CVD Prevention and Control (2010) 5, 27—34

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γ-Glutamyltransferase and mortality risk from heart disease and stroke in Japanese men and women: NIPPON DATA90

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Received 18 February 2010; accepted 12 March 2010
Available online 24 April 2010

KEYWORDS
γ-Glutamyltransferase;
Heart disease;
Stroke;
Mortality;
Asia

Summary
Background: Studies have shown that baseline serum γ-glutamyltransferase (GGT) is independently associated with cardiovascular disease (CVD) risk in men and women. However, less is known whether GGT is similarly associated with both stroke and heart disease (HD) risk in Asia. We examined an association between serum GGT and deaths from stroke and HD in Japanese men and women.

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doi:10.1016/j.cvdpc.2010.03.003

Methods: From 1990 to 2005, we followed 7488 adults (3089 men) randomly selected from 300 districts throughout Japan, aged 30—95 with no history of coronary disease nor stroke at baseline. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) according to sex-specific GGT strata.
Results: During the study period, observed deaths from HD and stroke were 165 (83 men), and 135 (66 men), respectively. After adjustment for confounding factors, HRs of HD death for 25th, 50th, 75th, and 90th GGT percentiles in reference to the lowest GGT stratum were 1.61, 2.28, 2.48, and 4.59 in women (P for trend = 0.001), and 0.90, 0.74, 1.42, and 1.56 in men (P for trend = 0.250). The corresponding HRs of total stroke death were 1.52, 0.95, 1.22, and 1.34 in women (P for trend = 0.785), and 0.75, 0.91, 1.26, and 1.02 in men (P for trend = 0.642). Results were similar when analysis was limited to never-drinkers.
Conclusion: This cohort study of representative Japanese men and women suggested that baseline GGT independently predicts future HD mortality risk, especially in women, but not stroke mortality risk in Asian.
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Introduction

Elevated serum γ-glutamyltransferase (GGT) level has been shown to predict cardiovascular diseases (CVD) incidence [1,2] and mortality [3] but less is known whether GGT is independently associated with both heart disease (HD) and stroke mortalities. For example, a meta-analysis that pooled prospective cohorts showed that GGT was associated with both incident coronary heart disease (CHD) and incident stroke [4], but many of the enrolled studies [2,3,5,6] did not take into account effect of alcohol consumption. Furthermore, current evidence on association between GGT and CVD risk is largely based on US and/or European populations. Asian populations are far less studied for association of GGT with risk of HD and stroke [7]. Although we previously reported an independent association between GGT and CVD death [8], we felt that events were too few to study an association with HD and stroke separately. In this study with extended follow-up period, we investigated whether serum GGT level at baseline is independently associated with long-term mortality from HD and stroke in both men and women in Japan. The question is of particular importance because stroke is more common in Asia compared to Europe and US. In addition, mortalities from CHD and ischemic stroke were examined as our secondary outcomes. We studied a cohort of representative Japanese men and women that has been followed up for 15 years.

Methods

Study participants

The National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged (NIPPON DATA) consists of two ongoing cohorts that are based on two national surveys conducted in Japan. Detailed methods in constructing the cohorts were described elsewhere [9—11]. In brief, they were constructed upon the National Survey of Circulatory Disorder conducted in 1980, and in 1990, which become the bases of ''NIPPON DATA80'' [9] and ''NIPPON DATA90'' [10], respectively. Both surveys included physical examination, laboratory tests, and self-administered questionnaire on lifestyle and medical information. The present study was based only on NIPPON DATA90 because the baseline survey of NIPPON DATA80 did not contain measurement of serum GGT level.

