Cardiovascular Diabetology

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Atherogenic lipid parameters in people with normal glucose tolerance: implications from elevated 1-hour post-load plasma glucose

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Abstract

Background Existing evidence suggests that elevated 1-hour post-load plasma glucose (1-h PG ≥ 8.6 mmol/L) during an oral glucose tolerance test (OGTT) is associated with atherogenic lipid parameters which are linked to an increased risk of cardiovascular disease (CVD). However, it remains unclear whether normal glucose tolerance (NGT) individuals with elevated 1-h PG (NGT-1hPG-high) should still be considered low-risk. Therefore, this study aims to demonstrate comprehensive lipid characteristics in individuals with different glycemic status stratified by 1-h PG, with a particular focus on those with NGT-1hPG-high.

Methods This cross-sectional study included individuals aged 25–55 years with high-risk of diabetes from the Daqing Diabetes Prevention Study II (Daqing DPS-II). Individuals were categorized into different glycemic status based on the World Health Organization's 1999 criteria and the International Diabetes Federation's 2024 position statement on 1-h PG. Traditional (TC, TG, HDL-C, LDL-C) and non-traditional lipid parameters [ApoA-1, ApoB, sdLDL-C, Lp(a), non-HDL-C, remnant cholesterol (RC), ApoB/ApoA-1, LDL-C/ApoB] were measured. Dyslipidemia was defined according to the 2023 Chinese Guidelines for Lipid Management. The China-PAR equation was used to estimate 10-year CVD risk. Spearman's correlation coefficients were calculated to evaluate the correlation between lipid parameters and 10-year CVD risk. Logistic and multiple linear regression models were performed to assess the association between 1-h PG and dyslipidemia as well as lipid parameters adjusting for covariates.

Results Among 2 469 individuals, 22.7% had NGT with normal 1-h PG (NGT-1hPG-normal), 19.9% had NGT-1hPG-high, 2.6% had prediabetes with normal 1-h PG (PDM-1hPG-normal), 34.2% had prediabetes with elevated 1-h PG (PDM-1hPG-high), and 20.6% had newly diagnosed diabetes. The prevalence of dyslipidemia did not significantly differ between NGT-1hPG-high and PDM-1hPG-high (*OR* = 1.13, 95%*CI*: 0.88–1.44, *P* > 0.05). Higher 1-h PG levels were consistently associated with an atherogenic lipid profile, characterized by increased TC, TG, LDL-C, ApoB, sdLDL-C, non-HDL-C, RC and ApoB/ApoA-1, along with decreased ApoA-1, HDL-C and LDL-C/ApoB (all *P* < 0.05). Among lipid

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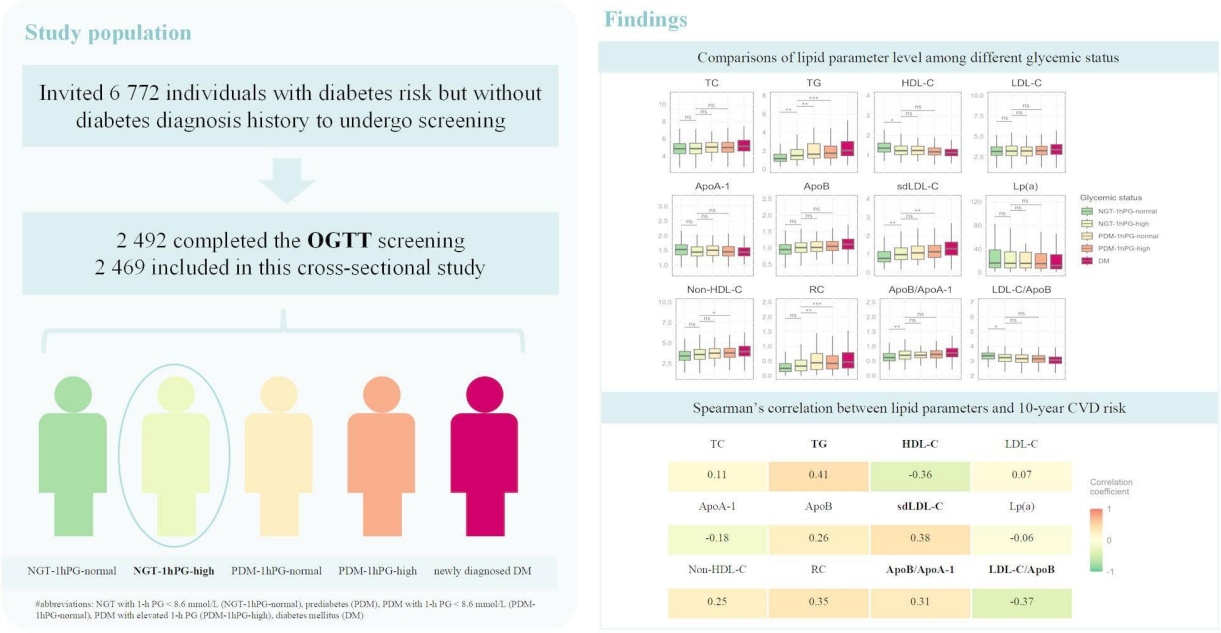
parameters, TG, sdLDL-C, RC, ApoB/ApoA-1, LDL-C/ApoB and HDL-C showed the strongest correlation with 10-year CVD risk, with Spearman's correlation coefficients of 0.41, 0.38, 0.35, 0.31, −0.37 and −0.36, respectively. In the NGT-1hPG-high, TG, sdLDL-C, and ApoB/ApoA-1 levels were significantly higher, while HDL-C and LDL-C/ApoB levels were significantly lower compared to counterparts with NGT-1hPG-normal (all $P < 0.05$). Moreover, except for TG and RC (both $P < 0.01$), the majority of lipid parameter levels in NGT-1hPG-high did not significantly differ from those in PDM (all $P > 0.05$).

Conclusions NGT-1hPG-high exhibited a similar atherogenic lipid profile to that observed in PDM. 1-h PG could serve as a potential indicator for the early identification of at-risk individuals who may otherwise go undetected among NGT population.

Graphical Abstract

Background: Existing evidence suggests that elevated 1-hour post-load plasma glucose (1-h PG ≥ 8.6 mmol/L) during an oral glucose tolerance test (OGTT) is associated with atherogenic lipid parameters which are linked to an increased risk of cardiovascular disease (CVD) risk.

