Atherosclerosis 265 (2017) 102–109

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Gamma-glutamyltransferase and cardiovascular mortality in Korean adults: A cohort study

Sang-Wook Yi [a, b, *], Sang-Hun Lee [c], Hee-Jin Hwang [b, d], Jee-Jeon Yi [e]

[a] Department of Preventive Medicine and Public Health, Catholic Kwandong University, College of Medicine, Gangneung, 25601, Republic of Korea
[b] Institute for Clinical and Translational Research, Catholic Kwandong University International St. Mary's Hospital, Incheon, 22711, Republic of Korea
[c] Department of Internal Medicine, Catholic Kwandong University International St. Mary's Hospital, Incheon, 22711, Republic of Korea
[d] Department of Family Medicine, Catholic Kwandong University International St. Mary's Hospital, Incheon, 22711, Republic of Korea
[e] Institute for Occupational and Environmental Health, Catholic Kwandong University, Gangneung, 25601, Republic of Korea

ARTICLE INFO

Article history:
Received 7 July 2017
Received in revised form
16 August 2017
Accepted 23 August 2017
Available online 26 August 2017

Keywords:
Asians
Cardiovascular diseases
Cohort studies
Gamma-glutamyltransferase
Ischemic heart disease
Mortality
Stroke

ABSTRACT

Background and aims: Insufficient evidence has been reported on the associations between gamma-glutamyltransferase (GGT) and cardiovascular disease (CVD) mortality from studies with an adequate number of participants.

Methods: 512,990 Korean adults who participated in routine health examinations during the period 2002–2003 were followed up until 2013. Hazard ratios (HRs) were calculated after adjusting for potential confounders.

Results: Each 1-unit higher natural-log-transformed GGT (Log_eGGT) level was associated with approximately 30–50% higher mortality risk of CVD (HR = 1.31): hypertensive diseases (HR = 1.31), ischemic heart diseases (IHD, HR = 1.29), total stroke (HR = 1.29), acute myocardial infarction (HR = 1.30), chronic IHD (HR = 1.27), heart failure (HR = 1.48), hemorrhagic stroke (HR = 1.42), and ischemic stroke (HR = 1.27). The associations with CVD mortality did not vary by sex, or alcohol use, whereas they were stronger in younger (<60 years), non-hypertensive (systolic blood pressure [SBP] <140 mmHg), physically more active, normal-weight (body mass index<25 kg/m^2), and normocholesterolemic (total cholesterol <200 mg/dL) adults than in their respective counterparts. Adding Log_eGGT to prediction models for CVD mortality increased AUC value (0.0020, $p < 0.001$), especially in persons aged <60 years (0.0055), with SBP <140 mmHg (0.0030), and with both age <60 years and SBP <140 mmHg (0.0086).

Conclusions: Higher GGT significantly increased the risk of mortality due to CVD and its subtypes. The relative risks were greater in subjects with younger age, no hypertension, more physical activity, normal weight, and normocholesterolemia than in their respective counterparts. In the general population, adding GGT to conventional CVD risk factors may improve the prediction of CVD mortality, especially in subjects younger than 60 years and in those without hypertension.

1. Introduction

Cardiovascular disease (CVD), including ischemic heart disease (IHD) and stroke, is currently the major cause of premature mortality and disability worldwide [1,2]. Several studies have shown that elevated gamma-glutamyltransferase (GGT) activity is associated with higher risk of CVD [3–5], although blood GGT levels have been mainly used as a liver function test and a marker of alcohol ingestion. Blood GGT is suggested to have the potential to be an indicator, or a risk factor, for cardiovascular risk prediction and evaluation [6–8].

The available evidence, however, is not consistent regarding the association of elevated GGT activity with the risk of the leading cause of premature mortality: IHD, particularly acute myocardial infarction (MI) [5,7,9]. Information from prospective studies on the associations between GGT and subcategories of CVD, such as heart failure and hemorrhagic stroke, is lacking [10,11]. It is unclear whether the associations between GGT and CVD differ by risk factors such as age [5,12], sex [13], alcohol intake [4,12], and metabolic

* Corresponding author. Department of Preventive Medicine and Public Health, College of Medicine, Catholic Kwandong University, Bumil-ro 579, Gangneung, Gangwon-do, 25601, Republic of Korea.
E-mail address: flyhigh@cku.ac.kr (S.-W. Yi).

http://dx.doi.org/10.1016/j.atherosclerosis.2017.08.028
0021-9150/

risk factors. Furthermore, despite some evidence linking GGT and CVD, it remains unclear whether GGT provides additional information on top of known conventional risk factors for the prediction of CVD, considering the existence of strong correlations between GGT and conventional risk factors [12,14].

Through a prospective cohort study that included approximately 513,000 participants, we aimed to examine whether blood GGT levels were associated with the risk of CVD mortality, and whether any such associations varied by individually specific factors such as sex, age, alcohol use, and blood pressure. Additionally, whether blood GGT provides an incremental benefit on top of known risk factors for the prediction of CVD mortality was examined.

2. Materials and methods

2.1. Study population and follow-up

The National Health Insurance Service (NHIS) provides compulsory health insurance that covers 97% of the Korean population [15]. The study cohort (n = 514,795) comprised a 10% random sample of 5.15 million NHIS beneficiaries aged 40–79 years in 2002 who participated in health examinations during the period 2002–2003. A total of 1805 people were excluded due to missing information (n = 1753) on GGT, serum glucose, systolic blood pressure, total cholesterol, and body mass index (BMI) or because they had an extremely high BMI (≥50 kg/m^2, n = 52). For the remaining 512,990 people, follow-up on underlying causes of death until December 31, 2013 was carried out using national death records. The International Classification of Diseases-10th Revision (ICD-10) was used to define death from CVD (I00-I99), and instances of CVD mortality were classified into hypertensive diseases (I10-I13), IHD (I20-I25), acute MI (I21), chronic IHD (I25), other heart diseases (I26-I51), heart failure (I50), total stroke (I60-I69), hemorrhagic stroke (I60-I62), and ischemic stroke (I63). For research in accordance with the conditions documented in Korean laws, health examination data can be provided without specific informed consent from the participants [16]. This study was approved by the Institutional Review Board of Catholic Kwandong University, Republic of Korea. Anonymized data were provided to the authors by the NHIS.

2.2. Data collection

GGT was measured using the method recommended by the International Federation of Clinical Chemistry (IFCC), or using the Szasz method. Fasting serum glucose and total cholesterol were assayed using enzymatic methods [17]. Blood pressure was measured in a seated position using a standard mercury sphygmomanometer. Weight and height were measured to the nearest kilogram and centimeter, respectively [15]. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters (kg/m^2). Smoking history, alcohol use, and known CVD were self-reported via a questionnaire. The health examinations and data collection followed a standard protocol officially documented by the Ministry of Health and Welfare. External quality assessments for clinical chemistry, such as GGT measurements, in hospitals was supervised by the Korean Association of Quality Assurance for Clinical Laboratory, and the quality of assays was regularly assessed [18].

