scientific reports

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Association of total cholesterol to high-density lipoprotein cholesterol ratio with diabetes risk: a retrospective study of Chinese individuals

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A common complication of type 2 diabetes is hypercholesterolemia in many patients. It is still unclear, nevertheless, how high-density lipoprotein cholesterol ratio (TC/HDL-C), total cholesterol, and diabetes are related. The purpose of this study is to look at the prediction ability and causal relationship between TC/HDL-C and diabetes. This study included 117,268 subjects who were undergoing physical examinations. The subjects were grouped into four equal groups according to the TC/HDL-C quartiles; the main outcome was the occurrence of diabetes events. TC/HDL-C is calculated as total cholesterol divided by high-density lipoprotein cholesterol. In 3.1 years (± 0.95) of follow-up, 795 women (0.68%) and 1,894 men (1.62%) received new diabetes diagnoses. TC/HDL-C is an independent predictor of new-onset diabetes, according to multivariable Cox regression analysis (HR 1.27 per SD increase, 95% CI: 1.09–1.48, *P* for trend < 0.001). It turned out that a cutoff value of 3.55 (area under the curve 0.64, sensitivity 0.66, specificity 0.56), was ideal for TC/HDL-C in predicting new-onset diabetes. A subgroup analysis demonstrated that the younger population had a significantly higher risk of TC/HDL-C-related diabetes than the middle-aged group (interaction *P* < 0.05). After controlling for confounding variables, this Chinese cohort study reveals a direct correlation between TC/HDL-C and diabetes, with a stronger independent association observed in younger and middle-aged individuals.

Keywords Diabetes, Cohort study, TC/HDL-C, Risk factor, Total cholesterol: high-density lipoprotein cholesterol ratio

A collection of metabolic illnesses collectively known as diabetes mellitus (DM) are typified by hyperglycemia, or high blood glucose levels[1–3]. Severe hyperglycemia can cause potentially fatal conditions like diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome, which can cause coma, in addition to classic symptoms like polyuria, polydipsia, fatigue, reduced work capacity, unexplained weight loss, visual disturbances, and susceptibility to infections[4,5]. In addition to impairing insulin secretion and/or function, chronic hyperglycemia raises the risk of cancer. It can cause long-term harm and dysfunction in several organs and tissues, including the kidneys, heart, blood vessels, eyes, and nerves[6,7]. Approximately 90% of the estimated 537 million cases of diabetes worldwide are type 2[8,9]. The number of afflicted people is skyrocketing, with a concerning trend among young adults and children (under 40 years)[10]. Sedentary lifestyles, bad eating habits, urbanization, and rapid economic development are thought to be the main environmental causes causing this spike[11]. Therefore, finding reliable and innovative diabetes predictors is crucial for proactive management and early detection, both of which are necessary to reduce or eliminate the burden of mortality and micro- and macrovascular complications.

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Abnormal glucose metabolism and dyslipidemia frequently occur[12,13]. This may be owing of the buildup of excess cholesterol, which lowers glucose tolerance, inhibits β-cell function, and influences insulin secretion. Elevated triglyceride levels, decreased high-density lipoprotein cholesterol (HDL-C), and elevated low-density lipoprotein cholesterol (LDL-C) are the usual markers of dyslipidemia[14,15]. Research has indicated that individuals with diabetes who have increased cholesterol levels are more susceptible to coronary artery disease[16]. The ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C) may be a more accurate indicator of diabetes than individual lipid markers. While there is evidence that TC/HDL-C can be used to predict cardiovascular risk[17], there hasn't been much discussion of the connection between TC/HDL-C and diabetes. The purpose of this study is to elucidate the relationship between diabetes and TC/HDL-C in the Chinese population.

Methods

Study population and design

The cohort research carried out by the Rich Healthcare Group in China is the source of this secondary analysis [18]. All methods are carried out according to the **Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)** guidelines[19]. Between 2011 and 2016, 685,277 adult participants getting medical tests from 11 Chinese cities were recruited for the Rich Healthcare Group cohort research. The project aimed to improve public health in China by assessing diabetes and its risk factors in specific and conducting regular health screenings and follow-up evaluations. Professor Chen uploaded the data utilized in this work to the Dryad database[20].

The terms of service of Dryad permit researchers to make unrestricted use of publicly accessible data for secondary studies, thereby enhancing the data's usefulness. No further ethical permission was needed for this analysis because the data had already been anonymized and the original study had received ethical approval.

