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The joint effect of cumulative metabolic parameters on the risk of type 2 diabetes: a population-based cohort study

Wen-Yan Xiong[1†], Yu-Hong Liu[1†], Yi-Bing Fan[1], Xiao-Lin Zhu[1], Kun Zhou[1] and Hui Li[1*]

Abstract

Background and aims This study aimed to examine the cumulative effects of body mass index (BMI), body roundness index (BRI), pulse pressure (PP), triglycerides (TG), high-density lipoprotein cholesterol (HDL) and fasting plasma glucose (FPG) on Type 2 diabetes (T2D) morbidity.

Methods A total of 78,456 participants aged older than 45 years were extracted from basic public health services in China. During the 2-year follow-up, 6,942 individuals had developed T2D. The binary logistic regression models and multinomial logistic regression models were conducted to investigate the effects of cumulative metabolic parameters on incident T2D, prediabetes regression and progression.

Results We found statistically deleterious impacts of exposure to high cumulative BMI, BRI, PP, TG and low cumulative HDL on T2D morbidity and prediabetes progression. Compared to the group with low cumulative of all five parameters, the adjusted ORs for new-onset T2D for participants presenting with 1–2, 3, and 4–5 elevated metabolic parameters were 1.41(1.31,1.52), 1.93(1.74,2.13) and 2.21(1.94,2.51), respectively. There was additive interaction between FPG level and cumulative metabolic parameters with T2D. Compared with participants with the lowest quartile of FPG and low cumulative of all 5 parameters, those with the highest quartile of FPG and high cumulative of 4–5 parameters had a 14.63 [95% CI (12.27, 17.42)] higher risk of incident T2D.

Conclusions Participants with more numbers of high-cumulative metabolic parameters were associated with a higher risk of incident T2D and prediabetes progression. A high level of normal FPG could enhance these risks.

Keywords Cumulative exposure, Metabolic parameters, T2D, Cohort study

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Introduction

Type 2 diabetes (T2D), a chronic metabolic disorder, predominantly presents with elevated blood glucose levels, insulin resistance, and a relative deficiency of insulin [1]. The prevalence of T2D has reached epidemic proportions globally, posing significant challenges to global health. International Diabetes Federation (IDF) reported that the number of diabetes patients is expected to increase to 783 million (12.2%) by 2045 [2]. T2D impacts individual health and quality of life and has profound implications for cardiovascular disease morbidity and mortality [3]. The Prediabetes population is a high-risk group for T2D. It was estimated that about 5-10% of prediabetes patients would develop T2D if not controlled [2]. The global rise in life expectancy and the resultant increase in the elderly demographic have led to a surge in the population at risk for chronic diseases, diabetes being a primary concern. Therefore, identify changeable risk factors is essential in mitigating the deleterious impacts of T2D.

An increasing body of research indicates a significant link between metabolic factors, including blood pressure, obesity, and lipid levels, and the development of T2D, with insulin resistance playing a key role [4–6]. Existing studies highlighted that individuals with impaired fasting glucose or insulin resistance show a higher propensity for progressing to T2D [7, 8]. Dysregulation in glucose metabolism, abnormal lipid levels, and obesity are recognized as a significant risk factor often present before the diagnosis of T2D [9, 10]. Emergency interventions taken for obesity and hypertension in adults with prediabetes could promote the reversion from prediabetes to normoglycemia [10, 11]. There is no doubt that prediabetes regression to normoglycemia could reduce the risk of T2D, as well as cardiovascular diseases [12].

Several studies have confirmed that cumulative exposure to elevated blood pressure [13] and triglyceride glucose-body mass index [14], could increase the risk of incident cardiovascular disease [15]. However, evidence for T2D is limited and falls short in explicating the cumulative high exposure of metabolic parameters to the incident diabetes in a large population. Besides, many studies are based on a single baseline metabolic parameter and ignore the long-term effect [16]. Given these insufficiencies, there is a need for more intensive, longitudinal studies that evaluate a broader spectrum of metabolic parameters that may offer insights into the preclinical stages of T2D and prediabetes.

Therefore, in our study, we sought to examine the relationship between cumulative metabolic parameters, including body mass index (BMI), body roundness index (BRI), pulse pressure (PP), triglycerides (TG), high-density lipoprotein cholesterol (HDL), and fasting plasma glucose (FPG) with the onset of T2D, and to determine if their combined effects significantly elevate T2D risk. In addition, the effect on prediabetes regression and progression was also examined.

Materials and methods

Study population

The data of our study was extracted from basic public health services in Nanchang, which are provided by the government to all residents free of charge. This project was mainly targeted at children, pregnant and postpartum women, the elderly, and patients with chronic diseases. In our study, we extracted data from individuals aged 45 and older who underwent annual health examinations between 2021 and 2023. The study complied with the Declaration of Helsinki and all participants were informed at enrollment. Participants under 45 years and those lacking metabolic parameters data, such as BMI, BRI, PP, TG, HDL, and FPG in 3 waves, were disqualified. Besides, we excluded people with T2D or missing data on T2D information in 2021. Ultimately, our analysis encompassed a total of 78,456 participants. Fig. 1 depicted the inclusion and exclusion criteria applied throughout our analytical process.

