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Application of the C-reactive protein-triglyceride glucose index in predicting the risk of new-onset diabetes in the general population aged 45 years and older: a national prospective cohort study

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Abstract

Objective Triglyceride-to-glucose index (TyG index) and inflammation are both independent risk factors for diabetes. However, only a few studies have combined TyG index with inflammation indices to predict diabetes risk. C-reactive protein-triglyceride-to-glucose index (CTI index), as a new type of lipid and inflammation marker, can comprehensively assess the severity of insulin resistance and inflammation. This study explores the association between CTI index and diabetes risk.

Methods We recruited a total of 6,728 participants from the China Health and Retirement Longitudinal Study (CHARLS) who had no history of diabetes at baseline. After determining the key predictors using the least absolute shrinkage and selection operator (LASSO) technique, the relationship between the CTI index and the risk of new-onset diabetes was assessed using multivariate COX regression, the mediating effect between insulin resistance and inflammatory indicators was explored, and restricted cubic splines (RCS) were applied to explore the association between the CTI index and the risk of new-onset diabetes. In addition, we used decision tree analysis to identify people at high risk of diabetes, calculated time-dependent Harrell's C index (95% CI) to assess the predictive ability of TyG, CRP, CTI and CRP + TyG for new-onset diabetes, and further calculated IDI and NRI to assess the predictive ability of CTI and TyG. Finally, we performed subgroup analyses for different subgroups using stratified COX proportional hazard regression models; and a series of sensitivity analyses were performed to verify the robustness of our results.

Results The incidence of diabetes was 15.9% during the 9-year follow-up. COX regression analysis showed that the risk ratio for diabetes increased gradually with an increase in the CTI index. The RCS curve confirmed the existence of a linear relationship between the CTI index and the risk of diabetes. Decision tree analysis showed that the CTI index was a key indicator of diabetes risk. In addition, the CTI index is a much better predictor of the onset of diabetes risk

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than the TyG index, as demonstrated by the integrated discrimination improvement (IDI) and net reclassification improvement (NRI).

Conclusion An increase in CTI levels is closely related to diabetes risk, and the CTI index may become a unique predictor of diabetes risk.

Clinical trial number Not applicable.

Keywords C-reactive protein-triglyceride glucose, New-onset diabetes, Aged 45 years and older, Cohort study, CHARLS

Introduction

Diabetes is the third leading cause of non-communicable disease after cardiovascular disease and tumours, and has become a major global healthcare issue [1–3]. Diabetes is the fastest growing disease of this century, and its morbidity and mortality rates are gradually increasing. By 2021, the number of adults with diabetes detected worldwide will reach 537 million, of which 6.7 million will die, and many people with diabetes will not be detected for various reasons [4–6]. As a country with an ageing population, China is experiencing a rapidly increasing burden of diabetes due to economic growth and urbanisation [7, 8]. Existing studies [7, 9, 10] have shown that the overall prevalence of diabetes in China has increased to 12.8%, and the number of adults with diabetes in China was estimated to be 111.6 million in 2019, and will reach 639 million by 2045. This has a serious impact on people's physical and mental health and quality of life, and can even lead to premature death from various diseases. Therefore, the identification and management of diabetes risk factors is crucial to building a healthy China.

However, most of the existing studies focus on the impact of insulin resistance on diabetes risk, ignoring the fact that inflammatory risk is also a key factor in the development of diabetes [11–15]. Therefore, we question the reliability of diabetes risk prediction models that rely solely on insulin resistance. The CTI index is an emerging indicator that combines C-reactive protein and the triglyceride glucose index (TyG index). In addition to being a good reflection of the body's metabolic state, it can also detect the collective impact of inflammation [16–18]. In addition, the CTI index has good predictive value in predicting the incidence of stroke in hypertensive populations, exploring the prognosis of cancer cachexia patients, the risk of erectile dysfunction, depressive symptoms, and cancer mortality in the general population [18–23]. However, no studies have yet investigated the association between the CTI index and the risk of developing diabetes. Therefore, this study sought to use data from the China Health and Retirement Longitudinal Study (CHARLS) to explore the effectiveness of the CTI index in predicting the risk of developing diabetes among middle-aged and elderly Chinese people, with a view to providing a new perspective on diabetes prevention and health care and treatment management.

Method

Study design

This is a prospective cohort study. All participants are from CHARLS, a national cohort study that began in 2011. The study focuses particularly on the middle-aged and elderly population in China, and promotes interdisciplinary research on China's ageing population by assessing the economic, social and health status of people aged 45 and above. So far, data surveys have been completed in 2011, 2013, 2015, 2018 and 2020. Initially, 17,708 participants from 10,257 households in 450 communities in 150 counties in 28 provinces were recruited using a multi-stage probability-proportional-to-size sampling method for the first wave of the CHARLS survey. Since then, 648 people under the age of 45, 6923 people with fasting blood glucose(FBG), triglycerides(TG), and C-reactive protein(CRP) deficiencies, 1660 people who already had diabetes at baseline, and 1749 people whose diabetes status was unknown during the follow-up process were excluded. A total of 6728 subjects participated in this study(Fig. 1). The CHARLS study received ethical approval from the Biomedical Ethics Committee of Peking University (IRB00001052-11015). All participants have signed informed consent forms. The data set related to this study is publicly accessible on the CHARLS project website.

