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Research article

Lp(a) and high-sensitivity C-reactive protein are predictive biomarkers for coronary heart disease in Chinese patients with type 2 diabetes mellitus

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ABSTRACT

Objective: Type 2 diabetes (T2DM) is a significant risk factor for coronary heart disease (CHD). This study aimed to assess the variations in biomarkers associated with CHD in T2DM patients across different age groups in the Han Chinese population.

Methods: A strict selection process was employed, involving three groups: a control group (n = 300) with no medical history, a new-onset T2DM group (n = 300), and a new-onset T2DM + CHD group (n = 300). Participants in each group were further categorized based on age: Group 1 (<60 years), Group 2 (60–75 years), and Group 3 (>75 years). Fasting glucose, hemoglobin A1c (HbA1c), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), ApoB/ApoA1 ratio, lipoprotein(a) [Lp(a)], high-sensitivity C-reactive protein (hsCRP), and homocysteine (HCY) levels were analyzed in all groups.

Results: Both T2DM and T2DM + CHD groups exhibited elevated levels of TG, TC, LDL-C, ApoB, ApoB/ApoA1, Lp(a), hsCRP, and HCY, alongside decreased levels of HDL-C and ApoA1 in comparison to the control group. Notably, when comparing the T2DM to the T2DM + CHD groups, significant increases were noted in ApoB, Lp(a), and hsCRP levels in the T2DM + CHD group, whereas other biomarkers did not show significant differences. Across all age groups, the patterns remained consistent, with the T2DM and T2DM + CHD groups showing elevated levels of TG, TC, LDL-C, ApoB, ApoB/ApoA1, Lp(a), hsCRP, and HCY, and decreased levels of HDL-C and ApoA1 compared to their respective age-matched control groups. Furthermore, within each age category, significant increases in ApoB, Lp(a), and hsCRP were specifically observed with advancing age in the T2DM + CHD group, with Lp(a) and hsCRP levels showing particularly notable elevations, underscoring their potential as significant indicators of CHD risk in the T2DM population.

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Conclusion: Lp(a) and hsCRP may serve as valuable risk biomarkers for the development of CHD in T2DM patients. Understanding the variations in these biomarkers across different age groups can assist in risk assessment and the development of personalized management strategies for CHD in T2DM patients.

1. Introduction

Coronary heart disease (CHD) is a critical global health issue, marked by inflammation and the accumulation of fatty deposits within the coronary arteries [1,2]. According to the British Heart Foundation (BHF), approximately 620 million individuals are dealing with heart and circulatory diseases as of the end of 2023 (data was collected from the 2023 factsheet of BHF). Key risk factors for CHD include diabetes, hypertension, obesity, physical inactivity, unhealthy diet, and smoking [1,3]. Concurrently, type 2 diabetes mellitus (T2DM), a chronic metabolic condition characterized by insulin resistance and elevated blood glucose levels, presents a parallel public health challenge [4,5]. Data from the International Diabetes Federation indicate that in 2021 around 537 million adults were living with diabetes, a number expected to escalate to 783 million by 2045, with a majority being T2DM cases [6]. The prevalence of T2DM is especially high in low- and middle-income countries [6]. T2DM is a significant contributor to CHD, emphasizing the urgent necessity for effective T2DM management strategies to reduce the risk and burden of cardiovascular complications [4,7].

Advancements in biomarker research have proven instrumental in refining cardiovascular risk assessment, offering insights into the mechanisms that intertwine T2DM with CHD [8]. Total cholesterol (TC) and its components, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), serve foundational roles in evaluating cardiovascular risk [9–11]. LDL-C contributes to atherosclerosis and HDL-C, whereas HDL-C is recognized for its CHD protective effects [10,11]. The risk of myocardial infarction is heightened by increased levels of TC and LDL-C due to their promotion of atherosclerotic plaque development [12]. Conversely, reduced HDL-C levels disrupt reverse cholesterol transport, exacerbating CHD risk in T2DM patients [12]. Triglycerides (TG) serve as indicators of metabolic dysregulation, a frequent occurrence in T2DM, and are closely associated with cardiovascular risk [13,14]. High TG levels are implicated in endothelial dysfunction, inflammation, and plaque development, thus aggravating CHD risk [15]. Beyond traditional lipid markers, high-sensitivity C-Reactive protein (hsCRP) offers a measure of systemic inflammation, emerging as a critical predictor of cardiovascular events independent of lipid levels [16,17]. Lipoprotein(a) [Lp(a)] promotes atherosclerosis by facilitating cholesterol deposition in arterial walls, leading to plaque formation and increasing a hereditary dimension to CHD risk assessment [18,19]. Homocysteine (HCY) levels are associated with endothelial dysfunction and increased cardiovascular risk, marking its significance in the metabolic landscape influencing CHD [20–22]. In T2DM, increased levels of hsCRP, Lp(a), and HCY are associated with a higher likelihood of CHD events, suggesting their potential as prognostic biomarkers [23,24]. Apolipoproteins A1 (ApoA-1) and B (ApoB) provide nuanced insights into the functional dynamics of lipoproteins, with ApoA-1 reflecting protective lipid processes and ApoB indicating atherogenic potential [25]. Imbalances between ApoA1 and ApoB contribute to an unfavorable lipid profile, promoting atherosclerosis and cardiovascular risk [25]. Lastly, hemoglobin A1c (HbA1c) is a biomarker that reflects the average blood glucose levels over the preceding two to three months, providing a measure of long-term glycemic control [26–28]. Its relevance to CHD risk assessment is underscored by the strong association between suboptimal glycemic control and an increased incidence of cardiovascular complications [26–28]. These biomarkers highlight the significance of lipid abnormalities, inflammation, oxidative stress, and glycemic control in the pathogenesis of CHD in T2DM patients, providing opportunities for risk assessment, early detection, and targeted interventions to reduce cardiovascular morbidity and mortality.

While previous studies have identified these biomarkers as potential predictors of CHD in diverse populations with T2DM, there remains a notable dearth of systematic and comprehensive research investigating their predictive sensitivity and accuracy specifically within the Chinese population. Thus, our study aimed to address this gap by recruiting three distinct cohorts: T2DM individuals, T2DM individuals with CHD, and healthy controls. Through this encompassing approach, we aim to ascertain the predictive accuracy of these biomarkers for CHD occurrence within the Chinese T2DM cohort.

