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Exposure of cumulative atherogenic index of plasma and the development of prediabetes in middle-aged and elderly individuals: evidence from the CHARLS cohort study

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Abstract

Background The impact of dynamic changes in the degree of atherosclerosis on the development of prediabetes remains unclear. This study aims to investigate the association between cumulative atherogenic index of plasma (CumAIP) exposure during follow-up and the development of prediabetes in middle-aged and elderly individuals.

Methods A total of 2,939 prediabetic participants from the first wave of the China Health and Retirement Longitudinal Study (CHARLS) were included. The outcomes for these patients, including progression to diabetes and regression to normal fasting glucose (NFG), were determined using data from the third wave. CumAIP was calculated as the ratio of the average AIP values measured during the first and third waves to the total exposure duration. The association between CumAIP and the development of prediabetes was analyzed using multivariable Cox regression and restricted cubic spline (RCS) regression.

Results During a median follow-up period of 3 years, 15.21% of prediabetic patients progressed to diabetes, and 22.12% regressed to NFG. Among the groups categorized by CumAIP quartiles, the proportion of prediabetes progressing to diabetes gradually increased (Q1: 10.61%, Q2: 13.62%, Q3: 15.65%, Q4: 20.95%), while the proportion regressing to NFG gradually decreased (Q1: 23.54%, Q2: 23.71%, Q3: 22.18%, Q4: 19.05%). Multivariable-adjusted Cox regression showed a significant positive linear correlation between high CumAIP exposure and prediabetes progression, and a significant negative linear correlation with prediabetes regression. Furthermore, in a stratified analysis, it was found that compared to married individuals, those who were unmarried (including separated, divorced, widowed, or never married) had a relatively higher risk of CumAIP-related diabetes.

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Conclusion CumAIP is closely associated with the development of prediabetes. High CumAIP exposure not only increases the risk of prediabetes progression but also hinders its regression within a certain range. These findings suggest that monitoring and maintaining appropriate AIP levels may help prevent the deterioration of blood glucose levels.

Keywords Cumulative atherogenic index of plasma, Atherogenic index of plasma, Progression to diabetes, Regression to normal fasting glucose

Background

Prediabetes is a common metabolic disorder during aging, representing the earliest identifiable stage of glucose dysregulation, characterized by plasma glucose levels between normal and diabetic thresholds [1, 2]. According to the American Diabetes Association (ADA) criteria, recent nationwide epidemiological surveys in China indicate a prediabetes prevalence of approximately 35.2%, with the rate approaching 50% among Chinese adults over 50 years old [3]. The development of prediabetes may result in progression to diabetes, maintenance of the prediabetic state, or regression to NFG [4, 5]. A recent meta-analysis of 103 prospective cohort studies reported that the cumulative incidence of prediabetes progressing to diabetes within five years ranges from 18 to 39%, while the rate of regression to NFG ranges from 33 to 59% [6]. It is noteworthy that the progression of prediabetes can exacerbate various cardiovascular and metabolic diseases, leading to severe adverse outcomes, whereas regression can significantly improve these outcomes [2, 7–9]. Therefore, it is essential to systematically evaluate the key factors influencing the progression and regression of prediabetes.

Contrary to the common belief that atherosclerosis is merely a complication of diabetes, atherosclerosis might also be a contributing factor to diabetes, as atherosclerotic burden has been found to exist before the onset of diabetes, accompanied by pro-atherosclerotic inflammation and vascular constriction [10–13]. In terms of lipid patterns, prediabetic individuals typically exhibit atherogenic dyslipidemia, characterized by increased triglycerides (TG), very low-density lipoprotein cholesterol (vLDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) [14, 15]. Moreover, clinical evidence has revealed that the AIP, representing atherosclerosis, is a risk factor for both prediabetes and diabetes in adults [16–22] and is negatively associated with prediabetes regression [22]. However, previous findings have overlooked the dynamic changes in atherosclerosis over time, which may significantly influence the transition of glycemic states. A previous cohort study of adolescents with type 1 diabetes suggested that changes in arterial stiffness might affect glycemic status. Lower insulin sensitivity at baseline appeared to be an important risk factor for increased arterial stiffness over time in these adolescents [23]. This finding further indicates the importance of assessing atherosclerosis dynamics over time for glucose metabolism. However, the association between cumulative exposure to atherosclerosis during follow-up and the progression or regression of prediabetes in adults remains unclear. To address this limitation, the current study aimed to analyze the CHARLS national survey follow-up data to assess the impact of CumAIP exposure during follow-up on the development of prediabetes in middle-aged and elderly Chinese.
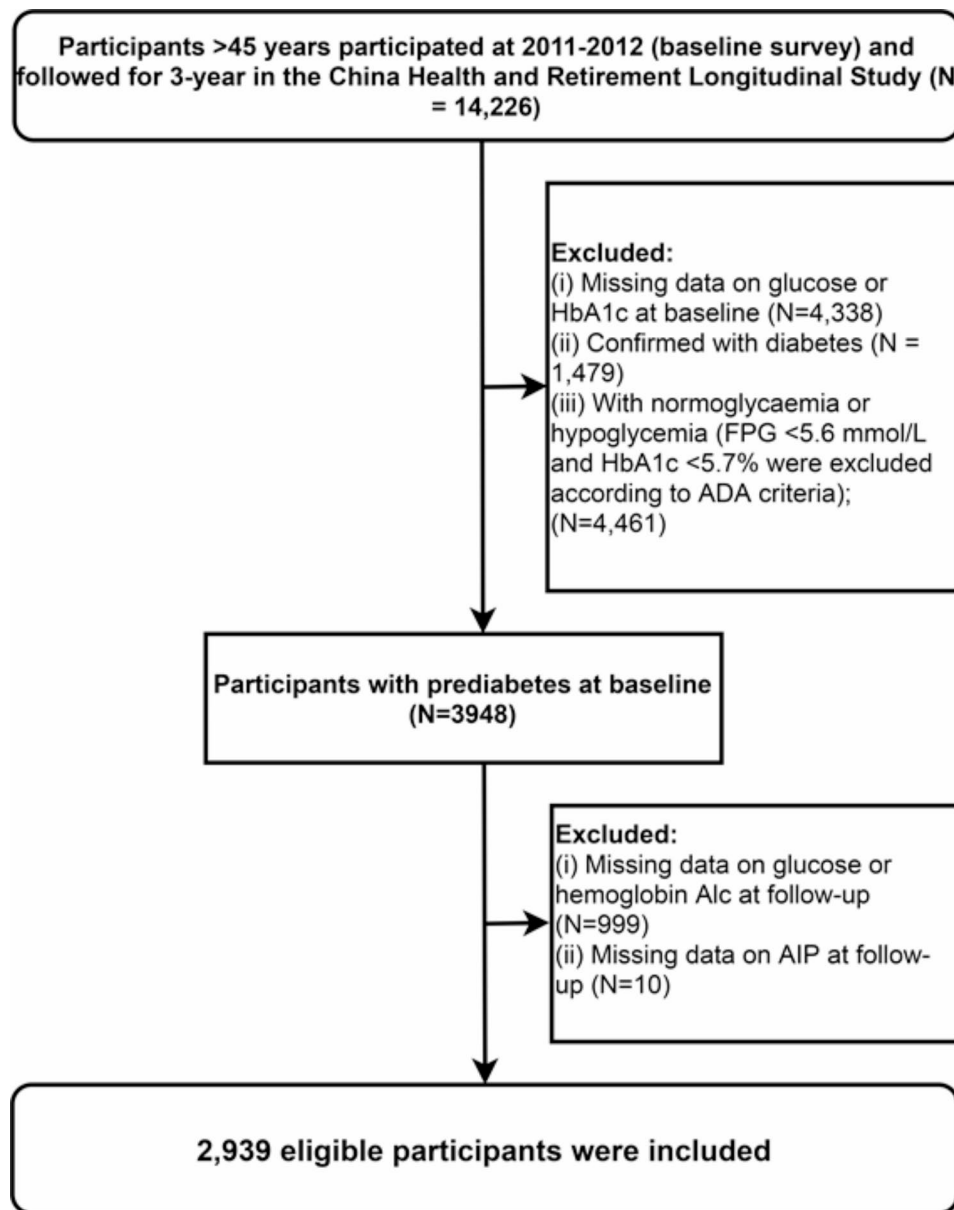
Methods

