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Transition of cardiometabolic status and the risk of type 2 diabetes mellitus among middle-aged and older Chinese: A national cohort study

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ABSTRACT

Aims/Introduction: The cardiometabolic index (CMI) has been proposed as a novel indicator of cardiometabolic status. This study aimed to investigate the effects of CMI and its longitudinal transitions on the development of type 2 diabetes mellitus in middle-aged and older Chinese.

Materials and Methods: We used data from the China Health and Retirement Longitudinal Study (2011–2018). CMI was calculated as the product of the waist circumference to height ratio and the triglyceride to high-density lipoprotein cholesterol ratio. At baseline in 2011, the subjects were classified into low- and high-CMI groups, and then divided into four transition patterns during follow-up, i.e. maintained-low, low-to-high, high-to-low, and maintained-high CMI. The hazard ratios (HRs) of different transition patterns for type 2 diabetes mellitus were calculated using multivariable Cox frailty models.

Results: During 2011–2018, 7,347 participants were included. Participants with a high-CMI at baseline had a significantly higher risk of new-onset type 2 diabetes mellitus than those with a low-CMI (HR = 1.78, 95% CI:1.55–2.05). For subjects with a low-CMI at baseline, the risk of developing type 2 diabetes mellitus increased by 75% if their CMI status changed to high during follow-up ($HR_{low\text{-}to\text{-}high}$ = 1.75, 95% CI:1.35–2.28). Meanwhile, for subjects with a maintained-high CMI, no significant risk reduction for type 2 diabetes mellitus was found when their CMI changed to low status ($HR_{high\text{-}to\text{-}low}$ = 0.77, 95% CI: 0.58–1.01).

Conclusions: Baseline CMI levels and longitudinal CMI transition patterns were associated with a higher risk of type 2 diabetes mellitus. Early anti-lipid measures should be taken to prevent type 2 diabetes mellitus in middle-aged and older Chinese.

INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder, is a rising global health concern. In 2019, it was estimated to be the ninth largest cause of mortality, accounting for approximately 4.2 million deaths globally[1–3]. Diabetes mellitus can cause a variety of acute and chronic complications and it is associated with numerous diseases, all of which together impair human health, or even endanger life[4]. Type 2 diabetes mellitus, the most common subtype of diabetes, is becoming dramatically prevalent in countries of all income levels[2,5]. China is one of the centers of the global type 2 diabetes mellitus epidemic[6]. Demographic

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aging, urbanization, and nutrition transition to western diets have resulted in an explosive increase in the prevalence of type 2 diabetes mellitus in China over the past 35 years (1.3% in 1980–1989 to 8.7% in 2010–2014), imposing a substantial burden on both individuals and healthcare systems[7,8].

The distribution of body fat accumulation is of great importance in the development of insulin resistance and diabetes[9,10]. Previous studies have established a strong association of several traditional obesity indicators, such as body mass index (BMI) and waist circumstance (WC), with type 2 diabetes mellitus. Furthermore, the waist-to-height ratio (WHtR) has been suggested to be superior to BMI and WC in detecting cardiovascular risk, including type 2 diabetes mellitus[11,12]. Another simple and reliable measurement of insulin resistance is the triglycerides-to-high-density lipoprotein cholesterol ratio (TG/HDL-C), whose effect on type 2 diabetes mellitus has been demonstrated widely[13–15]. The cardiometabolic index (CMI), a product of WHtR and TG/HDL-C, was initially proposed by Ichiro Wakabayashi for assessing the risk of cardiometabolic diseases and type 2 diabetes mellitus[16–21]. Compared with other indicators of adiposity and blood lipids including BMI, body adiposity index (BAI), WC, and triglyceride (TG), CMI was suggested to be a better predictor of type 2 diabetes mellitus and could be a useful marker for the discrimination of type 2 diabetes mellitus[17,22,23].

However, the status of CMI over time is not constant. Previous studies have successfully demonstrated the association of CMI status and the risk of type 2 diabetes mellitus, while it is still unclear whether the longitudinal transition of CMI levels might affect new-onset diabetes. Therefore, we conducted comprehensive analyses to investigate the associations of CMI status and its transition with the risk of type 2 diabetes mellitus in middle-aged and older Chinese, by using the China Health and Retirement Longitudinal Study (CHARLS), hoping to be helpful to the prevention and management of diabetes.

METHODS

Study design and study population

The current study utilized data from the CHARLS, a nationwide and representative study of Chinese aged 45 years and older (available at http://charls.pku.edu.cn/en). In brief, the participants in this survey were recruited from 150 county-level units from 28 Chinese provinces (the locations are shown in Figure S1 and Table S1) using a probability-proportional-to-size (PPS) sampling technique. Administrative villages in rural areas and communities in urban areas were considered as primary sample units (PSU), of which three were selected from each county by PPS sampling. The households of the chosen residents within each PSU were mapped by the "CHARLS-GIS" software. The overall household response rate was 80.5%. The baseline survey of CHARLS was implemented from June 2011 to March 2012. All participants and their spouses were followed-up by a face-to-face computer-assisted personal interview every 2 years. The follow-up studies were conducted in 2013, 2015, and 2018, respectively. Data on physical status were collected in each follow-up, and blood tests were conducted at baseline (2011) and at wave 3 (2015)[24–26].

Data collection

Data collection for CHARLS was composed of several crucial parts: an interview questionnaire, a physical examination, and a blood test. The questionnaire mainly covered the respondents' basic information (gender, age, marital status, place of origin, education level, etc.), family circumstances, self-assessed health status (self-reported health status, history of chronic disease, and health-related behaviors, etc.), and economic status.

