Moderate alcohol consumption and carotid intima-media thickness in type 2 diabetes

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ABSTRACT

Background and Objectives: Carotid intima-media thickness (IMT) is a risk predictor for myocardial infarction and stroke. Patients with type 2 diabetes mellitus are at higher risk for such conditions. The association of alcohol consumption with IMT is still controversial. **Methods and Study Design:** We undertook a cross-sectional study of patients hospitalized in the Department of Endocrinology at Zhoushan Hospital from January 1st, 2013 to December 31st, 2015. Patients with a past medical history of cerebrovascular events, acute myocardial ischemia or unable to provide a detailed alcohol consumption history were excluded. Carotid IMT, together with blood biochemical examinations were collected. Data were analyzed using least significant difference t test, Tamhane's T2 test, Levene test, χ^2-test and binary logistic regression model. **Results:** 281 patients were enrolled in the study. The number of patients with elevated carotid IMT in moderate alcohol consumers was apparently less than alcohol non/heavy-consumers. In addition, the number of participants with elevated carotid IMT in liqueur consumers was higher than alcohol non-consumers and rice wine/beer consumers. Systolic blood pressure, C-reactive protein, glycosylated hemoglobin, low density lipoprotein cholesterol, triglyceride, gamma glutamyl transpeptidase, uric acid, cholesterol and creatinine levels were higher in elevated IMT patients, while high density lipoprotein cholesterol level was levels were significantly lower (p value<0.05). **Conclusions:** Moderate alcohol consumption has a protective effect on atherosclerosis in patients with type 2 diabetes mellitus, requiring consideration to dietary intake and physical activity, among other influences. Inflammation theory and lipid metabolism could be involved in such prophylaxis effects.

Key Words: alcohol consumption, carotid intima-media thickness, diabetes, C-reactive protein, high-density lipoprotein cholesterol

INTRODUCTION

Carotid intima-media thickness (IMT), with its relative simplicity and non-invasive characteristics for B-ultrasonography investigations, has been studied as a risk predictor for myocardial infarction (MI) and stroke in the general population. A meta-analysis of 37,197 patients from eight relevant studies has demonstrated that as absolute carotid IMT was thickened by 0.1 mm, the risk of MI increased from 10% to 15%, with the risk of stroke increasing from 13% to 18%.[1]

Selected studies assessing associations among the three elements - alcohol intake, carotid IMT and atherosclerosis (AS)- have provided inconsistent results. The Cardiovascular Health Study, which focused on adults (aged 65 years or older) found that, in comparison with adults who abstained from alcohol, adults who consumed 1-6 drinks per week had a negative correlation with carotid AS whereas adults who consumed 14 or more drinks had a positive correlation.[2] Drinking patterns (heavy/acute intake of beer and spirits) had a positive association with the progression of carotid IMT and AS.[3] In addition, a different relationship between alcohol consumption and carotid IMT was observed among genders. Alcohol consumption has a negative relation with carotid IMT, though has a positive correlation with AS in men. The above phenomenon was not observed in women.[4] In contrast to such findings, elected studies did not support the postulation that alcohol consumption was a protective factor for carotid IMT.[5-8]

Patients with type 2 diabetes mellitus (T2DM) are at higher risk for MI and stroke than individuals with normal glucose metabolism. Type 1 and type 2 diabetes mellitus are associated with greater carotid IMT in comparison to normal glucose metabolism.[9-11] With the goal to assess the relationship between the level of alcohol consumption and carotid IMT in T2DM patients, we conducted a cross-sectional study evaluating 281 T2DM patients.

MATERIALS AND METHODS

T2DM patients who were hospitalized in the endocrinology department of Zhoushan Hospital between January 1st, 2013 to December 31st, 2015 were investigated in this study. This study was approved by the institutional review board of Zhoushan Hospital. Due to the retrospective nature of the study, informed consent was waived.

Alcohol consumption history was collected from each study participant once admitted to the hospital ward and recorded as part of the patient medical file. Whenever medical records were not detailed and the patient was discharged from hospital already, a follow-up telephone call was placed in order to obtain alcohol consumption history for complete accuracy regarding this study. The exclusion criteria consisted of a past medical history of cerebrovascular events or acute myocardial ischemia, inability to provide a detailed drinking history (including the types of alcohol consumption, daily alcohol tolerance/capacity and duration of alcohol consumption. Patients with acute or chronic inflammatory diseases, that could be confounders to C-reactive protein (CRP) results, were also excluded from the study.