Objective: To demonstrate comprehensive lipid characteristics in individuals with different glycemic status stratified by 1-h PG, with a particular focus on those with normal glucose tolerance (NGT) but elevated 1-h PG (NGT-1hPG-high).



Conclusions: NGT-1hPG-high exhibited a similar atherogenic lipid profile to that observed in PDM. 1-h PG could serve as a potential indicator for the early identification of at-risk individuals who may otherwise go undetected among NGT population.

Keywords 1-hour post-load plasma glucose, Dyslipidemia, Lipid parameters, Diabetes, Cardiovascular disease

Introduction

The prevalence of diabetes mellitus (DM) and prediabetes (PDM) has been rising rapidly worldwide, placing an increasing burden on global healthcare systems. The International Diabetes Federation (IDF) estimates that by 2045, the number of DM and PDM in adults aged 20–79 years will reach 783.7 million (11.2%) and 1.2 billion (17.5%), respectively [1]. Individuals with DM and PDM, or even early-stage of hyperglycemia often experience dyslipidemia, a well-established risk factor for atherosclerosis that significantly increases the risk of heart attacks, strokes, and other cardiovascular diseases (CVD) [2, 3].

To counteract the rising prevalence of DM, early identification and precise stratification of high-risk population of DM are crucial, as they allow timely interventions to manage glucose and lipid levels, and delay DM progression as well as reduce the risk of associated cardiovascular complications [4]. Recent studies have highlighted the

potential of 1-hour post-load plasma glucose (1-h PG) during an oral glucose tolerance test (OGTT) as a predictor of DM progression [5]. The IDF's 2024 position statement underscored that current glucose tests may be inadequate. Even among individuals with normal glucose tolerance (NGT), those with 1-h PG levels exceeding 8.6 mmol/L face a significantly higher risk of developing DM, DM related CVD and mortality [4].

Despite the growing recognition of 1-h PG as a valuable biomarker, existing studies on cardiometabolic characteristics have primarily focused on individuals with DM and PDM rather than those with NGT but elevated 1-h PG (NGT-1hPG-high). Existing study has shown that PDM is associated with lower high-density lipoprotein-cholesterol (HDL-C), higher total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B (ApoB) and triglycerides (TG) levels compared to NGT individuals [6]. These lipid abnormalities are even more pronounced in people with DM [7, 8]. Although a few studies have explored the association between 1-h PG and traditional lipid parameters (TG, TC, HDL-C and LDL-C) [9], further study is needed into non-traditional lipid parameters. Apolipoprotein, lipoprotein(a) [Lp(a)], small dense low-density lipoprotein cholesterol (sdLDL-C), non-HDL-C, remnant cholesterol (RC), ApoB/apolipoprotein A-1 (ApoA-1) and LDL-C/ApoB are critical in understanding atherogenesis and have gained increasing attention in recent research due to their associations with CVD [10–12]. For instance, sdLDL-C is a subtype of LDL-C whose particles are smaller and denser than typical LDL-C, enabling them to penetrate the arterial wall more easily and sustain oxidation, which promotes atherosclerotic plaque formation [13]. The LDL-C/ApoB ratio also reflects small LDL particle size and can predict CVD and all-cause mortality in the general population [14]. The ApoB/ApoA-1 ratio serves as a potential marker of plasma atherogenicity, assessing the balance between atherogenic and protective lipid factors [15]. However, evidence regarding these non-traditional lipid parameters in different glycemic status stratified by 1-h PG remains limited.

Therefore, this study aims to provide a comprehensive analysis of lipid characteristics in individuals with different glycemic status defined by 1-h PG. Particular attention is given to NGT-1hPG-high individuals to determine whether they should still be considered low-risk.

Materials and methods

Study design and participants

Data was obtained from the screening stage of "Daqing Diabetes Prevention Study II (Daqing DPS-II)", which included high-risk population screening stage and lifestyle intervention stage. The study was conducted in Daqing, Heilongjiang province in the northeast of China. We used 2023 health checkup data and an e-questionnaire for high-risk assessment to recruit employees aged 25–55 years from 8 oilfield factories. Those who met any one of the following conditions were considered high-risk: venous fasting plasma glucose (FPG) 5.6–6.9 mmol/L in 2023 health checkup data; capillary FPG 5.6–6.9 mmol/L; random capillary blood glucose 7.8–11.0 mmol/L; overweight or obese [body mass index (BMI) ≥ 24 kg/m^2]; family history of DM. For future lifestyle interventions, subjects were excluded if they met any one of the following exclusion criteria: self-reported presence of DM or regular use of hypoglycemic agents; persistent uncontrolled severe hypertension; pregnancy, lactation, or planned pregnancy within the next 36 months; severe diseases related to glucose metabolism disorder; active cancer, recent cancer treatment (within the past 6 months) or other conditions deemed inappropriate for participation by the researchers (Figure S1).

Eligible individuals were invited to undergo an OGTT, complete anthropometric measurements, and participate in a face-to-face structured questionnaire in the screening stage, which took place between August, 2023 and January, 2024. The study enrolled 2 492 individuals and data points with missing values were excluded. Ultimately, 2 469 (99.1%) subjects were included in the final analysis. Written informed consent was obtained from each individual. This study was approved by the Institutional Ethics Committee of the Chinese Academy of Medical Sciences & Peking Union Medical College (CAMS&PUMC-IEC-2022-061).

Glucose and lipid parameters measurement and 10-year CVD risk calculation

After fasting for at least 8 h, fasting blood samples were collected for examining FPG and other biochemical parameters. A 75 g OGTT was then performed, with additional blood samples taken at 60 and 120 min to assess post-load glucose and insulin tests. Plasma glucose was measured using the hexokinase method (Roche cobas® c701 analyzers, Germany), while insulin was measured using immunoradiometric assay kit (DiaSource® INS-IRMA, Belgium). Lipid parameters including TC, TG, HDL-C, LDL-C, sdLDL-C, Lp(a), ApoA-1 and ApoB were measured using enzymatic methods (Roche cobas® c701 analyzers, Germany). The following lipid indices were calculated: non-HDL-C = TC– HDL-C; RC = TC– HDL-C– LDL-C; ApoB/ApoA-1; LDL-C/ApoB. The 10-year CVD risk was calculated using the Prediction for Atherosclerotic cardiovascular disease Risk in China (China-PAR) equation as recommended by the Guideline on the assessment and management of cardiovascular risk in China [16, 17]. The gender-specific China-PAR equation was developed and validated using data from 4 large, contemporary, population-based Chinese cohorts.