The physical examination included height, weight, waist circumference, and blood pressure, conducted by professional interviewers in a standardized manner[25]. For height measurement (Seca 213 stadiometer), the respondents removed their shoes and held the prescribed position. For weight measurement (Omron, HN-286 scale), the respondents were required to take off shoes and bulky coats. Weight was divided by the square of the height (kg/m^2) to calculate BMI. With the respondents standing without jackets, the WC was measured with a tape wrapped around the respondent's waist with suitable flexibility horizontal to the navel. Blood pressure was taken three times on each respondent's left arm with a 45 s gap (Omron, HEM-7200 Monitor). The systolic and diastolic blood pressures (SBP and DBP) were recorded using the average of the three successive readings. To provide quality control, the physical examination process was chosen at random to be photographed.

For the blood test, professional nurses collected an 8 mL venous blood sample following an overnight fast of at least 12 h. The first tube of blood (2 mL) was used immediately for complete blood count testing at local county health centers. During travel, the remaining blood samples were kept strictly at 4°C. The second tube of blood (4 mL) was collected to acquire plasma and buffy coat, while the third tube of blood (2 mL) was obtained for glycosylated hemoglobin (HbA1c) assay. In wave 1, blood samples were cryopreserved at −20°C during transport to the Chinese Center for Disease Control and Prevention and then subsequently cryopreserved at −80°C before being analyzed at the Youanmen Center for Clinical Laboratory of Capital Medical University. In wave 3, the samples were sent to Peking University and assayed by KingMed Diagnostics, with the same temperature restrictions as before. Blood glucose was tested by the hexokinase method. Total cholesterol (TC) and TG levels were determined by the oxidase method[27]. Low-density lipoprotein cholesterol (LDL-C) and HDL-C were tested with corresponding direct methods, respectively[27]. The HbA1c levels were measured using high-performance liquid chromatography[27].

Definition of CMI and type 2 diabetes mellitus

The cardiometabolic index is an empirical-mathematical model which includes the anthropometric parameter (WHtR) and

functional parameters (HDL-C and TG)[28]. Centimeters were used for measuring WC and height, and WHtR was calculated by dividing WC by height. The calculation formula of CMI was as follows:

$$\text{CMI}: \frac{\text{TG(mmol/L)}}{\text{HDL}-C\text{(mmol/L)}} \times \text{WHtR} \quad (1)$$

At baseline (CHARLS 2011, June 2011 to March 2012), restricted cubic spline curves were used to classify the CMI levels as high-CMI (CMI score > 0.467) and low-CMI (CMI score ≤ 0.467) groups (Figure S2). Then, four patterns of CMI transitions during the follow-up (from CHARLS 2011 to CHARLS 2015) were defined as: (1) Maintained-low CMI: consistently low-CMI during follow-up; (2) Low-to-high CMI: low-CMI at baseline but transformed to high-CMI at follow-up; (3) High-to-low CMI: high-CMI at baseline but transformed to low-CMI at follow-up; (4) Maintained-high CMI: consistently high-CMI during follow-up.

The diagnosis of type 2 diabetes mellitus was determined by the American Diabetes Association's criteria in this study. An individual was diagnosed as having type 2 diabetes mellitus if his/her fasting plasma glucose was ≥126 mg/dL (7.0 mmol/L), and/or a random blood glucose was ≥200 mg/dL (11.1 mmol/L), and/or a HbA1c was ≥ 6.5%, and/or had a self-reported history of type 2 diabetes mellitus diagnosed by physician in the past, and/or currently was undergoing antihyperglycemic treatment[29].

Definition of covariates

Sociodemographic factors included age (45–49 years, 50–59 years, 60–69 years, and ≥70 years), sex (male and female), marital status (single, married/cohabiting), and education status (illiterate, literate, primary education, and middle school education and above). We used the tertiles of the natural logarithm of *per capita* expenditures (ln [PCE]) as an indication of family wealth[30,31] for evaluating the household economic status. The bottom, middle, and top tertiles of ln (PCE) represent the poor, moderate, and wealthy states, respectively. In terms of geographic features, the participant's residence was classified as North, Northeast, East, South-central, Southwest, and Northwest of China (Figure S1 and Table S1). As for health behaviors, we divided individuals into smokers and non-smokers, as well as drinkers and non-drinkers, respectively.

The nutritional status of the participants was divided into three categories based on the Working Group on Obesity in China (WGOC) criteria: normal (BMI < 24 kg/m^2), overweight (BMI ≥ 24 and < 28 kg/m^2), and obesity (BMI ≥ 28 kg/m^2)[32,33]. A WHtR of above 0.95 for males and over 0.85 for women was considered to be central obesity[30]. Hypertension was defined by SBP ≥ 140 mmHg, and/or DBP ≥ 90 mmHg, and/or a self-reported physician's diagnosis, and/or currently taking antihypertensive medicines, and/or under relevant treatment measures[30,34]. Elevated LDL-C was defined by >4.1 mmol/L (160 mg/dL), elevated TG was defined by >2.3 mmol/L (200 mg/dL), and lower HDL-C was defined by <1.0 mmol/L (40 mg/dL)[35].

Statistical analysis

Continuous variables were expressed as mean with standard deviation (SD) when they had a normal distribution, and as median with interquartile range (IQR) when they were asymmetric. Categorical variables were described in percentages with 95% confidence intervals (CIs). The basic characteristics of participants between urban and rural settings were compared using the Chi-square test. We calculated the person-years from the date of the baseline interview until the occurrence of type 2 diabetes mellitus events or until the end of follow-up (CHARLS 2018, August 2018), whichever came first. The Kaplan–Meier method was used to obtain the cumulative incidence rates of type 2 diabetes mellitus.

At the first stage, we investigated the association between baseline CMI status (low- and high- CMI) at CHARLS 2011 and incident type 2 diabetes mellitus with the log-rank test, which was stratified by setting (rural, urban, and overall). Considering the clustering effect of participants in the same province, the hazard ratios (HRs) for incident type 2 diabetes mellitus by CMI groups were calculated using multivariable Cox frailty models with a random effect. Three models were established: Model 1 was adjusted for age and sex; Model 2 was additionally adjusted for education, marital status, ln(PCE), region, hypertension, smoking, and drinking based on Model 1; Model 3 was further adjusted for TC and LDL-C based on Model 2.

