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Association Between the Trajectories of the Atherogenic Index of Plasma and Prediabetes Progression to Diabetes: A Retrospective Cohort Study

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Purpose: This study aims to analyze baseline profiles and longitudinal changes in Atherogenic Index of Plasma (AIP) among individuals with prediabetes to identify distinct AIP trajectories and assess their significance in predicting diabetes onset.

Methods: This retrospective cohort study analyzed data from 8346 participants who underwent multiple general health checks. Utilizing latent class trajectory modeling and Cox proportional hazards analyses, it examined the association between the AIP index and health outcomes.

Results: Over about 2 years, 2897 people progressed from prediabetes to diabetes. Individuals in the highest quartile of AIP had a higher diabetes risk compared to the lowest quartile (HR = 1.138, 95% CI1.013–1.278). Trajectory analysis revealed three groups: low-stable, moderate-stable, and high-stable, based on AIP index. The moderate-stable group showed a 1.117-fold risk of diabetes progression (95% CI1.026–1.217), while the high-stable group had an elevated risk (HR = 1.224, 95% CI1.059–1.415).

Conclusion: The study highlights a clear association between higher AIP index levels at baseline and an increased risk of diabetes progression. It underscores the significance of utilizing the AIP index as a predictive tool to identify those at risk, emphasizing the need for targeted preventive measures in managing diabetes progression.

Keywords: retrospective cohort study, atherogenic index of plasma, prediabetes progression, diabetes

Introduction

Prediabetes represents a crucial stage in the progression toward type 2 diabetes (T2DM), signaling heightened risks for future diabetes, cardiovascular diseases, microvascular complications, and related conditions.[1] Despite its importance, the global prevalence of prediabetes was 7.7% in 2017, impacting approximately 374 million individuals, with projections estimating that by 2045, approximately 548 million adults will have prediabetes, accounting for 8.6% of the global adult population.[2,3] Significantly, each year, 5% to 10% of adults with prediabetes advance to diabetes, with about 70% eventually developing diabetes.[4] Hence, effective intervention for individuals with prediabetes is crucial for averting diabetes onset.

Atherosclerosis, a fundamental process in cardiovascular diseases, is intricately linked to glucose dysregulation. The Atherogenic Index of Plasma (AIP), conceptualized by dobiášová et al[5] is characterized as the logarithm of the quotient of plasma triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C). It serves as a marker of lipid-related atherosclerosis, offering insights into cardiovascular risk. Previous research underscores the role of lipotoxicity in peripheral insulin resistance and dysfunction of pancreatic β-cells, key stages in T2DM pathogenesis.[6,7] Interventions

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targeting lipotoxicity can mitigate the natural progression of prediabetes by reducing endogenous insulin levels in patients with hypertriglyceridemia.[8] Recent observational studies reaffirm the significant association between AIP and prediabetes/diabetes onset.[9–12]

Despite recognizing the connection between atherosclerosis and glucose metabolism, comprehensive studies on baseline characteristics and longitudinal AIP trajectories in prediabetes, as well as its predictive value for diabetes progression, remain sparse. This retrospective cohort study seeks to clarify the association between plasma AIP trajectories and the transition from prediabetes to diabetes. By examining baseline profiles and longitudinal AIP changes among individuals with prediabetes, we aim to delineate distinct AIP trajectories and evaluate their predictive capacity for diabetes onset. Understanding the dynamic interplay between AIP trajectories and T2DM development holds clinical significance for risk assessment and preventive strategies.

Methods

Study Design and Setting

The foundational clinical data utilized in this analysis were acquired from individuals undergoing health assessments Health Promotion Center of Sir Run Run Shaw Hospital, Zhejiang University, located in Hangzhou, China. The data encompass the timeframe spanning from January 2017 to December 2021. Initially, a cohort of 381,768 individuals was considered. However, after applying exclusion criteria, the following groups were excluded: (1) individuals without completed diabetic history records, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), and HbA1c data (n = 145,972); (2) individuals who underwent the general health check only once (n = 26,385); (3) individuals who did not meet the prediabetes diagnostic criteria (n = 64,847). The exclusions led to a final sample size of 8346 individuals for analysis, as depicted in Figure 1.