2.3. Statistical analysis

GGT values were categorized into six groups using the 20th (reference), 40th, 60th, 80th, and 90th percentiles as sex-specific cut-points (quintiles, with the top quintile split). The cut-points corresponded to 20, 28, 40, 64, and 98 U/L in men, and 11, 15, 19, 26, and 35 U/L in women. The participants were also categorized into four groups based on quartiles for comparison with other research [19,20]. Natural-log transformed GGT (Log_eGGT) values were also analyzed as a continuous variable.

HRs for CVD mortality were calculated using Cox proportional hazards models stratified by age (years) at baseline (40–44, 45–54, 55–64, 65–74, 75–80) after adjustment for age at baseline (continuous variable within each age group), sex (when applicable), a history of heart disease or stroke (yes or no), smoking status (current smoker, former smoker, never-smoker, or missing information [n = 21,660]), alcohol use (frequency; rarely, 2 days/month to 2 days/week, 3–7 days/week, and missing information [n = 9657]), physical activity (at least once a week; yes or no), beneficiary income status (deciles; below 4 [low income], 4–7, 8–10 [high income]), systolic blood pressure (SBP; mmHg), serum total cholesterol (mg/dL), fasting serum glucose (mg/dL), and BMI (kg/m^2). Dose-response analysis using a restricted cubic spline transformation of Log_eGGT with 4 knots (5th, 35th, 65th, and 95th percentiles) with CVD mortality was done to evaluate the non-linearity of association.

The area under the curve (AUC) values were estimated using Proc Logistic (ROC statement). A prediction model with an AUC value of 1.0 or 0.5 represents a perfect or an uninformative model, respectively. When investigating changes in the AUC upon addition of GGT, a CVD mortality prediction model that included all variables in the fully adjusted analysis was used.

Subgroup analyses were done to examine evidence of differences in HRs according to individually specific characteristics, such as age, sex, and alcohol consumption. An inverse-variance weighted average method was used for the interaction test between subgroups [21]. Subgroup analyses were also used as a sensitivity test.

All *p*-values were 2-sided. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. General characteristics

During 5.3 million person-years of follow-up of 512,990 people (45.8% women), 4647 men and 3114 women died from CVD. At baseline, the mean (standard deviation) age was 53.1 (9.7) years and the mean Log_eGGT level was 3.26 (0.76) U/L (Table 1), with values of 3.59 (0.75) U/L for men and 2.87 (0.56) U/L for women. Subjects with higher GGT values tended to be more likely to be current smokers and to exhibit more frequent alcohol use, and less likely to be elderly (70 or above), than those with lower GGT levels. Higher GGT levels were generally associated with higher SBP, fasting glucose, total cholesterol, and BMI values (Table 1).

3.2. GGT and CVD mortality

Clear dose-response relationships between GGT and CVD mortality were observed in all participants (Fig. 1) and in both sexes (Supplementary Fig. 1 and 2). Compared with the lowest baseline GGT group, the sex-age adjusted HRs for CVD mortality were 1.06, 1.20, 1.32, 1.58, and 1.86 across the other five GGT categories (Fig. 1). After adjustment for age and sex, each 1-unit increase in Log_eGGT was associated with an approximately 35% higher risk of CVD mortality (HR per 1-unit increase in Log_eGGT = 1.35 [95% CI = 1.31–1.39]); and elevations of 33%–42% for deaths from hypertensive diseases, IHD, other heart diseases, and stroke (HRs of 1.42 [1.26–1.59], 1.33 [1.26–1.41], 1.35 [1.25–1.47], and 1.34

Table 1
Characteristics of participants according to GGT categories.

Characteristics	Total		Sex-specific GGT percentile											
			<20%		20% to <40%		40% to <60%		60% to <80%		80% to <90%		≥90%	
	N = 512,990		n = 89,774		n = 112,011		n = 104,014		n = 100,740		n = 53,164		n = 53,287	
GGT, U/L	37.9	±54.7	12.6	±4.0	17.8	±5.7	25.4	±8.7	36.9	±15.0	55.4	±25.1	131.5	±127.2
Log_eGGT, U/L	3.26	±0.76	2.47	±0.36	2.83	±0.33	3.17	±0.36	3.52	±0.43	3.90	±0.49	4.58	±0.73
Age, years	53.1	±9.7	53.3	±10.3	52.9	±9.9	53.0	±9.6	53.0	±9.4	53.0	±9.4	53.4	±9.2
SBP, mmHg	127.2	±18.3	123.4	±17.4	124.9	±17.8	126.9	±17.9	128.9	±18.1	130.6	±18.5	132.4	±19.2
FSG, mg/dL	98.4	±34.8	94.0	±28.5	95.1	±31.8	97.3	±33.1	100.1	±35.4	102.9	±39	107.6	±44.5
Total cholesterol, mg/dL	200.4	±38.8	188.3	±34.3	196.1	±36	201.1	±37	205.8	±38.9	209.1	±40.9	209.8	±45.3
BMI, kg/m^2	24.0	±3	22.9	±2.7	23.5	±2.8	24.0	±2.8	24.6	±2.9	24.9	±3	24.8	±3.2
Sex														
Women	234,743	(45.8)	34,661	(38.6)	57,241	(51.1)	47,436	(45.6)	45,728	(45.4)	24,355	(45.8)	25,322	(47.5)
Men	278,247	(54.2)	55,113	(61.4)	54,770	(48.9)	56,578	(54.4)	55,012	(54.6)	28,809	(54.2)	27,965	(52.5)
Age group														
< 60 years	370,540	(72.2)	63,171	(70.4)	80,915	(72.2)	75,657	(72.7)	73,478	(72.9)	38,953	(73.3)	38,366	(72.0)
60–69 years	104,822	(20.4)	18,316	(20.4)	22,392	(20.0)	21,019	(20.2)	20,679	(20.5)	10,858	(20.4)	11,558	(21.7)
≥ 70 years	37,628	(7.3)	8287	(9.2)	8704	(7.8)	7338	(7.1)	6583	(6.5)	3353	(6.3)	3363	(6.3)
Self-reported comorbidity														
Heart diseases, stroke	9692	(1.9)	1448	(1.6)	1814	(1.6)	1964	(1.9)	2103	(2.1)	1158	(2.2)	1205	(2.3)
Smoking status														
Never smoker	329,465	(64.2)	59,542	(66.3)	77,418	(69.1)	67,134	(64.5)	62,423	(62.0)	31,832	(59.9)	31,116	(58.4)
Past smoker	43,577	(8.5)	8336	(9.3)	8783	(7.8)	9090	(8.7)	8876	(8.8)	4549	(8.6)	3943	(7.4)
Current smoker	118,288	(23.1)	18,011	(20.1)	21,145	(18.9)	23,300	(22.4)	25,102	(24.9)	14,631	(27.5)	16,099	(30.2)
Missing	21,660	(4.2)	3885	(4.3)	4665	(4.2)	4490	(4.3)	4339	(4.3)	2152	(4.0)	2129	(4.0)
Alcohol use, frequency (days)														
Rarely	285,046	(55.6)	57,722	(64.3)	70,415	(62.9)	58,372	(56.1)	50,950	(50.6)	24,521	(46.1)	23,066	(43.3)
2/month-2/week	160,334	(31.3)	25,419	(28.3)	32,235	(28.8)	33,936	(32.6)	34,600	(34.3)	18,233	(34.3)	15,911	(29.9)
3–7/week	57,953	(11.3)	4683	(5.2)	7085	(6.3)	9733	(9.4)	13,441	(13.3)	9572	(18.0)	13,439	(25.2)
Missing	9657	(1.9)	1950	(2.2)	2276	(2.0)	1973	(1.9)	1749	(1.7)	838	(1.6)	871	(1.6)
Physical activity														
≥1 time/week	210,789	(41.1)	37,432	(41.7)	45,886	(41.0)	43,538	(41.9)	42,012	(41.7)	21,643	(40.7)	20,278	(38.1)
Income status														
<4 decile (low income)	118,061	(23.0)	19,576	(21.8)	26,062	(23.3)	23,778	(22.9)	22,989	(22.8)	12,448	(23.4)	13,208	(24.8)
4-7 decile	167,098	(32.6)	29,342	(32.7)	35,628	(31.8)	33,277	(32.0)	32,504	(32.3)	17,463	(32.8)	18,884	(35.4)
>7 decile (high income)	227,831	(44.4)	40,856	(45.5)	50,321	(44.9)	46,959	(45.1)	45,247	(44.9)	23,253	(43.7)	21,195	(39.8)

