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Association between atherogenic index of plasma and future risk of cardiovascular disease in individuals with cardiovascular-kidney-metabolic syndrome stages 0–3: a nationwide prospective cohort study

Gaoshu Zheng[1†], Jijie Jin[2†], Fei Wang[2†], Qianrong Zheng[2], Jiaxin Shao[2], Jiangnan Yao[2], Pan Huang[2*], Hao Zhou[1*] and Jianghua Zhou[1*]

Abstract

Background As an emerging concept, Cardiovascular-kidney-metabolic syndrome (CKM) elucidates the intricate interconnection between metabolic disorders(Mets), cardiovascular disease(CVD), and chronic kidney disease(CKD). Within this context, while numerous studies have demonstrated a correlation between the Atherogenic Index of Plasma (AIP) and CVD, the precise relationship between long-term fluctuations in the AIP and the incidence of CVD in patients with CKM syndrome remains unclear.

Method The CKM stages 0–3 population was obtained from the China Health and Retirement Longitudinal Study (CHARLS). The outcome CVD was defined as self-reported heart disease and/or stroke. AIP control level was classified using k-mean cluster analysis. Logistic regression was used to analyse the effect of cumulative AIP (cumAIP) on the incidence of CVD. Restricted cubic spline models (RCS) were used to explore the potential non-linear relationship between cumulative AIP and CVD risk at different CKM syndrome stages.

Results Of the 3429 CKM stages 0–3 participants, 620 patients developed CVD during the 3-year follow-up period. After adjusting for various confounders, the odds ratio (OR) for the well-controlled class 2 compared with the best AIP control class 1 were 1.37 (1.04, 1.81), the OR for the moderately-controlled class 3 were 1.54 (95% CI, 1.04–2.26), the poorly-controlled class 4 were 1.65 (95% CI, 1.13–2.41), and the worst-controlled class 5 were 2.14 (95% CI, 1.15–3.97).

†Gaoshu Zheng, Jijie Jin and Fei Wang contributed equally to this work.

*Correspondence:
Pan Huang
hpzyqzjh@wmu.edu.cn
Hao Zhou
wyzhouhao66@163.com
Jianghua Zhou
zhoujianghua@wmu.edu.cn

Full list of author information is available at the end of the article

In restricted cubic spline regression analyses, changes in AIP were linearly associated with the occurrence of CVD events. Further weighted quartiles and regression analyses indicated that triglyceride(TG) was a key variable for AIP in predicting CVD events in the CKM stages 0–3 population.

Conclusions Poor control level of AIP are associated with an increased risk of CVD events in the population of CKM stages 0–3. Long-term dynamic monitoring of changes in AIP may help in the early identification of patients at high risk of developing CVD in the individuals with CKM stages 0–3.

Keywords Atherogenic index of plasma, Cardiovascular-renal-metabolic syndrome, Cardiovascular disease

Introduction

With the increasingly close relationship among metabolic disease(Mets), cardiovascular disease(CVD), and chronic kidney disease(CKD), the American Heart Association (AHA) recently proposed the concept of Cardiovascular-kidney-metabolic syndrome (CKM), which is a multidirectional association between metabolic risk factors, CKD, and the cardiovascular system, eventually leading to adverse cardiovascular outcomes and increased multiple organ dysfunction [1]. Nowadays, more and more studies support the concept of CKM syndrome, emphasizing the complex interaction among these three, which is the current research hotspot and frontier [2]. Substantial epidemiologic data indicate that absolute CVD risk increases as CKM progresses from stage 0 to stage 3 [3]. Data show that more than 25% of Americans are likely to have CKM syndrome between 2015 and 2020, and more than 75% of healthcare costs will be spent on treating their associated conditions [4, 5]. The greatest clinical burden of CKM syndrome is disproportionately associated with CVD [6]. Therefore, the AHA emphasizes that studies in the CKM 0–3 population should focus on the prevention of CVD events [7], emphasizing the urgency of treating the three diseases as a whole to prevent CVD events.

The atherogenic index of plasma (AIP), a powerful predictive marker for CVD, diabetes, Mets, and CKD [8–13], is calculated from the log-transformed ratio of the molar concentrations of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-c) [14], and a study by Alifu et al. noted that high AIP increased the risk of major adverse cardiovascular events by 8-fold, demonstrating the significant predictive power of AIP on the prognosis of CVD patients [15].

Although many studies have validated the role of the AIP in the development of CVD, including myocardial infarction and coronary heart disease, as well as in the prognosis of patients [8, 11, 12, 16]. An inherent limitation of these studies is that the AIP is usually assessed at a single point in time, without analysing the relationship between changes in the dynamics of AIP and CVD during individual follow-up, which may not reflect the long-term exposure. There are relatively few studies on the longitudinal effects of repeated measures of the AIP on CVD risk. In the existing research, only a few studies have explored the association between changes in the AIP and the occurrence of CVD [14, 17]. However, studies on the association between long-term changes in the AIP and the occurrence of CVD in the CKM stages 0–3 population are still insufficient.