Definition of Outcome

The primary outcome investigated in this study was related to changes in glycemic status during follow-up in individuals initially diagnosed with prediabetes. The outcomes were defined following the criteria outlined by the American Diabetes Association, diabetes mellitus were determined based on fasting plasma glucose (FPG) levels.[13] Specifically, diabetes mellitus is defined as a self-reported diagnosis or FPG measurement of more than 7.0 mmol/L, or a hemoglobin A1c (HbA1c) level of more than 6.5% during the follow-up period. Prediabetes, on the other hand, is characterized by FPG levels between 5.6 mmol/L and 6.9 mmol/L with no prior diagnosis of diabetic disease.

Characteristics and Definition

The medical history was systematically collected by well-trained general practitioners at Zhejiang University Affiliated Sir Run Run Shaw Hospital. It included comprehensive information such as chief complaints, current medical conditions, past medical history, personal history, family history, and physical examinations. Hypertension was characterized as systolic blood pressure (SBP) equal to or exceeding 140 mmHg, and diastolic blood pressure (DBP) equal to or surpassing 90 mmHg, current use of antihypertensive medications, or a self-reported history of hypertension. Trained nurses conducted measurements of body weight, height, and blood pressure (BP). Body Mass Index (BMI) was computed as the weight (in kilograms) divided by the square of height (in meters). Various laboratory tests were conducted, including assessments of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). LDL-C was obtained directly from laboratory measurements of blood samples, with no estimation or use of formulas required. AIP was calculated as the logarithm base 10 of the ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C).[5]

Statistical Analyses

A comprehensive statistical analysis to investigate the relationship between the AIP index and diabetes progression. Descriptive statistics were utilized to summarize baseline AIP index quartiles, presenting mean ± standard deviation for normally distributed data, medians with interquartile ranges (IQRs) for skewed distributions, and frequencies with