Data are expressed as mean ± standard deviation or n (%). GGT categories: 1–19 (<20%), 20–27 (20% to <40%), 28–39 (40% to <60%), 40–63 (60% to <80%), 64–97 (80% to <90%), and ≥98 (≥90%) U/L in men, 1–10 (<20%), 11–14 (20% to <40%), 15–18 (40% to <60%), 19–25 (60% to <80%), 26–34 (80% to <90%), and ≥35 (≥90%) U/L in women. *p*-values, which were calculated by the Chi-squared test and 1-way analysis of variance across the GGT groups, were <0.001 for each variable including age at baseline. To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259. To convert glucose from mg/dL to mmol/L, multiply by 0.0555.
BMI, body mass index; FSG, fasting serum glucose; GGT, gamma-glutamyltransferase; SBP, systolic blood pressure.

[1.28–1.40], respectively). After further adjustment for person-specific factors including smoking status, frequency of alcohol use, and SBP, the HRs modestly changed (Table 2). The restricted cubic spline analysis showed that the association of Log_eGGT with CVD mortality was generally linear in both sexes ($p_{non\text{-}linearity}$ = 0.1999 in men, 0.4890 in women) and the pattern of association was similar between men and women (Supplementary Fig. 3).

Mortality was 33%–50% higher for every 1-unit higher Log_eGGT score for the various subtypes of heart diseases and stroke, including acute MI, chronic IHD, heart failure, hemorrhagic stroke, and ischemic stroke (HRs of 1.34 [95% CI = 1.25–1.43], 1.33 [95% CI, 1.15–1.54], 1.45 [95% CI, 1.24–1.70], 1.50 [95% CI, 1.39–1.69], and 1.33 [95% CI, 1.23–1.44], respectively), after adjusting for age and sex. When fully adjusted for potential confounders, mortality was on average 27%–48% higher for each 1-unit increment in Log_eGGT for the subtypes of heart disease and stroke (Supplementary Table 1). The magnitude of the HRs per 1-unit increase in Log_eGGT were similar between acute MI and chronic IHD, while it was greater for hemorrhagic stroke than for ischemic stroke (sex-age adjusted HR, 1.50 *vs.* 1.33, $p_{heterogeneity}$ = 0.029; fully adjusted HR, 1.42 *vs.* 1.27, $p_{heterogeneity}$ = 0.052), especially in men (fully adjusted HR, 1.58 *vs.* 1.22, $p_{heterogeneity}$<0.001).

When HRs were analyzed in various subgroups (Fig. 2), the HRs for CVD mortality generally did not vary between men and women, persons with or without self-reported heart diseases or stroke, never versus ever smokers, rare alcohol users versus regular alcohol users, high versus low income earners, and normoglycemic versus hyperglycemic persons. The association, however, was different between subgroups according to age ($p_{interaction}$ = 0.001), SBP ($p_{interaction}$ = 0.001), physical activity ($p_{interaction}$ = 0.052), BMI ($p_{interaction}$ = 0.026), and blood cholesterol levels ($p_{interaction}$ = 0.020). For IHD mortality, the estimated relative risk was greater in persons with lower blood pressure (Supplemental Fig. 4, $p_{interaction}$ = 0.001), while for total stroke mortality, it was greater in younger adults ($p_{interaction}$<0.001), men ($p_{interaction}$ = 0.006), and physically active persons ($p_{interaction}$ = 0.009) than their counterparts (Supplemental Fig. 5).

Additional analysis was performed after excluding persons with a history of liver disease, and further adjustment for alanine transaminase and aspartate transaminase in order to minimize the potential impact of liver disorders and to examine the associations of GGT independent of liver function. After such a restriction and further adjustment, the associations of GGT were not weakened (Supplemental Table 3).

3.3. GGT and prediction of CVD mortality

In persons without known heart disease or stroke, without GGT in the model, the fully adjusted prediction model showed a fairly good predictive ability for discriminating CVD mortality (AUC = 0.8442). When Log_eGGT was added into the model, the AUC