Study population and design

CHARLS is a prospective national cohort study conducted in China, utilizing a complex probabilities proportional to size sampling method to collect nationally representative health-related data from middle-aged and elderly populations in China [24]. The detailed study design is summarized in the online supplementary methods, with Supplementary Fig. 1 showing the screening process for the CHARLS cohort. The current study uses data from the first wave (2011–2012) of CHARLS as the baseline and data from the third wave (2015–2016) as the study endpoint, as these waves included blood samples from the participants. The entire study process adhered to the Declaration of Helsinki, and the study results were reported following the STROBE guidelines. The protocol for the CHARLS cohort was authorized by the Ethics Review Committee of Peking University (IRB00001052–11015), and all participants provided written informed consent at the time of participation.

Figure 1 shows the screening process for the study population in the current study. Among the 14,226 participants from the first wave who were followed up in the third wave, we excluded those lacking baseline blood glucose and glycated hemoglobin (HbA1c) information ($n=4,338$), those diagnosed with diabetes ($n=1,479$), and those with hypoglycemia or normal blood glucose ($n=4,461$). Additionally, participants lacking blood glucose and HbA1c information during follow-up ($n=999$) and those missing AIP information ($n=10$) were also excluded. Ultimately, 2,939 prediabetic participants were included in the current analysis.

Calculation of CumAIP

AIP=log10 [TG (mg/dL)/HDL-C(mg/dL)] [16].

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│ Participants >45 years participated at 2011-2012         │
│ (baseline survey) and followed for 3-year in the China   │
│ Health and Retirement Longitudinal Study (N = 14,226)    │
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Excluded:
(i) Missing data on glucose or HbA1c at baseline (N=4,338)
(ii) Confirmed with diabetes (N = 1,479)
(iii) With normoglycaemia or hypoglycemia (FPG <5.6 mmol/L and HbA1c <5.7% were excluded according to ADA criteria); (N=4,461)

Participants with prediabetes at baseline (N=3948)

Excluded:
(i) Missing data on glucose or hemoglobin Alc at follow-up (N=999)
(ii) Missing data on AIP at follow-up (N=10)

2,939 eligible participants were included

Fig. 1 Flow chart of study participants

CumAIP was calculated as the ratio of the average AIP values measured during the first and third waves to the total exposure duration, specifically as follows: (AIP2012+AIP2015)/2 * time (2012−2015) [25].

Determination and definition of prediabetes and its development

The determination of prediabetes and its development referred to the ADA diagnostic criteria. The development of prediabetes included progression to diabetes and regression to NFG. In the current study, we primarily assessed blood glucose status based on the ADA standards for impaired fasting glucose. NFG is defined as fasting plasma glucose (FPG)<5.6 mmol/L and HbA1c<5.7%; prediabetes is defined as FPG 5.6–6.9 mmol/L or HbA1c 5.7–6.4%; diabetes is defined as FPG≥7.0 mmol/L, HbA1c≥6.5%, or a self-reported history [26]. Additionally, for participants with random plasma glucose (RPG) measurements, RPG<7.8 mmol/L indicated normal glucose, while RPG>11.1 mmol/L indicated diabetes.

Covariates

As previously described [24], CHARLS utilized face-to-face computer-assisted personal interviews to collect data. A standardized structured questionnaire recorded demographic information (gender, age), disease information [hypertension, cardiovascular disease (CVD), stroke;

detailed diagnostic information available in the online supplementary methods], body measurements (height, weight, and blood pressure), health behaviors (smoking and drinking status), registered residence, and laboratory parameters. Laboratory parameters were analyzed using venous blood samples of subjects after they overnight fasting collected by professional healthcare workers. The blood samples were sent to the central laboratory in Beijing for biochemical analysis using standard methods, including measurements of total cholesterol (TC), TG, LDL-C, HDL-C, blood urea nitrogen (BUN), high-sensitivity C-reactive protein (hs-CRP), uric acid (UA), serum creatinine (Cr), plasma glucose, and HbA1c levels.

In addition, we also evaluated whether the study population engaged in physical exercise and drug treatment during follow-up based on the physical activity questionnaire and drug use information questionnaire, respectively, of the study population in the third wave of the survey. Drug treatment included antihypertensive and antidiabetic drug treatment, and physical exercise was divided into light activity, moderate activity, and intensive activity according to the intensity of exercise (See Supplementary Methods for details).