2. Methods

2.1. Study design and population

This study initially screened 4436 individuals from Hebei Province, China, for eligibility according to precise inclusion criteria. The participants were predominantly Han Chinese ethnicity from Hebei Province. For the control group (Group 1), which initially included 1219 individuals, the criteria were: age 18 years or older, age- and sex-matched, absence of T2DM or CHD diagnoses, no significant chronic disease history, and no medications taken within the past six months. Group 2, consisting of individuals with T2DM but without CHD (initially 1654 participants), required a new T2DM diagnosis per the American Diabetes Association (ADA) guidelines (HbA1c $\geq$ 6.5 %; fasting blood glucose $\geq$126 mg/dl; 2-h blood glucose $\geq$200 mg/dl) (American Diabetes Association, 2022), no current diabetes medication, and an absence of CHD history, with all participants being 18 years or older. Group 3 included 1563 participants with both T2DM and CHD, newly diagnosed according to ADA criteria, and CHD was confirmed via angiography, electrocardiogram, cardiac catheterization, and heart magnetic resonance imaging (MRI) scan, without current treatment for either condition, and aged 18 or above. Exclusion criteria applied across all groups encompassed: any prior pharmacological treatment for T2DM or CHD; the presence of acute or chronic inflammatory diseases; a cancer diagnosis; a major surgical procedure within the last six months; any

endocrine disorders other than T2DM; current pregnancy or breastfeeding status; a history of substance abuse or addiction; and recent participation in another clinical trial within 30 days. Additionally, the age is evenly distributed among three categories: below 60 years old, between 60 and 75 years old, and over 75 years old. Subsequent to stringent screening and confirmation, the final cohort was comprised of 314, 352, and 337 individuals meeting the criteria for the control group, the T2DM group, and the T2DM + CHD group, respectively. To standardize the sample sizes, 300 participants were selected for each group. These three groups were further divided into three age subgroups for a detailed analysis: subgroup 1 (<60 years), subgroup 2 (60–75 years), and subgroup 3 (>75 years) for comprehensive analysis. Each age subgroup included 100 participants, ensuring adequate representation across different age ranges.

All participants provided written informed consent prior to inclusion in the study and furnished comprehensive baseline demographic and clinical data, including age, blood pressure, risk factors, medication usage, and lifestyle factors as detailed in Table 1. No follow-up data were included in this study, as all data were collected from participants newly diagnosed during their physical examinations at Hebei Yanda Hospital. None of the participants had been involved in prior studies, and no previous publications have used this cohort. The ethical committee of Hebei Yanda Hospital granted approval for this study.

2.2. Blood sample collection and preparation

Blood samples were obtained from participants after an overnight fast. The blood samples were collected using standard venipuncture techniques and transferred to vacutainer tubes (BD Biosciences; Beijing, China; #367861). Serum and plasma were separated by centrifugation at 3000 rpm for 10 min at 4 °C. The serum and plasma samples were stored at −80 °C until further analysis.

2.3. Measurement of TC, LDL-C, HDL-C, TG, ApoA-1, and ApoB

The concentrations of TC, LDL-C, HDL-C, and TG were measured using enzymatic colorimetric methods. For these assays, commercially available diagnostic kits were employed, namely the Cholesterol Quantitation Kit (Sigma-Aldrich, Shanghai, China; #MAK043), HDL and LDL Quantitation Kit (Sigma-Aldrich; #MAK045), and TG Quantification Kit (Sigma-Aldrich; #MAK266), all of which were used in accordance with the protocols provided by the manufacturer. Additionally, the concentrations of ApoA-1 and ApoB were quantified using immunoturbidimetric assays conducted on a Siemens BNII nephelometric analyzer (Siemens Healthcare Diagnostics, Beijing, China).

2.4. Measurement of hsCRP, Lp(a), HCY, glucose, and HbA1c

The hsCRP concentration was measured using a high-sensitivity immunoturbidimetric kit (Roche Diagnostics; Shanghai, China; #4628918190) according to the manufacturer's instructions. Lp(a) levels were determined using a latex particle-enhanced immunoturbidimetric assay conducted on a Siemens BNII nephelometric analyzer. For HCY measurement, a high-performance liquid chromatography (HPLC) method was employed. Plasma samples were deproteinized using a sulfosalicylic acid reagent, and the resulting supernatant was injected into an HPLC system equipped with a fluorescence detector. The concentration of HCY was determined using a calibration curve. The HbA1c and glucose levels were determined using an immunoturbidimetric assay with the DCA HbA1c Reagent Kit (Siemens Healthcare Diagnostics; #06162000) and the Glucose (HK) Assay Kit (Sigma-Aldrich; #GAHK20), respectively, in accordance with the manufacturers' protocols.

Table 1
The demographic and clinical characteristics of study participants.

Characteristics	HC	T2DM (T2)	T2DM + CHD (T2C)	*P*-values (HC *vs* T2; HC *vs* T2C; T2 *vs* T2C)
Gender	157M/143F	160M/140F	154M/146F	N/A
Ages	68.43 ± 10.25	69.62 ± 12.84	69.87 ± 11.62	0.35; 0.26; 0.53
Ever smoked (n)	53	57	48	0.33; 0.39; 0.12
Hypertension (n)	36	51	53	0.041; 0.038; 0.68
BMI (kg/m^2)	22.84 ± 1.42	28.85 ± 2.21	29.33 ± 2.64	0.006; 0.003; 0.61
Glucose(mmol/L)	4.31 ± 0.46	9.59 ± 1.66	9.47 ± 1.38	0.0003; 0.0004; 0.47
HbA1c (%)	4.12 ± 0.38	9.37 ± 1.48	9.22 ± 1.19	0.0003; 0.0005; 0.39
TG (mmol/L)	1.05 ± 0.17	3.24 ± 0.42	3.06 ± 0.37	0.00008; 0.00007; 0.44
TC (mmol/L)	3.45 ± 0.46	7.02 ± 0.87	7.15 ± 0.68	0.0007; 0.0006; 0.61
LDL-C (mmol/L)	2.31 ± 0.33	6.43 ± 0.72	6.55 ± 0.84	0.0005; 0.0009; 0.54
HDL-C (mmol/L)	2.26 ± 0.47	0.85 ± 0.11	0.84 ± 0.09	0.00005; 0.00006; 0.76
ApoA1 (g/L)	1.49 ± 0.21	0.94 ± 0.1	0.91 ± 0.07	0.0005; 0.0006; 0.47
ApoB (g/L)	0.97 ± 0.07	1.43 ± 0.13	1.84 ± 0.11	0.014; 0.0007; 0.008
ApoB/ApoA1	0.68 ± 0.07	1.31 ± 0.17	1.93 ± 0.21	0.0009; 0.00007; 0.026
Lp(a) (mg/L)	112.32 ± 10.55	403.21 ± 42.65	611.23 ± 48.96	0.0007; 0.00003; 0.0008
HCY (mmol/L)	11.36 ± 1.69	68.49 ± 6.87	70.33 ± 6.47	0.0008; 0.0006; 0.58
hsCRP (mg/L)	2.03 ± 0.17	5.13 ± 0.49	8.69 ± 0.75	0.0007; 0.00005; 0.0009