Missing data processing

In our study, we found gender (119, 1.769%), hypertension (21, 0.312%), dyslipidemia (60, 0.892%), cardiovascular disease (8, 0.119%), alcohol status (8, 0.119%), smoking status (115, 1.709%), Systolic blood pressure(SBP)(931, 13.838%), Diastolic blood pressure(DBP) (932, 13.853%), Waist-height ratio(WHtR)(944, 14.031%), Low-dendity lipoproteins cholesterol(LDL-C) (1, 0.015%), Glycated hemoglobin(GHb) (50,0.743%), and education level (5, 0.074%). To reduce bias caused by missing variables, missing data were estimated using multiple interpolation. (The number of iterations was 5, and the regression model was linear regression.)

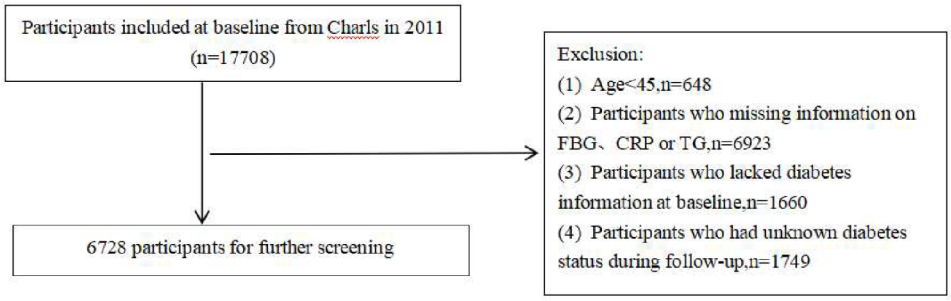

Fig. 1 A flow chart illustrating the selection of the study population

Data collection

Every two years, trained interviewers collected demographic information (e.g., age, sex, and marital status), health status (e.g., smoking and drinking), diagnosed chronic diseases, and health-related behaviours from the participants and their families using a standardised questionnaire administered through personal interviews. Notably, in 2011 and 2015, after obtaining information on the participants' height, weight, blood pressure, etc., venous blood samples were collected from each subject and analysed biochemically under the guidance of staff with professional medical training. Unfortunately, not all participants reported that they had fasted strictly for 8 h before blood collection.

Definition of new-onset diabetes

The diagnosis of new-onset diabetes was based on self-reported data and laboratory tests. Respondents were classified as diabetic when they answered 'yes' to the interviewer's question, 'Have you been diagnosed with diabetes by a doctor? Respondents were also classified as diabetic if they had a blood test indicator of FBG level ≥ 126 mg/dl and/or HbAlc level ≥ 6.5%. Subjects with diabetes in 2011 were excluded, and if patients were diagnosed with diabetes after this period until the follow-up period in 2020, they were included in the study according to our definition of diabetic patients. The interval between the assessment and the final assessment was calculated to determine the time of diabetes onset. For patients who did not report diabetes during follow-up, we determined the duration of follow-up based on the interval between the baseline assessment and the final survey. In addition, the incidence of diabetes was coded as binary (diabetes = 1, no diabetes = 0) as an outcome of interest during this study.

CTI calculation

CTI is defined as 0.412*Ln(CRP[mg/dl]) + Ln(TG[mg/dl]*FBG[mg/dl])/2.

Covariates

A selection of potential predictors that may influence diabetes were chosen based on socio-demographic characteristics, lifestyle behaviours, current health status and clinical expertise. These included gender (male, female), age (< 60, ≥ 60), place of residence (urban, rural), marital status (married, other), education level (below primary, primary, secondary and above), smoking and drinking status (never, past, current), hypertension, dyslipidemia, and cardiovascular disease. Laboratory data: DBP, SBP, BMI, FBG, GHb, total cholesterol (TC), TG, high-density lipoprotein (HDL-C), LDL-C, TyG index, CRP, CTI.

In addition, hypertension was defined as SBP ≥ 140 mmHg and DBP ≥ 90 mmHg according to the reference standards set by the World Health Organization, taking into account current use of antihypertensive medication or self-reported history of hypertension. Dyslipidemia was defined as a TC level ≥ 240 mg/dL, TG level ≥ 150 mg/dL, LDL-C level ≥ 160 mg/dL, HDL-C level < 40 mg/dL, current use of lipid-lowering medication, or self-reported history of dyslipidemia.

Statistical analysis

Data analysis was performed using IBM SPSS 26.0 and the R language. A two-sided P value of < 0.05 was considered statistically significant. Data are presented as the mean and standard deviation for continuous variables with normal or approximately normal distributions, and the median and interquartile range for continuous variables with non-normal distributions. Categorical variables are described using frequencies and percentages. An analysis of variance or rank sum test was performed on the baseline data in each group. In addition, the least absolute shrinkage and selection operator (LASSO) technique was used to identify key predictors. Furthermore, to assess the CTI index and the incidence of new-onset diabetes, we calculated the incidence rate per 1000 person-years for each outcome.