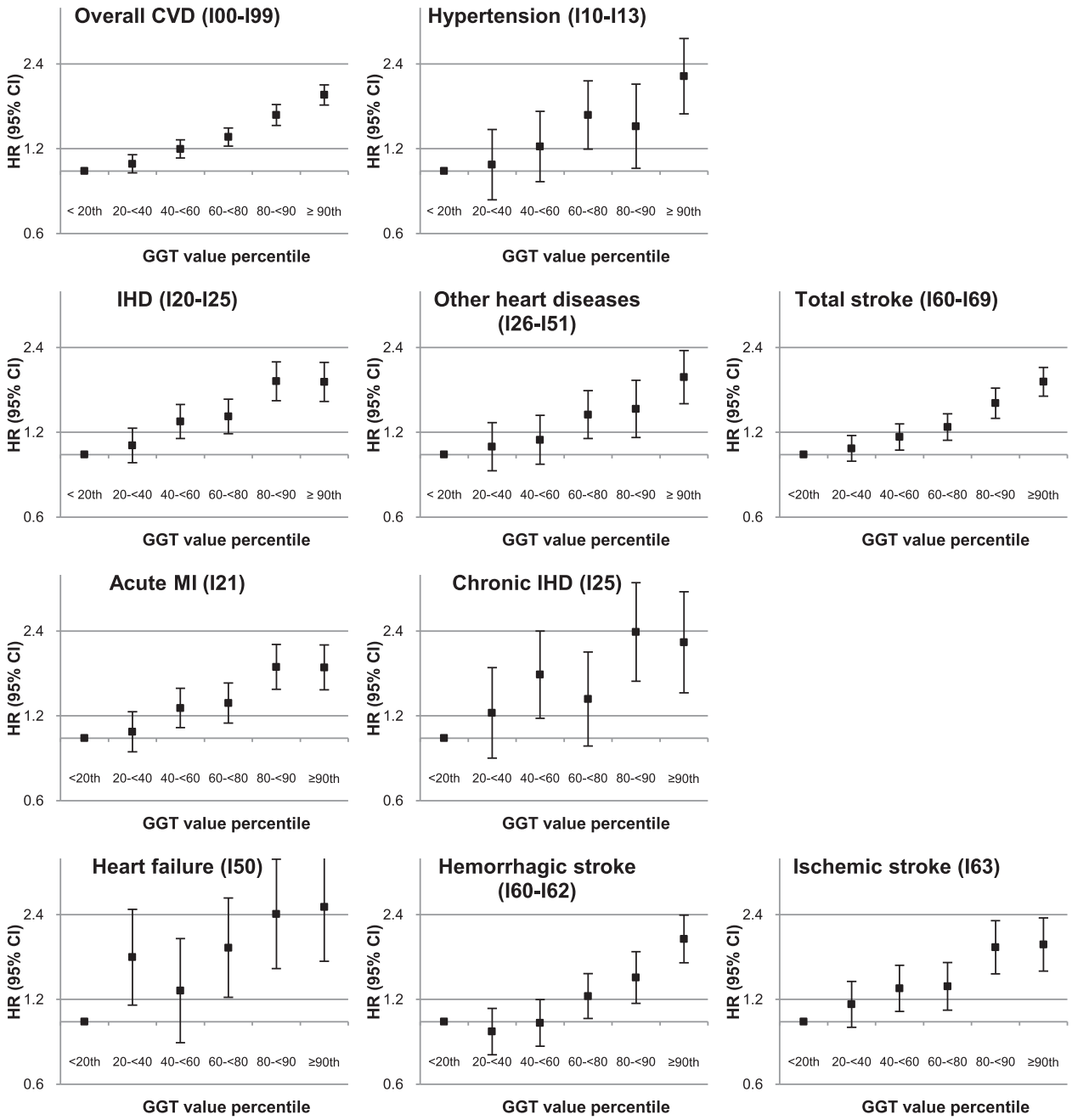

Fig. 1. Age and sex adjusted HRs* across 6 categories of baseline GGT for mortality from CVD and its subtypes.
GGT categories (1–19, 20–27, 28–39, 40–63, 64–97, and ≥98 U/L in men, 1–10, 11–14, 15–18, 19–25, 26–34, and ≥35 U/L in women). *HRs and 95% CIs were calculated using Cox proportional hazards models. CI, confidence interval; CVD, cardiovascular disease; GGT, gamma-glutamyltransferase; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction.

increased significantly (change in AUC, 0.0020, $p < 0.001$, Table 3). The increase in AUC upon the addition of GGT was greater in persons <60 years of age than in persons ≥60 years of age (0.0055 *vs.* 0.0021, $p_{heterogeneity} = 0.024$), in persons with no hypertension (SBP <140 mmHg) than in those with hypertension (0.0030 *vs.* 0.0013, $p_{heterogeneity} = 0.007$), and in persons <60 years of age with an SBP <140 mmHg than in those aged ≥60 years with an SBP <140 mmHg (0.0086 *vs.* 0.0030, $p_{heterogeneity} = 0.031$). When a model that only included Framingham risk score variables such as age, sex, smoking status, SBP, total cholesterol, and comorbid diabetes, but not high-density lipoprotein cholesterol due to the unavailability of that information, was fitted [22], among persons with an SBP <140 mmHg, the increase in the AUC upon the addition of GGT was also greater in persons aged <60 years than in persons aged ≥60 years (0.0088 *vs.* 0.0022, $p_{heterogeneity} = 0.008$).

4. Discussion

In our cohort study of 512,990 Korean adults, we found that higher blood GGT levels were associated with higher mortality from CVD and its subtypes. The presence of clear dose-response associations strengthens the evidence that GGT is a risk factor for

Table 2
Hazard ratios (HRs) for CVD mortality across GGT categories.

