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Article

Role of Circulating Lipids in Mediating the Pro-Diabetic Effect of Obesity

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Abstract

Background/Objectives: Obesity is a major risk factor for diabetes, but the underlying mechanisms remain incompletely understood. Obesity is associated with alterations in circulating lipids. This study aimed to determine whether, and to what extent, circulating lipids mediate the pro-diabetic effect of obesity. **Methods:** We analyzed data from 26,627 US adults. Mediation analysis was performed using the PROCESS Version 4.3 Macro for SPSS. Parallel mediation analysis included total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides as simultaneous mediators. Low-density lipoprotein (LDL) cholesterol was excluded from the parallel model due to collinearity with total cholesterol and was assessed separately using simple mediation analysis adjusted for confounders. **Results:** After adjustment for tested confounders, parallel mediation analysis showed that increases in triglycerides and reductions in HDL cholesterol mediated 24.0% (indirect effect coefficient = 0.23; 95% CI: 0.20–0.26; $p < 0.05$) and 3.8% (indirect effect coefficient = 0.04; 95% CI: 0.01–0.06; $p < 0.05$) of the pro-diabetic effect of obesity, respectively. An increase in total cholesterol negatively mediated the effect by 2.3% (indirect effect coefficient = -0.02; 95% CI: -0.03 to -0.01; $p < 0.05$). Simple mediation analysis indicated that LDL cholesterol was not a significant mediator. **Conclusions:** Triglycerides are the most influential circulating lipid in mediating the pro-diabetic effect of obesity, accounting for 24% of the total effect. Targeting triglyceride levels may represent an underrecognized therapeutic strategy to reduce obesity-related diabetes risk.

Keywords: lipids; type 2 diabetes; triglyceride; metabolic disease

1. Introduction

Obesity is defined as excessive fat accumulation in the body that can impair health [1]. Over the past three decades (1990–2021), global adult obesity prevalence has risen dramatically—by 105% in females (from 10.2% to 20.8%) and by 155% in males (from 5.8% to 14.8%) [2]. The World Health Organization (WHO) has classified obesity as a global epidemic [3]. According to the WHO, 890 million adults worldwide are living with diabetes, representing 16% of the global population [4]. Obesity in adults is particularly common in high-income countries, with prevalence rates of 28% in the UK [5], 29.5% in Canada [6], 32% in Australia [7], and 41.9% in the United States [8]. It is projected that by 2050, the number of adults with obesity will reach 1.95 billion [2].

Obesity has wide-ranging consequences for health and well-being [1]. Individuals with obesity often experience stigma and discrimination, which negatively impact quality of life [9,10] and increase the risk of depression [11]. Excess adipose tissue can also impair organ and tissue function; for example, it can damage joints, leading to osteoarthritis, pain, and reduced mobility [12].

Furthermore, obesity is a major risk factor for numerous diseases, including non-alcoholic fatty liver disease [13], chronic kidney disease, cardiovascular disease, and cancer [14,15].

Of particular concern, obesity substantially increases the risk of diabetes [16]. Currently, diabetes affects 537 million people worldwide [17], and both its prevalence and incidence continue to rise [17,18]. Diabetes can lead to severe complications, including blindness, kidney failure, heart attacks, stroke, and lower-limb amputation [19]. The World Obesity Federation and the International Diabetes Federation estimate that obesity accounts for 43% of type 2 diabetes cases [20], which itself represents approximately 90% of all diabetes diagnoses [21]. Both organizations emphasize that halting the global rise in type 2 diabetes requires prioritizing action on obesity [20].

Obesity contributes to diabetes through multiple mechanisms [16,22,23]. A key pathway involves obesity-induced insulin resistance and β -cell dysfunction [16], driven by increased oxidative stress and chronic inflammation [22,23]. Obesity is also strongly associated with dyslipidemia, characterized by elevated triglycerides [24], increased total cholesterol [25], higher low-density lipoprotein (LDL) cholesterol [26], and reduced high-density lipoprotein (HDL) cholesterol [27–29]. Approximately 60%–70% of individuals with obesity exhibit dyslipidemia [30]. However, the extent to which these circulating lipids mediate the pro-diabetic effect of obesity remains unclear.

To address this question, we analyzed data from 26,627 US adults who participated in the National Health and Nutrition Examination Survey (NHANES) between 1988 and 2014. Circulating lipids assessed included total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.

2. Materials and Methods

2.1. Study Participants

This study included US civilian noninstitutionalized individuals who attended the NHANES from 1988 to 2014. These surveys were organized by the National Center for Health Statistics (NCHS) within the Centers for Disease Control and Prevention (CDC) [31]. The inclusion criteria of the current study were age of ≥ 20 years and the presence of the following data: body mass index, fasting triglycerides, total cholesterol, HDL cholesterol, fasting plasma glucose, and blood hemoglobin A_{1c} (HbA_{1c}). This resulted in a group of 26,724 participants. The following participants were excluded from the analysis: unknown education status (n = 74), unknown smoking status (n = 13), and unknown physical activity status (n = 10). Therefore, 26,627 participants were included in the final analysis (Figure 1).

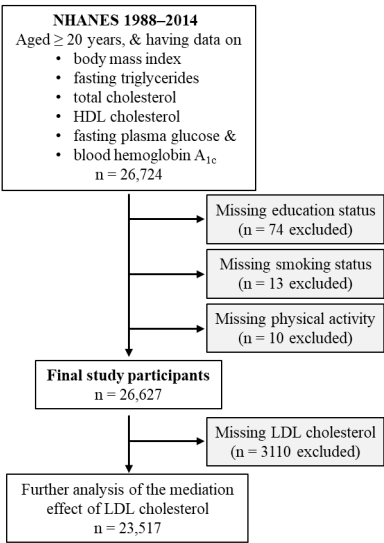


Figure 1. Flow diagram of the study participants. HDL, high-density lipoprotein; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey.