Next, we analysed the correlation between the CTI index and new-onset diabetes using a multivariate Cox proportional hazards regression model, assessed the risk assumption using Schoenfeld residuals, and did not

observe a significant violation of the proportional hazards assumption ($P > 0.05$), indicating that the model assumptions were met. Kaplan-Meier survival analysis was used to assess the cumulative incidence of the CTI index and new-onset diabetes and to generate a cumulative risk curve. using the log-rank test to assess group differences ($P < 0.005$) and testing for multiple co-linearity between covariates (VIF < 5). Four models were constructed: Model 1 (without adjustment for any covariates), Model 2 (adjusted for age and sex), Model 3 (adjusted for age, sex, marital status, place of residence, smoking and drinking status, education level and WHtR), and Model 4 (plus hypertension, dyslipidemia and cardiovascular disease). Also, to explore the interaction between CRP and TyG index, which constitute the CTI index, we conducted a mediation analysis.

In addition, to illustrate the dose-response relationship between the CTI index and the risk of new-onset diabetes, we used restricted cubic spline (RCS) function analysis with 4 knots. We then used decision tree analysis to identify people at high risk of developing new-onset diabetes. We calculated time-dependent Harrell's C index (95% CI) to assess the predictive ability of TyG, CRP, CTI and CRP + TyG for new-onset diabetes, and further calculated IDI and NRI to assess the predictive ability of CTI and TyG. Finally, we performed subgroup analyses for different subgroups (age, gender, marital status, education level, BMI, hypertension, dyslipidemia, and cardiovascular disease) using stratified COX proportional hazard regression models. We also performed a series of sensitivity analyses to verify the robustness of our results.

Results

Participants' baseline characteristics There were 6,728 participants in this study, including 3,024 men and 3,704 women. The mean age was 58.10 ± 8.66 years. After stratifying the participants into quartiles according to their CTI index, we found that FBG, GHb, TC, TG, DBP, SBP, WHtR, TyG, female, urban, dyslipidemia, hypertension, and cardiovascular disease significantly increased with increasing CTI index, while HDL-C, male, and rural decreased with increasing CTI index. LASSO regression was used to initially select risk factors, and 10-fold cross-validation was used to determine the optimal λ value. It was found that CTI, age, gender, marital status, place of residence, education level, smoking and drinking status, WHtR, hypertension, dyslipidemia, and cardiovascular disease may be predictors.(Table 1)(Fig. 2).

Incidence of new-onset diabetes

A total of 1069 participants in this study had diabetes, and the incidence of new-onset diabetes was 15.9%. The prevalence of new-onset diabetes in the CTI quartiles was Q1: 9.9%, Q2: 12.3%, Q3: 18.1%, and Q4: 23.2%. As the CTI index increases, the incidence of diabetes gradually increases (Table 2).

Association of CTI index with risk of new-onset diabetes

To explore the association between the CTI index and the risk of new-onset diabetes, we developed four COX proportional hazard regression models. The multivariable model (Model 4) showed that for every 10-unit increase in the CTI index, the risk of new-onset diabetes increased by 45% (HR = 1.45, 95%CI: 1.32–1.59). In addition, we further converted the CTI index from a continuous variable to a categorical variable based on quartiles. The multifactor model (Model 4) showed that participants in the third quartile (Q3) had a 59% increased risk of developing diabetes (HR = 1.59, 95%CI: 1.31–1.94) compared to those in the lowest quartile (Q1), and participants in the fourth quartile (Q4) had a 92% increased risk of developing diabetes (HR = 1.92, 95%CI: 1.57–2.36). (Table 3)(Fig. 3).

Mediating effect

In order to investigate whether there is a mutual influence between CRP and the TyG index, which form the CTI index, we conducted a mediating analysis. The mediating analysis showed that there is no influence between CRP and the TyG index.(Table 4).

Restricted cubic spline(RCS) study of the relationship between the CTI index and new-onset diabetes

To explore the trend between the CTI index and the risk of new-onset diabetes, we used a RCS curve model with 4 knots to model the association according to Model 4. In the fully adjusted model (Model 4), P for overall < 0.001, P for nonlinear = 0.648.(Fig. 4).

Decision tree analysis

The root node of this model shows that the incidence of new-onset diabetes is affected by factors such as the CTI index, hypertension, and cardiovascular disease. From our analysis, the DT model has an accuracy rate of 84.1%. The decision tree model results show that among Chinese middle-aged and elderly people aged 45 and above, the CTI index is the most important risk factor for new-onset diabetes.(Fig. 5).

Time-dependent Harrel's C index

To better explore the predictive ability of the CTI index, we calculated the time-dependent Harrel's C index for CTI, CRP, TyG, and CRP + TyG, respectively. We found that the CTI index showed the highest C index for new-onset diabetes.(Table 5).