Missing data handling

Given the substantial amount of missing blood glucose measurement data in the CHARLS dataset, we first compared the baseline characteristics of participants who provided blood glucose/HbAIc measurement information with those who did not, in both the first and third waves of the survey, before conducting the research analysis. The comparison results in Supplementary Tables 1 and 2 showed that most of the baseline characteristics of the group with missing blood glucose/HbAIc measurement information and the group without missing information exhibited similar distribution patterns. ($P>0.05$ or Standardized difference<0.1). This result suggested that the missing blood glucose/HbAIc in these two waves of surveys was completely random.

Supplementary Table 3 shows the missing baseline data in the current analysis, including 4 subjects with missing educational information, 3 subjects with missing marital status, 4 subjects with missing registered residence, 31 subjects with missing CVD information, 23 subjects with missing stroke information, 11 subjects with missing hypertension information, 13 subjects with missing drinking status, 369 subjects with missing blood pressure measurements, 354 subjects with missing height, 346 subjects with missing weight, and 1 subjects with missing LDL-C. To minimize potential bias due to missing data, we used multiple imputations by fully conditional specification to address the missing data issue [27].

Statistical analysis

For descriptive data, we provided flexible data presentation formats; qualitative variables were presented as frequencies and percentages, while quantitative variables were presented as medians and interquartile ranges or means and standard deviations. One-way ANOVA, Kruskal-Wallis H test, and Chi-square test were used to examine differences between groups.

Multivariable Cox regression models were used to examine the association between CumAIP exposure and the development of prediabetes, with 95% confidence intervals (CI) and hazard ratio (HR) estimated for the associations. For the development of prediabetes, we used a one-to-one method to split the data into binary datasets for each category [28, 29]. Considering collinearity (Supplementary Table 4), we included baseline covariates related to atherosclerosis and the development of diabetes in the multivariable models that incorporated time, including age, gender, education, registered residence, CVD, stroke, hypertension, smoking status, drinking status, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL-C, HbA1c, UA, Cr, BUN, and hs-CRP. Additionally, we constructed and visualized RCS regressions (with 4 knots) to test the dose-response relationship between CumAIP exposure and the development of prediabetes. Stratified analyses were also performed to explore whether the association between CumAIP exposure and the development of prediabetes varied by gender, age, education, marital status, registered residence, comorbidities (hypertension, CVD, stroke), and physical exercise or drug treatment during follow-up.

In sensitivity analyses, we evaluated the association between CumAIP exposure and the development of prediabetes based on the diagnostic criteria recommended by the World Health Organization (WHO) [30]. Secondly, given the adequate sample size in the current study, we followed the recommendations in "Regression Modeling Strategies" to apply an RCS analysis strategy with 5 knots to assess the dose-response relationship between CumAIP exposure and the development of prediabetes. Thirdly, considering the potential impact of unmeasured confounders, we calculated the minimum E-value needed to quantify the effect of potential confounders on the results based on the final model [31].

Data analysis in the current study was conducted using R statistical software (version 4.2.1) and Empower(R) (version 2.0). All statistical tests were two-sided, and a *P*-value less than 0.05 was considered significant.

Results

Study participants

In the current analysis, we included 1,357 male and 1,582 female prediabetic participants with an average age of 60

years. Table 1 presents the baseline characteristics of the study participants grouped by CumAIP quartiles. Participants with high CumAIP exposure were more likely to have adverse diabetes risk factors at baseline, and in further analysis, we also found that this unfavorable metabolic profile persisted during follow-up (Supplementary Table 5); including elevated SBP, DBP, weight, TC, TG, hs-CRP, glucose, UA, BUN, and lower HDL-C levels. Additionally, participants with high CumAIP exposure generally had lower education levels, a higher proportion were married, fewer had smoking or drinking habits and a higher proportion of subjects with comorbidities, including hypertension, CVD, stroke.

Summary of baseline characteristics according to follow-up outcomes

During a median follow-up period of 3 years, 15.21% of prediabetic patients progressed to diabetes, and 22.12% regressed to NFG. Table 2 summarizes the baseline characteristics of the study population according to the outcomes of prediabetes. Compared to participants who remained in a prediabetic state, those who progressed to diabetes had a higher proportion of lower education, were more likely to have CVD, hypertension and stroke, and had higher levels of DBP, weight, TG, hs-CRP, glucose, HbA1c, CumAIP, and lower levels of HDL-C and BUN. In addition, compared with subjects who remained prediabetic, participants who regressed to NFG were generally younger, had a higher proportion of higher education, and significantly lower levels of TC, TG, LDL-C, hs-CRP, HbA1c, and CumAIP at baseline.

Association between CumAIP exposure and the development of prediabetes

Table 3 presents the results of the association analysis between CumAIP and the progression to diabetes and regression to NFG. A positive correlation between CumAIP and progression to diabetes and a negative correlation between CumAIP and regression to NFG were observed in all three progressively adjusted multivariable models (All *P*-trend<0.05). According to the results of Model 3, after adjusting for age, gender, education, registered residence, CVD, stroke, hypertension, smoking status, drinking status, height, SBP, DBP, LDL-C, HbA1c, UA, Cr, BUN, and hs-CRP, the HR for CumAIP associated with progression to diabetes was 11.03 (3.76, 32.35), and the HR for regression to NFG was 0.40 (0.17, 0.96).

Dose-response relationship between CumAIP exposure and the development of prediabetes

In Fig. 2, we used RCS curves with 4 knots to flexibly model and visualize the relationship between CumAIP and the progression to diabetes and regression to NFG. It can be seen that, before and after adjusting for covariates,

CumAIP maintained a linear positive correlation with the progression to diabetes (Fig. 2) and a linear negative correlation with regression to NFG (Fig. 3).

While there was an overall linear negative correlation between CumAIP and regression of prediabetes to NFG, there seem to be special associations between both low and high levels of CumAIP and regression to NFG. Specifically, in the unadjusted model, Fig. 3a suggests that participants with very high CumAIP were again likely to regress to NFG. However, after fully adjusting for covariates, Fig. 3b shows that lower levels of CumAIP did not appear to show a tendency to regress to NFG. It is also important to mention that the confidence intervals for the association between CumAIP and regression to NFG were wide, spanning over/under the OR of 1 though most of the CumAIP range both in the adjusted and unadjusted setting.

Subgroup analysis

The association between CumAIP exposure and the development of prediabetes did not change with age, gender, registered residence, comorbidities (hypertension, CVD, stroke), education, and physical exercise or drug treatment during follow-up (Table 4). We only observed a significant interaction effect in the marital status subgroup, which showed that compared to married individuals, those in an unmarried state (including separated, divorced, widowed, or never married) had a relatively higher risk of CumAIP-related diabetes. Furthermore, the stratified analysis indicated that the use of antidiabetic drugs, antihypertensive drugs, as well as engaging in physical exercise during the follow-up, influenced the transition to pre-diabetic glycemic status. However, the wide confidence intervals and results from further interaction tests showed that these effects were not statistically significant.

