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Original Article

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Diabetes Mellitus Modifies the Association of Serum Triglycerides with Ischemic Cardiovascular Disease Mortality: The Ibaraki Prefectural Health Study (IPHS)

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Aim: Diabetes mellitus and hypertriglyceridemia may adversely interact with the development of ischemic cardiovascular disease, but epidemiological evidence on this issue is scarce. We hypothesized that the impact of hypertriglyceridemia on ischemic cardiovascular disease (ischemic heart disease and ischemic stroke) would differ according to the presence or absence of diabetes mellitus and tested our *a priori* hypothesis under a large population-based prospective study.

Methods: A total of 90,468 men and women aged 40–79 years in 1993 were enrolled in the Ibaraki Prefectural Health Study (IPHS), a community-based cohort study of Japanese. The participants' serum triglyceride levels (mostly nonfasting) were measured every 5 years, and the participants were followed up for mortality from ischemic cardiovascular disease through 2016. Hazard ratios (95% confidence intervals) were calculated according to 5-year updated triglyceride levels (<100, 100–149, 150–199, 200–299, and ≥ 300 mg/dl).

Results: During 1,795,877 person-years, there were 3,323 deaths from ischemic cardiovascular diseases (1,968 ischemic heart diseases and 1,355 ischemic strokes). We found no association between triglyceride levels and the risk of mortality from ischemic cardiovascular disease after adjustment for known cardiovascular risk factors. However, when stratified by the presence or absence of diabetes mellitus, excess mortality from ischemic cardiovascular disease appeared among participants with diabetes mellitus with triglyceride levels of ≥ 300 mg/dl. Further adjustment for high-density lipoprotein-cholesterol attenuated the association toward being statistically nonsignificant.

Conclusion: The impact of high serum triglyceride levels on the risk of ischemic cardiovascular disease mortality was confined to participants with diabetes mellitus.

Key words: Epidemiology, Cohort study, Diabetic dyslipidemia, Follow-up study, Risk factor, Cardiovascular disease

Introduction

Postprandial hypertriglyceridemia commonly occurs in patients with diabetes mellitus, accompanied by several clinical findings: increased production and defect in the clearance of very low-density lipoprotein (VLDL) triglycerides[1)], absence of the acute inhibitory effect of insulin on chylomicron production[2)], and increased levels of remnant-like lipoprotein particles[3, 4)]. Hypertriglyceridemia and hyperglycemia usually share underlying lifestyle and constitutional factors, such as high carbohydrate intake and visceral fat

accumulation. Accordingly, these metabolic conditions may adversely interact with the development of ischemic cardiovascular diseases. However, whether the impact of hypertriglyceridemia on ischemic cardiovascular disease, confirmed by previous studies[5-7], is modified by diabetes mellitus is uncertain.

We hypothesized that the impact of hypertriglyceridemia on ischemic cardiovascular disease is pronounced in the presence of diabetes mellitus and tested our *a priori* hypothesis under a large population-based prospective study[8]. This investigation could provide clinical implications for controlling risk factors among patients with diabetes.

Materials and Methods

Study Cohort

In 1993, the Ibaraki Prefectural Government initiated a community-based cohort study, the Ibaraki Prefectural Health Study (IPHS), to obtain information on the association between risk factor and disease for the purpose of health education and policy making[8]. The cohort included 97,043 individuals (63,912 women and 33,131 men) aged 40–79 years living in Ibaraki Prefecture, Japan, who completed an annual health checkup in 1993. We excluded 5,339 persons from the analyses because of a history of stroke or heart disease at baseline. We further excluded 1,236 persons because of missing baseline triglycerides (n=891) or follow-up data (n=345). Finally, 90,468 individuals (59,880 women and 30,588 men) were enrolled in the study.