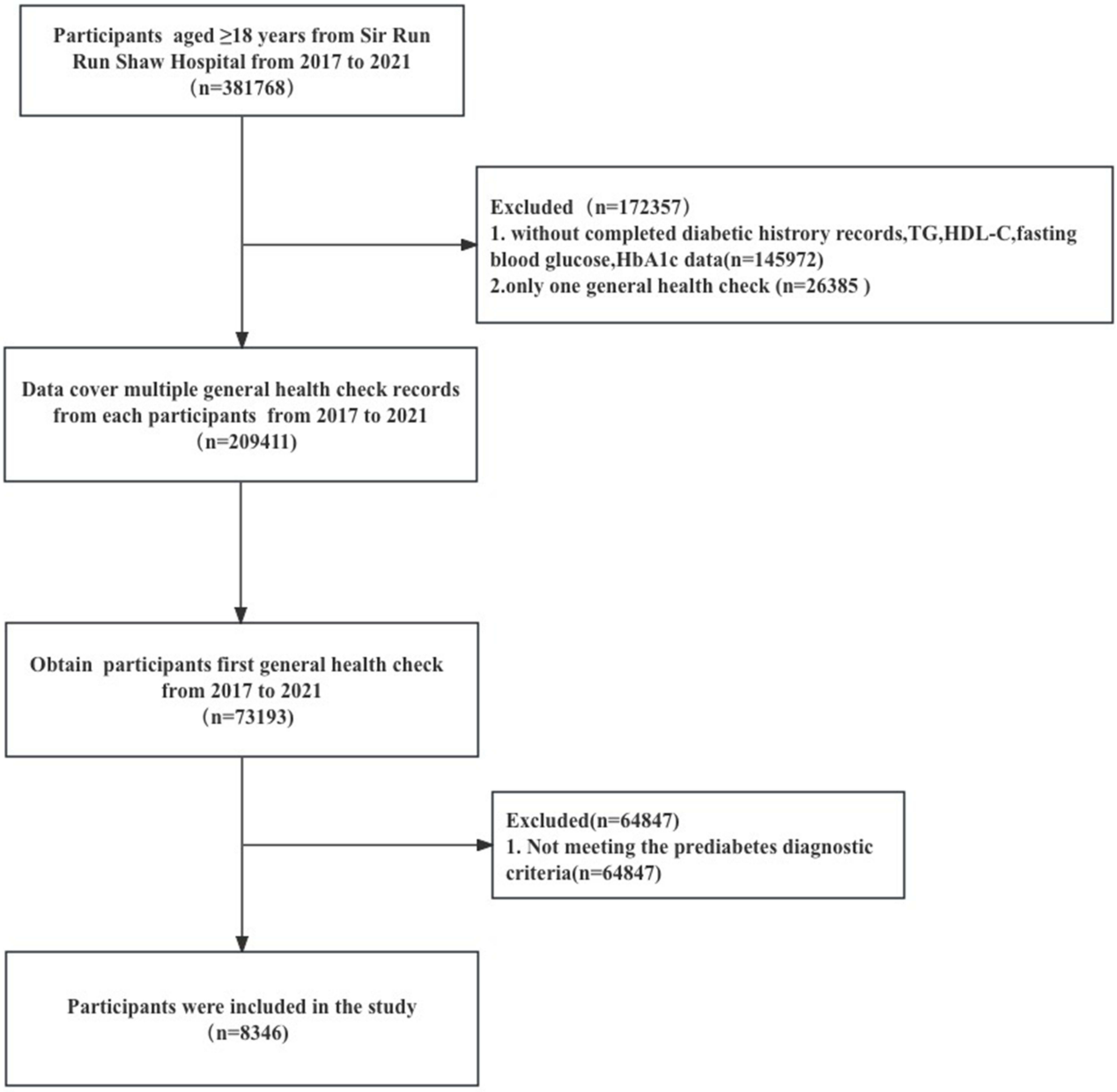

Figure 1 Flowchart of current study.

percentages (%) for categorical variables. To compare continuous variables across groups, we employed Mann–Whitney *U*-tests or Kruskal–Wallis H-tests, while categorical variables were assessed using the chi-squared test or Fisher's exact test. The Cox proportional hazards regression model was employed to investigate the relationship between baseline AIP index quartiles, AIP index per standard deviation change, and diabetes progression, while considering covariates including age, male sex, BMI, and hypertension.

In order to discern trajectories of the AIP index over time, we applied latent class trajectory models, a specialized form of finite mixture modeling.[14] These models identify latent classes of individuals with similar progressions of the AIP index over time or with age. The optimal number of trajectories was determined based on the minimum Bayesian Information Criterion, while ensuring posterior probabilities by class (>0.70) and class size (≥2% of the population). Trajectories were labeled for interpretability according to their modeled graphic patterns.

All statistical analyses were performed using IBM SPSS software (version 23.0, SPSS Inc., Chicago, IL) and RStudio (version 2022.02.3, Boston, MA) along with associated packages. Statistical significance was defined as two-tailed *P* values < 0.05.

Results

Baseline Characteristics of Study Participants

The baseline characteristics of the study population, categorized by quartiles of AIP, are presented in Table 1. The analysis included 8346 participants, with a mean age of 48.9 ± 12.0 years. The mean ± SD of AIP was calculated as 0.14 ± 0.32. Table 1 provides details on the demographic and clinical attributes at baseline across different AIP groups. Over a median follow-up duration of 756 days, 2897 individuals (35%) progressed from prediabetes to diabetes.

Associations Between Baseline AIP Index and Diabetes Progression

Table 2 illustrates a notable increase in the risk of diabetes progression with higher AIP quartiles. Following thorough adjustment for potential confounders, a 1-standard deviation increase in the AIP index was associated with a 16% increased risk of diabetes progression in the multivariate model, considering the AIP index as a continuous variable (HR

Table 1 Baseline Characteristics of Study Participants According to Quartiles of AIP Index