Table 1 Baseline characteristics of the study population based on new-onset diabetes

Characteristic	Total (*N* = 6728)	Q1 (*n* = 1682)	Q2 (*n* = 1682)	Q3 (*n* = 1682)	Q4 (*n* = 1682)	*P*
Age(years)	58.10 ± 8.66	57.19 ± 8.67	58.12 ± 8.75	58.57 ± 8.54	58.52 ± 8.61	<0.001
FBG(mg/dl)	100.30 ± 10.87	95.71 ± 11.04	99.03 ± 10.15	101.22 ± 9.84	105.25 ± 10.14	<0.001
GHb(%)	5.11 ± 0.39	5.06 ± 0.37	5.09 ± 0.39	5.12 ± 0.38	5.19 ± 0.41	<0.001
TC(mg/dl)	193.00 ± 37.10	182.45 ± 33.55	190.66 ± 34.51	195.33 ± 35.59	203.54 ± 41.13	<0.001
TG(mg/dl)	120.12 ± 74.64	66.20 ± 19.17	93.79 ± 26.76	123.11 ± 39.66	197.37 ± 100.29	<0.001
HDL-C(mg/dl)	52.08 ± 14.89	60.64 ± 14.82	54.92 ± 13.59	49.80 ± 12.84	42.95 ± 12.19	<0.001
LDL-C(mg/dl)	118.03 ± 33.56	110.80 ± 29.16	119.48 ± 31.35	122.61 ± 32.86	119.24 ± 38.94	<0.001
DBP(mmHg)	74.47 ± 11。98	72.22 ± 11.49	73.57 ± 11.77	75.22 ± 12.26	76.86 ± 11.89	<0.001
SBP(mmHg)	126.85 ± 20.50	122.66 ± 19.47	125.51 ± 19.73	128.25 ± 20.57	130.99 ± 21.26	<0.001
WHtR	0.53 ± 0.13	0.50 ± 0.07	0.53 ± 0.17	0.54 ± 0.16	0.56 ± 0.08	<0.001
CRP(mg/dl)	0.93 (0.52,1.92)	0.45 (0.32,0.67)	0.75 (0.49,1.21)	1.23 (0.73,2.12)	2.42 (1.29,5.05)	<0.001
TyG	8.56 ± 0.54	8.01 ± 0.30	8.40 ± 0.28	8.68 ± 0.33	9.14 ± 0.48	<0.001
CTI	5.74 ± 0.73	4.89 ± 0.28	5.46 ± 0.14	5.94 ± 0.15	6.71 ± 0.41	<0.001
Gender(%)						0.001
Male	3024 (44.9)	811 (48.2)	781 (46.4)	722 (42.9)	710 (42.2)	
Female	3704 (55.1)	871 (51.8)	901 (53.6)	960 (57.1)	972 (57.8)	
Residence status(%)						<0.001
Urban	2329 (41.9)	497 (29.5)	518 (30.8)	609 (36.2)	705 (41.9)	
Rural	4399 (58.1)	1185 (70.5)	1164 (69.2)	1073 (63.8)	977 (58.1)	
Marital status(%)						0.714
Married	6046 (89.9)	1523 (90.5)	1512 (89.9)	1504 (89.4)	1507 (89.6)	
Non-married	682 (10.1)	159 (9.5)	170 (10.1)	178 (10.6)	175 (10.4)	
Smoking status(%)						0.011
Never	4222 (62.8)	1029 (61.2)	1055 (62.7)	1071 (63.7)	1067 (63.4)	
Ever	514 (7.6)	104 (6.2)	132 (7.8)	130 (7.7)	148 (8.8)	
Current	1992 (29.6)	549 (32.6)	495 (29.4)	481 (28.6)	467 (27.8)	
Drinking status(%)						0.002
Never	3965 (58.9)	952 (56.6)	960(57.1)	1013 (60.2)	1040 (61.8)	
Ever	543 (8.1)	128 (7.6)	129 (7.7)	140 (8.3)	146 (8.7)	
Current	2220 (33.0)	602 (35.8)	593 (35.3)	529 (31.5)	496 (29.5)	
Education level(%)						0.019
Below elementary school	3138 (46.6)	791 (47.0)	783 (46.6)	805 (47.9)	759 (15.1)	
Elementary school	1451 (21.6)	341 (20.3)	406 (24.1)	332 (19.7)	372 (22.1)	
Secondary school and higher	2139 (31.8)	550 (32.7)	493 (29.3)	545 (32.4)	551 (32.8)	
Dyslipidemia(%)						<0.001
No	3717 (55.2)	1405 (83.5)	1193 (70.9)	816 (48.5)	303 (18.0)	
Yes	3011 (44.8)	277 (16.5)	489 (29.1)	866 (51.5)	1379 (82.0)	
Hypertension(%)						<0.001
No	2809 (41.8)	1164 (69.2)	1051 (62.5)	904 (53.7)	800 (47.6)	
Yes	3919 (58.2)	518 (30.8)	631 (37.5)	778 (46.3)	882 (52.4)	
Cardiovascular disease(%)						<0.001
No	5922 (88.0)	1540 (91.6)	1518 (90.2)	1457 (86.6)	1407 (83.7)	
Yes	806 (12.0)	142 (8.4)	164 (9.8)	225 (13.4)	275 (16.3)	
Diabetes(%)						<0.001
No	5659 (84.1)	1515 (90.1)	1475 (87.7)	1377 (81.9)	1292 (76.8)	
Yes	1069 (15.9)	167 (9.9)	207 (12.3)	305 (18.1)	390 (23.2)	

Improvement of the CTI index for predicting new-onset diabetes

We found that the CTI index with the addition of CRP resulted in an IDI of 0.003 (95% CI: 0.001–0.007, $P = 0.016$) and an NRI of 0.076 (95% CI: 0.009–0.126, $P = 0.024$) compared to the TyG index alone. This result shows that the CTI index has improved predictive ability compared to the TyG index.(Table 6).

