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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-092714
Article Type:	Original research
Date Submitted by the Author:	21-Aug-2024
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Keywords:	DIABETES & ENDOCRINOLOGY, Cardiovascular Disease, Body Mass Index, PUBLIC HEALTH

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Mediation Effect of Body Mass Index on the Association Between Glycated Albumin and 10-Year Atherosclerotic Cardiovascular Disease Risk in Hunan Residents of China: A Retrospective Study

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Abstract

Objectives: Glycated albumin (GA) and body mass index (BMI) have been linked to atherosclerotic cardiovascular disease (ASCVD). However, the role of BMI in the correlation between GA and 10-year ASCVD risk is still not fully understood.

Design: A Retrospective Study

Setting: This study retrospectively obtained data from 2,107 participants who received health checkups at the Health Management Medicine Center, Third Xiangya Hospital of Central South University from January 1, 2022 to December 30, 2023.

Participants: The inclusion criteria for this study included: a) age is greater than or equal to 18 years old; and b) subjects were long-term residents of Hunan province.

Primary and secondary outcome measures: The 10-year ASCVD risk was evaluated via the China-PAR equation. The link between GA and 10-year ASCVD risk was examined through a multivariable logistic regression model and the dose-response relationship was demonstrated using the restricted cubic spline. The potential mediation effect of BMI on this association was explored and the differences in this mediation effect across age and metabolic-associated fatty liver disease (MAFLD) subgroups were analyzed.

Results: Elevated GA levels were positively linked to an intensified 10-year ASCVD risk (OR=1.160, 95% CI =1.055–1.276). Additionally, BMI was negatively linked to GA and 10-year ASCVD risk. BMI mediated 13.9% of the connection between GA and 10-year ASCVD risk. Specifically, the mediating effect of BMI remained significant in the 40–60 years age subgroup and non-MAFLD subgroup, with mediation ratios of 43.7% and 8.5%, respectively.

Conclusions: GA is a key predictor of 10-year ASCVD risk, and BMI partially mediates this relationship in healthy populations. Therefore, targeted weight

management is recommended to reduce the adverse effect of GA on 10-year ASCVD risk in different populations.

Strengths and limitations of this study

1. This study firstly established body mass index (BMI) as a partial mediator in the association between Glycated albumin (GA) and 10-year atherosclerotic cardiovascular disease (ASCVD) risk using a mediation model.
2. We used multivariate logistic regression to explore the link between GA and 10-year ASCVD risk, developing three models to control confounding effects stepwise.
3. Restricted Cubic Splines (RCS) were applied to illustrate the dose-response relationship between GA and 10-year ASCVD risk.
4. Given the retrospective cross-sectional nature of this study, it is not feasible to establish the exact causality between GA and 10-year ASCVD risk.

Keywords: Glycated Albumin, Body Mass Index, Atherosclerotic Cardiovascular Disease Risk, Mediation, Metabolic Associated Fatty Liver Disease

1. Introduction

Cardiovascular diseases (CVDs) stand as primary culprits behind death and disability worldwide, presenting a substantial risk to human health. This category of diseases encompasses coronary artery disease (CAD), stroke, and myocardial infarction, which commonly arise due to arteriosclerosis, hypertension, hyperlipidemia, and diabetes[1-5]. Currently, glycated hemoglobin A1c (HbA1c) is recognized as a leading indicator in the clinical assessment of long-term blood sugar control. The latest KDIGO guidelines have recommended a target value of 6.5% to 8.0% for HbA1c in those with diabetes

and chronic kidney disease (CKD) to reduce cardiovascular risk[6]. Nevertheless, HbA1c can be influenced by hemoglobin levels, red blood cell lifespan, anemia, liver dysfunction, and kidney disease[7]. Concurrently, there is increasing interest in an alternative indicator, glycated albumin (GA), a novel index for glucose monitoring, reflecting average blood sugar levels over the past 2 to 3 weeks[8, 9] GA is calculated as the ratio of GA to total albumin concentration[10]. Unlike HbA1c, GA has the advantage of being independent of hemoglobin and red blood cell turnover and less affected by red blood cell lifespan, thus serving as a good marker for assessing blood glucose levels[11].

Numerous guidelines have recommended that the prevention and treatment of atherosclerotic CVD (ASCVD) be based on risk assessment. Traditional risk assessment methods, including the Framingham D'Agostino 2008 model, PCE white model, SCORE model, and QRI SK model, are recognized for their reliability in Western populations. However, the Chinese population presents distinct disease patterns and risk factors, making these models less suitable. Particularly, the Framingham D'Agostino model overestimates the CVD risk in men and underestimates it in women, a trend similarly observed in the PCE model[12]. S Since 2003, several large-sample prediction models for CVD risk have been established for Chinese adults. Among them, the 10-year risk prediction models for Chinese CVD[13, 14] and the China-PAR model for ASCVD[15] are notable. China-PAR model, a CVD risk assessment tool developed by Chinese scholars based on large-sample cohort data, is most often externally validated and is considered potentially a better option for predicting CVD risk in China[16]. It ultimately provides a 10-year and lifetime risk assessment based on relevant metrics, which benefits primary prevention and health management of CVD.

Obese people have a high prevalence of ASCVD, and body mass index (BMI), as an important indicator for assessing obesity in an individual, has a very close correlation with ASCVD risk. Similarly, the study of GA in predicting CVD risk has attracted much attention in recent years. GA, as an early glycated protein, may be more sensitive than other markers to reflect CVD and its complications[5, 17]. Several publications have found an link between GA and cardiovascular mortality in diabetes mellitus (DM) patients[9, 18, 19]. Notably, multiple studies confirm that GA is more strongly than HbA1C associated with CVD in CKD patients requiring dialysis[18, 20, 21]。 Several papers have noted a weak negative connection between GA and BMI in DM populations but with a narrow range for BMI or GA values[11, 22-27]. In contrast, an investigation of Caucasian populations with a median BMI of 38.4 (large body weight) similarly unveiled a marked negative link between BMI and GA[7]. Therefore, the association between GA and BMI in a wider population remains to be confirmed by further studies. There are few studies on the correlation among GA, BMI, and 10-year ASCVD risk in normal populations. Hence, this paper was to illustrate whether BMI mediates the link between GA and 10-year ASCVD risk in the normal population.

2.Methods

2.1 Participant Selection

This cross-sectional study obtained data from 4646 healthy subjects during health checkups at the Health Management Medicine Center, Third Xiangya Hospital of Central South University from January 1, 2022, to June 30, 2023. To control for potential biases, we included all health examination data during this period, rather than relying on random sampling.

The inclusion criteria for this study included: a) age is greater than or equal to 18 years

old; and b) subjects were long-term residents of Hunan province. The exclusion criteria of this study were a) subjects did not have complete data required for this study; and b) subjects did not provide written informed consent; and c) Subjects reported established family history and medical history of CVD and cerebrovascular diseases (including coronary heart disease, stroke, congestive heart failure, myocardial infarction, and angina) in questionnaires ;and d) Subjects was discovered severe liver or kidney dysfunction (which may affect GA results) in health checkups. According to the exclusion criteria, 84 participants under the age of 18 were excluded, 1237 participants lacking GA, BMI, and China-PAR equation-related data were excluded, 276 participants with self-reported CVD and cerebrovascular diseases on the questionnaire were excluded, 28 participants with severe liver or kidney dysfunction were excluded, and 914 participants with missing information on cardiovascular risk factors were excluded. Ultimately, 2107 participants were enrolled. The specific selection process is displayed in Figure 1. This retrospective study adhered to the institution and national research committee's ethical standards, and approval was obtained from the institutional ethics committee of the Third Xiangya Hospital of Central South University and review board (Ethics Approval Number: Quick24559).

2.2 Measurements

2.2.1 GA measurement

Compared to HbA1c testing, the detection methods for GA are not yet fully standardized. In this study, enzyme-linked immunosorbent assay (ELISA), a widely adopted and reliable technique[28] was employed to detect GA.

2.2.2 Cardiovascular Risk Estimation Based on China-PAR Project

The China-PAR score was employed to appraise ASCVD risk. The China-PAR model encompassed sex, age, systolic blood pressure (SBP), total cholesterol (TC), high-

density lipoprotein cholesterol (HDL-C), waist circumference (WC), smoking status, DM, region, urbanization, and family history of ASCVD. The participants were allocated into three risk subgroups based on the scores: <5% as low risk, 5–10% as medium risk, and ≥10% as high risk[15].

Health status and lifestyle information of the participants were collected through questionnaires during their health checkups. This questionnaire, designed based on the National Physical Examination Questionnaire[29], included details on the participants' and family history of CVDs and cerebrovascular diseases, and lifestyle information such as history of hypertension, CVDs, DM, smoking, alcohol consumption, and physical activity. Hypertension was diagnosed as SBP ≥140 mmHg and/or diastolic blood pressure (DBP)≥90 mmHg or receiving antihypertensive treatment. DM was set as fasting plasma glucose (FPG) ≥7.0 mmol/L, HbA1c ≥6.5%, or receiving hypoglycemic treatment. A family history of ASCVD was described as congestive heart failure, stroke, coronary heart disease, myocardial infarction, or angina in first-degree relatives. In this study, based on the three risk categories mentioned above, participants were allocated into medium-high risk group and low risk groups.

2.2.3 Covariate Assessment

Demographic data were obtained from physical examination reports. Age as a continuous variable was categorized into subgroups: 18-39 years, 40-60 years, or >60 years. During the physical examination, weight, height, WC, SBP, and DBP were gauged. BMI was presented as weight (kg) divided by height square (m^2). Laboratory tests covered routine blood tests, liver function tests, GA, FBG, glycated hemoglobin, fasting insulin, and blood lipids. All participants underwent liver and cervical vascular ultrasonography performed by an ultrasonologist. These reports were reviewed and confirmed by another senior ultrasonologist. The diagnoses of fatty liver (hepatic

steatosis) and cervical vascular plaques were based on liver and cervical vascular ultrasound scans using linear array or convex high-frequency probes with frequencies of 5-10 MHz. These scans evaluated the echo, size, and morphology of the liver, as well as intima-media thickness, plaque size, morphology, and location of cervical vessels. Furthermore, smoking history, alcohol consumption, and exercise frequency were recorded directly from the physical examination questionnaire. Smoking history was defined as smoking continuously or cumulatively for more than six months[29]. Alcohol consumption manifested as consuming over 10 grams of alcohol per day[30]. Physical activity represented moderate- or high-intensity physical activity at least three times per week, with each session lasting at least 30 minutes[31].

2.2.4 Diagnosis of MAFLD

According to Eslam et al.[32], metabolic-associated fatty liver disease (MAFLD) means steatosis in combination with metabolic dysfunction. The diagnostic criteria included hepatic steatosis through histology (liver biopsy), imaging techniques, or blood-based biomarkers and at least one of the following conditions: overweight/obesity, T2DM, and metabolic dysfunction. Metabolic dysfunction refers to at least two of the seven metabolic risk abnormalities (Figure 2).

2.3 Data Analysis

Continuous variables were denoted as median and interquartile spacing and compared utilizing the independent samples t-test. Categorical variables were depicted as unweighted frequencies, weighted percentages, and standard error (SE), and compared utilizing the chi-square test. Multiple regression analysis was used to test the correlation between GA (continuous exposure variable) and 10-year ASCVD risk (binary outcome variable). Variables showing between-group differences in the baseline information table ($P < 0.05$) were identified and included as potential confounders, serving as

covariates in subsequent analyses. Three models were constructed to progressively control for the effects of confounders: Unadjusted crude Model 1; Model 2 adjusted for age, sex, smoking status, sport status, BMI, WC, SBP, and DBP; and Model 3 adjusted for all covariates, such as albumin, platelet, TC, Triglyceride, HDL-C, Cervical vascular plaques, and MAFLD. Subsequently, restricted cubic spline (RCS) was adopted to demonstrate the dose-response relationship between GA and 10-year ASCVD risk. Finally, a logistic regression model was employed to illustrate the relationships among GA, BMI, and 10-year ASCVD risk. To analyze the mediation effect of BMI [(mediation effect/total effect) × 100%], a simple mediation model was used, with three paths (Figure 3). The total effect represented the impact of GA (exposure) on 10-year ASCVD risk (outcome). Path A assessed the effect of GA on BMI (mediator). Path B evaluated the link between BMI and 10-year ASCVD risk. Path C estimated the direct impact of GA on 10-year ASCVD risk. The mediated effect was calculated as (mediated effect/total effect) × 100%.

All statistical analyses, including mediation analysis, were done in the R statistical package. Statistical significance was delineated at a two-sided p-value of < 0.05.

3.Results

3.1. Characteristics of Participants

Table S1 displays the baseline characteristics of study participants. Based on the three risk categories mentioned above, participants were assigned to a medium-high-risk group (n=230) and a low-risk group (n=1877). The differences were statistically notable ($p < 0.001$) in age, BMI, WC, SBP, DBP, albumin, GA, platelet, FBG, TC, cervical vascular plaques, smoking status, and MAFLD.

Table S2 exhibits the multivariable logistic analysis results. In model 1, a higher GA

was greatly connected with higher odds of 10-year ASCVD risk (OR =1.138, 95% CI =1.094, 1.185). After adjusting for covariates (age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, TC, triglyceride, HDL-C, cervical vascular plaques, and MAFLD), GA was positively connected with 10-year ASCVD risk (OR =1.160, 95% CI =1.055, 1.276) in Model 3.

The RCS curve showed that increased GA levels were significantly linked to increased 10-year ASCVD risk (P for overall < 0.001), with a linear relationship (P for non-linear =0.2616) (Figure 4). The red solid line indicates the point estimate of OR, and the pink shaded area represents the 95% CI. The curve indicates that when GA levels are below 12.95%, the OR remains around 1, suggesting that GA does not significantly affect the risk within this range. However, when GA levels > 12.95%, the OR starts to increase significantly, indicating a marked correlation between higher GA levels and greater 10-year ASCVD risk.

3.2 Mediation Analysis of BMI

We then delved into the mediation effect of BMI on the link between GA and 10-year ASCVD risk. All mediation analyses were carried out after adjustment for age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, TC, triglyceride, HDL-C, cervical vascular plaques, and MAFLD.

GA was negatively correlated with BMI ($p < 0.001$) and positively correlated with 10-year ASCVD risk ($p < 0.001$). BMI was positively related to 10-year ASCVD risk ($p < 0.001$) (Table S3). It is estimated that BMI mediated 13.9% of the total link between GA and 10-year ASCVD risk.

Given the effect of age and MAFLD, subgroup analyses were implemented(Table S4). In the age group, BMI partially mediated the link between GA and 10-year ASCVD

risk. In the age subgroup 40–60 years, there was a 43.7% mediating effect of BMI on the link between GA and 10-year ASCVD risk. However, in the age subgroup < 40 years and > 60 years, no mediating effect of BMI was observed on the correlation between GA and 10-year ASCVD risk. Similarly, BMI mediated 8.5% of the total link between GA and 10-year ASCVD risk in the non-MAFLD group. However, the mediating effect was not observed in the MAFLD group.

4.Discussion

This study elucidated the relationship among GA, BMI, and 10-year ASCVD risk in the normal population undergoing physical examination and estimated the mediating role of BMI. This is the first study on their relationship, and our results confirm: 1. BMI mediated the link between GA and 10-year ASCVD risk, with 13.9% of the association mediated by BMI. 2. The mediating role of BMI varies by age and MAFLD subgroups. BMI plays a partially mediating role of 8.5% in the 40-60 age group and no mediating role in the 30-44 and over 60 age groups. Similarly, BMI has an 8.5% partial mediating effect on the non-MAFLD group, but no mediating effect was revealed in the MAFLD group.

