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The association between the ratio of triglyceride to high-density lipoprotein cholesterol and incident type 2 diabetes in Singapore Chinese men and women

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Abstract

Background—Increased triglycerides (TG) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels are risk factors for type 2 diabetes (T2D). However, previous studies reached inconsistent results between ratio of TG-to-HDL-C (TG/HDL-C) and T2D risk, and it was unclear whether the association was modified by gender, body mass index, or fasting status.

Methods—Blood biomarkers, including TG and HDL-C levels, were assayed among 571 T2D cases and 571 controls in a case-control study nested within Singapore Chinese Health Study. Participants were free of diagnosed diabetes, cardiovascular disease, and cancer at blood collections (1999-2004). Incident self-reported T2D cases were identified at follow-up II interview (2006-2010). Controls were 1:1 matched for age, sex, dialect group and date of blood collection. Multivariable logistic regression models were used to compute the odds ratio (OR) and 95% confidence interval (CI) between lipid profile and T2D risk with adjustment for diabetes risk factors.

Results—The OR (95% CI) of T2D was 1.70 (1.39-2.09) per 1-SD increment in TG, and 1.72 (1.37-2.17) per 1-SD increment in TG/HDL-C ratio. The relations were stronger among female than male (*P* for interaction = 0.028 and 0.017, respectively), and stronger among lean participants (<23 kg/m²) than their overweight/obese counterparts (*P* for interaction = 0.051 and 0.046, respectively). TG and TG/HDL-C ratio improved T2D prediction with similar magnitude.

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Conclusions—TG and TG/HDL-C ratio are independent risk factors for incident T2D, and they confer greater risk in women and in lean participants. TG/HDL-C ratio is not a better predictor of diabetes than TG alone.

Keywords

HDL cholesterol; nested case-control study; triglycerides; type 2 diabetes mellitus

Introduction

Dyslipidemia, especially increased triglycerides (TG) levels together with decreased high-density-lipoprotein cholesterol (HDL-C) levels, is strongly correlated with insulin resistance and type 2 diabetes (T2D).¹ Mechanistic studies suggested that high TG and low HDL-C levels may be causal factors for T2D,² and this inference was supported by various epidemiological and genetic studies. Prospective human studies have found that high TG and low HDL-C levels are independent risk factors for T2D, and TG and/or HDL-C values have been included in models to predict T2D risk.^{3, 4} Moreover, a recent Mendelian randomization study showed that genetic predisposition to high TG levels or low HDL-C levels were causally related to elevated T2D risk.⁵

Although recent studies demonstrated that the TG-to-HDL-C (TG/HDL-C) ratio could be better predictor for insulin resistance and cardiovascular disease than TG or HDL-C alone,^{6, 7} the association between TG/HDL-C ratio and T2D is not entirely clear yet. So far only a few prospective studies examined this issue,⁸⁻¹³ and the extent to which TG/HDL-C ratio is independently related to T2D risk has been variable. Some studies found positive association,⁸⁻¹² while one study showed null association.¹³ Moreover, few studies have explored whether the association is modified by gender,^{8, 10} and fasting status.¹⁰ One study reported a slightly stronger association between TG/HDL-C ratio in women compared to men,⁸ although formal interaction test was not performed. Another study found association between TG/HDL-C ratio and T2D risk in both men and women, regardless of fasting status.¹⁰ Additionally, previous studies have found ethnic differences in ability of TG/HDL-C ratio to identify insulin resistance.^{6, 14} Since Asians develop T2D at lower body mass index (BMI) compared to western populations,¹⁵ lipids may play a more important role in T2D development in relatively lean Asian populations. However, to our best knowledge, no study has explored whether the association between TG/HDL-C ratio and T2D risk is modified by BMI. Moreover, it is unknown whether TG/HDL-C ratio adds substantial predictive information for T2D. Two studies reported the predictive ability of TG/HDL-C ratio together with other risk factors for T2D, without presenting discrimination improvement by TG/HDL-C ratio alone.⁸ Another study reported TG/HDL-C ratio improved T2D prediction, however, the sample size was small (74 T2D cases).⁹

To address these issues, we conducted a nested case-control study within the Singapore Chinese Health Study (SCHS) to examine the relationship between TG/HDL-C ratio and risk of incident T2D as well as possible interaction with gender, obesity and fasting status. Moreover, we evaluated the predictive utility of TG/HDL-C ratio, TG alone, HDL-C alone, on top of other diabetes risk factors.

