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Longitudinal changes and patterns in cardiometabolic index and the natural course of prediabetes in the China health and retirement longitudinal study

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Abstract

Background Prediabetes is one of the most common metabolic disorders in the aging process. This study aims to investigate the longitudinal changes in the Cardiometabolic Index (CMI) and their relationship with the natural course of prediabetes in middle-aged and elderly populations.

Methods This study used longitudinal data from the China Health and Retirement Longitudinal Study. The natural course of prediabetes was used to describe the trend in glycemic development during follow-up, defined as progression to diabetes or regression to normoglycaemia. Longitudinal changes in CMI were categorized into CMI transition patterns (consistently-low, low-to-high, high-to-low, and consistently-high) and cumulative CMI (CumCMI) exposure. CumCMI was calculated as the ratio of the mean CMI values measured during the longitudinal surveys to the total duration of exposure.

Results According to the inclusion and exclusion criteria, a total of 2,544 prediabetic participants from the China Health and Retirement Longitudinal Study cohort were included in the study. During a median follow-up of 3 years, the rates of progression and regression of prediabetes were as follows in the consistently-low, low-to-high, high-to-low, and consistently-high CMI pattern groups: 9.94%, 16.55%, 11.72%, 20.32% for progression; and 24.97%, 22.37%, 23.81%, 20.42% for regression, respectively. Regarding prediabetes progression, our results found that a high baseline CMI level and high CumCMI exposure during follow-up significantly increased the risk of developing diabetes in prediabetic patients. Furthermore, during follow-up, compared to the low-to-high CMI pattern group, the consistently-low CMI pattern was protective for prediabetic patients. Concerning prediabetes regression, we only observed a negative correlation between baseline CMI and follow-up CumCMI exposure with outcomes in the elderly (age ≥ 60 years). Specifically, high baseline CMI levels and high follow-up CumCMI exposure significantly hindered prediabetes regression in the elderly.

Conclusion In this prospective cohort study of middle-aged and elderly populations, we found that longitudinal changes in CMI were associated with the progression and regression of prediabetes. High CumCMI exposure during follow-up significantly increased the risk of diabetes events and hindered the recovery of normoglycaemia

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in the elderly. Moreover, maintaining a consistently-low CMI pattern during follow-up reduced the risk of diabetes in prediabetic patients.

Keywords Cardiometabolic index, Cumulative cardiometabolic index exposure, Cardiometabolic index transition patterns, Natural course of prediabetes, CHARLS

Background

Prediabetes refers to an intermediate stage where blood glucose levels are elevated above normal but not yet high enough to be classified as diabetes. It is one of the most common metabolic disorders in the aging process [1, 2]. According to recent epidemiological analyses of the Chinese population, the prevalence of prediabetes among Chinese adults is approximately one-third, with middle-aged and elderly individuals accounting for nearly half of this population [3]. For individuals diagnosed with prediabetes, the primary objective is to improve the natural course of the condition, including delaying the progression from prediabetes to diabetes and restoring blood glucose levels to normal [4, 5]. Early intervention in prediabetes can significantly reduce the risk of future diabetes and various chronic complications [6–14]. From an epidemiological perspective, exploring modifiable factors that influence the natural course of prediabetes is of great value, as it may positively impact the management of this condition.

The Cardiometabolic Index (CMI) is a simple parameter developed by Ichiro Wakabayashi and his team in 2015 to assess metabolic diseases [15]. It is composed of height, waist circumference (WC), and lipid parameters including triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). Previous studies have shown that CMI has significant potential in risk assessment for cardiometabolic diseases [16], fatty liver disease [17–19], atherosclerosis [20], metabolic syndrome [21], hyperuricemia [22], ischemic stroke [23, 24], renal insufficiency [25, 26], and depression [27, 28]. Additionally, data from various countries consistently demonstrate that CMI is effective in identifying the risk of dysglycemia [29–31] and is closely associated with insulin resistance [29, 32]. Given the extensive application of the CMI in metabolic diseases, further evaluation of its dynamic changes could offer valuable insights for disease prevention and intervention strategies. In this context, we hypothesized that assessing longitudinal variations in CMI, based on measurements taken at different time points, could significantly contribute to understanding the natural course of prediabetes. To test this hypothesis, this study intends to evaluate the longitudinal changes in CMI, including the CMI transition patterns and cumulative CMI (Cum-CMI) exposure, utilizing data from the first national survey (2011–2012, baseline) and the third national survey (2015–2016, follow-up) of the China Health and Retirement Longitudinal Study (CHARLS); and further to evaluate the effects of baseline CMI and longitudinal changes in CMI on the natural course of prediabetes.

Methods

Study design and population

The CHARLS is a prospective, dynamic project focused on middle-aged and elderly populations in China [33]. The detailed study design is described in the online supplementary methods, with Supplementary Fig. 1 showing the screening process of the CHARLS cohort. Briefly, the nationwide CHARLS cohort began in 2011–2012, with subsequent national follow-up surveys conducted every 2–3 years. To date, CHARLS has completed five rounds of national surveys, with blood sample data provided by participants in the first wave (2011–2012) and the third wave (2015–2016). In the current study, we included prediabetic participants from the first wave of CHARLS and determined the natural course of these patients based on data from the third wave. The detailed study process was shown in Fig. 1.

Ethical approval

The CHARLS cohort was authorized by the Institutional Review Board of Peking University (IRB00001052–11015), and all participants provided written informed consent. The current study is observational, and our results is reported in accordance with the STROBE guidelines. The entire study process complies with the requirements of the Declaration of Helsinki.

Covariate assessment

From the CHARLS questionnaire, we extracted participants'demographic information (gender, age), disease information [including hypertension, cardiovascular disease (CVD), and stroke; detailed diagnostic information is available in the online supplementary methods], physical measurements [height, weight, WC, and blood pressure], health behaviors (smoking and drinking status), and biochemical parameters.

