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Original Article

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Hypertriglyceridemia Is an Independent Risk Factor for Cardiovascular Diseases in Korean Adults Aged 30–49 Years: a Nationwide Population-Based Study

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Conflict of Interest
The authors have no conflicts of interest to declare.

ABSTRACT

Objective: This study was conducted to estimate the incidence of cardiovascular disease (CVD) independently from low-density lipoprotein (LDL) cholesterol according to triglyceride (TG) levels in young adults.
Methods: Subjects aged 30–49 years with data from routine health check-ups provided by the National Health Insurance Service during 2009 were selected. The primary outcome was incident CVD, defined as a composite of ischemic heart disease and ischemic stroke during the follow-up period from 2009 to 2018.
Results: The mean age of study subjects (n=1,823,537) was 40.1±5.7 years, and the median follow-up period was 8.3 years. The quartiles of serum TG levels at the baseline were calculated: Q1, <74 mg/dL; Q2, 74–108 mg/dL; Q3, 109–166 mg/dL; and Q4: >166 mg/dL. The highest quartile of TG levels (Q4) had a significantly higher risk of the primary outcome than Q1 (hazard ratio [HR], 2.40 [95% confidence interval; CI, 2.33–2.47]). Q2 and Q3 also experienced the primary outcome more frequently than Q1 (HR, 1.37 [95% CI, 1.33–1.42] and HR, 1.80 [95% CI, 1.75–1.86], respectively). Even after adjustment for age, sex, obesity, alcohol drinking amount, smoking, LDL cholesterol, diabetes mellitus, hypertension, lipid-lowering medication use, and family history of CVD, there was a significant dose-response relationship between TG quartiles and the risk of the primary outcome (HR per quartile, 1.13 [95% CI, 1.12–1.14]).
Conclusion: In conclusion, in the Korean population aged 30–49 years, high TG levels independently increased future CVD risk in both men and women.

Keywords: Cardiovascular diseases; Triglycerides; Insurance claims analysis

INTRODUCTION

Conflicting data have been reported regarding whether plasma triglyceride (TG) levels increase the risk of cardiovascular disease (CVD) and mortality independently from low-density lipoprotein (LDL) cholesterol.[1,2] Although TG-lowering therapy failed to improve

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Author Contributions

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cardiovascular mortality,[3-5] it reduced the event rate of myocardial infarction (MI) and reperfusion therapy.[3,4] In addition, it brought an additional benefit to statins for protection against CVD in patients with diabetes who had hypertriglyceridemia.[5]

Ethnic differences in plasma TG levels have been reported, and the Korean population shows higher fasting plasma TG levels than Caucasian populations.[6] However, sparse data have been reported on the effect of hypertriglyceridemia on CVD risk in the Korean population. Only a single-center general health checkup—based study showed that plasma TG level 150 mg/dL or more increased the risk of CVD during 3 years of follow-up.[7] However, as all adults aged ≥20 years were included in that study (mean age, 48 years),[7] their findings cannot be extrapolated to a specific age group such as young adults. Age is a strong independent risk factors for CVD, and lipid levels are dependent on age and sex in both the Korean population[8] and Caucasian populations.[9] Considering the importance of the economic activity of young adults, as well as the effect of metabolic disorders in young adulthood on later life for each individual,[10] we focused on adults aged 30–49 years.

The National Health Insurance Service (NHIS) in Korea was initiated in 1977 and achieved universal coverage of the population by 1989. The NHIS covers the claims of 97% of the population in Korea; those of the remaining 3% of the population are covered by the Medical Aid Program. Accordingly, the NHIS database contains information on almost a full range of demographic and socioeconomic data, as well as insurance claims (including prescribed medications and procedures) for the Korean population of approximately 50 million.[11] The present study was performed to estimate the incidence of CVD according to TG level in the entire population of adults aged 30–49 years in South Korea using the NHIS database from 2009 to 2018.

MATERIALS AND METHODS

1. Data collection

We used the NHIS database between January 1, 2009 and December 31, 2009. After de-identification, the NHIS provided data including age, sex, diagnosis, date of hospital visits, drug prescriptions received during inpatient and outpatient visits, hospital admissions, medical procedures, and emergency department visits. Drug information included the brand name, generic name, prescription date, and duration and route of administration. Diagnoses were coded according to the International Classification of Disease (10th revision; ICD-10). As the NHIS offers national health examination programs biennially, the database also included body measurements, laboratory results, and additional information on smoking status, alcohol drinking habits, and menopausal status from self-reported questionnaires.[12] The dates of death of the participants in routine health check-ups provided by the NHIS were retrieved from National Death Registry by the Korea National Statistical Office. The study was approved by the Boramae Medical Center Institutional Review Board (IRB No.07-2020-033).

2. Study subjects

Adults aged 30–49 years who underwent routine health check-ups provided by the NHIS during 2009 were selected for the analysis (n=1,920,731). After the exclusion of individuals with insufficient data on clinical parameters including lipid profile (n=77,239), a previous history of ischemic stroke or ischemic heart disease (IHD) (n=15,476), or a follow-up duration less than 1 year (n=4,479), 1,823,537 subjects were included.