Baseline Measurements

At the checkups, height was measured with stocks on, and weight was measured with light clothing. Body mass index was calculated dividing weight in kilograms by the square of height in meters. Blood pressure was measured by a trained observer using a standard mercury sphygmomanometer. Blood sampling was done with the participants in a sitting position. Fasting was not required, and approximately 83% of the participants had blood drawn in nonfasting status (<8 hours from the last meal) at baseline. Serum total cholesterol and triglyceride levels were measured using enzymatic methods, high-density lipoprotein (HDL) cholesterol levels by the phosphotungstic acid magnesium method between 1993 and 1995 and direct methods thereafter, plasma glucose by the glucose oxidase electrode method between 1993 and 1996 and enzymatic methods thereafter, and serum creatinine by the Jaffe methods between 1993 and 2003 and enzymatic methods thereafter. The serum creatinine values were adjusted to the enzymatic method by subtracting 0.2 from the value measured using the Jaffe method. The estimated glomerular filtration rate was calculated using the Japanese version of the Chronic Kidney Disease Epidemiology Collaboration equation[9]. Low estimated glomerular filtration rate was defined as < 60 ml/min/1.73 m^2. Face-to-face interviews were conducted to obtain information on smoking status; number of cigarettes smoked per day; weekly intake of alcohol (in *go* unit, a traditional Japanese unit equivalent to 23 g ethanol); and history and treatment of stroke, heart disease, hypertension, dyslipidemia, and diabetes mellitus.

Follow-Up Surveillance

The dates of death or moving were obtained from local governments. Data regarding deaths were centralized at the Ministry of Health, Labour and Welfare, where the underlying causes of death were coded for the National Vital Statistics according to the International Classification of Diseases and Related Health Problems (ICD), 9th (1993–1994) and 10th (1995–2016) revisions. Deaths from total cardiovascular disease were identified as codes 393–459 in ICD-9 and as codes I00–I99 in ICD-10, ischemic heart disease as codes 410–414 in ICD-9 and as codes I20–I25 in ICD-10, and ischemic stroke as codes 433–434 and 437.7 in ICD-9 and as code I63 and I69.3 in ICD-10. Deaths from ischemic cardiovascular disease were defined as those from ischemic heart disease and ischemic stroke combined.

Statistical Analysis

The differences in the age-adjusted baseline characteristics across the triglyceride categories (< 100, 100–149, 150–199, 200–299, and ≥ 300 mg/dl) were tested using an analysis of covariance. Follow-up started from the 1993 baseline health checkups and ended at the date of death or emigration or at the end of 2016. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cause-specific mortality according to the triglyceride categories were tested using Cox proportional hazards regression models. The linear trend of HR across the categories was

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tested using a continuous value of log-transformed triglycerides. To reduce the impact of misclassification caused by changes on triglyceride status during follow-up, we updated the categories of triglycerides and the confounding factors listed below (except for sex) using the second (1998 ± 2) and third (2003 ± 2) follow-up health checkup data, in which 77% (n=69,814) and 61% (n=55,184) of the baseline (1993) participants participated, respectively[10]. For example, triglycerides from 1993 health checkups were related to the cardiovascular-related disease mortality occurring between 1993 and the second follow-up point, those from the second follow-up point were related to the mortality occurring between the second and third follow-up points, and those from the third checkups were related to the mortality occurring thereafter. For those who had not participated in the second or third follow-ups, values on the 1993 (or the second) follow-up point were used. Of note, the proportions of participants whose blood was drawn in nonfasting status were 83% at baseline, 66% at second follow-up, and 61% at third follow-up points. The following covariates were included: age (continuous), sex (dichotomous), cigarette smoking (never, ex, <20, 20–29, and ≥ 30 cigarettes/day), alcohol consumption (noncurrent, occasionally, <69 and ≥ 69 g ethanol/day), body mass index (continuous), systolic blood pressure (continuous), antihypertensive medication use (dichotomous), serum non-HDL cholesterol level (continuous), serum HDL cholesterol level (continuous), antidyslipidemic medication use (dichotomous), diabetes mellitus (dichotomous), low estimated glomerular filtration rate (dichotomous), and fasting status (time between the last meal and blood drawing: <8 or ≥ 8 hours). The analysis was further stratified by baseline diabetic status (excluding 75 participants with missing baseline diabetic status): with diabetes (fasting blood glucose ≥ 126 mg/dl or nonfasting blood glucose ≥ 200 mg/dl and/or use of antidiabetic medication) and no diabetes. For missing covariables, we assigned dummy variables and included them in the models. The multiplicative interactions of triglycerides with diabetic status in relation to mortality from each outcome were tested using cross-product terms. All statistical tests were two-sided, and values of P<0.05 were considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Ethics Approval

Informed consent was obtained from community representatives to conduct an epidemiological study. Individual consent was not required for the analysis of this study, since it was conducted as a secondary use of data obtained for public health practice on cardiovascular disease prevention in the local community at that time. Adhering to relevant guidelines and regulations afterward, the participants were retrospectively given the opportunity to withdraw their data from analysis, and the consent was considered to have been obtained if the participant did not decline in this study. The IPHS protocol was approved by the Ethics Committees of Ibaraki Prefecture and University of Tsukuba.

