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The Risk of Fasting Triglycerides and its Related Indices for Ischemic Cardiovascular Diseases in Japanese Community Dwellers: the Suita Study

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Aim: A prospective cohort study in a Japanese urban general population was performed to investigate whether triglyceride (TG) and its related indices were associated with the risk for the incidence of ischemic cardiovascular disease (CVD) after the adjustment for low-density lipoprotein cholesterol (LDL-C) in Asian community dwellers.

Methods: A 15.1-year prospective cohort study was performed in 6,684 Japanese community dwellers aged 30–79 years without a history of CVD and whose fasting TG levels were <400 mg/dL. After adjusting for covariates, including LDL-C, the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of the deciles (D) of TG and those of 1-standard deviation (SD) increment of log-transformed TG (1-SD of TG) according to LDL-C level (≥ 140 and <140 mg/dL) for ischemic CVD incidence were estimated. The multivariable-adjusted HRs and 95%CIs of the quintiles (Q) of TG, TG/HDL-C, and the cardiometabolic index (CMI) for ischemic CVD were also estimated.

Results: In 101,230 person-years, 464 ischemic CVD cases occurred. For D_{10} of TG, the HR (95%CI) was 1.56 (1.05–2.32), and for 1-SD of TG, it was 1.30 (1.00–1.70) in participants with LDL-C <140 mg/dL and 1.07 (0.77–1.50) in those with LDL-C ≥ 140 mg/dL. For Q_5 of the CMI, the multivariable-adjusted HR was higher than those of TG and TG/HDL-C.

Conclusions: Fasting TG was an independent predictor for ischemic CVD incidence after adjusting for LDL-C in Japanese community dwellers with TG <400 mg/dL. Among TG, TG/HDL-C, and the CMI, the CMI could be the most powerful predictor for ischemic CVD.

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Key words: TG/HDL-C ratio, Cardiometabolic index, Prospective cohort study, Hazard ratio, LDL-C

Introduction

Epidemiological studies in Western countries have reported moderate and significant associations between the levels of triglyceride (TG) and the risks of coronary artery disease (CAD)[1)] and stroke[2)]. Furthermore, elevated TG levels appear to be associated with a residual risk of atherosclerotic cardiovascular diseases (CVDs), despite the use of low-density lipoprotein cholesterol (LDL-C)-lowering

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statin therapy[3].

Previous studies in Asian[4] and Japanese[5] populations also showed an independent association between TG and the risk of ischemic CVD or CAD after the adjustment for total or high-density lipoprotein cholesterol (HDL-C). However, the association after adjusting for LDL-C or according to LDL-C level has not been well investigated in Asian prospective cohort studies. In addition, only a few studies have investigated the risk of fasting TG for CVD or CAD among Japanese general population[5, 6].

Furthermore, the TG/HDL-C ratio (TG/HDL-C) has been reported to be as powerful a predictor of CAD as isolated high LDL-C[7]. In addition, the cardiometabolic index (CMI), defined as TG/HDL-C multiplied by the waist/height ratio, has been demonstrated to be associated with the degree of atherosclerosis in the Japanese population[8]. However, whether these indices are associated with the risk for ischemic CVD after adjusting for LDL-C has not been well investigated in the Asian population.

Aim

A prospective cohort study in a Japanese urban general population was performed to investigate whether TG and its related indices are associated with the risk for the incidence of ischemic CVD after the adjustment for LDL-C in Asian community dwellers.

Methods

Study Participants

The Suita study, a cohort study of CVD, was established in 1989 in Suita City, Japan. The design of the cohort study and selection criteria for participants have already been described[9]. Briefly, 12,200 and 3,000 community dwellers aged 30–79 years were randomly selected in 1989 and 1996, respectively, from the municipal population registry of Suita City. Of these individuals, 6,485 and 1,329 individuals attended the baseline examination from 1989 to 1996 and from 1996 to 1998, respectively. In addition, 546 volunteer individuals attended the baseline study in 1992–2006. All individuals described above were the participants of the baseline survey.

In the present study, 688 individuals were excluded because of the presence of a CVD history at baseline or lost to follow-up. In addition, participants aged 80 years or more (n=36), those with missing data at the baseline survey (n=291), those with fasting < 10 hours (n=561), and those with TG ≥ 400 mg/dL (n=100) were excluded. Thus, 6,684 individuals were included in the analysis of the present study.

Written informed consent was obtained from each participant. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, and the protocol was approved by the Institutional Ethics Committee of the National and Cerebral and Cardiovascular Center (NCVC) (approval number M20-050-3).

Baseline Study

Well-trained nurses obtained information on smoking, alcohol drinking, and the medical history of each participant. If the participant answered yes to current drinker, alcohol consumption was determined by alcohol intake per typical week and calculated as ethanol intake per day. One drink was defined as 11.5 g of ethanol (half a gou, a traditional Japanese unit); this is nearly equal to one "standard" drink in most countries[10].

Well-trained physicians measured blood pressure (BP) three times in the right arm using a standard mercury sphygmomanometer while the participant was seated after a 5-minute rest. The average of the second and third measurements was used in the analyses. Height in stockings and weight in light clothing were measured, and body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Trained public health nurses and technicians measured waist circumference (WC) at the umbilical level while the participant was standing.

The blood samples were collected at the NCVC after fasting for at least 10 hours. The samples were immediately centrifuged, and a routine blood examination, which included serum total cholesterol (TC), HDL-C, TG, and glucose levels, was then conducted. LDL-C was calculated using the Friedewald formula. The CMI was calculated as TG/HDL-C multiplied by the waist/height ratio. Metabolic syndrome was defined by a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity in 2009[11].