Physical measurements were conducted by trained researchers using standardized equipment. Waist circumference (WC) was measured with the subject standing upright, using a soft tape measure positioned horizontally around the waist at the level of the

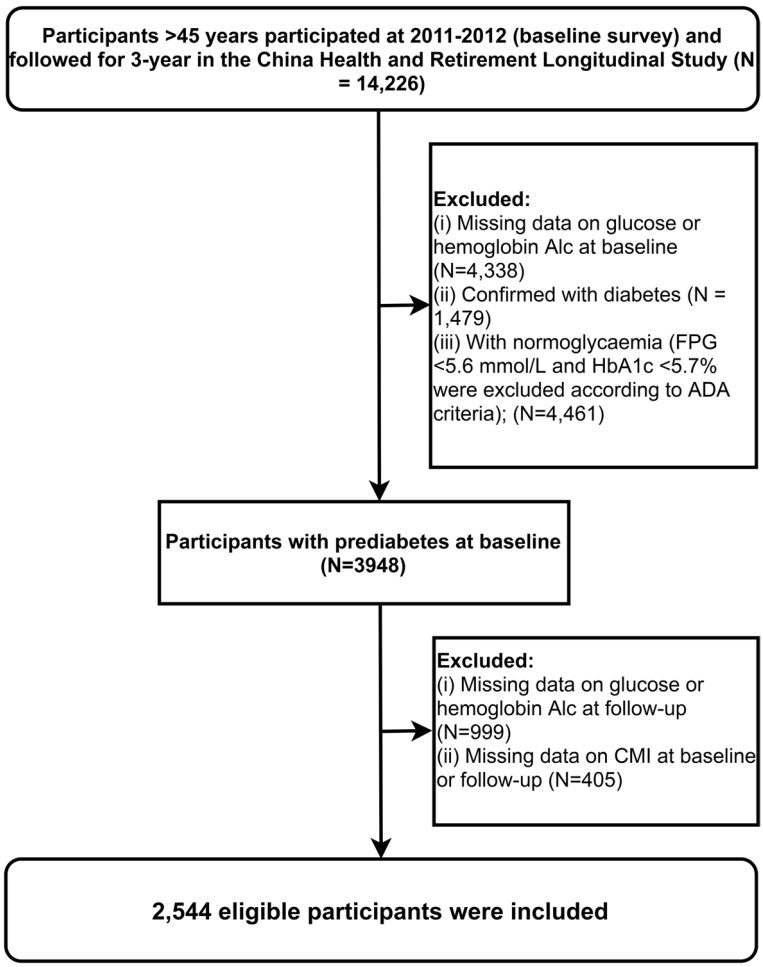

Fig. 1 Flow chart of study participants

umbilicus. Measurements were taken at the end of a calm expiration while holding the breath, with an accuracy of 0.1 cm.

Health behaviors, including smoking and drinking status, were assessed based on the following standardized questions: "Have you ever chewed tobacco, smoked a pipe, smoked self-rolled cigarettes, or smoked cigarettes/cigars?" or "Did you drink any alcoholic beverages, such as beer, wine, or liquor in the past year?".

After overnight fasting, venous blood samples were collected from the subjects by professionals from the Chinese Center for Disease Control and Prevention; the blood samples were then sent to the Youanmen Center for Clinical Laboratory of Capital Medical University for measurement of biochemical parameters. It should be noted that total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), HDL-C, and plasma glucose were measured using an enzymatic colorimetric test; Blood urea nitrogen (BUN) was measured using the enzymatic UV method with urease; Uric acid (UA) was measured using the UA Plus method; Serum creatinine (Cr) was measured using the Rate-blanked and compensated Jaffe creatinine method; Glycated haemoglobin (HbA1c) was measured using the high-performance liquid chromatography.

Exposure assessment

CMI was calculated as TG (mmol/L)/HDL-C (mmol/L) $\times$WC (cm)/Height (cm) [15, 16]. CMI transition patterns were categorized based on the median baseline CMI (CMI $=0.514$), dividing the study population into two groups, and then classified into four patterns based on their CMI during follow-up: consistently-low, low-to-high, high-to-low, and consistently-high.

The assessment of CumCMI was based on a widely used method for evaluating cumulative exposure [34–37]. It was calculated as the mean of the CMI values measured during the longitudinal surveys divided by the total duration of exposure: $(CMI_{2012} + CMI_{2015})/2 \times$time $(2015 - 2012)$.

Outcome assessment

The study outcomes were the natural course of prediabetes, specifically the trajectory of glycemic changes during the follow-up period, including progression to diabetes and regression to normoglycaemia. The diagnosis of diabetes, prediabetes, and normoglycaemia followed the criteria of the American Diabetes Association (ADA) [38], detailed in Table 1.

Statistical analysis

We used Cox regression models with a 3-year follow-up period as the time scale to evaluate the association between CMI and its changes with outcomes, calculating multivariable-adjusted hazard ratios (HRs) and corresponding 95% confidence intervals. For the outcomes of the study, we employed a one-to-one approach to split the data into binary datasets for each class [39, 40]. The multivariable adjustment model adjusted for factors such as age, gender, education, CVD, stroke, hypertension, smoking status, drinking status, height, systolic and diastolic blood pressure, LDL-C, HbA1c, UA, and Cr. Additionally, we constructed restricted cubic splines regression model with four knots to assess the dose–response relationship between CMI/CumCMI and the natural course of prediabetes. When a potential non-linear relationship was detected, we further used a segmented regression recursive algorithm to calculate meaningful inflection points where the non-linear relationship changes [41].