Here, this study evaluated the predictive ability of the control level of the AIP on the risk of CVD occurrence in the CKM stages 0–3 population using data from the China Health and Aged Care Longitudinal Study (CHARLS), with the aim of providing new perspectives on the early intervention and prevention strategies for patients with CKM syndrome stages 0–3.

Methods

Study population

The CHARLS is a long-term follow-up survey targeting Chinese adults aged 45 years and above. Its primary goal is to collect high-quality micro-data related to the aging status of China's population. Organized and conducted by the Chinese Academy of Social Sciences, Peking University, and other institutions [18]. CHARLS began as a national baseline survey in 2011. Since then, participants have been followed up every two years, resulting in five rounds of data collection to date (2011, 2013, 2015, 2018, and 2020). The dataset includes demographic information, results from 13 medical examinations, and analyses of blood samples [19]. The study adhered to the principles of the Declaration of Helsinki and received approval from the Biomedical Ethics Review Board of Peking University (IRB 000010052–11, 015). All field workers underwent systematic professional training and conducted face-to-face interviews using standardized questionnaires [19]. Written informed consent was obtained from all participants prior to their inclusion in the study. Further details about CHARLS are available on its official website (http://charls.pku.edu.cn/en).

In this study, wave 3 (2015) was set as the baseline. We used data from the baseline survey and wave 1 (2011) to evaluate dynamic changes in AIP, while subsequent follow-up surveys were utilized to track outcomes up to wave 5 (2020). Figure S1 presents the study population selection process. Of the 19,719 participants aged 45 years and above, we excluded 12,806 participants for the

following reasons: (1) lack of blood test data in both 2011 and 2015, (2) inability to calculate AIP, and (3) inability to define CKM syndrome stage. Additionally, 2,385 participants with CVD at baseline or who were lost to follow-up and 1,099 participants with missing baseline characteristic data were excluded. Finally, 3,429 eligible participants were included in the analysis.

Data assessment

Determination of CVD and calculation of AIP

In this study, we calculated the AIP by taking the logarithm of the ratio of TG to HDL-c obtained from blood samples collected at waves 1 and 3. Using these AIP values, we performed K-means cluster analysis to identify distinct patterns of AIP variation over time among the participants.

The exposure factor in this study was the changes in AIP from 2012 to 2015, and the cumulative AIP(cumAIP) was calculated as $(AIP_{2012} + AIP_{2015})/ 2 * (2015 - 2012)$ for assessing the impact of AIP changes on CVD incidence [17].

The outcome in this study was the incidence of CVD. In according to previous studies [20–22], incident CVD events were assessed by the following standardized questions: "Have you been told by a doctor that you have been diagnosed with a heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems?" or "Have you been told by a doctor that you have been diagnosed with a stroke?" Participants who reported heart disease or stroke during the follow-up period were defined as having incident CVD. Additionally, if a participant indicated a heart attack or stroke at a previous round of follow-up, they were required to verify the presence of CVD at a later round of follow-up. If participants denied a previous self-reported diagnosis of heart disease or stroke, these inconsistencies were corrected retrospectively. Our diagnoses of CVD were consistent with previous studies using CHARLS [20–22].

Definition of CKM syndrome stages 0 to 4

According to the American Heart Association Presidential Advisory Statement [1], CKM syndrome stages 0–4 are specified as follows: stage 0: no CKM health risk factors; stage 1: abdominal obesity and/or prediabetes; stage 2: metabolic disorders (type 2 diabetes mellitus, hypertension, and high triglycerides) or renal disorders; stage 3: subclinical CVD in the context of the CKM syndrome; stage 4: clinical CVD (coronary heart disease, heart failure, stroke, peripheral artery disease, atrial fibrillation) in CKM.

Data collection

The baseline survey collected demographic information such as age, gender, place of residence, education and marital status. Anthropometric measurements including body mass index (BMI), waist circumference(WC), diastolic blood pressure(DBP) and systolic blood pressure(SBP) were also taken. Related diseases and treatment factors included diabetes, antidiabetic treatment, dyslipidemia, antihyperlipidemic treatment, cancer, liver disease, CVD and CKM stage. Data on current alcohol consumption and smoking were also recorded. As part of the laboratory assessment, a number of blood chemistries were also collected, including total cholesterol (TC), TG, blood urea nitrogen (BUN), uric acid (UA), C-reactive protein (CRP), HDL-c, serum creatinine(Scr), fasting blood glucose (FBG) and glycated haemoglobin (HbA1c) AIP and cumAIP was assessed by further calculations.

Subjects were classified as hypertensive if they had a documented history of hypertension, had a SBP of 130 mmHg or greater, a DBP of 80 mmHg or greater, or were taking antihypertensive medication at the time of the baseline assessment [23].

Participants were diagnosed with diabetes if they had an FBG of 7.0 mmol/L (126 mg/dL) or greater, an HbA1c of 6.5% or greater, or had a history of diabetes or were being treated for diabetes [24].