Follow-Up and Endpoints

The method of follow-up has been described elsewhere[12]. Briefly, the participants were followed until December 31, 2013. The first step in the survey involved checking the health status of all participants by repeat visits to the NCVC every two years and yearly questionnaires conducted by mail or telephone interview. The second step involved reviewing the in-hospital medical records of the participants

suspected to have new-onset CAD or stroke or those who died because of the diseases. Reviews were performed by registered hospital physicians or research physicians blinded to the baseline information. Definite acute myocardial infarction (MI) and probable MI were defined according to the criteria of the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project[13]. The criteria for diagnosing CAD included sudden cardiac death within 24 hours after the onset of acute symptoms and CAD, followed by coronary bypass or angiography. Stroke was defined according to the National Survey of Stroke criteria[14], which require rapid onset of a variety of neurological deficits lasting at least 24 hours or until death. Strokes were classified as ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, or undetermined type. A definite stroke was defined by autopsy or diagnostic imaging, such as computed tomography or magnetic resonance imaging. Comprehensive systematic searches of death certificates were also performed to complete the surveillance of acute MI and stroke. The endpoint of the follow-up period for incident ischemic CVD was whichever of the following occurred first: (1) first diagnosis of CAD or ischemic stroke event, (2) death, (3) leaving Suita City, or (4) December 31, 2013.

Statistical Analysis

To compare baseline risk characteristics according to the quintiles of TG, analysis of variance was used for continuous variables, and the chi-squared test was used for dichotomous variables.

To investigate the associations of serum TG levels with the risk for the incidence of ischemic CVD (CAD and ischemic stroke) and its subtypes, a Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the deciles of TG compared to the sixth decile (D_6) for the incidence of ischemic CVD, CAD, and ischemic stroke. The models were adjusted for age, sex, the presence of hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, and/or medication for hypertension) and diabetes mellitus (glucose ≥ 126 mg/dL and/or medication for diabetes mellitus), medication for dyslipidemia, smoking (never, ex, current smoker), alcohol drinking (never; ex; current drinker, <4 drinks/day; and current drinker, ≥ 4 drinks/day), BMI, and LDL-C in model 1, and they were additionally adjusted for HDL-C in model 2. In addition, similar analyses were performed using the Cox proportional hazards model adjusted for the Suita risk score for 10-year risk of CVD[15]. In addition, the participants were classified into two groups according to LDL-C level (≥ 140 and <140 mg/dL), and the multivariable-adjusted HRs and 95%CIs of 1-standard deviation (SD) increment of log-transformed TG (1-SD of TG) for ischemic CVD, CAD, and ischemic stroke were estimated in the two groups after adjusting for the same covariates.

To investigate the associations of the TG-related indices (TG, TG/HDL-C, and the CMI) with the risk for the incidence of ischemic CVD and its subtypes, a Cox proportional hazards model was used to estimate the HRs and 95% CIs of the quintiles of those indices compared with the third quintile (Q_3) for the incidence of ischemic CVD, CAD, and ischemic stroke. The models were adjusted for the covariates in model 1 as mentioned above. Sex-specific analyses were also performed.

All statistical analyses were performed using SPSS, version 26.0 J (IBM, Tokyo, Japan). $P<0.05$ (two-tailed) was considered statistically significant.

Results

In 101,230 person-years, 464 ischemic CVD (268 CAD and 196 ischemic stroke) events occurred.

Table 1 shows the baseline characteristics of the participants according to the quintiles of TG level. The percentage of male participants, indices of obesity, TC, percentage of the presence of hypertension, TG/HDL-C, and CMI were significantly higher, and HDL-C was significantly lower in the participants with higher TG levels. The percentages of smoking and alcohol drinking were significantly different among the quintiles.

Table 2 shows the age- and sex-adjusted and multivariable-adjusted HRs (95%CI) of the deciles of TG for ischemic CVD, CAD, and ischemic stroke. The multivariable-adjusted HRs of D_9 and D_{10} for ischemic CVD was significantly increased compared with that of D_6 (98 ≤ TG ≤ 111 mg/dL) in model 1 (p for trend <0.05), although the increase of HRs of D_9 and D_{10} were not statistically significant after the additional adjustment for HDL-C in model 2. The multivariable-adjusted HRs of D_{10} for CAD was increased with borderline significance, and those of higher deciles for ischemic stroke were increased without statistical significance in model 1. In addition, the HRs of the deciles of TG for ischemic CVD and its subtypes adjusted for the Suita risk score were shown in **Supplemental Table 1**. The HRs were almost similar to those in **Table 2**; however, the risk of D_9 for ischemic CVD was significantly increased.

Table 3 shows the age- and sex-adjusted and multivariable-adjusted HRs (95%CI) of 1-SD of TG for ischemic CVD, CAD, and ischemic stroke

Table 1. Baseline characteristics of the participants according to the quintiles of serum TG: the Suita study (1989-2013)

	Quintiles of serum TG (mg/dL)					*p* value
	Q_1 (15-65)	Q_2 (66-86)	Q_3 (87-112)	Q_4 (113-154)	Q_5 (155-399)	
N	1355	1358	1337	1314	1320	
Age (years)	50 ± 13	55 ± 13	57 ± 13	57 ± 12	57 ± 12	< 0.001
Male (%)	31.1	38.6	47.3	54.2	63.5	< 0.001
Waist (cm)	74.4 ± 8.4	77.4 ± 8.9	80.3 ± 9.2	83.0 ± 8.7	85.0 ± 8.0	< 0.001
BMI (kg/m^2)	21.0 ± 2.7	21.7 ± 2.9	22.5 ± 3.0	23.2 ± 3.0	24.0 ± 2.8	< 0.001
Waist/height ratio	0.47 ± 0.05	0.49 ± 0.06	0.51 ± 0.06	0.52 ± 0.06	0.53 ± 0.05	< 0.001
Total cholesterol (mg/dL)	191 ± 32	203 ± 34	208 ± 34	214 ± 35	220 ± 38	< 0.001
HDL-C (mg/dL)	63 ± 14	59 ± 13	55 ± 13	51 ± 12	45 ± 11	< 0.001
LDL-C (mg/dL)	117 ± 29	129 ± 32	133 ± 32	136 ± 33	132 ± 37	< 0.001
Non-HDL cholesterol (mg/dL)	128 ± 30	144 ± 32	153 ± 32	163 ± 33	175 ± 37	< 0.001
Medication for dyslipidemia (%)	1.2	2.3	3.1	3.8	0.9	< 0.001
Hypertension (%)	16.4	26.2	33.2	36.5	40.5	< 0.001
Diabetes (%)	2.4	4.0	4.6	6.0	7.7	< 0.001
Smoking (%)						< 0.001
Never	66.5	59.6	54.7	47.9	41.5	
Ex	12.5	15.8	15.6	19.5	20.2	
Current	21.0	24.6	29.7	32.6	38.3	
Alcohol drinking (%)						< 0.001
Never	49.6	48.5	45.9	45.1	41.4	
Ex	2.1	2.6	2.8	1.9	2.6	
Current (< 4 drinks/day)	38.7	37.4	36.9	36.3	34.6	
Current (≥ 4 drinks/day)	9.6	11.5	14.4	16.7	21.4	
The Suita risk score[§]	6.7	13.8	17.3	19.4	21.2	< 0.001
Metabolic syndrome (%)	0.5	1.7	4.9	12.4	54.1	< 0.001
TG (mg/dL)[§]	54	76	98	131	200	< 0.001
TG/HDL-C ratio[§]	0.86	1.29	1.82	2.65	4.77	< 0.001
CMI[§]	0.40	0.63	0.92	1.37	2.52	< 0.001