We performed subgroup analyses based on gender (male/female), age (median: $<60/\geq 60$ years), hypertension/CVD/stroke (yes/no), education (below primary/middle school/high school and above), and marital status (married/other) to detect any population-dependent effects of CMI and CumCMI on the natural course of prediabetes. Effect modification was tested by including interaction terms between the natural course of prediabetes and potential effect modifiers in the final model.

All statistical analyses were conducted using R version 4.2.1 and Empower(R) version 2.20. A two-sided *P* value <0.05 was considered statistically significant. Baseline characteristics of the study population were compared using flexible methods and display formats according to the distribution and type of variables.

Table 1 Diagnose diabetes, prediabetes and normoglycaemia according to American Diabetes Association criteria

	Normoglycaemia	Prediabetes	Diabetes
FPG	< 5.6 mmol/L	5.6–6.9 mmol/L	≥ 7.0 mmol/L
HbA1c	< 5.7%	5.7–6.4%	≥ 6.5%
Diagnosed with diabetes by another physician			Yes

Abbreviations: *HbA1c* haemoglobin A1c, *FPG* fasting plasma glucose

For participants with random plasma glucose (RPG) measurements, RPG < 7.8 mmol/L indicated normal glucose, while RPG > 11.1 mmol/L indicated diabetes

Results

Baseline characteristics

A total of 2,544 middle-aged and elderly prediabetic participants were included in the analysis, with a mean age of 60 years. Overall, during a median follow-up period of 3 years, 391 participants (15.37%) progressed to diabetes, and 575 participants (22.60%) regressed to normoglycaemia. Regarding CMI transition patterns, 275 participants were classified as low-to high, 949 as consistently-low, 423 as high-to-low, and 897 as consistently-high. The rates of progression and regression of prediabetes in the consistently-low, low-to-high, high-to-low, and consistently-high CMI pattern groups were as follows: 9.94% and 24.97%, 16.55% and 22.37%, 11.72% and 23.81%, and 20.32% and 20.42%, respectively.

The baseline characteristics of the study population according to the natural course of prediabetes during follow-up were summarized in Table 2. The results revealed that, compared to participants who remained in a prediabetic state, those who progressed to diabetes were generally older, had higher weight, WC, WHtR, systolic blood pressure, TC, TG, glucose, HbA1c, CMI, and CumCMI (Fig. 2), and lower height, HDL-C, and LDL-C. Additionally, participants who progressed to diabetes were more likely to be female and had comorbid hypertension. Among participants who regressed to normoglycaemia, they were generally younger, more likely to be male, and had a significantly higher proportion of baseline non-comorbid hypertension/CVD/stroke. Furthermore, those who regressed to normoglycaemia had significantly lower baseline WC, WHtR, TC, TG, LDL-C, glucose, HbA1c, CMI, and higher levels of HDL-C and height.

Association of CMI, CMI transition patterns, and CumCMI with the natural course of prediabetes in the entire population

Before conducting regression analysis, we calculated the variance inflation factor for CMI, CMI transition patterns, CumCMI, and covariates to assess multicollinearity among variables. Variables with a variance inflation factor >5, indicating multicollinearity with other covariates, were excluded from the subsequent multivariable adjustment models (see Supplementary Tables 1–3).

Four stepwise-adjusted Cox regression models were constructed to explore the association between CMI, CMI transition patterns, CumCMI, and the natural course of prediabetes. The results showed (Table 3) that in all models based on the entire population, CMI, CMI

Table 2 Baseline characteristics summarized according to subjects'glycemic status during follow-up

	Glucose status during follow-up			*P*-value
	Prediabetes	Diabetes	Normoglycaemia	
No. of subjects	1578	391	575	
Age, years	59.64 (8.65)	60.54 (8.95)	58.23 (8.82)	< 0.001
Height, m	157.96 (8.63)	156.58 (8.05)	158.95 (8.37)	< 0.001
Weight, kg	59.11 (11.11)	61.70 (12.23)	59.41 (11.22)	< 0.001
WC, cm	84.92 (12.35)	88.29 (12.84)	83.95 (10.91)	< 0.001
WHtR	0.54 (0.08)	0.56 (0.08)	0.53 (0.07)	< 0.001
SBP, mmHg	131.11 (21.17)	132.84 (19.26)	128.95 (20.88)	0.015
DBP, mmHg	76.15 (11.92)	77.14 (11.78)	75.66 (11.84)	0.165
TC, mg/dL	200.30 (38.63)	200.69 (37.88)	190.57 (37.71)	< 0.001
TG, mg/dL	109.74 (77.88–160.85)	115.94 (84.96–182.31)	105.31 (75.22–155.76)	0.005
HDL-C, mg/dL	49.87 (40.98–60.70)	46.01 (37.50–57.80)	49.87 (40.59–61.08)	< 0.001
LDL-C, mg/dL	120.62 (98.58–143.43)	118.69 (99.36–144.20)	110.18 (89.01–133.18)	< 0.001
Glucose, mmol/L	108.08 (7.52)	110.96 (8.80)	107.60 (7.28)	< 0.001
HbA1c, %	5.25 (0.41)	5.40 (0.43)	5.05 (0.36)	< 0.001
Cr, mg/dL	0.76 (0.66–0.88)	0.73 (0.63–0.86)	0.77 (0.67–0.88)	0.075
UA, mg/dL	4.30 (3.61–5.17)	4.40 (3.67–5.28)	4.33 (3.63–5.14)	0.592
CMI	0.50 (0.30–0.89)	0.64 (0.34–1.13)	0.48 (0.29–0.86)	0.005
CumCMI	0.18 (0.12–0.30)	0.24 (0.16–0.39)	0.18 (0.11–0.29)	< 0.001
Gender				< 0.001
Male	716 (45.37%)	152 (38.87%)	306 (53.22%)	
Female	862 (54.63%)	239 (61.13%)	269 (46.78%)	
Smoking status				0.398
Never	988 (62.61%)	253 (64.71%)	344 (59.83%)	
Current	460 (29.15%)	102 (26.09%)	173 (30.09%)	
Quit	130 (8.24%)	36 (9.21%)	58 (10.09%)	
Drinking status				0.145
Current	400 (25.35%)	79 (20.26%)	156 (27.23%)	
Never	1073 (68.00%)	282 (72.31%)	384 (67.02%)	
Quit	105 (6.65%)	29 (7.44%)	33 (5.76%)	
Education, n (%)				0.053
Below primary	784 (49.68%)	204 (52.17%)	252 (43.83%)	
Primary schools	344 (21.80%)	89 (22.76%)	133 (23.13%)	
Middle school	330 (20.91%)	65 (16.62%)	131 (22.78%)	
High school and above	120 (7.60%)	33 (8.44%)	59 (10.26%)	
Marital status				0.895
Married	1382 (87.58%)	339 (86.70%)	503 (87.48%)	
Other	196 (12.42%)	52 (13.30%)	72 (12.52%)	
Hypertension				< 0.001
No	921 (58.37%)	183 (46.80%)	346 (60.17%)	
Yes	657 (41.63%)	208 (53.20%)	229 (39.83%)	
CVD				0.016
Yes	193 (12.31%)	67 (17.40%)	66 (11.60%)	
No	1375 (87.69%)	318 (82.60%)	503 (88.40%)	
Stroke				< 0.001
Yes	28 (1.78%)	19 (4.91%)	8 (1.40%)	
No	1545 (98.22%)	368 (95.09%)	564 (98.60%)	