In a further analysis investigating the effect of LDL cholesterol in mediating the pro-diabetic effect of obesity, 3110 participants were excluded due to missing LDL cholesterol values. Therefore, a total of 23,517 participants were included in this further analysis (Figure 1).

2.2. Exposure Variable

The exposure variable of this study was obesity, which was defined as a body mass index of ≥ 30 kg/m² [32,33]. In addition, body mass index (continuous) was used as the exposure variable in further analysis.

2.3. Outcome Variable

The outcome of the current study was diabetes, which was defined by one of the following criteria: HbA_{1c} $\geq 6.5\%$, fasting plasma glucose ≥ 126 mg/dL, 2-hour plasma glucose during oral glucose tolerance test ≥ 200 mg/dL, the use of hypoglycemic medications, or self-reported diagnosis of diabetes [34,35].

2.4. Candidate Mediators

The mediators assessed in this study included total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. Fasting blood samples were collected from participants who had fasted for at least 8 hours after their last caloric intake [35–37].

Total cholesterol was measured enzymatically using a series of coupled reactions: cholesteryl esters were hydrolyzed to cholesterol by cholesterol esterase; cholesterol was then oxidized by cholesterol oxidase, producing hydrogen peroxide; and hydrogen peroxide was converted into a red dye by peroxidase in the presence of 4-aminophenazone and phenol. The color intensity, directly proportional to cholesterol concentration, was determined photometrically at 500 nm [38].

HDL cholesterol was measured directly without removing apoB-containing lipoproteins [39]. A blocking reagent rendered LDL, very low-density lipoprotein (VLDL), and chylomicrons non-reactive with the enzymatic cholesterol reagent under assay conditions, effectively excluding them from detection. HDL cholesterol esters were converted to cholesterol by polyethylene glycol (PEG)-modified cholesterol esterase, then oxidized by cholesterol oxidase to Δ^4 -cholestenone and hydrogen peroxide. In the presence of peroxidase, hydrogen peroxide reacted with 4-amino-antipyrine and N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline (HSDA) to form a purple-blue dye. The color intensity, proportional to HDL cholesterol concentration, was measured photometrically.

Triglycerides were measured enzymatically through coupled reactions in which triglycerides were hydrolyzed to glycerol [40]. The resulting glycerol was phosphorylated and oxidized to produce hydrogen peroxide, which was then converted by peroxidase into a color product measured photometrically at 500 nm.

LDL cholesterol was not directly measured [41]. Instead, it was calculated using the Friedewald formula based on total cholesterol, HDL cholesterol, and triglyceride concentrations for participants with triglycerides ≤ 400 mg/dL [42].

2.4. Confounding Variables

The details of confounding covariables were described in previous publications [43–45]. The list included age (continuous), sex, ethnicity, education, poverty-income ratio, survey periods, physical activity, alcohol consumption, smoking, hypertension, and family history of diabetes.

2.5. Statistical Analyses

Baseline characteristics of participants were summarized as follows: categorical variables were presented as numbers (percentages), non-normally distributed continuous variables as medians (interquartile ranges), and normally distributed continuous variables as means (standard deviations) [46]. Differences in categorical variables were assessed using Pearson's chi-square test [47], while

differences in continuous variables were evaluated using Student’s t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables [48]. Correlations among the lipids were analysed using bivariate Pearson correlation analysis.

The association between obesity and diabetes was examined using binary logistic regression [49], with and without adjustment for potential confounders. Mediation analysis was performed using the PROCESS Version 4.3 Macro for SPSS [50,51]. First, a simple mediation analysis was conducted (Figure 2A), where candidate mediators (total cholesterol, HDL cholesterol, and triglycerides) were analyzed individually to estimate their separate mediation effects on the obesity–diabetes association. Subsequently, a parallel mediation analysis was performed (Figure 2B), in which all three mediators were included simultaneously in the model.