We followed a total of 8383 community residents (3504 men and 4879 women; age 30 or older) from 300 randomly selected districts across the nation until November 15, 2005. The overall population of ⩾30-year-old in all the districts was 10,956, and the participation rate in the survey was 76.5%. Of the 8383 participants, we excluded 895 participants for the following reasons; no baseline GGT measurement (n = 662), those with CHD and/or stroke at baseline (n = 222), and with missing pertinent covariates (n = 11), leaving 7488 individuals for analysis (3089 men, 4399 women). We utilized the National Vital Statistics to ascertain the cause of death. In accordance with Japan's Family Registration Law, all death certificates, issued by a physician, are to be forwarded to the Ministry of Health, Labour and Welfare via the public health center in the area of residency. The cause of death is then coded for the National Vital Statistics. The 9th International Classification for Disease (ICD9) was used for deaths occurring up to the end of 1994, and the 10th International Classification for Disease (ICD10) for deaths occurring thereafter. Permission was obtained from the Management and Coordination Agency of the Japanese Government for use of pertinent information from the National Vital Statistics. The respective codes for ICD9 and 10 used were as follows: heart disease (HD), 393—429 (ICD9), I01—I09, I11, I13, I20—I50 (ICD10); stroke, 430—438 (ICD9), I60—I69 (ICD10); coronary heart disease (CHD), 410—414 (ICD9), I20—I25 (ICD10); ischemic stroke 433, 434, 437.8a, 437.8b (ICD9), I63, I69.3 (ICD10). The study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 17—21, 2005).

Measurement

The baseline survey was conducted by a public health center in each area. Blood pressure was measured by a trained staff member using a standard mercury sphygmomanometer over the right arm of a seated participant after at least 5 min-rest. Body mass index (BMI) was calculated as weight in kilogram divided by square of height in meter. From the self-administered questionnaire, the following information

was obtained; physician-diagnosed diseases [Yes, No, Unknown] (stroke, myocardial infarction), status of clinical visit for the corresponding medical condition, and use of medication. Alcohol intake was first categorized into [Never, Current, Former], then further asked amount (''*go*'', the traditional Japanese unit for *sake*, per day; 1*gou* (180 mL) of *sake* contains 23 g of alcohol) of consumption for those who responded as ''current''. Based on these questions, we used three categories (never, past, current) in main analysis, and six categories (never, past, current <23 g of alcohol/day, current 23 g to <46 g/day, current 46 g to <69 g/day, and current $\geqslant$69 g/day) in sensitivity analysis. Smoking status was categorized into three groups; never-smoker, ex-smoker, and current-smoker. Exercise status was grouped into three categories; ''unable to exercise due to a health related reason'', ''unable to exercise due to a non-health related reason'', and ''exercise regularly''. Public health nurses confirmed information on smoking, drinking habits, and medical history.

Non-fasting blood samples were obtained and serum was separated and centrifuged immediately after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. Serum GGT was measured using 3-carboxyl-4-nitroanilide substrate methods based on International Federation of Clinical Chemistry and Laboratory Medicine with Hitachi 736-60 (Hitachi Ltd., Tokyo, Japan). Glutamyl oxaloacetic transaminase (GOT; also known as aspartate aminotransferase, AST) and glutamyl pyruvic transaminase (GPT; also known as alanine aminotransferase, ALT) were measured using ultraviolet methods. Serum total cholesterol and triglycerides (TG) as well as plasma glucose were measured enzymatically. High-density lipoprotein (HDL) cholesterol was measured by the precipitation method using heparin-calcium. Lipid measurements were standardized using the Lipids Standardization Program from the Centers for Disease Control/National Heart, Lung and Blood Institute. Diabetes mellitus was defined as serum glucose $\geqslant$200 mg/dL and/or presence of self-reported history. All samples were shipped to the central laboratory (SRL, Tokyo, Japan) for measurement.

