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Yiying Li, Yuke Zhang, Yu Zhang, Xinyu Yang & Yuehong Ni

Association between the atherogenic index of plasma and cognitive impairment

Yiying Li[1+], Yuke Zhang[1+], Yu Zhang[1+], Xinyu Yang[1], Yuehong Ni[2*]

[1] College of Medical Science, Huzhou University, Huzhou, Zhejiang, China.

[2] Huzhou Central Hospital, Affiliated Central Hospital of Huzhou University, Huzhou, Zhejiang , China.

*Corresponding Author: Yuehong Ni

Huzhou Central Hospital, Affiliated Central Hospital of Huzhou University, Huzhou, Zhejiang , China.

E-mail: nyh422804178@163.com, Tel: 15868237039

[+]These authors contributed equally to this work and shared the first authorship.

Abstract

The Atherogenic Index of Plasma (AIP), a burgeoning composite lipid marker that reflects overall lipid balance, has an incompletely understood longitudinal relationship with cognitive impairment. This study conducted a systematic investigation into the long-term, nonlinear association between AIP and the risk of cognitive impairment among middle-aged and older adults, utilizing longitudinal data from the China Health and Retirement Longitudinal Study (CHARLS) spanning from 2011 to 2020. The study encompassed 2,971 participants who were free from cognitive impairment at baseline and were followed for a period of up to 10 years. The cumulative incidence of new-onset cognitive impairment was found to be 40.46% in men and 54.45% in women. A multivariable-adjusted Cox regression analysis revealed that an elevated AIP, particularly within the 25th to 75th percentile range, was an independent risk factor for cognitive impairment ($P < 0.05$). Further analysis employing restricted cubic splines (RCS) uncovered a significant inverted U-shaped nonlinear association between AIP and cognitive impairment risk (P-nonlinear < 0.001), with a notably increased risk within the AIP range of 0.205 to 0.423. Subgroup analyses, stratified by sex, age, educational level, and BMI, showed consistent trends across various demographic groups. This study suggests that AIP, as a straightforward composite lipid marker, exhibits a significant nonlinear association with the risk of cognitive impairment in middle-aged and older adults. Monitoring AIP levels could assist in the early identification of individuals at high risk, and targeted interventions within specific AIP ranges, such as 0.205-0.423, could have significant public health implications, offering a new potential target for preventive strategies against cognitive decline.

Keywords: Atherogenic index of plasma; Cognitive impairment; CHARLS; Restricted cubic spline

1 Introduction

With the aging of the population and the increase in life expectancy in Chinese society, the health problems associated with older adults are becoming more prominent. Clinical studies have demonstrated that cognitive impairment is one of the most prevalent symptoms among the geriatric population and has emerged as a significant health challenge for older adults in China[1,2]. According to statistics, there are approximately 16.99 million dementia patients in China whose typical symptoms include memory loss, visual-spatial impairment, and dementia. These symptoms not only severely affect daily living but also frequently induce psychological problems such as depression and anxiety, creating a dual burden on both physical and mental health[3]. Notably, the disease often progresses insidiously in its early stages. Once it advances to dementia, effective treatments are lacking, underscoring the critical importance of early screening and intervention[4].

Metabolic disorders, such as dyslipidemia, have been demonstrated to be important risk factors for cognitive impairment[5-7]. Traditional lipid indices (e.g., total cholesterol, triglycerides [TG], and high-density lipoprotein cholesterol [HDL-C]) have been associated with the risk of cognitive impairment[8,9] but have limited predictive efficacy. In recent years, the atherosclerosis index (AIP, lg[TG(mmol/L)/HDL-C(mmol/L)) has gained widespread attention as a sensitive lipid profile indicator[10,11]. The AIP is more reliable and sensitive for assessing the risk of atherosclerosis than TG or HDL-C alone[12]. It is suitable for clinical practice due to its low cost and ease of implementation.

Atherosclerosis is recognized as a pivotal pathological underpinning of cognitive disorders. Empirical evidence suggests that vascular alterations, including carotid atherosclerosis, can precipitate vascular cognitive impairment by disrupting cerebral blood flow, inciting microembolic events, or leading to chronic cerebral hypoperfusion.[13]

Additionally, the inflammatory responses and endothelial dysfunction associated with atherosclerosis may intersect with the pathogenesis of Alzheimer's disease, including the deposition of β-amyloid proteins, thereby exacerbating cognitive decline.[14] In light of this, the AIP, as a sensitive marker of atherosclerotic risk, is likely to be intricately linked to cognitive performance.

However, existing studies exploring the relationship between AIP and cognitive impairment have several limitations. First, most studies employ a cross-sectional design, focusing solely on associations at a single point in time. This fails to capture the dynamic changes in AIP and cognitive impairment over time and makes it challenging to analyze interactions with the longitudinal evolution of cognitive function. Second, traditional regression models are difficult to analyze complex non-linear relationships and are prone to overfitting and covariance problems when dealing with data.

To address these gaps, this study investigates the dose-response relationship between AIP and cognitive impairment in middle-aged and older adults using the China Health and Retirement Longitudinal Study (CHARLS) cohort data with a restricted cubic spline model (RCS), which flexibly fits the non-linear relationship and alleviates the overfitting and covariance problems. Furthermore, the study provides new biomarkers and an evidence-based foundation for early warning, prevention, and control strategies for cognitive impairment through cohort design, Kaplan-Meier survival curves, and subgroup analysis.