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Serum TG levels were retrieved from the health check-up database provided by the NHIS, and hypertriglyceridemia was defined as TG ≥150 mg/dL.[13] The quartiles of serum TG level were also calculated, with Q1 and Q4 being the lowest and highest quartiles of TG levels, respectively.

Hypertension was defined as a blood pressure ≥140/90 mmHg or use of an antihypertensive medication under ICD-10 codes I10–13 and I15. Cases of diabetes mellitus were defined as subjects who were users of anti-diabetic medications, including insulin, under ICD-10 codes E11–14 at the point of the survey or had 8-hour fasting plasma glucose levels that were ≥126 mg/dL. Dyslipidemia was defined as total cholesterol ≥240 mg/dL or use of cholesterol-lowering agents under the ICD-10 code E78.

Based on the self-reported questionnaire, participants were classified according to their alcohol drinking habits into 3 groups: non-drinkers, mild drinkers (daily alcohol intake <30 g/day), and heavy drinkers (daily alcohol intake ≥30 g/day). Smoking history and family history of CVD were also assessed by self-reported questionnaires.

3. Study outcomes

The primary outcome was incident ischemic CVD, defined as a composite of IHD and ischemic stroke, during the follow-up period from 2009 to 2018. The secondary outcomes were MI and overall mortality, as well as each composite outcome of IHD and ischemic stroke. IHD and MI were diagnosed using hospitalization with the primary diagnostic ICD-10 codes I20–25 and I21–22, respectively.[14] Ischemic stroke was defined as hospitalization under ICD-10 codes I63–64 and having brain imaging such as computed tomography and magnetic resonance imaging during the admission. A previous history of IHD and MI was diagnosed using the codes I20–25 and I21–22, with more than 1 diagnosis during admission or at outpatient clinics, respectively.[14] The wash-out period for defining incident cases was 2002–2008.

4. Statistical analysis

All data were analyzed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org). To compare subjects' clinical characteristics according to the primary outcome, the Mood median test or analysis of variance for continuous variables and the chi-square test for categorical variables were used. The hazard ratio (HR) and 95% confidence interval (CI) for primary outcomes were calculated by multivariable Cox proportional hazards regression analysis. The variables incorporated in the Cox proportional hazards regression analysis were selected based on well-known factors affecting TG levels and CVD.[1,2,5,15] The HR of primary outcomes according to each quartile of serum TG level was compared to the lowest quartile, and trends in the HR according to the quartile of serum TG levels were also investigated. Since male sex and the presence of diabetes are major factors determining TG levels,[16,17] stratified analyses according to sex and diabetes status were performed. *p*-values <0.05 were considered to indicate statistical significance.

RESULTS

1. Baseline characteristics

The mean age of the study subjects (n=1,823,537) was 40.1±5.7 years, and the median follow-up period was 8.3 years (interquartile range, 8.1–8.5 years). The quartiles of serum TG levels

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Table 1. Baseline characteristics according to TG levels