Results

At baseline, age was inversely correlated with serum triglyceride levels for men but positively correlated with it for women **(Table 1)**. Body mass index, blood pressures, treatments for hypertension and hyperlipidemia, serum non-HDL cholesterol, and diabetes mellitus were positively correlated with triglyceride levels, while HDL cholesterol, the prevalence of current drinkers, and estimated glomerular filtration rate were negatively correlated. In women, the prevalence of current smokers was positively correlated with triglycerides. Of the participants, 66% were women.

During a 23.1-year median follow-up, there were 3,323 deaths from ischemic cardiovascular diseases including 1,968 deaths due to ischemic heart diseases and 1,355 ischemic strokes.

Serum triglyceride levels, as a whole, were positively associated with age and sex-adjusted mortality from ischemic cardiovascular disease **(Table 2)**. Adjustment for potential confounding factors, however, attenuated the associations, and the trend was no longer statistically significant.

Stratifying by the presence of diabetes **(Table 2)**, we found a positive association of serum triglyceride levels with mortality from ischemic cardiovascular disease among persons with diabetes mellitus. After further adjustment for cardiovascular risk factors, the excess risk of ischemic cardiovascular disease associated with triglycerides of ≥ 300 mg/dl remained (HR=1.56 [95% CI: 1.02–2.39]). Further adjustment for HDL cholesterol attenuated the association toward being statistically nonsignificant (HR=1.32 [95% CI: 0.84–2.09]). Among persons without diabetes mellitus, the associations were weak and not significant after further adjustment for cardiovascular risk factors. The interaction of triglycerides with diabetic status in relation to mortalities from ischemic cardiovascular disease reached statistical significance (p=0.003). Similar association and interaction were

Table 1. Sex-specific baseline cardiovascular risk factors in a cohort of 59, 880 women and 30, 588 men according to triglyceride category

	Triglyceride levels (mg/dl)					
	-99	100-149	150-199	200-299	300-	*P*-value‡
Men						
Median triglyceride, mg/dl	76	122	171	235	371	
Number at risk	10,397	8,863	5,145	4,164	2,019	
Age at baseline*, y	61.9 (9.8)	60.6 (9.9)	59.6 (9.9)	58.3 (10.0)	55.8 (9.9)	<0.001
Non-fasting status†, %	77.0	82.4	86.2	88.8	89.5	<0.001
Body mass index, kg/m^2	22.0	23.3	24.1	24.7	25.1	<0.001
Systolic blood pressure, mmHg	134	136	138	139	141	<0.001
Diastolic blood pressure, mmHg	80	81	82	83	84	<0.001
Treatment for hypertension, %	16.7	20.1	21.2	23.3	22.7	<0.001
Treatment for hyperlipidemia, %	0.5	1.1	1.5	2.0	2.8	<0.001
Serum non-HDL cholesterol, mg/dl	121	140	151	161	173	<0.001
Serum HDL-choelsterol, mg/dl	60	52	48	45	41	<0.001
Diabetes mellitus, %	6.4	6.9	7.5	9.9	11.2	<0.001
Current smoker, %	51.4	51.4	51.1	50.5	52.9	0.52
Current drinker, %	68.1	64.5	64.2	64.5	66.7	<0.001
Estimated GFR, mL/min/1.73m^2	80.0	78.6	77.9	77.2	77.2	<0.001
Women						
Median triglyceride, mg/dl	75	121	170	233	356	
Number at risk	23, 340	17, 856	9, 482	6, 855	2, 347	
Age at baseline*, y	55.0 (10.5)	58.7 (10.0)	59.8 (9.5)	60.5 (9.1)	60.2 (8.9)	<0.001
Non-fasting status†, %	75.5	84.4	89.4	91.9	93.9	<0.001
Body mass index, kg/m^2	22.5	23.7	24.4	25.0	25.5	<0.001
Systolic blood pressure, mmHg	129	132	134	135	137	<0.001
Diastolic blood pressure, mmHg	76	78	79	80	81	<0.001
Treatment for hypertension, %	16.1	19.4	21.7	25.1	27.2	<0.001
Treatment for hyperlipidemia, %	2.1	2.9	4.2	4.9	6.6	<0.001
Serum non-HDL cholesterol, mg/dl	134	152	164	173	184	<0.001
Serum HDL cholesterol, mg/dl	64	56	52	47	42	<0.001
Diabetes mellitus, %	3.3	3.6	4.2	5.4	8.6	<0.001
Current smoker, %	4.3	4.8	5.5	5.5	6.9	<0.001
Current drinker, %	10.8	9.0	8.7	8.7	8.4	<0.001
Estimated GFR, mL/min/1.73m^2	82.8	82.1	81.8	81.4	81.5	<0.001