It has demonstrated excellent performance in predicting atherosclerotic CVD risk with good internal consistency and external validation [16]. The equation accounts for sociodemographic, anthropometric, biochemical, lifestyle characteristics and family history, and is adjusted for baseline survival. Insulin resistance was evaluated using homeostasis model assessment of insulin resistance (HOMA-IR), calculated as follows: HOMA-IR = fasting insulin (μU/mL) × FPG (mmol/L)/22.5.

Definition of glycemic status

Based on the World Health Organization (WHO)'s 1999 criteria for the diagnosis of glycemic status and the IDF's 2024 position statement on 1-h PG for the diagnosis of intermediate hyperglycemia and DM [4, 18], the study population was classified as follows:

(1) NGT: FPG < 6.1 mmol/L and 2-h PG < 7.8 mmol/L

NGT-1hPG-normal: 1-h PG < 8.6 mmol/L
NGT-1hPG-high: 1-h PG ≥ 8.6 mmol/L

(2) PDM: FPG 6.1–6.9 mmol/L and/or 2-h PG 7.8–11.0 mmol/L

PDM-1hPG-normal: 1-h PG < 8.6 mmol/L
PDM-1hPG-high: 1-h PG ≥ 8.6 mmol/L

(3) DM: FPG ≥ 7.0 mmol/L and/or 2-h PG ≥ 11.1 mmol/L

Definition of dyslipidemia

Based on the 2023 Chinese guidelines for lipid management [19], individuals were defined as having dyslipidemia if they met either of the following criteria:

(1) TC ≥ 6.2 mmol/L or TG ≥ 2.3 mmol/L or LDL-C ≥ 4.1 mmol/L or HDL-C < 1.0 mmol/L.
(2) With a history of diagnosed dyslipidemia or the use of lipid-lowering drugs.

Covariates

To adjust for potential confounding factors, we collected a range of covariates. Body height, weight, waist circumference (WC) and blood pressure were measured by trained survey personnel. BMI was calculated as body weight (kg) divided by the square of body height (m^2). Blood pressure was measured three times for each individual after 5 minutes' rest (Omron HEM-7122, Japan), and with the average of the second and third measurements used for analysis.

A questionnaire was used to obtain information on sociodemographic characteristics, disease history and lifestyle information, including diet, physical activity, smoking status and frequency of alcohol consumption. Dietary quality was assessed using the Diet Quality Questionnaire (DQQ), and the Global Diet Recommendation (GDR) score which integrated various healthy and unhealthy food categories was calculated to evaluate individual's adherence to WHO global dietary recommendations [20–22]. Physical activity levels were assessed using the International Physical Activity Questionnaire– Short Form (IPAQ-SF) [23]. Smoking status and alcohol consumption frequency were investigated using a self-compiled questionnaire adapted from the China Chronic Disease and Risk Factor Surveillance survey. Individuals who were currently smoking were considered as current smokers. Those who had consumed alcohol within the past 12 months were considered as current drinkers. Hypertension was defined as an average systolic blood pressure ≥ 140 mmHg, or an average diastolic blood pressure ≥ 90 mmHg, or a self-reported history of hypertension diagnosis in the questionnaire [24]. Hyperuricemia was defined as serum uric acid ≥ 420 μmol/L or a self-reported history of hyperuricemia diagnosis in the questionnaire [25].

Statistical analysis

Data analysis was conducted using R statistical software (version 4.2.2). Categorical variables were described as n (%) and using with the Pearson's chi-square (χ^2) test or Fisher's exact test. Continuous variables were presented as mean (SD) or median (P_{25}, P_{75}) and tested using one-way ANOVA and Kruskal-Wallis rank sum test, respectively.

Individuals were categorized by glycemic status, or divided into 4 groups based on the number of elevated glucose indicators (FPG, 1-h PG, and 2-h PG). Then, logistic regression was used to estimate the association between glycemic status and dyslipidemia, as well as between the number of elevated glucose indicators and dyslipidemia. The Receiver Operating Characteristics (ROC) curve was employed to evaluate the performance of glucose indicators in identifying the dyslipidemia, with the area under curve (AUC) determined and tested using the DeLong's test. Subgroup analyses of the association between 1-h PG and dyslipidemia were also performed based on gender, age, hypertension, hyperuricemia, and 10-year CVD risk stratification (Supplementary material).

To identify the most atherogenic lipid parameters, we calculated Spearman's correlation coefficients between lipid parameters and 10-year CVD risk. Restricted cubic splines were used to examine nonlinear trends between 1-h PG (independent variable) and each lipid parameter (dependent variable) before conducting linear regression analysis. Multiple linear regression or log-log regression (if the distribution was significantly skewed) was applied to assess the correlation between 1-h PG (independent

variable) and each of the lipid parameters (dependent variables). Bonferroni post hoc correction was applied for lipid parameter comparisons among different glycemic status. The multivariate analyses mentioned above incorporated several potential confounding factors for model adjustment. Model 1 was a crude model without covariate adjustment. Model 2 was adjusted for age, gender, education and occupation. Model 3 was further adjusted for smoking status, alcohol consumption, GDR score and physical activity level based on Model 2. Model 4 included additional adjustments for BMI, hypertension and use of lipid-lowering drugs (LLDs) based on Model 3. All *P* values were two-sided with significance level of 0.05.

Results

A total of 2 469 subjects were included in the data analysis, of whom 60.1% were male, with an average age of 45.76 ± 6.20 years. Among the subjects, 560 (22.7%) had NGT-1hPG-normal, 492 (19.9%) had NGT-1hPG-high, 64 (2.6%) had PDM-1hPG-normal, 844 (34.2%) had PDM-1hPG-high, 509 (20.6%) had newly diagnosed DM.

Metabolic characteristics

Table 1 described the sociodemographic, anthropometric, biochemical and lifestyle characteristics of subjects by glycemic status. BMI and WC were higher in DM compared to counterparts with other glycemic status (both $P < 0.001$). TC, TG, ApoB, sdLDL-C, non-HDL-C, ApoB/ApoA-1, fasting insulin and the HOMA-IR index followed a similar trend, with the highest values observed in those with DM, followed by those with PDM-1hPG-high, PDM-1hPG-normal, NGT-1hPG-high and NGT-1hPG-normal (all $P < 0.001$). 1-h insulin levels were significantly higher in NGT-1hPG-high compared to others. Education and the 4 main lifestyles (diet, physical activity, smoking status and alcohol consumption) distributions differed significantly among groups and were therefore considered as covariates.