Measurements

Definition of cumulative metabolic parameters

Trained professionals conducted anthropometric evaluations, measuring waist circumference, weight, and height. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded by skilled nurses utilizing an automatic blood pressure monitoring device. In the morning, venous blood samples were collected from the study participants. Specialized equipment was employed to assess biochemical parameters, including total cholesterol (TC), low-density lipoprotein (LDL), TG, HDL, and FPG.

The calculation formulas for relevant metabolic parameters are as follows:

$BMI = \text{weight} / (\text{height})^2$; BRI [17] $= 364.2 - 365.5 \times \{1 - [(WC/2\pi) / (0.5 \times \text{height})]2\}^{1/2}$;

$PP = SBP - DBP$; The formula used for the calculation of the time-weighted mean Cum-metabolic parameters [18] was:

$[(cum_{2021} + cum_{2022})/2 \times (T2 - T1) + (cum_{2022} + cum_{2023}) / 2 \times (T3 - T2)] / (T3 - T1)$; where T1, T2, and T3 were the dates of follow-up during 2021, 2022, and 2023, respectively.

High cumulative exposure is identified as the highest quartile (Q4) of the cumulative index, representing the most significant exposure level (Cum-BRI ≥ 5.3, Cum-BMI ≥ 25.23, Cum-PP ≥ 60.28, Cum-TG ≥ 1.81), and low cumulative exposure is classified as falling within the first to third quartiles (Q1–Q3) of the cumulative index. While for Cum-HDL, we defined the lowest quartile (Q1) as high cumulative exposure (Cum-HDL ≤ 1.2).

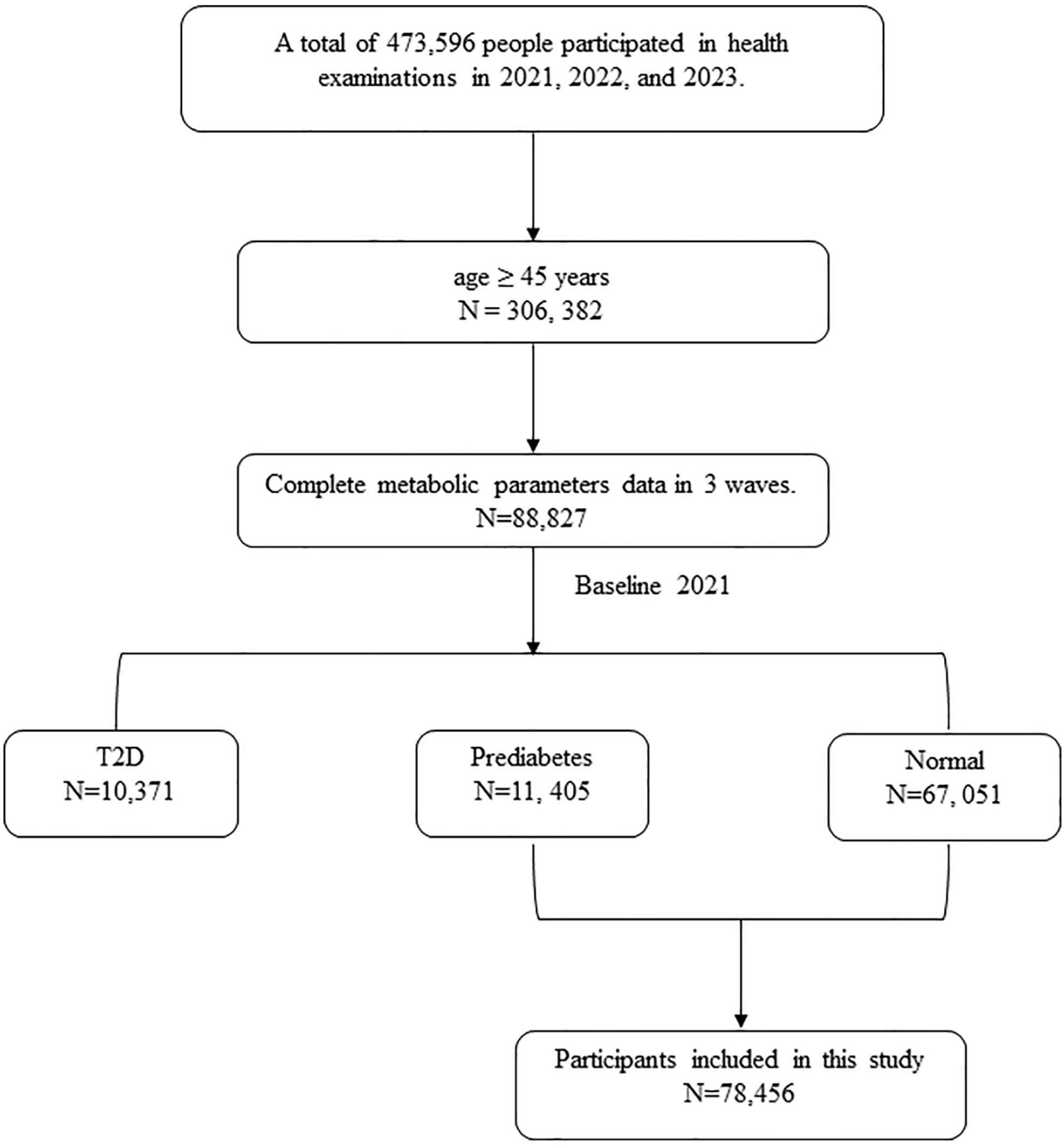

Fig. 1 Flow chart
Metabolic parameters: body mass index, body roundness index, pulse pressure, triglycerides, high-density lipoprotein cholesterol, fasting plasma glucose

Participants were classified into four groups based on their number of elevated cumulative metabolic parameters (BMI, BRI, PP, TG, HDL). Group 1 had none, Group 2 had one to two, Group 3 had three, and Group 4 had four to five elevated parameters.