Causes of death	GGT category	No. of deaths	Model 1			Model 2		
			p	HR	(95% CI)	*p*	HR	(95% CI)
Total CVD (I00-I99)	<20%	1365		1.00	(Reference)		1.00	(Reference)
	20% to <40%	1493	0.069	1.07	(0.99–1.15)	0.128	1.06	(0.98–1.14)
	40% to <60%	1489	<0.001	1.21	(1.12–1.30)	<0.001	1.18	(1.10–1.27)
	60% to <80%	1499	<0.001	1.34	(1.24–1.45)	<0.001	1.30	(1.20–1.40)
	80% to <90%	884	<0.001	1.59	(1.46–1.74)	<0.001	1.51	(1.38–1.65)
	≥90%	1031	<0.001	1.87	(1.72–2.04)	<0.001	1.72	(1.57–1.87)
	1 unit higher Log_eGGT	7761	<0.001	1.36	(1.32–1.40)	<0.001	1.31	(1.26–1.35)
Hypertensive diseases (I10-I13)	<20%	89		1.00	(Reference)		1.00	(Reference)
	20% to <40%	101	0.784	1.04	(0.78–1.39)	0.892	1.02	(0.76–1.36)
	40% to <60%	101	0.242	1.19	(0.89–1.59)	0.371	1.14	(0.85–1.53)
	60% to <80%	120	0.003	1.53	(1.15–2.03)	0.012	1.44	(1.08–1.92)
	80% to <90%	54	0.077	1.37	(0.97–1.94)	0.207	1.26	(0.88–1.79)
	≥90%	80	<0.001	2.04	(1.49–2.81)	<0.001	1.81	(1.31–2.50)
	1 unit higher Log_eGGT	545	<0.001	1.39	(1.23–1.57)	<0.001	1.31	(1.15–1.48)
IHD (I20-I25)	<20%	374		1.00	(Reference)		1.00	(Reference)
	20% to <40%	400	0.206	1.10	(0.95–1.26)	0.420	1.06	(0.92–1.22)
	40% to <60%	435	<0.001	1.34	(1.16–1.54)	0.001	1.27	(1.10–1.46)
	60% to <80%	411	<0.001	1.42	(1.23–1.64)	<0.001	1.31	(1.14–1.52)
	80% to <90%	268	<0.001	1.89	(1.61–2.23)	<0.001	1.70	(1.44–2.00)
	≥90%	265	<0.001	1.89	(1.61–2.24)	<0.001	1.66	(1.40–1.97)
	1 unit higher Log_eGGT	2153	<0.001	1.37	(1.29–1.45)	<0.001	1.29	(1.21–1.37)
Other heart disease (I26-I51)	<20%	190		1.00	(Reference)		1.00	(Reference)
	20% to <40%	214	0.405	1.09	(0.89–1.32)	0.390	1.09	(0.89–1.33)
	40% to <60%	200	0.158	1.16	(0.95–1.41)	0.148	1.16	(0.95–1.42)
	60% to <80%	226	<0.001	1.44	(1.18–1.76)	<0.001	1.45	(1.19–1.78)
	80% to <90%	117	0.001	1.52	(1.20–1.92)	0.001	1.52	(1.19–1.93)
	≥90%	149	<0.001	2.00	(1.59–2.50)	<0.001	1.97	(1.56–2.48)
	1 unit higher Log_eGGT	1096	<0.001	1.40	(1.29–1.53)	<0.001	1.39	(1.27–1.51)
Total stroke (I60-I69)	<20%	668		1.00	(Reference)		1.00	(Reference)
	20% to <40%	734	0.313	1.06	(0.95–1.17)	0.317	1.06	(0.95–1.17)
	40% to <60%	710	0.009	1.15	(1.04–1.28)	0.013	1.15	(1.03–1.28)
	60% to <80%	705	<0.001	1.25	(1.12–1.40)	<0.001	1.24	(1.11–1.38)
	80% to <90%	424	<0.001	1.50	(1.33–1.71)	<0.001	1.46	(1.28–1.66)
	≥90%	500	<0.001	1.77	(1.56–1.99)	<0.001	1.64	(1.45–1.86)
	1 unit higher Log_eGGT	3741	<0.001	1.33	(1.27–1.40)	<0.001	1.29	(1.23–1.35)

GGT categories: 1–19 (<20%), 20–27 (20% to <40%), 28–39 (40% to <60%), 40–63 (60% to <80%), 64–97 (80% to <90%), and ≥98 (≥90%) U/L in men, 1–10 (<20%), 11–14 (20% to <40%), 15–18 (40% to <60%), 19–25 (60% to <80%), 26–34 (80% to <90%), and ≥35 (≥90%) U/L in women.
CI, confidence interval; CVD, cardiovascular diseases; GGT, gamma-glutamyltransferase; IHD, ischemic heart disease.
Model 1: adjustment was done for age at baseline, sex, smoking status, alcohol use, physical activity, income status, and self-reported heart diseases or stroke.
Model 2: adjustment was done for model 1 plus systolic blood pressure, fasting glucose, total cholesterol, and body mass index.

CVD. Each 1-unit increase in the Log_eGGT value was on average associated with an approximately 30% higher risk of death from CVD (HR = 1.31), and a 30%–50% greater risk of death from the subgroups of CVD such as hypertensive diseases (HR = 1.31), IHD (HR = 1.29), other heart diseases (HR = 1.39), total stroke (HR = 1.29), acute MI (HR = 1.30), chronic IHD (HR = 1.27), heart failure (HR = 1.48), hemorrhagic stroke (HR = 1.42), and ischemic stroke (HR = 1.27), after full adjustment. In the subgroup analysis, the HRs for CVD mortality generally did not vary by sex, self-reported comorbidity of heart diseases or stroke, smoking status, frequency of alcohol use, income status, or blood glucose level. The association, however, was stronger in younger adults (below 60 years), non-hypertensive persons, physically more active persons, persons with normal weight (BMI <25 kg/m^2), and individuals with total cholesterol <200 mg/dL than in their respective counterparts. Upon the addition of Log_eGGT in the CVD mortality prediction model, which included age, sex, SBP, fasting glucose, total cholesterol, BMI, smoking status, alcohol use, income status, and physical activity, the AUC value showed a modest increase (0.0020, $p < 0.001$). The change in AUC values by including GGT was more profound in persons aged <60 years (0.0055), with an SBP <140 mmHg (0.0030), and with both age <60 years and SBP <140 mmHg (0.0086).

Through previous systematic reviews and our own literature search, six prospective cohort studies that reported associations between GGT and CVD in Asian populations were identified [9,13,20,23–25]. The results in Asian populations have been a source of heterogeneity in several meta-analyses [11,26], and the possibility that the association is weaker in Asians than in European-origin populations has been suggested [7,11]. The current study, however, suggests that the overall association is not substantially different between Asian and European-origin populations, since the magnitude of the associations of GGT with CVD found in this study (HR per 1-SD increase in Log_eGGT = 1.22 [95% CI = 1.19–1.25]), stroke (1.21 [1.17–1.25]), and heart failure (1.34 [1.19–1.52]) was similar to that of previous meta-analyses (1.23 [95% CI = 1.16–1.29] [3], 1.28, [95% CI = 1.16–1.43] [11], and 1.25 [95% CI = 1.07–1.46] [10], respectively).

IHD, especially its acute form, has been associated with controversial results; in several large studies, higher GGT activity was not associated with a greater risk of IHD, at least in a subgroup analysis according to sex [5,9,20,26]. In the current study, mortality from IHD, including acute MI, was positively associated with GGT levels in both sexes, and the magnitude of the HRs was found to be similar to those for other forms of CVD.