[§]: median. TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, CMI: cardiometabolic index, BMI: body mass index, LDL-C: low-density lipoprotein cholesterol.
The Suita risk score was calculated by a risk score for predicting 10-year risk of CVD [15].
Metabolic syndrome was defined by Joint statement from the IDF, AHA/NHLBI, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity in 2009 [11].

according to LDL-C level. The multivariable-adjusted HR for CAD was significantly increased and that for ischemic CVD was increased with borderline significance in the participants with LDL-C < 140 mg/dL in model 1; however, the increase of HRs was not statistically significant after further adjustment for HDL-C in model 2.

Fig. 1 shows the multivariable-adjusted HR of the quintiles of TG, TG/HDL-C, and the CMI for ischemic CVD, CAD, and ischemic stroke compared with that in Q_3 after adjusting for covariates, including LDL-C (model 1). For ischemic CVD, the HRs of Q_5 in TG and TG/HDL-C and those of Q_4 and Q_5 in the CMI were significantly increased, and the HR of Q_5 was the highest in the CMI among the three indices. For CAD, the HR of Q5 was significantly increased in three indices and that of the CMI was the highest among them. The HRs of the indices for ischemic stroke were not significantly increased; however, the increase of HR of Q_5 in the CMI showed borderline significance. The results of sex-specific analysis are presented in **Supplemental Tables 2 and 3**. For CVD, the HR of Q_5 of TG/HDL-C in women and those of Q_5 in the CMI in both sexes were significantly increased. For CAD, the tendencies of the results were almost the same as those for CVD without statistical significance. For ischemic stroke, the HRs of Q_2 and Q_5 of all indices tended to be increased in both sexes, especially in the CMI of women. In addition, higher CMI was associated with higher risk for ischemic CVD and CAD in the participants without metabolic syndrome with statistical significance of trend *p* (trend *p*: ischemic CVD, $p < 0.05$; CAD, $p < 0.01$); however, the

Table 2. Risk of the deciles of serum TG for ischemic CVD and its subtypes: the Suita study (1989-2013)

	N of participants	No. of events	Crude incidence (/1,000 person-years)	Age and sex-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI) (Model 1)	Multivariable-adjusted HR (95%CI) (Model 2)
Ischemic CVD						
D_1 (15-54)	699	20	1.8	0.86 (0.50-1.49)	1.15 (0.66-1.99)	1.27 (0.73-2.22)
D_2 (55-65)	656	29	2.8	1.05 (0.65-1.70)	1.25 (0.77-2.03)	1.36 (0.83-2.22)
D_3 (66-75)	660	37	3.7	1.18 (0.75-1.85)	1.25 (0.80-1.98)	1.34 (0.85-2.12)
D_4 (76-86)	698	38	3.6	1.03 (0.66-1.61)	1.15 (0.73-1.81)	1.21 (0.77-1.91)
D_5 (87-97)	629	47	5.0	1.41 (0.92-2.17)	1.45 (0.94-2.22)	1.47 (0.96-2.26)
D_6 (98-111)	667	38	3.8	1.00	1.00	1.00
D_7 (112-130)	686	54	5.4	1.37 (0.90-2.07)	1.31 (0.86-1.99)	1.29 (0.85-1.96)
D_8 (131-153)	641	60	6.3	1.48 (0.99-2.22)	1.43 (0.95-2.15)	1.37 (0.91-2.06)
D_9 (154-198)	675	70	6.9	1.68 (1.13-2.49)	1.52 (1.02-2.27)	1.44 (0.97-2.15)
D_{10} (199-399)	673	71	7.1	1.75 (1.18-2.60)	1.56 (1.05-2.32)	1.39 (0.93-2.09)
Trend p				$p<0.001$	$p<0.05$	$p=0.490$
CAD						
D_1 (15-54)	699	11	1.0	0.86 (0.41-1.79)	1.17 (0.56-2.46)	1.34 (0.64-2.83)
D_2 (55-65)	656	12	1.1	0.78 (0.38-1.58)	0.95 (0.47-1.94)	1.06 (0.51-2.17)
D_3 (66-75)	660	25	2.4	1.46 (0.82-2.61)	1.56 (0.87-2.80)	1.70 (0.94-3.05)
D_4 (76-86)	698	20	1.8	0.97 (0.53-1.80)	1.09 (0.59-2.02)	1.17 (0.63-2.16)
D_5 (87-97)	629	25	2.6	1.36 (0.76-2.43)	1.40 (0.79-2.51)	1.44 (0.81-2.57)
D_6 (98-111)	667	21	2.0	1.00	1.00	1.00
D_7 (112-130)	686	36	3.5	1.66 (0.97-2.85)	1.59 (0.93-2.73)	1.58 (0.92-2.71)
D_8 (131-153)	641	35	3.6	1.59 (0.93-2.73)	1.53 (0.89-2.63)	1.44 (0.84-2.48)
D_9 (154-198)	675	42	4.0	1.80 (1.06-3.04)	1.59 (0.94-2.70)	1.50 (0.88-2.54)
D_{10} (199-399)	673	41	4.0	1.82 (1.08-3.08)	1.70 (0.99-2.89)	1.48 (0.86-2.55)
Trend p				$p<0.01$	$p=0.060$	$p=0.484$
Ischemic stroke						
D_1 (15-54)	699	9	0.8	0.90 (0.40-2.03)	1.11 (0.49-2.52)	1.19 (0.52-2.73)
D_2 (55-65)	656	17	1.7	1.43 (0.73-2.80)	1.62 (0.82-3.19)	1.71 (0.86-3.39)
D_3 (66-75)	660	12	1.2	0.86 (0.41-1.81)	0.92 (0.44-1.92)	0.96 (0.45-2.02)
D_4 (76-86)	698	18	1.7	1.08 (0.56-2.10)	1.20 (0.62-2.34)	1.24 (0.64-2.42)
D_5 (87-97)	629	22	2.3	1.48 (0.78-2.78)	1.48 (0.78-2.78)	1.49 (0.79-2.82)
D_6 (98-111)	667	17	1.7	1.00	1.00	1.00
D_7 (112-130)	686	18	1.8	1.03 (0.53-2.00)	0.98 (0.51-1.91)	0.97 (0.50-1.89)
D_8 (131-153)	641	25	2.6	1.38 (0.75-2.55)	1.35 (0.73-2.51)	1.32 (0.71-2.44)
D_9 (154-198)	675	28	2.7	1.51 (0.83-2.76)	1.43 (0.78-2.62)	1.38 (0.75-2.54)
D_{10} (199-399)	673	30	2.9	1.67 (0.92-3.03)	1.36 (0.74-2.49)	1.26 (0.68-2.33)
Trend p				$p<0.05$	$p=0.491$	$p=0.876$

TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, CI: confidence interval, CVD: cardiovascular diseases.
Model 1: age, sex, hypertension, diabetes, medication for dyslipidemia, smoking, alcohol drinking, body mass index, and LDL-C were adjusted.
Model 2: the variables in model 1 and HDL-C were adjusted.

association between the CMI and the risks of ischemic CVD and its subtypes was not observed in the participants with metabolic syndrome (data not shown).

Discussion

In the present study, higher serum TG levels were significantly associated with the increased risk for the

Table 3. Risk of 1-SD increment of log-transformed serum TG for ischemic CVD and its subtypes according to LDL-C level: the Suita study (1989-2013)

	N of participants	No. of events	Crude incidence (/1,000 person-years)	Age and sex-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI) (Model 1)	Multivariable-adjusted HR (95%CI) (Model 2)
Ischemic CVD						
LDL-C <140 mg/dL						
ln TG	4307	260	4.0	1.46 (1.15-1.86)	1.30 (1.00-1.70)	1.22 (0.91-1.62)
LDL-C ≥ 140 mg/dL						
ln TG	2377	204	5.6	1.38 (1.00-1.90)	1.07 (0.77-1.50)	0.82 (0.57-1.18)
CAD						
LDL-C <140 mg/dL						
ln TG	4307	128	1.9	1.70 (1.04-2.06)	1.51 (1.03-2.20)	1.45 (0.96-2.18)
LDL-C ≥ 140 mg/dL						
ln TG	2377	140	3.7	1.42 (0.97-2.08)	1.09 (0.73-1.63)	0.76 (0.49-1.18)
Ischemic stroke						
LDL-C <140 mg/dL						
ln TG	4307	132	2.0	1.44 (1.03-2.01)	1.14 (0.79-1.64)	1.04 (0.70-1.55)
LDL-C ≥ 140 mg/dL						
ln TG	2377	64	1.7	1.32 (0.75-2.34)	1.07 (0.59-1.95)	1.00 (0.52-1.91)

TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, CI: confidence interval, CVD: cardiovascular diseases.
Model 1: age, sex, hypertension, diabetes, medication for dyslipidemia, smoking, alcohol drinking, body mass index, and LDL-C were adjusted.
Model 2: the variables in model 1 and HDL-C were adjusted.

incidence of ischemic CVD after the adjustment for CVD risk factors, including LDL-C, in Japanese general population with TG <400 mg/dL, although the association was attenuated after the additional adjustment for HDL-C. In addition, the association between TG and the risk for ischemic CVD and CAD was more evident in those with LDL-C <140 mg/dL. Furthermore, the risk of the top quintile of the CMI for ischemic CVD was higher than those of TG and TG/HDL-C.

In previous large meta-analyses of cohort studies in Western populations, significant associations between TG levels and the risk for CAD and stroke have been reported[1, 2]; however, another meta-analysis showed that TG was not an independent predictor for CAD and ischemic stroke after adjusting for HDL-C and non-HDL-C[16]. In the Asian-Pacific population, a meta-analysis showed that an elevated TG level was an independent risk factor for CAD after adjusting for the TC/HDL-C ratio[4]. In the Japanese population, Iso *et al.* showed a significantly increased risk of a high TG level for ischemic CVD after the adjustment for TC in community dwellers[5], and Satoh *et al.* showed that the risk of a high TG level for CAD was significantly increased after the adjustment for TC and HDL-C in middle-aged male workers[6]. However, the risks of the TG level for the incidence of CVD after adjusting for LDL-C have not been well investigated in the Asian general population fasting ≥ 10 hours. Because most of the blood samples were collected after fasting ≥ 10 hours and because there were only a few participants with TG ≥ 400 mg/dL at baseline in the Suita study, the model could be adjusted for LDL-C calculated using Friedewald formula in the present study. Thus, to the best of our knowledge, the present study is the first to show the risk of TG level for incident ischemic CVD and its subtypes after adjusting for LDL-C calculated using Friedewald formula in the Japanese general population. In addition, the present study is also the first to show the risk of the CMI for ischemic CVD in a prospective cohort study.

According to a previous study in Japan, the risk of patients with fasting TG >100 mg/dL for CVD events was significantly elevated compared with those with TG <100 mg/dL, after adjusting for confounders, including LDL-C and HDL-C[17]. However, because the participants of the previous study were patients with CAD, comparing the results in the previous and present study is difficult.