Definition of covariates

The covariates in our study include age (continuous), gender (female, male), health-related behaviors including smoking status (non-smoker, ex-smoker, current smoker), exercise (every day, more than once a week, occasionally, never), drinking status (non-drinker, ex-drinker, current drinker), and diet (balanced meat and vegetables, more vegetables, more meat). The data were

collected via structured questionnaires, which were administered by trained investigators. Dyslipidemia is defined as TC>6.2 mmol/L and/or TG>2.3 mmol/L and/or LDL>4.1 mmol/L and/or HDL<1 mmol/L [19]. Hypertension is characterized by either: a systolic blood pressure (SBP) of 140 mmHg or higher, a diastolic blood pressure (DBP) of 90 mmHg or above, a previous diagnosis of hypertension, or the current use of antihypertensive medication.

Outcome

T2D is categorized by fasting plasma glucose (FPG) levels equal to or exceeding 7.0 mmol/L, a self-reported history of T2D, or the use of anti-diabetic medications. Prediabetes is characterized by FPG levels ranging from 6.1 to 6.9 mmol/L.

Statistical analyses

Baseline characteristics were stratified by Cum-metabolic parameters groups and glycemic condition in 2023. Continuous variables were depicted as means (±standard deviations) or medians (interquartile ranges), while categorical variables were expressed in counts (percentages). Group differences were evaluated using Chi-square, ANOVA, or Kruskal-Wallis tests, depending on the data distribution. Furthermore, Spearman's correlation analysis was employed to examine the interrelations among metabolic parameters, offering a systematic understanding of their associations.

Firstly, binary logistic regression models were applied to assess both the combined and individual associations between cumulative metabolic parameters and the risk of T2D. The odds ratios (ORs), accompanied by 95% confidence intervals (CIs), were computed using three models: model 1, unadjusted; model 2, age and gender were adjusted; model 3, smoking status, exercise, drinking status, diet, SBP, DBP, FPG, TC, LDL, hypertension, and dyslipidemia were further adjusted based on model 2. Besides, we examined the interaction effect between FPG and cumulative metabolic parameters on T2D.

Next, multinomial logistic regression models were used to explore cumulative metabolic parameters with the prediabetes regression and progression, using the remained as prediabetes participants as the reference. In Models 2 and 3, we controlled for the same covariates, subsequently calculating the OR along with 95% CI.

In sensitive analysis, we performed subgroup analyses stratified by age, gender, hypertension, and dyslipidemia. In addition, restricted cubic spline (RCS) with 3 knots for cumulative metabolic parameters were further modeled to assess the shape of their associations with incident T2D adjusting covariates. Based on the outcomes of the RCS analysis, we classified the patients into groups using the cut-off values.

All statistical analyses were conducted utilizing R software version 4.1.2. All *P*-values were two-sided, with a threshold for statistical significance established at $P<0.05$.

Results

Baseline characteristics of study participants

A total of 78,456 individuals [mean (SD) age, 70.27 (7.61) years; 41.4% males] had complete metabolic parameters data in 3 waves were included in our analysis. During the 2-year follow-up period, 6,942 (8.8%) participants had developed T2D. The baseline characteristics of all the study participants across the joint cumulative metabolic parameters group are presented in Table 1. As indicated in Table 1, participants exhibiting a greater number of high cumulative metabolic parameters were predominantly women. Participants in Group 4 exhibited the highest baseline blood pressure (SBP, DBP, PP), obesity index (BMI, WC, BRI) and lipid parameters (TC, TG, LDL) ($P<0.001$). Besides, Participants in Group 4 had a higher prevalence of hypertension and dyslipidemia, and more people had developed T2D ($P<0.001$).

Among the included 11,405 [mean (SD) age, 70.18 (7.50) years; 39.0% males] participants with prediabetes at baseline, 2,876 remained as prediabetes, 3,150 progressed to diabetes, and 5,379 regressed to normoglycemia during the 2-year follow-up. Baseline characteristics of participants stratified by glycemic condition in 2023 are listed in Table S1.

The correlation between various metabolic parameters is depicted in Figure S1. There was correlation between various indicators, all correlation coefficients were significantly different from zero ($P<0.05$).

The relationship between cumulative metabolic parameters and the incidence of T2D

The association between combined metabolic parameters and the incidence of T2D is shown in Table 2. In our longitudinal analysis, after adjusting for potential confounders, individuals exhibit a significantly higher adjusted OR of 1.41(1.31,1.52) for Group 2, 1.93(1.74,2.13) for Group 3 and 2.21(1.94,2.51) for Group 4 for the development of T2D, compared to those with lower cumulative scores across all five parameters (Group 1). When participants were divided into quartiles of Cum-BRI, Cum-BMI, Cum-PP, and Cum-TG respectively, the risk of T2D showed a tendency to increase. Participants in the top quartile of Cum-BRI had a 1.72-fold (95% CI 1.57–1.89) increased likelihood of developing T2D. And the same tendency was shown in Cum-BMI, Cum-PP, and Cum-TG. In addition, Cum-HDL was negatively associated with the risk of T2D (Figure S2). When compared with the Cum-HDL in the first quartile, the adjusted ORs for new-onset T2D were 0.76 (0.69–0.83).