Methods

Study population

The design of the SCHS has been described previously.¹⁶ Briefly, the SCHS was established between 1993 and 1998, and recruited 63,257 Chinese adults aged 45-74 years. At recruitment, an in-person interview was conducted using a structured questionnaire to collect health-related information. Follow-up I was conducted via telephone between 1999 and 2004 to update selected lifestyle habit and medical history. A total of 52,322 participants were re-contacted successfully, and 32,535 consenting participants donated their bio-specimens. Follow-up II was conducted from 2006 to 2010, and 39,528 participants were re-contacted successfully. Among the 32,535 participants with available bio-specimens, 25,477 (78.3%) were contacted in the follow-up II. The study protocol was approved by the Institutional Review Boards at the National University of Singapore.

Ascertainment of diabetes and other covariates

History of physician-diagnosed diabetes was asked at baseline and both follow-ups by the question: "Have you been told by a doctor that you have diabetes?" If the answer was "yes", participants were also asked for the age at which they were first diagnosed. The robustness and accuracy (98.9%) of the self-reported diabetes data was validated in a separate study analyzing 1651 cohort participants (949 cases by medical records and 702 via phone interview).¹⁷

Body weight and height were self-reported at baseline and both follow-ups. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Alcohol consumption was coded as never, weekly and daily drinking and smoking status as never, former, and current smoking based on the follow-up I questionnaires. Weekly moderate-to-vigorous activity levels (<0.5, 0.5-3.9, and 4.0 hours/week) and education level (no, primary school, secondary school and above) were obtained from the baseline questionnaires.

Case and control selection

A nested case-control study of 571 cases and 571 matched controls within SCHS was established for the current analysis. All cases and controls were free of physician-diagnosed diabetes, cardiovascular disease and cancer at baseline interview as well as blood collection (1999-2004). Cases were those who reported to be diagnosed with incident diabetes during follow-up II visits (2006-2010). Controls were selected from the remaining participants who were free of T2D at follow-up II, and were matched for age (± 3 years), date (± 6 months) of blood collection, sex, and dialect group with the cases on a 1:1 ratio. In addition, the selected controls were screened for the presence of undiagnosed T2D at the time of blood donation by measuring haemoglobin A1c (HbA_{1C}) level. All matched controls with HbA_{1C} 6.0% were ineligible for the study and excluded, and a replacement control with the same matching criteria was randomly chosen among the remaining eligible controls.

Laboratory Procedures

20-mL peripheral blood was obtained from each consenting participant. The tubes were put on ice during transport from the participants' homes to the laboratory immediately after the blood collection. All specimens were separated into various components (plasma, serum, red blood cells, and buffy coat). All specimens were subsequently stored in -80°C freezers for long-term storage. Frozen plasma aliquots from cases and controls were selected for simultaneous analysis at the same batch at the National University Hospital Reference Laboratory.

Plasma concentrations of total cholesterol, TG, HDL-C and high-sensitivity C-reactive protein (CRP) were measured via colorimetric method on a chemistry analyzer (AU5800 Analyzer, Beckman Coulter, Brea, California). Adiponectin levels were measured by ELISA (Bio-Rad Laboratories, Hercules, California). LDL-C levels were calculated using the Friedewald formula: $\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides}/2.2$; where TG did not exceed 4.5 mmol/L. Thus, 44 participants had missing values for LDL cholesterol because of high TG levels.

Statistical Analysis

Based on the distribution among control participants, lipid measures (HDL-C, LDL-C, TG, and TG/HDL-C ratio) were divided into tertiles, and the lowest tertile served as the reference group. We used conditional logistic regression to model the association between lipid measures and T2D risk with adjustment for age at blood collection (continuous), smoking status (never, past, and current smoker), alcohol intake (never, weekly or daily), weekly moderate-to-vigorous activity levels (<0.5 , $0.5\text{--}3.9$, and 4.0 hours/week), education level (no, primary school, secondary or above), history of hypertension (yes, no), fasting status (yes, no), BMI (continuous), and plasma concentrations of CRP and adiponectin in tertiles. We also calculated the odds ratio of T2D per standard deviation (SD) increment in lipid measures with the same adjustment abovementioned. We tested potential interactions between lipid measures and gender, obesity, and fasting status. We used unconditional logistic regression models with additional adjustment for matching factors on gender (male, female) and dialect group (Cantonese, Hokkien) when performing stratified analysis on obesity and fasting status.