The present study examined a real-world normal population undergoing medical examinations and showed a positive correlation between GA and 10-year CVD risk. These associations remained after adjustment for established cardiovascular risk factors and socio-behavioral factors. Although GA is widely recognized to reflect blood glucose levels, relevant studies have focused on its application in diverse situations (e.g., anemia, abnormal liver function, and renal disease) where HbA1c accuracy may be impaired. However, there is controversy about the ability of GA to predict long-term ASCVD outcomes. Previous studies have manifested that GA upregulation is positively

linked to CAD and its severity in DM patients, whereas HbA1c levels are not as strongly correlated with CAD[33, 34]. Similarly, several publications have highlighted that after adjustment for HbA1c levels, the higher GA in dialysis-requiring patients with CKD and DM, the higher risk of cardiovascular mortality, all-cause mortality, CAD, major adverse cardiovascular events, and stroke; no correlation was found in non-DM individuals[9, 18, 19]. However, Copur et al. revealed a prominent correlation of GA levels with all-cause mortality in DM patients undergoing dialysis, but not with CVD mortality[35]. Additionally, high GA levels were independently linked to unfavorable intermediate-term efficacy in low-risk populations undergoing percutaneous coronary intervention, but the prognostic role was only present in the DM subgroup, and in the non-DM individuals, this association was not supported by clear evidence[36]. It is well known that atherosclerosis is the most important cause of CVDs[37]. Significant glycemic excursions or fluctuations potentiate oxidative stress and drive atherosclerosis, which can lead to ASCVD[38, 39]. We hypothesized that relative to HbA1c, GA may better indicate glycemic fluctuations (eg, acute hyperglycemia or significant postprandial glycemic excursion) before the onset of acute coronary syndrome (within a short period[38, 40], thereby promoting oxidative stress and accelerating atherosclerosis in both DM and non-DM subjects[41, 42]. In non-DM subjects, short-term glycemic fluctuations, especially significant postprandial glycemic excursion, may be manifested as small but notable differences in GA. The effect of HbA1c on non-DM participants may be confounded by non-glycemic factors, like abnormalities in liver and kidney function and differences in red blood cell lifespan. Therefore, further investigations are warranted to elucidate the complex pathophysiologic mechanisms that link GA to ASCVD risk.

Our experimental results showed that GA was negatively connected with BMI.

Research in normoglycemic populations, pre-DM patients, and T2DM patients has reported a link between BMI and HbA1c or GA/HbA1c[27, 43]. However, studies on the link between GA and BMI are very limited in normal populations in China. As mentioned earlier, several papers have demonstrated a weak negative connection between GA and BMI among DM populations, but mainly in normal-weight subjects with little fluctuation in BM[11, 22-27], or Caucasian populations with large body weights (mean BMI of 38.4). In contrast, the two papers that did not discover a negative correlation between GA and BMI were conducted in the Japanese population with type 1 DM with a mean BMI of 20.1[44] or without DM with a nearly constant GA[45]. Thereby, the negative link between BMI and GA may not be exclusively attributable to glycemic exposure, but that there are other factors. An increase in BMI increases renal blood flow, glomerular filtration rate, and tubular reabsorption, resulting in glomerular enlargement and obesity-associated glomerular disease[46, 47]. There is a difference in the rate of GA synthesis in participants with higher BMI and normal BMI[22]. BMI may affect GA clearance. A mild increment in BMI is related to an increased prevalence of microalbuminuria, which is a marker of early renal damage and is also closely related to cardiovascular prognosis[48]. Elevated GA levels may reflect the presence of microalbuminuria and cardiovascular events, but the exact mechanism is currently unknown. Therefore, future studies should refine the proteinuria and renal clearance of GA, which may influence the relationship between GA and BMI. Additional research utilizing labeled albumin in animal models of obesity and DM may offer valuable insight into this process.

Interestingly, the mediation analysis unraveled that BMI mediated 13.9% of the link between GA and 10-year ASCVD risk. This result emphasizes the importance of reducing BMI in lowering 10-year ASCVD risk, especially in high-GA populations,

regardless of DM. Overweight and obesity are drivers of insulin resistance[49, 50]. Insulin resistance is the core connecting several events of cardiometabolic disorders[49-54], molecularly due to impaired insulin signaling transduction via the PI3K pathway and intact signaling transduction via the MAPK pathway, leading to altered glucose-insulin homeostasis and increased glucose fluctuations. Significant shifts in blood glucose values facilitate oxidative stress and atherosclerosis[38, 39]. Similarly, elevated serum GA levels are notably related to augmented carotid intima-media thickness and vascular endothelial dysfunction, a sign of early atherosclerosis[55]. Vascular smooth muscle cell proliferation, vascular endothelial dysfunction, and overproduction of collagen and inflammatory cytokines contribute to atherosclerosis and adverse cardiovascular events. Patients in the high GA group were more susceptible to metabolic disorders and severe CAD than those in the low and mediate GA groups and therefore had an intensified risk of CAD. When GA levels are substantially elevated (in the higher range, e.g., more than 17.1%), the CAD risk augments by approximately two folds[36]. Akane Mihara et al. disclosed findings from 10-year follow-up of the Hisayama study, suggesting that the highest quartile of GA levels (≥15.7%) was connected with a 2.2-fold increase in CAD incidence and a 2.5-fold increase in stroke risk[56]. The exact mechanism of the mediating effect of BMI is currently unclear and may be different in different populations. Additional research is warranted to illustrate the mechanisms.

Interestingly, we found age and MAFLD were involved in the mediating role of BMI in the association between GA and 10-year ASCVD risk. Age-stratified subgroup analyses found that BMI did not mediate the association in the <40 and >60 groups. This finding suggests that BMI reduction in the <40 and >60 groups with increased GA may not be the cause for reducing 10-year CVD risk compared with the partial mediation effect in the 40-60 group. We suggest that in the 40-60 group, BMI reduction

will be the focus of reducing the 10-year CVD risk induced by increased GA. In addition, subgroup analyses by MAFLD discovered that the link between GA and 10-year CVD risk was partially mediated by BMI in the non-MAFLD group, whereas BMI had no mediating effect in the MAFLD group. This finding suggests that BMI reduction in the MAFLD group with increased GA may not be the cause for reducing 10-year CVD risk. In the non-MAFLD group, BMI reduction will be the focus of preventing 10-year CVD risk. Since GA is an indicator of short-term glucose fluctuations and insulin resistance is the main mechanism of MAFLD, it is primarily a long-term effect. Therefore, long-term monitoring of GA is of limited benefit in assessing 10-year CVD risk in MAFLD populations. This may provide new insights into assessing and reducing 10-year CVD risk in these two groups.

Our study first investigates the mediating role of BMI in the link between GA and 10-year ASCVD risk. Nevertheless, we must acknowledge certain inherent limitations of our study. Firstly, multiple multivariate models were adopted to unveil the independent link between GA and 10-year ASCVD risk. Essential confounding factors like alcohol consumption and smoking were obtained through self-reported data, which are potentially influenced by recall bias and misinterpretations and potentially affect the accuracy of our findings. Secondly, it is crucial to analyze the correlation between GA and proteinuria. However, since this study involved non-hospitalized population and the incidence of proteinuria among participants was exceedingly low, statistical analysis was not possible. This limitation underscores further investigations into the renal clearance of proteinuria and GA, which is pivotal in elucidating the link between BMI and GA. Lastly, given the cross-sectional nature, it is not feasible to establish the exact causality between GA and 10-year ASCVD risk. Thereby, prospective cohort studies are imperative to further unveil this relationship. Despite these limitations, our

study, based on a real-world context and substantial sample size, has fully adjusted for confounders, so the conclusions drawn are relatively reliable.

In conclusion, our cross-sectional study of 2,107 participants demonstrates for the first time that BMI effectively mediates the impact of GA on the 10-year ASCVD risk. Consequently, healthy populations, especially those aged 40-60 without MAFLD, should realize the beneficial effects of GA in reducing their 10-year ASCVD risk through lowering BMI, rather than just preventing diabetes. Prospective studies are crucial to validate these findings and elucidate intrinsic mechanisms, thus paving the way for targeted therapeutic strategies.

List of abbreviations

Glycated albumin (GA); atherosclerotic cardiovascular disease (ASCVD); Cardiovascular diseases (CVDs); coronary artery disease (CAD); hemoglobin A1c (HbA1c); chronic kidney disease (CKD); systolic blood pressure (SBP); waist circumference (WC); total cholesterol (TC); metabolic-associated fatty liver disease (MAFLD); standard error (SE)

Declarations

Ethics approval and consent to participate

This retrospective study adhered to the institution and national research committee's ethical standards, and approval was obtained from the institutional ethics committee of the Third Xiangya Hospital of Central South University and review board (Ethics Approval Number: Quick24559).

Data availability statement

The original contributions presented in the study are included in the

article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Consent for publication

Not applicable

Funding

This work was supported by grants from the National Natural Science Foundation of China (82304171) and the Hunan Province Natural Science Foundation (2022JJ40668); National Key Clinical Specialty Scientific Research Project (Z2023058) and Chinese Cardiovascular Association-ASCVD Fund (2023-CCA-ASCVD-018).

Author contributions

All authors contributed to the study conception and design. Writing - original draft preparation: XZ, YH, SX, NC, YZ, ML; Writing - review and editing: XZ; Conceptualization: YH, NC; Methodology: SX, YZ; Formal analysis and investigation: XZ, YH; Funding acquisition: ML, XZ; Resources: XZ; Supervision: ML, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

Not applicable.

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Figure legends

Figure 1: Flowchart for study population selection.

Figure 2: Diagnostic standard flowchart of MAFLD.

Figure 3: Path diagram of the mediation analysis models

Figure 4: Restricted Cubic Spline Curve for association between odds ratio of GA and 10-year ASCVD risk

Supplementary Materials

Table S1 Baseline characteristics of enrolled participants

Table S2. Logistic regression models of the link between GA and 10-year ASCVD risk

Table S3. Mediation effect of BMI on the association between GA and 10-year ASCVD risk

Table S4. Mediation effect of BMI on the link between GA and 10-year ASCVD risk by age and MAFLD

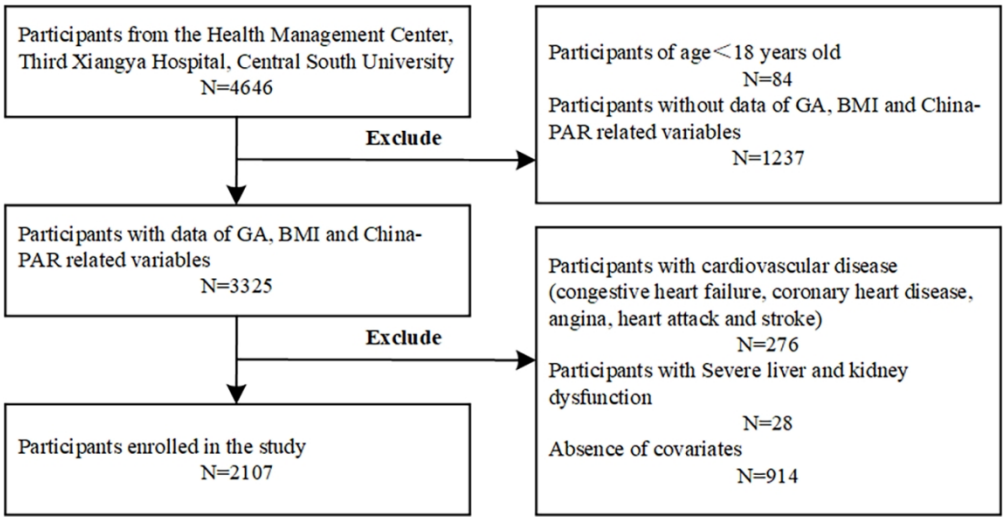

Figure 1: Flowchart for study population selection.

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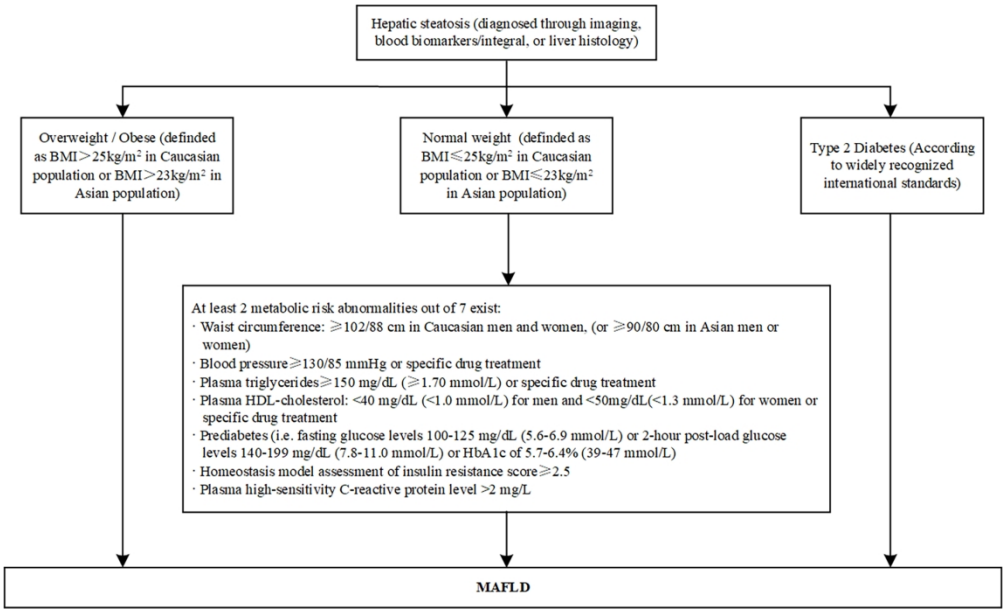

Figure 2: Diagnostic standard flowchart of MAFLD.