Table 1 Baseline characteristics of participants by joint cumulative exposure group

Characteristic	Total (*N* = 78,456)	Group 1 (*N* = 26,901)	Group 2 (*N* = 40,502)	Group 3 (*N* = 7,853)	Group 4 (*N* = 3,200)	*p*
age (years)	70.27 (7.61)	69.65 (7.82)	70.62 (7.53)	70.39 (7.40)	70.67 (7.01)	< 0.001
Gender (male, n, %)	32,501 (41.4)	12,273 (45.6)	16,770 (41.4)	2548 (32.4)	910 (28.4)	< 0.001
Smoking status (n, %)						
Non-smoker	68,653 (87.5)	23,492 (87.3)	35,250 (87.0)	7009 (89.3)	2902 (90.7)	< 0.001
Ex-smoker	1188 (1.5)	391 (1.5)	641 (1.6)	113 (1.4)	43 (1.3)	
Current smoker	8615 (11.0)	3018 (11.2)	4611 (11.4)	731 (9.3)	255 (8.0)	
Exercise (n, %)						
Every day	25,450 (32.4)	8012 (29.8)	13,188 (32.6)	2979 (37.9)	1271 (39.7)	< 0.001
More than once a week	4273 (5.4)	1512 (5.6)	2360 (5.8)	297 (3.8)	104 (3.2)	
Occasionally	4346 (5.5)	1932 (7.2)	1937 (4.8)	336 (4.3)	141 (4.4)	
Never	44,387 (56.6)	15,445 (57.4)	23,017 (56.8)	4241 (54.0)	1684 (52.6)	
Drinking status (n, %)						
Non-drinker	70,236 (89.5)	24,009 (89.2)	36,139 (89.2)	7126 (90.7)	2962 (92.6)	< 0.001
Ex- drinker	1823 (2.3)	639 (2.4)	964 (2.4)	162 (2.1)	58 (1.8)	
Current drinker	6397 (8.2)	2253 (8.4)	3399 (8.4)	565 (7.2)	180 (5.6)	
Diet (n, %)						
Balanced meat and vegetables	72,318 (94.3)	24,695 (94.3)	37,336 (94.1)	7301 (94.8)	2986 (95.2)	< 0.001
More vegetables	3553 (4.6)	1117 (4.3)	1969 (5.0)	342 (4.4)	125 (4.0)	
More meat	825 (1.1)	370 (1.4)	372 (0.9)	57 (0.7)	26 (0.8)	
Waistline (cm)	80.85 (8.42)	76.80 (7.04)	81.42 (7.72)	87.79 (7.73)	90.74 (7.78)	< 0.001
BMI (kg/m^2)	23.41 (3.00)	21.83 (2.05)	23.53 (2.78)	26.45 (2.83)	27.56 (2.57)	< 0.001
SBP (mmHg)	132.89 (15.48)	127.52 (12.52)	134.41(15.65)	139.43 (16.59)	142.75 (17.56)	< 0.001
DBP (mmHg)	78.37 (8.94)	77.55 (8.38)	78.54 (9.08)	79.75 (9.38)	79.80 (9.73)	< 0.001
Pulse pressure (mmHg)	54.52 (13.30)	49.97 (9.73)	55.87 (13.87)	59.68 (14.86)	62.95 (15.26)	< 0.001
FPG (mg/dl)	5.34 (0.68)	5.25 (0.67)	5.35 (0.68)	5.52 (0.68)	5.58 (0.68)	< 0.001
TC (mg/dl)	5.05 (1.01)	5.06 (0.91)	5.03 (1.05)	5.07 (1.04)	5.07 (1.04)	< 0.001
TG (mg/dl)	1.45 (0.91)	1.13 (0.42)	1.50 (0.95)	1.95 (1.20)	2.34 (1.26)	< 0.001
LDL (mg/dl)	2.79 (0.79)	2.75 (0.74)	2.80 (0.81)	2.89 (0.83)	2.93 (0.84)	< 0.001
HDL (mg/dl)	1.44 (0.44)	1.59 (0.43)	1.41 (0.44)	1.28 (0.38)	1.15 (0.29)	< 0.001
BRI	4.75 (0.83)	4.31 (0.62)	4.82 (0.78)	5.49 (0.80)	5.79 (0.70)	< 0.001
Hypertension (Yes, N, %)	21,456 (27.3)	6049 (22.5)	11,559 (28.5)	2686 (34.2)	1162 (36.3)	< 0.001
Dyslipidemia (Yes, N, %)	21,969 (28.4)	3501 (13.3)	12,855 (32.1)	3645 (46.7)	1968 (61.7)	< 0.001
T2D in 2023 (Yes, N, %)	6942 (8.8)	1550 (5.8)	3707 (9.2)	1123 (14.3)	562 (17.6)	< 0.001

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting plasma glucose, TC: total cholesterol, TG: triglycerides, LDL: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, BRI: body roundness index, T2D: Type 2 diabetes

The relationship between cumulative metabolic parameters and prediabetes regression and progression

Table 2 displays the results of multinomial logistic regression models. The cumulative metabolic parameters were identified as significant risk factors for prediabetes progression (OR = 1.21, 95%CI: 1.03–1.41 for Group 2; OR = 1.47, 95%CI: 1.21–1.79 for Group 3; OR = 1.69, 95%CI: 1.32–2.16 for Group 4) when compared with participants in the group of low cumulative of all 5 parameters (Group1), in the adjusted model. In addition, the cumulative metabolic parameters were negatively associated with prediabetes regression (OR = 0.70, 95%CI: 0.61–0.79 for Group 2; OR = 0.61, 95%CI: 0.51–0.73 for Group 3; OR = 0.56, 95%CI: 0.44–0.71 for Group 4).