2 Methods

2.1 Study Population

This study used data from CHARLS, a research project aimed at collecting high-quality microdata on households and individuals aged ≥45 years in China, which provides a rich data resource for analyzing

population aging in China and promoting interdisciplinary research on aging. The study used CHARLS data from 2011 to 2020, encompassing five two-year survey cycles. We adhered to CHARLS guidelines to ensure data consistency and accuracy. This study involved 2,971 participants, including 1,550 females and 1,421 males. (Figure.1) The CHARLS was performed in compliance with the Helsinki Declaration and received approval from the Biomedical Ethics Committee of Peking University (IRB00001052-11015), with all participants or their legal guardians providing informed consent following ethical research practices.

2.2 Definitions of the exposure and outcome variables

The exposure variable was AIP, which was derived from lg[TG(mmol/L)/HDL-C(mmol/L)], with both TG and HDL-C levels expressed in mmol/L[15]. Serum HDL-C was measured by direct immunoassay or precipitation according to the Centers for Disease Control and Prevention (CDC) standard protocol[16] and fasting venous blood was collected from each subject for TG measurement. The study population was subsequently categorized into four groups according to AIP quartiles.

The primary endpoint of the study was the prevalence of cognitive impairment. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) scale for participants in the CHARLS database. The MMSE comprehensively and accurately reflects cognitive deficits and intelligence levels, providing a research basis for neuropsychological diagnosis and treatment. It covers multiple cognitive domains, including memory, orientation, comprehension, attention, and reading comprehension. Cognitive function was evaluated on a scale of 0 to 30, with higher scores indicating better cognitive performance. This study defined cognitive impairment based on educational level: ≤17 points for the illiterate group, ≤20 points for the primary school group, and ≤24 points for the secondary education group.[17,18]

This study utilized the follow-up data from five survey rounds conducted in 2011, 2013, 2015, 2018, and 2020 from the CHARLS database for analysis. The exposure assessment was based on lipid indicators collected during the baseline survey in 2011, from which the AIP values were calculated. The index date was defined as the date when participants completed the baseline survey, including the collection of biological samples and cognitive assessments. The follow-up period commenced from this index date, with the endpoint event being the first occurrence of cognitive impairment. Censoring events included loss to follow-up, death, or the end of the study, whichever occurred first. For participants who did not experience the endpoint event, their last valid cognitive assessment date was used as the review time.

2.3 Potential covariates

We included several covariates that might have affected the results. These covariates included socio-demographic characteristics such as age (years), sex (Male/Female), marital status (Married/Divorced/Widowed/Unmarried), and level of education (Illiterate person/Primary School/Junior High School/High school education or above). Health behaviors included alcohol consumption (Never or rarely/Rarely or less than once a month/More than once). Other potential confounders were body mass index (kg/m^2), dyslipidemia (Yes/No), chronic lung disease (Yes/No), arthritis (Yes/No), and stroke (Yes/No). Additionally, Body mass index (BMI) is a common standard for assessing general obesity[19], corrected for height to minimize the effect of height on the assessment of obesity. It is calculated as body mass (kg) divided by the square of height (m). Studies have shown that BMI and body fatness are well correlated in the general population[20,21] and may reflect the risk of obesity-related diseases[22,23]. In this study, according to the National Health and Family Planning Commission of the People's Republic of China's Criteria of weight for adults[24], a BMI of less than

18.5 kg/m^2 is classified as wasting, up to 18.5 kg/m^2 and less than 24 kg/m^2 is considered normal, up to 24 kg/m^2 and less than 28 kg/m^2 is considered overweight, and up to or more than 28 kg/m^2 is considered obese.

2.4 Statistical analysis

Statistical analyses were conducted using SPSS version 27.0 and R version 4.4.3 software. In this case, for qualitative data, frequencies and percentages were used for description, and the Chi-square goodness-of-fit test was used to analyze the differences between different groups. We performed quartile grouping for AIP.

Variables that were statistically significant in the univariate analyses were included in the multivariate analyses, and the Cox proportional risk regression model was used to compare the effects of variables on cognitive impairment over time and to identify risk and protective factors for cognitive impairment. In addition, a non-linear fit between cognitive impairment and AIP was performed using RCS analysis, and the critical value of AIP was determined. Kaplan-Meier survival analyses were also performed to test the association between time to disease and the likelihood of disease at different AIP levels. In addition, subgroup analyses were used to test the effects of sex, age, education level, and BMI on the association between AIP and prevalence. A *p*-value less than 0.05 was considered to indicate a statistically significant difference.

3 Results

3.1 Baseline characteristics

A total of 2971 participants were finally included in the study, with a follow-up period of 10 years. Among them, 1550 (52.17%) were females, and 1421 (47.83%) were males. The results showed statistically significant (P <0.05) differences in age, sex, marital status, alcohol consumption, education level, dyslipidemia, chronic lung disease, arthritis, BMI, and AIP, as shown in Table 1.