This investigation is a post-hoc examination built upon earlier findings. The primary outcome of this trial was incident diabetes, and the exposure variable was defined as TC/HDL-C. Is TC/HDL-C an independent predictor of new-onset diabetes in the Chinese population? was the research hypothesis. The following were the exclusion standards for participants in research (Fig. 1): Those with diabetes at baseline; (2) those whose diabetes status was unclear at follow-up; (3) those whose follow-up period was shorter than two years; (4) those with incomplete or extreme gender, BMI, fasting plasma glucose (FPG), or lipid parameter values; (5) those without height or weight measurements; and (6) those who abstained from the study for unspecified reasons. Individuals without data on high-density lipoprotein cholesterol or total cholesterol were likewise disqualified. In all, 117,268 participants were included in the final analysis after meeting the inclusion criteria.

A standardized questionnaire was given to each participant, collecting information on their age, gender, blood pressure, height, weight, and status regarding drinking and/or smoking, as well as the results of a physical

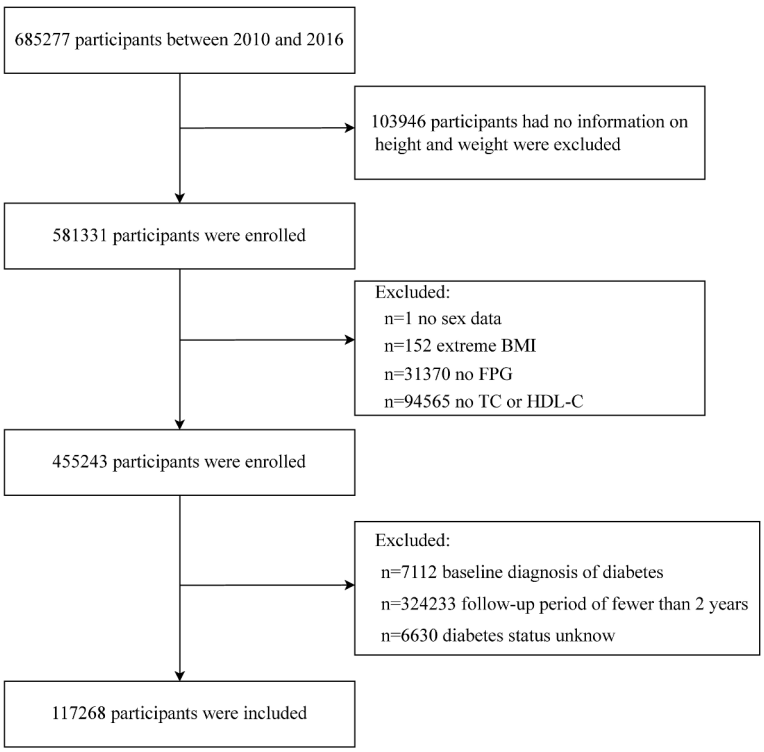

Fig. 1. Flow diagram of participants included. The exclusion criteria for the study population are shown in this flowchart, resulting in to the enrollment of 117,268 participants in total. BMI body mass index; FPG fasting plasma glucose; TC total cholesterol; HDL-C high-density lipoprotein cholesterol.

examination. Participants were measured indoors while wearing light clothing and going barefoot. In a peaceful setting, blood pressure was measured with a standard mercury sphygmomanometer. An automated analyzer (Beckman 5800) was used in standard laboratories to measure the plasma glucose levels in fasting venous blood samples obtained by trained workers. The glucose oxidase method was used to measure plasma glucose levels.

Definition and calculation

The first diabetes assessment by a clinician marked the start of the follow-up period, and the occurrence of a new diabetes incident was the endpoint. The primary site of follow-up was health examination facilities, and follow-up occurred annually.

Diabetes was identified as an FPG of ≥ 7.00 mmol/L at follow-up or a self-reported history of the disease[21]. Researchers confirmed the glucose levels of people with diabetes at the time of diagnosis or at their most recent visit.

Smoking/drinking status

Based on their history of drinking or smoking, participants were divided into three groups: current drinkers and smokers, ever drinkers and smokers, and never drinkers and smokers.

BMI was calculated as weight divided by height squared (kg/m^2).

Statistical analysis

STATA software (version 17), R (version 4.4.1) and Free Statistics analysis platform (Version 1.9, Beijing, China) were used for data analysis in this study. A two-sided *P*-value of less than 0.05 was deemed statistically significant.