When participants were divided into quartiles of Cum-BRI, Cum-BMI, Cum-PP, and Cum-TG, respectively, the risk of prediabetes progression showed a tendency to increase. It was negatively associated with prediabetes regression (Figure S3).

The relationship between cumulative metabolic parameters and the incidence of T2D in population with different levels of baseline FPG

In the estimation of the joint effects, significant additive interaction between FPG level and cumulative metabolic parameters with T2D was observed. Compared with participants with the lowest quartile of FPG and low cumulative of all 5 parameters, those with the highest quartile of FPG and high cumulative of 4–5 parameters had a 14.63 [95% CI (12.27, 17.42)] higher risk of incident T2D (Fig. 2). Fig. 3 depicts the association in populations with different FPG levels. There was an interaction

Table 2 The joint effect of cumulative metabolic parameters on T2D, prediabetes regression and progression

Group	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
T2D						
Group 1	Ref.		Ref.		Ref.	
Group 2	1.65(1.55,1.75)	< 0.001	1.66(1.57,1.77)	< 0.001	1.41(1.31,1.52)	< 0.001
Group 3	2.73(2.52,2.96)	< 0.001	2.79(2.57,3.03)	< 0.001	1.93(1.74,2.13)	< 0.001
Group 4	3.48(3.14,3.87)	< 0.001	3.59(3.23,3.98)	< 0.001	2.21(1.94,2.51)	< 0.001
Prediabetes regression						
Group 1	Ref.		Ref.		Ref.	
Group 2	0.69(0.62,0.77)	< 0.001	0.69(0.62,0.78)	< 0.001	0.70(0.61,0.79)	< 0.001
Group 3	0.59(0.51,0.68)	< 0.001	0.60(0.52,0.70)	< 0.001	0.61(0.51,0.73)	< 0.001
Group 4	0.53(0.43,0.66)	< 0.001	0.54(0.44,0.67)	< 0.001	0.56(0.44,0.71)	< 0.001
Prediabetes progression						
Group 1	Ref.		Ref.		Ref.	
Group 2	1.21(1.06,1.38)	0.004	1.25(1.09,1.42)	0.001	1.21(1.03,1.41)	0.017
Group 3	1.46(1.24,1.73)	< 0.001	1.54(1.30,1.82)	< 0.001	1.47(1.21,1.79)	< 0.001
Group 4	1.83(1.48,2.25)	< 0.001	1.95(1.57,2.41)	< 0.001	1.69(1.32,2.16)	< 0.001

Model 1: Unadjusted;

Model 2: Adjusted for age and gender;

Model 3: Model 2+smoking status, exercise, drinking status, diet, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, hypertension and dyslipidemia

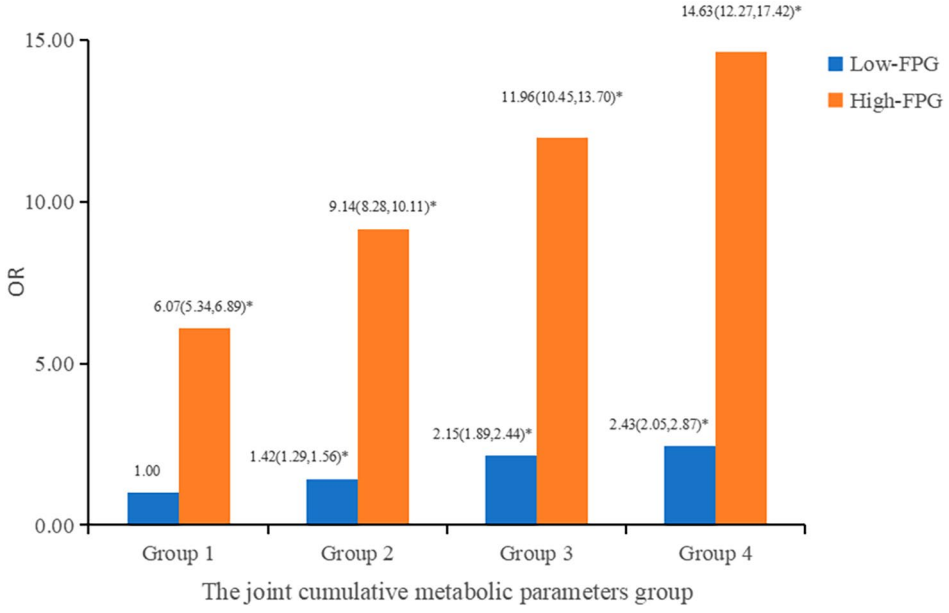

Fig. 2 Addition effect of cumulative metabolic parameters and baseline fasting plasma glucose level versus Type 2 diabetes incidence. Adjusted for age, gender, smoking status, exercise, drinking status, diet, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, hypertension and dyslipidemia

*$P<0.05$

between FPG and cumulative metabolic parameters (*P* for interaction = 0.034).