3.2 COX regression analysis between AIP and cognitive impairment

This study used a multivariate COX proportional risk model to assess the association of the AIP and other covariates with the risk of developing cognitive impairment. The model adjusted for confounders such as age, gender, marital status, drinking status, education level, chronic diseases (dyslipidemia, chronic lung disease, arthritis) and BMI. The results were shown in Table 2: AIP levels grouped by quartiles showed a significant non-linear risk trend, with the T2-T3 group showing a significantly higher risk of cognitive impairment compared to the reference group T1 in the T2 group (*HR*=1.412, 95% *CI*: 1.221-1.634), and the T3 group also had an increased risk (*HR*=1.227, 95% *CI*: 1.066-1.412). The T4 group showed an inverse reduction in risk (*HR*=0.475, 95% *CI*: 0.391-0.577), suggesting that very high levels of AIP may be associated with a decreased risk of cognitive impairment. Among other covariates, those aged 60-74 (*HR*=1.221, 95%*CI*: 1.087-1.370) and 75-89 (*HR*=2.208, 95% *CI*: 1.825-2.673) had a significantly higher risk than the reference group of 45-59; women had a higher risk than men (*HR*=1.188, 95% *CI*: 1.052-1.340); education was negatively correlated with risk. Negatively correlated with risk, e.g., the risk of those with high school education and above was only 9.7% of that of the illiterate group (*HR*=0.097, 95% *CI*: 0.065-0.144); frequency of drinking: the risk of those who drank more than once a month was significantly higher (*HR*=1.271, 95% *CI*: 1.065-1.517); BMI: the risk of those who were normal-weight (*HR*=0.806, 95% *CI*: 0.668-0.971), overweight (*HR*=0.735, 95% *CI*: 0.600-0.900) and obese (*HR*=0.725, 95% *CI*: 0.568-0.924) risk were all significantly lower than the wasting group. While marital status (divorced, unmarried), dyslipidemia, chronic lung disease, and arthritis were not statistically associated with the risk of cognitive impairment (all $P>0.05$).

3.3 A dose-response relationship study of AIP and cognitive impairment

The utilization of the RCS model to explore the potential nonlinear relationship between the AIP and the risk of cognitive impairment is considered optimal with the selection of 3 to 7 knots, as referenced. In the RCS model, the raw continuous AIP values are employed, with knots and reference points calculated by statistical software defaults, rather than being manually set. Based on the spline regression coefficients and the Akaike Information Criterion (*AIC*), this study found that the model related to cognitive dysfunction had the lowest *AIC* value of 21323.28 with 7 knots, as detailed in Table 4. Figure 2 depicts an inverted "U"-shaped relationship between AIP and the risk of cognitive impairment, indicating that AIP is a risk factor for cognitive impairment when its value falls between 0.205 and 0.423. The overall relationship between AIP and cognitive impairment is statistically significant (*P*-overall <0.001, *P*-nonlinear <0.001). These results advocate for the adoption of nonlinear models to characterize the dose-response relationship between AIP and the risk of cognitive impairment.

3.4 Kaplan-Meier survival curve analysis of AIP and cognitive impairment

This study assessed the cumulative risk of developing cognitive impairment in different AIP quartile groups (T1-T4) by Kaplan-Meier survival curves. Survival probabilities during 10 years of follow-up were shown: The probability of survival in the T2-T3 group decreased progressively with elevated AIP, with 10-year survival probabilities of 40% (T2) versus 30% (T3), suggesting that AIP was positively associated with cognitive risk in the intermediate tertile interval. The 10-year survival probability of cognitive impairment dropped to 60% in the T1 group; the T4 group had a significantly higher probability of survival than the other groups, with a 10-year survival probability of 80%, suggesting that very

high AIP levels may be associated with a reduced risk of cognitive impairment. (log-rank χ^2 = 368.424, P<0.001).The results are shown in Figure 3.

3.5 Subgroup analysis of AIP and cognitive impairment

There were no statistically significant interactions ($_{all}$ P >0.05) in the subgroups of age ($P_{\text{-interaction}}$=0.726), sex ($P_{\text{-interaction}}$=0.55), education level ($P_{\text{-interaction}}$=0.436) and BMI ($P_{\text{-interaction}}$=0.744), suggesting that AIP's protective effect did not show significant heterogeneity across subgroups. The results are shown in Figure 4.

3.6 Sensitivity analysis of AIP and cognitive impairment

To reduce the impact on the risk assessment of cognitive impairment arising from survival bias in the older age group, subjects aged ≥75 years were excluded from this study, and Cox regression analyses were re-run. As shown in Table 3, the association between AIP and cognitive impairment did not change significantly in the sensitivity analyses after the exclusion of subjects aged ≥75 years compared with the results of the analyses that included all subjects, suggesting that subjects aged ≥75 years had less influence on the main findings of this study, further confirming the robustness of the association between AIP and cognitive impairment.

4 Discussion

Based on national cohort data from the CHARLS, this study systematically explored for the first time the longitudinal association between AIP and the risk of developing cognitive impairment in a large sample of Chinese middle-aged and older adults. Furthermore, it revealed the non-linear dose-response relationship and gender heterogeneity between AIP and cognitive impairment using RCS. The study demonstrated that elevated levels of AIP, a comprehensive indicator of lipid metabolism disorders, were significantly associated with the risk of developing cognitive impairment in middle-aged and older

adults after adjusting for potential confounders, and this association showed a non-linear increasing trend.