At the second stage, the longitudinal influence of CMI transition on incident type 2 diabetes mellitus was explored. From CHARLS 2011 to CHARLS 2015, four patterns of CMI transitions were classified as, groups of maintained-low CMI, low-to-high CMI, high-to-low CMI, and maintained-high CMI. We first compared the risk difference between the maintained-low CMI group (reference) and the low-to-high CMI group. Moreover, the HR for the low-to-high group with the maintained-low group as reference, and the HR for the high-to-low group with the maintained-high group as reference were respectively calculated with adjustments for the following covariates: age, sex, education, region, hypertension, smoking, drinking, TC, and LDL-C level. The above investigations were also stratified according to rural and urban settings.

Furthermore, three kinds of sensitivity analyses were carried out to assess the robustness of results. First, multiple imputations by fully conditional specification (FCS) were used to impute missing data on sex, education, ln(PCE), BMI, obesity, hypertension, smoking, and drinking. The risks of new-onset type 2 diabetes mellitus by different CMI transition patterns in middle-aged and older Chinese were explored based on multiply imputed data sets. More details about the numbers of missing values are shown in Table S2. Second, we excluded participants who took medication for dyslipidemia from 2011

to 2015 and explored the relationship between different CMI groups and type 2 diabetes mellitus in the remaining population. Third, we also examined the associations between different CMI transition patterns from 2011 to 2015 and new-onset type 2 diabetes mellitus from 2016 to 2018.

Data analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). Statistical significance was assessed by two-sided tests and set as a P-value < 0.05.

RESULTS

Baseline characteristics of participants

At baseline, 17,708 participants were interviewed. Subjects with type 2 diabetes mellitus at baseline ($n = 8,223$), who did not reply to follow-up ($n = 531$), who were under 45 years old ($n = 194$), and who did not have sufficient data to generate CMI ($n = 1,413$) were excluded, leaving 7,347 participants in our analysis. There were a total of 471 (6.4%) and 444 (6.0%) participants taking medication for dyslipidemia in 2011 and 2015, respectively. The flow chart and comparison between included and excluded participants are shown in Figure S3 and Table S3.

Table 1 lists the baseline characteristics of the included subjects. Those participants, 4,942 from rural areas and 2,405 from urban areas, were followed for an average of 6.19 years. The majority were aged 50–59 years (35.7%) and 60–69 years (29.4%); most participants were married or cohabiting (88.1%). Almost one-third of the participants were from East China (30.1%). Compared with rural participants, urban participants had higher education and economic levels (all $P < 0.001$). Besides, there was a larger proportion of adults with general obesity (15.3 vs 9.8%), hypertension (43.5 vs 38.9%), elevated LDL-C (59.3 vs 55.2%), elevated TG (26.7 vs 21.7%), and lower HDL-C (45.1 vs 53.1%) in urban than in rural settings. Moreover, the average score of CMI in urban areas was significantly higher than that in rural areas (0.75 ± 0.76 vs 0.65 ± 0.85). Table S4 shows the baseline characteristics of the participants by CMI transition pattern (maintained-low, low-to-high, high-to-low, and maintained-high CMI).

Risk of type 2 diabetes mellitus by baseline CMI

The cumulative incidence rates of type 2 diabetes mellitus in both baseline CMI groups (low- and high-CMI) are demonstrated in Figure 1. From CHARLS 2011 to 2018, participants with high-CMI at baseline had a greater cumulative incidence than those with low-CMI (14.59 vs 8.36%).

The risks of type 2 diabetes mellitus by baseline CMI status (low- and high-CMI) are shown in Table 2. The high-CMI group showed a significantly higher risk of type 2 diabetes mellitus than the low-CMI group ($HR_{crude} = 1.78$, 95% CI: 1.55–2.05). Similar significant findings were observed after adjustments for age and sex ($HR_{model1} = 1.75$, 95% CI: 1.51–2.01), additional adjustments for education, marital status, economic status, region, hypertension, smoking, and drinking ($HR_{model2} = 1.38$, 95% CI: 1.17–1.63), and in the fully adjusted model ($HR_{model3} = 1.37$, 95% CI: 1.16–1.61). In subgroup analyses, we found a similar association of baseline CMI levels with type 2 diabetes mellitus in rural residents ($HR_{model3} = 1.44$, 95% CI: 1.19–1.76), whereas there was no significant association in urban residents ($HR_{model3} = 1.28$, 95% CI: 0.92–1.77). More details are described in Table S5.

Risk of type 2 diabetes mellitus by CMI transition pattern

Figure 2 and Figure 3 illustrate the differences in the cumulative incidence of type 2 diabetes mellitus among the four CMI transition patterns. As indicated in Figure 2c, the maintained-high CMI group had the highest cumulative incidence of type 2 diabetes mellitus (18.9%) in the overall settings, followed by the low-to-high CMI group (14.2%), the high-to-low CMI group (12.9%), and lastly the maintained-low CMI group (7.6%). Similar associations were also seen in both rural (Figure 2a) and urban (Figure 2b) settings.

Figure 3 shows the risks of type 2 diabetes mellitus by CMI transition patterns. Taking the maintained-low CMI group as reference, the low-to-high group showed a significant higher risk of new-onset type 2 diabetes mellitus in overall settings and rural areas ($HR_{overall} = 1.75$, 95% CI: 1.35–2.28; $HR_{rural} = 1.81$, 95% CI: 1.34–2.44); however, when taking the maintained-high CMI group as reference, no significant reduction for the risk of type 2 diabetes mellitus was found when the participants' CMI changed to low status ($HR_{overall} = 0.77$, 95% CI: 0.58–1.01; $HR_{rural} = 0.78$, 95% CI: 0.57–1.06; $HR_{urban} = 0.72$, 95% CI: 0.41–1.24) (Figure 3a). According to Figure 3b, all of three abnormal transitions (i.e. the low-to-high CMI group, high-to-low CMI group, and maintained-high CMI group) are associated with a higher risk of type 2 diabetes mellitus ($HR_{low\text{-}to\text{-}high} = 1.75$, 95% CI: 1.35–2.28; $HR_{high\text{-}to\text{-}low} = 1.50$, 95% CI: 1.10–2.05; $HR_{maintained\text{-}high} = 1.96$, 95% CI: 1.56–2.46). The associations in rural residents were similar to those in overall residents, whereas only the maintained-high CMI group had a significantly higher risk in urban settings.