HDL: high density lipoprotein; GFR: glomerular filtration rate
Age-adjusted means or percentages presented unless otherwise indicated.
*Unadjusted mean (standard deviation)
†Time between blood drawing and the last meal <8 hours.
‡*P*-values for overall difference across triglyceride categories based on analysis of covariance

found for ischemic heart disease **(Table 3)**. No such association or interaction was found for ischemic stroke, although the HRs in the highest category of triglycerides among participants with diabetes were similar between ischemic heart disease (1.67 [95% CI: 0.97–2.87]) and ischemic stroke (1.44 [95% CI: 0.72–2.89]).

When we used only the baseline triglyceride measurement, the excess risk of ischemic cardiovascular disease associated with triglycerides of ≥ 300 mg/dl were slightly attenuated probably due to the misclassification of triglycerides during follow-up: the multivariable HR in the highest category of triglycerides and *p* for trend among participants with diabetes was 1.44 (95% CI: 0.93–2.23) and 0.04, respectively (not shown in tables).

Discussion

In our cohort study, conducted over a median of 23 years and involving 90,468 men and women aged

Table 2. Age and sex-adjusted and multivariable hazard ratios and 95% confidence intervals of mortality from ischemic cardiovascular disease according to triglyceride categories, IPHS, 1993-2016

	Triglyceride levels (mg/dl)						*P* for interaction with diabetes
	-99	100-149	150-199	200-299	300-	Trend *P*	
Men and women							
Number at risk	33,737	26,719	14,627	11,019	4,366		
Person year	667,480	529,262	291,418	220,344	87,373		
Ischemic cardiovascular diseases (n)	1,095	973	601	474	180		
Age and sex-adjusted HR (95%CI)	1.0	1.03 (0.95-1.12)	1.07 (0.97-1.18)	1.14 (1.01-1.27)	1.33 (1.11-1.58)	<0.001	
Multivariable HR (95%CI)	1.0	0.96 (0.88-1.05)	0.95 (0.85-1.06)	0.98 (0.86-1.11)	1.07 (0.89-1.29)	0.55	
Further adjustment for HDL-cholesterol	1.0	0.93 (0.85-1.02)	0.90 (0.81-1.01)	0.91 (0.80-1.04)	0.97 (0.80-1.18)	0.46	
Participants with diabetes mellitus							
Number at risk	1,365	1,283	811	798	423		
Person year	24,372	22,927	14,941	14,414	7,466		
Ischemic cardiovascular diseases (n)	87	94	55	70	38		
Age and sex-adjusted HR (95%CI)	1.0	1.04 (0.79-1.38)	1.20 (0.88-1.64)	1.14 (0.81-1.60)	2.08 (1.43-3.03)	<0.001	
Multivariable HR (95%CI)	1.0	0.91 (0.68-1.22)	1.00 (0.71-1.41)	0.88 (0.60-1.28)	1.56 (1.02-2.39)	0.12	
Further adjustment for HDL-cholesterol	1.0	0.86 (0.64-1.16)	0.91 (0.64-1.30)	0.77 (0.52-1.15)	1.32 (0.84-2.09)	0.46	
Participants without diabetes mellitus							
Number at risk	32,344	25,415	13,801	10,214	3,939		
Person year	642,586	505,968	276,158	205,797	79,839		
Ischemic cardiovascular diseases (n)	1,006	876	545	404	142		
Age and sex-adjusted HR (95%CI)	1.0	1.03 (0.94-1.12)	1.04 (0.94-1.16)	1.12 (0.99-1.26)	1.12 (0.92-1.37)	0.007	0.004
Multivariable HR (95%CI)	1.0	0.97 (0.89-1.06)	0.95 (0.85-1.07)	1.00 (0.87-1.14)	0.97 (0.78-1.20)	0.87	0.003
Further adjustment for HDL-cholesterol	1.0	0.94 (0.86-1.04)	0.91 (0.80-1.02)	0.94 (0.81-1.08)	0.89 (0.72-1.11)	0.33	0.003

Multivariable model includes age, sex, cigarette smoking, alcohol consumption, body mass index, systolic blood pressure, antihypertensive medication use, serum non-HDL cholesterols, cholesterol lowering medication use, diabetes mellitus, low estimated glomerular filtration rate and fasting status.