The risk of cognitive impairment increases significantly with age in older adults[25,26]. BMI is a commonly used indicator of obesity and has a controversial relationship with cognitive function. Some studies suggest that a high BMI can lead to nerve fiber shortening and brain atrophy, potentially impacting cognitive function[27]. However, Nawab Qizilbash[28]et al. found that higher BMI may have a protective effect on cognitive function in middle-aged and older adults, consistent with the present study's findings. Several studies indicate that individuals with higher educational attainment have a lower risk of developing dementia compared to those with lower education levels. This protective effect of education may be explained by the composition of cognitive reserve, which may delay neurodegenerative diseases' cognitive and functional expression. In this study, higher levels of education were associated with higher levels of cognitive function, in line with the study by Nicolas Le Carret[29]et al. Additionally, Cox regression analysis revealed that women had a higher likelihood of suffering from cognitive impairment than men, with a 1.24 times greater risk. This finding is consistent with Nebel's s[30] research and may be explained by women's higher susceptibility to cognitive impairment risk factors such as depression and memory loss. During menopause, women experience a decline in estrogen levels, making them more prone to depression, which increases the risk of cognitive impairment[31,32]. Moreover, hippocampal function is impaired in women due to estrogen loss[33], further elevating their disease risk. Therefore, studying the independent relationship between cognitive function and atherosclerosis across genders is crucial for early intervention in cognitive impairment.

This study reveals for the first time an inverted U-shaped curvilinear relationship between AIP and the risk of cognitive impairment,

demonstrating a non-linear association through restricted cubic spline modeling. Elevating AIP within the 25th to 75th percentile range significantly increased the risk of cognitive impairment; however, the risk decreased when AIP reached the highest quartile. This finding challenges the traditional pathological hypothesis of linear association and provides new insights into the complex interaction between lipid metabolism and neurodegenerative diseases.

AIP, as a dual marker of atherosclerosis and lipid metabolism disorders, has been generally supported by previous studies (e.g., in a cross-sectional study among patients with type 2 diabetes by Fasihah Irfani Fitri et al.[34]) as having a linear positive correlation with cognitive impairment. It has been hypothesized that elevated AIP exacerbates the risk of cognitive impairment via two mechanisms: first, vascular pathways - elevated AIP promotes carotid atherosclerosis (CAS), leading to vascular cognitive impairment (VCI), which is significantly associated with the risk of cognitive impairment[35-37]; secondly, neurometabolic pathways - dyslipidemia may be involved in lipid metabolism in the brain and its pathways through multiple mechanisms thereby affecting cognitive function. Lipid abnormalities may be involved in the lipid metabolism of brain nerves and their pathways through various mechanisms, thus affecting cognitive function[38,39]. AIP is a composite metric whose increase or decrease is influenced by HDL-C and TG levels. Feinkohl et al. concluded that lower HDL-C and higher triglycerides are associated with cognitive impairment, defined as cognitive decline relative to the total sample[6]. Analyzed in terms of these two indicators that constitute AIP, HDL-C inhibits β-amyloid aggregation and promotes amyloid clearance, which in turn protects cognitive function[40], so that declining HDL-C levels are an independent risk marker for cognitive decline in old age[41], whereas higher HDL-C levels are associated with improved cognitive function[42]; Elevated TG interfere with leptin

transport across the blood-brain barrier and inhibit memory-related signaling pathways in the hippocampus[43,44]. The AIP value is the logarithm of serum triglycerides/serum HDL-C, which will increase in response to increasing serum triglyceride levels and decreasing blood HDL-C levels. The present study is in line with the findings of previous studies in the 25th to 75th percentile AIP interval.

This study reveals a "paradoxical phenomenon" where extremely high plasma AIP is associated with a reduced risk of cognitive impairment, which can be interpreted from its nature as an indicator of the dynamic balance between TG and HDL-C . Previous conclusions, based on studies with moderate to low AIP levels,[45] emphasized the dangers of elevated AIP. However, our longitudinal data analysis reveals a non-linear association: in the highest AIP percentile group (typically corresponding to extremely high TG and extremely low HDL-C), cognitive risk trends downward.This phenomenon may stem from complex metabolic adaptation mechanisms. A key empirical study published by Zhou et al.[46] in "Neurology" provides crucial evidence: after an average follow-up of 6.4 years with 18,294 community elderly, they found that higher TG levels were significantly associated with a lower risk of Alzheimer's disease and a slower rate of cognitive decline. Additionally, lipidomics studies indicate that specific triglyceride components containing long-chain polyunsaturated fatty acids are significantly reduced in patients with cognitive impairment, suggesting their protective role in maintaining the function of neuronal cell membranes.[47,48] Synthesizing existing evidence, we propose that in the extreme high range of AIP, extremely high TG levels may offset atherosclerotic risks to some extent by providing energy substrates or specific neuroprotective lipid components, thus exhibiting a seemingly paradoxical "adaptive protection" phenomenon. This profoundly reveals the complexity of the relationship between lipid metabolism and cognitive function, suggesting

that clinical assessments need to go beyond linear thinking and emphasizing the need for future research to use multi-omics technologies to further elucidate its biological mechanisms.