For subtypes of stroke, our study confirmed that the association of GGT was stronger for hemorrhagic stroke than for ischemic stroke. The majority of prospective studies [5,9,26,27], except for a few studies with a small number of stroke cases [13,28], showed similar evidence, but without formal statistical tests. A stronger

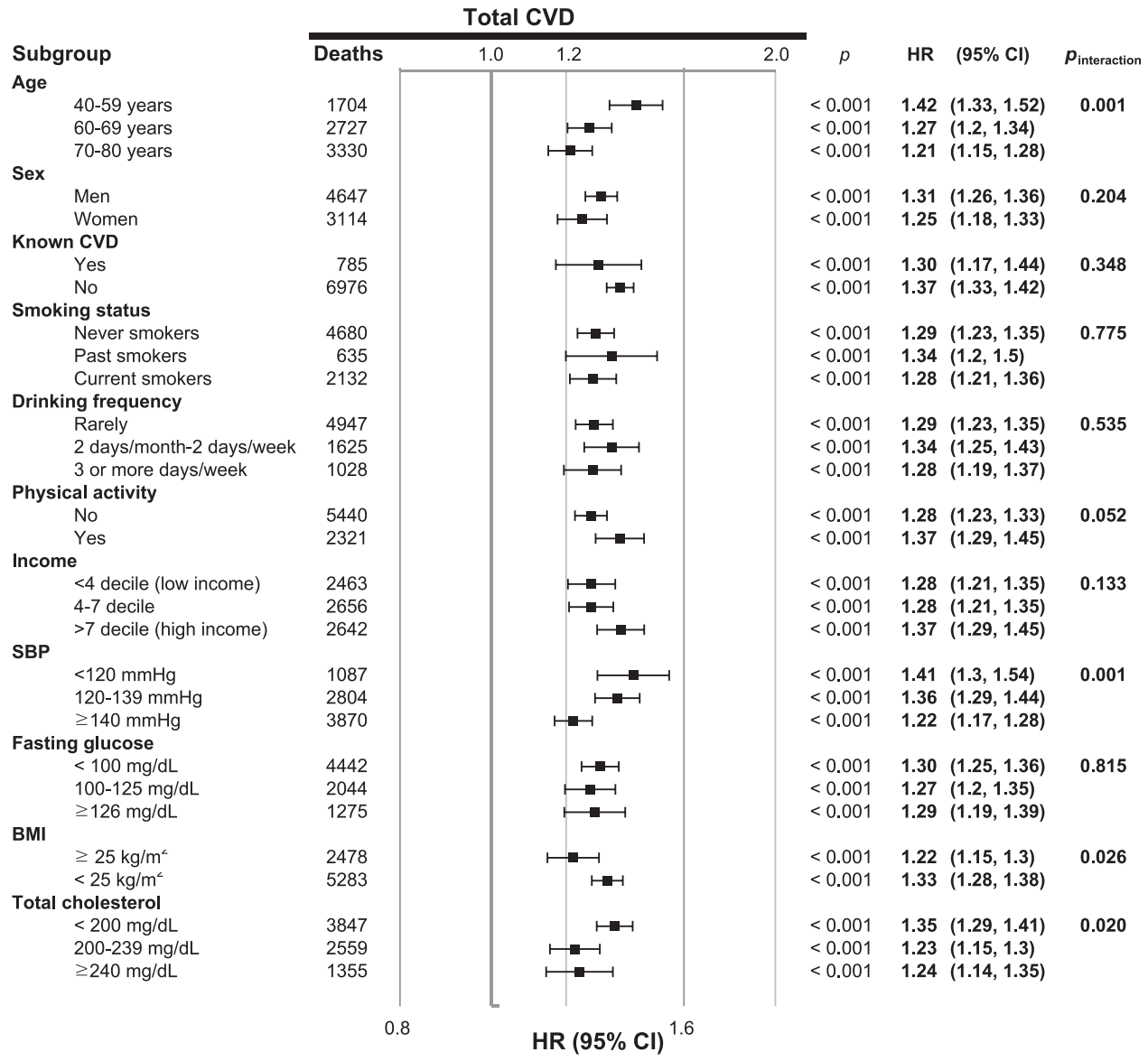

Fig. 2. HRs* per 1 unit increment in Log_eGGT for total CVD mortality by individual-specific characteristics.
*HRs and 95% CIs were calculated using Cox proportional hazards models stratified by baseline age (years: 40–44, 45–54, 55–64, 65–74, 75–80), after adjustment for age at baseline (continuous variable), sex, smoking status, alcohol use, physical activity, income status, a history of heart diseases or stroke, SBP, fasting glucose, total cholesterol and BMI. BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; Log_eGGT, natural-log transformed gamma-glutamyltransferase; SBP, systolic blood pressure.

Table 3
AUC changes upon addition of Log_eGGT to the CVD mortality prediction model in participants without self-reported heart disease or stroke at baseline.

Subgroup	No. of participants	No. of deaths	Without Log_eGGT		With Log_eGGT		Difference in AUC	p_{diff}	$p_{heterogeneity}$
			AUC	(95% CI)	AUC	(95% CI)			
Total	503,298	6976	0.8442	(0.8397–0.8486)	0.8461	(0.8417–0.8506)	0.0020	<0.001	
Age <60 y	366,850	1602	0.7627	(0.7512–0.7742)	0.7682	(0.7568–0.7795)	0.0055	<0.001	0.024
Age ≥60 y	136,448	5374	0.7332	(0.7266–0.7397)	0.7353	(0.7288–0.7418)	0.0021	<0.001	
SBP ≥ 140 mmHg	134,056	3525	0.7914	(0.7840–0.7988)	0.7927	(0.7854–0.8001)	0.0013	<0.001	0.007
SBP < 140 mmHg	369,242	3451	0.8490	(0.8424–0.8556)	0.8519	(0.8455–0.8584)	0.0030	<0.001	
Age <60 y, SBP <140 mmHg	287,456	877	0.7493	(0.7335–0.7651)	0.7579	(0.7422–0.7735)	0.0086	<0.001	0.031
Age ≥60 y, SBP <140 mmHg	81,786	2574	0.7374	(0.728–0.7467)	0.7403	(0.731–0.7496)	0.0030	0.002	

A prediction model with an AUC value of 1.0 or 0.5 represents a perfect or an uninformative model, respectively.
AUC, area under the receiver operating characteristics curve; CI, confidence interval; FRS, LogeGGT, natural log-transformed GGT; SBP, systolic blood pressure.
p_{diff}: p-value for the difference in the AUC value between models with or without Log_eGGT.
$p_{heterogeneity}$: p-value for heterogeneity of the difference in AUC value between models with or without Log_eGGT between age and SBP subgroups.
The prediction model includes age at baseline, sex, smoking status, alcohol use, physical activity, income status, SBP, fasting glucose, total cholesterol, and body mass index.

association for hemorrhagic than ischemic stroke, however, was found only in men in the current study. An additional analysis with 8 GGT groups (<15 [reference], 15–19, 20–24, 25–29, 30–39, 40–59, 60–79, and ≥80 U/L) revealed that only the highest GGT groups (60–79 and ≥ 80 U/L in both sexes combined and in men, ≥80 U/L in women) were associated with higher mortality from hemorrhagic stroke with a P-value <0.05, whereas GGT levels ≥25 U/L were generally associated with higher mortality from ischemic stroke in both sexes, compared with persons with a GGT level <15 U/L. These results suggest that the underlying mechanisms of the impact of GGT may be different between ischemic and hemorrhagic stroke to some degree.