Similar results were noted in the sensitivity analyses for data with multiple imputations (Tables S6–S7), for data excluded participants taking medication for dyslipidemia (Table S8), and for data of new-onset type 2 diabetes mellitus during 2016–2018 (Table S9).

DISCUSSION

In this nationwide, population-based prospective study, we discovered a positive association between CMI levels and the risk of new-onset type 2 diabetes mellitus in middle-aged and older Chinese. People with high-CMI were more likely to develop type 2 diabetes mellitus than those with low-CMI. Furthermore, people with a maintained-high, low-to-high, and high-to-low CMI transition during follow-up were 1.96, 1.75, and 1.50 times more likely to develop type 2 diabetes mellitus than those with maintained-low CMI, respectively.

Our research observed the deleterious effects of high CMI on the incidence of type 2 diabetes mellitus, which was in

Table 1 | **I** Demographic, socioeconomic and geographic characteristics of the included participants at baseline (CHARLS 2011)

Characteristic	Overall (n = 7,347)	Rural (n = 4,942)	Urban (n = 2,405)	$P^{\dagger}$
Age group				0.054
45–49 years	1,433 (19.5%)	932 (18.9%)	501 (20.8%)	
50–59 years	2,624 (35.7%)	1746 (35.3%)	878 (36.5%)	
60–69 years	2,163 (29.4%)	1,494 (30.2%)	669 (27.8%)	
≥70 years	1,127 (15.3%)	770 (15.6%)	357 (14.8%)	
Sex[‡]				0.113
Male	3,424 (46.6%)	2,335 (47.3%)	1,089 (45.3%)	
Female	3,917 (53.4%)	2,603 (52.7%)	1,314 (54.7%)	
Education[‡]				<0.001
Illiterate	2,151 (29.3%)	1,694 (34.3%)	457 (19.0%)	
Literate	1,396 (19.0%)	978 (19.8%)	418 (17.4%)	
Primary education	1,653 (22.5%)	1,144 (23.2%)	509 (21.2%)	
Middle or higher education	2,146 (29.2%)	1,125 (22.8%)	1,021 (42.5%)	
Marital status				0.265
Married or cohabiting	6,475 (88.1%)	4,341 (87.8%)	2,134 (88.7%)	
Single	872 (11.9%)	601 (12.2%)	271 (11.3%)	
Ln(PCE)[‡]				<0.001
Bottom tertile	2,149 (33.3%)	1,673 (38.1%)	476 (23.0%)	
Middle tertile	2,149 (33.3%)	1,440(32.8%)	709(34.3%)	
Top tertile	2,157 (33.4%)	1,276 (29.1%)	881(42.6%)	
Region				<0.001
North China	940 (12.8%)	662 (13.4%)	278 (11.6%)	
Northeast China	500 (6.8%)	301 (6.1%)	199 (8.3%)	
East China	2,210 (30.1%)	1,466 (29.7%)	744 (30.9%)	
South Central China	1739 (23.7%)	1,094 (22.1%)	645 (26.8%)	
Southwest China	1,356 (18.5%)	938 (19.0%)	418 (17.4%)	
Northwest China	602 (8.2%)	481 (9.7%)	121 (5.0%)	
BMI[‡]				<0.001
Mean ± SD	23.15 ± 3.42	22.82 ± 3.37	23.83 ± 3.42	
Waist circumference[‡]				<0.001
Mean ± SD	84.61 ± 9.91	83.70 ± 9.78	86.47 ± 9.91	
General obesity[‡]				<0.001
Normal	3,661 (50.5%)	2,681 (54.9%)	980 (41.4%)	
Overweight	2,748 (37.9%)	1722 (35.3%)	1,026 (43.3%)	
Obesity	841 (11.6%)	479 (9.8%)	362 (15.3%)	
Hypertension[‡]				<0.001
Normal	4,369 (59.6%)	3,014 (61.1%)	1,339 (56.5%)	
Hypertension	2,961 (40.4%)	1918 (38.9%)	1,021 (43.5%)	
Smoking[‡]				0.004
Non-smoker	4,471 (61.0%)	2,952 (59.9%)	1,519 (63.4%)	
Smoker	2,854 (39.0%)	1976 (40.1%)	878 (36.6%)	
Alcohol drinking[‡]				0.056
Non-drinker	5,055(68.8%)	3,366 (68.1%)	1,689 (70.3%)	
Drinker	2,288 (31.2%)	1,575 (31.9%)	713 (29.7%)	
Medication for dyslipidemia				
Yes	471 (6.4%)	276 (5.6%)	195 (8.1%)	
No	6,876 (93.6%)	4,666 (94.4%)	2,210 (91.9%)	
TC				0.136
≤ 200 mg/dL	4,537 (61.8%)	3,081 (62.3%)	1,456 (60.5%)	
> 200 mg/dL	2,810 (38.2%)	1861 (37.7%)	949 (39.5%)	
HDL-C				<0.001
≥50 mg/dL	3,706 (50.4%)	2,622 (53.1%)	1,084 (45.1%)	
< 50 mg/dL	3,641 (49.6%)	2,320 (46.9%)	1,321 (54.9%)	

Table 1. (*Continued*)