ApoA: Apolipoprotein A; ApoB: Apolipoprotein B; BMI: Body mass index; CHD: Coronary heart disease; HbA1c: Hemoglobin A1c; HC: Heathy control; HCY: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a); T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglycerides.

2.5. Statistical analysis

All statistical analyses were performed by using the SPSS (Statistical Package for the Social Sciences) software, version 22 (IBM, Chicago, Illinois, USA). Descriptive statistics were used to summarize the data. Continuous variables were expressed as mean ± standard deviation. Differences in biomarker levels among groups were assessed using Analysis of Variance (ANOVA) with subsequent post hoc tests for multiple comparisons. Statistical significance was set at $P < 0.05$.

The multivariate logistic regression was performed using Python's "statsmodels" library to assess the relationship between key biomarkers and the occurrence of CHD in patients with T2DM. The presence of CHD was our binary dependent variable, while independent variables included commonly assessed biomarkers such as glucose, HbA1C, TG, TC, LDL-C, HDL-C, ApoA1, ApoB, ApoB/ApoA1 ratio, HCY, hsCRP, and La(a). We evaluated the significance of each biomarker through calculated odds ratios (OR) and corresponding 95 % confidence intervals (95 % CI), considering *P*-values less than 0.05 as indicative of statistical significance. The analysis accounted for potential confounders and assessed the independent contribution of each biomarker to CHD risk.

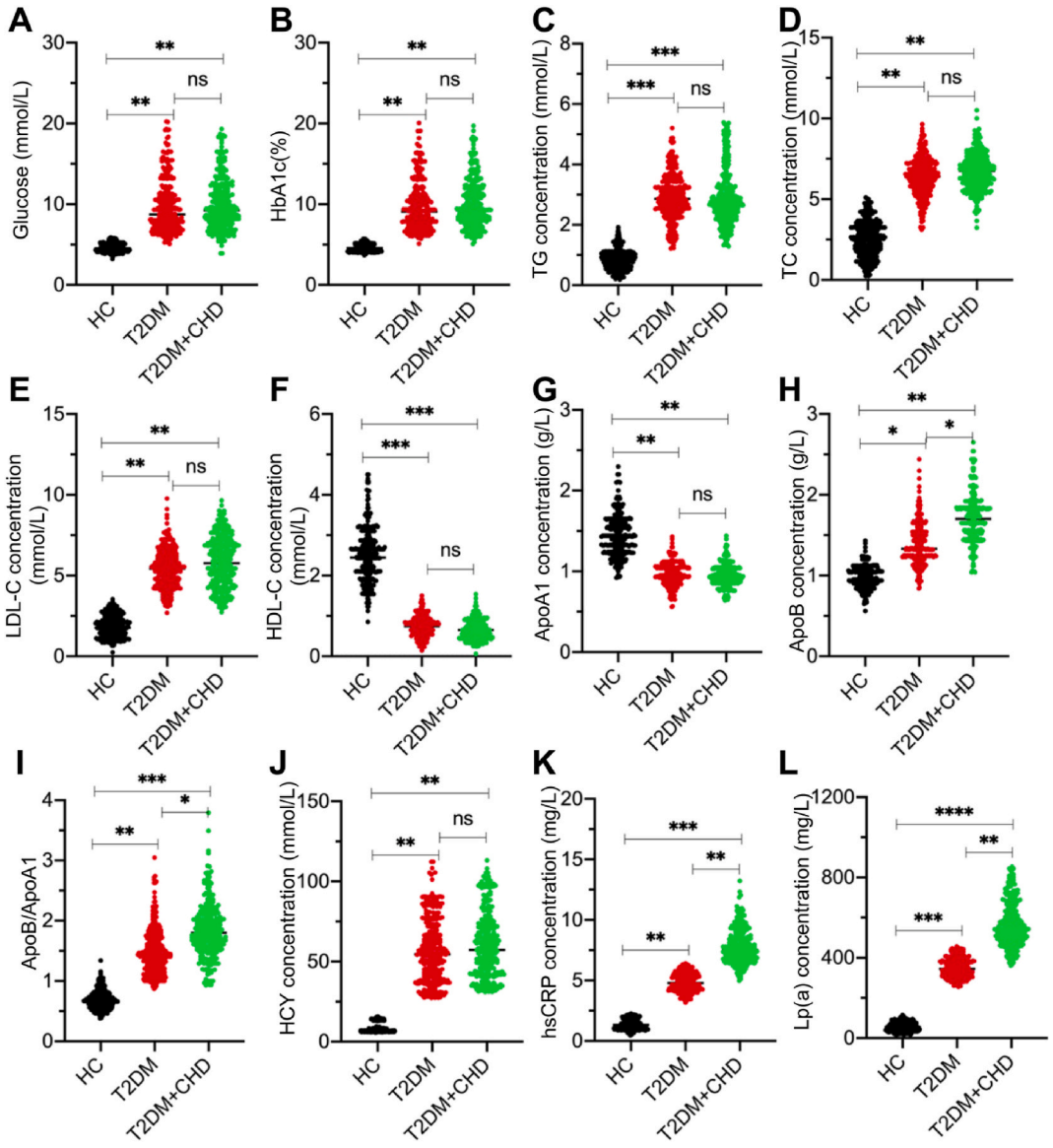

Fig. 1. Biomarker levels in HC, T2DM, and T2DM + CHD participants.
Blood samples were collected from three participant groups: HC, T2DM, and T2DM + CHD (n = 300 per group). The levels of fasting glucose **(A)**, HbA1c **(B)**, TG **(C)**, TC **(D)**, LDL-C **(E)**, HDL-C **(F)**, ApoA1 **(G)**, ApoB **(H)**, ApoB/ApoA1 **(I)**, HCY **(J)**, hsCRP **(K)**, and Lp(a) **(L)** were measured in each group. ns: no significant difference; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