Subgroup analysis

We examined possible variations in the association between the CTI index and the risk of new-onset diabetes

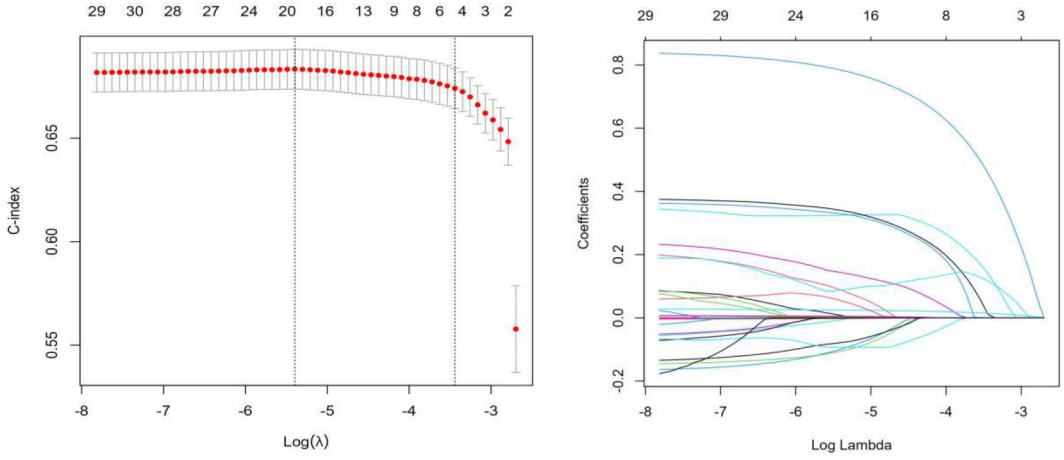

Fig. 2 Ten-fold cross-validation for the best variable selection The tenfold cross-validation filters λ

Table 2 Incidence of new onset diabetes

CTI	Participants(*n*)	Diabetes events(*n*)	Incidence rate(95%)(%)
Total	6728	1069	13.71 (12.94,14.47)
Q1	1682	167	9.03 (7.72,10.34)
Q2	1682	207	10.96 (9.55,12.37)
Q3	1682	305	15.35 (13.76,16.94)
Q4	1682	390	18.82 (17.14,20.51)
P for trend			<0.001

within different subgroups. We found that the association between the CTI index and the risk of new-onset diabetes was not affected by age, marital status, place of residence, education level, hypertension, dyslipidemia, and cardiovascular disease(P for interaction > 0.005). However, gender differences may have an impact on the association between the CTI index and the risk of new-onset diabetes(P for interaction < 0.005).(Table 7).

Sensitivity analysis

To assess the robustness of the results between the CTI index and the risk of new-onset diabetes. The CTI index

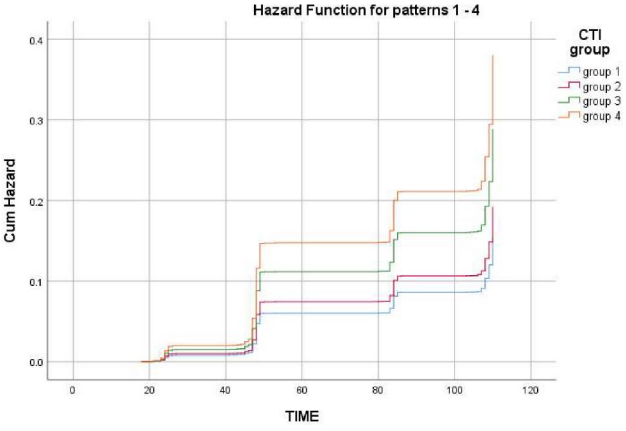

Fig. 3 K-M plot of diabetes incidence by CTI

was initially divided into quartiles, and then re-entered into the regression model in its modified categorical form. It was observed that the range of effect sizes between the groups was consistent, and this pattern of effect sizes was consistent with that observed when the CTI index was assessed as a continuous variable. (Table 3).

Table 3 Multifactor Cox proportional risk regression between CTI and risk of new-onset diabetes

	Incidence rate(1000PY)	Model 1	*P*	Model 2	*P*	Model 3	*P*	Model 4	*P*
CTI index									
Per SD increase	18.87	1.64 (1.52,1.77)	<0.001	1.62 (1.50,1.75)	<0.001	1.62 (1.50,1.75)	<0.001	1.45 (1.32,159)	<0.001
Quartiles									
Q1	11.79	Ref		Ref		Ref		Ref	
Q2	14.62	1.26 (1.03,1.55)	0.026	1.24 (1.01,1.52)	0.040	1.22 (0.99,1.50)	0.057	1.15 (0.94,0.141)	0.178
Q3	21.54	1.92 (1.59,2.31)	<0.001	1.86 (1.54,2.25)	<0.001	1.84 (1.52,2.22)	<0.001	1.59 (1.31,1.94)	<0.001
Q4	27.54	2.53 (2.11,3.03)	<0.001	2.46 (2.05,2.95)	<0.001	2.44 (2.03,2.93)	<0.001	1.92 (1.57,2.36)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001	

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, marital status, residence, smoking and drinking status, education level and WHtR