Characteristic	Overall, N = 8346	Q1, N = 2087	Q2, N=2086	Q3, N = 2086	Q4, N=2087	*P*-value
AIP index	0.14 ± 0.32	−0.25 ± 0.13	0.02 ± 0.06	0.23 ± 0.06	0.55 ± 0.20	<0.001
Age (years)	48.9 ± 12.0	49.1 ± 13.4	50.0 ± 12.5	48.4 ± 11.5	48.2 ± 10.5	<0.001
Gender						<0.001
F	2656 (32%)	1029 (49%)	709 (34%)	534 (26%)	384 (18%)	
M	5690 (68%)	1058 (51%)	1377 (66%)	1552 (74%)	1703 (82%)	
BMI, kg/m2	24.9 ± 3.2	23.5 ± 3.0	24.8 ± 3.0	25.5 ± 3.1	26.0 ± 3.1	<0.001
Hypertension	1446 (17%)	288 (14%)	372 (18%)	351 (17%)	435 (21%)	<0.001
TG, mmol/L	1.96 ± 1.67	0.86 ± 0.21	1.33 ± 0.27	1.88 ± 0.36	3.76 ± 2.45	<0.001
HDL-C, mmol/L	1.21 ± 0.30	1.51 ± 0.29	1.25 ± 0.21	1.11 ± 0.19	0.97 ± 0.18	<0.001
TC, mmol/L	5.09 ± 0.99	4.85 ± 0.94	5.01 ± 0.94	5.15 ± 0.94	5.33 ± 1.07	<0.001
LDL-C, mmol/L	2.88 ± 0.80	2.74 ± 0.78	2.99 ± 0.76	3.07 ± 0.77	2.72 ± 0.85	<0.001
FBG, mmol/L	5.95 ± 0.31	5.91 ± 0.29	5.94 ± 0.31	5.95 ± 0.30	5.99 ± 0.33	<0.001
HbA1c,%	5.60 ± 0.41	5.54 ± 0.41	5.60 ± 0.42	5.65 ± 0.40	5.63 ± 0.41	<0.001
Event status[#]	2897 (35%)	685 (33%)	707 (34%)	738 (35%)	767 (37%)	0.043

Note: [#]Event_status: participants from prediabetes to diabetes.
Abbreviations: BMI, body mass index; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; AIP index: Atherogenic Index of Plasma, calculated as the logarithm of the ratio of plasma triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C).

Table 2 Hazard Ratios (95% CI) for the Progression of Diabetes Across Baseline AIP Index Categories

AIP index	Diabetes Progression (N)	Unadjusted	*P*	Model 1	*P*	Model 2	*P*
		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Quartile 1	685/2087	Reference		Reference		Reference	
Quartile 2	707/2086	1.056 (0.951,1.173)	0.309	1.068 (0.961, 1.187)	0.225	1.037 (0.931, 1.154)	0.511
Quartile 3	738/2086	1.103 (0.994, 1.224)	0.064	1.135 (1.021, 1.262)	0.019	1.087 (0.975, 1.211)	0.133
Quartile 4	767/2087	1.152 (1.039, 1.277)	0.007	1.197 (1.076, 1.331)	< 0.001	1.138 (1.013, 1.278)	0.030
Per 1 SD	2897 /8346	1.159 (1.036,1.296)	0.010	1.214 (1.081, 1.364)	0.001	1.161 (1.012, 1.333)	0.034

Notes: Model 1: Adjusted for age and male. Model 2: Adjusted for age, male, BMI, hypertension, and TC, LDL-C.
Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.

= 1.161, 95% CI 1.012–1.333, $P = 0.034$, as shown in Table 2). Similar results were observed when individuals were categorized by AIP index quartiles, revealing the highest risk among those in the top quartile across three distinct adjusted models (all $P < 0.05$, as illustrated in Table 2). Significantly, the ultimate model presented hazard ratios (HRs) with 95% confidence intervals (CIs) for diabetes progression. Comparisons between the second, third, and fourth quartiles of the AIP index against the first quartile yielded values of 1.037 (95% CI 0.931–1.154), 1.087 (95% CI 0.976–1.211), and 1.138 (95% CI 1.013–1.278), respectively (as shown in Table 2). Figure 2, categorized by quartiles of the baseline AIP index, illustrates the Kaplan–Meier survival curves for diabetes progression (Log rank test, $P < 0.05$). These results emphasize the notable association between the baseline AIP index and diabetes progression.

Baseline Characteristics According to AIP Index Trajectories

Following thorough evaluation utilizing model-adequacy criteria and interpretability guidelines, three clearly defined trajectories of the AIP index were identified. Figure 3 displays the finalized models of latent class trajectory delineating the low-stable (n = 2745), moderate-stable (n = 4764), and high-stable AIP index trajectory groups (n = 837). Table 3 offers a comprehensive overview of the initial demographic and clinical traits pertaining to the AIP index trajectories. Aligned with the initial quartiles of the AIP index, heightened levels of the AIP index trajectory corresponded with elevated diabetes risk factors, correlating with an augmented risk of diabetes progression (Table 3). These outcomes underscore a significant correlation between the AIP index trajectory and diabetes progression. Moreover, Figure 4 displays the Kaplan–Meier survival curves for diabetes progression, with statistical significance determined by the Log rank test ($P < 0.05$).