All continuous variables were determined to have a skewed distribution after being tested for normality; as a consequence, they are all shown as medians (interquartile ranges). We used the Mann–Whitney U test for comparisons. The chi-square test was used to evaluate categorical variables, which are expressed as frequencies (percentages). Based on the quartiles of their TC: HDL-C ratio, participants were split into four groups: Q1 (< 2.95), Q2 (2.95–3.43), Q3 (3.43–4.11), and Q4 (> 4.11). We next used Cox proportional hazard curves to depict the cumulative incidence of diabetes.

The relationship between the TC: HDL-C ratio and diabetes risk was assessed using Cox proportional hazards regression analysis (Model 1: unadjusted). To lessen potential bias, two adjusted models were also created. Based on Model 1, age and sex adjustments were made in Model 2. Adding to Model 2, Model 3 was further adjusted for blood urea nitrogen (BUN), serum creatinine (Scr), smoking/alcohol status, cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP), diastolic blood pressure (DBP), cholesterol, and family history of diabetes.

Using stratified Cox regression models to do subgroup analyses, the connection between TC/HDL-C and diabetes was further investigated by looking at different age groups, genders, and BMI categories. While BMI stratification was based on the WHO classification for Asian people[22], age stratification was based on earlier studies[18]. To look for possible interactions and compare differences between strata, a likelihood ratio test was employed.

Finally, we used the "roctab" function in Stata to compute the area under the receiver operating characteristic (ROC) curve, as well as the sensitivity and specificity corresponding to distinct thresholds, in order to compare the predictive powers of TC, HDL, and the TC/HDL-C ratio for diabetes risk. The STATA module's "cutpt" command was used to calculate the cutoff values based on the ROC curve.

Results

Baseline characteristics of subjects

Following the elimination of participants who were not eligible, 117,268 eligible subjects with a median age of 41 years were included in the final analysis. These individuals were divided into 63,074 men and 54,194 females. The TC/HDL-C median was 3.43. Table 1 displays the anthropometric and biochemical parameters of the participants sorted by the existence or absence of recently diagnosed diabetes. Supplementary Table 1 presents baseline characteristics separated by gender.

The findings show that older guys without a family history of diabetes were more likely to develop diabetes in this study. Furthermore, there was a larger percentage of smokers and alcohol users among those with diabetes. In addition, the BMI, systolic/diastolic blood pressure (SBP/DBP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and serum creatinine (Scr) were all higher in the diabetic patients than in the non-diabetic group. The average age of males and females is similar, but males have higher biochemical markers and a greater number of smokers and drinkers compared to females. Additionally, the decline in HDL-C is significantly more pronounced in males than in females.

The incidence of new-onset diabetes

In a mean follow-up of 3.1 (0.95) years, 795 females (0.68%) and 1,894 males (1.62%) received a new diabetes diagnosis. The Q1 group experienced a cumulative incidence of diabetes of 0.98% (287/29,300), the Q2 group experienced 1.72% (505/29,284), the Q3 group experienced 2.69% (787/29,285), and the Q4 group experienced 3.78% (1110/29,404). The findings of the Cox regression analysis are shown in Fig. 2, which indicates that as the TC/HDL-C ratio grew, so did the cumulative incidence of diabetes.

Association of TC: HDL-C ratio with new-onset diabetes risk

A Cox regression model based on the TC/HDL-C quartiles was created to evaluate the relationship between the TC/HDL-C ratio and diabetes. Table 2 shows the construction of three multivariable-adjusted models, Model 1