To assess the predictive utility of each lipid measure, we established a parsimonious logistic regression model including education level, weekly activity, history of hypertension, and BMI using a forward selection procedure ($P < 0.05$). The improvement in discrimination was examined by comparing area under receiver-operating characteristic curve (AUC) between the parsimonious model and the model plus one lipid measure using the method from DeLong.¹⁸ Moreover, due to the limitation of AUC such as its insensitivity to model improvement,¹⁹ we also evaluated the category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI) statistics.²⁰ NRI is calculated from a sum of differences between higher predicted risk for events and lower predicted risk for non-events,²⁰ while IDI is based on differences in integrated average sensitivities and 'one minus specificities' between models with and without the new biomarker.²⁰ Furthermore, the goodness-of-fit of all models were assessed by Akaike information criteria (AIC), where a

lower AIC value indicates better model fit. Additionally, we tested the predictive utility of these lipid measures in different gender, and BMI groups. Analyses were performed with Stata software, version 11.0 (Stata Corp, College Station, Texas).

Results

Among T2D cases, the mean age of diagnosis (SD) was 63.2 (6.4) years and the mean duration (SD) between blood donation and diagnosis of T2D was 4.0 (1.7) years. The baseline characteristics of cases and controls are shown in Table 1. Cases had high-risk profiles except for the matching factors. They had higher BMI, and were more likely to have history of hypertension. No significant differences were found for education level, cigarette smoking, alcohol consumption, physical activity levels and fasting status. Cases had higher baseline levels of CRP, TG, and TG/HDL-C ratio, and lower adiponectin and HDL-C levels. LDL-C levels were not different between cases and controls.

Among the healthy control participants, TG/HDL-C ratio was inversely correlated with levels of HDL-C, LDL-C, and plasma adiponectin levels (Pearson's coefficient $r = -0.76$, -0.17 , and -0.49 , respectively; all $P < 0.001$), and positively correlated with TG level, BMI and plasma CRP levels (Pearson's coefficient $r = 0.95$, 0.19 and 0.14 , respectively; all $P < 0.01$; Supplementary table 1).

The associations between lipid measures and risk of incident T2D were presented in Table 2. Higher levels of TG and TG/HDL-C ratio were positively associated with risk of T2D, while increased HDL-C levels were inversely associated with T2D risk. However, LDL-C was not significantly associated with T2D risk. In the final model, T2D risk was increased by 70% per 1-SD increment in TG (odds ratio [OR] 1.70; 95% confidence interval [CI], 1.39-2.09), and 72% per 1-SD increment of TG/HDL-C ratio (OR 1.72; 95% CI, 1.37-2.17), while decreased by 32% per 1-SD increment in HDL-C (OR 0.68; 95% CI, 0.56-0.82).

We further performed stratified analysis to explore whether the observed associations were modified by gender (Table 3), BMI (Table 4), or fasting status (Supplementary table 2). The associations of TG and TG/HDL-C ratio with T2D risk were stronger among women than among men (P for interaction = 0.028 and 0.017, respectively), and stronger among lean participants ($< 23 \text{ kg/m}^2$) than among overweight/obese participants ($\geq 23 \text{ kg/m}^2$) (P for interaction = 0.051 and 0.046, respectively). The associations were consistent across all other subgroups and interaction tests were not statistically significant.

The summary statistics for the predictive performance of lipid measures was presented in Table 5. Compared with the AUC of the base model, inclusion of HDL-C, TG or TG/HDL-C ratio significantly improved AUCs ($P < 0.05$) with similar magnitude. Furthermore, the positive values of NRIs and IDIs also suggested that inclusion of lipid measures improved T2D risk prediction significantly (all $P < 0.001$). Although TG had slightly higher NRI and IDI than TG/HDL-C ratio and HDL-C, overall the three lipid measures had similar improvement in T2D prediction. Moreover, the NRI table stratified for T2D cases and controls was presented in Supplementary table 3. Specifically, the inclusion of HDL-C resulted in 24.3% of T2D cases correctly assigned to a higher predicted T2D risk and 6.5%

of controls correctly assigned to a lower predicted T2D risk. When TG and TG/HDL-C ratio was added to the model separately, 0.9% and -5.4% of cases were reclassified as higher T2D risk, while 40.4% and 42.9% of controls were reclassified as lower T2D risk, respectively. When stratified by gender, the improvement of three lipid measures in T2D prediction was only found in women (Supplementary table 4). However, when stratified by BMI level, the performance of lipid measures was consistent across all subgroups (Supplementary table 5).