Statistical analysis

K-means clustering is a rule-based method for determining the distance between data items (Fig. 1A). The advantage of this method is that it is simple and scalable. In our study, K-means clustering performed best when the number of clusters is equal to 5 [25, 26]. The specific groupings are as follows: Class 1: AIP increased slightly from 0.02 in 2012 to 0.05 in 2015, with a cumAIP of 0.09 ± 0.33, indicating that the AIP level has always remained in a low range with the best control; Class 2: AIP increased from 0.14 in 2012 to 0.35 in 2015, with a cumAIP of 0.75 ± 0.24, indicating that the AIP level was within the medium range with a slow upward trend, and the control was better; Class 3: AIP decreased from 0.51 in 2012 to 0.29 in 2015, with a cumAIP of 1.20 ± 0.31. Even though the AIP level had decreased from high to low, due to the higher AIP level in the early period, its cumAIP was higher than class 2, indicating a medium control effect; Class 4: AIP slightly increased from 0.49 in 2012 to 0.65 in 2015, with a cumAIP of 1.70 ± 0.28, indicating that the AIP level has been in the higher range for a long time, and the control is poor; Class 5: AIP decreased from 0.97 in 2012 to 0.84 in 2015, with a cumAIP of 2.71 ± 0.46, indicating that the AIP levels were always in the highest range and the control was the worst (Fig. 1B).

Descriptive statistics (mean and standard deviation SD for continuous data, percentages for categorical data) were used to report the basic characteristics of the data. The normality of continuous variables was tested by Kolmogorov-Smirnov test, and the skewed distribution

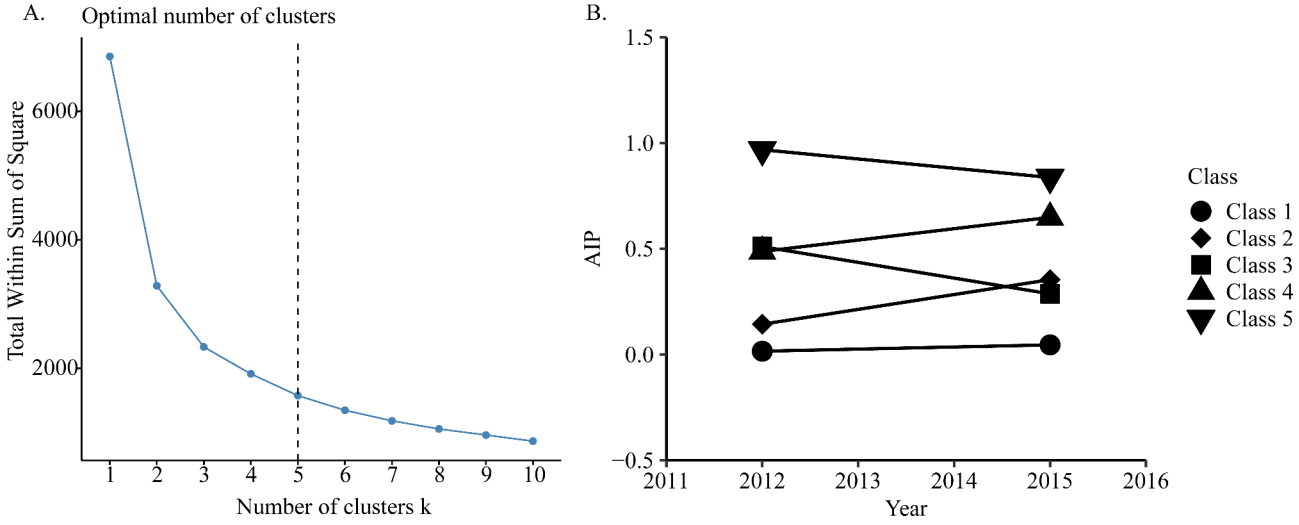

Fig. 1 **A** K-means clustering method for clustering the atherosclerosis index of plasma; **B** The AIP clustering by k-means clustering

variable CRP was expressed as median and interquartile range. One-way analysis of variance, Kruskal-Wallis H test (skewed distribution variables), and chi-square test were used for comparison between groups.

We analyzed the association between cumulative and AIP changes and the risk of CVD using univariate and multivariate logistic regression models. To explore the potential nonlinear relationship between cumulative AIP and CVD risk in the CKM syndrome stages 0–3 population, as well as in the CKM stages 0–2 (early) and CKM stage 3 (late) populations [27, 28], we used the restricted cubic spline (RCS) regression model to analyze the odds ratio (OR). At the same time, to explore the relationship between cumulative and AIP changes and CVD risk in different demographics, subgroup and interaction analyses were performed in different age groups (<60 years and ≥60 years), sex, place of residence, marital status, smoking status, drinking status, and different CKM syndrome stages. In the multicollinearity test (Table S1), the results showed that the variance inflation factor of each covariate was less than 5, indicating that there was no significant multicollinearity between the covariates.

In addition, the AIP was derived using a mathematical formula for the TG and HDL-c variables. In order to fully explain the formula, we employed a weighted quantile sum (WQS) regression model with 1000 iterations using the bootstrap resampling method. The WQS model helps to determine the weights assigned to TG and HDL-c, quantifying their respective contributions to the overall effect. These weights were restricted to a range of 0 to 1, with a cumulative sum of 1. Higher weights indicate greater importance of the corresponding metrics in the prediction of the CVD.