The Relationship Between AIP Index Trajectories and Diabetes Progression

Table 4 delineates the associations between AIP index trajectories and diabetes progression. In comparison with the low-stable group, both the moderate-stable group and the high-increasing group exhibited independent associations with diabetes progression. Following adjustments for age, sex, BMI, hypertension, TC, and LDL-C covariates, the moderate-

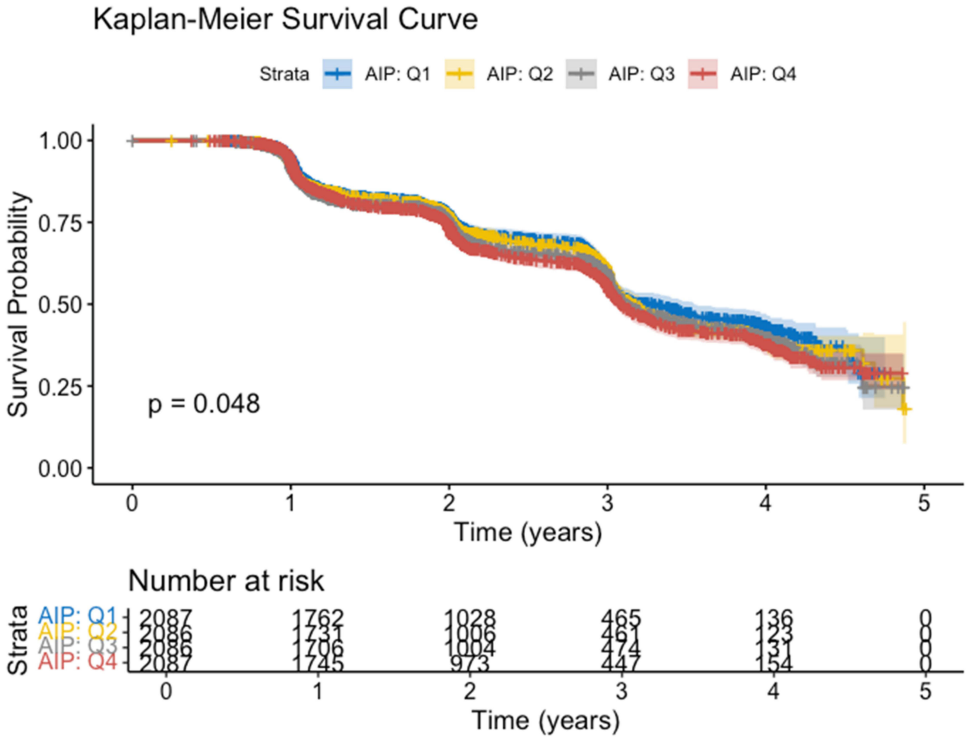

Figure 2 Kaplan-Meier survival analysis for diabetes progression stratified by AIP index.