Discussion

In this case-control study nested within the Singapore Chinese Health Study, we found that TG and TG/HDL-C ratio were associated with increased risk of incident T2D, while HDL-C was related to a lower risk of T2D. Moreover, the positive associations with TG and TG/HDL-C ratio were significantly stronger among women and lean participants compared to their counterparts. Furthermore, TG, HDL-C, and TG/HDL-C ratio all significantly improved T2D risk prediction, but TG/HDL-C ratio was not a better predictor than TG alone.

Our finding of positive association between TG/HDL-C ratio and T2D risk was supported by previous studies in Chinese,⁹ Iranian,^{8, 12} Japanese,¹⁰ and Caucasian men,¹¹ despite the heterogeneity in statistical methods (studies modeled TG/HDL-C ratio as continuous variable,^{8, 9} binary variable with a cutoff point,^{11, 12} or quartiles¹⁰). However, one prospective study showed null association.¹³ This study was conducted in a group of Iranian people (without diabetes) with family history of diabetes, and participants had much higher BMI and TG/HDL-C ratio compared to the current study (mean BMI: 29 vs. 23; TG/HDL-C ratio: 4.0 vs 1.3); therefore, TG/HDL-C ratio may not predict T2D risk in this specific high-risk population. In our study, we found similar strength of association with TG and TG/HDL-C ratio for diabetes risk, which was in accordance with previous studies.^{8, 9} Moreover, LDL-C was not associated with T2D risk in our study, which was in agreement with the findings from the Framingham Heart Study.²¹

The possible causal relation between high TG and low HDL-C levels and T2D risk was supported by several lines of evidence. Lipotoxicity, inflammation and endoplasmic reticulum stress are three widely-accepted mechanisms causing insulin resistance.²²⁻²⁴ Recent data indicate that high TG levels provoke lipotoxicity, cause overload of free fatty acids levels in the skeletal muscle and pancreas, and lead to insulin resistance, beta-cell dysfunction and apoptosis.²⁵ Meanwhile, high TG levels could directly promote inflammation or endoplasmic reticulum stress.¹ Additionally, low HDL-C levels may influence glucose homeostasis through reducing insulin secretion, insulin sensitivity and direct glucose uptake by muscle via the AMP-activated protein kinase.²² Results from prospective studies across ethnic groups also reported that high TG levels and low HDL-C levels were independent risk factors for T2D risk.^{3, 4} Moreover, clinical trials conducted in high-risk populations showed that drugs to decrease TG levels and increase HDL-C levels (e.g. bezafibrate) can lower the T2D risk.²⁶ Furthermore, a recent Mendelian randomization study testing 25 loci (account for 10% of the genetic variation) further supported the causal relation between high TG and low HDL-C levels with T2D risk,⁵ although a previous Mendelian randomization study with fewer loci (10 loci accounting for 3-5% of the genetic

variation) implied no causal relation.²⁷ Taken together, these findings suggested that we may be able to prevent T2D by modulating TG and HDL-C levels.

In addition, our study showed significant gender differences in the relation of TG and TG/HDL-C ratio with T2D risk, and the associations were significantly higher in women than men. Similarly, the same finding was also reported in an Iranian population, although formal interaction test was not performed.⁸ In addition, the observed gender difference in the association was also supported by other studies of TG and T2D risk prediction in a Japanese population,¹⁰ and of TG/HDL-C ratio and insulin resistance in population of primarily European ancestry.²⁸ However, further studies are warranted to confirm this finding in other populations. The underlying mechanism for the observed gender difference is unclear and we speculate that it may be due to sex hormones. Decline in estrogen levels after menopause leads to dysregulation of glucose and lipid metabolism,²⁹ and thus may put women under greater risk of developing T2D. Similar pattern has been observed for the association between TG levels and increased cardiovascular disease risks where it is stronger in women than men,³⁰ and the National Cholesterol Education Program has suggested more aggressive targets for HDL-C and TG in women to prevent cardiovascular disease compared to men.³¹ Therefore, the finding from the present study, along with previous studies,^{8, 10, 28} implied that the gender difference should be considered in T2D prevention as well.