Values were expressed as mean (standard deviation) or medians (quartile interval) or n (%)

Abbreviations: *WC* waist circumference, *WHtR* Waist-to-Height Ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HbA1c* haemoglobin A1c, *HDL-C* high-density lipoprotein-cholesterol, *LDL-C* low-density lipoprotein-cholesterol, *TC* total cholesterol, *TG* triglycerides, *UA* uric acid, *BUN* blood urea nitrogen, *Cr* creatinine, *CMI* cardiometabolic index, *CumCMI* cumulative CMI, *CVD* cardiovascular disease

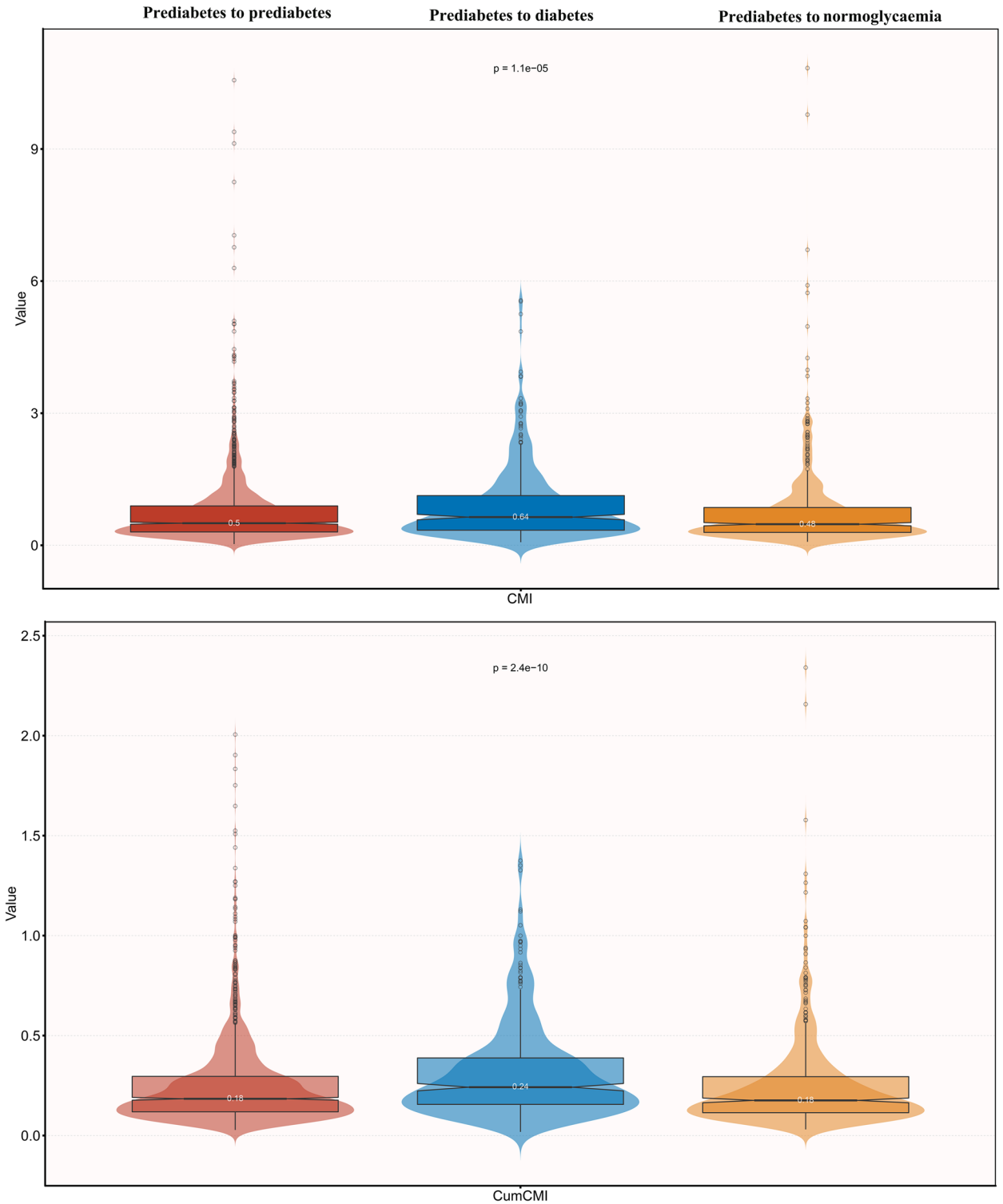

Fig. 2 Violin chart showing baseline characteristics of CMI and CumCMI according to glucose status during follow-up. CMI: cardiometabolic index; CumCMI: cumulative cardiometabolic index

transition patterns, and CumCMI were significantly associated with the progression of prediabetes to diabetes, but no statistically significant association was observed with prediabetes regression. Regarding prediabetes progression, in the unadjusted model, the HRs for the risk of diabetes associated with CMI and CumCMI were 1.14