A total of 281 patients were enrolled in our study. Information on alcohol consumption, age, height, weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and the number of patients with hypertension were collected.

The criteria used for diagnosis of T2DM consisted of symptoms of diabetes such as polyuria, polydipsia, weight loss, random plasma glucose concentration ≥11.1 mmol/L/fasting plasma glucose (FPG) ≥7.0 mmol/L/two hours postprandial plasma glucose ≥11.1 mmol/L during oral glucose tolerance test.

Drinking beer, spirits, yellow rice wine and red wine for a duration of over one year were defined as having a history of alcohol consumption. Otherwise, the individual study participant was deemed to be a non-alcohol consumer. Alcohol content in beer was defined as 3.8%, while spirits were defined to contain 38% alcohol, yellow rice wine and red wine were defined as containing 12% alcohol. The formula used included: Total alcohol consumption = drinking capacity per day × alcohol content × density of alcohol (0.8). Moderate alcohol consumers were defined as having a daily alcohol consumption <40 g for at least one year. Heavy alcohol consumers were defined as having a daily alcohol consumption ≥40 g for at least one year.[12]

Carotid IMT measurements were conducted by licensed professional ultrasound physicians that were blinded to alcohol consumption history of the patients. Carotid IMT, expressed in millimeters (mm), was measured by Siemens™ Acuson S1000 Ultrasound® (*9L4 linear array* transducer with the frequency being *9 MHz*). The normal value of carotid IMT is less than 1 mm. Once carotid IMT was over 1.3 mm, elevated IMT was deemed to exist.

FBG, glycosylated hemoglobin (HbA1c), CRP, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), cholesterol (CHOL), gamma glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL), creatinine (Cr), and uric acid (UA) were also collected.

Regarding descriptive statistics, mean and standard variances for continuous variables were determined. Data analyses employed Statistical Product and Service Solutions (SPSS®) 26. Participant profiles were compared using least significant difference (LSD) t test, Tamhane's T^2 test and Levene test for continuous variables, together with χ^2-test for categorical variables. Confounding factors with statistical significance were analyzed through univariate logistic regression. Receiver operating characteristic (ROC) curve analysis was taken to explore the relationship between alcohol content and carotid IMT. According to the univariate logistic regression results, selected confounding factors were determined to be placed within the multivariable model. Consequently, binary logistic regression model (Enter method) was applied for identifying relationships between alcohol intake and prevalence of increased carotid IMT, adjusted for selected confounding factors. All *p* values were two-sided, and a *p* value at <0.05 was considered to be statistically significant.

RESULTS

Patients enrolled in this study had an average age of 57.56±11.85 years old (ranging from 20-84 years old). Baseline characteristics of patients with varying IMT were summarized in Table 1. Compared to normal IMT patients, elevated IMT patients were older (*p* value<0.001). Moreover, the majority of patients with elevated IMT had a history of hypertension (*p* value<0.001), and had higher SBP than patients with normal IMT. Notably, in this study, non-smokers also tended to be alcohol non-consumers.

The number of patients with elevated carotid IMT according to alcohol consumption rate was summarized in Table 1. Normal carotid IMT was typically identified within alcohol non-consumers and moderate alcohol consumers. As shown in Figure 1, the number of study participants with elevated carotid IMT in moderate alcohol consumers (14.29%, 12/84) was apparently less than alcohol non-consumers (32.26%, 40/124) and heavy alcohol consumers (80.82%, 59/73), suggesting moderate alcohol consumption might have a correlation to elevated carotid IMT. People with elevated carotid IMT had increased alcohol consumption rates than those with normal carotid IMT [46(91) g/day to 2.5 (20.5) g/day *p* value<0.01], in conformity with the above results. ROC curve analysis was performed and determined that once alcohol consumption was >43g/day, patients were more likely to develop elevated carotid IMT (sensitivity=0.532, specificity=0.918, Supplementary figure 1). In addition, the number of study participants with elevated carotid IMT in liqueur consumers (78.0%, 32/41) were found to be higher than alcohol non-consumers (32.3%, 40/124, *p* value<0.01), rice wine consumers (41.8%, 23/55, *p* value<0.01) and beer consumers (25.9%, 15/58, *p* value<0.01). Since only three red wine consumers were collected, comparative analysis between red wine and other kinds of wine could not be properly performed. Finally, rice wine consumers and beer consumers had no statistical difference in carotid IMT.