	Total	Non-diabetes	Diabetes	P-value
No. of participants	117,268	114,579	2689	
Age (year)	41 (34, 53)	41 (34, 52)	57 (47, 65)	< 0.001
Sex, n (%)				< 0.001
Male	63,074 (53.8)	61,180 (53.4)	1894 (70.4)	
Female	54,194 (46.2)	53,399 (46.6)	795 (29.6)	
BMI (kg/m^2)	23.1 (21, 25.4)	23.1 (20.9, 25.3)	25.9 (23.7, 28)	< 0.001
SBP (mmHg)	118 (107, 130)	117 (107, 129)	131 (119, 143)	< 0.001
DBP (mmHg)	73 (66, 81)	73 (66, 81)	80 (72, 88)	< 0.001
FPG (mmol/L)	4.93 (4.56, 5.3)	4.91 (4.55, 5.3)	6.02 (5.46, 6.48)	< 0.001
Cholesterol (mmol/L)	4.7 (4.15, 5.32)	4.7 (4.14, 5.31)	5 (4.4, 5.67)	< 0.001
Triglyceride (mmol/L)	1.1 (0.76, 1.66)	1.1 (0.75, 1.64)	1.7 (1.17, 2.5)	< 0.001
HDL-C (mmol/L)	1.35 (1.16, 1.56)	1.35 (1.16, 1.56)	1.27 (1.08, 1.49)	< 0.001
LDL-C (mmol/L)	2.7 (2.29, 3.16)	2.69 (2.29, 3.16)	2.86 (2.39, 3.34)	< 0.001
ALT (U/L)	18 (13, 27.5)	18 (13, 27.1)	25.2 (18, 39.9)	< 0.001
AST (U/L)	22 (18.6, 26.8)	22 (18.6, 26.6)	25 (21, 31.7)	< 0.001
BUN (mmol/L)	4.57 (3.84, 5.4)	4.56 (3.84, 5.39)	4.9 (4.1, 5.77)	< 0.001
Scr (μmol/L)	69.6 (58, 81.2)	69.5 (58, 81.1)	72.93 (62, 82.3)	< 0.001
TC/HDL-C	3.43 (2.95, 4.11)	3.42 (2.94,4.09)	3.87 (3.33,4.70)	< 0.001
P for trend				< 0.001
Q1	29,300 (25.0)	29,013 (25.3)	287 (10.7)	
Q2	29,284 (25.0)	28,774 (25.1)	505 (18.8)	
Q3	29,285 (25.0)	28,498 (24.9)	787 (29.3)	
Q4	29,404 (25.1)	28,294 (24.7)	1110 (41.3)	
Smoking status, n (%)				< 0.001
Current smoker	6689 (20.4)	6431 (20.0)	258 (37.1)	
Ever smoker	1333 (4.1)	1287 (4.0)	46 (6.6)	
Never smoker	24,800 (75.6)	24,409 (76.0)	391 (56.3)	
Drinking status, n (%)				0.013
Current drinker	878 (2.7)	847 (2.6)	31 (4.5)	
Ever drinker	5553 (16.9)	5437 (16.9)	116 (16.7)	
Never drinker	26,391 (80.4)	25,843 (80.4)	548 (78.8)	
Family history of diabetes, n (%)	2657 (2.3)	2557 (2.2)	100 (3.7)	< 0.001

Table 1. Baseline characteristics of the study participants. Values were expressed as medians (quartile interval) or n (%). The differences among quintiles were evaluated by Mann–Whitney U test and Pearson's chi-squared test. After making a pairwise comparison between the diabetes and non-diabetes, the results showed that there were significant differences in two groups ($P < 0.05$). BMI Body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, FPG fasting plasma glucose, HDL-C high-density lipid cholesterol, LDL-C low-density lipid cholesterol, BUN blood urea nitrogen, Scr serum creatinine, ALT alanine aminotransferase, AST aspartate aminotransferase, TC total cholesterol.

being an unadjusted crude model. The findings showed a substantial positive association between TC/HDL-C and the chance of getting diabetes (HR 1.18 per SD increase, 95% CI: 1.16–1.21), and a higher risk of diabetes was seen as TC/HDL-C quartiles increased in comparison to the lowest quartile ($P < 0.001$). After adjusting for age and sex, Model 2 demonstrated that the relationship between TC/HDL-C and diabetes did not change. The positive relationship, including its quartiles, between TC/HDL-C and diabetes persisted even after accounting for additional significant variables found in the univariate analysis (Model 3). (HR 1.27 per SD increase, 95% CI: 1.09–1.48, $P = 0.003$). In conclusion, TC/HDL-C represents a separate risk factor for the onset of diabetes.

Stratified analyses

In order to investigate additional risk factors and particular populations that might impact the association between the TC/HDL-C ratio and diabetes, we conducted stratified analyses based on age, sex, and BMI. The results showed significant variations in the diabetes risk associated with TC/HDL-C across various age groups (*P* for interaction < 0.05).

Certain subpopulations had a noticeably increased risk of getting diabetes, as Table 3 illustrates. In the age-stratified study, the risk of TC/HDL-C-related diabetes was found to be considerably higher in younger persons as opposed to older adults [HR per SD increase: 20–30 years: 3.41, 31–40 years: 2.48, 41–50 years: 2.12 vs. 51–60 years: 1.30, 61–70 years: 0.93, > 70 years: 1.01].