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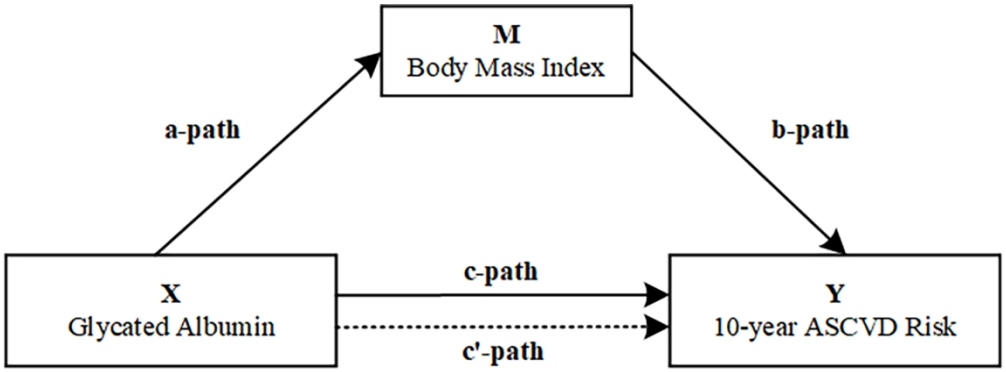

Figure 3: Path diagram of the mediation analysis models

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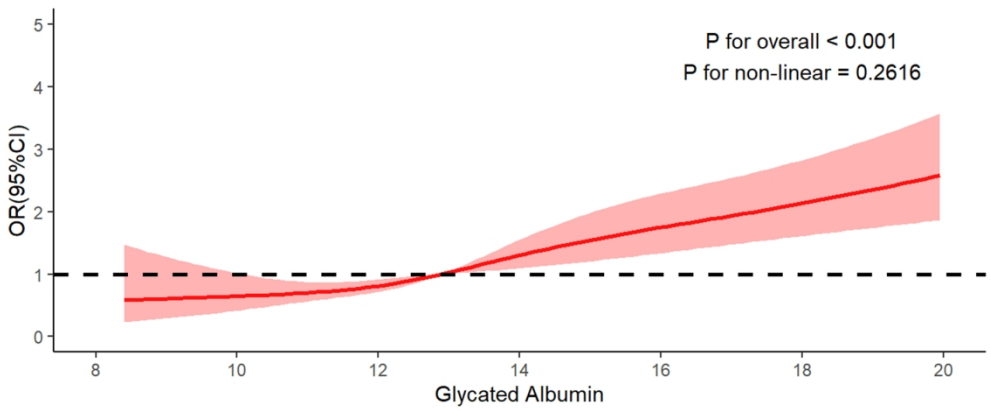

Figure 4: Restricted Cubic Spline Curve for association between odds ratio of GA and 10-year ASCVD risk

169x75mm (300 x 300 DPI)

Table 1 Baseline characteristics of enrolled participants

	Total	China-PAR		p-Value
	(n=2107)	Medium-high Risk Group (n=230)	Low Risk Group (n=1877)	
Characteristics [median (25th, 75th)]				
Age (year)	45.00 [36.00, 52.00]	59.00 [56.00, 66.00]	43.00 [35.00, 50.00]	<0.001
BMI*	24.20 [21.85, 26.50]	25.20 [23.63, 27.90]	24.00 [21.70, 26.20]	<0.001
Waist circumference	83.00 [74.00, 91.00]	89.00 [83.00, 96.00]	82.00 [73.00, 90.00]	<0.001
Systolic Pressure	119.00 [109.00, 130.00]	138.00 [130.00, 147.75]	118.00 [108.00, 127.00]	<0.001
Diastolic Pressure	73.00 [65.00, 81.00]	83.00 [77.00, 89.00]	71.00 [65.00, 80.00]	<0.001
albumin	45.50 [43.80, 47.60]	44.60 [42.90, 46.10]	45.70 [43.90, 47.70]	<0.001
GA*	12.90 [11.60, 14.20]	13.60 [12.20, 15.40]	12.80 [11.50, 14.10]	<0.001
platelet	227.00 [192.00, 261.00]	208.00 [176.25, 245.75]	229.00 [194.00, 262.00]	<0.001
ALT*	20.00 [14.00, 31.50]	20.00 [15.00, 28.00]	21.00 [14.00, 32.00]	0.391
AST*	22.00 [18.00, 27.00]	23.00 [20.00, 26.00]	22.00 [18.00, 27.00]	0.043
Fasting blood glucose	5.23 [4.90, 5.67]	5.74 [5.20, 6.51]	5.20 [4.87, 5.59]	<0.001
Total cholesterol	4.97 [4.42, 5.68]	5.18 [4.59, 5.92]	4.95 [4.41, 5.64]	0.006
triglyceride	1.42 [0.92, 2.26]	1.72 [1.05, 2.66]	1.38 [0.90, 2.22]	<0.001
HDL-C*	1.25 [1.07, 1.47]	1.21 [1.04, 1.40]	1.25 [1.07, 1.48]	0.006
LDL-C*	2.90 [2.39, 3.45]	2.94 [2.41, 3.55]	2.90 [2.39, 3.44]	0.408
Characteristics [n (%)]				
Sex				0.001
Female	1131 (53.7)	148 (64.3)	983 (52.4)	
Male	976 (46.3)	82 (35.7)	894 (47.6)	
Cervical vascular plaques				<0.001
No	1632 (77.5)	101 (43.9)	1531 (81.6)	
Yes	475 (22.5)	129 (56.1)	346 (18.4)	
Smoking status				<0.001
No	1538 (73.0)	131 (57.0)	1407 (75.0)	
Yes	569 (27.0)	99 (43.0)	470 (25.0)	
Drinking status				0.449
No	1344 (63.8)	141 (61.3)	1203 (64.1)	
Yes	763 (36.2)	89 (38.7)	674 (35.9)	
Sport status				0.012
No	854 (40.5)	75 (32.6)	779 (41.5)	
Yes	1253 (59.5)	155 (67.4)	1098 (58.5)	
MAFLD*				<0.001
No	1116 (53.0)	62 (27.0)	1054 (56.2)	
Yes	991 (47.0)	168 (73.0)	823 (43.8)	

Notes: Values are median (25th, 75th), or n (%). P values were computed utilizing Student's t-test or the Mann-Whitney U test for continuous variables, and the chi-squared test was adopted for categorical variables.

Table 2. Logistic regression models of the link between GA and 10-year ASCVD risk

	Model 1			Model 2			Model 3		
	OR	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
GA	1.138	(1.094, 1.185)	< 0.001	1.142	(1.049, 1.240)	0.002	1.160	(1.055, 1.276)	0.002

Notes: Model 1 = GA; Model 2 = Model 1 + Age + Sex + Smoking status + Sport status + BMI + WC + SBP +DBP; Model 3 = Model 2 + Albumin + Platelet + Total Cholesterol + Triglyceride + HDL-C + Cervical vascular plaques + MAFLD.

Table 3. Mediation effect of BMI on the association between GA and 10-year ASCVD risk

Mediator	Sample	Exposure to Mediator	Mediator to Outcome	Direct Effect	Mediated (Indirect Effect)	Total Effect (Exposure to Outcome)	Proportion Mediated (%)
BMI	2107	-0.146 (0.026) p<0.001 p<0.001	0.190 (0.015) p<0.001 p<0.001	0.229 (0.040) p<0.001 p<0.001	-0.028 (0.006) p<0.001 p<0.001	0.201 (0.040) p<0.001 p<0.001	13.9%

Notes: Exposure: GA; Outcome: 10-year ASCVD risk; Model adjusted for age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, TC, triglyceride, HDL-C, cervical vascular plaques, and MAFLD.

Table 4. Mediation effect of BMI on the link between GA and 10-year ASCVD risk by age and MAFLD

Mediator	Sample	Exposure to Mediator	Mediator to Outcome	Direct Effect	Mediated (Indirect Effect)	Total Effect (Exposure to Outcome)	Proportion Mediated (%)
Stratification by Age							
<40	743	-0.388 (0.064) p < .001	0.056 (0.005) p < .001	0.030 (0.022) p =.177	-0.022(0.007) 95%CI (-0.037, -0.011) p = .002	0.008 (0.023) p = .714	-
40-60	1214	-0.147 (0.030) p < .001	0.210 (0.016) p < .001	0.102 (0.029) p < .001	-0.031(0.007) 95%CI (-0.046, -0.020) p < .001	0.071 (0.030) p = .017	**43.7**
>60	150	0.136 (0.075) p =.270	0.185 (0.093) p < .05	0.415 (0.121) p < .001	0.025(0.022) 95%CI (-0.016, 0.069) p = .245	0.440 (0.117) p < .001	-
Stratification by MAFLD							
MALFD	991	-0.040 (0.029) p =.092	0.081 (0.029) p < .01	0.275 (0.043) p < .001	-0.003(0.003) 95%CI (-0.010, 0.002) p = .310	0.272 (0.043) p < .001	-
Non-MAFLD	1116	-0.107*** (0.029) p < .001	0.127*** (0.026) p < .001	0.178 (0.068) p = .009	-0.014(0.005) 95%CI (-0.025, -0.006) p = .004	0.164 (0.067) p = .014	**8.5**

Notes: Exposure: GA; Mediator: BMI; Outcome: 10-year ASCVD risk; Model adjusted for age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, total cholesterol, triglyceride, HDL-C, cervical vascular plaques, and MAFLD.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-092714.R1
Article Type:	Original research
Date Submitted by the Author:	01-Apr-2025
Complete List of Authors:	Zeng, Xi; Deparment of Health Management, The Third Xiangya Hospital, Central South University Hu, Yangliuzi; Department of Spinal Surgery, Third Xiangya Hospital, Central South University Xiao, Shujuan; Department of Epidemiology, Xiangya School of Public Health, Central South University; Hunan Provincial Key Laboratory of Clinical Epidemiology, Xiangya School of Public Health, Central South University, Changsha, Hunan, China Chen, Ni-Ni; Department of Health Management, The Third Xiangya Hospital, Central South University Zhou, Yang; Department of Epidemiology, Xiangya School of Public Health, Central South University; Hunan Provincial Key Laboratory of Clinical Epidemiology, Xiangya School of Public Health, Central South University, Changsha, Hunan, China Luo, Miyang; Central South University Xiangya School of Public Health, Department of Epidemiology; Hunan Provincial Key Laboratory of Clinical Epidemiology, Xiangya School of Public Health, Central South University
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, Cardiovascular Disease, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Body Mass Index

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Mediation Effect of Body Mass Index on the Association Between Glycated Albumin and 10-Year Atherosclerotic Cardiovascular Disease Risk in Hunan Residents of China: A Retrospective Cross-sectional Study

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Abstract

Objectives: Glycated albumin (GA) and body mass index (BMI) have been linked to atherosclerotic cardiovascular disease (ASCVD). However, the role of BMI in the correlation between GA and 10-year ASCVD risk is still not fully understood.

Design: A Retrospective Cross-sectional Study

Setting: In this retrospective cross-sectional study, 4,646 healthy subjects who received a full health checkup at the Health Management Medical Center, Third Xiangya Hospital of Central South University from January 1, 2022 to December 30, 2023, were initially identified. After applying the exclusion criteria, 2,107 participants were included in the final analysis.

Participants: The inclusion criteria for this study included: a) age is greater than or equal to 18 years old; and b) subjects were long-term residents of Hunan province.

Primary and secondary outcome measures: The 10-year ASCVD risk was evaluated via the China-PAR equation. The link between GA and 10-year ASCVD risk was examined through a multivariable logistic regression model and the dose-response relationship was demonstrated using the restricted cubic spline. The potential mediation effect of BMI on this association was explored and the differences in this mediation effect across age and metabolic-associated fatty liver disease (MAFLD) subgroups were analyzed.

Results: Elevated GA levels were positively linked to an intensified 10-year ASCVD risk (OR=1.160, 95% CI =1.055–1.276). Additionally, BMI was negatively linked to GA and 10-year ASCVD risk. BMI mediated 13.9% of the connection between GA and 10-year ASCVD risk. Specifically, the mediating effect of BMI remained significant in the 40–60 years age subgroup and non-MAFLD subgroup, with mediation ratios of 43.7% and 8.5%, respectively.

Conclusions: GA is a key predictor of 10-year ASCVD risk, and BMI partially mediates this relationship in healthy populations. Therefore, targeted weight management is recommended to reduce the adverse effect of GA on 10-year ASCVD risk in different populations.

Strengths and limitations of this study

1.We used a mediation model to identify BMI as a partial mediator in the association between GA and 10-year ASCVD risk.

2.We applied multivariate logistic regression to explore the link between GA and 10-year ASCVD risk, controlling confounding effects stepwise.A

3.Restricted Cubic Splines were used to illustrate the dose-response relationship between GA and 10-year ASCVD risk.

4.The study's retrospective cross-sectional design prevents establishing causality between GA and 10-year ASCVD risk and exploring the GA-BMI bidirectional relationship.

Keywords: Glycated Albumin, Body Mass Index, Atherosclerotic Cardiovascular Disease Risk, Mediation, Metabolic Associated Fatty Liver Disease

1. Introduction

Cardiovascular diseases (CVDs) stand as primary culprits behind death and disability worldwide, presenting a substantial risk to human health. This category of diseases encompasses coronary artery disease (CAD), stroke, and myocardial infarction, which commonly arise due to arteriosclerosis, hypertension, hyperlipidemia, and diabetes[1-5]. Currently, glycated hemoglobin A1c (HbA1c) is recognized as a leading indicator in

the clinical assessment of long-term blood sugar control. The latest KDIGO guidelines have recommended a target value of 6.5% to 8.0% for HbA1c in those with diabetes and chronic kidney disease (CKD) to reduce cardiovascular risk[6]. Nevertheless, HbA1c can be influenced by hemoglobin levels, red blood cell lifespan, anemia, liver dysfunction, and kidney disease[7]. Concurrently, there is increasing interest in an alternative indicator, glycated albumin (GA), a novel index for glucose monitoring, reflecting average blood sugar levels over the past 2 to 3 weeks[8,9] GA is calculated as the ratio of GA to total albumin concentration[10]. Unlike HbA1c, GA has the advantage of being independent of hemoglobin and red blood cell turnover and less affected by red blood cell lifespan, thus serving as a good marker for assessing blood glucose levels[11].

Numerous guidelines have recommended that the prevention and treatment of atherosclerotic CVD (ASCVD) be based on risk assessment. Traditional risk assessment methods, including the Framingham D'Agostino 2008 model, PCE white model, SCORE model, and QRI SK model, are recognized for their reliability in Western populations. However, the Chinese population presents distinct disease patterns and risk factors, making these models less suitable. Particularly, the Framingham D'Agostino model overestimates the CVD risk in men and underestimates it in women, a trend similarly observed in the PCE model[12]. S Since 2003, several large-sample prediction models for CVD risk have been established for Chinese adults. Among them, the 10-year risk prediction models for Chinese CVD[13,14] and the China-PAR model for ASCVD[15] are notable. China-PAR model, a CVD risk assessment tool developed by Chinese scholars based on large-sample cohort data, is most often externally validated and is considered potentially a better option for predicting CVD risk in China[16]. It ultimately provides a 10-year and lifetime risk assessment based on

relevant metrics, which benefits primary prevention and health management of CVD. Obese people have a high prevalence of ASCVD, and body mass index (BMI), as an important indicator for assessing obesity in an individual, has a very close correlation with ASCVD risk. Similarly, the study of GA in predicting CVD risk has attracted much attention in recent years. GA, as an early glycated protein, may be more sensitive than other markers to reflect CVD and its complications[5,17]. Several publications have found an link between GA and cardiovascular mortality in diabetes mellitus (DM) patients[9,18,19]. Notably, multiple studies confirm that GA is more strongly than HbA1C associated with CVD in CKD patients requiring dialysis[18,20,21]。 Several papers have noted a weak negative connection between GA and BMI in DM populations but with a narrow range for BMI or GA values[11,22-27]. In contrast, an investigation of Caucasian populations with a median BMI of 38.4 (large body weight) similarly unveiled a marked negative link between BMI and GA[7]. Therefore, the association between GA and BMI in a wider population remains to be confirmed by further studies. There are few studies on the correlation among GA, BMI, and 10-year ASCVD risk in normal populations. Hence, this paper was to illustrate whether BMI mediates the link between GA and 10-year ASCVD risk in the normal population.

2.Methods

2.1 Participant Selection

This cross-sectional study obtained data from 4646 healthy subjects during health checkups at the Health Management Medicine Center, Third Xiangya Hospital of Central South University from January 1, 2022, to June 30, 2023. To control for potential biases, we included all health examination data during this period, rather than relying on random sampling.