Individuals were also divided into 4 groups based on the number of elevated glucose indicators (FPG, 1-h PG, and 2-h PG): 0, 1, 2, and 3 elevated indicators (Table S1). As the number of elevated glucose indicators increased, the prevalence of dyslipidemia rose accordingly ($P < 0.001$). TC, TG, ApoB, sdLDL-C, non-HDL-C, RC, and ApoB/ApoA-1 ratio showed significant upward trends (all $P < 0.001$). In contrast, HDL-C, LDL-C/ApoB ratio and Lp(a) levels decreased (all $P < 0.01$, Table S1).

Dyslipidemia and glycemic status

There was no significant difference in the prevalence of dyslipidemia between NGT-1hPG-high and PDM-1hPG-high (*OR* = 1.13, 95%*CI*: 0.88–1.44; Table 2); however, NGT-1hPG-normal exhibited a statistically significant lower risk of dyslipidemia compared to NGT-1hPG-high (*OR* = 0.63, 95%*CI*: 0.48–0.81; Table 2).

Dyslipidemia and elevated 1-h PG

Among individuals with only 1 elevated glucose indicator, elevated 1-h PG was associated with a higher risk of dyslipidemia (*OR* = 1.60, 95%*CI*: 1.23–2.08), whereas no significant association was found for elevated FPG levels or 2-h PG levels (both $P > 0.05$; Table S2). Subgroup analysis across gender, age, hypertension and hyperuricemia demonstrated that elevated 1-h PG levels were consistently associated with an increased risk of dyslipidemia (all $P < 0.01$). A significant association between 1-h PG and dyslipidemia was observed in the low 10-year CVD risk subgroup ($P < 0.001$, Table S3).

Atherogenic lipid parameters and elevated 1-h PG

TG, sdLDL-C, RC, ApoB/ApoA-1, LDL-C/ApoB and HDL-C showed the strongest correlation with 10-year CVD risk, with Spearman's correlation coefficients of 0.41, 0.38, 0.35, 0.31, −0.37 and −0.36, respectively (Fig. 1). Higher 1-h PG levels were consistently and linearly associated with an atherogenic lipid profile, characterized by increased TC, TG, LDL-C, ApoB, sdLDL-C, non-HDL-C, RC and ApoB/ApoA-1, and decreased HDL-C, Lp(a), LDL-C/ApoB after adjusting for potential confounding factors (all $P < 0.01$, Table S4, Figure S2).

Atherogenic lipid parameters and glycemic status

NGT-1hPG-high showed significantly higher TG, sdLDL-C, and ApoB/ApoA-1 levels and lower HDL-C and LDL-C/ApoB levels compared to counterparts with NGT-1hPG-normal (all $P < 0.05$). There was no significant difference between NGT-1hPG-high and PDM in the majority of lipid parameters (all $P > 0.05$, Fig. 2), except for TG and RC (both $P < 0.01$, Fig. 2).

Discussion

Our study comprehensively investigated the correlation between 1-h PG and the atherogenic lipid parameters. The main findings were as follows: (1) Elevated 1-h PG was associated with an increased risk of dyslipidemia and the atherogenic lipid parameters; (2) NGT-1hPG-high individuals exhibited significantly more atherogenic lipid parameters relevant to 10-year CVD risk, including higher TG, sdLDL-C, ApoB/ApoA-1 and lower HDL-C, LDL-C/ApoB compared to counterparts with NGT-1hPG-normal. Additionally, their lipid profile resembled to that observed in PDM. Therefore, 1-h PG may serve as a valuable indicator for identifying NGT individuals with elevated CVD risk.

Our findings align with previous studies. Andreozzi et al. demonstrated that NGT individuals with elevated 1-h PG had significantly higher TG, TG/HDL-C, ApoB,

Table 1 Sociodemographic, anthropometric, biochemical and lifestyle characteristics according to glycemic status