3. Results

3.1. Comparison of biomarker levels in control, T2DM, and T2DM + CHD groups

To identify valuable biomarkers capable of predicting CHD incidence in T2DM patients, we implemented a stringent selection methodology. Our study cohort consisted of three distinct groups: healthy controls (HC), individuals newly diagnosed with T2DM, and those newly diagnosed with both T2DM and CHD (n = 300 for each group). We specifically included patients with recent diagnoses of T2DM and T2DM with CHD who had not yet begun any medication regimen to eliminate the potential confounding effects of pharmaceutical treatments. We conducted comprehensive biomarker profiling for each participant, which included measurements of fasting glucose, HbA1c, TG, TC, LDL-C, HDL-C, ApoA1, ApoB, ApoB/ApoA1, Lp(a), hsCRP, and HCY.

Significant variations were observed across all biomarkers when analyzing pooled data from each group. The pooled data from the T2DM and T2DM + CHD cohorts showed increased levels of fasting glucose, HbA1c, TG, TC, LDL-C, ApoB, ApoB/ApoA1, Lp(a), hsCRP, and HCY (Fig. 1A–L and Table 1). Conversely, the levels of HDL-C and ApoA1 were significantly decreased in both the T2DM and T2DM + CHD groups in comparison to the HC group (Fig. 1F and G, and Table 1).

Upon comparing the T2DM and T2DM + CHD groups, it was observed that only ApoB, ApoB/ApoA1, hsCRP, and Lp(a) displayed significant elevations in the T2DM + CHD group, while the other biomarkers did not exhibit any significant changes (Fig. 1 and Table 1). Specifically, ApoB levels were notably elevated, increasing from an average of 1.43 ± 0.13 g/L to 1.84 ± 0.11 g/L ($P < 0.05$) in the T2DM + CHD group (Fig. 1 and Table 1). Similarly, the ApoB/ApoA1 ratio rose from 1.31 ± 0.76 to 1.93 ± 0.21 ($P < 0.05$), hsCRP levels surged from 5.13 ± 0.49 mg/L to 8.69 ± 0.75 mg/L ($P < 0.01$), and Lp(a) concentrations increased from 403.21 ± 42.65 mg/L to 611.23 ± 48.96 mg/L ($P < 0.01$) in the T2DM + CHD group (Fig. 1 and Table 1). To determine the predictive utility of these biomarkers for CHD incidence in T2DM patients, multivariate logistic regression analysis was conducted. The analysis yielded OR and 95 % CI as follows: for ApoB, 1.565 (0.963–2.545, $P < 0.05$); for ApoB/ApoA1, 2.563 (0.473–13.881, $P = 0.275$); for hsCRP, 1.872 (1.533–2.286, $P < 0.0001$); and for Lp(a), 2.326 (1.673–3.233, $P < 0.0001$) (Table 2). These results indicated that ApoB, hsCRP, and Lp (a) might be significant biomarkers for CHD prediction in T2DM patients, particularly hsCRP and Lp(a).

3.2. Comparisons of fasting glucose, HbA1c, TG, TC, LDL-C, HDL-C, and HCY in different age subgroups of T2DM and T2DM + CHD participants

To enhance the investigation of biomarkers, participants within each group were stratified into three subgroups based on their age: Group 1 (<60 years), Group 2 (60–75 years), and Group 3 (>75 years). The variations in biomarker levels across these age-defined subgroups were analyzed. Elevated levels of fasting glucose and HbA1c were consistently observed across all age categories in both T2DM and T2DM + CHD groups, compared to their respective age-matched control subgroups (Fig. 2 and Table S1). However, within the various age subgroups of both T2DM and T2DM + CHD cohorts, no significant disparities were observed in the levels of glucose and HbA1c (Fig. 2 and Table S1). Furthermore, the outcomes of the multivariate logistic regression analysis revealed that the OR and 95 % CI for glucose and HbA1c did not demonstrate significant variances across the different age groups (Table 3). Consequently, these biomarkers were not effective predictors for the development of CHD within T2DM populations.

Comparative analyses of TG, TC, and LDL-C demonstrated that these biomarkers were significantly elevated in all three age subgroups within both T2DM and T2DM + CHD cohorts, in comparison to their respective HC subgroups (Fig. 3A–C and Table S1). In contrast, HDL-C levels were found to be lower in the three age subgroups of T2DM and T2DM + CHD, as opposed to the matching HC subgroups (Fig. 3D and Table S1). Nevertheless, within the T2DM and T2DM + CHD groups, comparisons among the different age subgroups did not reveal significant variations in levels of TG, TC, LDL-C, and HDL-C (Fig. 3 and Table S1). The multivariate logistic regression analysis demonstrated that TG, TC, LDL-C, and HDL-C were invalid biomarkers for predicting CHD with T2DM populations

Table 2
Multivariate logistic regression analysis results for predicting CHD occurrence in T2DM patients.