The inclusion criteria for this study included: a) age is greater than or equal to 18 years old; and b) subjects were long-term residents of Hunan province. The exclusion criteria of this study were a) subjects did not have complete data required for this study; and b) subjects did not provide written informed consent; and c) Subjects reported established family history and medical history of CVD and cerebrovascular diseases (including coronary heart disease, stroke, congestive heart failure, myocardial infarction, and angina) in questionnaires ;and d) Subjects was discovered severe liver or kidney dysfunction (which may affect GA results) in health checkups. According to the exclusion criteria, 84 participants under the age of 18 were excluded, 1237 participants lacking GA, BMI, and China-PAR equation-related data were excluded, 276 participants with self-reported CVD and cerebrovascular diseases on the questionnaire were excluded, 28 participants with severe liver or kidney dysfunction were excluded, and 914 participants with missing information on cardiovascular risk factors were excluded. Ultimately, 2107 participants were enrolled. The specific selection process is displayed in Figure 1. This retrospective study adhered to the institution and national research committee's ethical standards, and approval was obtained from the institutional ethics committee of the Third Xiangya Hospital of Central South University and review board (Ethics Approval Number: Quick24559).

2.2 Measurements

2.2.1 GA measurement

Compared to HbA1c testing, the detection methods for GA are not yet fully standardized. In this study, enzyme-linked immunosorbent assay (ELISA), a widely adopted and reliable technique[28] was employed to detect GA.

2.2.2 Cardiovascular Risk Estimation Based on China-PAR Project

The China-PAR score was employed to appraise ASCVD risk. The China-PAR model

encompassed sex, age, systolic blood pressure (SBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), waist circumference (WC), smoking status, DM, region, urbanization, and family history of ASCVD. The participants were allocated into three risk subgroups based on the scores: <5% as low risk, 5–10% as medium risk, and ≥10% as high risk[15].

Health status and lifestyle information of the participants were collected through questionnaires during their health checkups. This questionnaire, designed based on the National Physical Examination Questionnaire[29], included details on the participants' and family history of CVDs and cerebrovascular diseases, and lifestyle information such as history of hypertension, CVDs, DM, smoking, alcohol consumption, and physical activity. Hypertension was diagnosed as SBP ≥140 mmHg and/or diastolic blood pressure (DBP)≥90 mmHg or receiving antihypertensive treatment. DM was set as fasting plasma glucose (FPG) ≥7.0 mmol/L, HbA1c ≥6.5%, or receiving hypoglycemic treatment. A family history of ASCVD was described as congestive heart failure, stroke, coronary heart disease, myocardial infarction, or angina in first-degree relatives. In this study, based on the three risk categories mentioned above, participants were allocated into medium-high risk group and low risk groups.

2.2.3 Covariate Assessment

Demographic data were obtained from physical examination reports. Age as a continuous variable was categorized into subgroups: 18-39 years, 40-60 years, or >60 years. During the physical examination, weight, height, WC, SBP, and DBP were gauged. BMI was presented as weight (kg) divided by height square (m^2). Laboratory tests covered routine blood tests, liver function tests, GA, FBG, HbA1c, fasting insulin, and blood lipids. It should be noted that, considering GA rather than HbA1C was the primary focus of this study, and most research subjects did not have both measurements

above, HbA1C was not set as a mandatory enrollment criterion. All participants underwent liver and cervical vascular ultrasonography performed by an ultrasonologist after an overnight fast. These reports were reviewed and confirmed by another senior ultrasonologist. The diagnoses of fatty liver (hepatic steatosis) and cervical vascular plaques were based on liver and cervical vascular ultrasound scans using linear array or convex high-frequency probes with frequencies of 5-10 MHz. These scans evaluated the echo, size, and morphology of the liver, as well as intima-media thickness, plaque size, morphology, and location of cervical vessels. Furthermore, medication history, smoking history, alcohol consumption, and exercise frequency were recorded directly from the physical examination questionnaire. Medication history in this study was defined as medication use for diabetes mellitus, hypertension, and dyslipidemia. Smoking history was defined as smoking continuously or cumulatively for more than six months[29]. Alcohol consumption manifested as consuming over 10 grams of alcohol per day[30]. Physical activity represented moderate- or high-intensity physical activity at least three times per week, with each session lasting at least 30 minutes[31].

2.2.4 Diagnosis of MAFLD

According to Eslam et al.[32], metabolic-associated fatty liver disease (MAFLD) means steatosis in combination with metabolic dysfunction in the International Expert Consensus Statement on MAFLD. The diagnostic criteria included hepatic steatosis through histology (liver biopsy), imaging techniques, or blood-based biomarkers and at least one of the following conditions: overweight/obesity, T2DM, and metabolic dysfunction. Metabolic dysfunction refers to at least two of the seven metabolic risk abnormalities (Figure 2). In this study, all subjects were from a health - screening cohort. Thus, balancing feasibility, cost - effectiveness, and diagnostic accuracy in the screening population, we uniformly used liver ultrasonography after an overnight fast to assess

hepatic steatosis in all subjects, instead of other imaging techniques (e.g., vibration - controlled transient elastography or MRI elastography), blood - based biomarkers (e.g., FIB - 4, APRI et.al), or liver biopsy.

2.3 Data Analysis

Continuous variables were denoted as median and interquartile spacing and compared utilizing the independent samples t-test. Categorical variables were depicted as unweighted frequencies, weighted percentages, and standard error (SE), and compared utilizing the chi-square test. Multiple regression analysis was used to test the correlation between GA (continuous exposure variable) and 10-year ASCVD risk (binary outcome variable). Variables showing between-group differences in the baseline information table ($P < 0.05$) were identified and included as potential confounders, serving as covariates in subsequent analyses. Three models were constructed to progressively control for the effects of confounders: Unadjusted crude Model 1; Model 2 adjusted for age, sex, smoking status, sport status, BMI, WC, SBP, and DBP; and Model 3 adjusted for all covariates, such as albumin, platelet, TC, Triglyceride, HDL-C, Cervical vascular plaques, and MAFLD. Subsequently, restricted cubic spline (RCS) was adopted to demonstrate the dose-response relationship between GA and 10-year ASCVD risk. Finally, a logistic regression model was employed to illustrate the relationships among GA, BMI, and 10-year ASCVD risk. To analyze the mediation effect of BMI [(mediation effect/total effect) × 100%], a simple mediation model was used, with three paths (Figure 3). The total effect represented the impact of GA (exposure) on 10-year ASCVD risk (outcome). Path A assessed the effect of GA on BMI (mediator). Path B evaluated the link between BMI and 10-year ASCVD risk. Path C estimated the direct impact of GA on 10-year ASCVD risk. The mediated effect was calculated as (mediated effect/total effect) × 100%.

All statistical analyses, including mediation analysis, were done in the R statistical package. Statistical significance was delineated at a two-sided p-value of < 0.05.

3.Results

3.1. Characteristics of Participants

Table S1 displays the baseline characteristics of study participants. Based on the three risk categories mentioned above, participants were assigned to a medium-high-risk group (n=230) and a low-risk group (n=1877). The differences were statistically notable ($p < 0.001$) in age, BMI, WC, SBP, DBP, albumin, GA, platelet, FBG, TC, cervical vascular plaques, smoking status, and MAFLD.

Table S2 exhibits the multivariable logistic analysis results. In model 1, a higher GA was greatly connected with higher odds of 10-year ASCVD risk (OR =1.138, 95% CI =1.094, 1.185). After adjusting for covariates (age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, TC, triglyceride, HDL-C, cervical vascular plaques, and MAFLD), GA was positively connected with 10-year ASCVD risk (OR =1.160, 95% CI =1.055, 1.276) in Model 3.

The RCS curve showed that increased GA levels were significantly linked to increased 10-year ASCVD risk (P for overall < 0.001), with a linear relationship (P for non-linear =0.2616) (Figure 4). The red solid line indicates the point estimate of OR, and the pink shaded area represents the 95% CI. The curve indicates that when GA levels are below 12.95%, the OR remains around 1, suggesting that GA does not significantly affect the risk within this range. However, when GA levels > 12.95%, the OR starts to increase significantly, indicating a marked correlation between higher GA levels and greater 10-year ASCVD risk.

3.2 Mediation Analysis of BMI

We then delved into the mediation effect of BMI on the link between GA and 10-year ASCVD risk. All mediation analyses were carried out after adjustment for age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, TC, triglyceride, HDL-C, cervical vascular plaques, and MAFLD.

GA was negatively correlated with BMI ($p < 0.001$) and positively correlated with 10-year ASCVD risk ($p < 0.001$). BMI was positively related to 10-year ASCVD risk ($p < 0.001$) (Table S3). It is estimated that BMI mediated 13.9% of the total link between GA and 10-year ASCVD risk.

Given the effect of age and MAFLD, subgroup analyses were implemented (Table S4). In the age group, BMI partially mediated the link between GA and 10-year ASCVD risk. In the age subgroup 40–60 years, there was a 43.7% mediating effect of BMI on the link between GA and 10-year ASCVD risk. However, in the age subgroup < 40 years and > 60 years, no mediating effect of BMI was observed on the correlation between GA and 10-year ASCVD risk. Similarly, BMI mediated 8.5% of the total link between GA and 10-year ASCVD risk in the non-MAFLD group. However, the mediating effect was not observed in the MAFLD group.

3.3 Sensitivity Analysis

In sensitivity analyses, we adjusted for three medication status variables (antidiabetic, antihypertensive, and lipid-lowering drugs) as potential confounders. After excluding 23 cases with missing data, the analysis of 2,084 eligible participants demonstrated that the positive association between GA and 10-year cardiovascular risk remained highly consistent (OR = 1.153, 95% CI = 1.033–1.277; Table S5). Detailed results of the adjusted model are provided (Table S5). This finding further supported the robustness

of our primary analysis, indicating that GA maintained its independent predictive value for 10-year cardiovascular risk even after controlling for the influence of pharmacological interventions.

4.Discussion

This study elucidated the relationship among GA, BMI, and 10-year ASCVD risk in the normal population undergoing physical examination and estimated the mediating role of BMI. This is the first study on their relationship, and our results confirm: 1. BMI mediated the link between GA and 10-year ASCVD risk, with 13.9% of the association mediated by BMI. 2. The mediating role of BMI varies by age and MAFLD subgroups. BMI plays a partially mediating role of 8.5% in the 40-60 age group and no mediating role in the 30-44 and over 60 age groups. Similarly, BMI has an 8.5% partial mediating effect on the non-MAFLD group, but no mediating effect was revealed in the MAFLD group.

The present study examined a real-world normal population undergoing medical examinations and showed a positive correlation between GA and 10-year CVD risk. These associations remained after adjustment for established cardiovascular risk factors and socio-behavioral factors. Although GA is widely recognized to reflect blood glucose levels, relevant studies have focused on its application in diverse situations (e.g., anemia, abnormal liver function, and renal disease) where HbA1c accuracy may be impaired. However, there is controversy about the ability of GA to predict long-term ASCVD outcomes. Previous studies have manifested that GA upregulation is positively linked to CAD and its severity in DM patients, whereas HbA1c levels are not as strongly correlated with CAD[33,34]. Similarly, several publications have highlighted that after adjustment for HbA1c levels, the higher GA in dialysis-requiring patients with CKD and DM, the higher risk of cardiovascular mortality, all-cause mortality, CAD,

major adverse cardiovascular events, and stroke; no correlation was found in non-DM individuals[9,18,19]. Zhao et al. had found in the meta - analysis that GA had a stronger association with CVD outcomes (including cardiovascular mortality in non - dialysis patients and all - cause mortality in dialysis patients) than HbA1c, and its link with MACCE was independent of traditional risk factors and HbA1c levels[35]. However, Copur et al. revealed a prominent correlation of GA levels with all-cause mortality in DM patients undergoing dialysis, but not with CVD mortality[36]. Additionally, high GA levels were independently linked to unfavorable intermediate-term efficacy in low-risk populations undergoing percutaneous coronary intervention, but the prognostic role was only present in the DM subgroup, and in the non-DM individuals, this association was not supported by clear evidence[37]. It is well known that atherosclerosis is the most important cause of CVDs[38]. Significant glycemic excursions or fluctuations potentiate oxidative stress and drive atherosclerosis, which can lead to ASCVD[39,40]. We hypothesized that relative to HbA1c, GA may better indicate glycemic fluctuations (eg, acute hyperglycemia or significant postprandial glycemic excursion) before the onset of acute coronary syndrome (within a short period[39,41], thereby promoting oxidative stress and accelerating atherosclerosis in both DM and non-DM subjects[42,43]. In non-DM subjects, short-term glycemic fluctuations, especially significant postprandial glycemic excursion, may be manifested as small but notable differences in GA. The effect of HbA1c on non-DM participants may be confounded by non-glycemic factors, like abnormalities in liver and kidney function and differences in red blood cell lifespan. In summary, studies comparing GA and HbA1c for long - term ASCVD prediction had mainly focused on diabetic patients and those with renal dysfunction, and there had been a lack of research on the longitudinal comparison of GA and HbA1c changes in the normal population. Therefore, further investigations are warranted to elucidate the

complex pathophysiologic mechanisms that link GA to ASCVD risk.

Our experimental results showed that GA was negatively connected with BMI. Research in normoglycemic populations, pre-DM patients, and T2DM patients has reported a link between BMI and HbA1c or GA/HbA1c[27,44]. However, studies on the link between GA and BMI are very limited in normal populations in China. As mentioned earlier, several papers have demonstrated a weak negative connection between GA and BMI among DM populations, but mainly in normal-weight subjects with little fluctuation in BM[11,22-27], or Caucasian populations with large body weights (mean BMI of 38.4). In contrast, the two papers that did not discover a negative correlation between GA and BMI were conducted in the Japanese population with type 1 DM with a mean BMI of 20.1[45] or without DM with a nearly constant GA[46]. Thereby, the negative link between BMI and GA may not be exclusively attributable to glycemic exposure, but that there are other factors. An increase in BMI increases renal blood flow, glomerular filtration rate, and tubular reabsorption, resulting in glomerular enlargement and obesity-associated glomerular disease[47,48]. There is a difference in the rate of GA synthesis in participants with higher BMI and normal BMI[22]. BMI may affect GA clearance. A mild increment in BMI is related to an increased prevalence of microalbuminuria, which is a marker of early renal damage and is also closely related to cardiovascular prognosis[49]. Elevated GA levels may reflect the presence of microalbuminuria and cardiovascular events, but the exact mechanism is currently unknown. Therefore, future studies should refine the proteinuria and renal clearance of GA, which may influence the relationship between GA and BMI. Additional research utilizing labeled albumin in animal models of obesity and DM may offer valuable insight into this process.

Interestingly, the mediation analysis unraveled that BMI mediated 13.9% of the link

between GA and 10-year ASCVD risk. This result emphasizes the importance of reducing BMI in lowering 10-year ASCVD risk, especially in high-GA populations, regardless of DM. Overweight and obesity are drivers of insulin resistance[50,51]. Insulin resistance is the core connecting several events of cardiometabolic disorders[50-55], molecularly due to impaired insulin signaling transduction via the PI3K pathway and intact signaling transduction via the MAPK pathway, leading to altered glucose-insulin homeostasis and increased glucose fluctuations. Significant shifts in blood glucose values facilitate oxidative stress and atherosclerosis[39,40]. Our study results supported this hypothesis. Although antihypertensive, lipid-lowering, and antidiabetic drugs might influence ASCVD risk through different pathways, sensitivity analysis showed that GA's independent predictive value remained unweakened after adjusting for these clinical interventions. Similarly, elevated serum GA levels are notably related to augmented carotid intima-media thickness and vascular endothelial dysfunction, a sign of early atherosclerosis[56]. Vascular smooth muscle cell proliferation, vascular endothelial dysfunction, and overproduction of collagen and inflammatory cytokines contribute to atherosclerosis and adverse cardiovascular events. Patients in the high GA group were more susceptible to metabolic disorders and severe CAD than those in the low and mediate GA groups and therefore had an intensified risk of CAD. When GA levels are substantially elevated (in the higher range, e.g., more than 17.1%), the CAD risk augments by approximately two folds[37]. Akane Mihara et al. disclosed findings from 10-year follow-up of the Hisayama study, suggesting that the highest quartile of GA levels (≥15.7%) was connected with a 2.2-fold increase in CAD incidence and a 2.5-fold increase in stroke risk[57]. The exact mechanism of the mediating effect of BMI is currently unclear and may be different in different populations. Additional research is warranted to illustrate the mechanisms.