Correlations between other laboratory examinations and alcohol consumption were described in Table 1. In summary, SBP, CRP, HAb1c, LDL-C, TG, GGT, UA, CHOL and Cr levels were found to be higher within elevated IMT patients, rather than normal IMT patients (*p* value<0.05). Level of HDL-C was lower in heavy alcohol consumers, in comparison to moderate alcohol consumers (*p* value<0.05).

Possible association between alcohol consumption, CRP, LDL-C, HDL-C, TG, GGT, CHOL, UA, Cr, HbA1c, age, SBP, hypertension, smoking and carotid IMT were analyzed separately through univariate logistic regression (Supplementary table 1). Following multivariable logistic regression analyses, this study revealed alcohol consumption was influencing factors for increased carotid IMT (odds ratio=2.18, 95% CI=[1.38~3.45], *p* value <0.05, Table 2), adjusted for CRP, LDL-C, HDL-C, TG, GGT, Cr, age, hypertension and smoking. Stratified analysis was conducted according to smoking status (Supplementary table 2). Regarding non-smokers, alcohol consumption was also an influencing factor for increased carotid IMT (odds ratio=2.86, 95% CI=[1.17~7.00], *p* value<0.05). However, alcohol consumption had no correlation with increasing carotid IMT in smokers (odds ratio=1.64, 95% CI=[0.93~2.90], *p* value=0.086).

DISCUSSION

Through cross-sectional analysis of 281 T2DM hospitalized patients, this study determined that a moderate level of alcohol consumption was inversely associated with increased carotid IMT, in comparison with heavy- and non-alcohol consumers. The result was independent of factors such as CRP, LDL-C, HDL-C, TG, GGT, Cr, age, hypertension and smoking.

This study concluded that moderate alcohol consumption is a protective factor for carotid IMT, albeit only in non-smokers, with such a result being consistent with other studies.[2,13-15] A recent study considered that moderate alcohol consumption [(0.5) g/day for women and (10, 30) g/day for men] was inversely associated with carotid IMT and its progression.[16] Within this study, the daily alcohol content cut-off was 43 g in order to predict the risk of elevated carotid IMT for alcohol consumers, close to the cut off of 48 g/day in an alternate study.[12] Meanwhile, the definition of 'moderate' daily alcohol consumption of <40 g for at least one year was deemed to be reasonable. Wakabayashi et al[17] analyzed one cross-sectional study demonstrating that light alcohol consumption rates (less than 240g alcohol per week), though not heavy consumption, has benefit on preventing AS in patients with T2DM. However, in this particular study, aortic pulse wave velocity was employed to evaluate the degree of atherosclerotic progression instead of carotid IMT. Conversely, Petersen and colleagues[18] found alcohol consumption to be positively associated with common carotid artery IMT within populations that were not prescribed a lipid lowering medication using linear regression analysis. However, the finding did not take research details such as dividing into moderate drinking group or heavy drinking group, which could potentially mask an inverse association between moderate drinking and carotid IMT. Our study suggests that alcohol consumption is a predictive factor for carotid IMT, although it is important to note that this does not also infer that alcohol consumption is also a predictive factor for cardiovascular disease (CVD). A systematic review found that nine factors (hyperlipidemia, hyperhomocysteinemia, hypertension, hyperuricemia, smoking, metabolic syndrome, hypertriglyceridemia, diabetes, and higher LDL) were significantly associated with the presence of carotid plaque.[19] Nine factors were confounding parameters to speculate the relation between alcohol consumption and CVD. Besides, elevated carotid IMT was not equivalent to CVD.[20]

The relationship between the level of alcohol consumption and carotid IMT remains uncertain. A handful of studies found a U-shaped relationship between alcohol consumption and carotid IMT following cross-sectional analyses.[2,13,14] The same conclusion was reached in our study. However, selected studies did not find evidence supporting this U-shaped association between alcohol consumption and carotid IMT.[5-7,21] This study identified liqueur consumers to be more susceptible for developing carotid IMT, and 38 out of 41 participants were heavy alcohol consumers. This is an indication that liqueur consumers are always heavy alcohol consumers, and the type of wine is a possible explanation for the U-shaped association. Other possible explanations include drinking patterns, adjustments for confounding factors and reference groups. Such a conclusion requires further exploration.