Characteristic	Overall (n = 7,347)	Rural (n = 4,942)	Urban (n = 2,405)	$P^{\dagger}$
LDL-C				0.001
≤100 mg/dL	3,192 (43.4%)	2,212 (44.8%)	980 (40.7%)	
> 100 mg/dL	4,155 (56.6%)	2,730 (55.2%)	1,425 (59.3%)	
TG				<0.001
≤150 mg/dL	5,632 (76.7%)	3,870 (78.3%)	1762 (73.3%)	
> 150 mg/dL	1715 (23.3%)	1,072 (21.7%)	643 (26.7%)	
CMI score				<0.001
Median (IQR)	0.47 (0.29,0.81)	0.44 (0.27,0.75)	0.31 (0.53,0.90)	
CMI group				<0.001
Low-CMI	3,672 (50.0%)	2,622(53.1%)	1,051(43.7%)	
High-CMI	3,674 (50.0%)	2,320(46.9%)	1,354(56.3%)	

Data are presented as n (%) or mean with standard deviation (SDs); BMI, body mass index; CMI, cardiometabolic index; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PCE, *per capita* expenditures; TC, total cholesterol; TG, triglyceride. [†]Comparison between rural and urban settings. [‡]Data for some participants were missing.

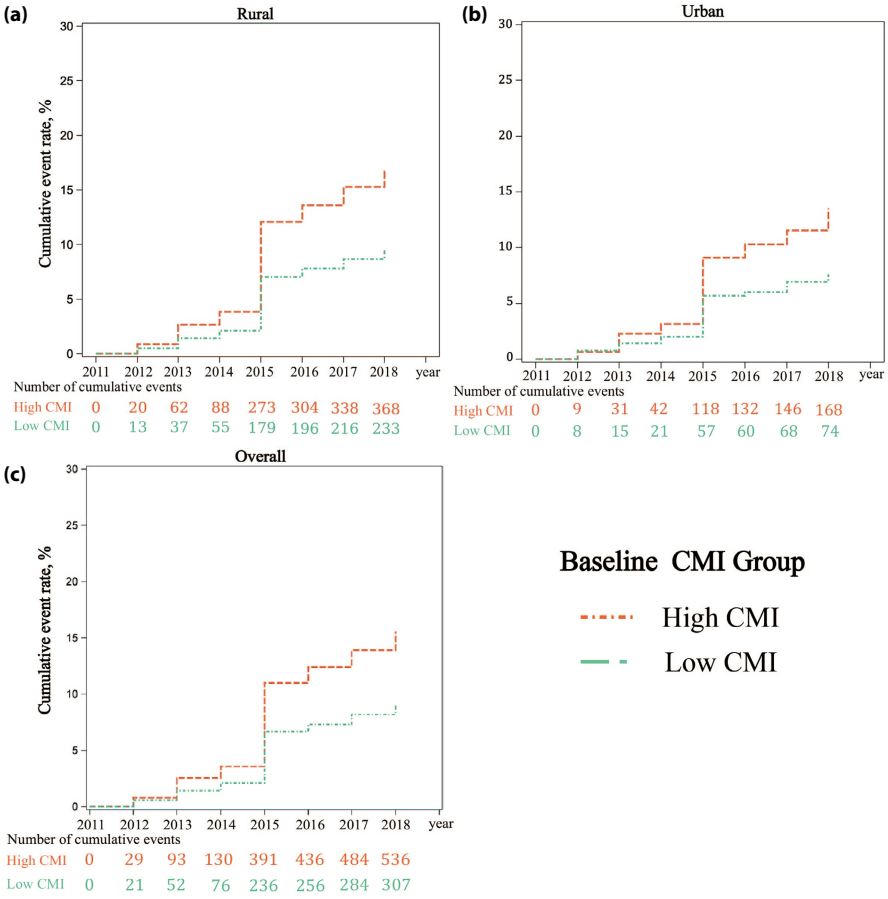

Figure 1 | I Cumulative incidence of type 2 diabetes mellitus for CMI phenotypes (Low- and High-) stratified by urban/rural settings from CHARLS 2011 to 2018. CMI, cardiometabolic index. The cumulative event rate of type 2 diabetes mellitus is significantly different between low-CMI and high-CMI in (a) rural, (b) urban, and (c) overall population.

Table 2 | Hazard ratios for type 2 diabetes mellitus by CMI groups in middle-aged and older Chinese, CHARLS 2011–2018

Model	CMI group		$P^{\dagger}$
	Low-CMI (n = 3,673)	High-CMI (n = 3,674)	
New-onset type 2 diabetes mellitus	307(8.36)	536(14.59)	
Overall			
Unadjusted	1 (reference)	1.78 (1.55, 2.05)	<0.001
Model 1	1 (reference)	1.75 (1.51, 2.01)	<0.001
Model 2	1 (reference)	1.38 (1.17, 1.63)	<0.001
Model 3	1 (reference)	1.37 (1.16, 1.61)	<0.001
Rural			
Unadjusted	1 (reference)	1.82 (1.54, 2.15)	<0.001
Model 1	1 (reference)	1.80 (1.52, 2.12)	<0.001
Model 2	1 (reference)	1.45 (1.20, 1.77)	<0.001
Model 3	1 (reference)	1.44 (1.19, 1.76)	<0.001
Urban			
Unadjusted	1 (reference)	1.79 (1.36, 2.35)	<0.001
Model 1	1 (reference)	1.71 (1.30, 2.25)	<0.001
Model 2	1 (reference)	1.31 (0.95, 1.81)	0.101
Model 3	1 (reference)	1.28 (0.92, 1.77)	0.137

Data are presented as n (%) or hazard ratios (95% CI); CMI, cardiometabolic index. Model 1 was adjusted for age and sex. Model 2 was adjusted for education, marital status, ln(PCE), region, hypertension, smoking, and drinking based on Model 1. Model 3 was adjusted for TC and LDL-C based on Model 2. †Hazard ratios for type 2 diabetes mellitus by CMI groups were calculated using multivariable Cox frailty models with random effect, by which means clustering of participants was accounted for.

agreement with previous studies[17,23,36]. Wen-Rui *et al.* conducted a cross-sectional study in rural areas of northeastern China and reported a strong positive correlation of CMI with type 2 diabetes mellitus. Similar findings were also found in the Japanese population, where CMI was strongly associated with hyperglycemia and type 2 diabetes mellitus[17]. Meanwhile, a prospective study conducted from 1992 to 2007 in an urban community in China suggested that CMI was an independent predictor of future diabetes (log_{10}-CMI [HR: 1.70 per SD])[23]. Comparatively, our study used CHARLS, a large-scale national prospective cohort study that included both urban and rural residents, which was highly representative.