Interestingly, we found age and MAFLD were involved in the mediating role of BMI in the association between GA and 10-year ASCVD risk. Age-stratified subgroup analyses found that BMI did not mediate the association in the <40 and >60 groups. This finding suggests that BMI reduction in the <40 and >60 groups with increased GA may not be the cause for reducing 10-year CVD risk compared with the partial mediation effect in the 40-60 group. We suggest that in the 40-60 group, BMI reduction will be the focus of reducing the 10-year CVD risk induced by increased GA. In addition, subgroup analyses by MAFLD discovered that the link between GA and 10-year CVD risk was partially mediated by BMI in the non-MAFLD group, whereas BMI had no mediating effect in the MAFLD group. This finding suggests that BMI reduction in the MAFLD group with increased GA may not be the cause for reducing 10-year CVD risk. In the non-MAFLD group, BMI reduction will be the focus of preventing 10-year CVD risk. Since GA is an indicator of short-term glucose fluctuations and insulin resistance is the main mechanism of MAFLD, it is primarily a long-term effect. Therefore, long-term monitoring of GA is of limited benefit in assessing 10-year CVD risk in MAFLD populations. This may provide new insights into assessing and reducing 10-year CVD risk in these two groups.

Our study first investigates the mediating role of BMI in the link between GA and 10-year ASCVD risk. Nevertheless, we must acknowledge certain inherent limitations of our study. Firstly, multiple multivariate models were adopted to unveil the independent link between GA and 10-year ASCVD risk. Essential confounding factors like alcohol consumption and smoking were obtained through self-reported data, which are potentially influenced by recall bias and misinterpretations and potentially affect the accuracy of our findings. Secondly, it is crucial to analyze the correlation between GA and proteinuria. However, since this study involved non-hospitalized population and

the incidence of proteinuria among participants was exceedingly low, statistical analysis was not possible. This limitation underscores further investigations into the renal clearance of proteinuria and GA, which is pivotal in elucidating the link between BMI and GA. Lastly, given the cross-sectional nature, it is not feasible to establish the exact causality as well as the bidirectional association between GA and 10-year ASCVD risk. Thereby, prospective cohort studies are imperative to further unveil this relationship. Despite these limitations, our study, based on a real-world context and substantial sample size, has fully adjusted for confounders, so the conclusions drawn are relatively reliable.

In conclusion, our cross-sectional study of 2,107 participants demonstrates for the first time that BMI effectively mediates the impact of GA on the 10-year ASCVD risk. Consequently, healthy populations, especially those aged 40-60 without MAFLD, should realize the beneficial effects of GA in reducing their 10-year ASCVD risk through lowering BMI, rather than just preventing diabetes. Prospective studies are crucial to validate these findings and elucidate intrinsic mechanisms, thus paving the way for targeted therapeutic strategies.

List of abbreviations

Glycated albumin (GA); atherosclerotic cardiovascular disease (ASCVD); cardiovascular diseases (CVDs); coronary artery disease (CAD); hemoglobin A1c (HbA1c); chronic kidney disease (CKD); systolic blood pressure (SBP); waist circumference (WC); total cholesterol (TC); metabolic-associated fatty liver disease (MAFLD); standard error (SE)

Declarations

Ethics approval and consent to participate

This retrospective study adhered to the institution and national research committee's ethical standards, and approval was obtained from the institutional ethics committee of the Third Xiangya Hospital of Central South University and review board (Ethics Approval Number: Quick24559).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Consent for publication

Not applicable

Funding

This work was supported by grants from the National Natural Science Foundation of China (82304171) and the Hunan Province Natural Science Foundation (2022JJ40668); National Key Clinical Specialty Scientific Research Project (Z2023058) and Chinese Cardiovascular Association-ASCVD Fund (2023-CCA-ASCVD-018).

Author contributions

All authors contributed to the study conception and design. Writing - original draft preparation: XZ, YH, SX, NC, YZ, ML; Writing - review and editing: XZ; Conceptualization: YH, NC; Methodology: SX, YZ; Formal analysis and investigation: XZ, YH; Funding acquisition: ML, XZ; Resources: XZ; the guarantor: ML; Supervision: ML, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial

or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

Not applicable.

Patient and Public Involvement

Not applicable

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Figure legends

Figure 1: Flowchart for study population selection.

Figure 2: Diagnostic standard flowchart of MAFLD.

Figure 3: Path diagram of the mediation analysis models

Figure 4: Restricted Cubic Spline Curve for association between odds ratio of GA and 10-year ASCVD risk

Supplementary Materials

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Table S2. Logistic regression models of the link between GA and 10-year ASCVD risk

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Table S5. Sensitivity Analysis Adjusted for Pharmacotherapy (Model 4)

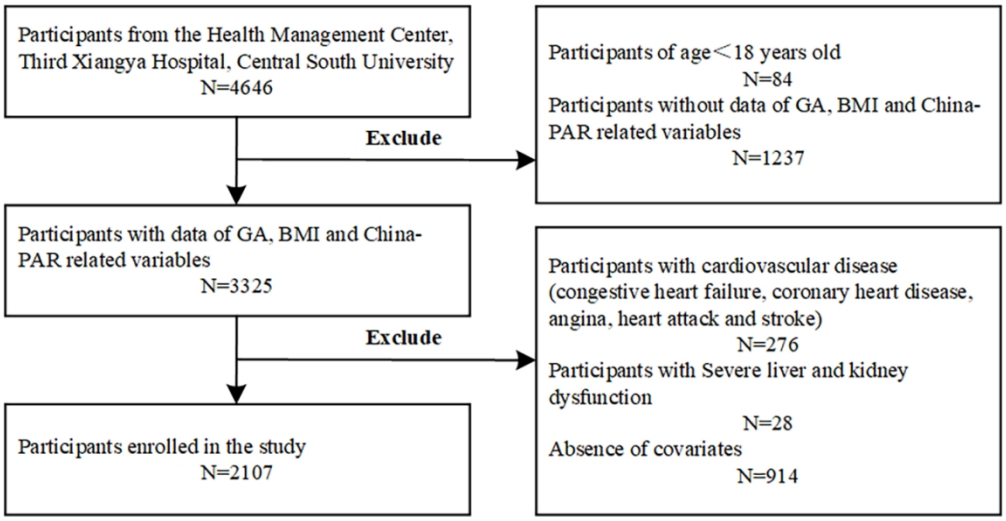

Figure 1: Flowchart for study population selection.

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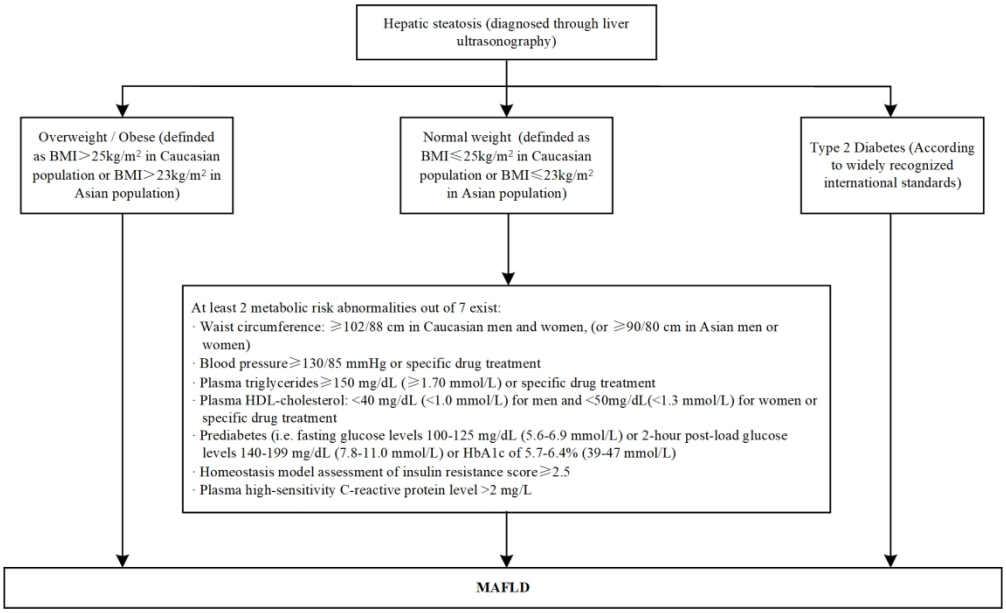

Diagnostic standard flowchart of MAFLD.

169x102mm (300 x 300 DPI)

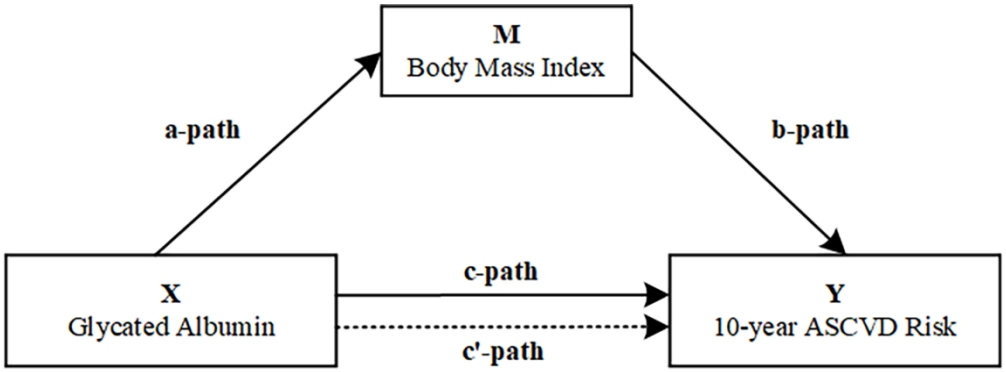

Figure 3: Path diagram of the mediation analysis models

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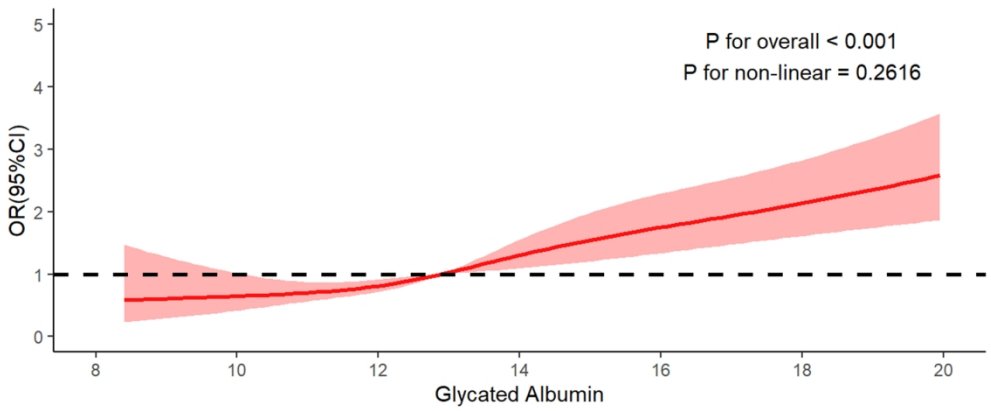

Figure 4: Restricted Cubic Spline Curve for association between odds ratio of GA and 10-year ASCVD risk

169x75mm (300 x 300 DPI)

Table S1 Baseline characteristics of enrolled participants

	Total	China-PAR		p-Value
	(n=2107)	Medium-high Risk Group (n=230)	Low Risk Group (n=1877)	
Characteristics [median (25th, 75th)]				
Age (year)	45.00 [36.00, 52.00]	59.00 [56.00, 66.00]	43.00 [35.00, 50.00]	<0.001
BMI*(kg/m^2)	24.20 [21.85, 26.50]	25.20 [23.63, 27.90]	24.00 [21.70, 26.20]	<0.001
Waist circumference(cm)	83.00 [74.00, 91.00]	89.00 [83.00, 96.00]	82.00 [73.00, 90.00]	<0.001
Systolic Pressure(mmHg)	119.00 [109.00, 130.00]	138.00 [130.00, 147.75]	118.00 [108.00, 127.00]	<0.001
Diastolic Pressure(mmHg)	73.00 [65.00, 81.00]	83.00 [77.00, 89.00]	71.00 [65.00, 80.00]	<0.001
albumin(g/L)	45.50 [43.80, 47.60]	44.60 [42.90, 46.10]	45.70 [43.90, 47.70]	<0.001
GA*(%)	12.90 [11.60, 14.20]	13.60 [12.20, 15.40]	12.80 [11.50, 14.10]	<0.001
platelet(10^9/L)	227.00 [192.00, 261.00]	208.00 [176.25, 245.75]	229.00 [194.00, 262.00]	<0.001
ALT*(U/L)	20.00 [14.00, 31.50]	20.00 [15.00, 28.00]	21.00 [14.00, 32.00]	0.391
AST*(U/L)	22.00 [18.00, 27.00]	23.00 [20.00, 26.00]	22.00 [18.00, 27.00]	0.043
Fasting blood glucose(mmol/L)	5.23 [4.90, 5.67]	5.74 [5.20, 6.51]	5.20 [4.87, 5.59]	<0.001
Total cholesterol(mmol/L)	4.97 [4.42, 5.68]	5.18 [4.59, 5.92]	4.95 [4.41, 5.64]	0.006
triglyceride(mmol/L)	1.42 [0.92, 2.26]	1.72 [1.05, 2.66]	1.38 [0.90, 2.22]	<0.001
HDL-C*(mmol/L)	1.25 [1.07, 1.47]	1.21 [1.04, 1.40]	1.25 [1.07, 1.48]	0.006
LDL-C*(mmol/L)	2.90 [2.39, 3.45]	2.94 [2.41, 3.55]	2.90 [2.39, 3.44]	0.408
Characteristics [n (%)]				
Sex				0.001
Female	1131 (53.7)	148 (64.3)	983 (52.4)	
Male	976 (46.3)	82 (35.7)	894 (47.6)	
Cervical vascular plaques				<0.001
No	1632 (77.5)	101 (43.9)	1531 (81.6)	
Yes	475 (22.5)	129 (56.1)	346 (18.4)	
Smoking status				<0.001
No	1538 (73.0)	131 (57.0)	1407 (75.0)	
Yes	569 (27.0)	99 (43.0)	470 (25.0)	
Drinking status				0.449
No	1344 (63.8)	141 (61.3)	1203 (64.1)	
Yes	763 (36.2)	89 (38.7)	674 (35.9)	
Sport status				0.012
No	854 (40.5)	75 (32.6)	779 (41.5)	
Yes	1253 (59.5)	155 (67.4)	1098 (58.5)	
MAFLD*				<0.001
No	1116 (53.0)	62 (27.0)	1054 (56.2)	
Yes	991 (47.0)	168 (73.0)	823 (43.8)	

Notes: Values are median (25th, 75th), or n (%). P values were computed utilizing Student's t-test or the Mann-Whitney U test for continuous variables, and the chi-squared test was adopted for categorical variables. *BMI: body mass index; GA: glycated albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MAFLD: metabolic associated fatty liver disease.