Table 3 Cox regression analysis of the association between CMI, CMI transition patterns, CumCMI and the natural course of prediabetes

	No. of case	HR (95%CI)			
		Non-adjusted model	Model I	Model II	Model III
Prediabetes to Diabetes					
CMI		1.14 (1.05, 1.24)	1.14 (1.05, 1.25)	1.13 (1.02, 1.24)	1.15 (1.03, 1.28)
CMI transition patterns					
Low-to-high	74 (16.55%)	1.0	1.0	1.0	
Consistently-low	82 (9.94%)	0.60 (0.44, 0.82)	0.60 (0.43, 0.82)	0.61 (0.45, 0.84)	0.63 (0.46, 0.86)
High-to-low	32 (11.72%)	0.71 (0.47, 1.07)	0.72 (0.48, 1.10)	0.72 (0.47, 1.09)	0.70 (0.46, 1.06)
Consistently-high	203 (20.32%)	1.23 (0.94, 1.60)	1.22 (0.94, 1.60)	1.15 (0.87, 1.50)	1.11 (0.83, 1.48)
CumCMI		2.24 (1.62, 3.09)	2.28 (1.64, 3.17)	2.08 (1.47, 2.95)	2.27 (1.51, 3.41)
Prediabetes to normoglycaemia					
CMI		0.98 (0.89, 1.08)	0.97 (0.88, 1.07)	0.99 (0.89, 1.09)	0.93 (0.84, 1.04)
CMI transition patterns					
Low-to-high	100 (22.37%)	1.0	1.0	1.0	
Consistently-low	206 (24.97%)	1.12 (0.88, 1.42)	1.11 (0.87, 1.41)	1.12 (0.88, 1.44)	1.19 (0.92, 1.52)
High-to-low	65 (23.81%)	1.06 (0.78, 1.45)	1.04 (0.76, 1.42)	1.07 (0.78, 1.47)	1.21 (0.87, 1.67)
Consistently-high	204 (20.42%)	0.91 (0.72, 1.16)	0.90 (0.71, 1.14)	0.92 (0.72, 1.18)	0.97 (0.74, 1.26)
CumCMI		0.80 (0.54, 1.18)	0.78 (0.52, 1.15)	0.82 (0.55, 1.22)	0.70 (0.46, 1.06)

Abbreviations: *HR* hazard ratios, *CI* confidence interval, *CMI* cardiometabolic index, *CumCMI* cumulative CMI

Model I adjust for age, gender, smoking status, drinking status

Model II adjust for age, gender, education, CVD, stroke, hypertension, smoking status, drinking status

Model III adjust for age, gender, education, CVD, stroke, hypertension, smoking status, drinking status, height, SBP, DBP, LDL-C, HbA1c, UA, Cr

(1.05–1.24) and 2.24 (1.62–3.09), respectively. Compared to participants with a low-to-high CMI pattern, those with a consistently-low CMI pattern had a 40% reduced risk of developing diabetes, while no significant associations were observed in the consistently-high and high-to-low CMI patterns. In the stepwise-adjusted models (Models I-III), the positive associations between CMI, CumCMI, and diabetes risk remained consistent, and the association between CMI transition patterns and diabetes progression was consistent with the unadjusted model.

Subgroup analysis

To further explore whether the association between CMI and CumCMI with the natural course of prediabetes varies across different populations, we conducted the same analysis based on Model III in subgroups defined by gender, age, hypertension/CVD/stroke, education, and marital status, and tested for interaction effects to assess significant differences in this association across subgroups. The results showed (Table 4) that no significant interactions were observed in all subgroups regarding the progression of prediabetes. However, for prediabetes regression, we observed a significant age-dependent association (P-interaction < 0.05). Specifically, we found a significant negative association between CMI and CumCMI with prediabetes regression only in the elderly (age ≥ 60), with HRs of 0.78 (0.62–0.99) and 0.32 (0.13–0.78), respectively. Overall, the association between CMI, CumCMI, and prediabetes regression was observed only in the elderly population.

Dose–response relationship between continuous variables CMI, CumCMI, and the natural course of prediabetes

Figures 3 and 4 show the dose–response relationship curves between CMI, CumCMI, and the natural course of prediabetes. A potential non-linear relationship was observed only in the association between CumCMI and diabetes progression. As shown in Fig. 4, the curve representing the association between CumCMI and the risk of diabetes progression changed at approximately 0.4, where the slope decreased and tended to flatten. We used segmented Cox regression to calculate this inflection point, which was determined to be 0.37 (Table 5). Before CumCMI reached 0.37, each unit increase in CumCMI was associated with a 956% increase in the risk of diabetes progression (HR 10.56, 3.40–32.80). After CumCMI exceeded 0.37, each unit increase in CumCMI was associated with only a 13% increase in the risk of diabetes progression (HR 1.13, 0.57–2.23).