All analyses were performed using R statistical software version 4.2.2 (R Foundation), and a two-sided $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of study participants

According to the inclusion and exclusion criteria, a total of 3,participants were included in the analysis of AIP changes. After an average follow-up of 5 years, 620 participants eventually developed CVD. Their baseline characteristics are shown in Table 1. The average age of the participants was 61.12 ± 8.50 years old, and males accounted for 45.49%. The mean AIP of the study population was 0.34 ± 0.33 in 2012 and 0.38 ± 0.28 in 2015, and the cumAIP was 1.07 ± 0.83.

Taking class as the reference group, it was observed that participants in other classes had lower drinking rates and lower levels of BUN, Scr, and HDL-c. In addition, the prevalence of liver disease was lower in participants in these classes. The levels of SBP, DBP, BMI, WC, TG, TC, UA, FBG and HbA1c were all high. At the same time, the prevalence of diabetes, dyslipidemia and cancer was high

The impact of changes in AIP on the incidence of CVD among individuals with CKM syndrome stages 0–3

The association of changes in AIP with risk of CVD was assessed using logistic regression models in a study population with CKM syndrome stages 0–Results showed that changes in AIP had significant effects on CVD risk, and this association remained statistically significant after multivariable adjustment (model II and Model III). In unadjusted model I, CVD risk was significantly increased in Class 5, the worst-controlled AIP group, compared with class 1, the best-controlled group (OR: 1.91, 95% CI: 1.38–2.64, $P<0.001$). In the fully adjusted model IV, the

Table 1 Baseline characteristics by categories of AIP change among individuals with CKM syndrome stages 0–3