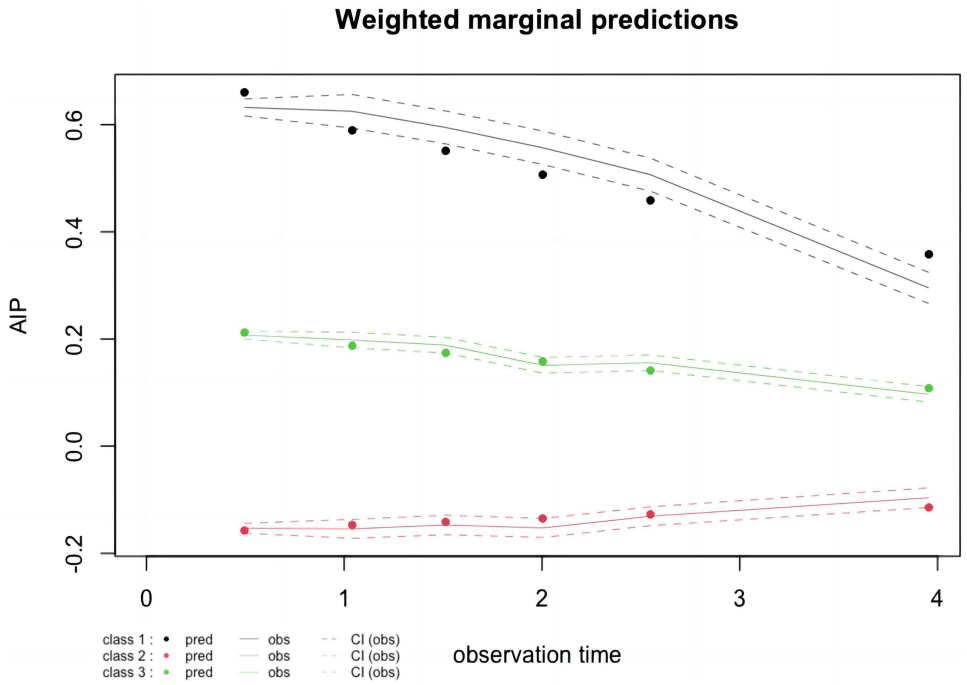

Figure 3 Trajectories of Over Time by AIP class.

stable group demonstrated a 1.117-fold (95% CI 1.0261–1.2168) increased risk of diabetes progression, while the high-stable group showed a 1.2244 -fold (95% CI 1.0593–1.4153) heightened risk of diabetes progression (Table 4).

Discussion

In this large retrospective cohort study, we found that the AIP was significantly associated with the risk of diabetes progression. Each 1-standard deviation increase in the AIP index was associated with a 16% higher risk of diabetes progression. In the fully adjusted multivariable model, individuals in the fourth quartile of AIP had a higher prevalence

Table 3 Baseline Characteristics of Study Participants Grouped by Trajectories of the AIP Index

Characteristic	Overall, N = 8346	Low-stable, N = 2745	Moderate-stable, N = 4764	High-stable, N = 837	*P*-value
AIP index	0.14 ± 0.32	−0.17 ± 0.17	0.22 ± 0.19	0.67 ± 0.24	<0.001
Age (years)	48.9 ± 12.0	49.3 ± 13.4	49.0 ± 11.6	47.2 ± 9.7	<0.001
Gender					<0.001
F	2656 (32%)	1305 (48%)	1264 (27%)	87 (10%)	
M	5690 (68%)	1440 (52%)	3500 (73%)	750 (90%)	
BMI, kg/m2	24.9 ± 3.2	23.8 ± 3.1	25.4 ± 3.1	26.0 ± 3.1	<0.001
Hypertension	1446 (17%)	401 (15%)	862 (18%)	183 (22%)	<0.001
TG, mmol/L	1.96 ± 1.67	1.01 ± 0.35	1.99 ± 0.88	4.88 ± 3.37	<0.001
HDL-C, mmol/L	1.21 ± 0.30	1.45 ± 0.29	1.13 ± 0.22	0.92 ± 0.17	<0.001
TC, mmol/L	5.09 ± 0.99	4.90 ± 0.92	5.14 ± 0.97	5.39 ± 1.19	<0.001
LDL-C, mmol/L	2.88 ± 0.80	2.80 ± 0.76	3.00 ± 0.79	2.46 ± 0.84	<0.001
FBG, mmol/L	5.95 ± 0.31	5.91 ± 0.30	5.96 ± 0.31	5.99 ± 0.33	<0.001
HbA1c,%	5.60 ± 0.41	5.56 ± 0.41	5.64 ± 0.41	5.58 ± 0.40	<0.001
Event status[#]	2897 (35%)	880 (32%)	1681 (35%)	336 (40%)	<0.001

Note: [#]Event_status: participants from prediabetes to diabetes.
Abbreviations: BMI, body mass index; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; AIP index: Atherogenic Index of Plasma, calculated as the logarithm of the ratio of plasma triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C).