Table 4 Exploratory subgroup analysis of the role and differences of CMI, CumCMI in assessing changes in glycemic status in prediabetes patients

	HR per 1 de/increase (95%CI)			
	CMI		CumCMI	
	Prediabetes to normoglycaemia	Prediabetes to diabetes	Prediabetes to normoglycaemia	Prediabetes to diabetes
Gneder				
Male	0.89 (0.76, 1.05)	1.19 (0.99, 1.43)	0.72 (0.41, 1.27)	2.71 (1.43, 5.14)
Female	0.96 (0.84, 1.10)	1.13 (0.99, 1.29)	0.68 (0.38, 1.21)	2.06 (1.25, 3.40)
P-interaction	0.4626	0.6584	0.8802	0.4952
Age, years				
45–59	0.98 (0.88, 1.10)	1.11 (0.96, 1.28)	0.91 (0.58, 1.44)	2.03 (1.19, 3.48)
≥ 60	0.78 (0.62, 0.99)	1.20 (1.02, 1.42)	0.32 (0.13, 0.78)	2.54 (1.42, 4.55)
P-interaction	0.0213	0.4296	0.0318	0.5624
Education, n (%)				
Below primary	0.92 (0.78, 1.09)	1.20 (1.04, 1.39)	0.70 (0.36, 1.34)	2.66 (1.53, 4.61)
primary schools	0.94 (0.78, 1.12)	1.09 (0.89, 1.33)	0.62 (0.29, 1.37)	1.73 (0.81, 3.71)
middle school	1.05 (0.85, 1.29)	1.15 (0.87, 1.52)	1.20 (0.57, 2.51)	2.41 (0.92, 6.31)
High school and above	0.80 (0.53, 1.19)	0.92 (0.57, 1.50)	0.38 (0.09, 1.53)	1.41 (0.34, 5.89)
P-interaction	0.6121	0.6632	0.4307	0.7187
Marital status				
Married	0.95 (0.86, 1.06)	1.10 (0.97, 1.24)	0.75 (0.49, 1.15)	2.00 (1.29, 3.09)
Other	0.86 (0.57, 1.30)	1.46 (1.12, 1.89)	0.55 (0.12, 2.48)	5.66 (1.93, 16.63)
P-interaction	0.6468	0.0736	0.6808	0.0961
Hypertension				
No	0.95 (0.83, 1.08)	1.13 (0.97, 1.31)	0.72 (0.42, 1.24)	2.39 (1.38, 4.16)
Yes	0.94 (0.79, 1.11)	1.15 (0.99, 1.34)	0.75 (0.41, 1.37)	2.04 (1.17, 3.56)
P-interaction	0.9005	0.8770	0.9128	0.6786
Heart Problems				
Yes	1.18 (0.92, 1.52)	1.16 (0.89, 1.51)	1.29 (0.44, 3.78)	2.44 (1.02, 5.81)
No	0.91 (0.81, 1.03)	1.14 (1.01, 1.28)	0.68 (0.44, 1.06)	2.16 (1.38, 3.38)
P-interaction	0.2571	0.9026	0.2941	0.8028
Stroke				
Yes	0.85 (0.16, 4.57)	0.89 (0.52, 1.52)	0.22 (0.00, 194.17)	0.94 (0.18, 4.94)
No	0.94 (0.85, 1.05)	1.15 (1.03, 1.29)	0.74 (0.49, 1.12)	2.34 (1.54, 3.55)
P-interaction	0.9038	0.3199	0.7127	0.2624

Abbreviations: *HR* hazard ratios, *CI* confidence interval, *CMI* cardiometabolic index, *CumCMI* cumulative CMI

Models adjusted for the same covariates as in model III (Table 3), except for the stratification variable

Discussion

In this prospective cohort study of middle-aged and elderly populations, our results suggest that assessing baseline CMI, CMI transition patterns during follow-up, and CumCMI exposure holds significant value for diabetes risk assessment. Additionally, in the evaluation of prediabetes regression, CMI and CumCMI play an important role in populations aged 60 years and older.

With the global trend of aging [42], prediabetes is becoming increasingly common. However, it is important to note that there is still no unified global standard for prediabetes, which poses a significant challenge for summarizing research related to prediabetes [1]. Currently, professional organizations such as the ADA, the World Health Organization, and the International Expert Committee have proposed several diagnostic criteria for prediabetes. Among them, the International Expert Committee and World Health Organization standards are more restrictive, while the ADA standard is the most inclusive [4]. In the current study, to ensure consistency in the results and discussion, we only included studies that defined prediabetes according to the ADA criteria.

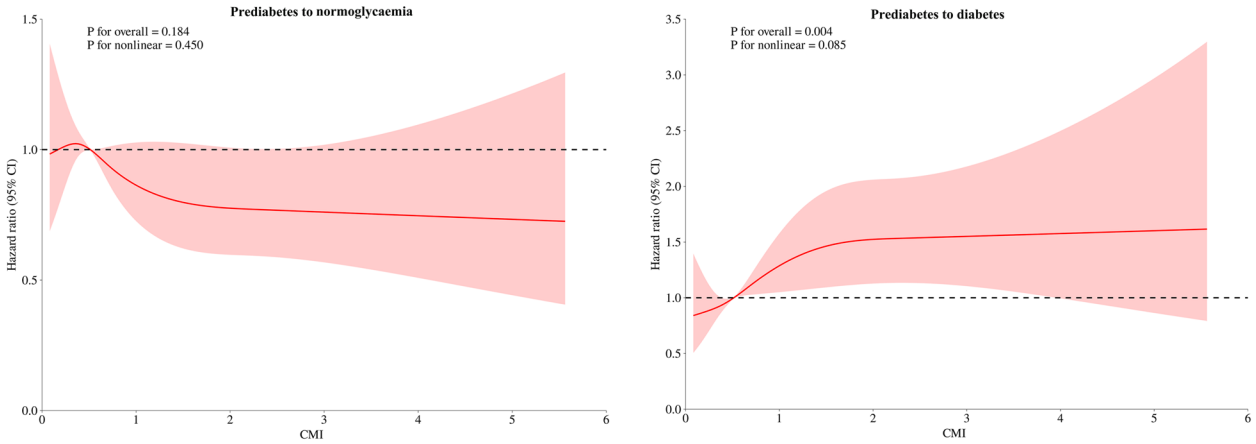

Fig. 3 Visualizing the relationship between CMI and the natural course of prediabetes in the entire population using 4-knots RCS. CMI: cardiometabolic index; RCS: restricted cubic splines