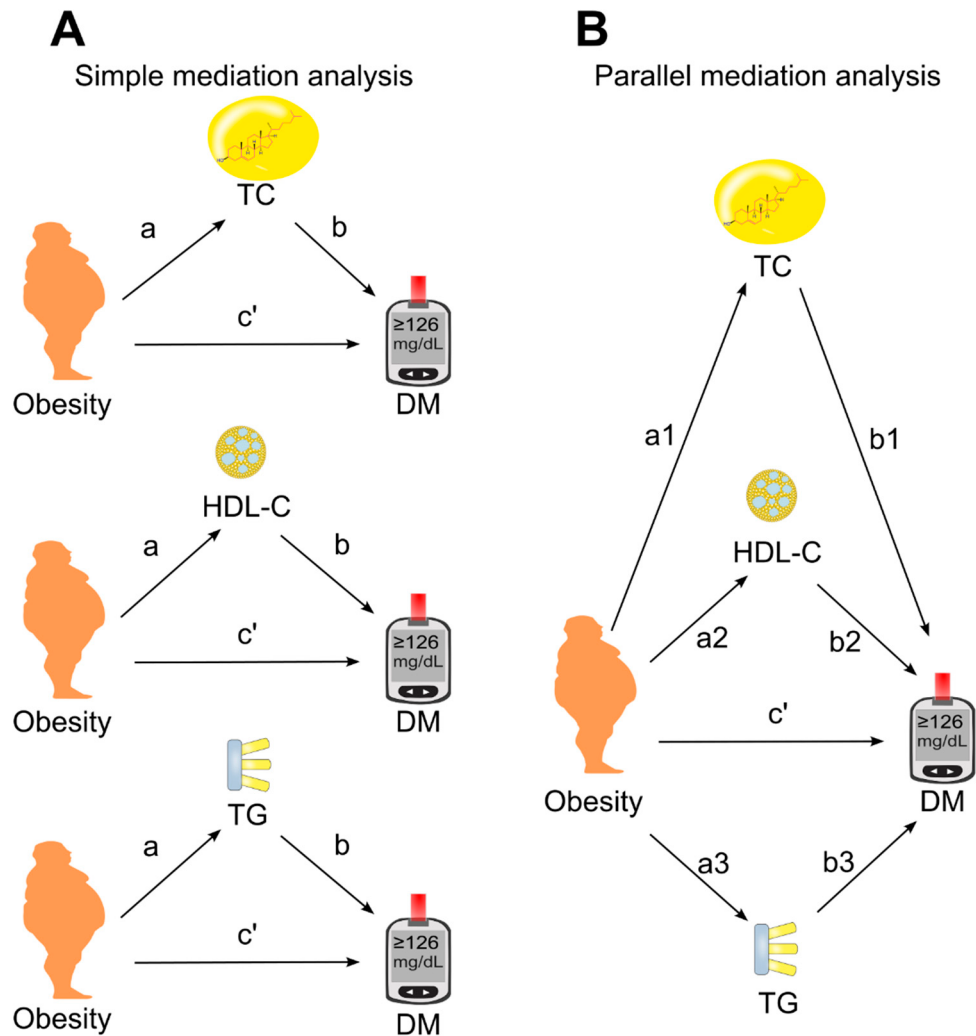


Figure 2. Mediation analysis models. **A**, Simple mediation. Total cholesterol, HDL cholesterol, or triglyceride was added as single mediator between obesity and diabetes. **B**, Parallel mediation. In this analysis, total cholesterol, HDL cholesterol, and triglycerides were added simultaneously to assess their mediation effects between obesity and diabetes. a, association coefficient between obesity and the tested mediator; b, association coefficient between the tested mediator and diabetes; c', also known as direct effect, referring to the association coefficient between obesity and diabetes in the presence of the tested mediator (simple mediation) or mediators (parallel mediation). DM, diabetes; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Further analyses assessed the mediation effect of LDL cholesterol. Participants lacking LDL cholesterol data (n = 3,310) were excluded, leaving 23,517 participants for this analysis (Figure 1). Because LDL cholesterol was highly correlated with total cholesterol (Pearson correlation coefficient

= 0.917, Table 1), it was excluded from the parallel mediation model to avoid collinearity. Instead, its mediation effect was examined using simple mediation analysis, adjusting for all tested confounders as well as HDL cholesterol and triglycerides.

Association coefficients were derived from mediation analysis (Figure 2). Coefficient a represented the association between obesity and the tested mediator, while coefficient b reflected the association between the mediator and diabetes. The direct effect (c') was the association between obesity and diabetes after accounting for the mediator(s). The indirect effect, also referred to as the mediation effect, was calculated as a × b [34]. The 95% confidence interval (CI) for the indirect effect was estimated using bootstrapping [52,53]. A mediation effect was considered statistically significant (p < 0.05) if the 95% CI did not include zero [54]. The proportion mediated was calculated using the formula: Proportion mediated=a × b/(a × b + c'). This metric indicates the extent to which the tested mediator explains the effect of obesity on diabetes [34,55].

Table 1. Bivariate Pearson correlation coefficient among the circulating lipids.

	Total cholesterol	HDL cholesterol	LDL cholesterol
HDL cholesterol	0.154		
LDL cholesterol	0.917	-0.070	
Triglycerides	0.367	-0.317	0.178

HDL-C, high-density lipoprotein; LDL, low-density lipoprotein.

Additional analyses were performed by replacing obesity with body mass index (continuous) in the mediation models.

Triglycerides, body mass index, total cholesterol, and HDL cholesterol were natural log-transformed to improve data distribution prior to inclusion in regression and mediation models [56]. The null hypothesis was rejected for two-tailed p-values < 0.05. All statistical analyses were conducted using SPSS version 27.0 (IBM SPSS Statistics for Windows, Armonk, NY, IBM Corporation).

3. Results

3.1. General Characteristics

This study included 26,627 US adult participants, with a mean age of 48 years. Among these participants, 3958 individuals (14.9%) had diabetes, and 8425 individuals (31.6%) were obese. Compared to non-obese individuals, those with obesity had a higher prevalence of diabetes and hypertension, higher levels of triglycerides, higher levels of total cholesterol, higher levels of LDL cholesterol, lower levels of HDL cholesterol, and less physical activity (Table 2).

Table 2. Characteristics of the 26,627 participants, stratified according to obesity¹.

	Non obese	Obese	Overall	p value
Sample size	18,202	8425	26,627	NA
BMI, kg/m ² , median (IQR)	25 (23–27)	34 (32–38)	27 (24–31)	<0.001
Diabetes, n (%)	1926 (10.6)	2032 (24.1)	3958 (14.9)	<0.001
Glucose, mg/dL, median (IQR)	95 (89–104)	101 (94–114)	97 (90–106)	<0.001
HbA _{1c} , %, median (IQR)	5.3 (5.1–5.6)	5.6 (5.3–6.0)	5.4 (5.1–5.8)	<0.001
TC, mg/dL, median (IQR)	196 (169–225)	198 (172–227)	196 (170–225)	<0.001
HDL-C, mg/dL, median (IQR)	52 (43–64)	46 (39–56)	50 (42–61)	<0.001
LDL-C ² , mg/dL, mean (SD)	119.3 (36.8)	121.3 (36.6)	120.0 (36.8)	<0.001
Triglycerides, mg/dL, median (IQR)	102 (72–150)	131 (91–189)	110 (77–163)	<0.001
Age, y, mean (SD)	48 (19)	49 (17)	48 (19)	<0.001
Sex (male), n (%)	9248 (50.8)	3503 (41.6)	12,751 (47.9)	<0.001
Ethnicity, n (%)				
Non-Hispanic white	8522 (46.8)	3464 (41.1)	11,986 (45)	<0.001