We further explored the long-term relationship of transition patterns of CMI with the development of type 2 diabetes mellitus, which had been rarely reported in previous studies[17,22,37,38]. We found that the risk of type 2 diabetes mellitus was higher in those with maintained-high, low-to-high, and high-to-low CMI transition groups than in the maintained-low CMI group. These results further suggested that being in a high CMI state was a risk factor for developing type 2 diabetes mellitus. In contrast, the risk difference between the maintained-high CMI group and the high-to-low CMI group was not significant. We could deduce that a high CMI, which implied a high WHtR and/or high TG and/or low HDL-C might lead to irreversible type 2 diabetes mellitus risks. These findings could be explained by the abnormal lipid metabolism among people with evaluated CMI. Excess-free fatty acids in obese people with high WHtR can block glucose from entering tissue cells, limiting insulin's role in glucose metabolism, and resulting in insulin resistance[39,40]. In people with abdominal obesity, the number of insulin receptors on target tissues has decreased, as has their binding affinity, lowering their capacity to handle glucose[41,42]. Meanwhile, a high TG status induces diabetes mellitus in a similar way to abdominal obesity. It may be regarded as a critical intermediate stage in the development of obesity to diabetes mellitus. Reduced HDL-C levels may have a detrimental impact on the function of β cells, reducing insulin output and sensitivity[41,43]. In conclusion, there is a "vicious cycle" between high CMI and type 2 diabetes mellitus.

The results of our subgroup analysis showed that participants living in rural regions had a higher risk of developing type 2 diabetes mellitus than those living in urban areas, which is in contrast to the findings from a study conducted by Wang *et al.*[44]. The possible reasons for this result include a lower education level and health literacy rates, inadequate medical facilities, and reduced physical labor due to mechanized agriculture in rural areas. A prior meta-analysis conducted in China showed type 2 diabetes mellitus was more common in rural regions than in urban areas in recent years[45]. And a study based on two consecutive population-based surveys in Shanghai also found that the increase of type 2 diabetes mellitus prevalence was more evident in rural residents ($P < 0.001$)[46]. Type 2 diabetes mellitus and obesity are often inextricably linked. So far, there have been studies that revealed the fact that the urban–rural gap in obesity was soon to disappear and reverse in China[47,48]. Based on this situation, it is understandable that a similar trend in the

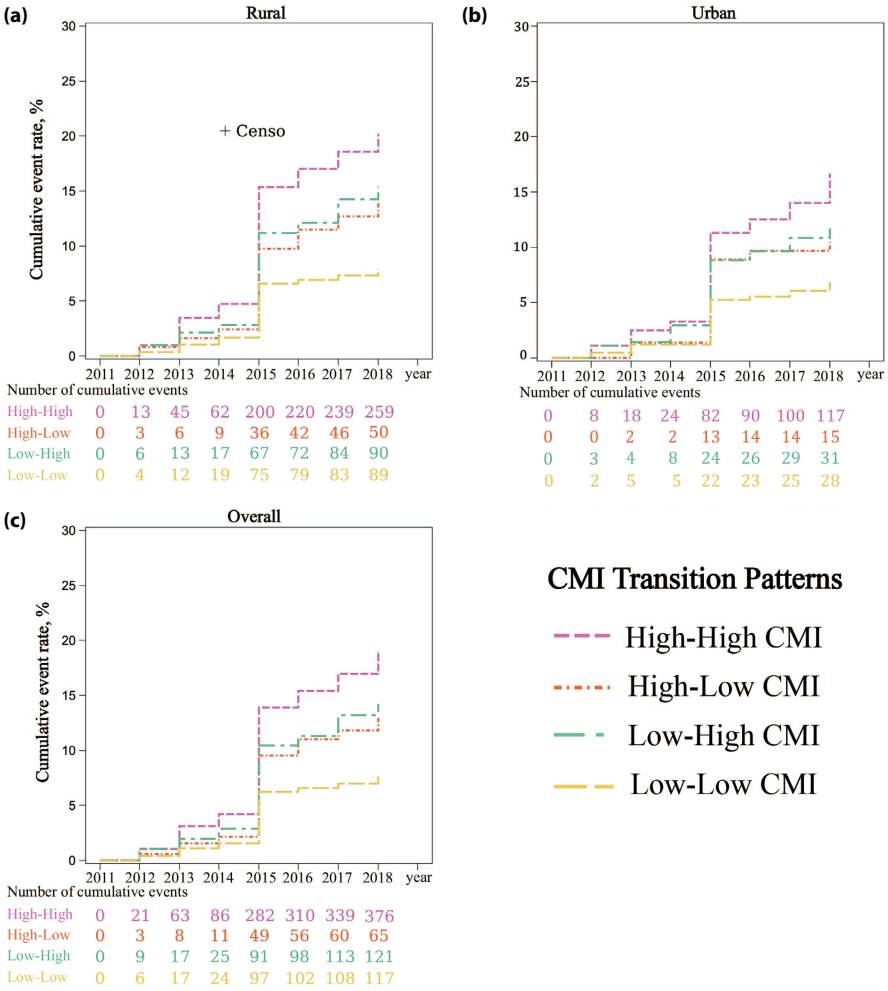

Figure 2 | I Cumulative incidence of type 2 diabetes mellitus for CMI transformations from CHARLS 2011 to 2018. CMI, cardiometabolic index. The cumulative event rate of type 2 diabetes mellitus is significantly different across four CMI transformations (high to high-, high to low-, low to high-, low to low-) in (a) rural, (b) urban, and (c) overall population.