Characteristics	Men					Women				
	Q1	Q2	Q3	Q4	*p* for trend	Q1	Q2	Q3	Q4	*p* for trend
Median TGs (mg/dL)*	60 (51–67)	91 (82–100)	134 (121–149)	233 (194–305)	<0.001	56 (47–65)	88 (80–98)	129 (118–144)	210 (184–262)	<0.001
Age (yr)	38.7±5.8	39.1±5.8	39.4±5.7	39.7±5.5	<0.001	40.4±5.5	41.5±5.4	42.1±5.2	42.5±5.2	<0.001
Body mass index (kg/m^2)	22.7±2.7	23.5±2.9	24.4±3.0	25.5±3.0	<0.001	21.8±2.7	22.7±3.0	23.7±3.3	24.82±3.58	<0.001
Current cigarette smoker	70,561 (42.4)	117,935 (47.5)	163,476 (50.9)	222,469 (57.0)	<0.001	7,510 (2.6)	7,358 (3.5)	5,900 (4.5)	3,920 (5.9)	<0.001
Alcohol drinking history					<0.001					<0.001
None	52,608 (31.6)	72,999 (29.4)	87,696 (27.3)	91,036 (23.3)		194,335 (67.4)	143,445 (68.4)	91,774 (69.2)	46,990 (70.1)	
Mild (<30 g/day)	97,154 (58.4)	146,681 (59.1)	189,957 (59.1)	227,470 (58.3)		91,661 (31.8)	63,949 (30.5)	38,863 (29.3)	18,660 (27.8)	
Heavy (≥30 g/day)	16,602 (10.0)	28,492 (11.5)	43,536 (13.6)	71,559 (18.4)		2,432 (0.8)	2,343 (1.1)	1,920 (1.5)	1,375 (2.1)	
Hypertension	16,814 (10.1)	32,320 (13.0)	54,618 (17.0)	93,599 (24.0)	<0.001	17,569 (6.1)	19,970 (9.5)	18,424 (13.9)	13,910 (20.8)	<0.001
Diabetes mellitus	4,291 (2.6)	8,759 (3.5)	16,096 (5.0)	35,871 (9.2)	<0.001	3,297 (1.1)	4,502 (2.2)	5,370 (4.1)	6,043 (9.0)	<0.001
Lipid medication	1,943 (1.2)	4,486 (1.8)	8,918 (2.8)	17,290 (4.4)	<0.001	2,275 (0.8)	3,310 (1.6)	3,719 (2.8)	3,531 (5.3)	<0.001
Total cholesterol (mg/dL)	178.7±33.7	188.8±33.9	197.9±40.2	210.7±41.6	<0.001	179.2±34.6	189.5±36.8	198.4±38.3	209.3±43.3	<0.001
LDL cholesterol (mg/dL)	113.9±193.4	120.7±168.2	124.6±154.3	116.3±167.4	<0.001	107.9±144.5	114.1±105.1	118.3±95.9	118.3±132.1	<0.001
HDL cholesterol (mg/dL)	59.2±23.7	55.5±19.7	52.99±29.0	49.3±35.0	<0.001	63.5±19.1	60.0±25.9	57.5±31.6	60.3±74.2	<0.001
Serum creatinine (mg/dL)	1.3±1.7	1.3±1.7	1.3±1.7	1.3±1.7	0.834	0.9±1.0	0.9±0.9	0.9±1.0	1.0±1.2	<0.001
Aspartate aminotransferase (IU/L)*	19 (15–26)	22 (16–30)	25 (19–36)	32 (23–46)	<0.001	14 (11–18)	15 (12–20)	16 (13–22)	19 (14–28)	<0.001
Alanine aminotransferase (IU/L)*	22 (19–27)	23 (19–28)	24 (20–29)	26 (22–34)	<0.001	19 (16–22)	19 (16–23)	20 (17–24)	21 (18–26)	<0.001
Family history of CVD					<0.001					<0.001
No	104,550 (62.8)	154,192 (62.1)	198,732 (61.9)	241,000 (61.8)		168,287 (58.4)	117,777 (56.2)	74,443 (56.2)	38,254 (57.1)	
Yes	12,855 (7.7)	20,292 (8.2)	27,697 (8.6)	34,524 (8.9)		24,569 (8.5)	19,105 (9.1)	12,400 (9.4)	6,422 (9.6)	
Unknown	48,959 (29.4)	73,688 (29.7)	94,760 (29.5)	114,541 (29.4)		95,572 (33.1)	72,855 (34.7)	45,714 (34.5)	22,349 (33.3)	

Values are presented as mean±standard deviation or number (%).
To compare the clinical characteristics according to TG quartiles, the Mood median test or analysis of variance for continuous variables and the χ^2 test for categorical variables were used.
TG, triglyceride; Q, quartile; IQR, interquartile range; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CVD, cardiovascular disease.
*Geometric mean (95% confidence interval).

at the baseline were calculated (Q1, <74 mg/dL; Q2, 74–108 mg/dL; Q3, 109–166 mg/dL; Q4, >166 mg/dL). In both sexes, mean age, body mass index (BMI), and LDL cholesterol levels increased as TG levels increased (p<0.001 for all; **Table 1**). Significant positive associations were also found between TG quartiles and current smoking, alcohol drinking amount, and family history of CVD (p<0.001 for all; **Table 1**).

During the follow-up period, the primary outcome was detected in 39,657 subjects (IHD, 33,509 cases; ischemic stroke, 7,292 cases; **Supplementary Tables 1** and **2**), and overall mortality was found in 17,030 subjects. Subjects with the primary outcome were significantly older (42.9±5.0 years vs. 40.0±5.7 years; p<0.001) and male-predominant (71.8% vs. 61.5%; p<0.001) compared to those without the primary outcome. They had higher prevalence of obesity (44.1% vs. 32.1%), diabetes mellitus (11.8% vs. 4.5%), and current smoking (42.8% vs. 32.6%; **Supplementary Table 1**). Although use of lipid-lowering agents was more common in subjects with the primary outcome, those subjects had significantly higher total cholesterol, TG, and LDL cholesterol levels and lower high-density lipoprotein cholesterol levels than subjects without the primary outcome (p<0.001 for all; **Supplementary Table 1**).

2. Incidence of CVD and mortality according to TG levels

In crude analysis, the highest quartile of TG levels (Q4) had a significantly higher risk of the primary outcome than Q1 (HR, 2.40 [95% CI, 2.33–2.47]; p<0.001). In addition, Q2 and Q3 also experienced the primary outcome more frequently than Q1 (HR, 1.37 [95% CI, 1.33–1.42]; and HR, 1.80 [95% CI, 1.75–1.86], respectively; **Table 2**). Even after adjustment for age, sex, obesity, alcohol drinking amount, smoking, LDL cholesterol, diabetes mellitus,

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Table 2. Incidence of CVD or mortality according to triglyceride levels