40–79 years, we found that nonfasting triglyceride levels were not associated with the risk of mortality from ischemic cardiovascular disease. Stratified by diabetic status, excess mortality from ischemic cardiovascular disease appeared among participants with diabetes mellitus with triglyceride levels of ≥ 300 mg/dl. Further adjustment for HDL cholesterol attenuated the association toward being statistically nonsignificant, probably because HDL cholesterol changes in sync with triglycerides.

Our finding of null associations between nonfasting triglyceride levels and mortality from ischemic cardiovascular disease was consistent with a previous pooled analysis from the Emerging Risk Factor Collaboration, which involved 302,430 people from 68 cohort studies of cardiovascular mortality and morbidity mostly in North America and Europe[11]. In their analysis, the HR for ischemic heart disease with one-standard deviation change in log-transformed triglycerides was 1.37 (95% CI: 1.31–1.42) after adjustment for nonlipid risk factors (age, sex, systolic blood pressure, smoking, body mass index, and history of diabetes), but it was reduced to 0.99 (95% CI: 0.94–1.05) after further adjustment for HDL cholesterol and non-HDL cholesterol. A similar pattern was observed for ischemic stroke: the respective HRs were 1.12 (95% CI: 1.05–1.19) and 1.02 (95% CI: 0.94–1.11). In contrast, most cohort studies of Asians[12-15] (but not all[16]) have shown a positive association of triglycerides with the incidence of or mortality from ischemic heart disease or cardiovascular disease after adjustment for HDL cholesterol. For example, the Circulatory Risk in Communities Study, which involved 5,641 Japanese men and women aged 40–69 in 1975–1980 at baseline who were followed up for 15.5 years, showed that the multivariable adjusted HR of incident ischemic heart disease was 3.21 (95% CI: 1.52–6.75) among the highest versus lowest quartiles of nonfasting triglycerides after adjustment for HDL cholesterol[12]. Another study from the same group (1975–1986 baseline and a median of 22 years follow-up) showed similar results for cardiovascular disease, but not for ischemic heart disease; the

Table 3. Age and sex-adjusted and multivariable hazard ratios and 95% confidence intervals of mortality from cardiovascular outcomes according to triglyceride categories, IPHS, 1993-2016