Statistical analysis

Because the relationship between GGT and CVD mortality was different by gender in our previous study [8], all analyses were performed separately in men and women. For main analysis, GGT level was categorized into five groups using sex-specific cut-off points of the 25th, 50th, 75th, and 90th percentiles computed over the each gender group, following previous works by Lee and the colleagues [1,12,13]. In estimating mortality risk, we first calculated crude total mortality rates according to the GGT strata. Then, multivariate-adjusted hazard ratios (HRs) were estimated using Cox proportional hazards model. Because distributions for GOT, GPT, and TG were right-skewed, values were natural log-transformed (ln-GOT, ln-GPT, ln-TG) when entering models as well as upon calculating linear trend across baseline GGT strata. Model 1 was adjusted for age only. Model 2 was further adjusted for systolic blood pressure (mmHg), BMI (kg/m^2), smoking status, regular exercise status, and total and HDL cholesterol (mg/dL), ln-TG, and diabetes mellitus at baseline. In Model 3, we further adjusted for alcohol intake. Model 4 further included ln-GOT and ln-GPT. We conducted a parallel procedure on the subgroup who reported as a never-drinker. To avoid instability in estimation, we used 25th and 50th percentiles combined as a reference group for secondary outcomes (CHD, ischemic stroke) due to their fewer events. Trends across the GGT strata were tested by regression with a median value used for a corresponding GGT stratum. All the statistical tests were two-tailed, and values of $P < 0.05$ were considered significant. Statistical analyses were conducted with SAS release 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the participants at baseline are shown in Table 1. Median age (years) at baseline was 51 for women and 52 for men. Median BMI (kg/m^2) was 22.5 for women and 22.9 for men. Only less than 7% of the women reported as a current-drinker whereas more than a half (59%) of the men did so. Majority (92%) of the women reported as a never-drinker. The 25th, 50th, 75th, and 90th percentile levels of GGT were 8, 12, 17, 26, and 52 U/L for women, and 15, 24, 41, 76, and 158 U/L for men. There was a clear gender difference in age distribution across GGT strata. As GGT level increased, the median age increased in women, whereas it decreased in men (P for trend < 0.001 for both). Despite such difference in age distribution, many cardiovascular risk factors were similarly associated with GGT level in both sexes; as GGT increases, BMI, total cholesterol, TG, systolic and diastolic blood pressure levels increased in both men and women (P for trend < 0.001 for all those variables in both sexes). The proportions of current-drinker and current-smoker were higher in higher GGT strata for both men and women, but there was a striking gender difference in absolute proportions such that both current-drinker and current-smoker were much fewer in women than in men even in the highest GGT group.

During the mean follow-up of 13.7 years, we observed 165 HD deaths (83 men), and 135 stroke deaths (66 men). Deaths due to CHD and ischemic stroke were 65 (40 men), and 83 (men 42), respectively. Estimated crude mortality rate, adjusted hazard ratios (HRs) for deaths from HD, CHD, total and ischemic stroke according to GGT strata are shown in Table 2 for women and in Table 3 for men.

In women, crude mortality rates (per 1000 person-years) were similar between HD and total stroke; 1.34, and 1.13, respectively (Table 2). By Cox regression models, we observed a significant graded positive association between GGT and HD mortality in women. After multivariate adjustment, the HRs of HD death of 25th, 50th, 75th, 90th GGT strata were 1.61, 2.28, 2.48, and 4.59 in reference to the lowest GGT group (Model 4, P for trend = 0.001). The association pattern of CHD death was similar to, and with apparently greater strength than HD (Table 2). In contrast, we observed no clear association between GGT and neither total stroke nor ischemic stroke death throughout the models.

In men, crude mortality rates (per 1000 person-years) were 2.00 for HD, and 1.59 for stroke, respectively (Table 3). In Models 3 and 4, we observed an apparent

J-shaped trend between GGT levels and HD death. The adjusted HRs for 25th, 50th, 75th, and 90th GGT percentiles in reference to the lowest GGT group were 0.90, 0.74, 1.42, and 1.56, respectively (Model 4, *P* for trend = 0.250). The J-shape association was more evident in CHD deaths with adjusted HRs for 50th, 75th, and 90th GGT percentiles being 0.47, 1.98, and 2.68. Similar to women, we observed no clear association between GGT and neither total nor ischemic stroke death throughout the models.

Table 1 Characteristics of the participants at baseline.