GGT has long been used as a marker of alcohol intake, and several studies have found evidence suggesting that the associations of GGT with CVD may be modified by alcohol consumption [12,20,29]. It has not been completely resolved whether GGT is associated with CVD independently of alcohol intake. Our study found that GGT was associated with higher CVD mortality in rare drinkers and that the associations were not modified by alcohol intake frequency. Thus, our study strengthens the evidence that higher GGT activity increases the risk of CVD mortality independently of alcohol intake.

Evidence from several previous studies has suggested that the relative risk of GGT for CVD may be higher at younger ages [5,8,12]. The current study demonstrated that the HRs of GGT for CVD mortality were greater in younger persons (<60 years) and normotensive individuals (SBP <140 mmHg) than in older adults (60 years old or above) and persons with hypertension (SBP ≥140 mmHg). In our study, the association of GGT was also stronger in persons who engaged in physical activity at least once a week, had a normal weight (BMI <25 kg/m^2), and had normal total cholesterol levels (<200 mg/dL) than in persons who engaged in no physical activity, were overweight or obese (BMI ≥25 kg/m^2), and had higher cholesterol levels (≥200 mg/dL). Wannamethee et al. similarly reported that the risk associated with elevated GGT was higher in persons with a lower cardiovascular risk score, but without providing detailed information about the specific variables [8]. Kunutsor et al. likewise reported similar findings, stating that subgroups with lower age, BMI, blood lipids, and SBP seemed to show stronger associations, although the *p*-value for interaction was below 0.05 only between the age subgroups [12].

Although it has been suggested that GGT measurements may be useful for CVD risk assessment [6,8], a few recent studies reported that adding GGT to the conventional CVD risk factors did not improve the prediction of risk for CVD or IHD-related mortality [12,14]. The current study found that upon the addition of Log_eGGT to the prediction model, the AUC showed a statistically significant increase (change in AUC, 0.0020, $p < 0.001$). The increase of 0.0020 in AUC can be deemed modest; however, the addition of GGT seemed to have the potential to provide an important improvement in risk prediction. For instance, when comparing AUC values with versus without a risk factor in our full model in persons without self-reported heart disease or stroke, only age (change in AUC, 0.1298), SBP (0.0067), and smoking status (0.0033) had more impact than GGT on the prediction of total CVD mortality, while sex, fasting glucose, total cholesterol, BMI, alcohol use, physical activity, and income status had a lower predictive ability than GGT. Furthermore, when we fitted the prediction model in younger adults and in persons with an SBP <140 mmHg, in whom the association of GGT was greatest, the predictive ability (AUC) upon addition of GGT increased from 0.0020 to 0.0055 in persons <60 years, and to 0.0086 in persons aged <60 years with an SBP <140 mmHg. These findings suggest that GGT measurements have the potential to improve the prediction of CVD mortality, especially in persons younger than 60 years old and with an SBP <140 mmHg. Additionally, since GGT levels increased the AUC more than other cardiometabolic risk factors, except SBP, upon addition into the prediction model, GGT has the potential to replace other conventional risk factors for the prediction of CVD mortality, not to mention that GGT is stable in storage and that measuring GGT is simple, inexpensive, and does not require fasting for measurements to be made.

Several putative mechanisms have been suggested to explain the association of elevated GGT with increased CVD risk [7]. GGT may be a marker of antioxidant inadequacy, oxidative and nitrosative stress, and systemic inflammation [7,30], potentially independent of cardiometabolic risk factors [31]. The direct role of GGT in the formation of atheromatous plaque was also proposed [6].

4.1. Strengths and limitations of the study

A large number of participants, a prospective design, and complete follow-up for death are clear strengths of this study. However, it has several limitations. Non-IFCC methods for measuring GGT, which are associated with lower accuracy [32], were used in some hospitals. However, since lower accuracy was not related to CVD mortality, this may not contribute to an overestimation of the HRs of GGT for CVD mortality. Second, collection of alcohol use information via questionnaire may have some limitations. For example, rare drinkers in the current study were not necessarily lifelong abstainers. However, since the associations were similar across alcohol intake subgroups, this potential misclassification is unlikely to significantly affect the observed associations in rare drinkers. Furthermore, we performed a validation analysis of alcohol measure by examining associations of alcohol with the mortality risk of alcoholic liver disease, which showed that our alcohol measure was fairly reliable and valid. Third, several risk factors, such as C-reactive protein and subgroups of lipids (such as low-density and high-density lipoprotein cholesterol, as well as triglycerides) and several predictors including anti-hypertensive and lipid-lowering medications were not adjusted for in the current study. Although additional adjustment for such factors did not substantially change the associations in other studies [10,33], this remains a limitation. Fourth, relative risk estimation using a single baseline measurement of GGT may underestimate its true association, due to the regression dilution effect [34]. Fifth, several medications use, such as anti-epilepsy drugs [35], that may affect both GGT levels and CVD risk, were not adjusted for. Non-adjustment for such medications use might affect the results. Finally, the fact that the study population was homogeneously Korean may affect its generalizability. Some results, such as the magnitude of the relative risk estimation associated with GGT or the magnitude of the change in AUC upon addition of GGT to the risk prediction model, may need to be assessed in other ethnic and regional populations with varying distributions of environmental and individual risk factors, as well as of subtypes of CVD morbidity.

4.2. Conclusions

Our cohort study of 512,990 Korean adults suggests that higher blood GGT levels increase mortality from CVD and its subtypes. The associations were stronger in younger, non-hypertensive, physically more active, normal-weight, and normocholesterolemic persons than in their respective counterparts. In the general population, GGT measurements have the potential to improve and to replace other conventional risk factors in the prediction of CVD mortality risk, especially in persons aged <60 years old without hypertension.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

Health examinations were funded and managed by the NHIS of Korea. This work was supported by research funds from Catholic Kwandong University (201601750001). Catholic Kwandong University had no role in study design, data collection, the writing of the manuscript, or the decision to submit it for publication.

Author contributions

SWY conceived the study concept and design, and acquired data. SWY analyzed the data and wrote the first draft. SWY, SHL, HJH, and JJY interpreted data and contributed to critical revision of the manuscript. All authors have read and approved of the final submitted version of the manuscript. SWY is the study guarantor.

Acknowledgements

The authors thank the staff at the Big Data Steering Department at the NHIS for providing the data and support.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2017.08.028.