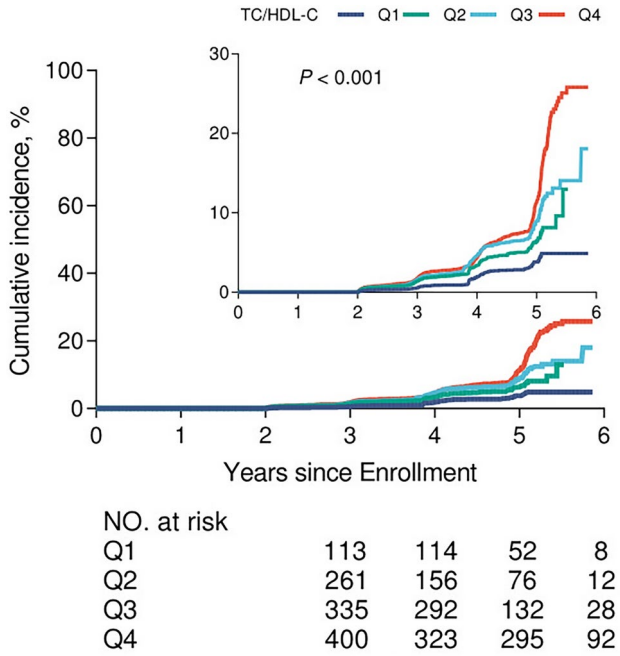

Fig. 2. Associations between the TC/HDL-C and new-onset diabetes. Shown is the cumulative incidence curve of the diabetes outcome. The result was estimated with the use of Log rank test ($P < 0.001$). The inset shows the same data on an expanded y axis.

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*- value	HR (95% CI)	*P*- value	HR (95% CI)	*P*-value
TC/HDL-C	1.18 (1.16–1.21)	< 0.001	1.1 (1.07–1.13)	< 0.001	1.27 (1.09–1.48)	0.003
TC/HDL-C (Quartile)						
Q1	Ref		Ref		Ref	
Q2	1.90 (1.64–2.19)	< 0.001	1.54 (1.33–1.78)	< 0.001	2.72 (1.52–4.84)	0.001
Q3	2.49 (2.18–2.85)	< 0.001	1.68 (1.47–1.93)	< 0.001	2.33 (1.29–4.20)	0.005
Q4	2.95 (2.59–3.36)	< 0.001	1.70 (1.49–1.94)	< 0.001	3.87 (2.09–7.16)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

Table 2. Univariate and multivariate Cox proportional hazards regression analyses for the association between TC: HDL-C ratio and new-onset diabetes in different models. Model 1 crude model. Model 2 adjusted for age, sex. Model 3 adjusted for age, sex, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, BUN, Scr, smoking status, drinking status and family history of diabetes. HR hazard ratio, CI confidence interval, BMI Body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, FPG fasting plasma glucose, HDL-C high-density lipid cholesterol, LDL-C low-density lipid cholesterol, BUN blood urea nitrogen, Scr serum creatinine, ALT alanine aminotransferase, AST aspartate aminotransferase, TC total cholesterol, TG Triglyceride.

Predictive value of TC/HDL-C in new-onset diabetes

The researchers used ROC curve analysis to examine the predictive value of TC/HDL-C for incident diabetes (Fig. 3). The AUCs for TC/HDL-C, TC, and HDL-C were 0.64 (95% CI: 0.63061–0.65082), 0.59 (95% CI: 0.58154–0.60344), and 0.42 (95% CI: 0.40832–0.43040), respectively, for the prediction of new-onset diabetes. When compared to either TC or HDL-C alone, the AUC for TC/HDL-C was considerably greater (both $P < 0.001$). With a sensitivity of 0.66 and specificity of 0.56, the ideal cut-off value for TC/HDL-C was 3.55 (Table 4).

Discussion

TC/HDL-C was found to be independently and positively linked with the incidence of new-onset diabetes in this retrospective cohort study based on a Chinese population, even after full adjustment for confounders, regardless of whether it was examined as a categorical or continuous variable. In terms of predicting new-onset diabetes, ROC analysis showed that TC/HDL-C was more accurate than both TC and HDL-C.