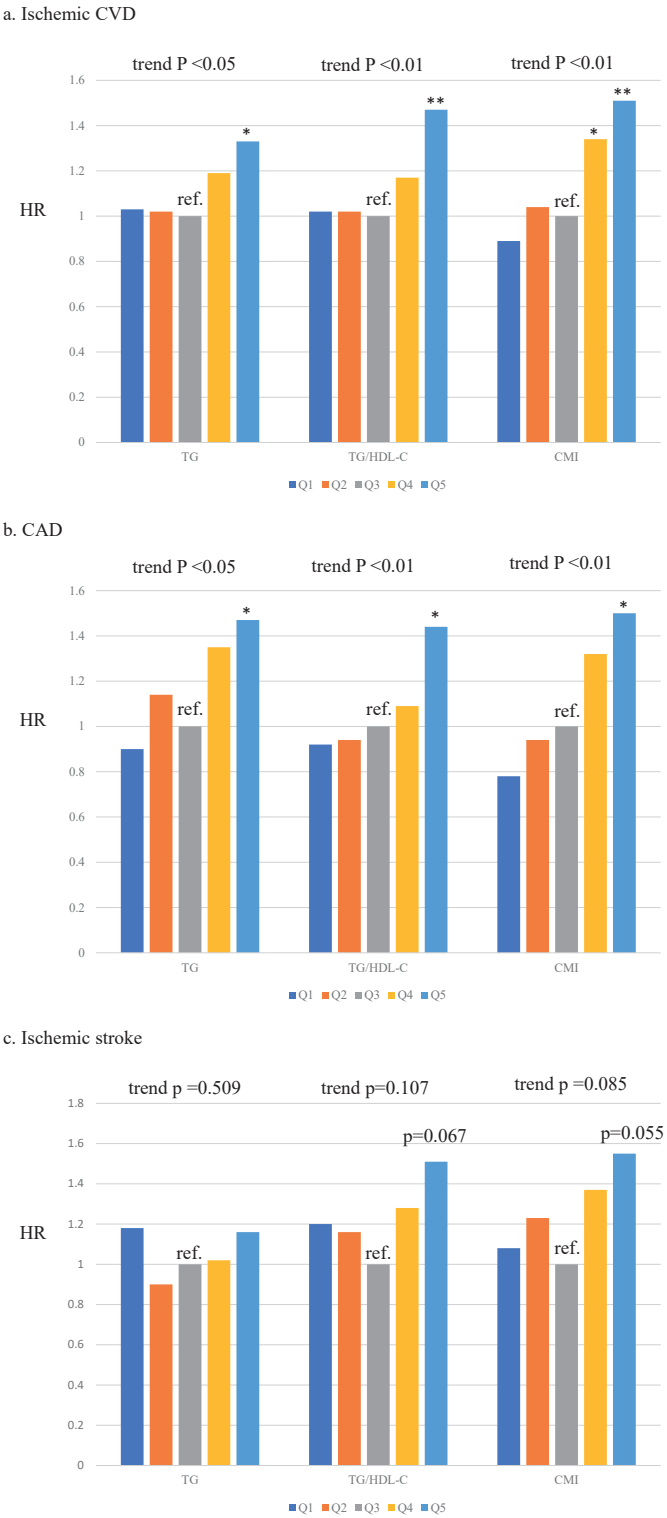

Fig. 1. Risk of TG-related indices for ischemic CVD and its subtypes: the Suita study (1989-2013)

TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, CMI: cardiometabolic index, HR: hazard ratio.
Quintiles of TG (mg/dL): Q_1 15–65, Q_2 66–86, Q_3 87–112, Q_4 113–154, Q_5 155–399.
Quintiles of TG/HDL-C: Q_1 0.17–1.05, Q_2 1.06–1.52, Q_3 1.53–2.15, Q_4 2.16–3.39, Q_5 3.40–16.86.
Quintiles of CMI: Q_1 0.06–0.50, Q_2 0.51–0.75, Q_3 0.76–1.11, Q_4 1.12–1.78, Q_5 1.79–8.82.
The HRs age, sex, hypertension, diabetes, medication for dyslipidemia, smoking, alcohol drinking, body mass index, and low-density lipoprotein cholesterol were adjusted.

Furthermore, only a few previous studies have investigated the risk of fasting TG for ischemic CVD or CAD among Asian general population[4-6]. Thus, the cutoff value of fasting TG for the risk of ischemic CVD should be further investigated among Asian general population in future.

In the present study, the risk of TG for ischemic CVD and CAD was more evident in the participants with LDL-C <140 mg/dL than those with LDL-C ≥ 140 mg/dL. In the previous study in Western population[16], the risk of non-HDL-C according to HDL-C level was investigated; however, studies investigating the risk of TG according to LDL-C level in the Asian general population are few. The present study showed the importance of controlling TG levels for CAD prevention, even in individuals with LDL-C <140 mg/dL.

Among several TG-related indices, TG/HDL-C and the CMI were selected in the present study. Although the lipid accumulation product (LAP) is also an index that includes TG in its formula[18], the LAP is not always useful for the Japanese population because WC is lower than 65 cm in some men or 58 cm in some women. In addition, as we have previously reported, the CMI was more strongly associated with both the cardio-ankle vascular index in a Japanese general population and the degree of atherosclerotic progression in patients with PAD than the LAP[7, 19]. In addition, according to previous studies, HDL-C was independent of the TG concentration[15], and the waist/height ratio is a predictive factor for CVD[20]. Thus, TG/HDL-C and the CMI could be candidate predictors in identifying individuals at high risk for ischemic CVD. The present study suggests that the CMI could be the most significant predictor for future ischemic CVD risk among the three TG-related indices; it also provides a message for the strategy of lipid control, "to prevent ischemic CVD, in addition to controlling LDL-C, keep lower WC, lower TG, and higher HDL-C," which is a concept of the metabolic syndrome.

In the sex-specific analyses of the present study, the association between higher quintiles of TG-related indices and ischemic CVD risk was more evident in women than in men. Iso *et al.* showed a significant increase of ischemic CVD risk for the highest quartile of fasting TG in men, but not in women, due to the small number of fasting women[5]. In the ARIC study, the age-adjusted relative ratio of the top quintile of TG for CAD was greater in women than in men[21]. In other previous studies that investigated the risk of TG/HDL-C for incident CVD, sex-specific analyses were not performed[22], or only the risk assessment of TG/HDL-C >3.5 for men and TG/HDL-C >2.5 for women was performed[23]. In addition, few studies have investigated the risk of the CMI for the incidence of CVD. Although the reason for the higher HRs of the higher quintiles of TG-related indices in women than in men is not clear in the present study, a much lower incidence in the reference quintile of women than of men might be one reason for the difference. In addition, higher risks for ischemic CVD and stroke among women with lower quintiles of the indices were found in the present study, which few previous studies have reported. Because the risk of lower TG-related indices might not yet have been fully investigated, especially in sex-specific analyses, larger epidemiological studies, including sex-specific analyses, are needed for the further assessment of the risks of TG-related indices.