CRP is one of the inflammatory indices, while LDL-C, HDL-C, TG and CHOL are lipid metabolism indices. This study determined that the laboratory investigation results are correlated to alcohol consumption. Inflammation theory and lipid metabolism could be involved in the prevention of CVD through moderate alcohol consumption. Selected studies have struggled to explore such potential mechanisms. Higher levels of HDL-C and adiponectin, together with lower levels of fibrinogen, provide indirect pathophysiological support.[22] Intake of wine, but not of spirits or beer, is positively and independently associated with coronary heart disease in women.[23]

Study limitations and strengths

We obtained alcohol intake data through a patient self-reporting method, resulting in recall bias. In addition, confounders that were not collected such as drinking patterns, sex, physical activity and dietary intake could have affected our findings. In future studies, such datasets will be collected, together with expanding the sample size to crystallize further the effects of alcohol consumption on the cardiovascular system.

Conclusions

Here in our study moderate drinking was found to be inversely associated with carotid IMT in patients with T2DM. And, liqueur consumers are more likely to develop elevated carotid IMT. However, the conclusion was not adjusted by dietary intake, physical activity and other confounding factors. Inflammation theory and lipid metabolism could be involved in such protection. Given our findings, we advocate patients who have already consumed alcohol to drink moderately rather than abstain. And, it is not recommended for patients who never consumed alcohol (prior to diagnosis) to embark on alcohol consumption. In essence, it is also significant to consider that long-term, moderate alcohol consumption can still do harm to the liver, nervous system, digestive system and other organs.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Table 1. Baseline characteristics for elevated/normal IMT patients

	Elevated IMT (N, %)	Normal IMT (N, %)	*p* values
no alcohol consumers	32.26%	67.74%	/
moderate alcohol consumers	14.29%	85.71%	/
heavy alcohol consumers	80.82%	19.18%	/
Age (years old)	61.06+11.61	55.28+11.47	<0.001
Height (cm)	170.51+3.28	170.62+3.47	0.802
Weight (kg)	64.25+9.81	65.31+9.13	0.359
BMI (kg/cm^2)	22.11+3.39	22.58+3.22	0.243
SBP (mmHg)	132.56+15.05	128.95+12.22	0.028
DBP (mmHg)	75.29+9.62	75.21+7.68	0.941
CRP (mg/L)	6.71+4.97	4.70+2.56	<0.001
HbA1c (%)	9.56+2.07	8.85+2.09	0.006
LDL-C (mmol/L)	3.09+0.80	2.31+1.26	<0.001
HDL-C (mmol/L)	0.99+0.33	1.26+0.41	<0.001
TG (mmol/L)	2.47+1.29	1.48+1.17	<0.001
GGT (U/L)	84.75+122.14	36.01+31.26	<0.001
UA (μmol/L)	327.75+87.83	287.70+92.68	<0.001
CHOL (mmol/L)	5.28+1.19	4.31+1.35	<0.001
Cr (μmol/L)	100.81+95.70	80.80+23.17	0.033
FPG (mmol/L)	9.30+3.56	8.97+3.32	0.432
ALT (U/L)	28.75+27.75	29.05+22.36	0.921
AST (U/L)	27.70+23.44	25.24+16.91	0.307
TBIL (μmol/L)	15.48+8.48	15.66+11.03	0.884
ALP (U/L)	83.44+37.43	80.88+27.71	0.511

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; HbA1c: glycosylated haemoglobin; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglyceride; GGT: gamma glutamyl transpeptidase; UA: uric acid; CHOL: cholesterol; Cr: creatinine; FPG: fasting plasma glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; ALP: alkaline phosphatase.
Continuous variables are presented as the mean value ±SD or median values with interquartile ranges (25th to 75th), while categorical variable is presented as percentages