Sensitivity analysis

When we analyzed the study population based on the WHO-recommended criteria, we observed similar results to those under the ADA criteria (Supplementary Table 6). The RCS with 5 knots showed similar linear association results to those with 4 knots (Supplementary Figs. 2 and 3). Finally, based on the results of Model 3, the E-values calculated were 9.03 (for progression to diabetes) and 3.16 (for regression to NFG).

Discussion

In this prospective cohort study involving middle-aged and elderly Chinese adults, we were the first to identify that high CumAIP exposure is a significant risk factor for the progression of prediabetes and is detrimental to the regression of prediabetes. Moreover, compared to unmarried individuals, being married significantly

Table 1 Summary of baseline characteristics of the study population according to CumAIP quartile group

	CumAIP quartile				*P*-value
	Q1(-0.14-0.06)	Q2(0.06–0.12)	Q3(0.12–0.18)	Q4(0.18–0.45)	
No. of subjects	735	734	735	735	
Age, years	60.72 (9.06)	60.20 (8.70)	58.98 (8.67)	57.61 (8.42)	< 0.001
SBP, mmHg	128.67 (21.22)	129.69 (20.29)	131.21 (21.55)	133.14 (20.06)	< 0.001
DBP, mmHg	73.65 (11.67)	75.48 (11.54)	77.15 (12.01)	78.95 (11.97)	< 0.001
Height, m	1.58 (0.08)	1.57 (0.09)	1.58 (0.08)	1.58 (0.09)	0.045
Weight, kg	55.30 (10.37)	58.33 (11.14)	61.98 (11.21)	65.28 (11.58)	< 0.001
TC, mg/dL	193.84 (34.61)	195.23 (39.91)	197.63 (37.63)	203.75 (39.66)	< 0.001
LDL-C, mg/dL	115.21 (95.10-132.41)	120.43 (100.90-144.97)	122.17 (101.68–147.10)	114.43 (91.43-139.95)	< 0.001
TG, mg/dL	66.38 (54.87–82.31)	92.92 (77.88-115.71)	126.56 (103.55-157.09)	206.21 (163.72-279.66)	< 0.001
HDL-C, mg/dL	64.95 (56.44-75.00)	52.96 (45.62–60.70)	46.39 (40.98–52.19)	36.73 (32.09–42.53)	< 0.001
hs-CRP, mg/L	0.75 (0.45–1.71)	0.85 (0.51–1.78)	1.16 (0.63–2.18)	1.31 (0.71–2.79)	0.091
Glucose, mmol/L	107.50 (7.02)	107.71 (8.04)	108.40 (7.93)	110.03 (8.16)	< 0.001
HbA1c, %	5.22 (0.41)	5.23 (0.42)	5.24 (0.42)	5.22 (0.44)	0.800
UA, mg/dL	4.13 (3.45–4.99)	4.16 (3.55–5.03)	4.40 (3.71–5.21)	4.62 (3.87–5.49)	< 0.001
Cr, mg/dL	0.75 (0.65–0.86)	0.75 (0.64–0.87)	0.76 (0.66–0.88)	0.76 (0.66–0.88)	0.405
BUN, mg/dL	15.80 (13.11–19.12)	15.08 (12.69–18.42)	14.96 (12.63–18.23)	14.82 (12.46–17.59)	< 0.001
Gender					< 0.001
Male	400 (54.42%)	344 (46.87%)	309 (42.04%)	304 (41.36%)	
Female	335 (45.58%)	390 (53.13%)	426 (57.96%)	431 (58.64%)	
Education, n (%)					0.031
Below primary	364 (49.52%)	371 (50.54%)	361 (49.12%)	321 (43.67%)	
Primary schools	176 (23.95%)	157 (21.39%)	160 (21.77%)	165 (22.45%)	
Middle school	150 (20.41%)	148 (20.16%)	143 (19.46%)	173 (23.54%)	
High school and above	45 (6.12%)	58 (7.90%)	71 (9.66%)	76 (10.34%)	
Marital status					0.012
Married	638 (86.80%)	628 (85.56%)	637 (86.67%)	668 (90.88%)	
Other	97 (13.20%)	106 (14.44%)	98 (13.33%)	67 (9.12%)	
Registered residence					< 0.001
Village	641 (87.21%)	619 (84.33%)	606 (82.45%)	578 (78.64%)	
City	94 (12.79%)	115 (15.67%)	129 (17.55%)	157 (21.36%)	
CVD					0.004
Yes	72 (9.80%)	95 (12.94%)	116 (15.78%)	109 (14.83%)	
No	663 (90.20%)	639 (87.06%)	619 (84.22%)	626 (85.17%)	
Stroke					0.033
Yes	9 (1.22%)	19 (2.59%)	16 (2.18%)	26 (3.54%)	
No	726 (98.78%)	715 (97.41%)	719 (97.82%)	709 (96.46%)	
Hypertension					< 0.001
No	480 (65.31%)	448 (61.04%)	430 (58.50%)	359 (48.84%)	
Yes	255 (34.69%)	286 (38.96%)	305 (41.50%)	376 (51.16%)	
Smoking status					0.007
Never	426 (57.96%)	466 (63.49%)	492 (66.94%)	473 (64.35%)	
Current	244 (33.20%)	213 (29.02%)	178 (24.22%)	196 (26.67%)	
Quit	65 (8.84%)	55 (7.49%)	65 (8.84%)	66 (8.98%)	
Drinking status					< 0.001
Current	235 (31.97%)	182 (24.80%)	160 (21.77%)	168 (22.86%)	
Never	454 (61.77%)	512 (69.75%)	533 (72.52%)	509 (69.25%)	
Quit	46 (6.26%)	40 (5.45%)	42 (5.71%)	58 (7.89%)	

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

SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides; UA, uric acid; BUN, blood urea nitrogen; Cr, creatinine; CumAIP, cumulative atherogenic index of plasma