Variable	Coefficient	SE	z-Value	OR (95 % CI)	P-Value
Glucose	0.203	0.504	0.403	1.225 (0.456–3.290)	0.687
HbA1C	0.237	0.456	0.52	1.267 (0.519–3.098)	0.603
TG	0.441	0.603	0.731	1.554 (0.477–5.068)	0.465
TC	0.311	0.557	0.558	1.365 (0.458–4.066)	0.576
LDL-C	0.502	0.689	0.729	1.652 (0.428–6.375)	0.466
HDL-C	−0.221	0.643	−0.344	0.802 (0.227–2.827)	0.731
ApoA1	−0.335	0.739	−0.453	0.715 (0.168–3.045)	0.65
ApoB	0.448	0.248	1.806	1.565 (0.963–2.545)	0.031
AopB/ApoA1	0.941	0.862	1.092	2.563 (0.473–13.881)	0.275
HCY	0.662	0.917	0.722	1.939 (0.321–11.697)	0.47
HsCRP	0.627	0.102	6.147	1.872 (1.533–2.286)	<0.0001
Lp(a)	0.844	0.168	5.024	2.326 (1.673–3.233)	<0.0001

ApoA: Apolipoprotein A; ApoB: Apolipoprotein B; CHD: Coronary heart disease; 95 % CI: 95 % confidence intervals; HbA1c: Hemoglobin A1c; HC: Heathy control; HCY: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a); OR: Odds ratio; SE: Standard Error; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglycerides.

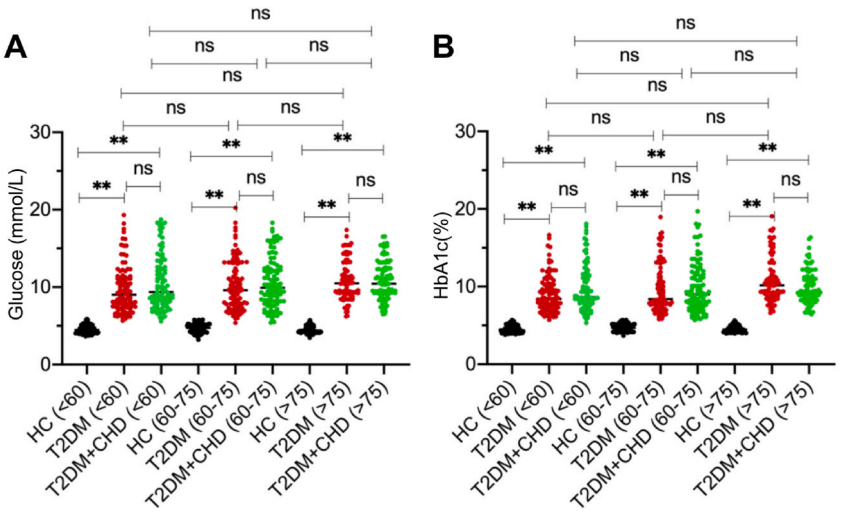

Fig. 2. Levels of fasting glucose and HbA1c in different age subgroups of HC, T2DM, and T2DM + CHD participants.
Participants from HC, T2DM, and T2DM + CHD groups were categorized into three subgroups: Group 1 (<60), Group 2 (60–75), and Group 3 (>75) (n = 100 per subgroup). The levels of fasting glucose **(A)** and HbA1c **(B)** were assessed within each subgroup. ns: no significant difference; *$P < 0.01$.

(Table 3).

Furthermore, elevated levels of HCY were noted across all age subgroups of participants with T2DM and T2DM + CHD, compared with the corresponding HC subgroups (Fig. 4A and Table S1). However, no significant differences in HCY levels were detected between the subgroups of individuals with T2DM and those with T2DM + CHD (Fig. 4A and Table S1). The outcomes of the multivariate logistic regression analysis indicated that HCY levels were not a viable marker for predicting the occurrence of CHD within the T2DM population, as indicated by a *P*-value greater than 0.05 (Table 3).

3.3. Comparisons of ApoA1, ApoB, and ApoB/AopA1 in different age subgroups of T2DM and T2DM + CHD participants

Decreased levels of ApoA1 were observed in all age subgroups of T2DM and T2DM + CHD participants in comparison to their respective HC subgroups (Fig. 4B and Table S1). Nonetheless, no significant variances were detected between the T2DM and T2DM + CHD subgroups (Fig. 4B and Table S1).

Conversely, elevated levels of ApoB were observed in all age subgroups of individuals with T2DM and T2DM + CHD compared to the corresponding HC subgroups (Fig. 4C and Table S1). When analyzing ApoB levels among the three subgroups of T2DM and T2DM + CHD participants, no significant difference was identified between subgroup 1 (<60 years) of T2DM and T2DM + CHD (Fig. 4C and Table S1). However, in both subgroup 2 (60–75 years) and subgroup 3 (>75 years) of T2DM + CHD participants, ApoB levels were significantly higher than those in subgroup 2 (60–75 years) and subgroup 3 (>75 years) of T2DM participants (Fig. 4C and Table S1). The patterns observed in the ApoB/ApoA1 ratios mirrored those of the ApoB levels. Specifically, in subgroup 2 (60–75 years) and subgroup 3 (>75 years) of T2DM + CHD participants, the ApoB/ApoA1 ratios were significantly elevated compared to those in subgroup 2 (60–75 years) and subgroup 3 (>75 years) of T2DM participants (Fig. 4D and Table S1). In the multivariate logistic regression analysis, significant variations in the ORs and 95 % CIs were observed for ApoB, but not for ApoA1 or the ApoB/ApoA1 ratio (Table 3). The age-related changes in ApoB were as follows: for the <60 subgroup, the OR was 1.514 with a 95 % CI of 0.861–2.455 ($P = 0.161$); in the 60–75 subgroup, the OR was 1.664 with a 95 % CI of 1.059–2.613 ($P < 0.05$); and in the >75 subgroup, the OR was 1.738 with a 95 % CI of 1.074–2.814 ($P < 0.05$) (Table 3). These findings suggest that ApoB may serve as a modest biomarker for predicting CHD in T2DM who are aged 60 years and above.

3.4. Comparisons of hsCRP and Lp(a) in different age subgroups of T2DM and T2DM + CHD participants

Within each age category, we conducted a comparison of hsCRP and Lp(a) levels, identifying significant elevations in both biomarkers across all age subgroups of T2DM and T2DM + CHD participants in contrast to their respective HC counterparts (Fig. 5 and Table S1). Furthermore, an age-specific significant increase in hsCRP and Lp(a) levels was observed particularly within the T2DM + CHD cohort (Fig. 5 and Table S1). The mean hsCRP concentration among the different T2DM subgroups remained relatively stable, averaging about 5 mg/L (Fig. 5A and Table S1). In the T2DM + CHD cohort, the mean hsCRP concentration in group 1 (<60) was recorded at 6.23 ± 0.42 mg/L, which escalated to 7.69 ± 0.55 mg/L in group 2 (60–75), and further increased to 9.31 ± 0.62 mg/L in group 3 (>75) (Fig. 5A and Table S1).