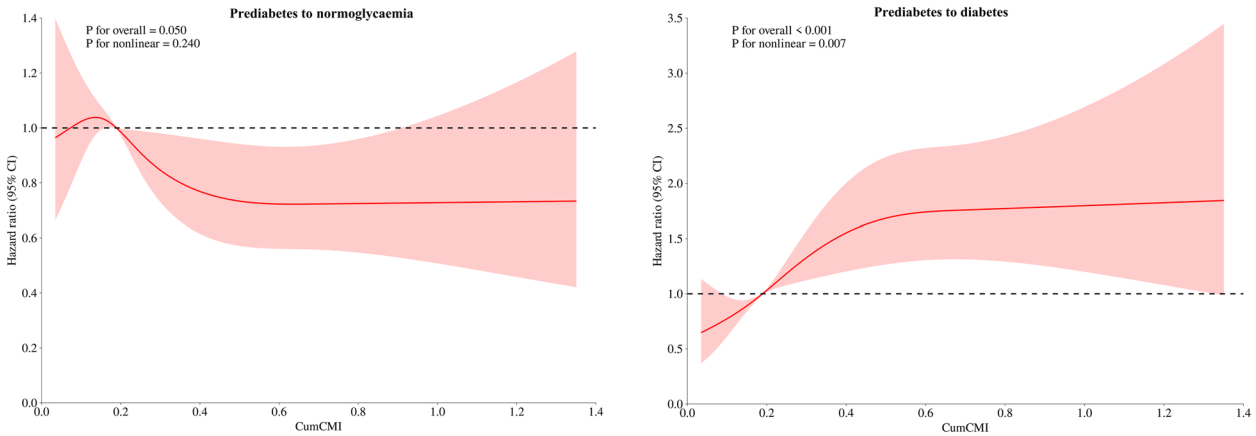

Fig. 4 Visualizing the relationship between CumCMI and the natural course of prediabetes in the entire population using 4-knots RCS. CumCMI: cumulative cardiometabolic index; RCS: restricted cubic splines

Table 5 The result of the two-piecewise Cox regression model

	HR (95%CI)	*P*-value
Fitting model by two-piecewise cox regression		
The inflection point of CumCMI	0.37	
< 0.37	10.56 (3.40, 32.80)	< 0.0001
> 0.37	1.13 (0.57, 2.23)	0.7351
P for log likelihood ratio test	0.004	

Abbreviations: *HR* hazard ratios, *CI* confidence interval, *CumCMI* cumulative CMI

Epidemiologically, the prevalence of prediabetes in China is currently around 35.2%, with this figure approaching 50% among adults over 50 years of age. This trend is similar to the global prevalence [3, 43, 44]. According to recent global meta-analyses, approximately 18% of individuals with prediabetes defined by the ADA criteria will progress to diabetes within five years [45, 46], and about 31% will regress to normoglycaemia [47]. In our current analysis, based on nationally representative data from CHARLS, we observed a prediabetes regression rate of 22.60% and a progression rate of 15.37% over a median follow-up of 3 years. Comparatively, the prediabetes progression rate in the CHARLS cohort is similar to global reports, while the regression rate is slightly lower than that reported in systematic reviews. This discrepancy may be related to the design and population of the current study: unlike the randomized controlled trials included in systematic reviews [47], the CHARLS cohort is non-interventional, which has a significant impact on prediabetes regression. Secondly, the CHARLS cohort is a national survey of middle-aged and elderly populations (with a mean age of 60 years in the current analysis), which aligns with age-related impaired glucose metabolism [2, 48].

In the current study, our analysis of CMI further confirmed previous findings that high CMI is significantly positively associated with diabetes [15, 29–31, 49]. It is noteworthy that in a recent study by Qiu et al. [49], they employed a particularly clever: they used restricted cubic splines analysis results (linear association) to set a CMI cutoff value of 0.467 to distinguish between low and high CMI and further classified CMI transition patterns into four categories: consistently-low, low-to-high, high-to-low, and consistently-high. Their findings indicated that compared to participants with a consistently-low CMI pattern, those with low-to-high, high-to-low, and consistently-high CMI patterns had a significantly increased risk of diabetes. In the current study, we also evaluated the impact of CMI transition patterns during follow-up on the progression to diabetes. Unlike Qiu et al.'s design [49], we used the median baseline CMI (CMI = 0.514) to dichotomize the study population and then evaluated their transition patterns during follow-up in relation to prediabetes progression. Our analysis results were similar to those of Qiu et al. [49], suggesting that maintaining a low CMI level is ideal for reducing diabetes risk. Compared to Qiu et al. and previous similar studies [15, 29–31, 49], our study included a different participant population, providing evidence for using CMI to assess future diabetes risk in prediabetic patients. Moreover, our study further evaluated the impact of baseline CMI and CMI transition patterns during follow-up on prediabetes regression. Unfortunately, despite the statistical data on incidence rates showing that the proportions of participants regressing to normoglycaemia were lowest and highest in the consistently-high and consistently-low CMI pattern groups, respectively (low-to-high 22.37%, consistently-low 24.97%, high-to-low 23.81%, consistently-high 20.42%), no statistically significant associations were observed in further analyses. Further research is needed to validate these findings.