Triglyceride quartiles	Total (n=1,823,537)			Men (n=1,125,790)			Women (n=697,747)		
	Event	HR (95% CI)		Event	HR (95% CI)		Event	HR (95% CI)	
		Model 1	Model 2		Model 1	Model 2		Model 1	Model 2
Primary outcome									
Q1	6,054	(Reference)	(Reference)	2,710	(Reference)	(Reference)	3,344	(Reference)	(Reference)
Q2	8,333	1.37 (1.33–1.42)*	1.15 (1.11–1.19)*	4,978	1.23 (1.18–1.29)*	1.12 (1.07–1.17)*	3,355	1.38 (1.32–1.45)*	1.18 (1.12–1.24)*
Q3	10,829	1.80 (1.75–1.86)*	1.30 (1.26–1.35)*	8,163	1.57 (1.50–1.64)*	1.29 (1.23–1.34)*	2,666	1.74 (1.66–1.83)*	1.28 (1.21–1.35)*
Q4	14,441	2.40 (2.33–2.47)*	1.45 (1.40–1.50)*	12,640	2.01 (1.93–2.09)*	1.43 (1.37–1.50)*	1,801	2.34 (2.21–2.48)*	1.43 (1.34–1.52)*
Per 1Q		1.34 (1.32–1.35)*	1.13 (1.12–1.14)*		1.27 (1.25–1.28)*	1.13 (1.12–1.14)*		1.32 (1.30–1.35)*	1.12 (1.10–1.15)*
IHD									
Q1	5,096	(Reference)	(Reference)	2,259	(Reference)	(Reference)	2,837	(Reference)	(Reference)
Q2	7,091	1.39 (1.34–1.44)*	1.17 (1.12–1.21)*	4,238	1.26 (1.20–1.33)*	1.14 (1.09–1.20)*	2,853	1.39 (1.32–1.46)*	1.18 (1.12–1.24)*
Q3	9,091	1.80 (1.74–1.86)*	1.30 (1.26–1.35)*	6,848	1.58 (1.50–1.65)*	1.30 (1.24–1.36)*	2,243	1.73 (1.63–1.83)*	1.26 (1.19–1.34)*
Q4	12,231	2.41 (2.33–2.49)*	1.47 (1.41–1.52)*	10,716	2.04 (1.95–2.14)*	1.47 (1.40–1.54)*	1,515	2.32 (2.18–2.47)*	1.41 (1.32–1.50)*
Per 1Q		1.34 (1.32–1.35)*	1.13 (1.12–1.45)*		1.27 (1.25–1.29)*	1.14 (1.12–1.15)*		1.32 (1.29–1.34)*	1.12 (1.10–1.14)*
Stroke									
Q1	1,128	(Reference)	(Reference)	537	(Reference)	(Reference)	591	(Reference)	(Reference)
Q2	1,458	1.28 (1.19–1.39)*	1.06 (0.98–1.14)	880	1.10 (0.99–1.22)	0.98 (0.88–1.09)	578	1.35 (1.20–1.51)*	1.14 (1.02–1.28)*
Q3	2,053	1.83 (1.70–1.97)*	1.30 (1.26–1.35)*	1,555	1.50 (1.36–1.66)*	1.19 (1.08–1.32)*	498	1.84 (1.63–2.07)*	1.33 (1.17–1.50)*
Q4	2,653	2.35 (2.19–2.52)*	1.45 (1.40–1.50)*	2,301	1.83 (1.67–2.01)*	1.23 (1.11–1.36)*	352	2.57 (2.25–2.93)*	1.51 (1.31–1.74)*
Per 1Q		1.34 (1.31–1.37)*	1.11 (1.08–1.13)*		1.25 (1.22–1.28)*	1.09 (1.06–1.12)*		1.37 (1.31–1.42)*	1.12 (1.10–1.15)*
MI									
Q1	619	(Reference)	(Reference)	346	(Reference)	(Reference)	273	(Reference)	(Reference)
Q2	1,060	1.70 (1.54–1.88)*	1.24 (1.12–1.37)*	798	1.55 (1.36–1.76)*	1.36 (1.20–1.54)*	262	1.32 (1.11–1.56)*	1.10 (0.93–1.31)
Q3	1,710	2.78 (2.53–3.04)*	1.55 (1.41–1.70)*	1,502	2.25 (2.00–2.53)*	1.75 (1.56–1.97)*	208	1.66 (1.38–1.99)*	1.16 (0.97–1.40)
Q4	2,850	4.60 (4.22–5.02)*	1.97 (1.80–2.17)*	2,689	3.33 (2.98–3.72)*	2.22 (1.98–2.49)*	161	2.54 (2.09–3.08)*	1.42 (1.15–1.75)
Per 1Q		1.66 (1.62–1.70)*	1.26 (1.22–1.29)*		1.48 (1.44–1.52)*	1.29 (1.25–1.33)*		1.34 (1.26–1.43)*	1.11 (1.04–1.19)†
Death									
Q1	3,282	(Reference)	(Reference)	1,821	(Reference)	(Reference)	1,461	(Reference)	(Reference)
Q2	3,951	1.20 (1.14–1.25)*	1.00 (0.95–1.04)	2,751	1.01 (0.96–1.08)	0.95 (0.89–1.01)	1,200	1.13 (1.05–1.22)†	1.04 (0.96–1.12)
Q3	4,530	1.39 (1.32–1.45)*	0.99 (0.95–1.04)	3,621	1.03 (0.97–1.09)	0.91 (0.86–0.97)‡	909	1.35 (1.25–1.47)*	1.15 (1.05–1.25)*
Q4	5,267	1.60 (1.53–1.67)*	0.95 (0.90–0.99)	4,679	1.10 (1.04–1.16)†	0.87 (0.82–0.92)†	588	1.73 (1.58–1.91)*	1.31 (1.19–1.45)*
Per 1Q		1.17 (1.15–1.18)*	0.98 (0.97–1.00)‡		1.03 (1.02–1.05)*	0.95 (0.94–0.97)*		1.19 (1.16–1.23)*	1.09 (1.06–1.12)*