Table S2. Logistic regression models of the link between GA and 10-year ASCVD risk

	Model 1			Model 2			Model 3		
	OR	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
GA	1.138	(1.094, 1.185)	< 0.001	1.142	(1.049, 1.240)	0.002	1.160	(1.055, 1.276)	0.002

Notes: Model 1 = GA; Model 2 = Model 1 + Age + Sex + Smoking status + Sport status + BMI + WC + SBP +DBP; Model 3 = Model 2 + Albumin + Platelet + Total Cholesterol + Triglyceride + HDL-C + Cervical vascular plaques + MAFLD.

Table S3. Mediation effect of BMI on the association between GA and 10-year ASCVD risk

Mediator	Sample	Exposure to Mediator	Mediator to Outcome	Direct Effect	Mediated (Indirect Effect)	Total Effect (Exposure to Outcome)	Proportion Mediated (%)
BMI	2107	-0.146 (0.026) p<0.001	0.190 (0.015) p<0.001	0.229 (0.040) p<0.001	-0.028 (0.006) p<0.001	0.201 (0.040) p<0.001	13.9%

Notes: Exposure: GA; Outcome: 10-year ASCVD risk; Model adjusted for age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, TC, triglyceride, HDL-C, cervical vascular plaques, and MAFLD.

Table S4. Mediation effect of BMI on the link between GA and 10-year ASCVD risk by age and MAFLD

Mediator	Sample	Exposure to Mediator	Mediator to Outcome	Direct Effect	Mediated (Indirect Effect)	Total Effect (Exposure to Outcome)	Proportion Mediated (%)
Stratification by Age							
<40	743	-0.388 (0.064) p < .001	0.056 (0.005) p < .001	0.030 (0.022) p =.177	-0.022(0.007) 95%CI (-0.037, -0.011) p = .002	0.008 (0.023) p = .714	-
40-60	1214	-0.147 (0.030) p < .001	0.210 (0.016) p < .001	0.102 (0.029) p < .001	-0.031(0.007) 95%CI (-0.046, -0.020) p < .001	0.071 (0.030) p = .017	**43.7**
>60	150	0.136 (0.075) p =.270	0.185 (0.093) p < .05	0.415 (0.121) p < .001	0.025(0.022) 95%CI (-0.016, 0.069) p = .245	0.440 (0.117) p < .001	-
Stratification by MAFLD							
MALFD	991	-0.040 (0.029) p =.092	0.081 (0.029) p < .01	0.275 (0.043) p < .001	-0.003(0.003) 95%CI (-0.010, 0.002) p = .310	0.272 (0.043) p < .001	-
Non-MAFLD	1116	-0.107*** (0.029) p < .001	0.127*** (0.026) p < .001	0.178 (0.068) p = .009	-0.014(0.005) 95%CI (-0.025, -0.006) p = .004	0.164 (0.067) p = .014	**8.5**

Notes: Exposure: GA; Mediator: BMI; Outcome: 10-year ASCVD risk; Model adjusted for age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, total cholesterol, triglyceride, HDL-C, cervical vascular plaques, and MAFLD.

Table S5. Sensitivity Analysis Adjusted for Pharmacotherapy (Model 4)

	Model 4		
	OR*	**95%CI***	**p**
GA*	1.153	(1.033, 1.277)	0.008

Notes: Model 4 adjusted for antihypertensive drugs, lipid-lowering drugs, and glucose-lowering drugs. Analysis was conducted on 2,084 participants after excluding 23 cases with missing medication data. *OR: odds ratio; CI: confidence interval; GA: glycated albumin;

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-092714.R2
Article Type:	Original research
Date Submitted by the Author:	08-May-2025
Complete List of Authors:	Zeng, Xi; Deparment of Health Management, The Third Xiangya Hospital, Central South University Hu, Yangliuzi; Department of Spinal Surgery, Third Xiangya Hospital, Central South University Xiao, Shujuan; Department of Epidemiology, Xiangya School of Public Health, Central South University; Hunan Provincial Key Laboratory of Clinical Epidemiology, Xiangya School of Public Health, Central South University, Changsha, Hunan, China Chen, Ni-Ni; Department of Health Management, The Third Xiangya Hospital, Central South University Zhou, Yang; Department of Epidemiology, Xiangya School of Public Health, Central South University; Hunan Provincial Key Laboratory of Clinical Epidemiology, Xiangya School of Public Health, Central South University, Changsha, Hunan, China Luo, Miyang; Central South University Xiangya School of Public Health, Department of Epidemiology; Hunan Provincial Key Laboratory of Clinical Epidemiology, Xiangya School of Public Health, Central South University
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, Cardiovascular Disease, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Body Mass Index

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Mediation Effect of Body Mass Index on the Association Between Glycated Albumin and 10-Year Atherosclerotic Cardiovascular Disease Risk in Hunan Residents of China: A Retrospective Cross-sectional Study

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Abstract

Objectives: Glycated albumin (GA) and body mass index (BMI) are associated with the risk of atherosclerotic cardiovascular disease (ASCVD). However, the role of BMI in the association between GA and 10-year ASCVD risk is still not fully understood.

Design: A Retrospective Cross-sectional Study

Setting: In this retrospective cross-sectional study, 4,646 healthy subjects who received a full health examination at the Health Management Medical Center, Third Xiangya Hospital of Central South University from January 1, 2022 to December 30, 2023, were initially identified. According to the exclusion criteria, 2,107 participants were included in the final analysis.

Participants: The inclusion criteria for this study included: a) age is greater than or equal to 18 years old; and b) subjects were long-term residents of Hunan province.

Primary and secondary outcome measures: The 10-year ASCVD risk was evaluated via the China-PAR equation. The link between GA and 10-year ASCVD risk was examined through a multivariable logistic regression model and the dose-response relationship was demonstrated using the restricted cubic spline. The potential mediation effect of BMI on this association was explored and the differences in this mediation effect across age and metabolic-associated fatty liver disease (MAFLD) subgroups were analyzed.

Results: Elevated GA levels were positively linked to an intensified 10-year ASCVD risk (OR=1.160, 95% CI =1.055–1.276). Additionally, BMI was negatively linked to GA and 10-year ASCVD risk. BMI mediated 13.9% of the connection between GA and 10-year ASCVD risk. Specifically, the mediating effect of BMI remained significant in the 40–60 years age subgroup and non-MAFLD subgroup, with mediation ratios of 43.7% and 8.5%, respectively.

Conclusions: GA is a key predictor of 10-year ASCVD risk, and BMI partially mediates this relationship in healthy populations. Therefore, targeted weight management is recommended to reduce the adverse effect of GA on 10-year ASCVD risk in different populations.

Strengths and limitations of this study

1. We used a mediation model to identify BMI as a partial mediator in the association between GA and 10-year ASCVD risk.
2. We applied multivariate logistic regression to explore the link between GA and 10-year ASCVD risk, controlling confounding effects stepwise.
3. Restricted Cubic Spline curves were used to illustrate the dose-response association between GA and 10-year ASCVD risk.
4. The study's retrospective cross-sectional design prevents establishing causality between GA and 10-year ASCVD risk and exploring the GA-BMI bidirectional relationship.

Keywords: Glycated Albumin, Body Mass Index, Atherosclerotic Cardiovascular Disease Risk, Mediation, Metabolic Associated Fatty Liver Disease

1. Introduction

Cardiovascular diseases (CVDs) represent the primary culprits behind deaths and disability worldwide, presenting a substantial risk to human health. This category of diseases encompasses coronary artery disease (CAD), stroke, and myocardial infarction, which commonly arise due to arteriosclerosis, hypertension, hyperlipidemia, and diabetes[1-5]. Currently, glycated hemoglobin A1c (HbA1c) is recognized as a leading

indicator in the clinical assessment of long-term blood glucose control. The latest KDIGO guidelines have recommended a target value of 6.5% to 8.0% for HbA1c in those with diabetes and chronic kidney disease (CKD) to reduce CVD risk[6]. Nevertheless, HbA1c can be influenced by hemoglobin levels, red blood cell lifespan, anemia, liver dysfunction, and kidney disease[7]. Concurrently, there is increasing interest in an alternative indicator, glycated albumin (GA), a novel index for glucose monitoring, reflecting average blood glucose levels over the past 2 to 3 weeks[8, 9] GA is calculated as the ratio of GA to total albumin concentration[10]. Unlike HbA1c, GA has the advantage of being independent of hemoglobin and red blood cell turnover and less affected by red blood cell lifespan, thus serving as a favorable marker for assessing blood glucose levels[11].

Numerous guidelines have recommended that the prevention and treatment of atherosclerotic CVD (ASCVD) be based on risk assessment. Traditional risk assessment methods, including the Framingham D'Agostino 2008 model, PCE white model, SCORE model, and QRI SK model, are recognized for their reliability in Western populations. However, the Chinese population presents distinct disease patterns and risk factors, making these models less suitable. Particularly, the Framingham D'Agostino model overestimates the CVD risk in men and underestimates it in women, a trend similarly observed in the PCE model[12]. Since 2003, several large-sample prediction models for CVD risk have been established for Chinese adults. Among them, the 10-year risk prediction models for Chinese CVD[13, 14] and the prediction for ASCVD risk in China (China-PAR) model for ASCVD[15] are notable. China-PAR model, a CVD risk assessment tool developed by Chinese scholars based on large-sample cohort data, is most often externally validated and is considered potentially a better option for predicting CVD risk in China[16]. The China-PAR model

estimates the 10-year ASCVD risk based on validated demographic, clinical, and lifestyle indicators, including age, sex, family history, blood pressure (systolic blood pressure, diastolic blood pressure), lipid profiles (total cholesterol, high-density lipoprotein cholesterol), smoking, diabetes, abdominal obesity (waist circumference), urban/rural residence, and regional cardiovascular epidemiology.

Obese people have a high prevalence of ASCVD, and body mass index (BMI), as an important indicator for assessing obesity in an individual, has a very close link with ASCVD risk. Similarly, the performance of GA in predicting CVD risk has attracted much attention in recent years. GA, as an early glycated protein, may be more sensitive than other markers to CVD and its complications[5, 17]. Several publications have found a link between GA and cardiovascular mortality in diabetes mellitus (DM) patients[9, 18, 19]. Notably, multiple studies confirm that GA is more strongly than HbA1C associated with CVD in CKD patients requiring dialysis[18, 20, 21]. Several papers have noted a weak negative connection between GA and BMI in DM populations but with a narrow range for BMI or GA values[11, 22-27]. In contrast, an investigation of Caucasian populations with a median BMI of 38.4 (large body weight) similarly unveiled a marked negative link between BMI and GA[7]. Therefore, the association between GA and BMI in a wider population remains to be confirmed by further studies. There are few studies on the association among GA, BMI, and 10-year ASCVD risk in normal populations. Hence, this paper was to illustrate whether BMI mediates the link between GA and 10-year ASCVD risk in the normal population.

2. Methods

2.1 Participant Selection

This cross-sectional study obtained data from 4646 healthy subjects during health

checkups at the Health Management Medicine Center, Third Xiangya Hospital of Central South University from January 1, 2022, to June 30, 2023. To control for potential biases, we included all health examination data during this period, rather than relying on random sampling.

The inclusion criteria for this study included: a) age is greater than or equal to 18 years old; and b) subjects were long-term residents of Hunan province. The exclusion criteria of this study were a) subjects did not have complete data required for this study; b) subjects did not provide written informed consent; c) Subjects reported established family history and medical history of CVD and cerebrovascular diseases (including coronary heart disease, stroke, congestive heart failure, myocardial infarction, and angina) in questionnaires; and d) Subjects was discovered severe liver or kidney dysfunction (which may affect GA results) in health checkups. According to the exclusion criteria, 84 participants under the age of 18 were excluded, 1237 participants lacking GA, BMI, and China-PAR equation-related data were excluded, 276 participants with self-reported CVD and cerebrovascular diseases on the questionnaire were excluded, 28 participants with severe liver or kidney dysfunction (defined as a history of severe liver impairment, liver cirrhosis, CKD stage 3 or higher, or end-stage renal disease, which may affect GA results) were excluded, and 914 participants with missing information on cardiovascular risk factors were excluded. Ultimately, 2107 participants were enrolled. The specific selection process is displayed in Figure 1. This retrospective study adhered to the institution and national research committee's ethical standards, and approval was obtained from the institutional ethics committee of the Third Xiangya Hospital of Central South University and the review board (Ethics Approval Number: Quick24559).

2.2 Measurements

2.2.1 GA measurement

Compared to HbA1c testing, the detection methods for GA are not yet fully standardized. In this study, enzyme-linked immunosorbent assay (ELISA), a widely adopted and reliable technique[28] was employed to detect GA.

2.2.2 Cardiovascular Risk Estimation Based on China-PAR Project

The China-PAR score was employed to appraise ASCVD risk. The China-PAR model encompassed sex, age, systolic blood pressure (SBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), waist circumference (WC), smoking status, diabetes, region, urbanization, and family history of ASCVD. The participants were allocated into three risk subgroups based on the scores: <5% as low risk, 5–10% as medium risk, and ≥10% as high risk[15].

Health status and lifestyle information of the participants were collected through questionnaires during their health checkups. This questionnaire, designed based on the National Physical Examination Questionnaire[29], included details on the participants' and family history of CVDs and cerebrovascular diseases, and lifestyle information such as history of hypertension, CVDs, DM, smoking, alcohol consumption, and physical activity. Hypertension was diagnosed as SBP ≥140 mmHg and/or diastolic blood pressure (DBP)≥90 mmHg or receiving antihypertensive treatment. Diabetes was diagnosed as fasting plasma glucose (FPG) ≥7.0 mmol/L, HbA1c ≥6.5%, or receiving hypoglycemic treatment. A family history of ASCVD was described as congestive heart failure, stroke, coronary heart disease, myocardial infarction, or angina in first-degree relatives. Based on the Chinese guideline on the primary prevention of cardiovascular diseases (2020) [30], which prioritizes actionable thresholds for public health interventions, participants were allocated into a medium-high risk group and low-risk groups in this study.

2.2.3 Covariate Assessment

Demographic data were obtained from physical examination reports. Age as a continuous variable was categorized into subgroups: 18-39 years, 40-60 years, or >60 years. During the physical examination, weight, height, WC, SBP, and DBP were gauged. BMI was presented as weight (kg) divided by height square (m^2). Laboratory tests covered routine blood tests, liver function tests, GA, FBG, HbA1c, fasting insulin, and blood lipids. It should be noted that GA rather than HbA1C was the primary focus of this study, and most research subjects did not have both measurements above, HbA1C was not set as a mandatory enrollment criterion. All participants underwent liver and cervical vascular ultrasonography performed by an ultrasonologist after an overnight fast. These reports were reviewed and confirmed by another senior ultrasonologist. The diagnoses of fatty liver (hepatic steatosis) and cervical vascular plaques were based on liver and cervical vascular ultrasound scans using linear array or convex high-frequency probes with frequencies of 5-10 MHz. These scans evaluated the echo, size, and morphology of the liver, as well as intima-media thickness, plaque size, morphology, and location of cervical vessels. Furthermore, medication history, smoking history, alcohol consumption, and exercise frequency were recorded directly from the physical examination questionnaire. Medication history in this study was defined as medication used for diabetes mellitus, hypertension, and dyslipidemia. Smoking history was defined as smoking continuously or cumulatively for more than six months[29]. Alcohol consumption manifested as consuming over 10 grams of alcohol per day[31]. Physical activity represented moderate- or high-intensity physical activity at least three times per week, with each session lasting at least 30 minutes[32].