Non-Hispanic black	3567 (19.6)	2265 (26.9)	5832 (21.9)	
Hispanic	4963 (27.3)	2463 (29.2)	7426 (27.9)	
Other	1150 (6.3)	233 (2.8)	1383 (5.2)	
Education, <i>n</i> (%)				
< High School	5790 (31.8)	2786 (33.1)	8576 (32.2)	0.01
High School	4651 (25.6)	2209 (26.2)	6860 (25.8)	
> High School	7761 (42.6)	3430 (40.7)	11,191 (42.0)	
Poverty-income ratio, <i>n</i> (%)				
< 130%	5008 (27.5)	2585 (30.7)	7593 (28.5)	<0.001
130%-349%	6714 (36.9)	3136 (37.2)	9850 (37.0)	
≥ 350%	4929 (27.1)	2032 (24.1)	6961 (26.1)	
Unknown	1551 (8.5)	672 (8.0)	2223 (8.3)	
Physical activity, <i>n</i> (%)				
Active	5351 (29.4)	1696 (20.1)	7047 (26.5)	<0.001
Insufficiently active	6807 (37.4)	3115 (37.0)	9922 (37.3)	
Inactive	6044 (33.2)	3614 (42.9)	9658 (36.3)	
Alcohol consumption, <i>n</i> (%)				
0 drink/week	2957 (16.2)	1775 (21.1)	4732 (17.8)	<0.001
< 1 drink/week	3846 (21.1)	2166 (25.7)	6012 (22.6)	
1-6 drinks/week	4004 (22.0)	1392 (16.5)	5396 (20.3)	
≥ 7 drinks/week	2606 (14.3)	829 (9.8)	3435 (12.9)	
Unknown	4789 (26.3)	2263 (26.9)	7052 (26.5)	
Smoking status, <i>n</i> (%)				
Past smoker	4435 (24.4)	1587 (18.8)	6022 (22.6)	<0.001
Current smoker	4413 (24.2)	2260 (26.8)	6673 (25.1)	
Nonsmoker	9354 (51.4)	4578 (54.3)	13,932 (52.3)	
Hypertension, <i>n</i> (%)				
No	11,963 (65.7)	3919 (46.5)	15,882 (59.6)	<0.001
Yes	5991 (32.9)	4377 (52.0)	10368 (38.9)	
Unknown	248 (1.4)	129 (1.5)	377 (1.4)	
Family history of diabetes, <i>n</i> (%)				
Yes	7239 (39.8)	4340 (51.5)	11,579 (43.5)	<0.001
No	10,626 (58.4)	3931 (46.7)	14,557 (54.7)	
Unknown	337 (1.9)	154 (1.8)	491 (1.8)	

¹Obesity was defined as BMI ≥30 kg/m². ²LDL cholesterol was calculated in 23,517 participants, as 3110 participants did not have the data. Abbreviations: BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; *n*, number; NA, not applicable; SD, standard deviation; TC, total cholesterol.

3.2. Association of Obesity with Diabetes Diagnosis

Obesity was associated with a 2.44-fold higher risk of diabetes (odds ratio, OR, 2.44; 95% CI, 2.25–2.65; *p* <0.001; Model 4, Table 3) after adjustment for risk factors except for the tested mediators (i.e., total cholesterol, HDL cholesterol, and triglycerides). After further adjustment for these tested mediators, obesity remained associated with a higher risk of diabetes (OR, 2.03; 95% CI, 1.87–2.21; *p* <0.001; Model 8, Table 3). This indicates that any mediation by total cholesterol, HDL cholesterol, or triglycerides is partial rather than complete [57].

Table 3. Obesity-associated risk for diabetes in 26,627 participants.

Models	Odds ratio	95% CI	<i>p</i> value
Model 1	2.69	2.51–2.88	<0.001
Model 2	3.11	2.88–3.35	<0.001
Model 3	2.84	2.63–3.07	<0.001

Model 4	2.44	2.25–2.65	<0.001
Model 5 (Model 4 + TC)	2.44	2.25–2.65	<0.001
Model 6 (Model 4 + HDL-C)	2.14	1.97–2.32	<0.001
Model 7 (Model 4 + TG)	2.13	1.96–2.31	<0.001
Model 8 (Model 4 + TC + HDL-C + TG)	2.03	1.87–2.21	<0.001

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. Model 1: Not adjusted; Model 2: Adjusted for age, sex, and ethnicity; Model 3: Adjusted for factors in Model 2 plus poverty-income ratio, education, physical activity, alcohol consumption, smoking status, and survey period; Model 4: Adjusted for factors in Model 3 plus hypertension and family history of diabetes.

3.3. Role of Circulating Lipids in Mediating the Effect of Obesity on Diabetes

The mediation coefficients of total cholesterol, HDL cholesterol, and triglycerides for the effect of obesity on diabetes are displayed in Figures 3–5. When total cholesterol, HDL cholesterol, and triglycerides was added as single mediator in the mediation analysis (simple mediation), all of the three tested parameters were found to play a role in mediating the association between triglycerides and diabetes (Figure 3A), with triglycerides as the most dominant mediator (indirect effect coefficient, 0.18; 95% CI, 0.17–0.20; $p < 0.05$) which accounted for 18% of the total effect of obesity on diabetes (Figure 3A).