The mechanism of the involvement of TGs in the onset of ischemic CVD is considered as follows. According to Ohmura[24], "the core TGs comprising chylomicrons (CMs) and very low-density lipoproteins (VLDLs) are rapidly catabolized in the circulating blood by lipoprotein lipase (LPL) on the blood vessel walls, and CM and VLDL remnants are produced. VLDL and VLDL remnants penetrate the arterial intima and are taken up by macrophages directly without undergoing oxidative modification. Moreover, LPL on the endothelial surface or within the arterial intima degrades TGs in VLDL and VLDL remnants, with liberation of free fatty acids and monoacylglycerols, both of which cause tissue toxicity and precipitate in local inflammation. Thus, serum TGs are associated with low-grade inflammation and accelerated foam cell formation via macrophage uptake directly at the arterial wall, followed by the development of atherosclerosis." In addition, high TG levels are associated with increased small-density LDL particles, which could be more atherogenic than larger LDL particles because of their increased susceptibility to oxidation[25].

Previous studies have reported that non-fasting TG is a superior predictor for risk of CVD events over fasting TG[26], because the elevated levels of non-fasting TG is considered to reflect elevated remnant lipoprotein levels[26, 27]. In addition, according to the previous study, the obvious superiority of non-fasting TG over fasting TG was observed in TG measured in 2 to <4 hours after meal[26]. Because TG levels progressively decrease with longer periods of fasting in a person and because a predictive ability of non-fasting TG for ischemic CVD events has not been well investigated according to fasting hours in Asian population, further investigation about the usefulness of non-fasting TG is needed among Asian population in the future.

The present study has several limitations. First, single TG measurement at the baseline survey might have underestimated the association between TG and ischemic CVD because of regression dilution bias. The longitudinal trend for CVD risk factors and information about medications after the baseline survey were also not investigated, although hypertriglyceridemia is associated with the future onset of metabolic syndrome components, such as hypertension and diabetes[28, 29]. Second, because the blood samples were collected after an overnight fast in the Suita study, the risk of non-fasting TG was not assessed. Third, serum lipoprotein (a), which showed to be a strong risk factor for CAD in a previous study, was not measured[21]. Fourth, ischemic stroke in the present study included cerebral infarction other than atherothrombotic cerebral infarction.

Conclusion

Higher serum TG level was significantly associated with the increased risk for the incidence of ischemic CVD after the adjustment for CVD risk factors, including LDL-C, in Japanese general population with TG <400 mg/dL. Because the association between TG and the risk for ischemic CVD and CAD was more evident in those with LDL-C <140 mg/dL, TG should be well controlled in individuals with higher TG level whose LDL-C is not evidently high. Furthermore, because the CMI could be the most powerful predictive factor for future ischemic CVD among TG, TG/HDL-C, and the CMI, TG control combined with HDL-C elevation and WC reduction, in addition to LDL-C control, could be effective for the prevention of ischemic CVD.

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Supplemental Table 1. Risk of the deciles of serum TG for ischemic CVD and its subtypes adjusted for the Suita risk score: the Suita study (1989-2013)

	N of participants	No. of events	Crude incidence (/1,000 person-years)	Multivariable-adjustedHR (95%CI)
Ischemic CVD				
D_1 (15-54)	699	20	1.8	1.18 (0.68-2.05)
D_2 (55-65)	656	29	2.8	1.26 (0.77-2.06)
D_3 (66-75)	660	37	3.7	1.32 (0.84-2.09)
D_4 (76-86)	698	38	3.6	1.19 (0.75-1.87)
D_5 (87-97)	629	47	5.0	1.38 (0.89-2.14)
D_6 (98-111)	667	38	3.8	1.00
D_7 (112-130)	686	54	5.4	1.34 (0.88-2.03)
D_8 (131-153)	641	60	6.3	1.41 (0.93-2.13)
D_9 (154-198)	675	70	6.9	1.51 (1.02-2.25)
D_{10} (199-399)	673	71	7.1	1.37 (0.92-2.04)
Trend *p*				*p*=0.278
CAD				
D_1 (15-54)	699	11	1.0	1.20 (0.57-2.52)
D_2 (55-65)	656	12	1.1	0.90 (0.43-1.88)
D_3 (66-75)	660	25	2.4	1.68 (0.93-3.03)
D_4 (76-86)	698	20	1.8	1.14 (0.61-2.12)
D_5 (87-97)	629	25	2.6	1.27 (0.69-2.33)
D_6 (98-111)	667	21	2.0	1.00
D_7 (112-130)	686	36	3.5	1.66 (0.96-2.87)
D_8 (131-153)	641	35	3.6	1.59 (0.92-2.75)
D_9 (154-198)	675	42	4.0	1.68 (0.99-2.86)
D_{10} (199-399)	673	41	4.0	1.46 (0.85-2.50)
Trend *p*				*p*=0.186
Ischemic stroke				
D_1 (15-54)	699	9	0.8	1.18 (0.52-2.66)
D_2 (55-65)	656	17	1.7	1.71 (0.87-3.37)
D_3 (66-75)	660	12	1.2	0.94 (0.45-1.97)
D_4 (76-86)	698	18	1.7	1.20 (0.62-2.34)
D_5 (87-97)	629	22	2.3	1.49 (0.79-2.80)
D_6 (98-111)	667	17	1.7	1.00
D_7 (112-130)	686	18	1.8	0.97 (0.50-1.88)
D_8 (131-153)	641	25	2.6	1.25 (0.67-2.32)
D_9 (154-198)	675	28	2.7	1.32 (0.72-2.41)
D_{10} (199-399)	673	30	2.9	1.27 (0.70-2.31)
Trend *p*				*p*=0.858

Multivariable-adjusted HR: the scores calculated by the Suita risk score[15] were adjusted.