Model 4: plus hypertension, dyslipidemia and cardiovascular disease

Table 4 Mediating effect between CRP and TyG

Intermediate variable	CRP and TyG Association		Proportion mediated
	Total HR(95%)	Direct HR(95%)	
Model 1			
CRP	0.087 (0.071,0103)	0.087 (0.071,0.103)	0%
TyG	0.003 (0.001,0.004)	0.003 (0.001,0.004)	0%
Model 2			
CRP	0.087 (0.071,0103)	0.087 (0.071,0103)	0%
TyG	0.002 (0.001,0.004)	0.002 (0.001,0.004)	0%
Model 3			
CRP	0.083 (0.067,0.099)	0.083 (0.067,0.099)	0%
TyG	0.002 (0.001,0.004)	0.002 (0.001,0.004)	0%
Model 4			
CRP	0.059 (0.039,0.078)	0.060 (0.040,0.079)	0%
TyG	0.002 (0.001,0.003)	0.002 (0.001,0.004)	0%

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, marital status, residence, smoking and drinking status, education level and WHtR

Model 4: plus hypertension, dyslipidemia and cardiovascular disease

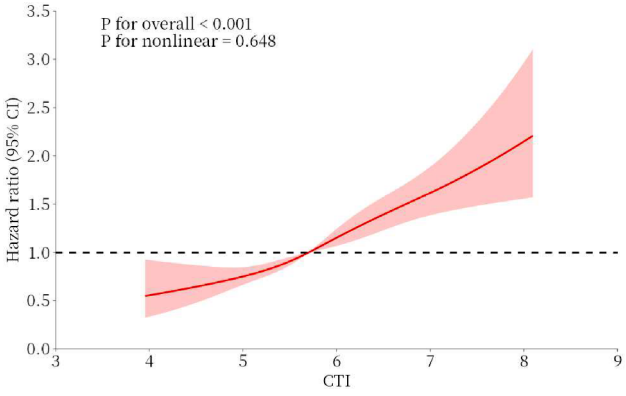

Fig. 4 RCS curve between CTI and diabetes incidence

In addition, to further verify the relationship between the CTI index and the risk of new-onset diabetes, the CTI index was grouped using tertiles. The multivariable model (Model 4) showed that a CTI index in the middle tertile was associated with a 36% increased risk of new diabetes, and a CTI index in the high tertile was associated with an 81% increased risk of new diabetes.(Table 8).

Finally, additional analyses were conducted to verify the strength and consistency of the relationship between CTI and risk of new diabetes by focusing on specific populations and adjusting for various health factors. Based on all sensitivity analyses, our findings are robust.(Table 9).

Table 5 Time-dependent Harrel's C index

	Cindex	*P*
CTI	0.611(0.593–0.629)	<0.001
CRP	0.571(0.553–0.589)	<0.001
TYG	0.595(0.577–0.613)	<0.001
CRP + TYG	0.598(0.590–0.616)	<0.001

Table 6 Improvement of the CTI index for predicting new-onset diabetes

	Est.	Lower	Upper	*p*-value
IDI	0.003	0.001	0.007	0.016
NRI	0.076	0.009	0.126	0.024

Discussion

Our study found that the CTI index, as a new composite index of IR level and inflammation, has high research value in predicting the risk of diabetes. In addition, our study found that there is a linear relationship between the CTI index and the outcome of diabetes, indicating that a higher CTI index is associated with a higher risk of diabetes. Mediation analysis showed that CRP and TyG index, which constitute the CTI index, have no interaction in the risk of diabetes. In addition, this study also showed that the CTI index is more valuable in predicting the risk of diabetes than the TyG index. Subgroup analysis showed that the CTI index was not affected by age, gender, marital status, place of residence, education level, BMI, hypertension, dyslipidemia, and cardiovascular disease.