Table 2. Association between clinical variables and carotid IMT

Clinical variables	Odds ratios	95% CI	*p* values
Alcohol consumption	2.18	(1.38, 3.45)	0.001
CRP (mg/L)	1.24	(1.07, 1.43)	0.004
LDL-C(mmol/L)	1.46	(1.07, 1.99)	0.017
HDL-C(mmol/L)	0.14	(0.05, 0.39)	<0.001
TG (mmol/L)	2.00	(1.37, 2.91)	<0.001
CHOL (mmol/L)	1.55	(1.14, 2.13)	0.006
Cr (μmol/L)	1.01	(0.99,1.02)	0.289
HbA1c (%)	1.16	(0.97,1.40)	0.107
Age (years old)	1.08	(1.04, 1.12)	<0.001
Hypertension	2.97	(1.39, 6.37)	0.005
smoking	3.59	(1.60, 8.08)	0.002

CRP: C-reactive protein; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; CHOL: cholesterol; Cr: creatinine; HbA1c: glycosylated hemoglobin.
Continuous variables are presented as the mean value ±SD or median values with interquartile ranges (25th to 75th), while categorical variable is presented as percentages

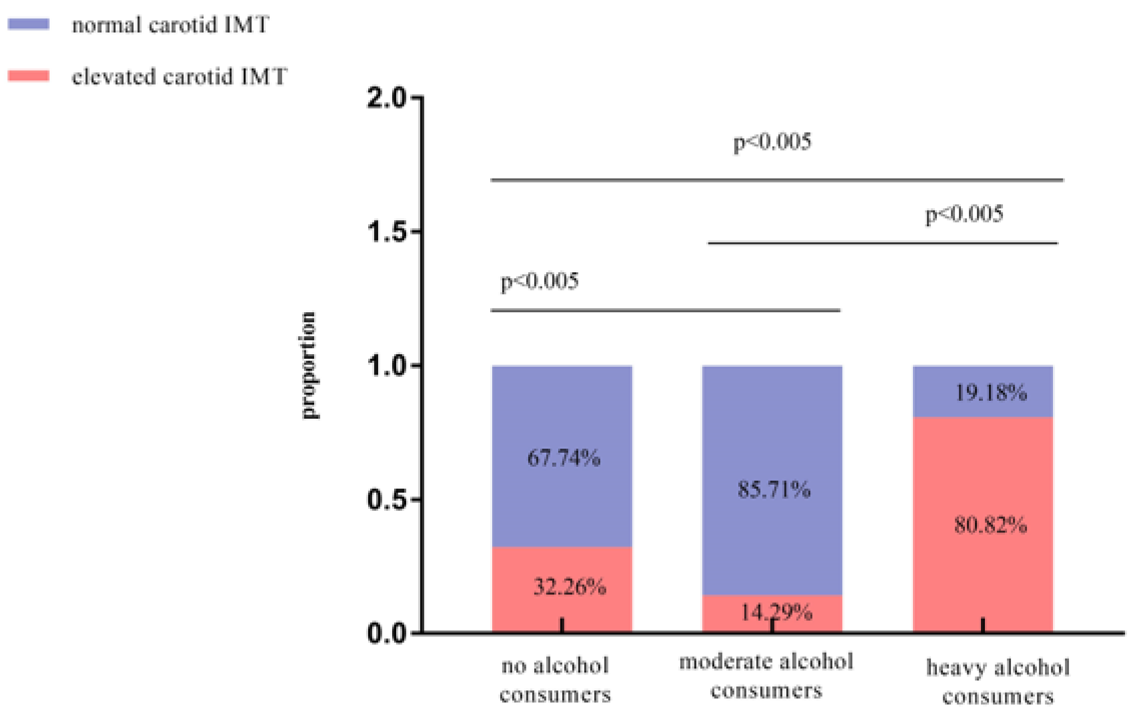
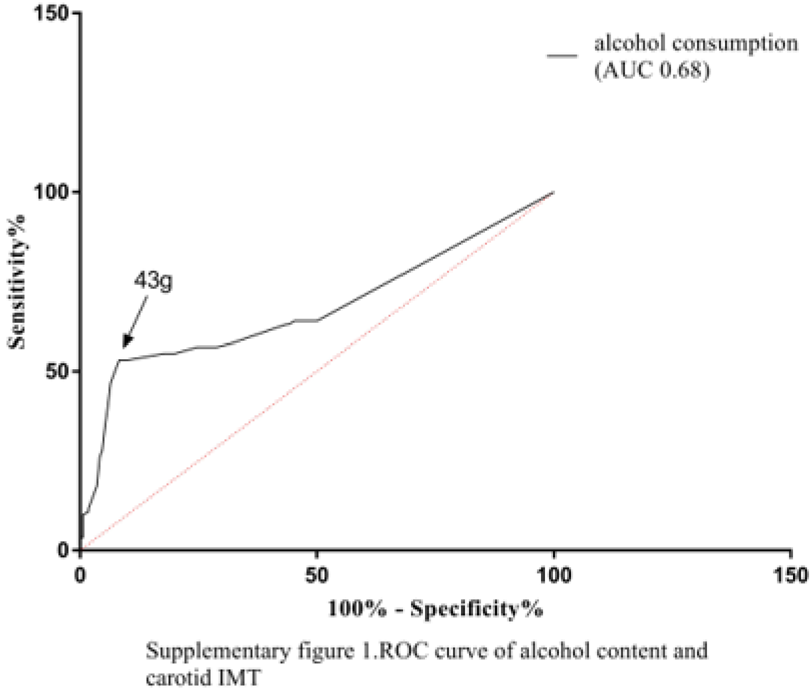