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

	Glucose status during follow-up			*P*-value	G1 vs. G2 comparison	G1 vs. G3 comparison	G2 vs. G3 comparison
	Prediabetes to prediabetes (G1)	Prediabetes to diabetes (G2)	Prediabetes to NFG (G3)		*P*-value	*P*-value	*P*-value
No. of subjects	1842	447	650				
Age, years	59.59 (8.71)	60.39 (8.97)	58.10 (8.78)	< 0.001	0.194	< 0.001	< 0.001
SBP, mmHg	130.67 (21.16)	132.98 (19.39)	129.13 (20.83)	0.011	0.090	0.235	0.007
DBP, mmHg	76.09 (11.95)	77.63 (11.89)	76.02 (11.97)	0.040	0.039	0.991	0.073
Height, m	1.58 (0.09)	1.56 (0.08)	1.59 (0.08)	< 0.001	0.006	0.010	< 0.001
Weight, kg	59.79 (11.48)	62.19 (12.28)	60.10 (11.79)	< 0.001	< 0.001	0.822	0.010
TC, mg/dL	199.80 (38.37)	200.28 (37.23)	189.59 (37.26)	< 0.001	0.969	< 0.001	< 0.001
LDL-C, mg/dL	120.43 (98.58-143.33)	120.23 (99.74-142.85)	109.79 (89.40-133.18)	< 0.001	0.961	< 0.001	< 0.001
TG, mg/dL	109.74 (77.88-161.96)	115.94 (84.96-182.31)	104.43 (73.45-155.76)	0.016	0.008	0.243	0.001
HDL-C, mg/dL	49.87 (40.98–61.08)	46.39 (37.50-57.99)	49.29 (40.59–60.31)	< 0.001	< 0.001	0.497	0.015
hs-CRP, mg/L	1.02 (0.56–2.18)	1.23 (0.66–2.63)	0.85 (0.50–1.73)	0.006	0.001	0.002	< 0.001
Glucose, mmol/L	108.07 (7.52)	111.22 (9.41)	107.44 (7.19)	< 0.001	< 0.001	0.172	< 0.001
HbA1c, %	5.25 (0.41)	5.41 (0.43)	5.04 (0.36)	< 0.001	< 0.001	< 0.001	< 0.001
UA, mg/dL	4.32 (3.61–5.18)	4.43 (3.71–5.29)	4.32 (3.58–5.15)	0.251	0.415	0.732	0.229
Cr, mg/dL	0.75 (0.66–0.88)	0.75 (0.63–0.87)	0.77 (0.67–0.88)	0.091	0.428	0.284	0.078
BUN, mg/dL	15.15 (12.72–18.37)	14.57 (12.25–17.77)	15.45 (12.91–18.57)	0.015	0.031	0.648	0.013
CumAIP	0.13 (0.09)	0.15 (0.09)	0.12 (0.09)	< 0.001	< 0.001	0.041	< 0.001
Gender				< 0.001			
Male	838 (45.49%)	176 (39.37%)	343 (52.77%)				
Female	1004 (54.51%)	271 (60.63%)	307 (47.23%)				
Education, n (%)				0.090			
Below primary	893 (48.48%)	235 (52.57%)	289 (44.46%)				
Primary schools	413 (22.42%)	98 (21.92%)	147 (22.62%)				
Middle school	390 (21.17%)	76 (17.00%)	148 (22.77%)				
High school and above	146 (7.93%)	38 (8.50%)	66 (10.15%)				
Marital status				0.641			
Married	1615 (87.68%)	385 (86.13%)	571 (87.85%)				
Other	227 (12.32%)	62 (13.87%)	79 (12.15%)				
Registered residence				0.980			
Village	1530 (83.06%)	373 (83.45%)	541 (83.23%)				
City	312 (16.94%)	74 (16.55%)	109 (16.77%)				
CVD				< 0.001			
Yes	232 (12.60%)	87 (19.46%)	73 (11.23%)				
No	1610 (87.40%)	360 (80.54%)	577 (88.77%)				
Stroke				0.002			
Yes	35 (1.90%)	21 (4.70%)	14 (2.15%)				
No	1807 (98.10%)	426 (95.30%)	636 (97.85%)				
Hypertension				< 0.001			
No	1111 (60.31%)	209 (46.76%)	397 (61.08%)				
Yes	731 (39.69%)	238 (53.24%)	253 (38.92%)				
Smoking status				0.494			
Never	1164 (63.19%)	293 (65.55%)	400 (61.54%)				
Current	529 (28.72%)	114 (25.50%)	188 (28.92%)				
Quit	149 (8.09%)	40 (8.95%)	62 (9.54%)				
Drinking status				0.145			
Current	481 (26.11%)	93 (20.81%)	171 (26.31%)				

Table 2 (continued)

	Glucose status during follow-up			P-value	G1 vs. G2 comparison	G1 vs. G3 comparison	G2 vs. G3 comparison
	Prediabetes to prediabetes (G1)	Prediabetes to diabetes (G2)	Prediabetes to NFG (G3)		P-value	P-value	P-value
Never	1241 (67.37%)	323 (72.26%)	444 (68.31%)				
Quit	120 (6.51%)	31 (6.94%)	35 (5.38%)				

Quantitative variables were expressed as mean (standard deviation) or medians (quartile interval), and the differences among groups were evaluated by the Kruskal Wallis H test and Steel Dwass test or one-way ANOVA and Tukey's HSD test; qualitative variables were presented as frequencies and percentages, and the chi-square test will be used to examine differences between groups;

SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides; UA, uric acid; BUN, blood urea nitrogen; Cr, creatinine; CumAIP, cumulative atherogenic index of plasma

Table 3 Multivariate Cox regression analysis of the role of CumAIP in assessing changes in glycemic status in patients with prediabetes

		HR (95% CI)		
	No of case	Model 1	Model 2	Model 3
Prediabetes to diabetes				
CumAIP		18.36 (6.80, 49.54)	11.70 (4.21, 32.51)	11.03 (3.76, 32.35)
CumAIP (quartile)				
Q1	78 (10.61%)	1.0	1.0	1.0
Q2	100 (13.62%)	1.29 (0.96, 1.74)	1.22 (0.90, 1.64)	1.18 (0.87, 1.59)
Q3	115 (15.65%)	1.51 (1.13, 2.02)	1.42 (1.06, 1.90)	1.34 (1.00, 1.80)
Q4	154 (20.95%)	2.09 (1.59, 2.75)	1.86 (1.40, 2.46)	1.76 (1.32, 2.34)
P-trend		< 0.0001	< 0.0001	< 0.0001
Prediabetes to NFG				
CumAIP		0.38 (0.16, 0.91)	0.39 (0.16, 0.96)	0.40 (0.17, 0.96)
CumAIP (quartile)				
Q1	173 (23.54%)	1.0	1.0	1.0
Q2	174 (23.71%)	1.00 (0.81, 1.23)	1.00 (0.81, 1.24)	1.06 (0.85, 1.31)
Q3	163 (22.18%)	0.91 (0.73, 1.13)	0.91 (0.73, 1.13)	0.98 (0.79, 1.23)
Q4	140 (19.05%)	0.76 (0.61, 0.96)	0.77 (0.61, 0.97)	0.79 (0.62, 0.99)
P-trend		0.0138	0.0190	0.0402