Moreover, our study found slightly higher relations of TG and TG/HDL-C ratio with T2D risk in lean people than their heavier counterparts. Although the underlying mechanism is unclear yet, we thought that one possible explanation for the observed interaction with obesity might be due to the differences in the dominant pathogenesis pathway driving T2D development between lean and obese individuals. In lean people, dyslipidemia may play a more important causal role in T2D development, while in obese counterparts, other mechanism related to adiposity, such as low-grade inflammation, may play a more prominent role. Alternatively, in obese people, the increased T2D risk by increased TG may be attenuated by other mechanisms. For example, adiponectin was associated with significantly decreased risk of T2D in obese people, but its effect was less apparent in non-obese counterparts in Western and Asian populations.^{32, 33} Nevertheless, the sample size for the subgroup analysis was small and the results should be interpreted cautiously.

The finding also highlights that lean appearance does not necessarily equal to being healthy. Therefore, it is important for clinical practice to identify lean people with high TG levels as high risk population of developing T2D, and lean people may receive greater benefit from decreasing T2D risk by altering lipid levels compared to overweight/obese people. However, Asians tend to develop T2D at lower BMI compared to western populations,¹⁵ which may partly due to their propensity to store fat viscerally rather than subcutaneously.³⁴ In addition, compared with non-Asian populations, Asians are more insulin resistant even in relatively lean individuals, and had lower beta cell function to overcome insulin resistance.³⁵ Due to the biological differences between Asians and non-Asians, whether the observed interaction with BMI in the current study remains in non-Asian populations is unclear.

Our study found that TG, HDL-C, and TG/HDL-C ratio improved T2D risk prediction with similar magnitude. In line with our study, Hadaegh et al⁸ also found same improvements in

AUCs by TG, HDL-C (only in women) and TG/HDL-C ratio. Additionally, He et al⁹ also found similar AUC improvements between TG and TG/HDL-C, and the value was similar to the present study. Although recent studies suggested that TG/HDL-C ratio could be better predictor for insulin resistance and cardiovascular disease than TG or HDL-C alone,^{6, 7, 36} the superiority of TG/HDL-C ratio in disease prediction was not observed for T2D.

The strength of the current study was the prospective design and hence the presumed lack of recalled bias in exposure data (questionnaires, collected bio-specimen) prior to T2D diagnosis. However, there are some limitations as well. First, we measured TG and HDL-C only once at baseline, thus may not represent long-term lipid profile. However, these would lead to non-differential misclassification and may underestimate the association. Second, incident diabetes was obtained from self-reported information, although our validation study suggested that individuals who reported to have diabetes were more likely to be true diabetes cases, undiagnosed diabetes may still exist in the population. Third, more than 70% of blood samples were non-fasting, and therefore may influence the lipid levels. However, we performed stratified analysis among fasting and non-fasting group, and found similar associations between lipid measures and T2D risk in two groups, indicating non-fasting status did not influence the associations in the present study. Recent European clinical guideline also concluded that “fasting is not routinely required for determination of a lipid profile”.³⁷ Moreover, current study used matched case-control study design, although it is valid in studying associations, recent studies pointed out it may introduce bias when studying predictive utility of biomarkers.^{38, 39}

Conclusion

In conclusion, the current study demonstrated a strong, dose-dependent relation of TG and TG/HDL-C ratio with T2D risk, and the association was stronger in women and in lean participants compared to their counterparts. Additionally, both TG and TG/HDL-C ratio improved T2D risk prediction significantly, but TG/HDL-C ratio was not a better predictor than TG alone. Our findings suggest that women and lean people may receive greater benefit from decreasing T2D risk by altering lipid levels compared to men and overweight/obese people. Further research is needed to validate the findings and investigate the biochemical and genetic mechanisms for the associations and the heterogeneity observed between TG levels and the development of T2D.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key points

1. Significant findings of the study
 - TG and TG/HDL-C ratio was independently associated with increased risk of incident type 2 diabetes. Both associations were significantly stronger in women and lean participants compared to their counterparts.
 - TG and TG/HDL-C ratio improved T2D prediction with similar magnitude.
2. What this study adds
 - This study conducted formal interaction tests and showed that the association between TG/HDL-C ratio and T2D risk was stronger in women and in lean participants. Additionally, the predictive utility of TG/HDL-C ratio for T2D is no better than TG alone.