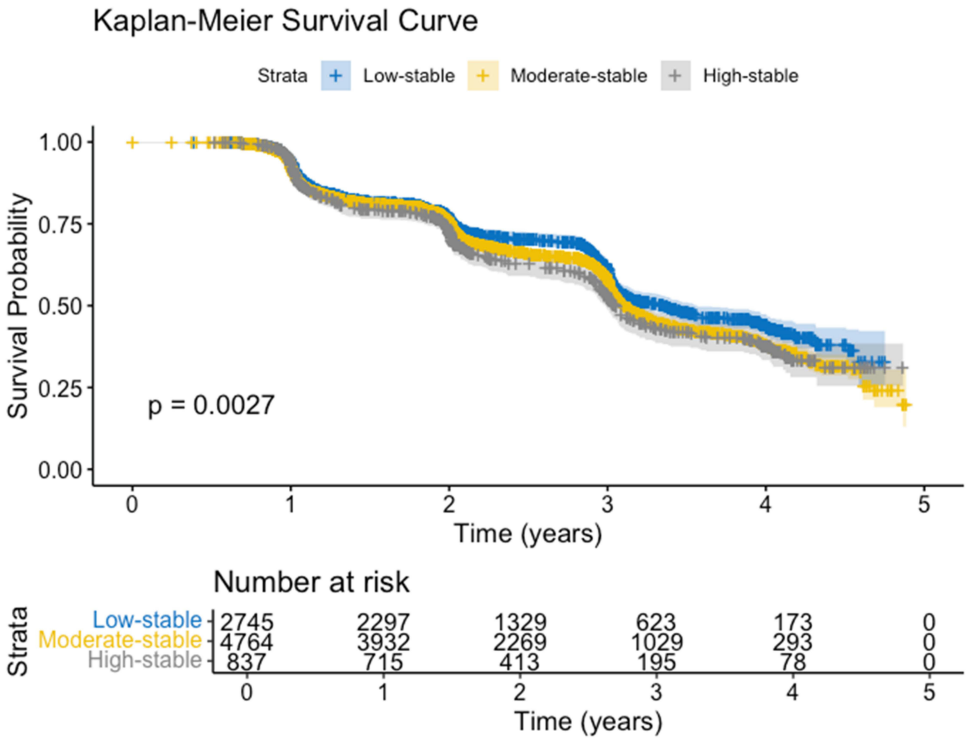

Figure 4 Kaplan–Meier survival analysis curves for diabetes progression stratified by trajectories of the baseline AIP index.

of diabetes compared to those in the first quartile. Trajectory analysis identified low-stable, moderate-stable, and high-stable AIP groups, with both moderate-stable and high-stable trajectories showing increased risks of diabetes progression. These findings underscore the potential of AIP as a predictive marker for identifying individuals at risk of diabetes progression and highlight the importance of targeted preventive measures among high-risk individuals.

In recent years, AIP has been firmly established as a non-traditional lipid parameter for assessing the risk of atherosclerosis, significantly contributing to the evaluation and prediction of vascular-related diseases.[15–17] Dyslipidemia associated with atherosclerosis serves as a modifiable risk factor for diabetes and cardiovascular events among prediabetic individuals, garnering increasing recognition for intensified lipid management by endocrinologists and researchers.[18] Studies such as Wan et al suggest that lipid control effectively improves the natural course of prediabetes.[19] In our current investigation focusing on prediabetic individuals, we observed a significant positive correlation between AIP and the incidence of diabetes. Following thorough adjustment for confounding factors, our results indicate that for each unit increase in AIP, the risk of diabetes onset among prediabetic patients increases by 16%. These findings align with previous reports predominantly centered on Chinese and other ethnic populations, indicating that elevated AIP levels heighten the risk of diabetes onset.[9,12,20] However, most prior studies have primarily focused on baseline or single-level AIP indices, with limited data on dynamic changes over time. Leveraging healthcare screening systems, researchers collected multiple AIP measurements across various visits, enabling the identification of long-term AIP trajectories in real-world studies. Importantly, compared to analyzing solely baseline AIP levels, this investigation for the first time elucidates the impact of long-term AIP trends on the incidence of diabetes among prediabetic participants, providing insights into the cumulative burden of AIP on diabetes incidence.

The progression of diabetes is highly intricate, involving a myriad of factors such as insulin resistance, impaired pancreatic β-cell function, oxidative stress, and endothelial dysfunction—all interacting in a complex manner.[21] However, the underlying mechanisms of the relationship between Atherogenic Index of Plasma (AIP) and the onset of diabetes remain elusive. One plausible explanation is that AIP, calculated based on triglycerides (TG) and high-density lipoprotein (HDL), correlates with the development of diabetes in connection with decreased HDL-C levels and elevated TG levels.[22] Current research indicates that lipotoxicity plays a crucial role in two key aspects of type 2 diabetes mellitus

Table 4 Hazard Ratios (95% CI) for Diabetes Progression Across Trajectory Groups of the AIP Index

AIP Index Trajectories	Diabetes Progression (N)	Unadjusted	*P*	Model 1	*P*	Model 2	*P*
		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Low-stable	880/2745	Reference		Reference		Reference	
Moderate-stable	1681/4764	1.129 (1.040, 1.225)	0.00365	1.156 (1.063, 1.256)	<0.001	1.117 (1.026, 1.217)	0.0110
High-stable	336/837	1.204 (1.062, 1.366)	0.00374	1.265 (1.112, 1.439)	<0.001	1.224 (1.059, 1.415)	0.006

Notes: Model 1: Adjusted for age and male; Model 2: Adjusted for age, male, BMI, hypertension, and TC, LDL-C.
Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.