HR: hazard ratios; CI: confidence interval; other abbreviations as in Table 1

Model 1 adjust for age, gender, education, registered residence;

Model 2 adjust for age, gender, education, registered residence, heart problem, stroke, hypertension, smoking status, drinking status, height, SBP, DBP

Model 3 adjust for age, gender, education, registered residence, heart problem, stroke, hypertension, smoking status, drinking status, height, SBP, DBP, LDL-C, HbA1c, UA, Cr, BUN, CRP

reduces the risk of prediabetes progression associated with high CumAIP exposure.

With the rapid global aging population [32], atherosclerosis is becoming increasingly prevalent [33, 34]. Previous studies have shown that AIP, representing atherosclerosis, is closely associated with prediabetes and diabetes [16–21], and further follow-up studies have indicated a nonlinear relationship between AIP and prediabetes and diabetes [17, 22]. Additionally, recent research has emphasized the clinical application potential of AIP in glycemic metabolic diseases. Studies have shown that AIP can be directly used for risk assessment of diabetes and prediabetes [17–20, 22] and for evaluating cardiovascular and metabolic complications in diabetic patients [35–38]. Despite the substantial evidence highlighting the importance of AIP in adult glycemic metabolic diseases, a limitation of previous studies is that they assessed AIP at a single time point, lacking repeated measurements of AIP. This has hindered a more comprehensive understanding of how changes in AIP affect disease progression. Notably, in a recent cohort study, Yi et al. conducted a bold design to investigate the impact of AIP transition patterns on diabetes [39]. They categorized baseline and follow-up AIP into low and high groups based on specific cutoff values and examined the effects of four transition patterns (maintaining high, maintaining low, high to low, and low to high) on diabetes. The study found that maintaining high AIP, high to low AIP, and low to high AIP transition patterns were positively associated with diabetes occurrence. However, the finding that the high to low AIP transition pattern was identified as a risk factor for diabetes warrants further verification, as it seems counterintuitive. We believe this particular result reported by Yi et al. is primarily related to the cutoff values used for AIP, where minor changes around the cutoff values could significantly affect the AIP transition patterns and further impact the study results. In the current study, we adopted an approach similar to some previous studies [24, 40, 41], combining baseline and repeated measurements of AIP with follow-up duration to calculate the continuous variable CumAIP. Our results showed that high CumAIP exposure was associated with a higher risk of diabetes,
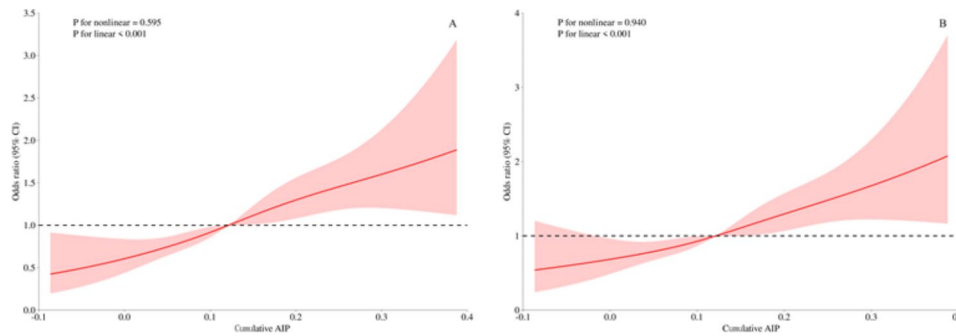
Fig. 2 Visualizing the relationship between CumAIP and progression from prediabetes to diabetes using 4-knots RCS (A: unadjusted; B: adjusted). CumAIP: cumulative atherogenic index of plasma; RCS: restricted cubic spline
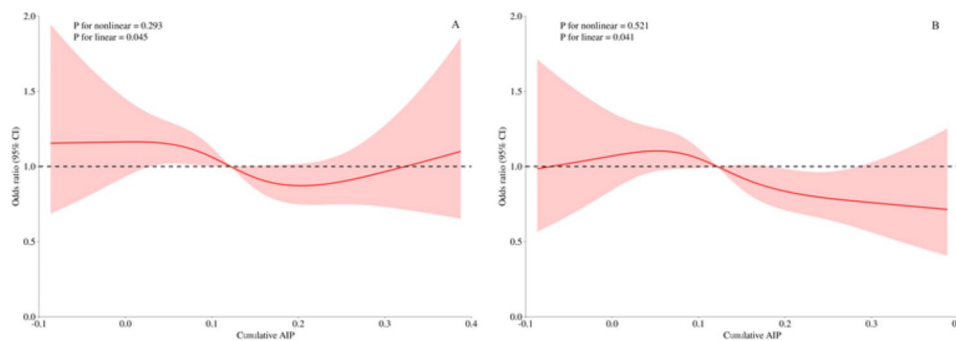
Fig. 3 Visualizing the relationship between CumAIP and regression of prediabetes to NFG using 4-knots RCS (A: unadjusted; B: adjusted). CumAIP: cumulative atherogenic index of plasma; RCS: restricted cubic spline

providing more direct evidence that monitoring and maintaining appropriate AIP levels is crucial for diabetes prevention.