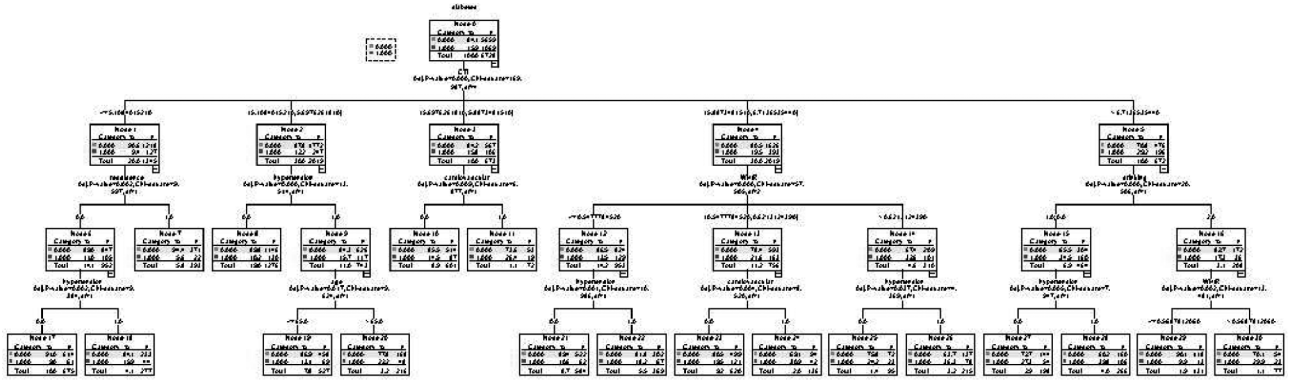

Fig. 5 CTI decision tree analysis

Table 7 Subgroup analysis

Subgroups	HR (95%CI)	*P*	*P* for interaction
Age			0.680
<60	1.48 (1.31,1.68)	<0.001	
≥ 60	1.40 (1.22,1.61)	<0.001	
Gender			0.018
Male	1.22 (1.05,1.40)	0.009	
Female	1.61 (1.42,1.83)	<0.001	
Marital status			0.921
Married	1.46 (1.32,1.62)	<0.001	
Non-married	1.31 (1.01,1.69)	0.042	
Residence status			0.182
Urban	1.56 (1.32,1.83)	<0.001	
Rural	1.36 (1.21,1.53)	<0.001	
Education level			0.933
Below elementary school	1.44 (1.27,1.64)	<0.001	
Elementary school	1.46 (1.20,1.79)	<0.001	
Secondary school and higher	1.42 (1.18,1.70)	<0.001	
Hypertension			0.598
No	1.50 (1.31,1.72)	<0.001	
Yes	1.66 (1.27,2.16)	<0.001	
Dyslipidemia			0.255
No	1.55 (1.33,1.82)	<0.001	
Yes	1.40 (1.24,1.57)	<0.001	
Cardiovascular			0.598
No	1.45 (1.31,1.61)	<0.001	
Yes	1.27 (1.01,1.60)	0.039	

Association of TyG index with diabetes

The CTI index was initially used as a new comprehensive indicator combining the inflammatory biomarker CRP and the IR index TyG to assess the degree of inflammation and IR. It was initially used as a tool for cancer prognosis assessment by Ruan and colleagues [20]. Previous studies have shown [24–26] that there is a significant correlation between the TyG index and the risk of diabetes. TyG levels can not only be used to determine early signs of diabetes [27], but also to assess the progression of diabetes [28]. Therefore, regular assessment of the TyG index may be of great significance in the early prevention, development and control of diabetes. In addition, the TyG index is also a reliable predictor of diabetes and its complications in the general population or specific populations, including non-diabetics, those with comorbid cardiovascular disease, diabetic nephropathy, etc [11, 29–34].

The association between CRP and diabetes

Inflammation is an important physiological response in the development of diabetes [35–39]. On the one hand, a chronic inflammatory state in the body over a long period of time can lead to an imbalance in the internal environment, which in turn can lead to increased insulin resistance, destruction of pancreatic cells, and weakened pancreatic function, thereby inducing diabetes. On the other hand, a chronic low-grade inflammatory state in diabetic patients over a long period of time can cause weakened body resistance and immunity, which in turn can lead to the occurrence of diabetes complications. A REGARD study on CRP and diabetes incidence found [40] that higher CRP is a risk factor for diabetes, but the disproportionate burden of diabetes in black adults is only seen in people with lower CRP. It has also been found that elevated serum CRP levels in early pregnancy may be a risk factor for gestational diabetes [41]. In addition, a cross-sectional study of data from the National Health and Nutrition Examination Survey in the United States showed that an increase in the concentration of CRP in the body with diabetes can lead to an increased risk of death [42]. Thus, CRP is a key factor mediating the development of diabetes.

Potential mechanism of CTI in predicting new-onset diabetes

Considering that insulin resistance and inflammation have been identified as independent risk factors for diabetes, and that insulin resistance and inflammatory responses are known to interact with each other, when assessing the risk of developing diabetes in individuals, not only should the effects of insulin resistance be considered, but also inflammatory variables should be taken into account. We hypothesised that CTI, which combines insulin resistance and an inflammatory marker (CRP), can predict diabetes risk. Previous studies have also highlighted the complex relationship between the triglyceride-to-glucose index, CRP and diabetes outcomes [43–47]. This further supports our findings. Furthermore,

Table 8 Relationship between the tertiary CTI index and the risk of new-onset diabetes

Variables	Incidence rate(1000PY)	HR(95%CI)	*P*	HR(95%CI)	*P*	HR(95%CI)	*P*	HR(95%CI)	*P*
Low CTI	12.07	Ref		Ref		Ref		Ref	
Medium CTI	18.06	1.54,(1.30,182)	<0.001	1.50 (1.27,1.77)	<0.001	1.49 (1.26,1.77)	<0.001	1.36 (1.15,1.62)	<0.001
High CTI	26.47	2.36 (2.01,2.76)	<0.001	2.30 (1.96,2.69)	<0.001	2.28 (1.95,2.67)	<0.001	1.81 (1.52,2.16)	<0.001

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, marital status, residence, smoking and drinking status, education level and WHtR

Model 4: plus hypertension, dyslipidemia and cardiovascular disease

Table 9 Relationship between CTI index and risk of new-onset diabetes in different sensitivity analyses