(T2DM) pathogenesis: peripheral insulin resistance and pancreatic β-cell dysfunction.[6,7] Additionally, individuals with hypertriglyceridemia exhibit decreased endogenous intestinal insulin levels.[23] High-density lipoprotein particles may confer protection by facilitating reverse cholesterol transport, exerting antioxidative and anti-inflammatory effects, as well as influencing skeletal muscle glucose uptake and safeguarding pancreatic β-cell function to ameliorate glucose regulation.[24–26] However, in the context of diabetes, these defensive functions of high-density lipoprotein particles appear compromised.

In addition to the biochemical mechanisms mentioned above, it is important to consider the impact of lifestyle factors such as weight gain and poor dietary habits on AIP and its relationship with diabetes.[27] Increased body weight, especially when associated with an unhealthy diet rich in saturated fats and sugars, is a well-established risk factor for both dyslipidemia and the development of type 2 diabetes.[28] In such cases, the typical lipid profile is characterized by low HDL-C levels and high triglyceride (TG) levels, which directly contribute to a higher AIP.[29,30] This suggests that AIP may serve as a marker not only for lipid abnormalities but also for the adverse effects of unhealthy lifestyle choices.

Therefore, while AIP has been shown to correlate with the onset of diabetes, further studies are needed to investigate the potential mechanistic pathways linking AIP, body weight, diet, and diabetes development. In particular, assessing AIP as a predictive tool for diabetes risk could be valuable in clinical settings, where early intervention and lifestyle modification could help mitigate the progression of the disease.

Strengths and Limitations of the Study

The study's primary strength lies in its utilization of a large, longitudinal population cohort featuring repeated measurements of AIP index profiles. This approach allowed for the establishment of baseline and follow-up relationships between the AIP index and diabetes progression, thereby enabling the effective monitoring of AIP trajectory patterns and bolstering the robustness and reliability of the findings. Additionally, the implementation of the longitudinal lipid trajectory method, facilitated through LCTM, offered detailed insights into lipid trajectory changes over time.

Several limitations necessitate acknowledgment in this study. Firstly, its single-center nature in China highlights the need for inclusion and validation of results from multicenter samples across various provinces to improve the generalizability of the findings. Secondly, the predominance of Chinese individuals with T2D in the study population may constrain the applicability of the results to other racial or ethnic groups. Thirdly, participant data obtained from general health checkups relied on self-reported conditions, thus potentially overlooking influential variables such as family history, diet, lifestyle, and medications, which could affect the study outcomes.

Given these limitations, future investigations should prioritize large-scale prospective cohort studies to validate and expand upon these initial findings, fostering a more comprehensive understanding of the relationship between the AIP index and diabetes progression across diverse populations and settings.

Conclusions

Our study suggests that the higher the baseline AIP, the higher the risk of progression to diabetes in individuals with prediabetes. This association was further highlighted by trajectory analysis, suggesting that both moderately stable and highly stable AIP trajectories indicate an increased risk of diabetes progression, emphasizing that AIP is a valuable predictive marker for identifying individuals at risk of transitioning from prediabetes to diabetes.

Data Sharing Statement

The datasets produced and analyzed in the present study can be obtained from the corresponding author upon reasonable inquiry.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Helsinki Declaration (2013 revision) and received approval from the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Approval No: 2024-2095-01). Informed consent from individual patients was waived by the Ethics Committee (Sir Run Run Shaw Hospital, Zhejiang University School of Medicine) due to the retrospective nature of the study, involving the analysis of data

derived from previous clinical diagnoses and treatments. Notably, medical records of patients who explicitly refused consent were excluded from the study. The research did not adversely affect the rights and health of the subjects, and stringent measures were implemented to protect the privacy and personal identity information of the participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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