	Sex-specific GGT[a]					Total	
	<25th	25 to <50th	50 to <75th	75 to <90th	⩾90th		
Women							
No.	960	1138	1124	719	458	4399	
Age (years)	45	49	52	56	56	51	(41—62)
BMI (kg/m^2)	21.5	21.9	22.8	23.6	23.9	22.5	(20.5—24.8)
Total cholesterol (mg/dL)	192	200	206	214	220	203	(179—231)
HDL-C (mg/dL)	57	57	55	55	53	56	(46—66)
Triglycerides (mg/dL)	82	95	103	116	130	101	(71—145)
GOT (U/L)	18	19	20	22	27	20	(17—24)
GPT (U/L)	12	14	16	20	28	16	(12—22)
SBP (mmHg)	126	128	132	138	140	130	(118—146)
DBP (mmHg)	76	78	80	82	82	80	(70—88)
Use of antihypertensives (%)	12.5	16.0	21.4	29.1	31.2	20.3	
Diabetes mellitus (%)	2.1	3.0	3.7	6.5	7.9	4.1	
Smoking							
Never (%)	91.9	88.4	87.5	86.2	83.4	88.1	
Former (%)	1.9	3.6	2.5	2.1	2.4	2.6	
Current (%)	6.3	8.0	10.0	11.7	14.2	9.4	
Drinking							
Never (%)	96.7	93.7	92.1	90.4	84.1	92.4	
Former (%)	0.4	1.1	1.1	1.3	0.9	1.0	
Current (%)	2.9	5.2	6.9	8.3	15.1	6.7	
Regular exercise							
Not, for health (%)	5.8	6.0	6.0	8.3	9.4	6.7	
Not, for other reason (%)	78.1	74.3	75.6	71.8	71.8	74.8	
Yes (%)	16.0	19.7	18.3	19.9	18.8	18.5	
Men							
No.	681	831	795	472	310	3089	
Age (years)	56	55	51	49	49	52	(41—63)
BMI (kg/m^2)	21.4	22.4	23.4	24.2	24.0	22.9	(20.8—24.9)
Total cholesterol (mg/dL)	182	194	200	203	204	195	(174—221)
HDL-C (mg/dL)	48	48	48	47	51	48	(40—58)
Triglycerides (mg/dL)	93	108	132	154	172	119	(83—181)
GOT (U/L)	20	22	24	27	34	24	(19—29)
GPT (U/L)	16	19	24	31	42	22	(16—32)
SBP (mmHg)	132	132	136	140	138	136	(124—150)
DBP (mmHg)	80	80	84	88	88	84	(76—90)
Use of antihypertensives (%)	14.5	17.8	16.5	20.3	17.1	17.1	
Diabetes mellitus (%)	6.2	6.4	6.9	8.9	9.4	7.2	
Smoking							
Never (%)	26.3	21.8	20.0	17.4	12.6	20.7	
Former (%)	22.9	25.5	23.6	21.6	18.7	23.2	
Current (%)	50.8	52.7	56.4	61.0	68.7	56.1	
Drinking							
Never (%)	57.1	42.7	28.4	15.5	10.0	34.8	
Former (%)	6.8	8.2	5.9	4.7	3.5	6.3	
Current (%)	36.1	49.1	65.7	79.9	86.5	59.0	

Table 1 (*continued*)

	Sex-specific GGT[a]					Total
	<25th	25 to <50th	50 to <75th	75 to <90th	⩾90th	
Regular exercise						
Not, for health (%)	5.0	5.3	4.5	4.9	1.3	4.6
Not, for other reason (%)	71.2	72.0	72.8	75.8	76.8	73.1
Yes (%)	23.8	22.7	22.6	19.3	21.9	22.3

Values are expressed in median unless otherwise specified. Numbers in parenthesis are inter-quartile ranges.
Abbreviations: GGT, γ-glutamyltransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
[a] Cut-off GGT values (U/L) for 25th, 50th, 75th, and 90th percentile were 8, 12, 17, 26 and 52 in women and 15, 24, 41, 76 and 158 in men, respectively.