When total cholesterol, HDL cholesterol, and triglycerides were included together as mediators in a parallel mediation model, all three continued to mediate the relationship between obesity and diabetes, both without adjustment (Figure 4A) and after adjusting for confounders (Figure 5A). After further adjustment for all the tested confounding factors, increases in triglycerides and reductions in HDL cholesterol mediated 24.0% and 3.8% of the total effect, respectively, whereas an increase in total cholesterol negatively mediated 2.3% of the total effect (Figure 5A).

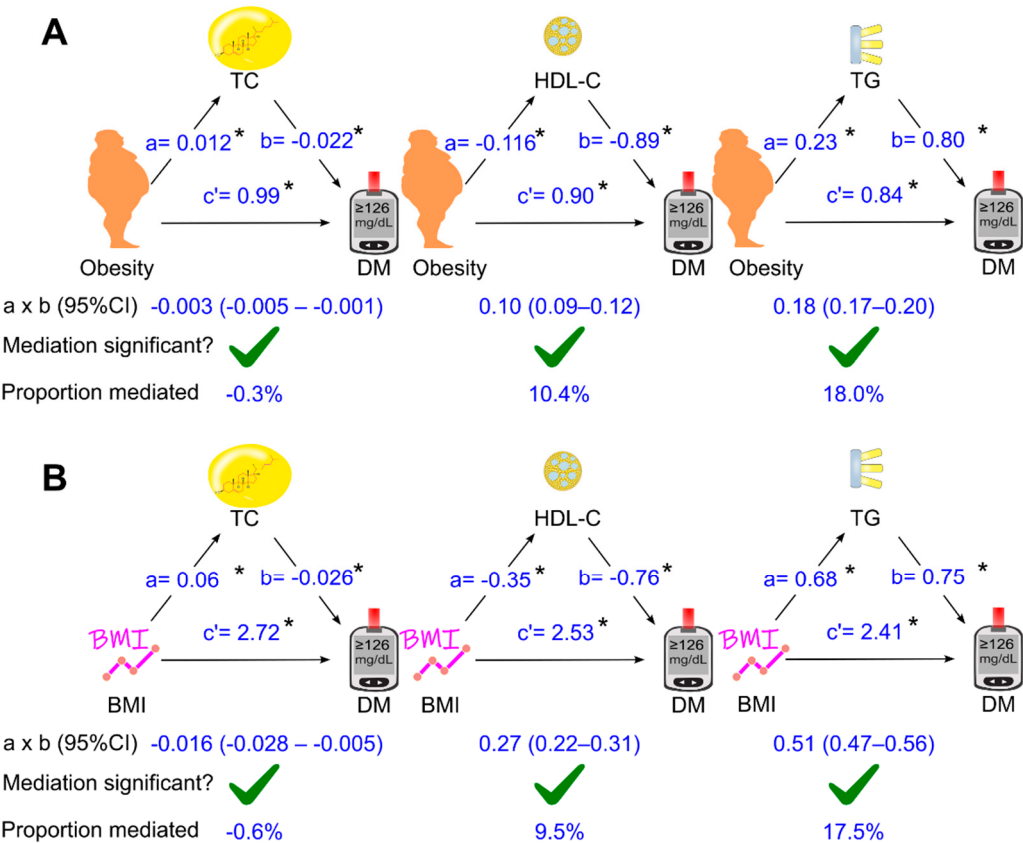


Figure 3. Simple mediation analysis. Total cholesterol, HDL cholesterol, or triglyceride was added as single mediator for the effect of obesity or BMI on diabetes. a, association coefficient between obesity and the tested mediator or between BMI and the tested mediator; b, association coefficient between the tested mediator and

diabetes; c' , association coefficient between obesity and diabetes or between BMI and diabetes in the presence of the tested mediator. BMI, body mass index; CI, confidence interval; DM, diabetes; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. Green tick=yes.