References

[1] GBD 2015 DALYs Hale Collaborators, Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet 388 (2016) 1603–1658.
[2] GBD 2015 Mortality Causes of Death Collaborators, Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet 388 (2016) 1459–1544.
[3] S.K. Kunutsor, T.A. Apekey, H. Khan, Liver enzymes and risk of cardiovascular disease in the general population: a meta-analysis of prospective cohort studies, Atherosclerosis 236 (2014) 7–17.
[4] D.H. Lee, K. Silventoinen, G. Hu, et al., Serum gamma-glutamyltransferase predicts non-fatal myocardial infarction and fatal coronary heart disease among 28,838 middle-aged men and women, Eur. Heart J. 27 (2006) 2170–2176.
[5] E. Ruttmann, L.J. Brant, H. Concin, et al., Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults, Circulation 112 (2005) 2130–2137.
[6] J.E. Mason, R.D. Starke, J.E. Van Kirk, Gamma-glutamyl transferase: a novel cardiovascular risk biomarker, Prev. Cardiol. 13 (2010) 36–41.
[7] G. Ndrepepa, A. Kastrati, Gamma-glutamyl transferase and cardiovascular disease, Ann. Transl. Med. 4 (2016) 481.
[8] S.G. Wannamethee, L. Lennon, A.G. Shaper, The value of gamma-glutamyltransferase in cardiovascular risk prediction in men without diagnosed cardiovascular disease or diabetes, Atherosclerosis 201 (2008) 168–175.
[9] S. Ebrahim, J. Sung, Y.M. Song, et al., Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study, BMJ 333 (2006) 22.
[10] S.K. Kunutsor, J.A. Laukkanen, D.A. Bluemke, et al., Baseline and long-term gamma-glutamyltransferase, heart failure and cardiac arrhythmias in middle-aged Finnish men: prospective study and pooled analysis of published evidence, Eur. J. Prev. Cardiol. 23 (2016) 1354–1362.
[11] X.W. Zhang, M. Li, W.S. Hou, et al., Association between gamma-glutamyltransferase level and risk of stroke: a systematic review and meta-analysis of prospective studies, J. Stroke Cerebrovasc. Dis. 24 (2015) 2816–2823.
[12] S.K. Kunutsor, S.J. Bakker, J.E. Kootstra-Ros, et al., Circulating gamma glutamyltransferase and prediction of cardiovascular disease, Atherosclerosis 238 (2015) 356–364.
[13] Y. Shimizu, H. Imano, T. Ohira, et al., gamma-Glutamyltranspeptidase and incident stroke among Japanese men and women: the Circulatory Risk in Communities Study (CIRCS), Stroke 41 (2010) 385–388.
[14] A.P. Kengne, S. Czernichow, E. Stamatakis, et al., Gamma-glutamyltransferase and risk of cardiovascular disease mortality in people with and without diabetes: pooling of three British Health Surveys, J. Hepatol. 57 (2012) 1083–1089.
[15] S.W. Yi, H. Ohrr, S.A. Shin, et al., Sex-age-specific association of body mass index with all-cause mortality among 12.8 million Korean adults: a prospective cohort study, Int. J. Epidemiol. 44 (2015) 1696–1705.
[16] S.C. Seong, Y.Y. Kim, Y.H. Khang, et al., Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea, Int. J. Epidemiol. (2016), http://dx.doi.org/10.1093/ije/dyw253.
[17] E.Y. Lee, Y.H. Lee, S.W. Yi, et al., BMI and all-cause mortality in normoglycemia, impaired fasting glucose, newly diagnosed diabetes, and prevalent diabetes: a cohort study, Diabetes Care 40 (2017) 1026–1033.
[18] W.K. Min, K.D. Kim, D.J. Kim, et al., Annual report on external quality assessment in clinical chemistry in Korea, J. Laboratory Med. Qual. Assur. 25 (2003) (2002) 1–14.
[19] G. Du, Z. Song, Q. Zhang, Gamma-glutamyltransferase is associated with cardiovascular and all-cause mortality: a meta-analysis of prospective cohort studies, Prev. Med. 57 (2013) 31–37.
[20] Y. Li, H. Iso, R. Cui, et al., Serum gamma-glutamyltransferase and mortality due to cardiovascular disease in Japanese men and women, J. Atheroscler. Thromb. 23 (2016) 792–799.
[21] J.J. Deeks, D.G. Altman, M.J. Bradburn, Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis, in: Systematic Reviews in Health Care, BMJ Publishing Group, 2001, pp. 285–312.
[22] R.B. D'Agostino Sr., R.S. Vasan, M.J. Pencina, et al., General cardiovascular risk profile for use in primary care: the Framingham Heart Study, Circulation 117 (2008) 743–753.
[23] A. Fujiyoshi, K. Miura, A. Hozawa, et al., Gamma-Glutamyltransferase and mortality risk from heart disease and stroke in Japanese men and women: NIPPON DATA90, CVD Prev. Control 5 (2010) 27–34.
[24] A. Hozawa, T. Okamura, T. Kadowaki, et al., gamma-Glutamyltransferase predicts cardiovascular death among Japanese women, Atherosclerosis 194 (2007) 498–504.
[25] K.C. Sung, S. Ryu, B.S. Kim, et al., Gamma-Glutamyl transferase is associated with mortality outcomes independently of fatty liver, Clin. Chem. 61 (2015) 1173–1181.
[26] A. Fraser, R. Harris, N. Sattar, et al., Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British Women's Heart and Health Study and Meta-Analysis, Arterioscler. Thromb. Vasc. Biol. 27 (2007) 2729–2735.
[27] M.L. Bots, J.T. Salonen, P.C. Elwood, et al., Gamma-glutamyltransferase and risk of stroke: the EUROSTROKE project, J. Epidemiol. Community Health 56 (Suppl 1) (2002) i25–29.
[28] P. Jousilahti, D. Rastenyte, J. Tuomilehto, Serum gamma-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke, Stroke 31 (2000) 1851–1855.
[29] C.F. Liu, Y.T. Gu, H.Y. Wang, et al., Gamma-glutamyltransferase level and risk of hypertension: a systematic review and meta-analysis, PLoS One 7 (2012) e48878.
[30] G. Koenig, S. Seneff, Gamma-glutamyltransferase: a predictive biomarker of cellular antioxidant inadequacy and disease risk, Dis. Markers 2015 (2015) 818570.
[31] S.S. Ali, E.T. Oni, M.J. Blaha, et al., Elevated gamma-glutamyl transferase is associated with subclinical inflammation independent of cardiometabolic risk factors in an asymptomatic population: a cross-sectional study, Nutr. Metab. (Lond) 13 (2016) 37.
[32] S. Bulusu, M. Sharma, What does serum gamma-glutamyltransferase tell us as a cardiometabolic risk marker? Ann. Clin. Biochem. 53 (2016) 312–332.
[33] C. Weikert, D. Drogan, R. di Giuseppe, et al., Liver enzymes and stroke risk in middle-aged German adults, Atherosclerosis 228 (2013) 508–514.
[34] A.M. Strasak, C.C. Kelleher, J. Klenk, et al., Longitudinal change in serum gamma-glutamyltransferase and cardiovascular disease mortality: a prospective population-based study in 76,113 Austrian adults, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 1857–1865.
[35] N. Katsiki, D.P. Mikhailidis, D.R. Nair, The effects of antiepileptic drugs on vascular risk factors: a narrative review, Seizure 23 (2014) 677–684.