Variables	Overall, *N* = 2 469	NGT		PDM		DM, *n* = 509	*P*-value
		1-h PG normal, *n* = 560	1-h PG high, *n* = 492	1-h PG normal, *n* = 64	1-h PG high, *n* = 844		
Sociodemographic characteristics							
Gender (male)	1 485 (60.1%)	251 (44.8%)	314 (63.8%)	41 (64.1%)	527 (62.4%)	352 (69.2%)	< 0.001
Age, y	45.76 (6.20)	44.14 (6.63)	44.98 (6.83)	45.77 (5.66)	46.55 (5.72)	46.98 (5.40)	< 0.001
Ethnicity group (Han)	2 382 (96.5%)	536 (95.7%)	474 (96.3%)	60 (93.8%)	813 (96.3%)	499 (98.0%)	0.136
Education (High school or below)	1 106 (44.8%)	223 (39.8%)	190 (38.6%)	31 (48.4%)	402 (47.6%)	260 (51.1%)	< 0.001
Marital status (married)	2 162 (87.6%)	483 (86.3%)	419 (85.2%)	60 (93.8%)	747 (88.5%)	453 (89.0%)	0.116
Occupation (Manual labour)	1 558 (63.4%)	345 (61.7%)	294 (60.0%)	41 (64.1%)	538 (64.3%)	340 (66.8%)	0.204
Anthropometric and biochemical characteristics							
BMI, kg/m^2	26.46 (3.99)	24.52 (3.47)	25.86 (3.57)	25.88 (3.68)	27.08 (3.93)	28.23 (4.03)	< 0.001
WC, cm	87.53 (11.64)	81.34 (10.78)	86.37 (10.57)	85.97 (10.82)	89.11 (11.12)	93.06 (11.14)	< 0.001
Hypertension	993 (40.2%)	114 (20.4%)	173 (35.2%)	22 (34.4%)	407 (48.2%)	277 (54.4%)	< 0.001
Hyperuricemia	760 (30.8%)	113 (20.2%)	157 (31.9%)	20 (31.3%)	277 (32.8%)	193 (37.9%)	< 0.001
Dyslipidemia	1 474 (59.7%)	227 (40.5%)	285 (57.9%)	40 (62.5%)	540 (64.0%)	382 (75.0%)	< 0.001
LLDs use	177 (7.17%)	18 (3.21%)	26 (5.28%)	3 (4.69%)	74 (8.77%)	56 (11.0%)	< 0.001
FPG, mmol/L	6.08 (0.94)	5.45 (0.33)	5.67 (0.28)	6.07 (0.48)	6.10 (0.46)	7.15 (1.41)	< 0.001
2-h PG, mmol/L	8.54 (3.22)	5.84 (0.93)	6.51 (0.90)	7.30 (1.42)	8.67 (1.39)	13.42 (2.98)	< 0.001
1-h PG, mmol/L	10.88 (3.19)	7.02 (1.13)	10.17 (1.25)	7.74 (0.88)	11.66 (1.66)	14.92 (2.52)	< 0.001
HbA1c, %	5.59 (0.54)	5.26 (0.28)	5.38 (0.30)	5.47 (0.27)	5.59 (0.35)	6.19 (0.71)	< 0.001
TC, mmol/L	5.03 (0.95)	4.90 (0.92)	4.93 (0.96)	5.06 (0.87)	5.07 (0.91)	5.20 (1.03)	< 0.001
TG, mmol/L	1.58 (1.09, 2.37)	1.15 (0.85, 1.63)	1.47 (1.05, 2.15)	1.62 (1.20, 2.82)	1.75 (1.23, 2.55)	2.05 (1.47, 3.13)	< 0.001
HDL-C, mmol/L	1.27 (0.33)	1.42 (0.37)	1.28 (0.34)	1.25 (0.30)	1.23 (0.31)	1.16 (0.26)	< 0.001
LDL-C, mmol/L	3.29 (0.87)	3.20 (0.78)	3.27 (0.92)	3.24 (0.83)	3.29 (0.82)	3.40 (0.96)	0.008
ApoA-1, g/L	1.49 (0.24)	1.55 (0.26)	1.47 (0.24)	1.50 (0.22)	1.48 (0.24)	1.46 (0.21)	< 0.001
ApoB, g/L	1.04 (0.24)	0.96 (0.22)	1.02 (0.25)	1.05 (0.22)	1.06 (0.22)	1.12 (0.26)	< 0.001
sdLDL-C, mmol/L	1.12 (0.51)	0.88 (0.42)	1.06 (0.49)	1.13 (0.52)	1.17 (0.48)	1.33 (0.54)	< 0.001
Lp(a), nmol/L	16.70 (7.70, 44.50)	18.90 (8.80, 50.20)	17.40 (8.10, 43.20)	19.95 (8.20, 44.25)	16.30 (7.70, 39.15)	13.50 (6.20, 43.20)	0.003
Non-HDL-C, mmol/L	3.76 (0.95)	3.48 (0.89)	3.54 (0.94)	3.81 (0.89)	3.84 (0.89)	4.04 (1.03)	< 0.001
RC, mmol/L	0.33 (0.15, 0.60)	0.20 (0.07, 0.37)	0.29 (0.12, 0.51)	0.40 (0.20, 0.69)	0.46 (0.24, 0.82)	0.46 (0.24, 0.82)	< 0.001
ApoB/ApoA-1 ratio	0.72 (0.20)	0.64 (0.19)	0.71 (0.21)	0.72 (0.18)	0.74 (0.19)	0.79 (0.21)	< 0.001
LDL-C/ApoB ratio	3.15 (0.41)	3.32 (0.35)	3.19 (0.37)	3.09 (0.45)	3.09 (0.40)	3.00 (0.42)	< 0.001
Fasting insulin, μIU/mL	20.54 (12.10, 27.16)	12.46 (10.33, 20.88)	14.09 (11.63, 23.75)	14.81 (11.77, 24.90)	21.61 (13.15, 28.48)	26.20 (20.49, 34.56)	< 0.001
1-h insulin, μIU/mL	110.47 (80.64, 186.94)	91.03 (66.60, 153.52)	152.90 (91.50, 199.54)	94.66 (70.14, 134.63)	118.50 (88.37, 201.73)	109.76 (79.82, 183.25)	< 0.001
2-h insulin, μIU/mL	105.66 (73.16, 188.37)	69.85 (50.13, 98.57)	93.85 (70.45, 154.71)	82.22 (59.69, 159.22)	157.45 (93.00, 218.05)	168.48 (97.63, 230.64)	< 0.001
HOMA-IR index	5.26 (3.14, 7.57)	3.09 (2.44, 5.22)	3.60 (2.90, 6.10)	4.26 (3.24, 6.92)	5.97 (3.50, 7.88)	8.41 (5.75, 11.21)	< 0.001
Estimated 10-year CVD risk (%)	3.22 (1.21, 6.53)	1.25 (0.65, 3.28)	2.52 (1.05, 5.54)	2.90 (1.30, 5.60)	3.40 (1.51, 6.93)	6.23 (3.77, 11.17)	< 0.001
Lifestyle variables							
GDR score	10.80 (1.90)	10.92 (1.90)	10.87 (1.96)	10.39 (1.65)	10.81 (1.97)	10.63 (1.77)	0.025
Current smoker	751 (30.4%)	115 (20.5%)	162 (32.9%)	21 (32.8%)	264 (31.3%)	189 (37.1%)	< 0.001
Current drinker	1 404 (56.9%)	282 (50.4%)	295 (60.0%)	37 (57.8%)	503 (59.6%)	287 (56.4%)	0.007
Moderate PA ≥ 150 min/week	833 (33.7%)	203 (36.3%)	192 (39.0%)	25 (39.1%)	271 (32.1%)	142 (27.9%)	0.002

Values are presented as n (%), mean (SD) or median (P_{25}, P_{75}). *P*-values were calculated using Pearson's Chi-squared test or Fisher's exact test, one-way ANOVA analysis, Kruskal-Wallis rank sum test

Table 2 Odd ratios (*ORs*) and 95% confidence intervals (*CIs*) of dyslipidemia with different glycemic status

Group	Model 1			Model 2			Model 3			Model 4		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
NGT-1hPG-high (ref.)	–	–	–	–	–	–	–	–	–	–	–	–
NGT-1hPG-normal	0.50	0.39, 0.63	< 0.001	0.55	0.43, 0.71	< 0.001	0.56	0.44, 0.72	< 0.001	0.63	0.48, 0.81	< 0.001
PDM-1hPG-normal	1.21	0.71, 2.10	0.485	1.20	0.70, 2.09	0.516	1.19	0.69, 2.08	0.533	1.20	0.69, 2.13	0.520
PDM-1hPG-high	1.29	1.03, 1.62	0.028	1.30	1.03, 1.64	0.026	1.31	1.04, 1.66	0.024	1.13	0.88, 1.44	0.329
DM	2.18	1.67, 2.86	< 0.001	2.11	1.61, 2.78	< 0.001	2.10	1.59, 2.77	< 0.001	1.66	1.25, 2.22	0.001