The primary outcome was incident ischemic CVD, defined as a composite of IHD and ischemic stroke during the follow-up period.
Data are shown as below: model 1, without adjustment; model 2, with adjustment for age, sex, obesity, smoking, alcohol drinking, low-density lipoprotein cholesterol, diabetes mellitus, hypertension, lipid-lowering medication use, and family history of CVD.
CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; Q, quartile; IHD, ischemic heart disease; MI, myocardial infarction.
*p<0.001, †p<0.01, ‡p<0.05.

hypertension, lipid-lowering medication use, and family history of CVD, there was a significant dose-response relationship between TG quartiles and the risk of the primary outcome (HR per quartile, 1.13 [95% CI, 1.12–1.14]; p<0.001; model 2 in **Table 2**). In that model, Q4 had a 1.45 times higher risk of the primary outcome than Q1 (HR, 1.45 [95% CI, 1.40–1.50]; p<0.001). Q4 also had a significantly higher risk of each composite endpoint than Q1 (for IHD: HR, 1.47 [95% CI, 1.41–1.52]; p<0.001; for ischemic stroke: HR, 1.45 [95% CI, 1.40–1.50]; p<0.001; and for MI risk: HR, 1.97 [95% CI, 1.80–2.17]; p<0.001). Interestingly, even in Q2, the risks of the primary outcome, IHD, and MI were significantly higher than in Q1 (HR, 1.15 [95% CI, 1.1–1.19], 1.17 [95% CI, 1.12–1.21], and 1.24 [95% CI, 1.12–1.37], respectively). There was no difference in overall mortality according to quartile (**Table 2**).

The sex-stratified analysis also showed similar trends in the risk of outcomes according to TG levels except for overall mortality (**Table 2**). In men, Q3 and Q4 showed a significantly lower risk of mortality than Q1 in the fully adjusted model (HR, 0.91 [95% CI, 0.86–0.97], p=0.011; HR, 0.87 [95% CI, 0.82–0.92], p=0.001, respectively); by contrast, in women, Q3 and Q4 had a higher risk of mortality than Q1 (HR, 1.15 [95% CI, 1.05–1.25], p=0.001; HR, 1.31 [95% CI, 1.19–1.45], p<0.001, respectively; model 2 in **Table 2**).

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Table 3. Incidence of CVD or mortality according to triglyceride levels in men with and without DM