Most previous studies on the development of prediabetes have focused on the progression to diabetes [42–44]. However, it is also important to note that the regression of prediabetes deserves attention as it is closely associated with reduced risks of diabetes and related complications [2, 7–9]. The progression and regression rates of prediabetes largely depend on the criteria used, which remains a significant challenge in this field [2]. The ADA criteria are the most inclusive, while the International Expert Committee and WHO criteria are more restrictive [45]. According to ADA criteria, a recent meta-analysis of 103 prospective studies reported that 18% of prediabetic patients progressed to diabetes within five years [6, 8]. Furthermore, another meta-analysis in 2022, based on 35 randomized controlled trials (RCTs) involving 10,164 prediabetic adults, showed that 31% of participants regressed to NFG within 1.6 years [9]. In the current national survey data based on CHARLS, 15.21% of prediabetic patients progressed to diabetes, and 22.12% regressed to NFG during a median follow-up of three years. Regarding diabetes progression, our study's data are similar to international analysis results. However, the regression rate to NFG in our analysis is slightly lower than in the meta-analysis data [9]. We

believe this is due to several reasons: (1) Compared to RCTs [9], our study is observational and did not include interventions specific to the study population. Instead, our findings are more reflective of the real-world situation in China. (2) Our study primarily involved middle-aged and elderly individuals, who are generally older and may have poorer metabolic conditions [1]. (3) Our analysis did not include oral glucose tolerance test data, which could lead to the omission of some patients with impaired glucose tolerance [45]. In this study, we also investigated the association between CumAIP exposure and prediabetes regression. Multivariate Cox regression showed a negative correlation, which further RCS analyses confirmed to be linear. Notably, in the dose-response relationship plots, the RCS analyses with both knots 4 and 5 showed wide confidence intervals for the associations between CumAIP and regression to NFG. Most of the CumAIP-related HRs crossed the reference line both before and after adjustments, regardless of whether the levels of CumAIP were high or low. These findings suggest that the use of CumAIP in assessing regression to NFG involves some uncertainty, and the results are relatively unstable. Regarding the RCS analysis results of CumAIP and regression to NFG, we have the following considerations: (1) Compared with the diagnostic criteria for diabetes, the threshold for diagnosing prediabetes based on blood glucose parameters is relatively loose,

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

	HR (95% CI)	
	Prediabetes to NFG	Prediabetes to diabetes
Gender		
Male	0.51 (0.16, 1.68)	7.06 (1.35, 36.84)
Female	0.39 (0.11, 1.39)	13.84 (3.39, 56.48)
P-interaction	0.7473	0.5314
Age, years		
45–59	0.77 (0.26, 2.27)	6.62 (1.47, 29.94)
≥ 60	0.15 (0.03, 0.64)	17.03 (3.71, 78.11)
P-interaction	0.0708	0.3846
Education, n (%)		
Below primary	0.55 (0.15, 2.05)	15.15 (3.52, 65.13)
Primary schools	0.12 (0.02, 0.69)	11.19 (1.33, 94.35)
Middle school	1.01 (0.19, 5.44)	5.40 (0.46, 62.97)
High school and above	0.21 (0.01, 2.90)	6.87 (0.20, 238.32)
P-interaction	0.3088	0.8969
Marital status		
Married	0.46 (0.18, 1.14)	7.54 (2.40, 23.75)
Other	0.13 (0.01, 1.89)	184.83 (9.61, 3554.36)
P-interaction	0.3809	0.0492
Registered residence		
Village	0.42 (0.16, 1.08)	9.47 (2.97, 30.22)
City	0.33 (0.04, 2.70)	26.39 (1.81, 384.91)
P-interaction	0.8287	0.4861
Antidiabetic drugs		
Yes	inf (0.00, Inf)	0.07 (0.00, 17.41)
No	inf (0.00, Inf)	1.56 (0.03, 96.56)
P-interaction	1.00	0.3806
Antihypertensive drugs		
Yes	0.31 (0.05, 1.96)	0.32 (0.01, 10.39)
No	0.61 (0.04, 10.53)	11.30 (1.99, 64.25)
P-interaction	0.6930	0.6240
Physical exercise		
No activity	0.74 (0.02, 29.07)	21.38 (0.50, 913.76)
Light activity	0.21 (0.02, 2.80)	25.86 (1.04, 643.47)
Moderate activity	0.35 (0.04, 2.72)	9.45 (0.49, 181.91)
Intensive activity	0.32 (0.04, 2.55)	79.39 (6.63, 950.45)
P-interaction	0.9593	0.7377
Hypertension		
No	0.39 (0.13, 1.17)	17.68 (3.85, 81.21)
Yes	0.43 (0.11, 1.66)	7.27 (1.71, 30.85)
P-interaction	0.8988	0.3955
Heart Problems		
Yes	1.02 (0.07, 14.57)	12.83 (1.18, 139.25)
No	0.36 (0.15, 0.91)	10.66 (3.28, 34.62)
P-interaction	0.4705	0.8893
Stroke		
Yes	7.99 (0.03, 2078.50)	1.01 (0.01, 103.16)

Table 4 (continued)

	HR (95% CI)	
	Prediabetes to NFG	Prediabetes to diabetes
No	0.38 (0.16, 0.91)	12.62 (4.19, 38.04)
P-interaction	0.4330	0.2893

HR: hazard ratios; CI: confidence interval; inf: infinite; other abbreviations as in Table 1

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

which may lead to some subjects who actually have normal blood glucose metabolism to be inappropriately classified as prediabetic patiens; It is necessary to improve and unify the criteria for prediabetes diagnosis as soon as possible [45], and then verify the current research results according to the latest standards. (2) The exclusion of a larger number of subjects with missing blood measurement information in the current study may somewhat contribute to the relative lack of sample size leading to a decrease in test efficacy, and validation of the results in further large sample cohorts is needed.

After establishing the relationship between CumAIP exposure and the progression or reversal of prediabetes in middle-aged and elderly populations, we further investigated the differences in this association among various subgroups. The results of the study showed that no significant specific population dependencies in almost all subgroups, indicating that the current findings are relatively stable, which was further confirmed by sensitivity analyses. However, we did find some notable differences within the marital status subgroup. Specifically, compared to married individuals, those who were unmarried (including separated, divorced, widowed, or never married) had a relatively higher risk of CumAIP-related diabetes. Previous studies have shown that being unmarried or having a poor marital relationship significantly increases atherosclerotic burden [46, 47] and negatively impacts cardiovascular health [48]. Additionally, evidence from the United States and Korea suggests that being unmarried also significantly promotes glucose deterioration and adverse metabolic outcomes [49, 50]. These findings provide context for our results, indicating that being unmarried may influence diabetes progression through atherosclerosis and glucose metabolism. These results suggest that marital status should be considered in diabetes risk assessment, and further research into atherosclerosis-related diabetes outcomes based on marital status is warranted.