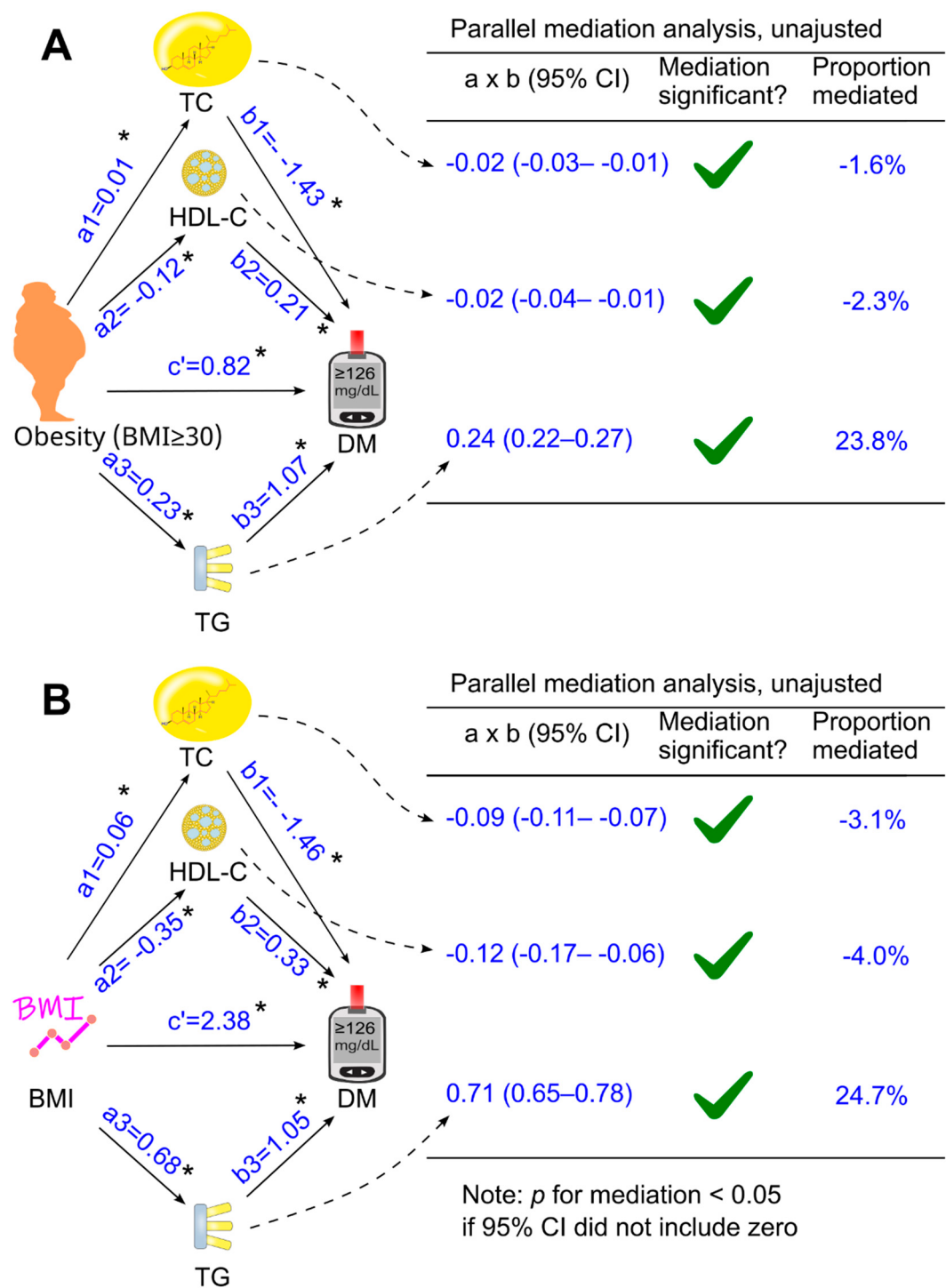


Figure 4. Unadjusted parallel mediation analysis. Total cholesterol, HDL cholesterol, and triglycerides were added as parallel mediators for the effect of obesity (or BMI as continuous variable) on diabetes without adjustment for confounding factors. a , association coefficient between obesity and the tested mediator or between BMI and the teste mediator; b , association coefficient between the tested mediator and diabetes; c' , association coefficient between obesity and diabetes or between BMI and diabetes. BMI, body mass index; CI, confidence interval; DM, diabetes; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. Green tick = yes. Red cross = no.