incidence of type 2 diabetes mellitus would arise. Hence, strengthening type 2 diabetes mellitus prevention and management in rural regions is critical. However, we found that only maintained-high CMI was significantly hazardous compared with maintained-low CMI in urban residents. Due to the excellent medical infrastructure, convenient medical treatment, and generally high education level, the participants in urban settings are more likely to address and prevent type 2 diabetes mellitus when their CMI is high. However, because of the above-mentioned "vicious cycle", it might be difficult for people with a maintained-high CMI to reduce their risk of type 2 diabetes mellitus. Therefore, the risk remains substantial, emphasizing the importance of early detection and intervention.

To our best knowledge, this is the first nationwide study in China that explored the long-term effects of CMI and its transition patterns on type 2 diabetes mellitus. The quality of our research is reliable, given the extensive geographic coverage (28 of 31 provinces in China), a huge number of samples, and blood samples analyzed by established techniques in the standard laboratory.

However, our study has several limitations. First, the participants included were all middle-aged and older Chinese adults; the effect of CMI on younger people remains unclear. Second, since a large proportion of participants was excluded from the analysis owing to missing data, the representativeness of the population and the extrapolation of the study's findings should be interpreted with caution. However, significant associations of CMI and its transitions with new-onset type 2 diabetes mellitus remained after multiple imputations of missing variables, suggesting the robustness of our results. Third, blood samples were only collected in 2011 and 2015 to define type 2 diabetes mellitus; in other years, the type 2 diabetes mellitus status was self-reported. Therefore, the current study may be subject to recall bias. Fourth, due to the lack of relative information in the

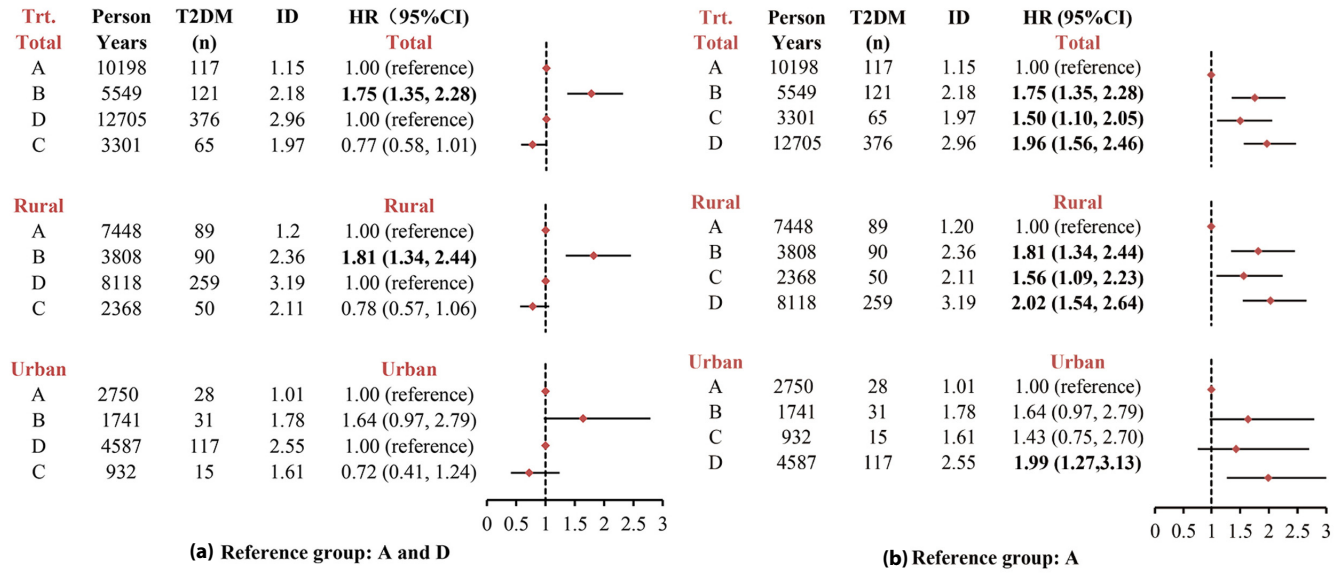

Figure 3 | Risk of new-onset type 2 diabetes mellitus by different CMI transitions in middle-aged and older Chinese. Data are presented as *n*, hazard ratios (95% CI) and incidence density (person-year), adjusted for age, sex, education, region, hypertension, smoking, drinking, TC and LDL-c level. Hazard ratios for type 2 diabetes mellitus by CMI transitions were calculated using multivariable Cox frailty models with random effect, by which means clustering of participants was accounted for. (A), Group A and Group D were set as reference groups; (B), Group A was set as reference groups. Significant values are shown in bold format. ID, incidence density; CMI, cardiometabolic index; Trt., transition types during follow-up, the definition from group A to D are listed as follows: Group A, maintained Low CMI during follow-up; Group B, Low CMI at baseline turned to High CMI at follow-up; Group C, High CMI at baseline turned to Low CMI at follow-up; Group D, maintained High CMI during follow-up.

CHARLS dataset, several confounding factors, such as physical activity and diet were not accounted for in our multivariable analyses. Moreover, the results on the risk of type 2 diabetes mellitus by CMI transition may have been influenced by the duration of the high-CMI state. For example, the later that people achieve the low-to-high CMI transition, the less time they are at risk for high-CMI. More research into the impact of the ongoing CMI transition process for developing type 2 diabetes mellitus is called for. Finally, covariates were collected at baseline, and any changes in follow-up might result in unanticipated exposure and influence our findings.