The high prevalence and rapid growth of prediabetes worldwide have imposed a significant burden on society [2, 3]. Despite numerous RCTs indicating the potential of pharmacological treatments for prediabetes [9], no drugs have been approved for prediabetes treatment by regulatory agencies. Current evidence and clinical policies

favor lifestyle changes for prediabetes management [26, 51], underscoring the importance of effectively implementing diabetes prevention strategies. In the current study, we also investigated the relative impact of physical exercise on the evolution of prediabetes during the follow-up period. Although the final interaction analyses did not detect significant modulatory effects, results from stratified analyses suggest that moderate activity may help reduce the risk of diabetes associated with CumAIP, whereas intensive activity appears to hinder diabetes prevention. Additionally, our study found that any level of physical exercise promotes the regression of CumAIP-related prediabetes. Similar findings have been reported in several previously conducted RCTs [52–55]. Overall, physical exercise can improve the progression of various chronic diseases and has a beneficial effect on glycaemic control in prediabetic patients [56]. Although conclusive evidence is lacking on the impact of physical exercise on CumAIP-related glycemic metabolism, from a pathophysiological perspective, atherosclerosis results from the interaction between metabolic and inflammatory pathways. Exercise can beneficially modulate these pathways, including lipid, inflammatory, and glucose metabolism [56]. Therefore, findings of the current study can be interpreted as moderate physical exercise exerting a beneficial effect on atherosclerosis, which may, in turn, promote favourable changes in glycaemic metabolism. Of course, the impact of physical exercise is multifaceted, as it influences both atherosclerosis and glycaemic metabolism, creating a positive feedback loop that prevents the progression of various chronic diseases.

The significance of the current study lies in further clarifying the impact of changes in AIP over follow-up periods on the development of prediabetes, building on previous research. High exposure to CumAIP during the follow-up period may reflect an important factor indicating ongoing adverse metabolic conditions. Given the simplicity and convenience of calculating and obtaining CumAIP [16], along with its crucial role in assessing cardiovascular and cerebrovascular diseases risk [24, 40, 57] and its relevance to glycaemic metabolic disorders, CumAIP holds significant potential for clinical applications and prognostic evaluation. China currently bears one of the highest global burdens of atherosclerotic disease, making the use of simple tools to quantify cumulative atherosclerotic exposure particularly significant [58, 59]. We believe that incorporating CumAIP into clinical practice could be instrumental in reducing the burden of atherosclerotic diseases and could inform primary prevention strategies for the regression of prediabetes. It is important to note that calculating CumAIP is a straightforward task for clinicians, with the main challenge being the repeated measurement of AIP. This is due to the relatively low rate of annual physical examination

(APE) among middle-aged and elderly populations in China, which ranges from approximately 35–65%, with significant regional and urban-rural disparities [60–62]. Despite free APE services being available to older adults in China, a considerable proportion of them do not utilize these services, highlighting the importance of identifying barriers to APE uptake. It is recommended that government agencies establish health consultation centers for middle-aged and elderly individuals in communities and rural areas, enhance health education, and raise awareness of the importance of APE. In addition to the difficulty in obtaining repeated AIP measurements, there are currently no clear recommendations for maintaining appropriate CumAIP levels, as related studies remain limited and further research is needed.

Strengths and limitations

This study has several strengths, including its prospective design and dynamic assessment methods, which elucidate the association between atherosclerosis fluctuations and the development of prediabetes, thus enhancing its clinical significance. Additionally, the design involving repeated measurements of AIP adds a novel aspect to the study.

However, there are several limitations to consider when interpreting our results: (i) The diagnosis of prediabetes in the current analysis did not include oral glucose tolerance test data, potentially missing some patients with impaired glucose tolerance [45], which could lead to an underestimation of both the incidence of diabetes and the regression rate to NFG [45]. (ii) A substantial number of participants were excluded due to missing blood glucose data, which may introduce sampling bias. (iii) Considering the increasing trend of atherosclerosis in younger populations, our findings may also apply to younger adults, adolescents, and children [11, 63], but caution is needed when extrapolating our results based on middle-aged and elderly populations.

(iv) The study participants were Chinese, so caution is required when applying these findings to other racial or ethnic groups. (v) As with all observational studies, despite our efforts to account for relevant confounders, some residual confounding factors may still be present. Nonetheless, sensitivity analyses estimating the minimum E-value needed to account for unmeasured confounders indicated that our findings are relatively robust. (vi) Since this is a non-interventional study, we cannot infer the specific impact of lifestyle interventions on the progression and regression of prediabetes associated with cumulative CumAIP. (vii) Since the Wave 3 survey did not include information on lipid-lowering drug use, the impact of these drugs on the development of CumAIP-associated prediabetes during follow-up could not be assessed in this analysis. In addition, we only

obtained information on the use of antihypertensive drugs, antidiabetic drugs, and physical exercise information during follow-up for no more than half of the subjects, which brought certain obstacles to the production of meaningful results in subgroup analysis and also further research is needed. (viii) The first wave of CHARLS national data was applied as the baseline information in the current study. Since prediabetes was diagnosed based on blood glucose measurement parameters and the questionnaire lacked detailed data on the history of prediabetes, the duration of prediabetes in the study population could not be confirmed in the current study for the time being, which is an important help for further interpretation of the results [9], and further research is needed. (ix) Estimates of CumAIP for the current study were calculated using AIP data from waves 1 and 3. Although this cumulative exposure assessment method has been widely used in many studies [24, 40, 41], it should be noted that the calculation of CumAIP includes measurement data at the time of the study outcome, which may influence the results and necessitates further prospective research.

Conclusion

This prospective cohort study of middle-aged and elderly Chinese adults demonstrates that CumAIP is closely associated with the progression and regression of prediabetes. High CumAIP exposure increases the risk of prediabetes progression and hinders its regression. These findings suggest that monitoring and maintaining appropriate AIP levels may help prevent the deterioration of blood glucose levels.

Abbreviations

CumAIP	Cumulative atherogenic index of plasma
CHARLS	China Health and Retirement Longitudinal Study
RCS	Restricted cubic spline
NFG	Normal fasting glucose
HR	Hazard ratio
CI	Confidence interval
ADA	American Diabetes Association
TG	Triglycerides
vLDL-C	Very low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
Hb	Hemoglobin
CVD	Cardiovascular disease
FPG	Fasting plasma glucose
RPG	Random plasma glucose
TC	Total cholesterol (TC)
BUN	Blood urea nitrogen
hs-CRP	High-sensitivity C-reactive protein
UA	Uric acid
Cr	Creatinine
SBP	Systolic blood pressure
DBP	diastolic blood pressure
WHO	World Health Organization
RCTs	Randomized controlled trials
APE	Annual physical examination

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02449-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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 entire study process adhered to the Declaration of Helsinki, and the study results were reported following the STROBE guidelines. The protocol for the CHARLS cohort was authorized by the Ethics Review Committee of Peking University (IRB00001052–11015), and all participants provided written informed consent at the time of participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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