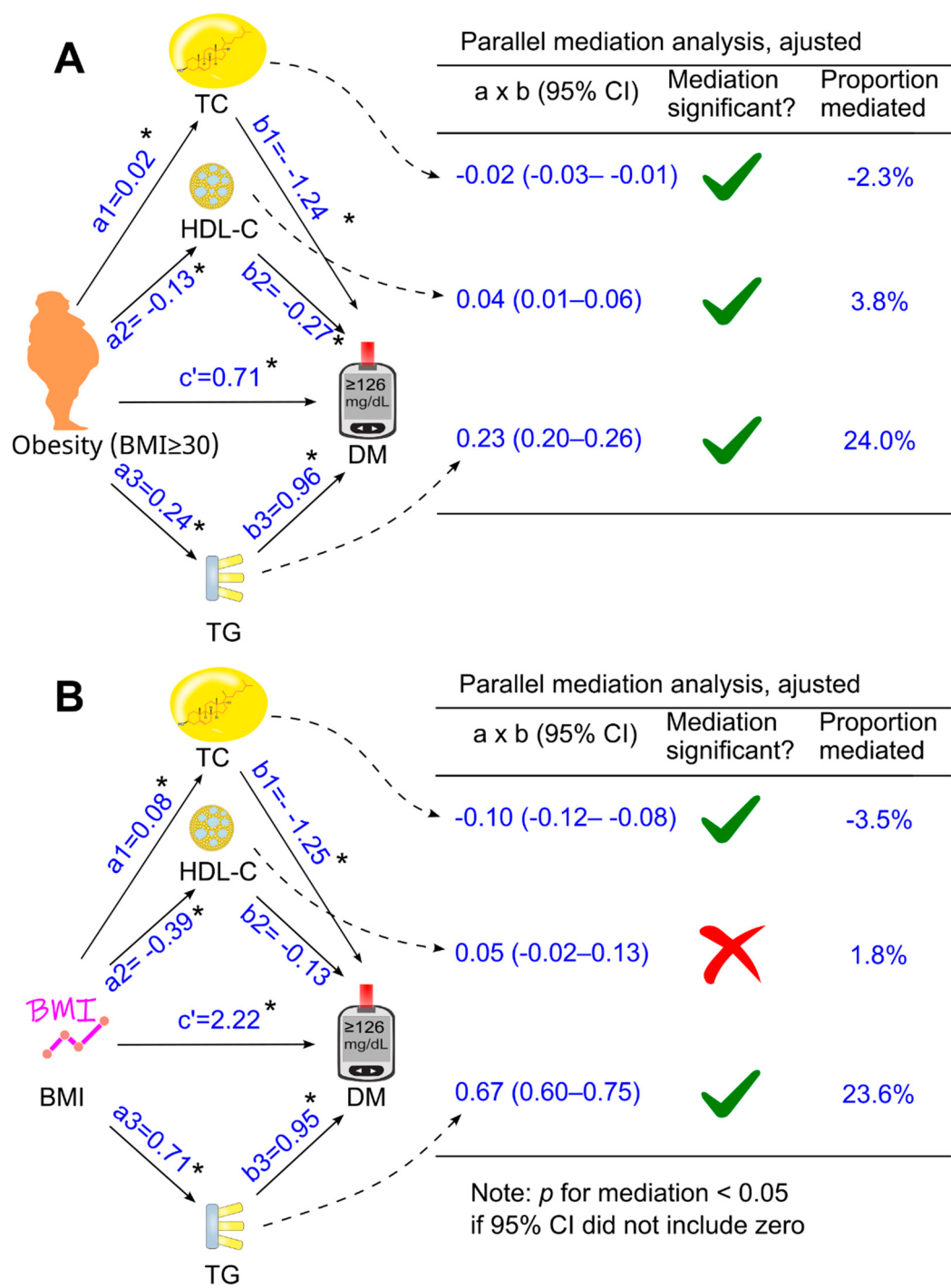


Figure 5. Parallel mediation analysis with adjustment for confounding factors. Total cholesterol, HDL cholesterol, and triglycerides were placed simultaneously into the analysis as parallel mediators for the effect of obesity or BMI on diabetes. This analysis was adjusted for confounding factors, including age, sex, ethnicity, poverty-income ratio, education, survey period, lifestyle confounding factors (physical activity, alcohol consumption, and smoking status), clinical confounding factors (hypertension and family history of diabetes). Abbreviations: a, association coefficient between obesity and the tested mediator, or between BMI and the tested mediator; b, association coefficient between the tested mediator and diabetes; c', association coefficient between obesity and diabetes or between BMI and diabetes in the presence of the tested mediators. BMI, body mass index; CI, confidence interval; DM, diabetes; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. The green tick represented yes and the red cross represented no.

3.4. Role of Circulating Lipids in Mediating the Effect of Body Mass Index on Diabetes

Further analyses were conducted when obesity was replaced with a continuous variable, i.e., body mass index (Figures 3B, 4B & 5B). After adjustment for all the tested confounders, the parallel mediation analysis showed that triglycerides remained the most dominant mediator among the three tested mediators, mediated 23.6% of the association between body mass index and diabetes, and total cholesterol remained to slightly and negatively mediate the association by 3.5% (Figure 5B). However, HDL cholesterol did not mediate the effect of body mass index on diabetes (Figure 5B, $p > 0.05$)

3.5. Further Analyses of the Role of LDL Cholesterol in Mediating the Effect of Obesity (or Body Mass Index) on Diabetes

Further analyses were conducted in a sub-cohort of 23,517 participants after 3110 participants were excluded due to missing LDL cholesterol. After adjustment for all the tested confounders, an increase in LDL cholesterol negatively mediated 1% of the effect of obesity on diabetes, but this mediation effect was not significant ($p > 0.05$, Figure 6). However, when obesity was replaced by the body mass index, an increase in LDL cholesterol negatively mediated 3% of the effect of body mass index on diabetes ($p < 0.05$, Figure 6).

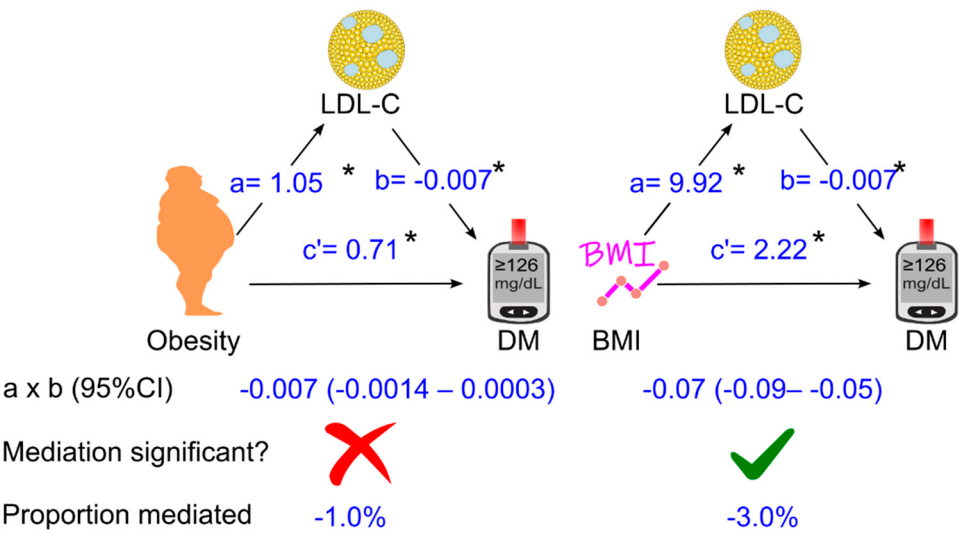


Figure 6. Association coefficients of LDL cholesterol for mediating the effect of obesity or BMI on diabetes in 23,517 participants. The analysis was adjusted for age, sex, ethnicity, poverty-income ratio, education, survey period, lifestyle confounding factors (physical activity, alcohol consumption, and smoking status), clinical confounding factors (hypertension and family history of diabetes, HDL cholesterol and total cholesterol). Abbreviations: a, association coefficient between obesity and LDL cholesterol, or between BMI and LDL cholesterol; b, association coefficient between LDL cholesterol and diabetes; c', association coefficient between obesity and diabetes or between BMI and diabetes in the presence of the tested mediators and confounders. BMI, body mass index; CI, confidence interval; DM, diabetes; HDL, high-density lipoprotein. The green tick represented yes and the red cross represented no.

4. Discussion

Utilizing a large sample of US adults ($n = 26,627$), this study found that the increase in triglycerides and the decrease in HDL cholesterol mediated 24.0% ($p < 0.05$) and 3.8% ($p < 0.05$) of the pro-diabetic effect of obesity, respectively, after adjusting for tested confounders. In contrast, total cholesterol negatively mediated the effect by 2.3% ($p < 0.05$), and LDL cholesterol was not a significant

mediator. These findings indicate that triglycerides are the most influential circulating lipid mediating the pro-diabetic effect of obesity.