Table 1
Baseline characteristics and plasma biomarkers of diabetes cases and matched controls.*

	Cases (n =571)	Controls (n =571)	P-value
Age (years) at blood taken	59.6 ± 6.1	59.7 ± 6.2	-
Gender (Female)	335 (58.7)	335 (58.7)	-
Dialect (%)			-
Cantonese	287 (50.3)	287 (50.3)	
Hokkien	284 (49.7)	284 (49.7)	
Body mass index (kg/m ²)	24.8 ± 3.6	22.8 ± 3.3	<0.001
Level of education (%)			0.26
No formal education	104 (18.2)	99 (17.3)	
Primary school	255 (44.7)	233 (40.8)	
Secondary and above	212 (37.1)	239 (41.9)	
History of Hypertension (%)	265 (46.4)	148 (25.9)	<0.001
Cigarette smoking (%)			0.15
Never smokers	410 (71.8)	425 (74.4)	
Former smoker	63 (11.0)	71 (12.4)	
Current smokers	98 (17.2)	75 (13.1)	
Weekly moderate activity (%)			0.11
<0.5 hours/week	456 (79.9)	454 (79.5)	
0.5-3.9 hours/week	82 (14.4)	68 (11.9)	
4 hours/week	33 (5.8)	49 (8.6)	
Alcohol Intake (%)			0.81
Abstainers	498 (87.2)	497 (87.0)	
Weekly drinkers	55 (9.6)	59 (10.3)	
Daily drinkers	18 (3.2)	15 (2.6)	
Fasting status (yes)	178 (31.2)	156 (27.3)	0.15
TC, mmol/L	5.3 ± 1.0	5.2 ± 0.9	0.05
HDL-C, mmol/L	1.1 ± 0.2	1.2 ± 0.3	<0.001
LDL-C, mmol/L	3.2 ± 0.9	3.2 ± 0.8	0.77
TG, mmol/L	2.2 (1.5-3.0)	1.5 (1.1-2.2)	<0.001
TG/HDL-C ratio	2.0 (1.3-3.1)	1.3 (0.8-2.1)	<0.001
Adiponectin, µg/mL	7.0 ± 2.7	9.1 ± 3.8	<0.001
C-reactive protein, mg/L	1.8 (1.0-3.5)	1.2 (0.6-2.3)	<0.001

Abbreviations: TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TG/HDL-C ratio, triglyceride-to-high density lipoprotein cholesterol ratio.

* Cases and controls are matched on age at blood taken (±3 years), gender, dialect, and date of blood collection (±6 months). Data are expressed as mean ± standard deviation for continuous variables (normally distributed) and median (interquartile range) for continuous variables (skewed distributed), and n (percentage) for categorical variables. P values based on the McNemar's Chi-square test for categorical variables, paired Student's t-test for normally-distributed continuous variables and Wilcoxon signed-rank test for skewed continuous variables.

Table 2
Odds ratios (95% confidence intervals) of type 2 diabetes associated with different levels of plasma lipid measures

Variables	Teriles of lipid measures			P for trend*	R ²	Per 1 SD increment
	T1	T2	T3			
HDL-C						
Cases/controls	294/191	195/190	82/190			
Model 1 [†]	1.00	0.67 (0.49-0.90)	0.27 (0.18-0.39)	<0.001	10%	0.52 (0.44-0.62)
Model 2 [‡]	1.00	0.71 (0.51-0.98)	0.30 (0.20-0.44)	<0.001	14%	0.55 (0.46-0.66)
Model 3 [§]	1.00	0.82 (0.58-1.15)	0.47 (0.31-0.73)	0.001	18%	0.68 (0.56-0.82)
LDL-C						
Cases/controls	187/189	182/187	167/186			
Model 1 [†]	1.00	1.06 (0.76-1.47)	0.89 (0.60-1.30)	0.62	6%	1.03 (0.90-1.18)
Model 2 [‡]	1.00	1.07 (0.75-1.52)	0.87 (0.61-1.24)	0.43	11%	1.04 (0.91-1.20)
Model 3 [§]	1.00	1.03 (0.70-1.52)	0.88 (0.60-1.29)	0.51	17%	1.08 (0.93-1.26)
TG						
Cases/controls	81/194	158/187	332/190			
Model 1 [†]	1.00	2.23 (1.52-3.28)	5.29 (3.56-7.88)	<0.001	13%	2.09 (1.71-2.55)
Model 2 [‡]	1.00	2.15 (1.42-3.24)	5.21 (3.42-7.94)	<0.001	17%	2.01 (1.65-2.46)
Model 3 [§]	1.00	1.61 (1.04-2.50)	3.59 (2.30-5.61)	<0.001	20%	1.70 (1.39-2.09)
TG/HDL-C ratio						
Cases/controls	69/191	171/190	331/190			
Model 1 [†]	1.00	2.51 (1.70-3.72)	5.35 (3.57-8.01)	<0.001	13%	2.22 (1.79-2.77)
Model 2 [‡]	1.00	2.42 (1.59-3.66)	5.14 (3.36-7.89)	<0.001	17%	2.14 (1.71-2.68)
Model 3 [§]	1.00	1.87 (1.21-2.89)	3.31 (2.09-5.23)	<0.001	19%	1.72 (1.37-2.17)