The discrepancies between the present study and previous studies may stem from differences in AIP intervals and research methodologies. Previous studies typically concluded that elevated AIP is linearly and positively associated with cognitive impairment, focusing mainly on results derived from the low and medium AIP ranges while neglecting the 'protective adaptation' pattern induced by very high AIP. Additionally, most prior studies employed cross-sectional designs, making it challenging to capture dynamic changes over time. In contrast, the restricted cubic spline model in the present study uncovered an inverted 'U-shaped' nonlinear relationship, indicating that extremely high AIP may trigger compensatory protective mechanisms or reflect survival bias. This study enhances causal inference credibility by clarifying the temporal sequence of exposure and outcome through the cohort design. It reduces confounding bias caused by simultaneous measurement of exposure and outcome in cross-sectional studies. It also enables dynamic observation of the association between indicator changes and disease progression. The paradoxical phenomenon revealed in this study prompts a re-evaluation of traditional perceptions, encouraging a more comprehensive understanding of the potential impact of AIP on cognitive function. It underscores the necessity to revisit the dynamic association between lipid metabolic markers and cognitive function. Future studies should incorporate imaging and molecular markers to elucidate further the specific pathways AIP affects cognition.

5 Strengths and limitations

This study possesses several strengths. First, it is a prospective cohort study utilizing a large national database with long-term follow-up. Second, all blood samples were tested in the same cycle using a

standardized protocol, significantly reducing potential bias. Third, this paper uses the RCS model to explore the link between atherosclerosis and cognitive function in greater detail, providing more informative insights. Fourth, the atherosclerosis measurements employed in this study are simpler and more cost-effective than those used in most other studies. The calculation of AIP requires only the measurement of blood triglyceride and HDL cholesterol levels without the need for sophisticated testing equipment. This simplicity makes it highly tractable for widespread use in clinical practice; moreover, we adjusted for covariates and performed subgroup analyses to explore these associations in different populations and observed non-linear associations.

While this study has yielded significant insights, several limitations should be acknowledged. Firstly, these analyses can only identify the association between AIP and the prevalence of cognitive impairment. Although the prospective cohort design helps to establish the temporal sequence where exposure (baseline AIP) precedes the outcome (incident cognitive impairment), it does not entirely rule out the possibility of reverse causality. The causality of this association requires further validation with additional prospective data. Second, the data for this study came from the CHARLS database of Chinese adults, and further research is needed to assess the applicability of the results of this study to other populations of different economic and geographic statuses. Finally, although this study accounted for relevant confounding factors, there may still be unadjusted potential confounders at play, such as the apolipoprotein E ε4 allele status, specific dietary patterns, or inflammatory markers that could simultaneously influence lipid profiles and cognition, potentially creating spurious associations. It is recommended that future research endeavors to collect this information whenever possible, or employ more rigorous causal exploration methods,

such as genetic instrumental variables.

6 Perspectives and clinical applications

This study suggests that monitoring AIP levels is an effective way to assess the risk of cognitive impairment. Keeping AIP at a certain level may have a positive effect on reducing the prevalence of cognitive impairment. While further research is necessary to elucidate the mechanisms underlying this effect, this study offers valuable insights into potential prevention strategies.

7 Conclusions

Middle-aged and older adults receiving long-term follow-up showed a significant correlation between AIP and cognitive impairment. In this study, We discovered that the likelihood of developing cognitive impairment was significantly elevated when $0.205<AIP<0.423$. Given this, it is crucial to adjust risk assessment and management programs according to AIP in the context of China's current rapidly aging population.

Abbreviations

CHARLS: China health and retirement longitudinal study

AIP: atherogenic index of plasma

TG: triglycerides

RCS: restricted cubic spline model

CDC: Centers for Disease Control and Prevention

MMSE: Mini-Mental State Examination

BMI: Body mass index

CAS: carotid atherosclerosis

VCI: vascular cognitive impairment

MCT: medium-chain triglyceride

PUDG: long-chain polyunsaturated fatty acid-containing triglycerides

AD: Alzheimer's disease

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki and all participants signed informed consents before participation. Approval was granted by the Ethical Review Committee at Peking University (IRB00001052-11015).

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are available in the website of China Health and Retirement Longitudinal Study (https://charls.pku.edu.cn/).

Competing interests

We declare no competing interests.

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None.

Authors' contributions

Yiyng Li, Yu Zhang: Study design and data acquisition; Xinyu Yang: data analysis; Yuke Zhang,Yu Zhang and Xinyu Yang: manuscript editing; Yiying Li and Yuehong Ni: manuscript review. All authors approved the final version of the study.

