizability of the results. Multiple sensitivity analyses further supported the robustness of the findings.

Nevertheless, several limitations should be acknowledged. First, some CMM-related disease information was primarily obtained through self-reports, which may have introduced reporting bias and disease misclassification. Second, TTR calculations relied on anthropometric measurements collected at limited time points and therefore may not fully capture short-term fluctuations. Future studies with higher-frequency measurements are needed for further validation. Third, as an observational study, residual confounding factors, such as dietary patterns, physical activity levels, and medication use, cannot be completely excluded despite multivariable adjustment. Fourth, the study population mainly consisted of middle-aged and older adults; therefore, whether these findings can be generalized to younger populations requires further investigation. Finally, this study could not distinguish whether weight changes resulted from intentional weight loss or disease-related unintentional weight loss, which may have different metabolic implications.

5. CONCLUSIONS

Higher BMI-TTR, WC-TTR, and WHtR-TTR were associated with a lower risk of incident cardiometabolic multimorbidity, with approximately linear dose‑response relationships. These associations were more pronounced among women, whereas no significant associations were observed among men. WC-TTR demonstrated the best discriminatory performance and the most consistent cross-cohort reproducibility in the HRS and ELSA cohorts. These findings suggest that long-term maintenance of waist circumference within the recommended range may help reduce the risk of cardiometabolic multimorbidity among middle-aged and older women.

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List of abbreviations

BMI: body mass index

CMM: cardiometabolic multimorbidity

CI: confidence interval

ELSA: English Longitudinal Study of Ageing

HDL-C: high-density lipoprotein cholesterol

HR: hazard ratio

HRS: Health and Retirement Study

LDL-C: low-density lipoprotein cholesterol

RCS: restricted cubic spline

ROC: receiver operating characteristic

TTR: time in target range

WC: waist circumference

WHtR: waist-to-height ratio

CHARLS: China Health and Retirement Longitudinal Study

Author Contributions

Yibo Lin was responsible for formal analysis, methodology, and writing—original draft; Haimei Zhong was responsible for data curation and writing—original draft; Qintong Ruan ,Yingen Feng and

yupeng huang were responsible for data curation and literature retrieval; Jianfeng Zheng was responsible for data validation and resource collection; Zhuguo Wu was responsible for data collation and supplementary analysis; Yu Zhao was responsible for methodology improvement and project administration; Zilong Wen was responsible for conceptualization, statistical supervision, and writing—review & editing; Haibing Yu was responsible for study design, funding acquisition, project administration, and writing—review & editing. All authors reviewed and approved the final manuscript.

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Data availability

The datasets analyzed in this study are publicly available from the China Health and Retirement Longitudinal Study (CHARLS), the Health and Retirement Study (HRS), and the English Longitudinal Study of Ageing (ELSA). Data can be accessed through their respective official data platforms following registration and approval in accordance with the corresponding data-use policies.

Declarations

Ethics approval and consent to participate: This study was a secondary analysis of publicly available data from CHARLS, HRS, and ELSA. The original studies obtained ethical approval from their respective institutional review boards or ethics committees, and informed consent was obtained from all participants. Therefore, no additional ethical approval was required for the present secondary analysis.

Consent for publication: Not applicable.

Competing interests: The authors declare no competing interests.

Clinical trial number: not applicable

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