Being the third largest cause of death worldwide and the fourth largest cause of years lived with a handicap adjusted for life, diabetes is a major public health concern[23]. Globally, the prevalence of diabetes is expected to increase yearly to 10.9% (or 700 million people) by 2045. The frequency is higher in high-income nations

Subgroup	No. of participants	Unadjusted HR (95%CI)	Adjusted HR (95%CI)	*P* for interaction
Age (years)				0.0011
20–30	11,236	3.41 (1.52–7.67)	–	
31–40	42,225	2.48 (1.89–3.26)	1.75 (0.48–6.29)	
41–50	27,246	2.12 (1.73–2.58)	0.89 (0.35–2.28)	
51–60	19,615	1.30 (1.12–1.52)	1.47 (0.85–2.55)	
61–70	12,041	0.93 (0.79–1.10)	0.48 (0.19–1.20)	
> 70	4905	1.01 (0.83–1.24)	2.26 (0.25–20.63)	
Sex				0.9810
Men	63,074	1.25 (1.13–1.38)	1.37 (0.92–2.03)	
Women	54,194	2.79 (2.40–3.23)	1.14 (0.45–2.88)	
BMI (kg/m^2)				0.8640
< 18.5	6029	1.60 (0.61–4.18)	–	
18.5–23	63,813	1.99 (1.71–2.31)	1.02 (0.50–2.07)	
23–27.5	37,232	1.02 (0.90–1.15)	1.01 (0.55–1.84)	
> = 27.5	10,154	0.89 (0.75–1.07)	1.38 (0.61–3.14)	

Table 3. Stratified association between TC/HDL-C and diabetes by age, sex, and BMI. HR hazard ratios, CI confidence interval, BMI Body mass index. Note: Models adjusted for the same covariates as in model 3 (Table 2), except for the stratification variable.