In a similar analysis, the mean concentration of Lp(a) remained relatively constant at approximately 400 mg/L among the various subgroups of T2DM participants. Conversely, within the cohort of T2DM + CHD, a progressive increase in the mean Lp(a)

Table 3
Multivariate logistic regression analysis results for predicting CHD occurrence in different age groups of T2DM patients.

Variable	Age	Coefficient	SE	z-Value	OR (95 % CI)	P-Value
Glucose	<60	0.213	0.469	0.454	1.237 (0.493–3.106)	0.650
	60–75	0.247	0.405	0.610	1.280 (0.579–2.831)	0.542
	>75	0.351	0.285	1.232	1.420 (0.813–2.483)	0.218
HbA1C	<60	0.198	0.505	0.392	1.219 (0.453–3.280)	0.695
	60–75	0.244	0.410	0.595	1.276 (0.572–2.850)	0.552
	>75	0.265	0.377	0.702	1.303 (0.622–2.731)	0.483
TG	<60	0.374	0.267	1.399	1.454 (0.861–2.455)	0.162
	60–75	0.407	0.246	1.656	1.502 (0.928–2.432)	0.098
	>75	0.425	0.235	1.806	1.739 (0.964–2.454)	0.071
TC	<60	0.275	0.361	0.762	1.316 (0.641–2.660)	0.446
	60–75	0.329	0.303	1.086	1.390 (0.756–2.430)	0.277
	>75	0.308	0.322	0.956	1.361 (0.717–2.505)	0.339
LDL-C	<60	0.448	0.236	1.898	1.565 (0.976–2.459)	0.058
	60–75	0.552	0.18	3.067	1.737 (1.206–2.731)	0.072
	>75	0.509	0.197	2.584	1.663 (1.142–2.668)	0.087
HDL-C	<60	−0.193	0.517	−0.373	0.824 (0.448–3.226)	0.709
	60–75	−0.224	0.448	−0.5	0.799 (0.519–2.890)	0.617
	>75	−0.251	0.398	−0.63	0.778 (0.576–2.752)	0.529
ApoA1	<60	−0.318	0.314	−1.013	0.728 (0.699–2.569)	0.311
	60–75	−0.392	0.255	−1.537	0.943 (0.591–2.444)	0.124
	>75	−0.377	0.266	−1.418	0.862 (0.686–2.457)	0.156
ApoB	<60	0.415	0.267	1.400	1.514 (0.861–2.455)	0.161
	60–75	0.509	0.230	2.21	1.664 (1.059–2.613)	0.037
	>75	0.553	0.246	2.25	1.738 (1.074–2.814)	0.021
AopB/ApoA1	<60	0.806	0.665	1.212	2.239 (0.608–8.244)	0.226
	60–75	0.913	0.628	1.454	2.492 (0.728–8.531)	0.139
	>75	0.955	0.683	1.398	2.599 (0.681–9.914)	0.142
HCY	<60	0.584	0.482	1.212	1.793 (0. 697–4.611)	0.226
	60–75	0.654	0.45	1.454	1.923 (0.796–4.644)	0.146
	>75	0.712	0.509	1.398	2.038 (0.751–5.530)	0.162
HsCRP	<60	0.856	0.208	4.123	2.354 (1.567–3.536)	<0.001
	60–75	0.942	0.206	4.567	2.565 (1.712–3.843)	<0.001
	>75	1.053	0.192	5.489	2.866 (1.968–4.175)	<0.001
Lp(a)	<60	0.925	0.224	4.123	2.522 (1.625–3.915)	<0.001
	60–75	1.015	0.193	5.256	2.759 (1.890–4.029)	<0.001
	>75	1.142	0.191	5.978	3.133 (2.155–4.556)	<0.001

ApoA: Apolipoprotein A; ApoB: Apolipoprotein B; CHD: Coronary heart disease; 95 % CI: 95 % confidence intervals; HbA1c: Hemoglobin A1c; HC: Heathy control; HCY: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a); SE: Standard Error; OR: Odds ratio; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglycerides.

concentration was observed: in subgroup 1 (<60 years), the level elevated to 513.26 ± 40.11 mg/L; it further rose to 603.25 ± 38.21 mg/L in subgroup 2 (60–75 years); and reached its zenith at 732.44 ± 40.69 mg/L in subgroup 3 (>75 years) (Fig. 5B and Table S1).

Furthermore, multivariate logistic regression analysis was conducted to ascertain the predictive capabilities of hsCRP and Lp(a) across different age subgroups. The analysis revealed significant differences in the ORs and 95 % CIs for both biomarkers across all age categories. Specifically, for hsCRP, the ORs (95 % CIs) in the subgroups <60, 60–75, and >75 were 2.354 (1.567–3.536, $P < 0.0001$), 2.565 (1.712–3.843, $P < 0.0001$), and 2.866 (1.968–4.175, $P < 0.0001$), respectively. For Lp(a), the ORs (95 % CIs) in the subgroups <60, 60–75, and >75 were 2.522 (1.625–3.915, $P < 0.0001$), 2.759 (1.890–4.029, $P < 0.0001$), and 3.133 (2.155–4.556, $P < 0.0001$), respectively. These findings indicate that both hsCRP and Lp(a) serve as robust biomarkers for predicting the risk of CHD within T2DM populations across all age groups.

4. Discussion

The prediction and management of CHD have significantly advanced through the identification and application of various biomarkers [29–31]. These indicators shed light on the pathophysiological underpinnings of CHD, enabling risk assessment and the customization of prevention and treatment plans [30,31]. Traditional biomarkers for CHD prediction include lipid profile components such as LDL-C, HDL-C, TG, and TC, with dyslipidemia indicated by elevated LDL-C and TG alongside low HDL-C levels, marking a substantial risk for atherosclerosis and CHD [30,31]. Additionally, other biomarkers like Lp(a), HCY, hsCRP, N-terminal pro-b-type natriuretic peptide (NT-proBNP), oxidized LDL (oxLDL), high-sensitivity cardiac troponin (hs-cTn), adhesion molecules like VCAM-1, ICAM-1, and E-selectin, heart-type fatty acid binding protein (H-FABP), growth differentiation factor-15 (GDF-15) and soluble urokinase plasminogen activator receptor (suPAR), have emerged as predictors of CHD, though their predictive accuracy varies across populations and is complicated by the presence of comorbidities such as T2DM and cancer [30–37].