	Incidence rate(1000PY)	Model 1	*P*	Model 2	*P*	Model 3	*P*	Model 4	*P*	Mode 5	*P*
CTI index											
Per SD increase	18.87	1.47 (1.34,1.61)	<0.001	1.49 (1.36,1.64)	<0.001	1.53 (1.41,1.66)	<0.001	1.46 (1.33,1.60)	<0.001	1.64 (1.52,1.77)	<0.001
Quartiles											
Q1	11.79	Ref		Ref		Ref		Ref		Ref	
Q2	14.62	1.17 (0.95,1.43)	0.138	1.18 (0.96,1.45)	0.115	1.18 (0.96,1.45)	0.107	1.15 (0.94,1.41)	0.180	1.24 (1.01,1.52)	0.041
Q3	21.54	1.63 (1.34,1.98)	<0.001	1.68 (1.38,2.04)	<0.001	1.70 (1.41,2.06)	<0.001	1.60 (1.31,1.95)	<0.001	1.88 (1.56,2.27)	<0.001
Q4	27.54	1.98 (1.6,2.42)	<0.001	2.06 (1.68,2.53)	<0.001	2.18 (1.81,2.62)	<0.001	1.94 (1.58,2.38)	<0.001	2.50 (2.09,3.01)	<0.001

Model 1: adjusted for age, gender, marital status, residence, smoking and drinking status, education level, hypertension, dyslipidemia, and coronary heart disease

Model 2: adjusted for age, gender, marital status, residence, smoking and drinking status, education level, WHtRI, dyslipidemia, and coronary heart disease

Model 3: adjusted for age, gender, marital status, residence, smoking and drinking status, education level, hypertension, WHtR, and coronary heart disease

Model 4: adjusted for age, gender, marital status, residence, smoking and drinking status, education level, hypertension, dyslipidemia, WHtR

Model 5: adjusted for age, gender, marital status, residence, smoking and drinking status, education level

the linear association between the CTI index and diabetes highlights the importance of monitoring CRP and the TyG index for diabetes. Therefore, approaches to reduce insulin resistance and inflammation, such as moderate exercise, lifestyle modification, weight loss and careful pharmacological treatment, may all reduce the risk of diabetes.

This study provides new insights into the prediction of diabetes risk. Although our study points to the potential effect of the combined assessment of insulin resistance and CRP in predicting diabetes risk, the specific mechanism remains unclear. In addition, based on previous studies, we hypothesised that the combined assessment of inflammation and insulin resistance would be predictive of diabetes events, but the specific mechanism of the interaction between CRP and the triglyceride glucose index in diabetes risk events and the specific mechanism of the CTI in predicting diabetes risk remain unknown. Third, as this study is based on a national study design of middle-aged and elderly people in China, it provides us with a large sample size and good representativeness. Finally, strict quality control and standardised measurements were carried out throughout our study, so the quality of the current study can be guaranteed.

Our study has several limitations. First, this study only involved Chinese people aged 45 and above, and may not be applicable to other regions and age groups. Second, some diabetes-related indicators, such as family history and drug use, were not included in the original data, which may have had an impact on the results. Third, the CHARLS database is a self-reported database, although it is supported by certain laboratory tests, which may still result in recall bias and sampling bias. Fourth, as with all observational studies, although adjustments were made for confounding factors, uncontrolled confounding factors may still occur. Fifth, 298 participants were excluded due to missing data, which may introduce a greater degree of error. Sixth, the included studies lacked data on physical activity levels, failing to take into account the impact of physical activity on the development of diabetes, which is something we need to pay attention to in future studies. In addition, because insulin resistance levels and inflammation change over time, it is impossible to determine the association between the CTI index trajectory and diabetes risk. Finally, given that this is an observational study, the causal relationship between the CTI index and diabetes risk has not been established.

Conclusion

In summary, our study found that the novel composite index of insulin resistance and inflammation, the CTI index, is more valuable than the individual insulin resistance indicator (TyG index) in predicting diabetes risk. The results showed that there is a linear association between the CTI index and diabetes risk, and that a higher CTI index is associated with a higher risk of diabetes. This provides a reference for the timely diagnosis, early prevention, optimal treatment, and slowing of the progression of diabetes.

Abbreviations

CHARLS	China Health and Retirement Longitudinal Study
TyG	Triglyceride glucose
FBG	Fasting plasma glucose
CRP	C-Reactive Protein
GHb	Glycated hemoglobin
TC	Total cholesterol
TG	Triglyceride
LDL-C	Low-dendity lipoproteins cholesterol
HDL-C	High-dendity lipoproteins cholesterol
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
BMI	Body mass index

HR	Hazard ratio
CI	Confidence interval
ROC	Receiver Operating Characteristic
AUC	Area under the curve
RCS	Restricted cubic spline
CTI	C-reactive protein-triglyceride glucose

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Author contributions
S is responsible for writing the paper, G is responsible for research design and review of the article, and L is responsible for review of the article.

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Data availability
All the data generated during the fire analysis of this study can be in online access at http://www.isss.pku.edu.cn/cfps/. To get the data, you need to register as a user on the website. Once your registration has been reviewed and approved, you can download the dataset by following the instructions provided.

Declarations

Ethics approval and consent to participate
This study was conducted and approved by the Biomedical Ethics Review Committee of Peking University in accordance with the principles of the Declaration of Helsinki. In addition, all participants provided written informed consent to participate in the study (IRB approval number IRB00001052-11015). This study does not disclose any personal privacy of the participants and does not violate data protection laws.The research has been performed in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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