Model 1: Crude model

Model 2: Adjusted for age, gender, education and occupation

Model 3: Adjusted for smoking status, alcohol consumption, GDR score and physical activity level based on Model 2

Model 4: Adjusted for BMI, hypertension and LLDs use based on Model 3

and ApoB/ApoA-1 and lower HDL-C compared to NGT-1hPG-normal individuals, resembling the lipid profiles of individuals with impaired glucose tolerance (IGT) [9]. Similarly, Shimodaira et al. reported a negative correlation between 1-h PG levels and HDL-C levels, as well as a positive correlation between 1-h PG levels and TG/HDL-C ratio in NGT individuals [26]. Oduncu et al. highlighted significant differences in HDL-C and TG levels between individuals with 1-h PG > 8.6 mmol/L and those with 1-h PG ≤ 8.6 mmol/L in PDM [27]. It is well-established that these lipid parameters play a crucial role in atherosclerosis and CVD. Elevated TG levels are associated with a higher risk of CVD, and should be routinely evaluated in all patients, even those considered to be at low-risk [28, 29]. A U-shaped relationship has been observed between HDL-C levels and CVD risk, with both low (< 40 mg/dL in men, < 50 mg/dL in women) and very high (≥ 80 mg/dL in men) HDL-C values being linked to increased risks of CVD and overall mortality [30]. The ApoB/ApoA-1 ratio reflects the balance between atherogenic and anti-atherogenic lipoproteins, with a high ApoB/ApoA-1 ratio being strongly correlated with stroke [31] and major adverse cardiovascular events (MACEs), and may also signal an increased risk of cardiovascular events decades before their onset [32]. These findings suggest that elevated 1-h PG in individuals with NGT may be associated with a higher risk of atherosclerosis and CVD.

We also observed elevated levels of sdLDL-C and a decreased LDL-C/ApoB ratio in NGT-1hPG-high individuals. Growing attention has been directed toward sdLDL-C, a specific form of LDL-C comprising smaller and denser particles [33]. The enhanced atherogenicity of sdLDL-C may be explained by its lower affinity for the LDL-C receptor, greater ability to penetrate arterial walls, increased retention due to proteoglycan binding [34], and heightened susceptibility to oxidation [35]. As these sdLDL-C particles contain less cholesterol, their presence may not be reflected by LDL-C levels and can often be overlooked [36]. Furthermore, the LDL-C/ApoB ratio, a more accessible and cost-effective tool for estimating LDL particle size, has been shown to independently predict both CVD and all-cause mortality [14]. Additionally, our study corroborated the previously reported phenomenon of the "Lp(a) paradox". To date, there is no evidence to suggest that lowering Lp(a) has a negative impact on cardiovascular outcomes [37]. Therefore, non-traditional parameters involved in CVD pathogenesis should not be disregarded and further investigation is warranted.

The natural progression from normal glucose regulation to DM can be described in three distinct stages [4, 38]. Initially, β-cells compensate for reduced insulin sensitivity by increasing insulin production. In the second phase, although β-cell function is still preserved,

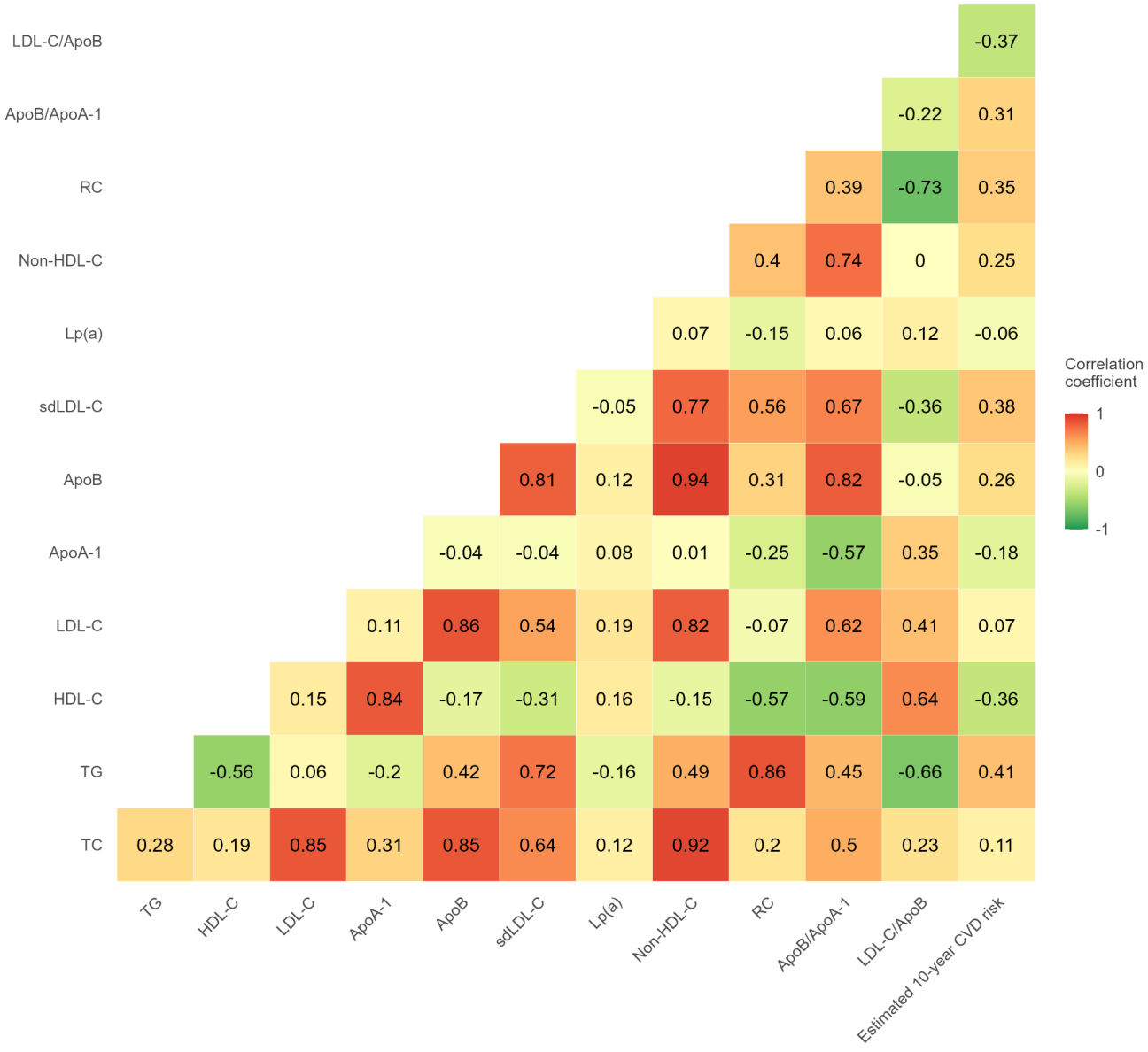


Fig. 1 Correlation between lipid parameters and 10-year CVD risk. This heatmap displays the Spearman's correlation coefficients between lipid parameters and 10-year CVD risk. The color gradient represents the strength and direction of correlations, where red indicates positive correlations and green indicates negative correlations