Characteristics	Total (*n* = 3429)	Class 1 (*n* = 806)	Class 2 (*n* = 876)	Class 3 (*n* = 699)	Class 4 (*n* = 722)	Class 5 (*n* = 326)	*P* value
Age, Mean ± SD	61.12 ± 8.50	62.24 ± 8.58	60.91 ± 8.89	61.40 ± 8.16	60.19 ± 8.34	60.39 ± 8.05	< 0.001
Male, n(%)	1560 (45.49)	424 (52.61)	386 (44.06)	321 (45.92)	289 (40.03)	140 (42.94)	< 0.001
Married, n(%)	2897 (84.49)	681 (84.49)	734 (83.79)	586 (83.83)	608 (84.21)	288 (88.34)	0.368
Rural residence, n(%)	2350 (68.53)	607 (75.31)	606 (69.18)	472 (67.53)	474 (65.65)	191 (58.59)	< 0.001
Educational attainment, n(%)							0.080
Elementary school or below	2362 (68.88)	562 (69.73)	628 (71.69)	478 (68.38)	486 (67.31)	208 (63.80)	
Middle school or above	1067 (31.12)	244 (30.27)	248 (28.31)	221 (31.62)	236 (32.69)	118 (36.20)	
SBP (mmHg)	126.74 ± 19.60	123.81 ± 18.89	125.49 ± 19.92	127.51 ± 19.94	128.63 ± 18.65	131.56 ± 20.42	< 0.001
DBP (mmHg)	74.84 ± 11.78	72.79 ± 11.38	74.10 ± 11.91	74.62 ± 10.83	76.74 ± 12.06	78.14 ± 12.45	< 0.001
BMI (kg/m2)	24.26 ± 18.20	22.20 ± 10.43	23.70 ± 9.10	24.86 ± 27.00	26.03 ± 25.11	25.63 ± 3.94	< 0.001
WC (cm)	84.26 ± 13.34	77.51 ± 14.42	83.02 ± 13.08	84.87 ± 12.52	89.61 ± 10.43	91.14 ± 9.72	< 0.001
TG (mg/dL)	140.53 ± 89.56	71.05 ± 17.16	118.02 ± 33.08	102.96 ± 26.87	207.58 ± 72.34	304.82 ± 119.74	< 0.001
TC (mg/dL)	185.62 ± 36.63	180.89 ± 32.46	182.81 ± 33.26	183.88 ± 34.82	190.67 ± 37.01	197.46 ± 51.41	< 0.001
BUN(mg/dL)	15.69 ± 4.59	16.41 ± 5.00	15.53 ± 4.46	15.98 ± 4.73	14.98 ± 4.19	15.28 ± 4.04	< 0.001
UA(mg/dL)	4.85 ± 1.37	4.52 ± 1.28	4.80 ± 1.33	4.83 ± 1.39	5.08 ± 1.33	5.32 ± 1.51	< 0.001
CRP(mg/dL)*	1.30 (0.70, 2.50)	0.90 (0.50,1.70)	1.10 (0.70,2.02)	1.20 (0.70,2.10)	2.00 (1.30,3.20)	2.45 (1.60,4.20)	< 0.001
HDL-c (mg/dL)	51.98 ± 12.00	63.32 ± 13.00	51.07 ± 8.52	52.16 ± 9.34	44.90 ± 7.27	41.62 ± 7.69	< 0.001
Scr(mg/dL)	0.80 ± 0.29	0.82 ± 0.40	0.80 ± 0.24	0.81 ± 0.25	0.79 ± 0.24	0.78 ± 0.26	0.312
FBG (mg/dL)	102.19 ± 31.93	95.96 ± 24.13	99.97 ± 29.78	99.32 ± 27.24	107.18 ± 35.67	118.64 ± 45.35	< 0.001
HbA1c (%)	5.96 ± 0.92	5.82 ± 0.74	5.86 ± 0.74	5.91 ± 0.80	6.08 ± 1.16	6.39 ± 1.23	< 0.001
AIP_{2012}	0.34 ± 0.33	0.02 ± 0.17	0.14 ± 0.13	0.51 ± 0.16	0.49 ± 0.16	0.97 ± 0.23	< 0.001
AIP_{2015}	0.38 ± 0.28	0.05 ± 0.12	0.35 ± 0.11	0.29 ± 0.12	0.65 ± 0.13	0.84 ± 0.21	< 0.001
Cumulative AIP	1.07 ± 0.83	0.09 ± 0.33	0.75 ± 0.24	1.20 ± 0.31	1.70 ± 0.28	2.71 ± 0.46	< 0.001
Current smoker, n(%)	955 (27.85)	249 (30.89)	242 (27.63)	202 (28.90)	187 (25.90)	75 (23.01)	0.054
Current drinker, n(%)	1209 (35.26)	353 (43.80)	289 (32.99)	239 (34.19)	220 (30.47)	108 (33.13)	< 0.001
Diabetes, n(%)	601 (17.53)	85 (10.55)	129 (14.73)	108 (15.45)	159 (22.02)	120 (36.81)	< 0.001
Antidiabetic agents, n(%)	149 (4.35)	22 (2.73)	22 (2.51)	33 (4.72)	37 (5.12)	35 (10.74)	< 0.001
Dyslipidemia, n(%)	391 (11.40)	37 (4.59)	66 (7.53)	96 (13.73)	106 (14.68)	86 (26.38)	< 0.001
Antihyperlipidemic agents, n(%)	159 (4.64)	14 (1.74)	25 (2.85)	38 (5.44)	41 (5.68)	41 (12.58)	< 0.001
Cancer, (n%)	39 (1.14)	5 (0.62)	13 (1.48)	8 (1.14)	6 (0.83)	7 (2.15)	0.170
Liver disease, n(%)	170 (4.96)	43 (5.33)	43 (4.91)	38 (5.44)	33 (4.57)	13 (3.99)	0.832
CVD, n(%)	620 (18.08)	114 (14.14)	153 (17.47)	132 (18.88)	143 (19.81)	78 (23.93)	0.001
CKM stage, n(%)							< 0.001
0	158 (4.61)	81 (10.05)	44 (5.02)	33 (4.72)	0 (0.00)	0 (0.00)	
1	651 (18.99)	278 (34.49)	179 (20.43)	181 (25.89)	10 (1.39)	3 (0.92)	
2	1363 (39.75)	172 (21.34)	335 (38.24)	227 (32.47)	436 (60.39)	193 (59.20)	
3	1257 (36.66)	275 (34.12)	318 (36.30)	258 (36.91)	276 (38.23)	130 (39.88)	

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; TG, Triglyceride; TC, total cholesterol; BUN, Blood urea nitrogen; UA, Uric acid; CRP, C-reactive protein; HDL-c, high density lipoprotein cholesterol; Scr, Serum creatinine; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; AIP, atherogenic index of plasma; CVD: cardiovascular diseases; CKM: Cardiovascular-Kidney-Metabolic

Continuous variables were expressed as mean ± standard deviation (SD) in case of normal distribution and compared between the two groups by Kruskal-Wallis rank sum test. If the theoretical number of count variables was less than 10, Fisher's exact probability test was used. Categorical variables were expressed as counts (percentages) and compared by chi-square test.

* Present as median (interquartile range).

ORs of class 2, Class 3, Class 4 and class 5 were 1.37 (95% CI: 1.04–1.81), 1.54 (95% CI: 1.04–2.26), and 1.65 (95% CI: 1.13–2.41) and 2.14 (95% CI: 1.15–3.97) respectively. This showed that among those with CKM syndrome stages 0–3, participants in class 2, Class 3, Class 4, and Class 5 had a 34%, 54%, 65%, and 114% increased risk of CVD respectively, compared with class 1 (Table 2)

To further explore the relationship between changes in AIP and CVD risk, subgroup and interaction analyzes were performed for different age groups, gender, smoking status, and drinking status (Table S2). The results showed that among different demographic characteristics, there was no significant interaction between changes in AIP and CVD risk (P for interaction > 0.05).