Sensitive analysis

Subgroups analyses were performed to stratify the association between joint cumulative metabolic parameters and T2D by age, gender, hypertension status and dyslipidemia status, as depicted in Figure S4. The results of the subgroup analyses were consistent with the result of total participants analysis for T2D risk.

In the restricted cubic spline regression models, the association between Cum-BRI, Cum-BMI, Cum-PP, Cum-TG, and Cum-HDL with risk of incident T2D was nonlinear ($P_{Nonlinear} < 0.05$) (Fig. 4). When the

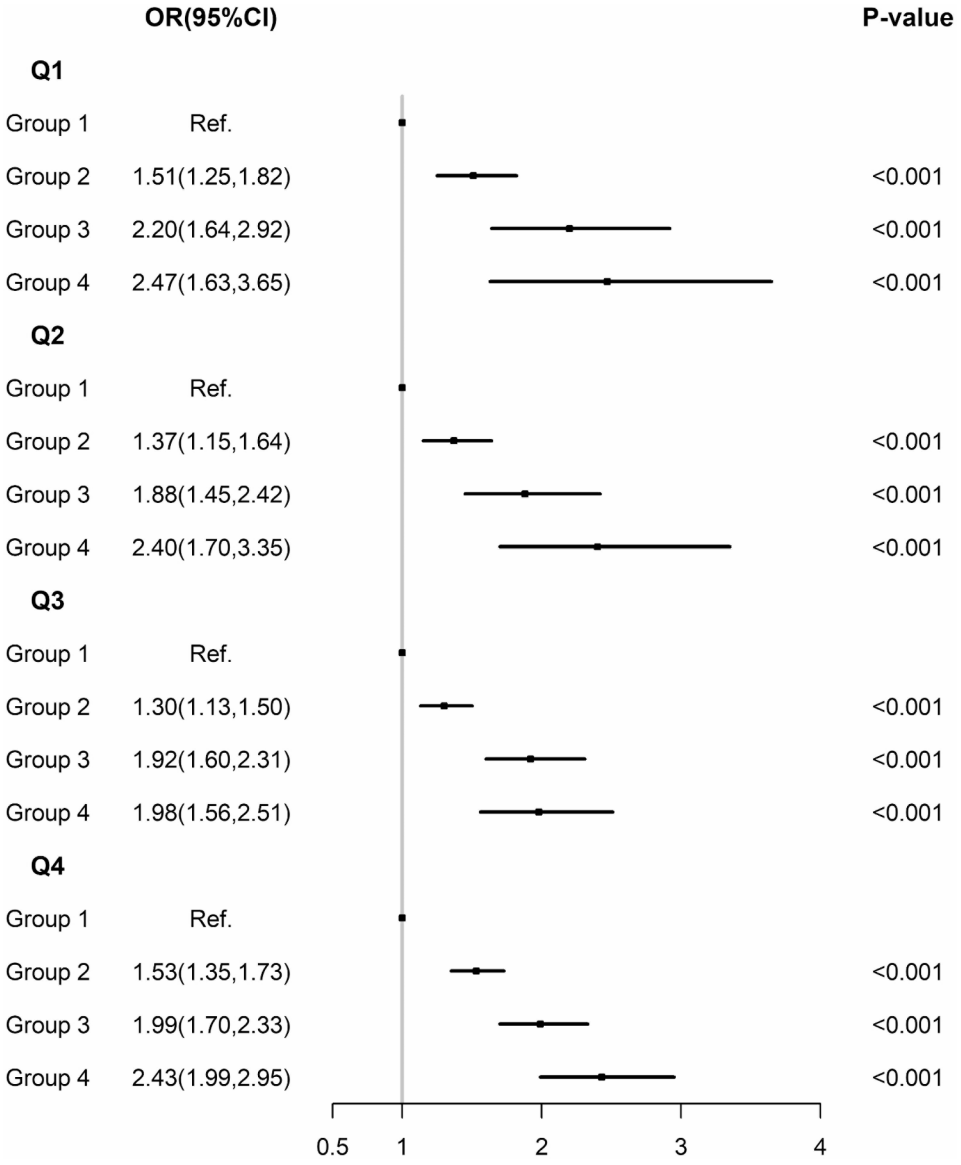

Fig. 3 The joint effect of cumulative metabolic parameters on Type 2 diabetes in populations with different baseline fasting plasma glucose levels. *P* for interaction = 0.034. Adjusted for age, gender, smoking status, exercise, drinking status, diet, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, hypertension and dyslipidemia

Cum-BRI ≥ 4.75, Cum-BMI ≥ 23.25, Cum-PP ≥ 53.45, Cum-TG ≥ 1.37, and cum-HDL ≤ 1.38, the risk of incident T2D increases rapidly. We categorized the patients into two distinct groups by employing the cut-off values derived from the RCS analysis. The baseline characteristics of all the study participants across the cumulative metabolic parameters group are presented in Table S2. We got the same results in the analysis of the joint effect of cumulative metabolic parameters on T2D. The adjusted ORs for new-onset T2D were 1.40(1.19,1.65) for Group 2, 1.87(1.59,2.21) for Group 3 and 2.33(1.98,2.76) for Group 4, when compared with Group 1 (Table 3).