Abbreviations: R², the coefficient of determination; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TG/HDL-C ratio, the ratio of triglyceride to high-density lipoprotein cholesterol.

^{*} Linear trend was tested using the median level of each tertile of blood lipid profile.

[†] Model 1: adjusted for age at blood taken (continuous), smoking (never, past, current smoker), alcohol intake (never, weekly or daily), weekly activity (<0.5, 0.5-3 hours/week, and 4 hours/week), education level (no, primary school, secondary or above), history of hypertension (yes, no), and fasting status (yes, no);

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Model 2: Model 1 plus adjusted for body mass index (continuous);
Model 3: Model 2 plus adjusted for plasma concentrations of C-reactive protein (mmol/L) and adiponectin ($\mu\text{g/mL}$) (both in tertiles).

Table 3
Odds ratios (95% confidence intervals) of type 2 diabetes associated with tertile levels of plasma lipid measures in men and women separately.*

	T1	T2	T3	P for trend [†]	Per 1 SD increment
HDL-C					
Men					
Cases/controls	116/79	84/79	36/79		
OR (95% CI)	1.00	0.89 (0.54-1.47)	0.56 (0.29-1.05)	0.09	0.71 (0.53-0.94)
Women					
Cases/controls	188/112	101/112	46/111		
OR (95% CI)	1.00	0.73 (0.44-1.19)	0.48 (0.26-0.88)	0.02	0.69 (0.53-0.90)
LDL-C					
Men					
Cases/controls	78/77	71/77	66/76		
OR (95% CI)	1.00	1.19 (0.65-2.15)	0.89 (0.46-2.15)	0.82	1.06 (0.83-1.36)
Women					
Cases/controls	111/112	107/111	103/109		
OR (95% CI)	1.00	0.92 (0.53-1.61)	0.81 (0.49-1.34)	0.44	1.03 (0.84-1.27)
TG [‡]					
Men					
Cases/controls	46/79	69/79	121/78		
OR (95% CI)	1.00	1.09 (0.60-1.98)	2.25 (1.16-4.36)	0.007	1.61 (1.16-2.24)
Women					
Cases/controls	42/115	86/111	207/109		
OR (95% CI)	1.00	1.82 (0.98-3.39)	5.03 (2.58-9.81)	<0.001	1.85 (1.40-2.44)
TG/HDL-C ratio [§]					
Men					
Cases/controls	46/79	69/79	121/78		
OR (95% CI)	1.00	1.01 (0.53-1.90)	1.98 (1.04-3.79)	0.01	1.61 (1.12-2.34)
Women					
Cases/controls	35/112	80/112	220/111		

	T1	T2	T3	P for trend [‡]	Per 1 SD increment
OR (95% CI)	1.00	1.68 (0.87-3.26)	4.98 (2.48-10.0)	<0.001	1.80 (1.34-2.39)

Abbreviations: OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TG/HDL-C ratio, the ratio of triglyceride to high-density lipoprotein cholesterol.

* Multivariate model adjusted for age at blood taken (continuous), smoking (never, past, current smoker), alcohol intake (never, weekly or daily), physical activity (<0.5, 0.5-3.9, and 4 hours/week), education level (no, primary school, secondary or above), history of hypertension (yes, no), BMI (continuous), plasma concentrations of C-reactive protein (mmol/L) and adiponectin (µg/mL) (both in tertiles).

[‡] Linear trend was tested using the median level of each tertile of blood lipid profile.

^{‡‡} P for interaction between TG and sex is 0.028.