	Triglyceride levels (mg/dl)						*P* for interaction with diabetes
	-99	100-149	150-199	200-299	300-	Trend *P*	
Men and women							
Number at risk	33,737	26,719	14,627	11,019	4,366		
Person year	667,480	529,262	291,418	220,344	87,373		
Ischemic heart disease (n)	609	575	348	315	121		
Age and sex-adjusted HR (95%CI)	1.0	1.05 (0.95-1.18)	1.15 (1.01-1.31)	1.27 (1.10-1.47)	1.44 (1.15-1.79)	<0.001	
Multivariable HR (95%CI)	1.0	0.97 (0.86-1.08)	1.00 (0.86-1.15)	1.06 (0.90-1.25)	1.11 (0.88-1.41)	0.04	
Further adjustment for HDL-cholesterol	1.0	0.93 (0.82-1.04)	0.93 (0.80-1.08)	0.97 (0.82-1.15)	0.98 (0.77-1.25)	0.48	
Ischemic stroke (n)	486	398	253	159	59		
Age and sex-adjusted HR (95%CI)	1.0	1.01 (0.89-1.14)	0.97 (0.82-1.14)	0.95 (0.79-1.15)	1.17 (0.88-1.56)	0.90	
Multivariable HR (95%CI)	1.0	0.96 (0.84-1.10)	0.89 (0.75-1.06)	0.86 (0.70-1.06)	1.02 (0.75-1.38)	0.11	
Further adjustment for HDL-cholesterol	1.0	0.94 (0.82-1.08)	0.87 (0.73-1.04)	0.82 (0.66-1.02)	0.96 (0.70-1.32)	0.04	
Participants with diabetes mellitus							
Number at risk	1,365	1,283	811	798	423		
Person year	24,372	22,927	14,941	14,414	7,466		
Ischemic heart disease (n)	50	62	37	51	25		
Age and sex-adjusted HR (95%CI)	1.0	1.21 (0.85-1.73)	1.50 (1.02-2.21)	1.45 (0.96-2.20)	2.17 (1.34-3.51)	<0.001	
Multivariable HR (95%CI)	1.0	1.05 (0.73-1.52)	1.25 (0.82-1.89)	1.14 (0.72-1.81)	1.67 (0.97-2.87)	0.07	
Further adjustment for HDL-cholesterol	1.0	0.98 (0.67-1.42)	1.09 (0.71-1.69)	0.96 (0.59-1.57)	1.33 (0.75-2.38)	0.40	
Ischemic stroke (n)	37	32	18	19	13		
Age and sex-adjusted HR (95%CI)	1.0	0.83 (0.52-1.32)	0.79 (0.46-1.39)	0.70 (0.37-1.33)	2.00 (1.09-3.66)	0.28	
Multivariable HR (95%CI)	1.0	0.73 (0.45-1.18)	0.68 (0.37-1.24)	0.52 (0.26-1.05)	1.44 (0.72-2.89)	0.87	
Further adjustment for HDL-cholesterol	1.0	0.71 (0.44-1.16)	0.65 (0.35-1.22)	0.50 (0.24-1.02)	1.34 (0.63-2.85)	0.94	
Participants without diabetes mellitus							
Number at risk	32,344	25,415	13,801	10,214	3,939		
Person year	642,586	505,968	276,158	205,797	79,839		
Ischemic heart disease (n)	558	510	311	264	96		
Age and sex-adjusted HR (95%CI)	1.0	1.03 (0.92-1.16)	1.10 (0.95-1.26)	1.23 (1.05-1.43)	1.23 (0.96-1.59)	<0.001	0.02
Multivariable HR (95%CI)	1.0	0.96 (0.85-1.09)	0.97 (0.84-1.13)	1.07 (0.90-1.27)	1.02 (0.78-1.33)	0.10	0.02
Further adjustment for HDL-cholesterol	1.0	0.93 (0.82-1.05)	0.92 (0.78-1.07)	0.98 (0.82-1.18)	0.91 (0.69-1.21)	0.58	0.02
Ischemic stroke (n)	448	366	234	140	46		
Age and sex-adjusted HR (95%CI)	1.0	1.02 (0.90-1.17)	0.98 (0.83-1.15)	0.97 (0.79-1.18)	0.97 (0.69-1.35)	0.48	0.14
Multivariable HR (95%CI)	1.0	0.99 (0.86-1.13)	0.92 (0.77-1.10)	0.90 (0.73-1.12)	0.89 (0.63-1.27)	0.08	0.14
Further adjustment for HDL-cholesterol	1.0	0.97 (0.84-1.12)	0.89 (0.74-1.07)	0.87 (0.69-1.09)	0.85 (0.59-1.21)	0.03	0.14

Multivariable model includes age, sex, cigarette smoking, alcohol consumption, body mass index, systolic blood pressure, antihypertensive medication use, serum non-HDL cholesterols, cholesterol lowering medication use, diabetes mellitus, low estimated glomerular filtration rate and fasting status.

multivariable adjusted HR of incident cardiovascular disease was 1.48 (95% CI: 1.08–2.02) among the highest versus lowest quartiles of triglycerides after adjustment for HDL cholesterol[14]. The Asia-Pacific Cohort Study, which involved 96,224 men and women from 26 studies in Asia-Pacific region, showed a 70% greater risk of fatal ischemic heart disease and an 80% greater risk of fatal and nonfatal ischemic heart disease among the highest versus lowest quartiles of triglycerides even after adjustment for total-to-HDL cholesterol ratio[13].

The reasons for the effect modification with diabetic status in relation to the triglycerides–ischemic cardiovascular disease association warrant discussion. Postprandial triglycerides include chylomicron remnants, and their concentration reflects delayed clearance of chylomicron remnants[17, 18]. In addition, the catabolism of lipoprotein could be interrupted with diabetes mellitus, resulting in the increased levels of chylomicron remnants and VLDL remnants[3, 4].