In conclusion, our study demonstrated that high CMI was a detrimental factor of new-onset type 2 diabetes mellitus. Additionally, there were significant associations between transitions of CMI status and type 2 diabetes mellitus. For better prevention of type 2 diabetes mellitus, health workers should devote more attention to the general healthy population, and take measures to prevent their CMI progressing from low to high levels. The value of CMI as a reliable and efficient indicator of the early prevention of type 2 diabetes mellitus should be further investigated.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: Ethical approval for all the CHARLS waves was granted from the Institutional Review Board at Peking University. The IRB approval number for the main household survey, including anthropometrics, is IRB00001052-11015; the IRB approval number for biomarker collection, was IRB00001052-11014.
Informed consent: All individual participants included in the study gave their informed consent.
Approval date of registry and the registration no. of the study/-trial: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | The six geographic regions in China. Twenty-eight provinces in Mainland China were randomly chosen in CHARLS, except for Hainan province, Ningxia Hui Autonomous Region, and Tibet province, which are marked in white.

Figure S2 | Association between type 2 diabetes mellitus and CMI using restricted cubic spline with 4 knots. CMI, cardiometabolic index.

Figure S3 | Flow chart for subjects included in this study. Incomplete data refer to any incomplete information on age, sex, educational attainment, marital status, setting, economic status, geographic region. CMI, cardiometabolic index.

Table S1 | Investigated provinces in six geographic regions in CHARLS. Twenty-eight provinces in Mainland China were randomly chosen in CHARLS, except for Hainan province, Ningxia Hui Autonomous Region, and Tibet province

Table S2 | Number of missing values and corresponding dispositions. Ln(PCE), the natural logarithm of *per capita* expenditures; BMI, body mass index

Table S3 | Comparison of general characteristics between the included and non-included subjects in the CHARLS 2011 survey. Data are presented as *n* (%); [a]*P*, comparison between included and excluded subjects; PCE, *per capita* expenditures; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride

Table S4 | Comparison of general characteristics in participants among four CMI transition patterns during the follow up. Data are presented as *n* (%); [a]*P*, comparison between our CMI transition patterns; PCE, *per capita* expenditures; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride

Table S5 | Hazard ratios for type 2 diabetes mellitus in middle-aged and older Chinese, CHARLS 2011–2018. Data are presented as hazard ratios (95% CI); Associations between CMI and type 2 diabetes mellitus were conducted using multivariable Cox frailty models with random effect to account for clustering of participants in each province; CMI, cardiometabolic index; PCE, *per capita* expenditures; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; NA, not available; [a]$P < 0.05$. Model 1 adjusted for age and sex. Model 2 adjusted for education, marital status, ln(PCE), region, smoking, drinking hypertension, general obesity, and central obesity based on Model 1. Model 3 adjusted for TC and LDL-C based on Model 2

Table S6 | Hazard ratios for type 2 diabetes mellitus by baseline CMI levels in middle-aged and older Chinese based on multiply imputed data sets All analyses are based on multiply imputed data sets. Data are presented as hazard ratios (95% CI); Associations between CMI and type 2 diabetes mellitus were conducted using multivariable Cox frailty models with random effect to account for clustering of participants in each province; CMI, cardiometabolic index; PCE, *per capita* expenditures; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; NA, not available; [a]$P < 0.05$. Model 1 adjusted for age and sex. Model 2 adjusted for education, marital status, ln(PCE), region, smoking, drinking hypertension, general obesity, and central obesity based on Model 1. Model 3 adjusted for TC and LDL-C based on Model 2

Table S7 | Risk of new-onset type 2 diabetes mellitus by different CMI transition patterns in middle-aged and older Chinese based on multiply imputed data sets. All analyses are based on multiply imputed data sets. Data are presented as hazard ratios (95% CI), adjusted for age, sex, education, region, hypertension, smoking, drinking, TC, and LDL-C level; Hazard ratios for type 2 diabetes mellitus by CMI transitions were calculated using multivariable Cox frailty models with random effect, by which means clustering of participants was accounted for; [a]$P < 0.05$. ID, incidence density; CMI, cardiometabolic index; the definition from group A to D are listed as follows: Group A, maintained low-CMI during follow-up; Group B, low-CMI at baseline turned to high-CMI during follow-up; Group C, high-CMI at baseline turned to low-CMI during follow-up; Group D, maintained high-CMI during follow-up

Table S8 | Hazard ratios for type 2 diabetes mellitus by CMI groups in middle-aged and older Chinese (excluded the participants taking medication for dyslipidemia), CHARLS 2011–2018. Data are presented as hazard ratios (95% CI); † Hazard ratios for type 2 diabetes mellitus by CMI groups were calculated using multivariable Cox frailty models with random effect, by which means clustering of participants was accounted for. CMI, cardiometabolic index. Model 1 was adjusted for age and sex. Model 2 was adjusted for education, marital status, ln(PCE) by setting, region, hypertension, smoking, and drinking based on Model 1. Model 3 was adjusted for TC and LDL-C based on Model 2

Table S9 | Risk of new-onset type 2 diabetes mellitus (during 2016–2018) by different CMI transition patterns (during 2011–2015) in middle-aged and older Chinese. All analyses are based on multiply imputed data sets. Data are presented as hazard ratios (95% CI), adjusted for age, sex, education, region, hypertension, smoking, drinking, TC and LDL-C level. Hazard ratios for type 2 diabetes mellitus by CMI transitions were calculated using multivariable Cox frailty models with random effect, by which means clustering of participants was accounted for; [a]$P < 0.05$. ID, incidence density; CMI, cardiometabolic index; the definition from group A to D are listed as follows: Group A, maintained low-CMI during follow-up; Group B, low-CMI at baseline turned to high-CMI during follow-up; Group C, high-CMI at baseline turned to low-CMI during follow-up; Group D, maintained high-CMI during follow-up