Figure 1. Separate proportion of elevated and normal carotid IMT within varying alcohol consumers.

Supplementary Figure and Tables



Supplementary figure 1. ROC curve of alcohol content and carotid IMT .

Supplementary table 1. Association between clinical variables and carotid IMT analyzed by univariate logistic regression

Clinical variables	Odds ratios	95% CI	*p* values
Alcohol consumption	2.49	(1.81, 3.43)	<0.001
CRP (mg/L)	1.21	(1.10, 1.33)	<0.001
LDL-C (mmol/L)	2.17	(1.64, 2.87)	<0.001
HDL-C (mmol/L)	0.11	(0.05, 0.26)	<0.001
TG (mmol/L)	2.40	(1.18, 3.19)	<0.001
GGT (U/L)	1.018	(1.007, 1.029)	<0.001
CHOL (mmol/L)	1.78	(1.44, 2.18)	0.007
UA (μmol/L)	1.01	(1.00,1.01)	0.001
Cr (μmol/L)	1.02	(1.01,1.03)	0.006
HbA1c (%)	1.18	(1.05,1.32)	0.006
Age (years old)	1.04	(1.02, 1.07)	<0.001
SBP (mmHg)	1.02	(1.00, 1.04)	0.030
Hypertension	2.091	(1.379, 6.929)	0.006
smoking	3.84	(1.531, 8.390)	0.003

Supplementary table 2. Association between clinical variables and carotid IMT analyzed by stratified univariate logistic regression (according to smoking status)

	Nonsmokers			Smokers		
Clinical variables	Odds ratios	95% CI	*p* value	Odds ratios	95% CI	*p* value
Alcohol consumption	2.86	(1.17, 7.00)	0.021	1.64	(0.93, 2.90)	0.086
CRP (mg/L)	1.37	(1.04, 1.80)	0.026	1.22	(1.02, 1.47)	0.032
LDL-C (mmol/L)	1.27	(0.84, 1.93)	0.264	2.06	(1.20, 3.53)	0.009
HDL-C (mmol/L)	0.08	(0.01, 0.67)	0.019	0.12	(0.03, 0.49)	0.003
TG (mmol/L)	4.58	(1.76, 11.93)	0.002	1.49	(0.96, 2.30)	0.074
CHOL (mmol/L)	1.71	(0.99, 2.98)	0.056	1.53	(1.00, 2.34)	0.050
Cr (μmol/L)	1.01	(0.97,1.05)	0.622	1.00	(0.99,1.02)	0.616
HbA1c (%)	1.14	(0.82,1.59)	0.429	1.13	(0.89,1.43)	0.325
Age (years old)	1.14	(1.05, 1.24)	0.002	1.07	(1.02, 1.12)	0.003
Hypertension	3.03	(0.71, 12.88)	0.133	3.21	(1.25, 8.27)	0.016