Triglyceride quartiles	Men without DM (n=1,060,773)					Men with DM (n=65,017)				
	Event	Model 1		Model 2		Event	Model 1		Model 2	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Primary outcome										
Q1	2,524	(Reference)		(Reference)		186	(Reference)		(Reference)	
Q2	4,545	1.22 (1.16–1.28)	<0.001	1.11 (1.06–1.17)	<0.001	433	1.14 (0.96–1.36)	0.132	1.10 (0.93–1.31)	0.270
Q3	7,247	1.53 (1.46–1.60)	<0.001	1.28 (1.22–1.34)	<0.001	916	1.32 (1.13–1.54)	<0.001	1.24 (1.06–1.45)	0.008
Q4	10,387	1.90 (1.82–1.98)	<0.001	1.42 (1.36–1.49)	<0.001	2,253	1.46 (1.26–1.69)	<0.001	1.39 (1.19–1.62)	<0.001
Per 1Q		1.24 (1.23–1.26)	<0.001	1.13 (1.11–1.14)	<0.001		1.13 (1.09–1.17)	<0.001	1.12 (1.08–1.16)	<0.001
IHD										
Q1	2,113	(Reference)		(Reference)		146	(Reference)		(Reference)	
Q2	3,894	1.25 (1.19–1.32)	<0.001	1.14 (1.08–1.20)	<0.001	344	1.15 (0.95–1.14)	0.148	1.12 (0.92–1.35)	0.269
Q3	6,096	1.54 (1.46–1.62)	<0.001	1.29 (1.22–1.35)	<0.001	752	1.38 (1.15–1.64)	<0.001	1.30 (1.08–1.55)	0.005
Q4	8,881	1.94 (1.85–2.03)	<0.001	1.46 (1.39–1.53)	<0.001	1,835	1.51 (1.28–1.79)	<0.001	1.44 (1.21–1.71)	<0.001
Per 1Q		1.25 (1.23–1.26)	<0.001	1.13 (1.12–1.15)	<0.001	3,077	1.14 (1.09–1.19)	<0.001	1.13 (1.08–1.18)	<0.001
Stroke										
Q1	481	(Reference)		(Reference)		56	(Reference)		(Reference)	
Q2	775	1.09 (0.97–1.22)	0.136	0.98 (0.87–1.10)	0.716	105	0.92 (0.66–1.27)	0.598	0.89 (0.62–1.23)	0.464
Q3	1,340	1.48 (1.33–1.64)	<0.001	1.21 (1.09–1.34)	0.001	215	1.02 (0.76–1.37)	0.893	0.97 (0.72–1.31)	0.856
Q4	1,781	1.70 (1.53–1.88)	<0.001	1.23 (1.11–1.36)	<0.001	520	1.11 (0.84–1.46)	0.472	1.07 (0.81–1.41)	0.650
Per 1Q		1.21 (1.18–1.98)	<0.001	1.09 (1.06–1.12)	<0.001		1.06 (0.99–1.14)	0.093	1.06 (0.98–1.14)	0.140
MI										
Q1	326	(Reference)		(Reference)		20	(Reference)		(Reference)	
Q2	711	1.48 (1.30–1.68)	<0.001	1.30 (1.14–1.48)	<0.001	87	2.13 (1.31–3.46)	0.002	2.04 (1.25–3.32)	0.004
Q3	1,311	2.14 (1.90–2.42)	<0.001	1.70 (1.49–1.91)	<0.001	191	2.55 (1.61–4.03)	<0.001	2.37 (1.49–3.77)	<0.001
Q4	2,208	3.11 (2.77–3.49)	<0.001	2.16 (1.92–2.44)	<0.001	481	2.88 (1.84–4.50)	<0.001	2.76 (1.76–4.33)	<0.001
Per 1Q		1.46 (1.41–1.50)	<0.001	1.29 (1.25–1.33)	<0.001		1.24 (1.14–1.36)	<0.001	1.24 (1.14–1.36)	<0.001
Death										
Q1	1,667	(Reference)		(Reference)		154	(Reference)		(Reference)	
Q2	2,471	1.00 (0.94–1.07)	0.916	0.95 (0.90–1.02)	0.136	280	0.89 (0.73–1.08)	0.242	0.88 (0.72–1.07)	0.199
Q3	3,159	1.01 (0.95–1.07)	0.823	0.92 (0.87–0.98)	0.009	462	0.80 (0.67–0.96)	0.015	0.80 (0.67–0.96)	0.019
Q4	3,724	1.02 (0.97–1.08)	0.446	0.87 (0.82–0.93)	<0.001	955	0.94 (0.62–0.88)	0.001	0.76 (0.64–0.91)	0.002
Per 1Q		1.01 (0.99–1.03)	0.389	0.96 (0.94–0.97)	<0.001		0.91 (0.87–0.95)	<0.001	0.92 (0.88–0.97)	<0.001

The primary outcome was incident ischemic CVD, defined as a composite of IHD and ischemic stroke during the follow-up period.
Data are shown as below: model 1, without adjustment; model 2: with adjustment for age, obesity, smoking, alcohol drinking, low-density lipoprotein cholesterol, hypertension, lipid-lowering medication use, and family history of CVD.
CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; Q, quartile; IHD, ischemic heart disease; MI, myocardial infarction.

3. Incidence of CVD and mortality according to sex and diabetes mellitus

As there was a significant difference between the sexes according to the primary outcome and the association between mortality and TG levels, we performed a stratified analysis according to sex. Since insulin resistance and hyperglyceridemia are well-known determinants of serum TG levels,[2] subsequent stratification according to diabetes status was performed.

In men, an increasing trend of risk for IHD, stroke, and MI, as well as the primary outcome, according to increasing TG quartiles was found irrespective of diabetes status. However, in those with diabetes, there was no significant difference in stroke risk according to TG quartiles (HR per quartile, 1.06 [95% CI, 0.98–1.14]; **Table 3**), which corresponded to the findings for TG levels ≥150 mg/dL (HR for stroke, 1.05 [95% CI, 0.91–1.21]; **Supplementary Table 3**). An inverse correlation between overall mortality and TG quartiles was also found in men with and without diabetes (**Table 3**).

The finding of an increasing trend of risk of IHD and stroke according to TG in all women was maintained in the stratified analysis according to diabetes (**Table 4**). Unlike men, the HR of stroke for each 1-quartile increase in TG in women with diabetes was 1.41 (95% CI, 1.21–1.63), which was comparable to that in women who did not have diabetes (HR, 1.12; 95%

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Table 4. Incidence of CVD or mortality according to triglyceride levels in women with and without DM