Taken together, high triglycerides in participants without diabetes mellitus (mostly under normal insulin state) may reflect short-term postprandial hypertriglyceridemia, which may have less adverse effects, and result in a null or weak association of triglycerides. As for epidemiological studies, a meta-analysis of a maximum of 31 prospective studies from various countries and involving a maximum of 132,044 people with diabetes mellitus showed an association between triglycerides and cardiovascular disease: pooled relative risk=1.30 (1.16–1.46) for the highest versus the lowest categories of triglycerides from 11 studies (although nonsignificant when further adjusted for other lipid parameters; respective relative risk=1.39 [0.92–2.10] from three studies)[19]. Additionally, some cohort studies of general populations showed that high triglyceride-glucose index (although it was based on fasting triglycerides and glucose) was associated with a higher risk of incidence for ischemic heart disease or myocardial infarction[20-22]. These findings were partly in line with our observation. On the other hand, a pooling analysis of studies from the Asia-Pacific region showed that the positive association between triglycerides and fatal ischemic heart disease was similarly observed for participants either with or without diabetes mellitus[13].

The effect modification by diabetes mellitus was statistically significant for ischemic cardiovascular disease and ischemic heart disease, but not for ischemic stroke, although the HRs of the highest category of triglycerides among participants with diabetes mellitus were similar between ischemic heart disease and ischemic stroke. This may be caused by the small number of ischemic strokes in the stratum of participants with diabetes mellitus. Another reason is that ischemic stroke deaths included not only atherothrombotic stroke but also lacunar and cardioembolic strokes, which are unlikely to be associated with lipid metabolism.

The strengths of the current study include the largest number of study participants from Asia with triglyceride measurement involving persons both with and without diabetes mellitus and a standardized manner of triglyceride measurement at a single laboratory. The repeat measurements of triglycerides and confounding variables approximately every 5 years would be another strength, which allowed us to account for the changes in them over 20 years of follow-up. Some limitations applied, as with other cohort studies, including observational design, residual confounding, and undetermined external validity. Because the participation in the health checkups was voluntary, the healthy participant effect was unavoidable. We did not have data on the incidence of cardiovascular disease, and the association of triglycerides with the incidence of cardiovascular disease may differ from that of mortality from cardiovascular disease.

Based on clinical trials, pharmacological treatment for elevated triglycerides has generally shown to reduce the risk of cardiovascular disease[23, 24], although no study have been specifically designed to recruit patients with hypertriglyceridemia so far[24]. Among patients with diabetes mellitus, the risk reduction by fibrates has been less clear[25, 26], but their sub-analyses suggested a potential benefit of treating triglycerides among patients with diabetes with marked (≥ 204 mg/dl) hypertriglyceridemia[27] or hypertriglyceridemia accompanied with low HDL cholesterol[27, 28].

In conclusion, the impact of high serum triglyceride levels on the risk of ischemic cardiovascular disease mortality was confined to participants with diabetes mellitus. Taken together with currently available findings from clinical trials, the present study underscores the importance of careful triglyceride monitoring among patients with diabetes mellitus.

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Conflict of Interest

The authors declare that there is no conflict of interest.