β-cells mass begins to diminish, leading to reduced insulin responsiveness. Eventually in the third phase, β-cells can no longer produce sufficient insulin, resulting in the breakdown of glucose homeostasis and the onset of DM. Insulin resistance is a potential mechanism linking hyperglycemia to atherogenic lipid parameters. Impaired insulin sensitivity may hinder glucose uptake for glycogen synthesis in peripheral tissues, such as skeletal muscle, resulting in a redirection of excess glucose to the liver [39]. This process promotes hepatic lipogenesis, ultimately contributing to elevated circulating lipid levels and atherogenic lipid parameters. In NGT-1hPG-high individuals, insulin resistance may result in a delayed insulin peak and prolonged postprandial hyperglycemia [40], which could potentially explain the association between 1-h PG and atherogenic lipid parameters. Our findings support this observation, as 1-h insulin levels were the highest in NGT-1hPG-high compared to those with other glycemic status, indicating an abnormal insulin peak.

Data from the HOMA-IR index suggest that NGT-1hPG-high represents an intermediate state of insulin resistance, positioned between NGT-1hPG-normal and PDM. Under insulin-resistance conditions, very low-density lipoprotein (VLDL) levels increase, facilitating the exchange of cholesterol esters and TG between

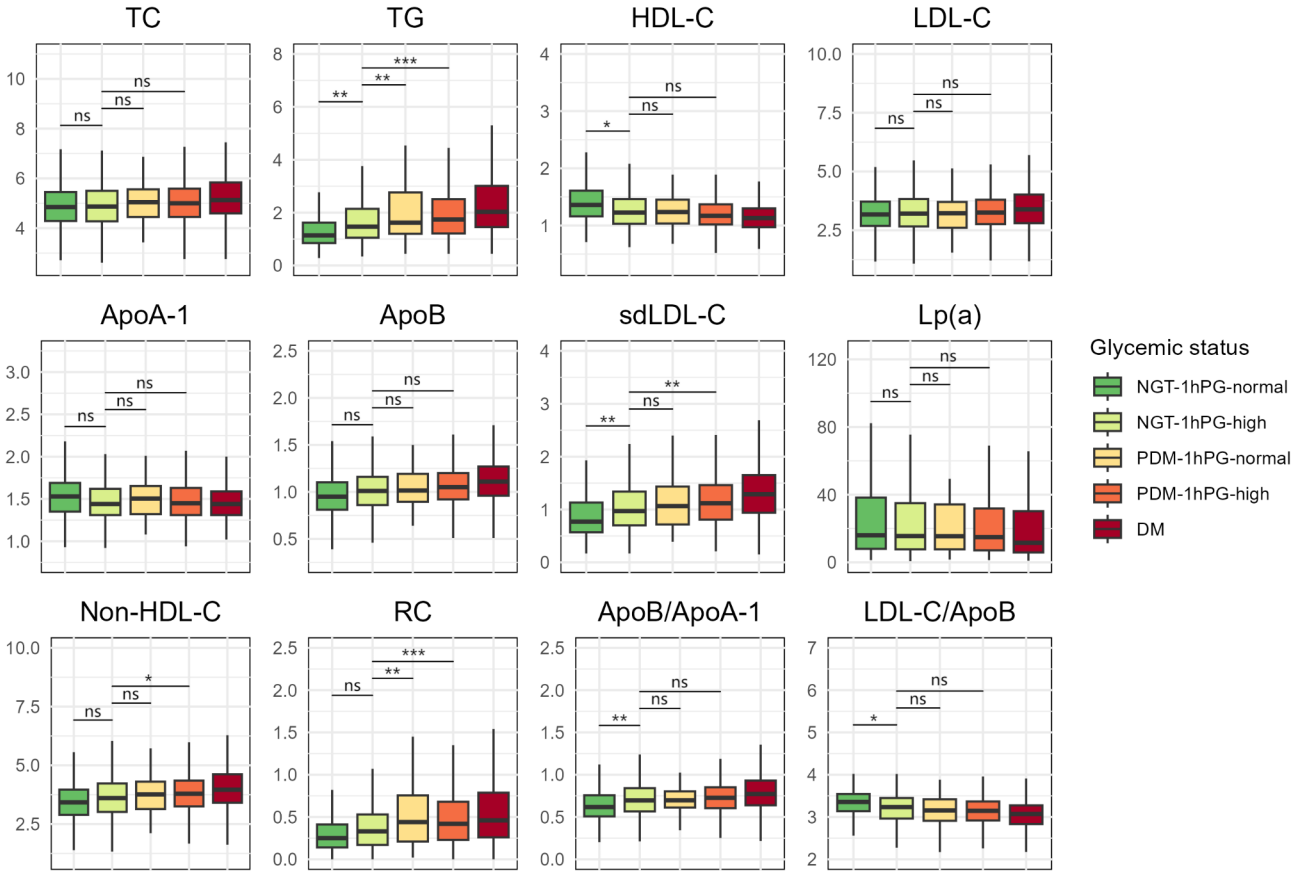


Fig. 2 Comparisons of lipid level among different glycemic status. Box plots showed the median and interquartile range (IQR). Group differences were assessed using a general linear model adjusted for covariates (age, gender, education, occupation, smoking status, alcohol consumption, GDR score, physical activity level, BMI, LLDs use and hypertension) with post-hoc Bonferroni correction. ns = no significant difference; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

VLDL and low-density lipoprotein (LDL) [41]. This process produces TG-rich LDL particles that are depleted of cholesterol esters. These particles serve as an optimal substrate for hepatic lipase, which hydrolyzes their TG content, leading to the formation of small dense LDL particles [42]. Additionally, the increased presence of TG-rich VLDL and LDL fosters the redistribution of TG to high-density lipoprotein (HDL) via lecithin-cholesterol acyltransferase and cholesterol ester transfer protein, accelerating HDL catabolism [9]. As a result, NGT-1hPG-high individuals exhibit a lipid pattern similar to PDM, including increased TG and sdLDL-C, as well as decreased LDL-C/ApoB and HDL-C, suggesting that NGT-1hPG-high should no longer to be considered low-risk.