Triglyceride quartiles	Women without DM (n=678,535)					Women with DM (n=19,212)				
	Event	Model 1		Model 2		Event	Model 1		Model 2	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Primary outcome										
Q1	3,248	(Reference)		(Reference)		96	(Reference)		(Reference)	
Q2	3,177	1.36 (1.30–1.43)	<0.001	1.17 (1.12–1.23)	<0.001	178	1.36 (1.06–1.74)	0.015	1.24 (0.96–1.59)	0.097
Q3	2,407	1.67 (1.58–1.76)	<0.001	1.26 (1.20–1.33)	<0.001	259	1.67 (1.32–2.12)	<0.001	1.46 (1.15–1.85)	0.002
Q4	1,455	2.11 (1.98–2.24)	<0.001	1.40 (1.31–1.50)	<0.001	346	1.99 (1.59–2.50)	<0.001	1.66 (1.32–2.09)	<0.001
Per 1Q		1.28 (1.26–1.31)	<0.001	1.12 (1.10–1.14)	<0.001		1.24 (1.16–1.32)	<0.001	1.18 (1.10–1.26)	<0.001
IHD										
Q1	2,750	(Reference)		(Reference)		87	(Reference)		(Reference)	
Q2	2,704	1.37 (1.30–1.44)	<0.001	1.18 (1.12–1.24)	<0.001	149	1.25 (0.96–1.55)	0.199	1.13 (0.87–1.48)	0.364
Q3	2,019	1.65 (1.56–1.75)	<0.001	1.25 (1.18–1.32)	<0.001	224	1.59 (1.24–2.04)	<0.001	1.37 (1.07–1.76)	0.013
Q4	1,231	2.11 (1.97–2.25)	<0.001	1.40 (1.30–1.50)	<0.001	284	1.80 (1.41–2.29)	<0.001	1.47 (1.15–1.88)	0.002
Per 1Q		1.28 (1.25–1.30)	<0.001	1.14 (1.09–1.14)	<0.001		1.21 (1.13–1.30)	<0.001	1.14 (1.06–1.22)	<0.001
Stroke										
Q1	575	(reference)		(Reference)		16	(Reference)		(Reference)	
Q2	543	1.31 (1.17–1.48)	<0.001	1.13 (1.00–1.27)	0.047	35	1.60 (0.89–2.89)	0.120	1.49 (0.83–2.70)	0.186
Q3	449	1.75 (1.55–1.98)	<0.001	1.31 (1.16–1.49)	<0.001	49	1.88 (1.07–3.31)	0.028	1.72 (0.97–3.05)	0.061
Q4	260	2.12 (1.83–2.45)	<0.001	1.37 (1.18–1.60)	<0.001	92	3.15 (1.85–5.35)	<0.001	2.83 (1.64–4.86)	<0.001
Per 1Q		1.30 (1.24–1.35)	<0.001	1.12 (1.07–1.18)	<0.001		1.45 (1.25–1.67)	<0.001	1.41 (1.21–1.63)	<0.001
MI										
Q1	266	(Reference)		(Reference)		7	(Reference)		(Reference)	
Q2	241	1.26 (1.06–1.50)	0.010	1.07 (0.90–1.27)	0.463	21	2.19 (0.93–5.16)	0.072	1.99 (0.84–4.70)	0.116
Q3	178	1.50 (1.24–1.81)	<0.001	1.10 (0.91–1.34)	0.324	30	2.63 (1.16–5.99)	0.021	2.29 (1.00–5.26)	0.051
Q4	126	2.22 (1.79–2.74)	<0.001	1.40 (1.12–1.75)	0.003	35	2.73 (1.21–6.13)	0.016	2.22 (0.97–5.08)	0.058
Per 1Q		1.28 (1.20–1.37)	<0.001	1.10 (1.03–1.18)	0.008		1.27 (1.04–1.55)	0.020	1.19 (0.97–1.46)	0.098
Death										
Q1	1,421	(Reference)		(Reference)		40	(Reference)		(Reference)	
Q2	1,146	1.12 (1.04–1.21)	0.004	1.04 (0.96–1.12)	0.374	54	0.98 (0.65–1.48)	0.947	0.97 (0.64–1.46)	0.886
Q3	839	1.32 (1.22–1.44)	<0.001	1.15 (1.05–1.25)	0.002	70	1.07 (0.73–1.58)	0.722	1.05 (0.71–1.56)	0.817
Q4	494	1.63 (1.47–1.80)	<0.001	1.32 (1.18–1.47)	<0.001	94	1.28 (0.89–1.85)	0.190	1.21 (0.83–1.78)	0.327
Per 1Q		1.17 (1.13–1.21)	<0.001	1.09 (1.05–1.12)	<0.001		1.10 (0.98–1.23)	0.109	1.08 (0.96–1.22)	0.213

The primary outcome was incident ischemic CVD, defined as a composite of IHD and ischemic stroke during the follow-up period.
Data are shown as below: model 1, without adjustment; model 2, with adjustment for age, obesity, smoking, alcohol drinking, low-density lipoprotein cholesterol, hypertension, lipid-lowering medication use, and family history of CVD.
CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; Q, quartile; IHD, ischemic heart disease; MI, myocardial infarction.

CI, 1.07–1.18). In women with diabetes, MI and mortality during follow-up period were only found in 93 and 258 out of 19,121 subjects, respectively; there was no significant difference in MI or mortality events according to TG quartiles (**Table 4**).

Adopting TG ≥150 mg/dL as the hypertriglyceridemia cutoff confirmed that a TG level ≥150 mg/dL significantly increased the risk of IHD irrespective of sex and diabetes mellitus status (**Supplementary Table 3**).

DISCUSSION

Using a nationwide database of the Korean population aged 30–49 years, we found that as serum TG levels increased, the future risk of the primary outcome (a composite of IHD and ischemic stroke) significantly increased in both men and women, even after adjusting for important CVD risk factors including LDL cholesterol levels. The relationship between TG levels and mortality differed by sex. In women, mortality increased at higher TG levels; in contrast, an inverse relationship between TG level and mortality was found in men.