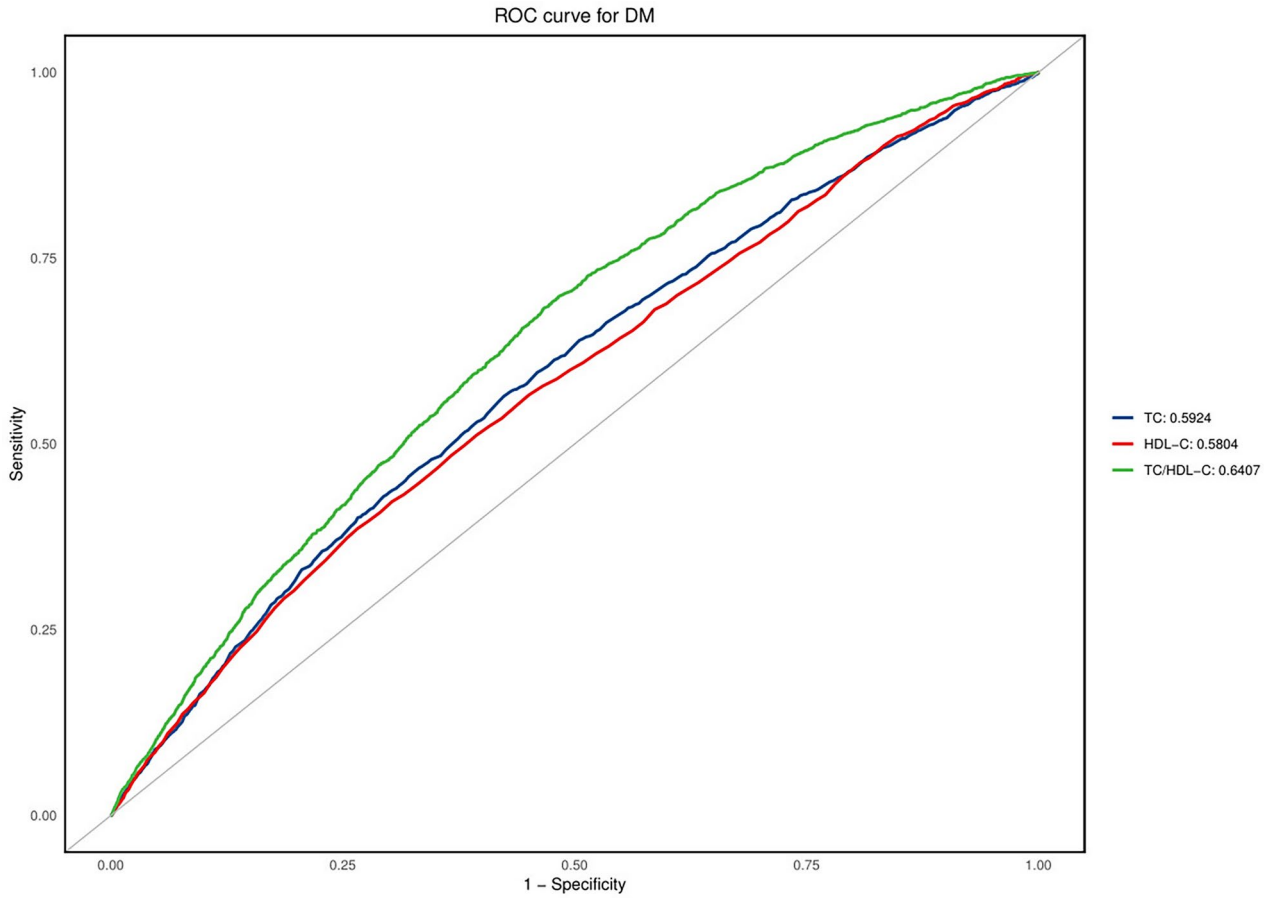

Fig. 3. Receiver operating characteristic (ROC) curve analyses to predict diabetes. The predictive value of TC/HDL-C for incident diabetes was investigated by the researchers using ROC curve analysis. The AUC for TC/HDL-C was significantly higher than that of either TC or HDL-C alone (both P < 0.001). AUC: area under the curve; DM diabetes mellitus, HDL-C high-density lipid cholesterol, TC total cholesterol.

	AUC	95% confidence interval	Best threshold	Sensitivity	Specificity
TC/HDL-C	0.64	0.6306–0.6508	3.55	0.66	0.56
Cholesterol*	0.59	0.5815–0.6034	4.87	0.56	0.58
HDL-C*	0.42	0.4083–0.4304	1.35	0.39	0.51

Table 4. Areas under the receiver operating characteristic curves for each evaluated parameters in identifying diabetes. AUC area under the curve; HDL-C high-density lipid cholesterol, LDL-C low-density lipid cholesterol, TC total cholesterol. *$P < 0.0001$, compare with TC/HDL-C.

(10.4%) than in low-income countries (4.0%), and in urban areas (10.8%) than in rural regions (7.2%)[24]. Obesity is a common condition among type 2 diabetic patients, and obesity exacerbates insulin resistance[25]. Elevated TG, TC, and LDL-C values combined with decreased HDL-C are frequently observed in patients with dyslipidemia[26]. The widespread consensus is that HDL-C protects against diabetes[27]. A vicious loop of insulin resistance[28,29] is created when lower HDL-C levels decrease β-cell activity in the pancreas[30]. Diabetes patients who received recombinant HDL-C infusions saw a higher drop in blood glucose than controls, according to a small randomized controlled experiment[31]. This shows that in tissues that are susceptible to insulin, HDL-C may help to improve insulin sensitivity and glucose absorption.

As opposed to HDL-C's protective role, TC increases the risk of diabetes. Regardless of the presence of diabetes, the Asia Pacific Cohort Studies Collaboration discovered that high total cholesterol raised the risk of cardiovascular disease[32]. According to other research, abnormal cholesterol accumulation not only raises the risk of cardiovascular disease but also interferes with the function of pancreatic β-cells[33–35]. Insulin secretion was hindered in mice when the β-cell-specific deletion of the ABCG1 gene, which controls cholesterol efflux, resulted in elevated intracellular cholesterol levels[36]. Contradictory findings, however, were found in a recent multicenter cross-sectional research of an elderly Taiwanese population, which indicated a higher risk of type 2 diabetes was linked to lower TC levels. According to that research, aggressive lipid-lowering therapy may not always be advantageous. A significant lipid parameter linked to the risk of type 2 diabetes has been identified by recent studies as the TC/HDL-C, a combination index that is computed by dividing TC by HDL-C[37,38]. Uncertainty surrounds the link between the TC/HDL-C and the occurrence of diabetes, though. According to our research, the TC/HDL-C is an independent risk factor for diabetes. As far as we are aware, this is the first study to demonstrate this connection, offering insightful information for the primary prevention of diabetes.