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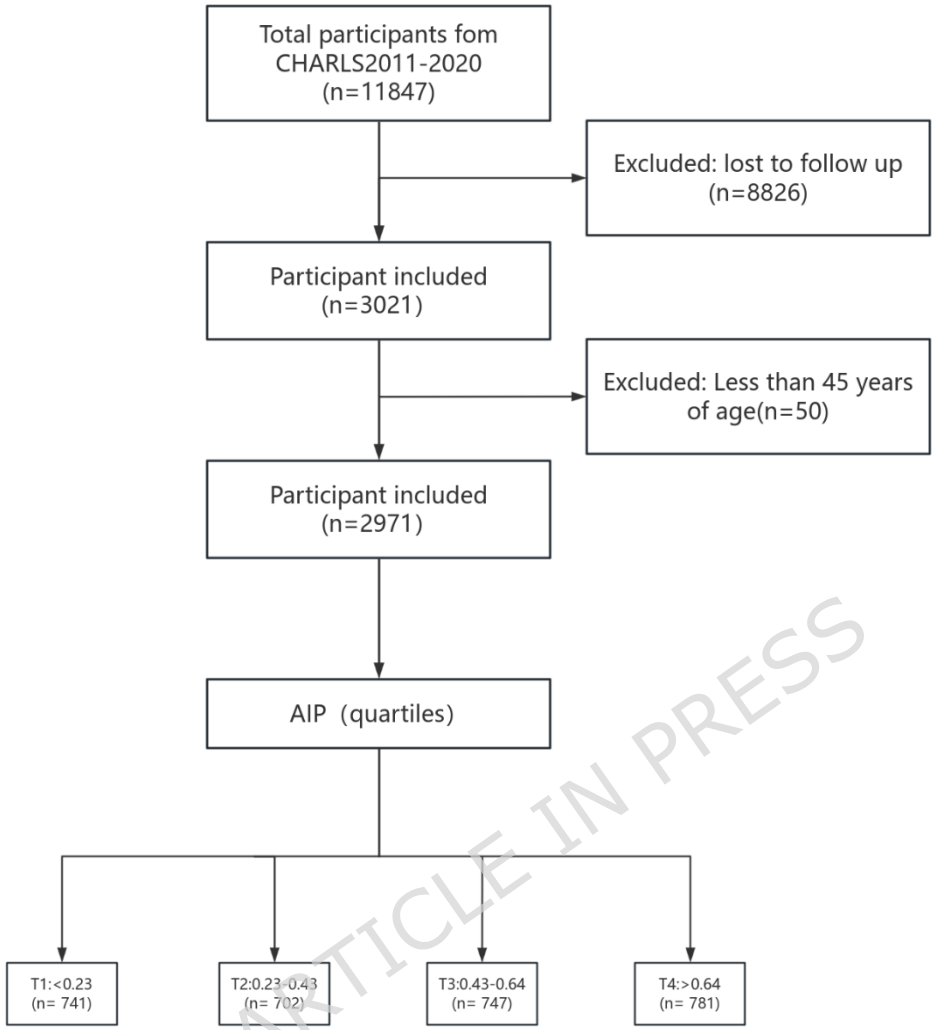
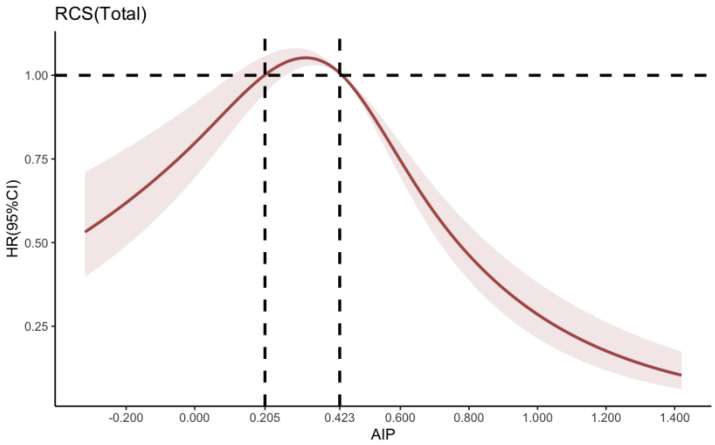
Fig.1 Flow diagram of subjects included in the cohort study



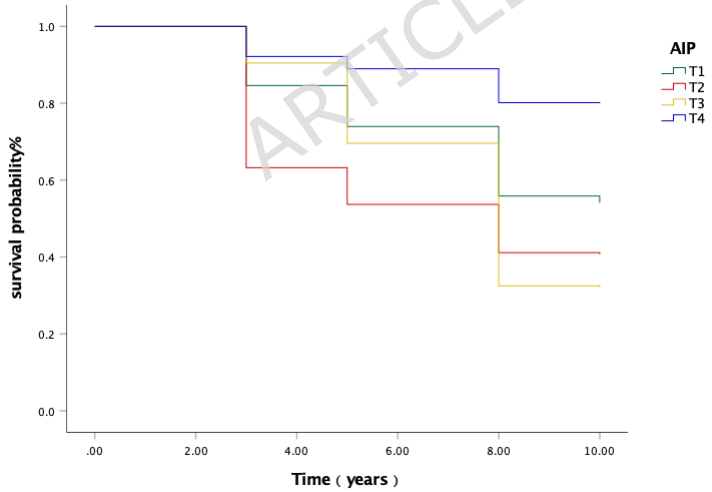
Note: CHARLS: China Health and Retirement Longitudinal Study; AIP: Atherogenic Index of Plasma;