Testing of 1-h PG in high-risk populations is essential for precise stratification. Because the progression from normal glucose regulation to DM can span over a decade, during which the traditional glucose indicators, like FPG and 2-h PG, may still remain within normal ranges [4]. The San Antonio Heart Study (SAHS) revealed that individuals with NGT and 1-h PG ≥ 8.6 mmol/L had a significantly higher 8-year risk (15.3%) of developing to type 2 diabetes (T2D), comparable to those with IFG (10.8%) or IGT (17.8%) but with 1-h PG < 8.6 mmol/L [43]. The Botnia Study reported similar findings [44]. Moreover, extensive research highlights that individuals with NGT but elevated 1-h PG exhibit an adverse cardio-metabolic risk profile, including elevated plasma biomarkers of systemic inflammation increasing their risk of cardiovascular target-organ damage [4]. Among patients with coronary heart disease, those with NGT but elevated 1-h PG demonstrated more severe coronary artery lesions and faced a higher risk of adverse cardiovascular events and hospital re-admission [45]. Therefore, despite normal FPG and 2-h PG levels, maintained due to residual β-cell function, elevated 1-h PG could still serve as an early indicator for future DM and CVD risk, as it signals underlying metabolic dysfunctions not yet detected by traditional glucose tolerance tests [4, 46, 47]. Our subgroup analysis, showing a significant association between 1-h PG and dyslipidemia in the low 10-year CVD risk group, further underscores its potential as an early predictor of cardio-metabolic abnormalities. From a clinical perspective, 1-h PG should be considered in OGTT, as it may provide additional prognostic value beyond traditional FPG and

2-h PG measurements. Incorporating 1-h PG testing in diabetes screening could allow for more precise stratification of high-risk population and the identification of at-risk people, who might otherwise go undetected. Additionally, it could refine current risk assessments and provides a new perspective on the prevention of DM and CVD.

This study offers several advantages. First, it includes a large sample size of participants with varying glycemic status categorized by 1-h PG, providing a novel and comprehensive understanding of lipid parameters and cardiometabolic characteristics across different glycemic conditions. The identification of NGT-1hPG-high as an undetected at-risk population highlights the potential for early intervention and improved cardiovascular risk management. Additionally, standardized screening protocols and rigorous quality control measures ensure the reliability and robustness of the results.

However, our study also has several limitations. First, the cross-sectional design limits our ability to assess changes in risk factors or outcomes over time, necessitating further prospective longitudinal studies for confirmation. Second, although we exclusively included individuals with self-reported no prior history of DM or the use of hypoglycemic agents, potential selection bias may have occurred because the individuals with NGT in our study were selected from a high-risk population rather than the general population. This could have led to an overestimation of the associations with cardiovascular risk factors and limited the generalizability to the broader population. Third, although our results have adjusted for LLDs use, the potential influence of other medications on the outcomes cannot be entirely excluded. Fourth, although the 10-year CVD risk was calculated using the China-PAR equations, which was validated and widely used in the Chinese population, it remains an estimation, rather than data directly derived from long-term follow-up. Finally, despite applying multivariate adjustments and conducting subgroup analyses, residual confounding remains a possibility. Although our findings provide important insights, caution should be exercised when extrapolating these results to other populations or settings.

Conclusion

NGT-1hPG-high exhibited an atherogenic lipid profile similar to that observed in PDM. 1-h PG could serve as a potential indicator for the early identification of undetected at-risk individuals among NGT population.

Abbreviations

NGT	Normal glucose tolerance
PDM	Prediabetes
DM	Diabetes mellitus
NGT-1hPG-normal	NGT with normal 1-h PG
NGT-1hPG-high	NGT with elevated 1-h PG
PDM-1hPG-normal	PDM with normal 1-h PG
PDM-1hPG-high	PDM with elevated 1-h PG
BMI	Body Mass Index
WC	Waist circumference
FPG	Fasting plasma glucose
1-h PG	1-hour post-load plasma glucose
2-h PG	2-hour post-load plasma glucose
LLDs	Lipid-lowering drugs
ApoA-1	Apolipoprotein A-1
ApoB	Apolipoprotein B
Lp(a)	Lipoprotein (a)
sdLDL-C	Small dense low-density lipoprotein-cholesterol
TC	Total cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein-cholesterol
LDL-C	Low-density lipoprotein-cholesterol
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
Non-HDL-C	Non-high-density lipoprotein-cholesterol
RC	Remnant cholesterol
VLDL	Very low-density lipoprotein
China-PAR	Prediction for atherosclerotic cardiovascular disease risk in China
HOMA-IR	Homeostatic model assessment for insulin resistance
GDR	Global diet recommendation
PA	Physical activity
OGTT	Oral glucose tolerance test
CVD	Cardiovascular disease
Daqing DPS-II	Daqing Diabetes Prevention Study II
WHO	World Health Organization
IDF	International Diabetes Federation
OR	Odds ratio
CI	Confidence Interval
SD	Standard deviation
ANOVA	Analysis of variance
ROC	Receiver operating characteristic
AUC	Area under curve
MACEs	Major adverse cardiovascular events

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

CY.Y: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Validation, Visualization, Writing—original draft, Writing—review & editing. X.C: Data curation, Formal analysis, Investigation, Validation, Visualization, Writing—original draft, Writing—review & editing. YC.W: Data curation, Investigation, Validation, Visualization, Writing—review & editing. D.L, DL.Z, KP.L: Data curation, Investigation, Validation. JP.W: Project administration, Supervision, Validation. ZW.Y: Project administration, Supervision, Funding acquisition. QH.G: Project administration, Validation. J.Z: Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing—review & editing. RT.S: Conceptualization, Funding acquisition, Supervision, Validation, Writing—review & editing.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Chinese Academy of Medical Sciences & Peking Union Medical College under approval number [CAMS-PUMC-IEC-2022-061]. Written informed consent was obtained from all participants prior to their inclusion in the study.

Consent for publication
All participants provided written informed consent for the publication of anonymized data.

Competing interests
The authors declare no competing interests.

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