Table 2 Logistic regression results for the association of changes in AIP and cumulative AIP with CVD among individuals with CKM syndrome stages 0–3

	Model I		Model II		Model III		Model IV	
	OR(95%CI)	*P* value	OR(95%CI)	*P* value	OR(95%CI)	*P* value	OR (95%CI)	*P* value
Changes in AIP								
Class 1	Reference		Reference		Reference		Reference	
Class 2	1.28 (0.99, 1.67)	0.063	1.31 (1.01, 1.71)	0.046	1.37 (1.04, 1.81)	0.026	1.37 (1.04, 1.81)	0.027
Class 3	1.41 (1.07, 1.86)	0.013	1.43 (1.09, 1.89)	0.011	1.54 (1.05, 2.26)	0.027	1.54 (1.04, 2.26)	0.029
Class 4	1.50 (1.14, 1.96)	0.003	1.56 (1.18, 2.04)	0.002	1.63 (1.12, 2.38)	0.011	1.65 (1.13, 2.41)	0.010
Class 5	1.91 (1.38, 2.64)	< 0.001	1.99 (1.44, 2.75)	< 0.001	2.17 (1.18, 4.00)	0.013	2.14 (1.15, 3.97)	0.016
Cumulative AIP								
Continuous	1.23 (1.11, 1.36)	< 0.001	1.25 (1.12, 1.38)	< 0.001	1.32 (1.00, 1.73)	0.046	1.33 (1.01, 1.75)	0.040
Q1	Reference		Reference		Reference		Reference	
Q2	1.17 (0.90, 1.52)	0.255	1.16 (0.89, 1.51)	0.274	1.21 (0.91, 1.61)	0.200	1.22 (0.91, 1.63)	0.178
Q3	1.48 (1.15, 1.90)	0.003	1.50 (1.16, 1.94)	0.002	1.59 (1.15, 2.21)	0.006	1.61 (1.16, 2.24)	0.005
Q4	1.66 (1.29, 2.14)	< 0.001	1.72 (1.33, 2.21)	< 0.001	1.83 (1.17, 2.85)	0.008	1.92 (1.22, 3.00)	0.005
P for trend		< 0.001		< 0.001		0.005		0.003

Model I: crude model

Model II: adjusted for Age, Gender

Model III: adjusted for Age, Gender, Rural residence, Smoking statues, Drinking statues, Education level, Marital status, BMI, Cancer, Liver disease, BUN, Scr, CRP, HbA1C, FBG, Baseline AIP

Model IV: adjusted for Age, Gender, Rural residence, Smoking statues, Drinking statues, Education level, Marital status, BMI, Cancer, Liver disease, BUN, Scr, CRP, HbA1C, FBG, Baseline AIP, Antidiabetic agents, Antihyperlipidemic agents

Abbreviations: AIP: Atherogenic index of plasma, CVD: Cardiovascular disease, CKM: Cardiovascular-Kidney-Metabolic, BMI: Body mass index, BUN, Blood urea nitrogen, Scr, Serum creatinine, CRP: C-reactive protein, HbA1c: Glycated Hemoglobin A1c, FBG: Fasting plasma glucose, OR: Odds ratio, CI: Confidence interval

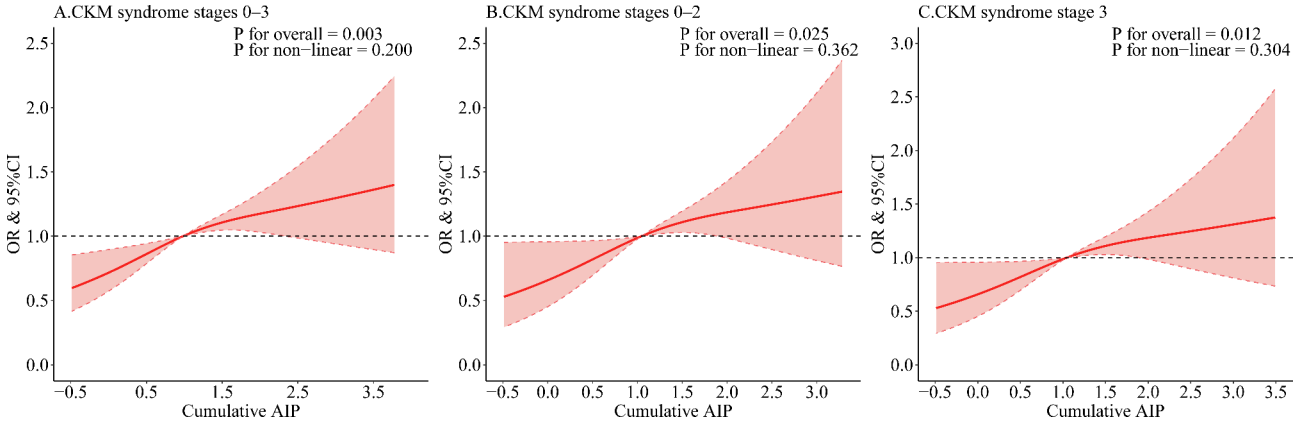

Fig. 2 A cubic model of the association between different CKM stages and cumulative AIP, **A** CKM stages 0–3 **B** CKM stages 0–2 (early stage) **C** CKM stage 3(late stage)

The impact of cumAIP on the incidence of CVD among individuals with CKM syndrome stages 0–3

Multivariable logistic regression analysis showed a positive linear association between cumAIP and CVD risk, with an adjusted OR of 1.33 (95% CI: 1.01–1.75, $P = 0.040$). Further analysis by quartile group showed a significant cumAIP trend effect (P for trend = 0.003). Compared with Q1 (lowest quartile), the CVD risk in Q3 and Q4 groups was significantly higher, 1.61-fold (95% CI: 1.16–2.24, $P = 0.005$) and 1.92-fold (95% CI: 1.22-3.00, $P = 0.005$) (Table 2).