Discussion

Our study brings forth a comprehensive analysis focusing on the joint effects of cumulative metabolic parameters (BRI, BMI, PP, TG, and HDL) on the risk of T2D development, prediabetes regression and progression in the Chinese population. We presented further proof of the harmful effects of metabolic parameters on diabetes morbidity. Besides, high exposure to BMI, BRI, PP, TG, and low exposure to HDL in the long term could increase the risk of prediabetes progression to diabetes. The cumulative metabolic parameters combined with high levels of normal FPG could significantly increase the risk of developing T2D. Therefore, it is necessary to continuously monitor the metabolic parameters and FPG levels

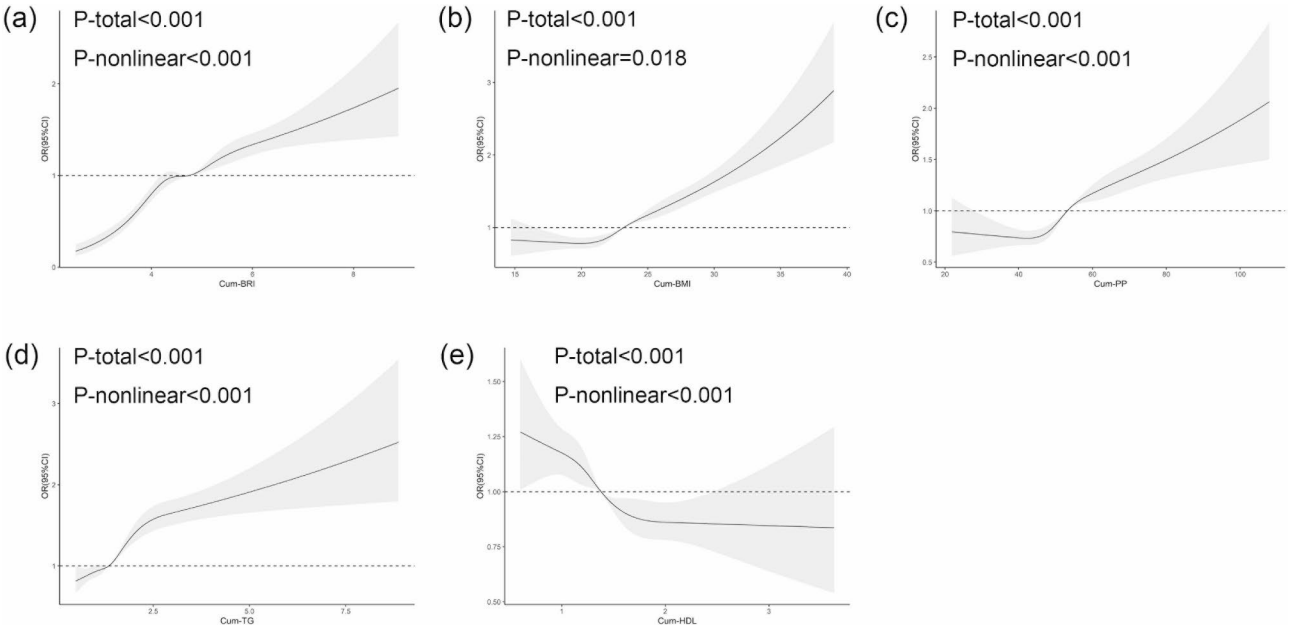

Fig. 4 Adjusted cubic spline model of the association between cumulative metabolic parameters and risk of Type 2 diabetes
Adjusted for age, gender, smoking status, exercise, drinking status, diet, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, hypertension and dyslipidemia

Table 3 The joint effect of cumulative metabolic parameters on T2D in sensitive analysis

Group	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Group 1	Ref.		Ref.		Ref.	
Group 2	1.42(1.25,1.62)	< 0.001	1.43(1.26,1.63)	< 0.001	1.40(1.19,1.65)	< 0.001
Group 3	2.21(1.94,2.53)	< 0.001	2.26(1.98,2.58)	< 0.001	1.87(1.59,2.21)	< 0.001
Group 4	3.17(2.79,3.61)	< 0.001	3.25(2.86,3.71)	< 0.001	2.33(1.98,2.76)	< 0.001

Model 1: Unadjusted;

Model 2: Adjusted for age and gender;

Model 3: Model 2+smoking status, exercise, drinking status, diet, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, hypertension and dyslipidemia

of middle-aged and older adults. Effective intervention in populations with high metabolic parameters and high level of normal FPG could reduce the risk of T2D.

The elevation of BRI and BMI as indicators of adiposity and obesity are established as a significant risk for T2D development [20, 21], and our study further substantiates these findings. BMI has been recognized as a traditional risk factor for T2D and has been confirmed in many studies [22, 23]. Findings from the Coronary Artery Risk Development in Young Adults study showed that the cumulative burden of higher BMI was associated with a higher risk of incident prediabetes (HR=2.064, 95% CI: 1.793–2.377) [24]. Results were consistent in our analyses. The BRI was a new body measure, combined height, waistline, and weight, that can more comprehensively reflect visceral fat [17]. A high level of baseline BRI was associated with a higher risk of T2D, hypertension and cardiovascular disease [23, 25, 26]. Our study confirmed that cumulative exposure to high BRI can significantly increase the risk of T2D and increase the risk of prediabetes progressing to diabetes. The potential mechanisms of obesity increase the risk of T2D are diverse and complex, involving an intricate interplay between genetic, metabolic, and lifestyle factors. These mechanisms can be broadly categorized into those related to insulin resistance [27], β-cell dysfunction [28] and inflammation [29].