After completing the analysis of CMI transition patterns on the natural course of prediabetes, we engaged in some deeper reflections. From the data analysis perspective, the advantage of evaluating CMI transition patterns during follow-up is that it provides direct evidence for identifying relatively low-risk groups, such as the consistently-low CMI group. However, one concern is that the setting of the CMI cutoff value may significantly impact the study results, especially for slight changes near the cutoff value during follow-up. This is a limitation that is difficult to avoid when converting continuous variables into categorical ones [50, 51], even in high-quality randomized controlled trials. For example, even when LDL-C levels are controlled below normal in coronary heart disease patients after treatment, they still face a high residual risk of events [52, 53]. To address this issue, researchers have proposed a new approach to evaluating cumulative exposure to independent variables over time (e.g., long-term high-concentration LDL-C exposure exacerbates atherosclerosis) [54]. In the current study, we adopted a widely used method for evaluating cumulative exposure [34–37] and assessed the association between cumulative CMI exposure during follow-up and the progression and regression of prediabetes. Our further analysis results showed that CumCMI was positively associated with the future risk of diabetes in prediabetic patients and negatively associated with prediabetes regression in those aged ≥ 60 years. The analysis results indicate that compared to baseline CMI, CumCMI has a much-improved ability to assess the progression and regression of prediabetes [Prediabetes to diabetes (HR): CMI 1.15 vs CumCMI 2.27; Prediabetes to normoglycaemia (age ≥ 60, HR): CMI 0.78 vs CumCMI 0.32]. In simple terms, the longer and higher the CMI exposure, the more likely diabetes events are to occur, and it hinders prediabetes regression in the elderly. These findings further suggest that monitoring and maintaining appropriate CMI levels may help prevent glucose deterioration.

The reason why the association between CMI, CumCMI, and prediabetes regression was only observed in the elderly population remains unclear. However, based on the stratified analysis results, the association between CMI, CumCMI, and diabetes progression also appears to be relatively stronger in the elderly population. Although further interaction analysis did not detect significant differences in age subgroups, this does not affect our observation of this trend. Based on the results of the age subgroup, we speculate that CMI and CumCMI may have age-related high sensitivity in assessing glucose metabolism. We found some corroboration from completed studies related to CMI. For example, in a recent study by Wu et al. [32], they noted a significantly higher correlation between CMI and insulin resistance in people aged 60 years and older. Similar results have been reported for cardiometabolic diseases [16]. Additionally, regarding diabetes progression, Song et al., supported by a large sample (n = 21,304), found that the risk of glucose deterioration was significantly higher in those aged 60 years and older (P-interaction < 0.01) [29]. Besides these examples, similar age-specific findings have also been reported in the evaluation of metabolic syndrome [21] and chronic kidney disease [25]. Based on the findings from the above CMI-related studies and the results of the current study, we believe that CMI may be a good risk identification factor for metabolic diseases, particularly for age-related glucose metabolism disorders.

Strengths and limitations

The strengths of the current study stem from the prospective design and dynamic monitoring of the CHARLS cohort, which allowed us to evaluate the impact of CMI and its longitudinal changes on the natural course of prediabetes. The analysis of CMI transition patterns and cumulative exposure not only greatly enhanced the innovation of the current study but also provided valuable evidence for future research in this field.

Several limitations of the current study should be noted: (1) The diagnosis of prediabetes: The oral glucose tolerance test was not included in the CHARLS cohort survey items, which may lead to the omission of some individuals with impaired glucose tolerance [4]. (2) The CHARLS cohort is a survey study targeting middle-aged and elderly Chinese populations, so caution should be exercised when extrapolating the findings to the general population [55, 56]. (3) While the use of large study populations can minimize sampling bias and better represent real-world practice, some participants were excluded from the current analysis because they did not have blood glucose measurements, which may introduce some sampling bias. (4) The CHARLS cohort is a non-interventional observational study, so it is not possible to determine the impact of interventions on cumulative CMI exposure. (5) As with all observational studies, our study is subject to residual confounding [57], as the relative size of the study sample makes it impossible to fully account for a wide range of covariates.

Conclusion

In this prospective cohort study of middle-aged and elderly populations, we found that longitudinal changes in CMI were associated with the progression and regression of prediabetes. High CumCMI exposure during follow-up significantly increased the risk of diabetes events and hindered the recovery of normoglycaemia in older adults. Furthermore, maintaining a low CMI pattern during follow-up can significantly reduce the risk of diabetes in prediabetic patients.

Abbreviations

CMI	Cardiometabolic Index
CHARLS	China Health and Retirement Longitudinal Study
CumCMI	Cumulative CMI
WC	Waist circumference
TG	Lipid parameters including triglycerides
HDL-C	High-density lipoprotein cholesterol
CVD	Cardiovascular disease
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
BUN	Blood urea nitrogen
UA	Uric acid
Cr	Creatinine
ADA	American Diabetes Association

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

GB-X and YZ: Conceptualization, methodology, supervision, and project administration. YZ, CY-J and HY-Y: writing-original draft preparation. GB-X, SM-H and GT-S: writing-reviewing and editing. YZ and SM-H: software. YZ and GB-X: formal analysis and validation. YZ and GB-X: data curation. All authors read and approved the final manuscript.

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Data availability

CHARLS datasets are available for download at the CHARLS home website (http://charls.pku.edu.cn/en).

Declarations

Ethics approval and consent to participate

The CHARLS cohort was authorized by the Institutional Review Board of Peking University (IRB00001052–11015), and all participants provided written informed consent. The current study is observational, and our results is reported in accordance with the STROBE guidelines. The entire study process complies with the requirements of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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