Fig.2 RCS curves for the associations of the AIP of the overall population



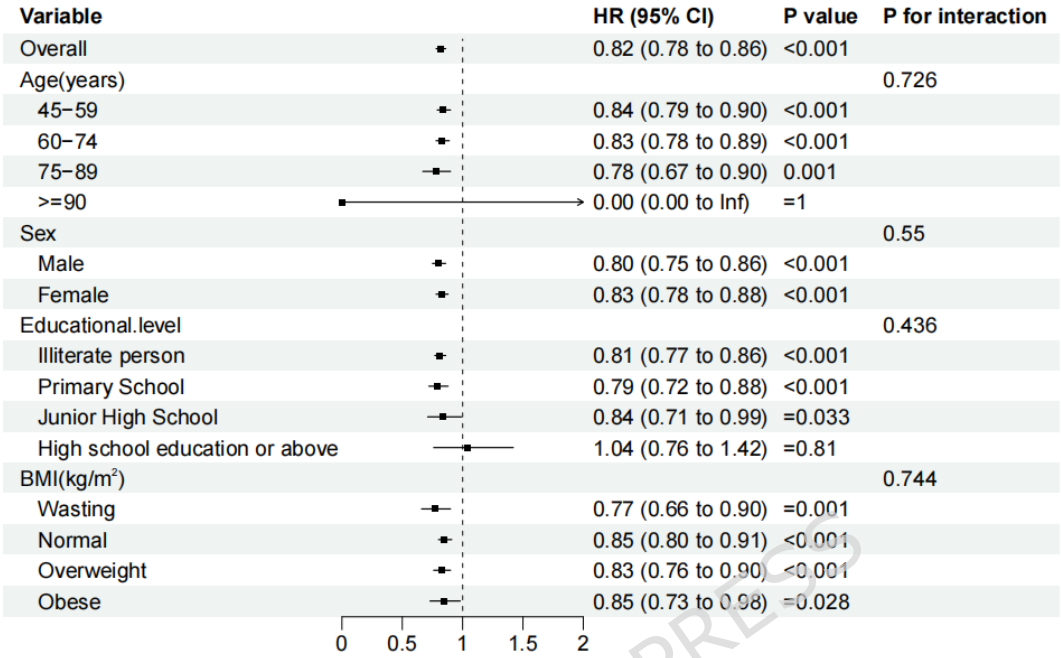
Note: AIP: Atherogenic Index of Plasma; *HR*: Hazard Ratio; *CI*: Confidence Interval. The shaded area represents the 95% confidence interval. The dashed line is the reference line (*HR*=1).. The figure indicates the AIP range where the risk significantly increases (0.205-0.423).

Fig.3 Kaplan-Meier survival curves of different degrees of AIP population



Note: AIP: Atherogenic Index of Plasma. T1-T4 represent four quartile groups of AIP from low to high (cut-off points: <0.23, 0.23-0.42, 0.43-0.63, ≥0.64). The survival probability is defined as the probability of not developing cognitive impairment.

Fig.4 Subgroup analysis of association of AIP with cognitive impairment



Note: BMI: Body Mass Index; *HR*: Hazard Ratio; *CI*: Confidence Interval. The black dots represent the HR for each subgroup, with the horizontal lines indicating the 95% CI. The vertical dashed line represents the overall HR reference line. The HR for each subgroup is calculated based on continuous AIP values.

Table 1 Baseline characteristics of participants（n=2971）

Variables		Cognitive		*P*
		No	Yes	
Age(years)	45-59	991(63.9)	581(40.9)	<0.001
	60-74	532(34.3)	674(47.5)	
	75-89	29(1.9)	162(11.4)	
	≥90	0(0.0)	2(0.1)	
Sex	Male	846(54.5)	575(40.5)	<0.001
	Female	706(45.5)	844(59.5)	
Marital status	Married	1443(93.0	1198(84.4	<0.001
	Divorced	12(0.8)	3(0.2)	
	Widowed	92(5.9)	209(14.7)	
	Unmarried	5(0.3)	9(0.6)	
Smoking	Yes	644(41.5)	541(38.1)	0.061
	No	908(58.5)	878(61.9)	
Drinking	Never or rarely	1281(82.5	1114(78.5	0.011
	Rarely or less than	145(9.3)	149(10.5)	
	More than once	126(8.1)	156(11.0)	
Education level	Illiterate person	317(20.4)	1024(72.2	<0.001
	Primary School	441(28.4)	276(19.5)	
	Junior High School	501(32.3)	93(6.6)	
	High school education	293(18.9)	26(1.8)	
Dyslipidemia	Yes	177(11.4)	104(7.3)	<0.001
	No	1375(88.6	1315(92.7	
Chronic lung diseases	Yes	126(8.1)	156(11.0)	0.008
	No	1426(91.9	1263(89.0	
Arthritis	Yes	491(31.6)	549(38.7)	<0.001
	No	1061(68.4	870(61.3)	
Stroke	Yes	22(1.4)	34(2.4)	0.050
	No	1530(98.6	1385(97.6	
Hypertension	Yes	373(24.0)	378(26.6)	0.103
	No	1179(76.0	1041(73.4	
Heart disease	Yes	195(12.6)	147(10.4)	0.060
	No	1357(87.4	1272(89.6	
AIP	<0.23(T1)	401(25.8)	340(24.0)	<0.001
	0.23-0.42(T2)	286(18.4)	416(29.3)	
	0.43-0.63(T3)	240(15.5)	507(35.7)	
	≥0.64(T4)	625(40.3)	156(11.0)	
BMI(kg/m^2)	Wasting	50(3.2)	133(9.4)	<0.001
	Normal	755(48.6)	757(53.3)	
	Overweight	518(33.4)	381(26.8)	
	Obese	229(14.8)	148(10.4)	

Note: BMI: Body Mass Index; AIP: Atherogenic Index of Plasma.