Given T2DM's role as a significant CHD risk factor, this study aimed to identify biomarkers that signal CHD risk in T2DM patients,

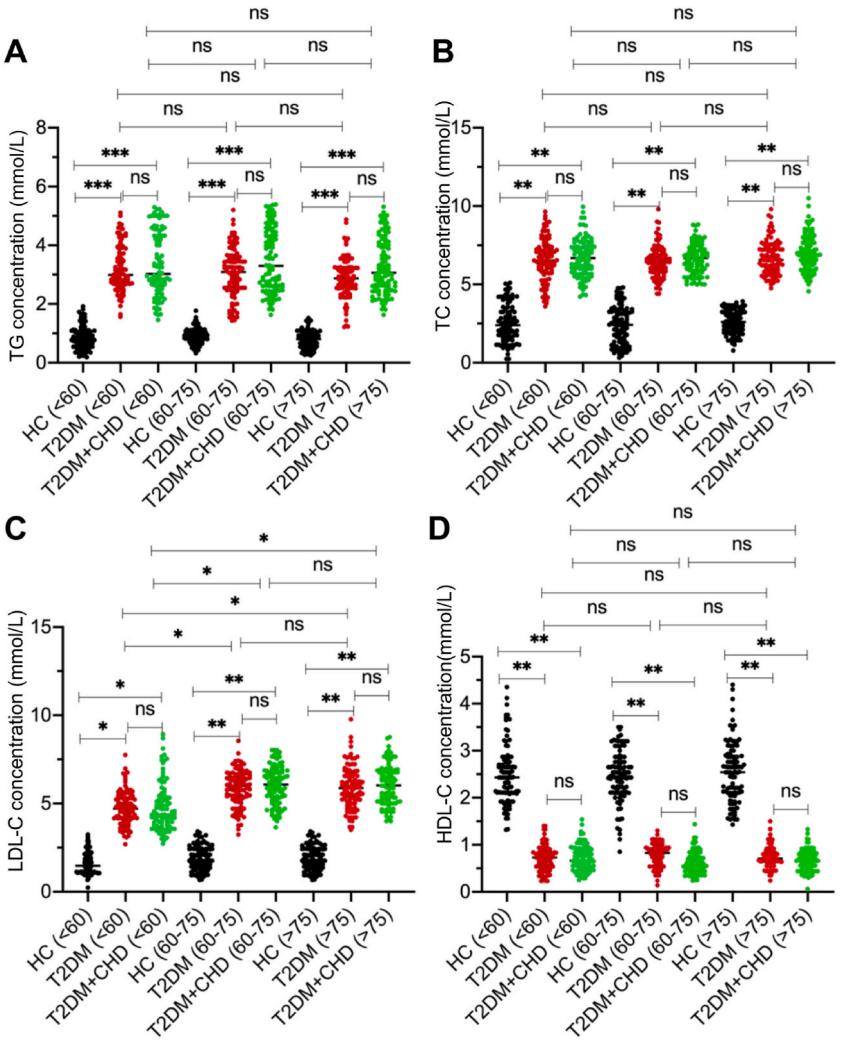

Fig. 3. Levels of TG, TC, LDL-C, and HDL-C in different age subgroups of HC, T2DM, and T2DM + CHD participants.
Participants from HC, T2DM, and T2DM + CHD groups were categorized into three subgroups: Group 1 (<60), Group 2 (60–75), and Group 3 (>75) (n = 100 per subgroup). The levels of TG **(A)**, TC **(B)**, LDL-C **(C)**, and HDL-C **(D)** were assessed within each subgroup. ns: no significant difference; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

focusing on age-related biomarker variations. We found that hsCRP and Lp(a) levels increase with age in T2DM + CHD patients compared to T2DM patients alone, suggesting their potential as CHD risk indicators in the T2DM population and highlighting the importance of considering age in CHD risk management. The exclusion of participants on lipid-lowering or glycemic medications ensured an accurate assessment of baseline biomarker levels, underscoring the natural relationship between these biomarkers and CHD risk in T2DM.

Apart from hsCRP, Lp(a), and ApoB, the T2DM and T2DM + CHD groups consistently showed higher levels of TG, TC, LDL-C, and HCY levels, along with elevated ApoB/ApoA1 ratio. In contrast, HDL-C and ApoA1 levels were lower when compared to the HC group. These observations emphasize the critical role of these biomarkers as primary indicators of dyslipidemia and inflammation, both of which are pivotal in the onset and progression of T2DM. These results align with numerous prior studies [38–42], demonstrating that TG, TC, LDL-C, HCY, HDL-C, and ApoA1 may serve as biomarkers for T2DM.

This study is subject to two main limitations. First, it did not evaluate all known biomarkers associated with the prediction of CHD. While we have identified two significant biomarkers [hsCRP and Lp(a)] and one less pronounced biomarker (ApoB) with the capacity to predict the occurrence of CHD in the T2DM population, the predictive capabilities of other unassessed biomarkers, including NT-proBNP, oxLDL, VCAM-1, ICAM-1, E-selectin, GDF-15, H-FABP, hs-cTn, and suPAR, in T2DM remain unexplored. Second, the study was limited by an insufficient sample size, suggesting that further research with a larger cohort is necessary to firmly establish hsCRP and Lp(a) as reliable predictive biomarkers for CHD within the T2DM context.