Supplemental Table 2. Risk of the quintiles of serum TG, TG/HDL-C, and the CMI for ischemic CVD by sex: the Suita study (1989-2013)

	N of participants	No. of events	Crude incidence (/1,000 person-years)	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI)
TG (mg/dL)					
Men					
Q_1 (28-73)	610	45	5.1	0.90 (0.61-1.34)	1.08 (0.72-1.62)
Q_2 (74-98)	649	61	6.8	1.10 (0.77-1.59)	1.25 (0.87-1.81)
Q_3 (99-128)	627	54	6.0	1.00	1.00
Q_4 (129-175)	617	69	7.8	1.31 (0.92-1.87)	1.28 (0.89-1.83)
Q_5 (176-399)	626	68	7.4	1.34 (0.94-1.91)	1.26 (0.88-1.81)
Trend p				$p<0.05$	$p=0.406$
Women					
Q_1 (15-59)	703	16	1.4	1.08 (0.58-1.99)	1.33 (0.71-2.49)
Q_2 (60-77)	726	24	2.0	0.98 (0.57-1.67)	1.07 (0.62-1.83)
Q_3 (78-98)	707	30	2.7	1.00	1.00
Q_4 (99-134)	714	37	3.4	1.10 (0.68-1.79)	1.10 (0.68-1.78)
Q_5 (135-397)	705	60	5.5	1.57 (1.01-2.44)	1.37 (0.88-2.15)
Trend p				$p<0.05$	$p=0.266$
TG/HDL-C ratio					
Men					
Q_1 (0.34-1.29)	625	40	4.4	0.73 (0.48-1.09)	0.84 (0.56-1.27)
Q_2 (1.30-1.91)	632	56	6.4	1.10 (0.76-1.59)	1.14 (0.79-1.66)
Q_3 (1.92-2.72)	623	56	6.2	1.00	1.00
Q_4 (2.73-4.13)	623	69	7.6	1.24 (0.87-1.76)	1.09 (0.77-1.56)
Q_5 (4.14-16.86)	626	76	8.4	1.44 (1.02-2.04)	1.37 (0.96-1.94)
Trend p				$p<0.01$	$p<0.05$
Women					
Q_1 (0.17-0.93)	716	16	1.4	1.10 (0.58-2.08)	1.31 (0.68-2.50)
Q_2 (0.94-1.27)	712	25	2.2	1.45 (0.82-2.56)	1.50 (0.85-2.64)
Q_3 (1.28-1.77)	714	23	2.0	1.00	1.00
Q_4 (1.78-2.65)	706	36	3.2	1.35 (0.80-2.27)	1.42 (0.84-2.40)
Q_5 (2.66-13.90)	707	67	6.2	2.30 (1.43-3.70)	2.08 (1.28-3.38)
Trend p				$p<0.001$	$p<0.01$
CMI					
Men					
Q_1 (0.16-0.62)	642	42	4.6	0.79 (0.53-1.18)	0.94 (0.62-1.43)
Q_2 (0.63-0.93)	610	53	6.0	1.06 (0.72-1.54)	1.11 (0.76-1.62)
Q_3 (0.94-1.37)	632	54	6.0	1.00	1.00
Q_4 (1.38-2.14)	621	68	7.7	1.25 (0.88-1.79)	1.13 (0.79-1.63)
Q_5 (2.15-8.82)	624	80	8.9	1.52 (1.08-2.15)	1.43 (1.00-2.05)
Trend p				$p<0.001$	$p<0.05$
Women					
Q_1 (0.06-0.43)	719	16	1.4	1.25 (0.66-2.36)	1.52 (0.79-2.92)
Q_2 (0.44-0.62)	703	25	2.2	1.34 (0.76-2.34)	1.43 (0.81-2.52)
Q_3 (0.63-0.91)	728	24	2.0	1.00	1.00
Q_4 (0.92-1.42)	695	33	3.1	1.19 (0.71-2.02)	1.20 (0.70-2.04)
Q_5 (1.43-8.82)	710	69	6.4	2.20 (1.38-3.51)	1.89 (1.16-3.08)
Trend p				$p<0.001$	$p<0.05$

TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, CMI: cardiometabolic index, HR: hazard ratio, CI: confidence interval, CVD: cardiovascular diseases.
Multivariable-adjusted HR: age, sex, hypertension, diabetes, medication for dyslipidemia, smoking, alcohol drinking, body mass index, and low-density lipoprotein cholesterol were adjusted.

Supplemental Table 3. Risk of the quintiles of TG, TG/HDL-C ratio, and the CMI for CAD and ischemic stroke by sex: the Suita study (1989-2013)

	N of participants	No. of events	Crude incidence (/1,000 person-years)	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI)
CAD					
TG (mg/dL)					
Men					
Q_1 (28-73)	610	27	3.0	0.86 (0.52-1.43)	1.06 (0.63-1.78)
Q_2 (74-98)	649	32	3.4	0.91 (0.56-1.47)	1.04 (0.64-1.70)
Q_3 (99-128)	627	34	3.7	1.00	1.00
Q_4 (129-175)	617	43	4.7	1.28 (0.82-2.01)	1.23 (0.79-1.94)
Q_5 (176-399)	626	38	4.0	1.17 (0.74-1.86)	1.14 (0.71-1.82)
Trend p				$p=0.118$	$p=0.589$
Women					
Q_1 (15-59)	703	9	0.8	0.97 (0.43-2.19)	1.33 (0.58-3.02)
Q_2 (60-77)	726	10	0.8	0.67 (0.31-1.45)	0.78 (0.36-1.71)
Q_3 (78-98)	707	18	1.6	1.00	1.00
Q_4 (99-134)	714	23	2.0	1.12 (0.61-2.08)	1.15 (0.62-2.13)
Q_5 (135-397)	705	34	3.0	1.48 (0.83-2.62)	1.27 (0.71-2.28)
Trend p				$p<0.05$	$p=0.370$
TG/HDL-C ratio					
Men					
Q_1 (0.34-1.29)	625	23	2.5	0.73 (0.43-1.25)	0.87 (0.50-1.49)
Q_2 (1.30-1.91)	632	30	3.3	0.98 (0.60-1.61)	1.03 (0.62-1.69)
Q_3 (1.92-2.72)	623	33	3.5	1.00	1.00
Q_4 (2.73-4.13)	623	46	4.9	1.41 (0.90-2.20)	1.21 (0.77-1.91)
Q_5 (4.14-16.86)	626	42	4.5	1.34 (0.85-2.12)	1.32 (0.83-2.10)
Trend p				$p<0.05$	$p=0.103$
Women					
Q_1 (0.17-0.93)	716	8	0.7	0.88 (0.37-2.11)	1.12 (0.47-2.71)
Q_2 (0.94-1.27)	712	11	1.0	1.01 (0.46-2.23)	1.06 (0.48-2.35)
Q_3 (1.28-1.77)	714	14	1.2	1.00	1.00
Q_4 (1.78-2.65)	706	23	2.0	1.40 (0.72-2.73)	1.44 (0.74-2.82)
Q_5 (2.66-13.90)	707	38	3.4	2.12 (1.15-3.93)	1.85 (0.98-3.49)
Trend p				$p<0.01$	$p<0.05$
CMI					
Men					
Q_1 (0.16-0.62)	642	24	2.6	0.78 (0.46-1.33)	0.94 (0.54-1.62)
Q_2 (0.63-0.93)	610	28	3.1	0.95 (0.57-1.57)	0.98 (0.59-1.63)
Q_3 (0.94-1.37)	632	32	3.4	1.00	1.00
Q_4 (1.38-2.14)	621	45	4.9	1.41 (0.90-2.22)	1.24 (0.78-1.96)
Q_5 (2.15-8.82)	624	45	4.9	1.45 (0.92-2.28)	1.41 (0.88-2.25)
Trend p				$p<0.01$	$p=0.066$
Women					
Q_1 (0.06-0.43)	719	8	0.7	0.80 (0.35-1.86)	1.03 (0.43-2.42)
Q_2 (0.44-0.62)	703	9	0.8	0.61 (0.28-1.36)	0.65 (0.29-1.45)
Q_3 (0.63-0.91)	728	18	1.5	1.00	1.00
Q_4 (0.92-1.42)	695	19	1.7	0.91 (0.47-1.73)	0.89 (0.46-1.71)
Q_5 (1.43-8.82)	710	40	3.6	1.68 (0.96-2.94)	1.44 (0.80-2.61)
Trend p				$p<0.01$	$p<0.05$