Table 2 Multivariate Cox Regression Analysis Showing the Association between AIP and Other Covariates with the Risk of Cognitive Impairment (Analysis of the Entire Population)

Variables		*β*	*SE*	*P*	*HR(95%CI)*
	45-59(Reference)			<0.0	
Age(years)	60-74	0.19	0.0	0.00	1.221(1.087-
	75-89	0.79	0.0	<0.0	2.208(1.825-
	>=90	0.85	0.7	0.23	2.341(0.574-
Sex	Male(Reference)				
	Female	0.17	0.0	0.00	1.188(1.052-
Marital status	Married(Reference)			0.08	
	Divorced	0.05	0.5	0.92	1.054(0.338-
	Widowed	0.17	0.0	0.03	1.187(1.013-
	Unmarried	0.51	0.3	0.13	1.670(0.860-
Drinking	Never or			0.01	
	Rarely or less than	0.13	0.0	0.14	1.139(0.954-
	More than once	0.24	0.0	0.00	1.271(1.065-
Educational	Illiterate			<0.0	
	Primary School	-0.8	0.0	<0.0	0.439(0.383-
	Junior High School	-1.6	0.1	<0.0	0.190(0.153-
	High school education	-2.3	0.2	<0.0	0.097(0.065-
Dyslipidemia	Yes(Reference)				
	No	0.10	0.1	0.31	1.111(0.906-
Chronic lung	Yes(Reference)				
	No	-0.0	0.0	0.99	0.999(0.842-
Arthritis	Yes(Reference)				
	No	-0.0	0.0	0.30	0.945(0.84-1.
AIP	<0.23(T1)(Reference)			<0.0	
	0.23-0.42(T2)	0.34	0.0	<0.0	1.412(1.221-
	0.43-0.63(T3)	0.20	0.0	0.00	1.227(1.066-
	≥0.64(T4)	-0.7	0.0	<0.0	0.475(0.391-
BMI(kg/m^2)	Wasting(Reference)			0.02	
	Normal	-0.2	0.0	0.02	0.806(0.668-
	Overweight	-0.3	0.1	0.00	0.735(0.600-
	Obese	-0.3	0.1	0.00	0.725(0.568-

Note: BMI: Body Mass Index; AIP: Atherogenic Index of Plasma；*HR*: Hazard Ratio; *CI*: Confidence Interval.

Table 3 Multivariate Cox Regression Analysis Showing the Association between AIP and Other Covariates with the Risk of Cognitive Impairment (Sensitivity Analysis: Excluding Participants Aged 75 and Above)

Variables		*β*	*SE*	*P*	*HR(95%CI)*
Age(years)	45-59(Reference)				
	60-74	0.19	0.0	0.00	1.210(1.077-
Sex	Male(Reference)				
	Female	0.17	0.0	0.00	1.192(1.049-
Marital status	Married(Reference)			0.15	
	Divorced	-0.2	0.7	0.72	0.775(0.192-
	Widowed	0.16	0.0	0.07	1.179(0.986-
	Unmarried	0.49	0.3	0.17	1.635(0.808-
Drinking	Never or			0.02	
	Rarely or less than	0.15	0.0	0.10	1.163(0.967-
	More than once	0.22	0.0	0.01	1.252(1.040-
Educational	Illiterate			<0.0	
	Primary School	-0.8	0.0	<0.0	0.432(0.374-
	Junior High School	-1.7	0.1	<0.0	0.180(0.143-
	High school education	-2.3	0.2	<0.0	0.093(0.062-
Dyslipidemia	Yes(Reference)				
	No	0.06	0.1	0.53	1.069(0.865-
Chronic lung	Yes(Reference)				
	No	0.01	0.0	0.86	1.016(0.845-
Arthritis	Yes(Reference)				
	No	-0.0	0.0	0.30	0.941(0.839-
AIP	<0.23(T1)(Reference)			<0.0	
	0.23-0.42(T2)	0.37	0.0	<0.0	1.451(1.241-
	0.43-0.63(T3)	0.23	0.0	0.00	1.264(1.089-
	≥0.64(T4)	-0.7	0.1	<0.0	0.474(0.386-
BMI(kg/m^2)	Wasting(Reference)			0.00	
	Normal	-0.3	0.1	0.00	0.714(0.582-
	Overweight	-0.4	0.1	<0.0	0.652(0.524-
	Obese	-0.4	0.1	0.00	0.645(0.500-

Note: BMI: Body Mass Index; AIP: Atherogenic Index of Plasma；*HR*: Hazard Ratio; *CI*: Confidence Interval.

Table4 Bare Pool Information Criterion for different node models.

Nodes	*AIC*	*P* total	*P* nonlinearity
Nodes=3	21741.74	<0.001	<0.001
Nodes=4	21743.72	<0.001	<0.001
Nodes=5	21380.68	<0.001	<0.001
Nodes=6	21408.21	<0.001	<0.001
Nodes=7	21323.28	<0.001	<0.001