In conclusion, the present study provides evidence that Lp(a) and hsCRP are two independent predictors of CHD in patients with T2DM. These biomarkers offer valuable information for risk assessment and could potentially guide the development of personalized

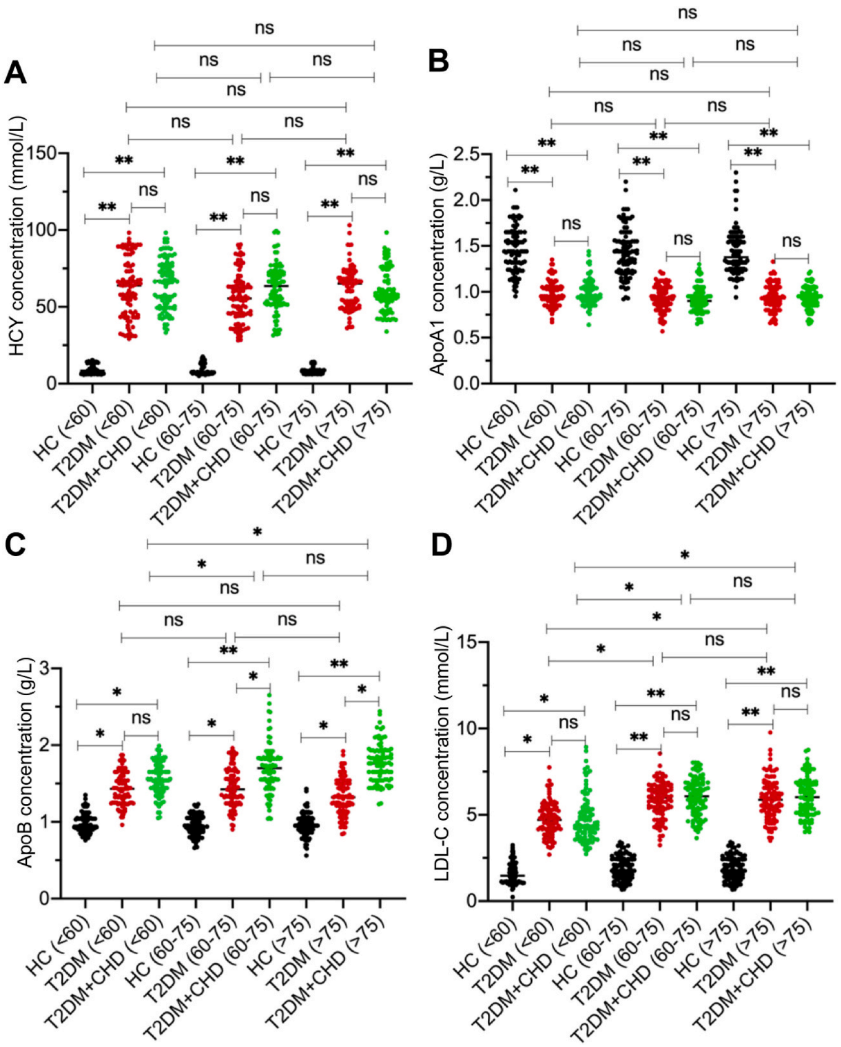

Fig. 4. Levels of HCY, ApoA1, ApoB, and ApoB/ApoA1 in different age subgroups of HC, T2DM, and T2DM + CHD participants.
Participants from HC, T2DM, and T2DM + CHD groups were categorized into three subgroups: Group 1 (<60), Group 2 (60–75), and Group 3 (>75) (n = 100 per subgroup). The levels of HCY **(A)**, ApoA1 **(B)**, ApoB **(C)**, and ApoB/ApoA1 **(D)** were assessed within each subgroup. ns: no significant difference; $^{*}P < 0.05$; $^{**}P < 0.01$.

preventive strategies in this vulnerable population. Further research is needed to validate these findings and explore the underlying mechanisms linking hsCRP and CHD in T2DM patients.

CRediT authorship contribution statement

Qinghan Meng: Methodology, Investigation, Formal analysis. **Haina Ma:** Funding acquisition, Formal analysis, Data curation. **Nannan Tian:** Investigation, Formal analysis, Data curation. **Zheng Wang:** Investigation, Formal analysis, Data curation. **Liwen Cai:** Validation, Software, Resources, Formal analysis. **Yuqi Zhang:** Software, Data curation. **Qian Wang:** Software, Resources. **Ruiwang Zhen:** Validation, Methodology. **Jinwen Zhao:** Resources, Methodology. **Menghan Wang:** Resources, Methodology, Formal analysis. **Xinqi Wang:** Software, Resources. **Haifei Liu:** Resources, Methodology. **Yuan Liu:** Software, Resources, Data curation. **Xinyu Wang:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition. **Li Wang:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition.

Data availability statement

The data associated with this study will be made available upon request.

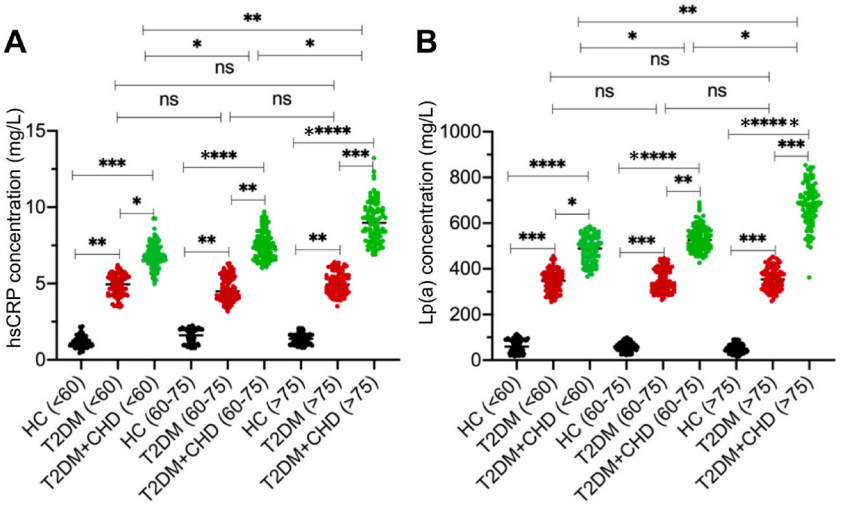

Fig. 5. Levels of hsCRP and Lp(a) in different age subgroups of HC, T2DM, and T2DM + CHD participants.
Participants from HC, T2DM, and T2DM + CHD groups were categorized into three subgroups: Group 1 (<60), Group 2 (60–75), and Group 3 (>75) (n = 100 per subgroup). The levels of hsCRP **(A)** and Lp(a) **(B)** were assessed within each subgroup. ns: no significant difference; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$; *****$P < 0.00001$.

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of Hebei Yanda Hospital (Approval No. 2020-041D). All participants provided informed consent to participate in the study, as well as informed consent for the publication of the findings.

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Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40074.

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