In RCS analyses, we further explored potential nonlinear relationships between cumAIP and CVD risk. The results showed that in the overall population of CKM syndrome stages 0–3, cumAIP was positively correlated with CVD risk (P for non-linear = 0.200). As the cumAIP level increased, the risk of CVD gradually increased (Fig. 2A). In a staged analysis, cumulative AIP was also significantly positively associated with CVD risk in CKM syndrome stages 0–2 (early stage of CKM, Fig. 2B) and stage 3 (late stage of CKM, Fig. 2C) populations. Furthermore, subgroup analysis (Figure S2) showed no significant interaction between subgroup variables (P for interaction > 0.05). Of note, the association of cumAIP with CVD risk was more significant in those with CKM syndrome stage 3 ($P < 0.05$).

WQS analyses

To explore the association between TG and HDL-c levels and CVD risk, we made extensive use of the WQS regression model (Figure. S3). The results of the WQS regression analyses show that among the variables assessed, TG had the highest relative contribution weights to CVD risk in 2012 and 2015, with weights of 0.651 and 0.669 respectively, suggesting that TG plays an important role in modifying CVD risk over time.

Discussion

The results of this study show that changes in AIP and cumAIP are significantly associated with CVD risk in people with CKM stages 0–3. After adjusting for confounding factors such as age, gender, education level, smoking, alcohol consumption, and baseline AIP, the risk of cardiovascular events was significantly increased in the group with greater variation in AIP, suggesting that AIP is not only an independent risk factor for CVD in patients with CKM stages 0–3, but also its dynamic changes have important predictive value. In addition, the study reveals the cumulative effect of cumAIP on CVD risk, further emphasizing the importance of comprehensive monitoring of AIP dynamics. These findings lay the foundation for the application of AIP in CVD risk assessment, which help us identify at-risk populations and guide more effective risk management strategies.

AIP, as an emerging biomarker, has been proposed for assessing dyslipidemia and predicting insulin resistance(IR) risk [29]. It indicates the severity of IR in addition to reflecting lipid profiles [30]. Numerous studies have confirmed that IR is an independent risk factor for CVD [31, 32], and it disrupts glucose metabolism by impeding insulin signaling, which in turn triggers endothelial dysfunction and hastens the progression of atherosclerosis [33]. Also most cardiovascular events are attributed to atherosclerosis, a process significantly facilitated by abnormal lipid metabolism. From a pathophysiological point of view, TG-rich residual particles have been shown to contribute to the formation and progression of atherosclerotic plaques [34]. Furthermore, in addition to their reverse cholesterol transport function, HDL-c particles exhibit a wide range of beneficial biological activities such as anti-atherosclerotic effects [35]. Therefore, in patients with CKM stages 0–3, the AIP, as an economical, easy-to-use indicator, may be an effective predictor of CVD development and progression.

According to WQS analysis, TG has a large weight in AIP control, so controlling TG levels is crucial to controlling AIP Personalized intervention strategies should be adopted for CKM patients at different stages. For patients with early CKM, attention should be paid to primary prevention, preventing the development of excessive or dysfunctional metabolic risk factors, and improving lipid metabolism and insulin sensitivity through measures such as increasing exercise and controlling weight [36–38]. For patients with advanced CKM, the disease burden is heavy. A combined treatment that includes both glucose and lipid metabolism drugs is essential to improve the health prognosis of CKM patients, which delays disease progression and reduces the occurrence of complications [34].

This study focused on the relationship between AIP and CVD risk in the CKM stages 0–3 population. Increased AIP is often associated with changes in TG and HDL-c levels, indicating abnormal lipid metabolism. This imbalance leads to the accumulation of visceral fat, which contributes to central obesity [39]. Visceral fat disrupts the insulin signaling pathway by releasing proinflammatory cytokines like tumor necrosis factor-alpha and interleukin-6 [40, 41]. This causes IR and worsens glucose metabolism disorders. Additionally, higher AIP is closely linked to endothelial dysfunction. Elevated TG and low HDL-c levels impair endothelial cell function, reduce nitric oxide production [42], limit blood vessel dilation, and increase vascular resistance, leading to hypertension [43]. High blood sugar further promotes CKD by increasing the accumulation of advanced glycation end products and oxidative stress [44]. This damages endothelial cells and renal microvessels. Increased AIP is also associated with kidney fibrosis, which accelerates kidney function deterioration through endothelial injury and ongoing inflammation [30]. Overall, AIP plays a central role in the development of CKM syndrome. It affects lipid metabolism, insulin sensitivity, blood vessel function, and kidney structure. Therefore, targeting AIP for intervention can provide important clinical insights to help prevent and delay the progression of CKM.