Our analysis showed that total cholesterol negatively mediated the pro-diabetic effect of obesity by 2.3%, a small but statistically significant magnitude. LDL cholesterol showed a negative mediation of 1%, which was not statistically significant. However, when body mass index was used instead of obesity, LDL cholesterol significantly and negatively mediated the effect on diabetes, though the magnitude remained small (3.0%).

Overall, these results suggest that although obesity is associated with increased total and LDL cholesterol, these lipids do not play a major role in mediating its pro-diabetic effect. They may even provide slight protection against obesity-related diabetes risk. The mechanisms underlying these observations remain unclear. Nevertheless, our findings align with existing literature showing that lowering cholesterol and LDL cholesterol with statins slightly increases type 2 diabetes risk by approximately 10%–12% [58–62]. Statins reversibly and competitively inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis [63], thereby reducing cholesterol production and circulating total cholesterol. Additionally, statin-induced reductions in intracellular cholesterol upregulate LDL receptors (LDLR) in the liver and peripheral tissues, enhancing LDL clearance and lowering circulating LDL cholesterol [62,64].

This study also found that HDL cholesterol mediated 3.8% of the effect of obesity on diabetes. Obesity was associated with decreased HDL cholesterol, consistent with previous reports [27–29]. This reduction contributed to increased diabetes risk, supporting evidence that HDL cholesterol protects against type 2 diabetes [65,66] through mechanisms such as stimulating pancreatic insulin synthesis and secretion [67] and enhancing skeletal muscle glucose uptake [68]. Similarly, treatment with cholesteryl ester transfer protein (CETP) inhibitors to raise HDL cholesterol improved glycemic control in patients with type 2 diabetes [69]. Notably, the reduction in HDL cholesterol played only a minor role (3.8%) in mediating the pro-diabetic effect of obesity, and this effect disappeared when body mass index replaced obesity in the analysis.

Triglycerides, unlike total cholesterol, LDL cholesterol, and HDL cholesterol, played a substantially greater role in mediating the pro-diabetic effect of obesity, accounting for 24% of the total effect. We observed that obesity was associated with elevated triglyceride levels, consistent with previous reports [24,26,70]. Furthermore, this increase in triglycerides was linked to a higher risk of diabetes, in agreement with existing literature [36,71,72]. Mechanistically, elevated circulating triglycerides promote intracellular triglyceride accumulation and reduce the capacity of cells to store excess glucose as triglycerides, thereby inducing insulin resistance [73]. In addition, high triglyceride levels contribute to β -cell dysfunction [74,75] and apoptosis [76], as well as increased hepatic gluconeogenesis [73,77,78]. Collectively, these mechanisms underscore the role of triglycerides in diabetes development.

The significance of triglycerides in mediating the pro-diabetic effect of obesity is further supported by evidence from bariatric surgery. Weight loss induced by bariatric surgery improves glycemic control and often leads to diabetes remission [79–81]. Notably, these improvements occur without significant changes in total cholesterol [79,81] or LDL cholesterol [80,81], reinforcing our observation that these lipids play only a minor role in mediating obesity's pro-diabetic effect. Although bariatric surgery is frequently associated with increased HDL cholesterol [79,80], HDL cholesterol does not appear to be a major contributor to the anti-diabetic effect. For example, Genua et al. reported that blood glucose levels declined within three months post-surgery, while HDL cholesterol decreased during this period; although HDL cholesterol subsequently increased and remained elevated for up to five years, changes in body mass index were not associated with changes in HDL cholesterol [81].

In contrast, bariatric surgery consistently reduces circulating triglyceride levels [79,80,82,83]. This reduction parallels a decrease in intracellular triglyceride deposition in the liver and skeletal muscle [84]. These findings suggest that triglycerides may play a central role in mediating the anti-

diabetic effects of weight loss, consistent with our observation that triglycerides accounted for 24% of the total effect of obesity.

Evidence from dietary energy restriction-induced weight loss further supports our findings. Lim et al. [85] reported that dietary energy restriction led to weight loss and reduced blood glucose levels within one week of intervention. However, at this time point, no changes in HDL cholesterol or LDL cholesterol were observed, suggesting that these lipids may not play a major role in mediating the antidiabetic effect of dietary energy restriction-induced weight loss—consistent with our results. In contrast, Lim et al. [88] found that the antidiabetic effect of dietary energy restriction-induced weight loss was accompanied by a reduction in circulating triglycerides. Moreover, a decline in intracellular triglyceride content in the pancreas was associated with restored insulin secretion, while a similar decline in the liver corresponded with reduced hepatic glucose production and lower fasting plasma glucose [85,86]. These findings suggest that lowering circulating triglycerides may contribute significantly to the antidiabetic effect of dietary energy restriction-induced weight loss.

Taken together, our results and evidence from weight-loss studies [79–86], support the notion that circulating triglycerides—rather than total cholesterol, HDL cholesterol, or LDL cholesterol—play a key role in mediating the pro-diabetic effect of obesity. Therefore, targeting circulating triglycerides may represent a promising therapeutic strategy to reduce obesity-induced diabetes risk.

Strengths of this study include its large sample size and adjustment for multiple confounding factors. However, the findings were based on US participants and may not be generalizable to other populations.

5. Conclusions

This study demonstrates that among circulating lipids, triglycerides play the central mediating role in the pro-diabetic effect of obesity. Consequently, targeting circulating triglycerides may be an underrecognized therapeutic approach for managing obesity-related diabetes

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Abbreviations

The following abbreviations are used in this manuscript:

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CETP	Cholesteryl ester transfer protein
CI	Confidence interval
DM	Diabetes
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol

HSDA	N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline
IQR	Interquartile range
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
n	Number;
NA	Not applicable
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PEG	Polyethylene glycol
SD	Standard deviation
TC	Total cholesterol
TG	Triglyceride
VLDL	Very low-density lipoprotein
WHO	World Health Organization

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