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TG-rich lipoproteins can penetrate the arterial wall and are taken up by macrophages, which transform into foam cells.[18] They result in endothelial dysfunction, increased expression of adhesion molecules in endothelial cells, and production of oxidized free fatty acids and inflammatory cytokines, which promote atherogenesis and thrombogenesis.[19] Previous epidemiological studies have shown positive correlations between CVD risk and circulating TG levels,[1,2,7,20] and our study confirmed that correlation in relatively young adults aged 30–49 years using a prospective nationwide database. However, conflicting data have been reported regarding whether TG levels independently increase CVD risk,[1,2,7,20] which might be due to heterogeneity of the study populations. The effect of TG levels on CVD was more prominent in women,[20] young adults (<50 years vs. ≥50 years),[20] and those without other CVD risk factors.[7] The current study selected a study population with narrow age range (30–49 years) and confirmed that TG was an independent risk factor for IHD and stroke in this population. In addition, consistent findings were found for subjects with diabetes, although there was statistical attenuation due to a small number of stroke events in the subgroup analysis.

Interestingly, the relationship between TG levels and mortality differed according to sex in the current study. In women, an increasing trend for mortality was found as TG levels increased, which corroborates previous epidemiological studies.[20,21] However, among men, an inverse relationship between TG levels and mortality was found in the present study. A recent meta-analysis of prospective studies on the effect of TG levels on overall mortality showed that increased TG levels, even in the range of 150–200 mg/dL, increased the risk of CVD mortality compared to TG levels <150 mg/dL[20]; however, this relationship was not found in studies with less than 15 years of follow-up.[20] A long-term prospective study with 22 years of follow-up confirmed that the effect of hypertriglyceridemia was more prominent after 5 years.[21] Even though the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid trial failed to show an additional benefit of fenofibrate to statin therapy,[5] a beneficial reduction in CVD events was observed in an extended follow-up study (ACCORD Follow-On),[22] which implies that TG levels might require a relatively long time to affect clinical outcomes. Studies with a follow-up duration of less than 5 years even showed an inverse association between TG and mortality in the population with IHD.[23,24] Moreover, low TG levels are an independent risk factor for mortality within 1 year after acute CVD events.[25-27] The median follow-up duration of the current study was 8.3 years, which might have affected the observed association between TG levels and mortality. In addition, adjustment for BMI might impact the association between TG levels and mortality. In the Korean population, mortality in those with a BMI <23 kg/m^2 was higher than in the normal-weight group[28,29]; this relationship was more prominent in men than in women,[29] and the BMI with the lowest mortality was higher in men compared to women.[29,30] Considering that the positive correlation between TG levels and BMI was more prominent in men in the current study, adjustment for BMI might reverse the relationship between TG levels and mortality in men. More studies are needed to confirm the finding of an inverse correlation between TG levels and mortality in young men aged 30–49 years.

The major limitation of the current study is that the events during the following period were assessed using claims data. Even though the sensitivity and positive predictive values of claims data with identical definitions for CVD to those used in the current study were reported to be as high as 90% in a previous validation study in Korea,[31] the findings might have been affected both by underestimation of the real incidence of CVD, especially for ischemic stroke,[32] and overestimation due to the low sensitivity of claims-based definitions.[31,33] In addition, clinical data during the follow-up period were not considered.

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Furthermore, claims data provide limited information on disease severity, co-morbid conditions, past history, and specific treatment. Second, as there was no intervention for TG levels, the findings regarding the relationship between TG levels and clinical outcomes, especially mortality, cannot be explained. In addition to previous TG-lowering clinical trials to prove CVD benefits,[5] the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes study is ongoing to demonstrate the effect of a selective peroxisome proliferator-activated receptor alpha modulator on CVD outcomes, including all-cause mortality,[34] which might provide insights into the effects of TG levels on mortality. Third, we did not have cause-specific mortality data, which makes it more difficult to explain the observed inverse relationship between TG level sand overall mortality found in men. In addition, we excluded subjects with previous history of stroke or IHD and those with insufficient follow-up duration, which might have resulted in selection bias. Lastly, there was no consideration of multicollinearity between TG levels and covariates. Collinearity between BMI and TG levels might have influenced the sex difference in the association between TG levels and mortality. Nevertheless, the current study was based on nationwide claims data covering 97.0% of the population in Korea, and the median follow-up duration reached 8.3 years. In addition to claims data, the current study incorporated baseline clinical characteristics, including biochemical data from health checkups, which could enable adjustments for CVD risk factors other than TG levels. Furthermore, the wash-out period was long (7 years), which might have reduced the risk of confounding from a previous history of CVD.

In conclusion, in the Korean population aged 30–49 years, high TG levels independently increased future CVD risk both in men and women. The sex difference in the relationship between TG levels and overall mortality found in the current study should be further investigated in diverse populations.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics according to development of the primary outcome

Click here to view

Supplementary Table 2

Number at risk and event rate during the follow-up period

Click here to view

Supplementary Table 3

Incidence of CVD or mortality according to a triglyceride level cut-off of ≥150 mg/dL

Click here to view

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