Although the exact mechanisms behind the relationship between TC/HDL-C and diabetes are unknown, a number of reasonable theories exist. When significantly lower plasma HDL-C levels are paired with normal or higher plasma TC levels, a high TC/HDL-C is generally observed in diabetes individuals[39]. One steady and independent characteristic of diabetes is thought to be a notable reduction in HDL-C[40]. Studies have found that patients at high risk of coronary heart disease with a high TC/HDL-C ratio exhibit significantly increased insulin resistance[41], suggesting a correlation between TC/HDL-C ratio and insulin resistance. Changes in cholesterol homeostasis may be a mechanism via which TC and HDL-C regulate pancreatic β-cells[42]. This in turn impacts the synthesis, movement, and exocytosis of insulin granules. Consequently, insulin secretion may be further decreased and diabetes may develop when TC levels are unusually high or HDL-C levels are abnormally low.

The stratified analysis of our current study also produced some intriguing results. With advancing age, the TC/HDL-C-associated diabetes risk declined. There are various ways to explain the mechanisms underlying this variation in the age-related impact. On the one hand, the correlation between the TC/HDL-C and diabetes may be weakened by age-related increases in insulin resistance, comorbidities, and general health decline [43]. On the other hand, total cholesterol levels in elderly men generally decrease with age, while high-density lipoprotein cholesterol remains relatively stable[44]. Additionally, the widespread use of lipid-lowering medications, such as statins, in the elderly population[45] may further weaken the relationship between the TC:HDL-C ratio and diabetes risk. While our analysis did not find any significant differences across BMI subgroups, prior research has demonstrated that an increase in BMI is associated with worsening insulin resistance and an increased risk of acquiring diabetes[46].

Study strength and limitations

Several significant strengths of this study are as follows: (1) It is the first to look at the connection between diabetes and TC/HDL-C, and the stratified analysis identifies unique populations, offering new approaches to precise diabetes screening, prevention, and intervention. (2) A large sample size and a wide age distribution were used to ensure that the study population was representative of the Chinese population, as it was gathered from various places throughout China. (3) The study used subgroup analysis and other sophisticated statistical analyses. The study's findings were reliable since the positive relationship between the TC/HDL-C and the risk of diabetes persisted even after controlling for confounding variables.

Nevertheless, there are other limitations on this study: (1) Its diagnostic criteria failed to distinguish between type 1 and type 2 diabetes. However, since type 2 diabetes accounts for more than 95% of all instances of diabetes, the results might be more useful in predicting type 2 diabetes risk [47]. (2) Participants' self-reports or FPG ≥ 7.0 mmol/L at follow-up were used to diagnose diabetes, which could have resulted in an underestimating of the actual prevalence of the disease. However, in a small number of patients, we showed a strong correlation between the TC/HDL-C and diabetes. (3) Because this is a retrospective cohort study, residual confounding from measurement error and the lack of data on some unmeasured characteristics cannot be eliminated out even after controlling for a wide range of confounding factors. (4) The findings are particularly relevant to communities in

southern China because they are based on a cohort that is primarily from that region; more research is required for populations of northern Chinese and non-Chinese populations. (5) The possible influence of HDL-C dysfunction on glucose metabolism could not be ruled out because this study did not differentiate between different forms of HDL-C, which could have an impact on the relationship between TC/HDL-C and diabetes. The various functions of HDL-C and its subtypes should be further examined in future studies[48].

Conclusion

In conclusion, among Chinese individuals, the TC: HDL-C ratio represents a risk factor for diabetes on its own. The risk of diabetes is positively connected with an increase in the TC: HDL-C ratio, and this association holds true for all populations that have been studied. Notably, a high ratio of total cholesterol to high-density lipoprotein cholesterol is linked to a higher risk of developing diabetes, especially in younger and middle-aged people. According to these results, the TC: HDL-C ratio could be a viable lipid target for diabetes therapy and prevention.

Data availability

The datasets generated and/or analysed during the current study are available in the "Dryad" repository, (https://doi.org/https://doi.org/10.5061/dryad.ft8750v).

Received: 3 November 2024; Accepted: 17 January 2025
Published online: 09 May 2025

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Funding

This work was supported by the Shandong Province Traditional Chinese Medicine Science & Technology Project (No. Z2023116), SHENNONG:A Real-world, Prospective, Observational Study Assessing the Effectiveness of Repatha Used in Combination with Standard of Care Compared with Standard of Care Alone on Major Cardiovascular Events in Chinese Patients with Established Atherosclerotic Cardiovascular Disease(No.20180442) and Jining City Science and Technology Key Research and Development Program (No. 2021YXNS069).

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Due to the retrospective nature of the study, the need of obtaining approval was waived.

Informed consent

Due to the retrospective nature of the study, (Institutional Review Board) waived the need of obtaining informed consent.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-87277-0.

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