2.2.4 Diagnosis of MAFLD

According to Eslam et al.[33], metabolic-associated fatty liver disease (MAFLD)

means steatosis in combination with metabolic dysfunction in the International Expert Consensus Statement on MAFLD. The diagnostic criteria included hepatic steatosis through histology (liver biopsy), imaging techniques, or blood-based biomarkers and at least one of the following conditions: overweight/obesity, T2DM, and metabolic dysfunction. Metabolic dysfunction refers to at least two of the seven metabolic risk abnormalities (Figure 2). In this study, all subjects were from a health screening cohort. Thus, balancing feasibility, cost-effectiveness, and diagnostic accuracy in the screening population, we uniformly used liver ultrasonography after an overnight fast to assess hepatic steatosis in all subjects, instead of other imaging techniques (e.g., vibration-controlled transient elastography or MRI elastography), blood-based biomarkers (e.g., FIB-4, APRI), or liver biopsy.

2.3 Data Analysis

Continuous variables were denoted as median and interquartile spacing and compared utilizing the independent samples t-test. Categorical variables were depicted as unweighted frequencies, weighted percentages, and standard error (SE), and compared utilizing the chi-square test. Multivariate logistic regression analysis was performed to assess the association between GA (a continuous exposure variable) and 10-year ASCVD risk (a binary outcome variable). Variables showing between-group differences in the baseline information table ($P < 0.05$) were identified and included as potential confounders, serving as covariates in subsequent analyses. Given the strong association of fasting glucose and HbA1c with the 10-year ASCVD risk, they were excluded from the logistic regression model. Three models were constructed to progressively control for the effects of confounders: Unadjusted crude Model 1; Model 2 adjusted for age, sex, smoking status, sport status, BMI, WC, SBP, and DBP; and Model 3 adjusted for all covariates, such as albumin, platelet, TC, triglyceride, HDL-

C, cervical vascular plaques, and MAFLD. Subsequently, restricted cubic spline (RCS) analysis was adopted to demonstrate the dose-response relationship between GA and 10-year ASCVD risk. Finally, a logistic regression model was employed to illustrate the relationships among GA, BMI, and 10-year ASCVD risk. To analyze the mediation effect of BMI [(mediation effect/total effect) × 100%], a simple mediation model was used, with three paths (Figure 3). The total effect represented the impact of GA (exposure) on 10-year ASCVD risk (outcome). Path A assessed the effect of GA on BMI (mediator). Path B evaluated the link between BMI and 10-year ASCVD risk. Path C estimated the direct impact of GA on 10-year ASCVD risk. The mediated effect was calculated as (mediated effect/total effect) × 100%.

All statistical analyses, including mediation analysis, were performed in the R statistical package. Statistical significance was delineated at a two-sided p-value of < 0.05.

3. Results

3.1. Characteristics of Participants

Table S1 displays the baseline characteristics of study participants. Based on the three risk categories mentioned above, participants were assigned to a medium-high-risk group (n=230) and a low-risk group (n=1877). The differences were statistically notable ($p < 0.001$) in age, BMI, WC, SBP, DBP, albumin, GA, platelet, FBG, TC, cervical vascular plaques, smoking status, and MAFLD.

Table S2 exhibits the multivariate logistic analysis results. In Model 1, a higher GA was greatly associated with higher odds of 10-year ASCVD risk (OR =1.138, 95% CI =1.094, 1.185). After adjusting for covariates (age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, TC, triglyceride, HDL-C, cervical vascular plaques, and MAFLD), GA was positively associated with 10-year ASCVD risk

(OR =1.160, 95% CI =1.055, 1.276) in Model 3.

The RCS curve showed that increased GA levels were significantly linked to an increased 10-year ASCVD risk (P for overall < 0.001), with a linear relationship (P for non-linear =0.2616) (Figure 4). The red solid line indicates the point estimate of OR, and the pink shaded area represents the 95% CI. The curve indicates that when GA levels are below 12.95%, the OR remains around 1, suggesting that GA does not significantly affect the risk within this range. However, when GA levels > 12.95%, the OR starts to increase significantly, indicating a marked association between higher GA levels and greater 10-year ASCVD risk.

3.2 Mediation Analysis of BMI

We then delved into the mediation effect of BMI on the link between GA and 10-year ASCVD risk. All mediation analyses were carried out after adjustment for age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, TC, triglyceride, HDL-C, cervical vascular plaques, and MAFLD.

GA was negatively associated with BMI ($p < 0.001$) and positively associated with 10-year ASCVD risk ($p < 0.001$). BMI was positively related to 10-year ASCVD risk ($p < 0.001$) (Table S3). It is estimated that BMI mediated 13.9% of the total link between GA and 10-year ASCVD risk.

Given the effect of age and MAFLD, subgroup analyses were implemented (Table S4). In the age group, BMI partially mediated the link between GA and 10-year ASCVD risk. In the age subgroup 40–60 years, there was a 43.7% mediating effect of BMI on the link between GA and 10-year ASCVD risk. However, in the age subgroup < 40 years and > 60 years, no mediating effect of BMI was observed on the association between GA and 10-year ASCVD risk. Similarly, BMI mediated 8.5% of the total link

between GA and 10-year ASCVD risk in the non-MAFLD group. However, the mediating effect was not observed in the MAFLD group.

3.3 Sensitivity Analysis

In sensitivity analyses, we adjusted for three medication status variables (antidiabetic, antihypertensive, and lipid-lowering drugs) as potential confounders. After excluding 23 cases with missing data, the analysis of 2,084 eligible participants demonstrated that the positive association between GA and 10-year cardiovascular risk remained highly consistent (OR = 1.153, 95% CI = 1.033–1.277; Table S5). Detailed results of the adjusted model are provided (Table S5). This finding further supported the robustness of our primary analysis, indicating that GA maintained its independent predictive value for 10-year cardiovascular risk even after controlling for the influence of pharmacological interventions.

4. Discussion

This study elucidated the association among GA, BMI, and 10-year ASCVD risk in the normal population undergoing physical examination and estimated the mediating role of BMI. This is the first study on their associations, and our results confirm: 1. BMI mediates 13.9% of the association between GA and 10-year ASCVD risk. 2. The mediating role of BMI varies by age and MAFLD subgroups. BMI plays a partially mediating role of 8.5% in the 40-60 age group and no mediating role in the 30-44 and over 60 age groups. Similarly, BMI has an 8.5% partial mediating effect on the non-MAFLD group, but no mediating effect was revealed in the MAFLD group.

The present study examined a real-world normal population undergoing medical examinations and showed a positive association between GA and 10-year CVD risk.

The association remained after adjustment for established cardiovascular risk factors and socio-behavioral factors. Although GA is widely recognized to reflect blood glucose levels, relevant studies have focused on its application in diverse situations (e.g., anemia, abnormal liver function, and renal disease) where HbA1c accuracy may be impaired. However, there is controversy about the ability of GA to predict long-term ASCVD outcomes. Previous studies have manifested that GA upregulation is positively linked to CAD and its severity in DM patients, whereas HbA1c levels are not as strongly correlated with CAD[34, 35]. Similarly, several publications have highlighted that after adjustment for HbA1c levels, the higher GA in dialysis-requiring patients with CKD and DM, the higher risk of cardiovascular mortality, all-cause mortality, CAD, major adverse cardiovascular events, and stroke; no association was found in non-DM individuals[9, 18, 19]. Zhao et al. found in the meta-analysis that GA had a stronger association with CVD outcomes (including cardiovascular mortality in non-dialysis patients and all-cause mortality in dialysis patients) than HbA1c, and its link with MACCE was independent of traditional risk factors and HbA1c levels[36]. However, Copur et al. revealed a prominent association of GA levels with all-cause mortality in DM patients undergoing dialysis, but not with CVD mortality[37]. Additionally, high GA levels were independently linked to unfavorable intermediate-term efficacy in low-risk populations undergoing percutaneous coronary intervention, but the prognostic role was only present in the DM subgroup, and in the non-DM individuals, this association was not supported by clear evidence[38]. It is well known that atherosclerosis is the most important cause of CVDs[39]. Significant glycemic excursions or fluctuations potentiate oxidative stress and drive atherosclerosis, which can lead to ASCVD[40, 41]. We hypothesized that relative to HbA1c, GA may better indicate glycemic fluctuations (eg, acute hyperglycemia or significant postprandial glycemic excursion) before the

onset of acute coronary syndrome (within a short period[40, 42], thereby promoting oxidative stress and accelerating atherosclerosis in both DM and non-DM subjects[43, 44]. In non-DM subjects, short-term glycemic fluctuations, especially significant postprandial glycemic excursion, may be manifested as small but notable differences in GA. The effect of HbA1c on non-DM participants may be confounded by non-glycemic factors, like abnormalities in liver and kidney function and differences in red blood cell lifespan. In summary, studies comparing GA and HbA1c for long-term ASCVD prediction had mainly focused on diabetic patients and those with renal dysfunction, and there had been a lack of research on the longitudinal comparison of GA and HbA1c changes in the normal population. Therefore, further investigations are warranted to elucidate the complex pathophysiologic mechanisms that link GA to ASCVD risk.

Our experimental results showed that GA was negatively associated with BMI. Research in normoglycemic populations, pre-DM patients, and T2DM patients has reported a link between BMI and HbA1c or GA/HbA1c[27, 45]. However, studies on the link between GA and BMI are very limited in normal populations in China. As mentioned earlier, several papers have demonstrated a weak negative connection between GA and BMI among DM populations, but mainly in normal-weight subjects with little fluctuation in BM[11, 22-27], or Caucasian populations with large body weights (mean BMI of 38.4). In contrast, the two papers that did not discover a negative association between GA and BMI were conducted in the Japanese population with type 1 DM with a mean BMI of 20.1[46] or without DM with a nearly constant GA[47]. Thereby, the negative link between BMI and GA may not be exclusively attributable to glycemic exposure, but there are other factors. An increase in BMI increases renal blood flow, glomerular filtration rate, and tubular reabsorption, resulting in glomerular

enlargement and obesity-associated glomerular disease[48, 49]. There is a difference in the rate of GA synthesis in participants with higher BMI and normal BMI[22]. BMI may affect GA clearance. A mild increment in BMI is related to an increased prevalence of microalbuminuria, which is a marker of early renal damage and is also closely related to cardiovascular prognosis[50]. Elevated GA levels may reflect the presence of microalbuminuria and cardiovascular events, but the exact mechanism is currently unknown. Therefore, future studies should refine the proteinuria and renal clearance of GA, which may influence the relationship between GA and BMI. Additional research utilizing labeled albumin in animal models of obesity and DM may offer valuable insight into this process.

Interestingly, the mediation analysis unraveled that BMI mediated 13.9% of the link between GA and 10-year ASCVD risk. This result emphasizes the importance of reducing BMI in lowering 10-year ASCVD risk, especially in high-GA populations, regardless of DM. Overweight and obesity are drivers of insulin resistance[51, 52]. Insulin resistance is the core connecting several events of cardiometabolic disorders[51-56], molecularly due to impaired insulin signaling transduction via the PI3K pathway and intact signaling transduction via the MAPK pathway, leading to altered glucose-insulin homeostasis and increased glucose fluctuations. Significant shifts in blood glucose values facilitate oxidative stress and atherosclerosis[40, 41]. Our study results supported this hypothesis. Although antihypertensive, lipid-lowering, and antidiabetic drugs might influence ASCVD risk through different pathways, sensitivity analysis showed that GA's independent predictive value remained unweakened after adjusting for these clinical interventions. Similarly, elevated serum GA levels are notably related to augmented carotid intima-media thickness and vascular endothelial dysfunction, a sign of early atherosclerosis[57]. Vascular smooth muscle cell proliferation, vascular

endothelial dysfunction, and overproduction of collagen and inflammatory cytokines contribute to atherosclerosis and adverse cardiovascular events. Patients in the high GA group were more susceptible to metabolic disorders and severe CAD than those in the low and mediate GA groups and therefore had an intensified risk of CAD. When GA levels are substantially elevated (in the higher range, e.g., more than 17.1%), the CAD risk augments by approximately two folds[38]. Akane Mihara et al. disclosed findings from a 10-year follow-up of the Hisayama study, suggesting that the highest quartile of GA levels (≥15.7%) was connected with a 2.2-fold increase in CAD incidence and a 2.5-fold increase in stroke risk[58]. The exact mechanism of the mediating effect of BMI is currently unclear and may be different in different populations. Additional research is warranted to illustrate the mechanisms.

Interestingly, we found age and MAFLD were involved in the mediating role of BMI in the association between GA and 10-year ASCVD risk. Age-stratified subgroup analyses found that BMI did not mediate the association in the <40 and >60 groups. This finding suggests that BMI reduction in the <40 and >60 groups with increased GA may not be the cause for reducing 10-year CVD risk compared with the partial mediation effect in the 40-60 group. We suggest that in the 40-60 group, BMI reduction will be the focus of reducing the 10-year CVD risk induced by increased GA. In addition, subgroup analyses by MAFLD discovered that the link between GA and 10-year CVD risk was partially mediated by BMI in the non-MAFLD group, whereas BMI had no mediating effect in the MAFLD group. This finding suggests that BMI reduction in the MAFLD group with increased GA may not be the cause for reducing 10-year CVD risk. In the non-MAFLD group, BMI reduction will be the focus of preventing 10-year CVD risk. Since GA is an indicator of short-term glucose fluctuations and insulin resistance is the main mechanism of MAFLD, it is primarily a long-term effect.

Therefore, long-term monitoring of GA is of limited benefit in assessing 10-year CVD risk in MAFLD populations. This may provide new insights into assessing and reducing 10-year CVD risk in these two groups.

Our study first investigates the mediating role of BMI in the link between GA and 10-year ASCVD risk. Nevertheless, we must acknowledge certain inherent limitations of our study. Firstly, multiple multivariate models were adopted to unveil the independent link between GA and 10-year ASCVD risk. Essential confounding factors like alcohol consumption and smoking were obtained through self-reported data, which are potentially influenced by recall bias and misinterpretations and potentially affect the accuracy of our findings. Secondly, it is crucial to analyze the association between GA and proteinuria. However, since this study involved non-hospitalized populations and the incidence of proteinuria among participants was exceedingly low, statistical analysis was not possible. This limitation underscores further investigations into the renal clearance of proteinuria and GA, which is pivotal in elucidating the link between BMI and GA. Lastly, given the cross-sectional nature, it is not feasible to establish the exact causality as well as the bidirectional association between GA and 10-year ASCVD risk. Therefore, prospective cohort studies are imperative to further unveil this relationship. Despite these limitations, our study, based on a real-world context and substantial sample size, has fully adjusted for confounders, so the conclusions drawn are relatively reliable.

In conclusion, our cross-sectional study of 2,107 participants demonstrates for the first time that BMI effectively mediates the impact of GA on the 10-year ASCVD risk. Consequently, healthy populations, especially those aged 40-60 without MAFLD, should realize the beneficial effects of GA in reducing their 10-year ASCVD risk through lowering BMI, rather than just preventing diabetes. Prospective studies are

crucial to validate these findings and elucidate intrinsic mechanisms, thus paving the way for targeted therapeutic strategies.

List of abbreviations

Glycated albumin (GA); atherosclerotic cardiovascular disease (ASCVD); cardiovascular diseases (CVDs); coronary artery disease (CAD); hemoglobin A1c (HbA1c); chronic kidney disease (CKD); systolic blood pressure (SBP); waist circumference (WC); total cholesterol (TC); metabolic-associated fatty liver disease (MAFLD); standard error (SE)

Declarations

Ethics approval and consent to participate

This retrospective study adhered to the institution and national research committee's ethical standards, and approval was obtained from the institutional ethics committee of the Third Xiangya Hospital of Central South University and review board (Ethics Approval Number: Quick24559).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Consent for publication

Not applicable

Funding

This work was supported by grants from the National Natural Science Foundation of China (82304171) and the Hunan Province Natural Science Foundation (2022JJ40668);

National Key Clinical Specialty Scientific Research Project (Z2023058) and Chinese Cardiovascular Association-ASCVD Fund (2023-CCA-ASCVD-018).