(Cont. Supplemental Table 3)

	N of participants	No. of events	Crude incidence (/1,000 person-years)	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI)
Ischemic stroke					
TG (mg/dL)					
Men					
Q_1 (28-73)	610	18	2.0	0.99 (0.52-1.86)	1.14 (0.59-2.18)
Q_2 (74-98)	649	29	3.1	1.40 (0.79-2.47)	1.53 (0.86-2.71)
Q_3 (99-128)	627	20	2.2	1.00	1.00
Q_4 (129-175)	617	26	2.9	1.35 (0.75-2.41)	1.34 (0.75-2.40)
Q_5 (176-399)	626	30	3.2	1.59 (0.90-2.80)	1.43 (0.80-2.53)
Trend *p*				$p=0.135$	$p=0.571$
Women					
Q_1 (15-59)	703	7	0.6	1.23 (0.48-3.15)	1.35 (0.52-3.52)
Q_2 (60-77)	726	14	1.2	1.44 (0.67-3.12)	1.48 (0.68-3.22)
Q_3 (78-98)	707	12	1.1	1.00	1.00
Q_4 (99-134)	714	14	1.3	1.04 (0.48-2.26)	1.00 (0.46-2.17)
Q_5 (135-397)	705	26	2.3	1.66 (0.84-3.30)	1.49 (0.74-3.00)
Trend *p*				$p=0.284$	$p=0.590$
TG/HDL-C ratio					
Men					
Q_1 (0.34-1.29)	625	17	1.9	0.75 (0.40-1.41)	0.84 (0.44-1.59)
Q_2 (1.30-1.91)	632	26	2.9	1.20 (0.69-2.11)	1.23 (0.70-2.16)
Q_3 (1.92-2.72)	623	23	2.5	1.00	1.00
Q_4 (2.73-4.13)	623	23	2.5	0.99 (0.56-1.76)	0.92 (0.51-1.65)
Q_5 (4.14-16.86)	626	34	3.7	1.56 (0.92-2.65)	1.42 (0.83-2.44)
Trend *p*				$p<0.05$	$p=0.152$
Women					
Q_1 (0.17-0.93)	716	8	0.7	1.45 (0.56-3.76)	1.57 (0.60-4.13)
Q_2 (0.94-1.27)	712	14	1.2	2.13 (0.92-4.92)	2.14 (0.92-4.97)
Q_3 (1.28-1.77)	714	9	0.8	1.00	1.00
Q_4 (1.78-2.65)	706	13	1.2	1.22 (0.52-2.85)	1.28 (0.54-3.01)
Q_5 (2.66-13.90)	707	29	2.6	2.48 (1.17-5.26)	2.31 (1.07-4.98)
Trend *p*				$p=0.057$	$p=0.145$
CMI					
Men					
Q_1 (0.16-0.62)	642	18	1.9	0.84 (0.45-1.56)	0.99 (0.52-1.90)
Q_2 (0.63-0.93)	610	25	2.8	1.22 (0.69-2.16)	1.28 (0.72-2.29)
Q_3 (0.94-1.37)	632	22	2.4	1.00	1.00
Q_4 (1.38-2.14)	621	23	2.5	1.04 (0.58-1.87)	0.99 (0.55-1.79)
Q_5 (2.15-8.82)	624	35	3.8	1.63 (0.96-2.78)	1.48 (0.86-2.57)
Trend *p*				$p<0.05$	$p=0.215$
Women					
Q_1 (0.06-0.43)	719	8	0.7	2.62 (0.90-7.60)	2.98 (1.01-8.82)
Q_2 (0.44-0.62)	703	16	1.4	3.55 (1.39-9.08)	3.89 (1.51-10.03)
Q_3 (0.63-0.91)	728	6	0.5	1.00	1.00
Q_4 (0.92-1.42)	695	14	1.3	1.99 (0.77-5.20)	2.00 (0.76-5.23)
Q_5 (1.43-8.82)	710	29	2.6	3.64 (1.51-8.78)	3.11 (1.26-7.69)
Trend *p*				$p=0.098$	$p=0.365$

TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, CMI: cardiometabolic index, HR: hazard ratio, CI: confidence interval, CAD: coronary artery disease.
Multivariable-adjusted HR: age, sex, hypertension, diabetes, medication for dyslipidemia, smoking, alcohol drinking, body mass index, and low-density lipoprotein cholesterol were adjusted.