Through subgroup analysis, we further investigated the relationship between changes in AIP and CVD risk in population with CKM syndrome stages 0–3. There was no statistical interaction between AIP and CVD risk in the groups with CKM syndrome stages 0–3, suggesting a generality of results. It was worth noting that individuals with CKM stages 0–3 who were male, over 60, living in rural areas, and had a history of alcohol and/or tobacco use were more likely to have CVD. This is consistent with the results of the China Health Statistical Yearbook 2022, which shows that the rural CVD mortality rate has been higher than that in urban areas since 2009 [45]. Physiologically, first of all, CVD risk increases with age due to the additional burden of age-related changes (e.g. arterial stiffness, inflammation, organ function) [46, 47]. Secondly, the 20-year follow-up research found that men had a higher overall lifetime risk of CVD than women of the same age [48]. This is related to estrogen acting in target tissues through estrogen receptors, thereby reducing the risk of CVD [49]. Moreover, nicotine and carbon

monoxide in cigarettes damage vascular endothelial cells, causing vasospasm, endothelial dysfunction, and increasing the risk of atherosclerosis [50]. At the same time, alcohol stimulates the release of inflammatory factors in the body, aggravates the vascular inflammatory response, and can also indirectly trigger the activation of Renin-Angiotensin-Aldosterone System, resulting in increased blood pressure [51]. These results have clinical implications for understanding the role of AIP in individuals at risk for CVD.

Our study had several strengths. First, there were few studies on the relationship between AIP and new-onset CVD in the CKM stages 0–3 population. This study confirmed that the dynamic changes in individual AIP levels can help identify high-risk groups. Based on the changes in AIP levels, we divided the population into well-controlled and poorly controlled groups. We found that lowering AIP significantly reduced the incidence of cardiovascular events. Second, we used data from a large-scale national longitudinal survey. We also adjusted for multiple confounding factors, which allowed us to better understand the link between AIP control and CVD in the CKM stages 0–3 population. Finally, our study highlighted the clinical value of AIP as a low-cost and easy-to-use indicator for preventing new-onset CVD in this population. These biochemical parameters can be easily obtained from a single blood sample, offering an approach to improve the long-term prognosis for patients with cardiorenal metabolic abnormalities.

However, there were some limitations in this study. First, studies had relied on self-reports to identify CVD due to the absence of clinical markers, which may compromise accurate assessments of CVD incidence and be affected by recall bias. Fortunately, data collected through face-to-face interviews, structured questionnaires and validation of CVD history by a review committee ensured some accuracy of the data. Second, the drugs analyzed in this study was based on individuals self-reported drugs in the CHARLS, which was retrospective and may lead to recall bias. Third, all participants in this study were Chinese. While the results may be applicable to other populations, further research is needed to confirm this in diverse groups. Therefore, similar international studies are necessary to validate the global applicability of these findings. Despite these limitations, the innovation and reliability of this study provide important insights for future research in this area.

Conclusions

In middle-aged and elderly participants with CKM syndrome stages 0–3, constant higher AIP with worst control may have a higher incidence of CVD. Monitoring long-term changes in AIP will contribute to early identification of high risk of CVD among individuals with CKM syndrome stages 0–3.

Abbreviations

AIP	Atherogenic index of plasma
CKM	Cardiovascular-kidney-metabolic
CVD	Cardiovascular disease
CHARLS	China Health and Retirement Longitudinal Study
cumAIP	Cumulative AIP
OR	Odds ratio
TG	Triglyceride
HDL-c	High-density lipoprotein cholesterol
AHA	American Heart Association
CKD	Chronic kidney disease
IR	Insulin resistance
BMI	Body mass index
WC	Waist circumference
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triglycerides
BUN	Blood urea nitrogen
UA	Uric acid
CRP	C-reactive protein
Scr	Serum creatinine
FBG	Fasting blood glucose
HbA1c	Hemoglobin A1c
RCS	Restricted cubic spline
Mets	Metabolic disease
SD	Standard deviation
WQS	Weighted quantile sum

Supplementary Information

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Supplementary Material 1

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Author contributions

Gaoshu Zheng: conceptualization, writing-original draft and resources. Jijie Jin: data curation, software. Wang Fei: writing-original draft, software. Qianrong Zheng: investigation, software. Jiaxin Shao: investigation, data curation. Jiangnan Yao: investigation, data curation. Pan Huang: investigation, data curation. Hao Zhou: investigation, supervision. Jianghua Zhou: research design.

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Availability of data and materials

Online repositories contain the datasets used in this investigation. The names of the repositories and accession numbers can be found at http://charls.pku.edu.cn/en.

Declarations

Ethical approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Review Committee of Peking University. The patients/participants provided their written informed consent to participate in this study.

Competing interests

The authors declare no competing interests.

Author details
[1]Department of Cardiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou Medical University, Wenzhou, China
[2]College of Nursing, Wenzhou Medical University, Wenzhou, China

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