References

1) Howard BV: Lipoprotein metabolism in diabetes mellitus. J Lipid Res, 1987; 28: 613-628
2) Nogueira JP, Maraninchi M, Beliard S, Padilla N, Duvillard L, Mancini J, Nicolay A, Xiao C, Vialettes B, Lewis GF and Valero R: Absence of acute inhibitory effect of insulin on chylomicron production in type 2 diabetes. Arterioscler Thromb Vasc Biol, 2012; 32: 1039-1044
3) Watanabe N, Taniguchi T, Taketoh H, Kitagawa Y, Namura H, Yoneda N, Kurimoto Y, Yamada S and Ishikawa Y: Elevated remnant-like lipoprotein particles in impaired glucose tolerance and type 2 diabetic patients. Diabetes Care, 1999; 22: 152-156
4) Schaefer EJ, McNamara JR, Shah PK, Nakajima K, Cupples LA, Ordovas JM and Wilson PW: Elevated remnant-like particle cholesterol and triglyceride levels in diabetic men and women in the Framingham Offspring Study. Diabetes Care, 2002; 25: 989-994
5) Hokanson JE and Austin MA: Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk, 1996; 3: 213-219
6) Labreuche J, Touboul PJ and Amarenco P: Plasma triglyceride levels and risk of stroke and carotid atherosclerosis: a systematic review of the epidemiological studies. Atherosclerosis, 2009; 203: 331-345
7) Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT and Gudnason V: Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation, 2007; 115: 450-458
8) Irie F, Sairenchi T, Iso H and Shimamoto T: [Prediction of mortality from findings of annual health checkups utility for health care programs]. Nihon Koshu Eisei Zasshi, 2001; 48: 95-108 (in Japanese with English abstract)
9) Horio M, Imai E, Yasuda Y, Watanabe T and Matsuo S: Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis, 2010; 56: 32-38
10) SAS Institute Inc.: The PHREG Procedure. In: SAS/STAT®131 User's Guide, SAS Institute Inc., Cary, NC, 2013
11) Emerging Risk Factors Collaboration: Major lipids, apolipoproteins, and risk of vascular disease. JAMA, 2009; 302: 1993-2000
12) Iso H, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, Shimamoto T, Iida M and Komachi Y: Serum triglycerides and risk of coronary heart disease among Japanese men and women. Am J Epidemiol, 2001; 153: 490-499
13) Asia Pacific Cohort Studies Collaboration: Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation, 2004; 110: 2678-2686
14) Iso H, Imano H, Yamagishi K, Ohira T, Cui R, Noda H, Sato S, Kiyama M, Okada T, Hitsumoto S, Tanigawa T and Kitamura A; for the CIRCS Investigators: Fasting and non-fasting triglycerides and risk of ischemic cardiovascular disease in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). Atherosclerosis, 2014; 237: 361-368
15) Hirata A, Okamura T, Hirata T, Sugiyama D, Ohkubo T, Okuda N, Kita Y, Hayakawa T, Kadota A, Kondo K, Miura K, Okayama A and Ueshima H: Relationship between non-fasting triglycerides and cardiovascular disease mortality in a 20-year follow-up study of a Japanese general population: NIPPON DATA90. J Epidemiol, (in press); doi: 10.2188/jea.JE20200399
16) Higashiyama A, Wakabayashi I, Okamura T, Kokubo Y, Watanabe M, Takegami M, Honda-Kohmo K, Okayama A and Miyamoto Y: The risk of fasting triglycerides and its related indices for ischemic cardiovascular diseases in Japanese community dwellers: the Suita Study. J Atheroscler Thromb, 2021; 28: 1275-1288
17) Zilversmit DB: Atherogenesis: a postprandial phenomenon. Circulation, 1979; 60: 473-485
18) Nakajima K, Nakano T, Moon HD, Nagamine T, Stanhope KL, Havel PJ and Warnick GR: The correlation between TG vs remnant lipoproteins in the fasting and postprandial plasma of 23 volunteers. Clin Chim Acta, 2009; 404: 124-127
19) Ye X, Kong W, Zafar MI and Chen LL: Serum triglycerides as a risk factor for cardiovascular diseases in type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. Cardiovasc Diabetol, 2019; 18: 48
20) Sánchez-Íñigo L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado J and Martínez JA: The TyG index may predict the development of cardiovascular events. Eur J Clin Invest, 2016; 46: 189-197
21) Li S, Guo B, Chen H, Shi Z, Li Y, Tian Q and Shi S: The role of the triglyceride (triacylglycerol) glucose index in the development of cardiovascular events: a retrospective cohort analysis. Sci Rep, 2019; 9: 7320
22) Tian X, Zuo Y, Chen S, Liu Q, Tao B, Wu S and Wang A: Triglyceride-glucose index is associated with the risk of myocardial infarction: an 11-year prospective study in the Kailuan cohort. Cardiovasc Diabetol, 2021; 20: 19
23) Marston NA, Giugliano RP, Im K, Silverman MG, O'Donoghue ML, Wiviott SD, Ference BA and Sabatine MS: Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: A systematic review and meta-regression analysis of randomized controlled trials. Circulation, 2019; 140: 1308-1317
24) Esan O and Wierzbicki AS: Triglycerides and cardiovascular disease. Curr Opin Cardiol, 2021; 36: 469-477
25) The FIELD study investigators: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet, 2005; 366: 1849-1861
26) ACCORD Study Group: Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med, 2010; 362: 1563-1574
27) Scott R, O'Brien R, Fulcher G, Pardy C, D'Emden M, Tse D, Taskinen MR, Ehnholm C, Keech A and on behalf of the Fenofibrate Intervention and Event Lowering in

Diabetes (FIELD) Study Investigators: Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care, 2009; 32: 493-498
28) Elam MB, Ginsberg HN, Lovato LC, Corson M, Largay J, Leiter LA, Lopez C, O'Connor PJ, Sweeney ME, Weiss D, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm R, Ismail-Beigi F, Goff DC, Jr., Fleg JL, Rosenberg Y and Byington RP; for the ACCORDION Study Investigators: Association of fenofibrate therapy with long-term cardiovascular risk in statin-treated patients with type 2 diabetes. JAMA Cardiol, 2017; 2: 370-380