The scientific evidence consistently suggests that hypertension substantially increases the risk of developing T2D [30, 31]. Previous studies mainly focused on the impact of elevated systolic or diastolic blood pressure on diabetes [32, 33]. Increased pulse pressure, a marker of arterial stiffness [34], emerged from our analyses as a notable risk factor. A retrospective cohort study conducted by Jia et al. [35]. demonstrated the relationship between PP and diabetes. However, they only found this association in females but not in males. There are few existing associations between PP and the risk of developing T2D, and the conclusions are inconsisten [36–38].

The reason for inconsistent results may be due to an inconsistent study population. Our results showed that high-level cumulative PP increased the risk of T2D and prediabetes progression not only in females but also in males. Hypertension is often accompanied by hyperinsulinemia and impaired insulin-mediated glucose uptake [39]. Elevated blood pressure can lead to endothelial dysfunction and impair the delivery of insulin and glucose to skeletal muscle cells, augmenting insulin resistance [40]. Our data provide fresh insights into the long-term relationship and pay attention to the role taken by PP in prediabetes, which may be of clinical interest in devising strategies for early intervention in individuals with elevated PP, an aspect not extensively explored in previous diabetes risk assessments.

In recent years, many studies have proposed that triglyceride-glucose index (TyG) and TG/HDL can be used as alternative indicators of insulin resistance and are related to the risk of diabetes, hypertension and CVD [41, 42]. A cohort study confirmed that cumulative higher TG and lower HDL levels were associated with increased diabetes risk [43], aligning with our results. TG and HDL cholesterol are essential considerations when investigating metabolic risk factors for T2D [43]. The relationship between them is bidirectional, where increased TGs can contribute to insulin resistance and T2D, and vice versa. An overproduction of very low-density lipoprotein (VLDL), the primary carrier of TGs in the bloodstream, is a characteristic feature of insulin resistance. Excessive delivery of FFAs to the liver stimulates VLDL synthesis, and increased VLDL release into the circulation contributes to the elevated levels of TGs. This high TG state may exacerbate insulin resistance by impairing insulin signal and exacerbating glucose intolerance [44]. HDL through its various components like apolipoprotein A-I and sphingosine-1-phosphate, is posited to influence glucose metabolism by modulating pancreatic β-cell function and enhancing insulin sensitivity [45, 46].

Furthermore, we examined the potential influence of baseline FPG level on the observed associations between metabolic parameters and T2D onset. Our analysis suggests that these associations may be more pronounced in high-level FPG. Previous studies have shown that individuals with higher FPG are more likely to develop T2D, even at normal levels [47]. Our study extrapolates upon their interaction, illustrating a more pronounced T2D risk when these abnormality parameters cluster together.

This study had several advantages. To our knowledge, our study firstly quantified the separate and joint cumulative effects of metabolic parameters on T2D morbidity based on a large population. Secondly, we also explored the effect on prediabetes regression and progression, which has been ignored in other studies. In addition, we investigated the interaction effect of FPG and cumulative metabolic parameters on the association. However, our study is susceptible to some restrictions. First, our follow-up time is relatively short, and the cumulative effects of exposure may vary after a longer follow-up time. In the future, we will conduct longer follow-up studies to further verify this association. Second, our study did not control for family history and medication history, which may affect our results.

Conclusion

In summary, we discovered that high cumulative exposure to BRI, BMI, PP, TG and low cumulative exposure to HDL could significantly increase the risk for T2D morbidity. Participants with more high-cumulative metabolic parameters were associated with higher risk of incident T2D. The combination of high-cumulative metabolic parameters and high-level FPG significantly enhances the risk of T2D. Furthermore, these associations should not be ignored in prediabetes regression and progression. Our research provides a basis for the prevention and control of T2D. Populations exposed to high metabolic parameters for a long time should be focused on. Besides, it is also necessary for early primary prevention and management of individuals with healthy blood sugar levels.

Abbreviations

BMI	Body mass index
BRI	Body roundness index
PP	Pulse pressure
TG	Triglycerides
HDL	High-density lipoprotein cholesterol
FPG	Fasting plasma glucose
T2D	Type 2 diabetes
IDF	International Diabetes Federation
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TC	Total cholesterol
LDL	Low density lipoprotein
OR	Odds ratio
CI	Confidence interval
RCS	Restricted cubic spline
VLDL	Very low-density lipoprotein

Supplementary Information

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Supplementary Material 1

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Author contributions

WY.X., YH.L. and H.L. conceived of and designed the study. WY.X., YH.L., YB.F., XL.Z., K.Z., and H.L. acquired the data. WY.X., YH.L conducted the data analysis. YB.F., XL.Z. and K.Z. searched the literature. WY.X. and YH.L interpreted the data and drafted the manuscript. H.L. was the project leader and participated in all the work. All authors read and approved the final manuscript.

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Data availability
The datasets are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study complied with the Declaration of Helsinki and all participants were informed at enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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