[§] P for interaction between TG/HDL and sex is 0.017.

Odds ratios (95% confidence intervals) of type 2 diabetes associated with tertile levels of plasma lipid measures stratified by level of body mass index (BMI).*

Table 4

	T1	T2	T3	P for trend [†]	Per 1 SD increment
HDL-C					
BMI <23 kg/m ²					
Cases/controls	95/106	69/106	22/106		
OR (95% CI)	1.00	0.94 (0.59-1.50)	0.40 (0.21-0.76)	0.01	0.65 (0.50-0.85)
BMI 23 kg/m ²					
Cases/controls	189/85	122/84	74/84		
OR (95% CI)	1.00	0.69 (0.45-1.06)	0.55 (0.45-1.06)	0.02	0.75 (0.61-0.93)
LDL-C					
BMI <23 kg/m ²					
Cases/controls	58/105	61/106	53/103		
OR (95% CI)	1.00	1.02 (0.62-1.66)	0.90 (0.55-1.49)	0.58	1.10 (0.89-1.36)
BMI 23 kg/m ²					
Cases/controls	120/83	130/84	114/81		
OR (95% CI)	1.00	1.09 (0.71-1.68)	1.05 (0.67-1.63)	0.24	1.04 (0.87-1.25)
TG[‡]					
BMI <23 kg/m ²					
Cases/controls	18/107	54/105	114/106		
OR (95% CI)	1.00	2.56 (1.33-4.93)	5.06 (2.65-9.68)	<0.001	1.88 (1.45-2.44)
BMI 23 kg/m ²					
Cases/controls	75/85	101/84	209/84		
OR (95% CI)	1.00	1.24 (0.76-2.00)	2.14 (1.33-3.43)	0.001	1.33 (1.06-1.67)
TG/HDL-C ratio[§]					
BMI <23 kg/m ²					
Cases/controls	19/106	50/106	117/106		
OR (95% CI)	1.00	2.30 (1.21-4.40)	4.85 (2.51-9.35)	<0.001	1.88 (1.42-2.49)
BMI 23 kg/m ²					

	T1	T2	T3	P for trend [‡]	Per 1 SD increment
Cases/controls	61/85	125/84	199/84		
OR (95% CI)	1.00	1.69 (1.03-2.75)	2.38 (1.44-3.95)	0.002	1.30 (1.01-1.67)

Abbreviations: BMI, body mass index; OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TG/HDL-C ratio, the ratio of triglyceride to high-density lipoprotein cholesterol.

* Multivariate model adjusted for age at blood taken (continuous), gender (male, female), dialect group (Cantonese, Hakkien), smoking (never, past, current smoker), alcohol intake (never, weekly or daily), physical activity (<0.5, 0.5-3.9, and ≥4 hours/week), education level (no, primary school, secondary or above), history of hypertension (yes, no), fasting status (yes, no), plasma concentrations of C-reactive protein (mmol/L) and adiponectin (μg/mL) (both in tertiles).

[‡] Linear trend was tested using the median level of each tertile of blood lipid profile.

[‡] P for interaction between TG and BMI (<23 kg/m², 23.0 kg/m²) is 0.051.

[§] P for interaction between TG/HDL and BMI (<23 kg/m², ≥23.0 kg/m²) is 0.046.

Table 5
Summary statistics to evaluate the improved classification of type 2 diabetes by plasma lipid measures

Variable	Multivariate model [*]			
	Discrimination (AUC [95% CI])	Calibration (AIC)	NRI (%)	IDI (%)
Base model	0.69 (0.66-0.72)	670		
HDL-C	0.72 (0.69-0.74) [†]	622	30.8	3.64
TG	0.73 (0.70-0.75) [†]	615	41.3	4.31
TG/HDL-C ratio	0.72 (0.70-0.75) [†]	618	37.5	3.99

Abbreviations: AUC, area under ROC curve; CI, confidence interval; AIC, Akaike information criterion; NRI, net reclassification improvement; IDI, integrated discrimination improvement; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TG/HDL-C ratio, the ratio of triglyceride to high-density lipoprotein cholesterol.

Base model included education level (no, primary school, secondary and above), physical activity (<0.5, 0.5-3.9, 4 hours/week), history of hypertension (yes, no), and body mass index (continuous).

^{*} Multivariate model adjusted for all the variables included in the base model.

[†] Compare with the base model, the increment in AUC value is statistically significant ($P < 0.05$).