Author contributions

All authors contributed to the study conception and design. Writing - original draft preparation: XZ, YH, SX, NC, YZ, ML; Writing - review and editing: XZ; Conceptualization: YH, NC; Methodology: SX, YZ; Formal analysis and investigation: XZ, YH; Funding acquisition: ML, XZ; Resources: XZ; the guarantor: ML; Supervision: ML, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

Not applicable.

Patient and Public Involvement

Not applicable

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Figure legends

Figure 1: Flowchart for study population selection.

Figure 2: Diagnostic standard flowchart of MAFLD.

Figure 3: Path diagram of the mediation analysis models

Figure 4: Restricted Cubic Spline Curve for association between odds ratio of GA and 10-year ASCVD risk

Supplementary Materials

Table S1 Baseline characteristics of enrolled participants

Table S2. Logistic regression models of the link between GA and 10-year ASCVD risk

Table S3. Mediation effect of BMI on the association between GA and 10-year ASCVD risk

Table S4. Mediation effect of BMI on the link between GA and 10-year ASCVD risk by age and MAFLD

Table S5. Sensitivity Analysis Adjusted for Pharmacotherapy (Model 4)

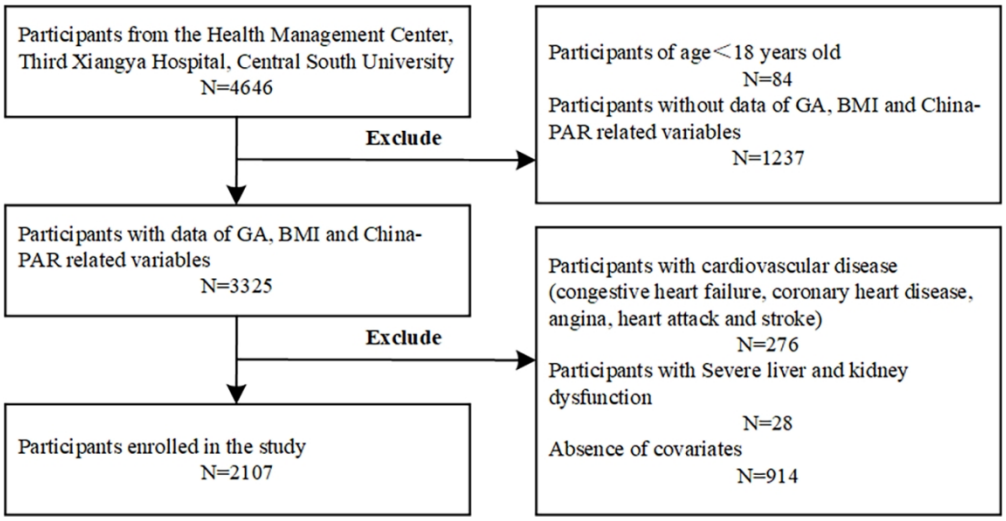
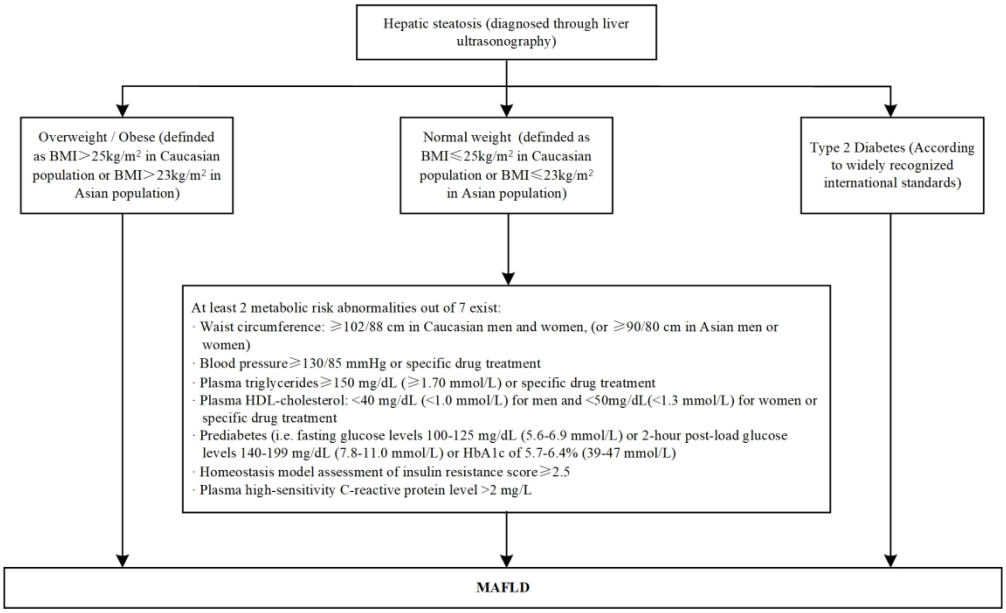


Figure 1: Flowchart for study population selection.

112x57mm (300 x 300 DPI)



Diagnostic standard flowchart of MAFLD.

169x102mm (300 x 300 DPI)

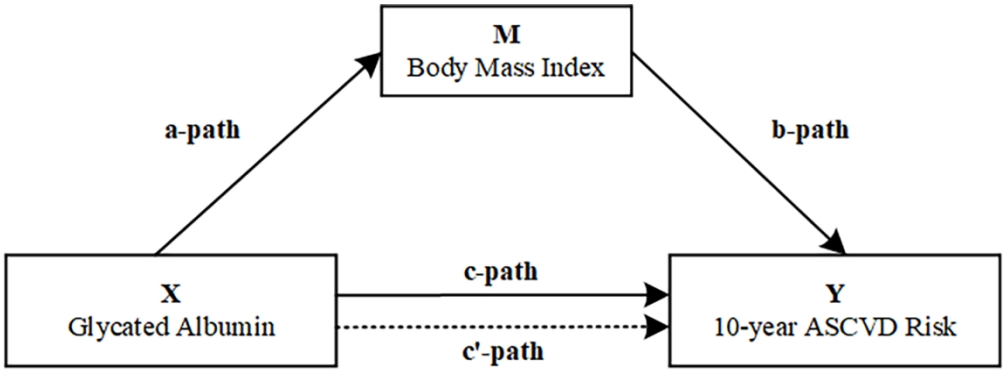


Figure 3: Path diagram of the mediation analysis models

169x63mm (300 x 300 DPI)

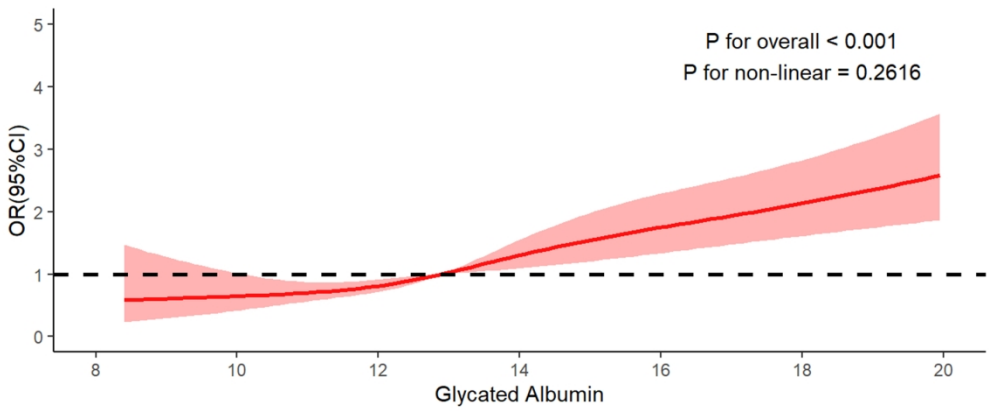


Figure 4: Restricted Cubic Spline Curve for association between odds ratio of GA and 10-year ASCVD risk

169x75mm (300 x 300 DPI)

Table S1 Baseline characteristics of enrolled participants

	Total	China-PAR		p-Value
	(n=2107)	Medium-high Risk Group (n=230)	Low Risk Group (n=1877)	
Characteristics [median (25th, 75th)]				
Age (year)	45.00 [36.00, 52.00]	59.00 [56.00, 66.00]	43.00 [35.00, 50.00]	<0.001
BMI*(kg/m^2)	24.20 [21.85, 26.50]	25.20 [23.63, 27.90]	24.00 [21.70, 26.20]	<0.001
Waist circumference(cm)	83.00 [74.00, 91.00]	89.00 [83.00, 96.00]	82.00 [73.00, 90.00]	<0.001
Systolic Pressure(mmHg)	119.00 [109.00, 130.00]	138.00 [130.00, 147.75]	118.00 [108.00, 127.00]	<0.001
Diastolic Pressure(mmHg)	73.00 [65.00, 81.00]	83.00 [77.00, 89.00]	71.00 [65.00, 80.00]	<0.001
albumin(g/L)	45.50 [43.80, 47.60]	44.60 [42.90, 46.10]	45.70 [43.90, 47.70]	<0.001
GA*(%)	12.90 [11.60, 14.20]	13.60 [12.20, 15.40]	12.80 [11.50, 14.10]	<0.001
platelet(10^9/L)	227.00 [192.00, 261.00]	208.00 [176.25, 245.75]	229.00 [194.00, 262.00]	<0.001
ALT*(U/L)	20.00 [14.00, 31.50]	20.00 [15.00, 28.00]	21.00 [14.00, 32.00]	0.391
AST*(U/L)	22.00 [18.00, 27.00]	23.00 [20.00, 26.00]	22.00 [18.00, 27.00]	0.043
Fasting blood glucose(mmol/L)	5.23 [4.90, 5.67]	5.74 [5.20, 6.51]	5.20 [4.87, 5.59]	<0.001
Total cholesterol(mmol/L)	4.97 [4.42, 5.68]	5.18 [4.59, 5.92]	4.95 [4.41, 5.64]	0.006
triglyceride(mmol/L)	1.42 [0.92, 2.26]	1.72 [1.05, 2.66]	1.38 [0.90, 2.22]	<0.001
HDL-C*(mmol/L)	1.25 [1.07, 1.47]	1.21 [1.04, 1.40]	1.25 [1.07, 1.48]	0.006
LDL-C*(mmol/L)	2.90 [2.39, 3.45]	2.94 [2.41, 3.55]	2.90 [2.39, 3.44]	0.408
Characteristics [n (%)]				
Sex				0.001
Female	1131 (53.7)	148 (64.3)	983 (52.4)	
Male	976 (46.3)	82 (35.7)	894 (47.6)	
Cervical vascular plaques				<0.001
No	1632 (77.5)	101 (43.9)	1531 (81.6)	
Yes	475 (22.5)	129 (56.1)	346 (18.4)	
Smoking status				<0.001
No	1538 (73.0)	131 (57.0)	1407 (75.0)	
Yes	569 (27.0)	99 (43.0)	470 (25.0)	
Drinking status				0.449
No	1344 (63.8)	141 (61.3)	1203 (64.1)	
Yes	763 (36.2)	89 (38.7)	674 (35.9)	
Sport status				0.012
No	854 (40.5)	75 (32.6)	779 (41.5)	
Yes	1253 (59.5)	155 (67.4)	1098 (58.5)	
MAFLD*				<0.001
No	1116 (53.0)	62 (27.0)	1054 (56.2)	
Yes	991 (47.0)	168 (73.0)	823 (43.8)	

Notes: Values are median (25th, 75th), or n (%). P values were computed utilizing Student's t-test or the Mann-Whitney U test for continuous variables, and the chi-squared test was adopted for categorical variables. *BMI: body mass index; GA: glycated albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MAFLD: metabolic associated fatty liver disease.

Table S2. Logistic regression models of the link between GA and 10-year ASCVD risk

	Model 1			Model 2			Model 3		
	OR	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
GA	1.138	(1.094, 1.185)	< 0.001	1.142	(1.049, 1.240)	0.002	1.160	(1.055, 1.276)	0.002

Notes: Model 1 = GA; Model 2 = Model 1 + Age + Sex + Smoking status + Sport status + BMI + WC + SBP +DBP; Model 3 = Model 2 + Albumin + Platelet + Total Cholesterol + Triglyceride + HDL-C + Cervical vascular plaques + MAFLD.

Table S3. Mediation effect of BMI on the association between GA and 10-year ASCVD risk

Mediator	Sample	Exposure to Mediator	Mediator to Outcome	Direct Effect	Mediated (Indirect Effect)	Total Effect (Exposure to Outcome)	Proportion Mediated (%)
BMI	2107	-0.146 (0.026) p<0.001	0.190 (0.015) p<0.001	0.229 (0.040) p<0.001	-0.028 (0.006) p<0.001	0.201 (0.040) p<0.001	13.9%

Notes: Exposure: GA; Outcome: 10-year ASCVD risk; Model adjusted for age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, TC, triglyceride, HDL-C, cervical vascular plaques, and MAFLD.

Table S4. Mediation effect of BMI on the link between GA and 10-year ASCVD risk by age and MAFLD

Mediator	Sample	Exposure to Mediator	Mediator to Outcome	Direct Effect	Mediated (Indirect Effect)	Total Effect (Exposure to Outcome)	Proportion Mediated (%)
Stratification by Age							
<40	743	-0.388 (0.064) p < .001	0.056 (0.005) p < .001	0.030 (0.022) p =.177	-0.022(0.007) 95%CI (-0.037, -0.011) p = .002	0.008 (0.023) p = .714	-
40-60	1214	-0.147 (0.030) p < .001	0.210 (0.016) p < .001	0.102 (0.029) p < .001	-0.031(0.007) 95%CI (-0.046, -0.020) p < .001	0.071 (0.030) p = .017	**43.7**
>60	150	0.136 (0.075) p =.270	0.185 (0.093) p < .05	0.415 (0.121) p < .001	0.025(0.022) 95%CI (-0.016, 0.069) p = .245	0.440 (0.117) p < .001	-
Stratification by MAFLD							
MALFD	991	-0.040 (0.029) p =.092	0.081 (0.029) p < .01	0.275 (0.043) p < .001	-0.003(0.003) 95%CI (-0.010, 0.002) p = .310	0.272 (0.043) p < .001	-
Non-MAFLD	1116	-0.107*** (0.029) p < .001	0.127*** (0.026) p < .001	0.178 (0.068) p = .009	-0.014(0.005) 95%CI (-0.025, -0.006) p = .004	0.164 (0.067) p = .014	**8.5**

Notes: Exposure: GA; Mediator: BMI; Outcome: 10-year ASCVD risk; Model adjusted for age, sex, smoking status, sport status, BMI, WC, SBP, DBP, albumin, platelet, total cholesterol, triglyceride, HDL-C, cervical vascular plaques, and MAFLD.

Table S5. Sensitivity Analysis Adjusted for Pharmacotherapy (Model 4)

	Model 4		
	OR*	**95%CI***	**p**
GA*	1.153	(1.033, 1.277)	0.008

Notes: Model 4 adjusted for antihypertensive drugs, lipid-lowering drugs, and glucose-lowering drugs. Analysis was conducted on 2,084 participants after excluding 23 cases with missing medication data. *OR: odds ratio; CI: confidence interval; GA: glycated albumin;