Table 2 Crude rates and multivariate-adjusted HR for heart disease and stroke deaths in women.

GGT category (value in U/L)	<25th (1—10)	25 to <50th (11—14)	50 to <75th (15—21)	75 to <90th (22—36)	⩾90th (37—385)	Total
Person-years	13,467	15,933	15,698	9844	6072	61,012
Heart disease death						
No.	10	16	21	19	16	82
Crude rate (per 1000 person-years)	0.74	1.00	1.34	1.93	2.64	1.34
						P for trend
Model 1	1	1.44	1.90	2.15	3.52	<0.001
Model 2	1	1.61	2.31	2.54	4.81	<0.001
Model 3	1	1.61	2.31	2.57	4.88	<0.001
Model 4	1	1.61	2.28	2.48	4.59	0.001
CHD death						
No.	5		7	7	6	25
Crude rate (per 1000 person-years)	0.17		0.45	0.71	0.99	0.41
						P for trend
Model 1	1		2.72	3.39	5.66	0.005
Model 2	1		3.27	4.40	7.95	0.001
Model 3	1		3.35	4.46	7.59	0.002
Model 4	1		3.56	5.01	10.31	0.002
Total stroke death						
No.	14	22	13	13	7	69
Crude rate (per 1000 person-years)	1.04	1.38	0.83	1.32	1.15	1.13
						P for trend
Model 1	1	1.40	0.84	1.06	1.10	0.890
Model 2	1	1.48	0.94	1.14	1.27	0.881
Model 3	1	1.50	0.93	1.15	1.32	0.819
Model 4	1	1.52	0.95	1.22	1.34	0.785
Ischemic stroke death						
No.	27		4	7	3	41
Crude rate (per 1000 person-years)	0.92		0.25	0.71	0.49	0.67
						P for trend
Model 1	1		0.30	0.64	0.57	0.298
Model 2	1		0.33	0.68	0.66	0.455
Model 3	1		0.32	0.67	0.69	0.483
Model 4	1		0.32	0.70	0.67	0.552

Model 1 was adjusted for age. Model 2 further included systolic blood pressure, BMI, smoking, exercise, total cholesterol, HDL-cholesterol, ln-TG, and diabetes mellitus. Model 3 further included alcohol intake (never, past, current). Model 4 further included ln-GOT and ln-GPT.
Abbreviations: CHD, coronary heart disease; GGT, γ-glutamyltransferase; BMI, body mass index; HDL, high-density lipoprotein; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

Table 3 Crude rates and multivariate-adjusted HR for heart disease and stroke deaths in men.

GGT category (value in U/L)	<25th (1—18)	25 to <50th (19—30)	50 to <75th (31—57)	75 to <90th (58—110)	⩾90th (111—1803)	Total
Person-years	8939	11,114	10,862	6488	4140	41,542
Heart disease death						
No.	30	24	14	10	5	83
Crude rate (per 1000 person-years)	3.36	2.16	1.29	1.54	1.21	2.00
						P for trend
Model 1	1	0.72	0.53	0.84	0.80	0.754
Model 2	1	0.81	0.62	1.02	1.08	0.704
Model 3	1	0.87	0.69	1.30	1.43	0.324
Model 4	1	0.90	0.74	1.42	1.56	0.250
CHD death						
No.	25		4	7	4	40
Crude rate (per 1000 person-years)	1.62		0.37	1.08	0.97	0.96
						P for trend
Model 1	1		0.38	1.39	1.49	0.343
Model 2	1		0.41	1.52	2.05	0.134
Model 3	1		0.46	1.97	2.74	0.048
Model 4	1		0.47	1.98	2.68	0.060
Total stroke death						
No.	20	16	16	10	4	66
Crude rate (per 1000 person-years)	2.24	1.44	1.47	1.54	0.97	1.59
						P for trend
Model 1	1	0.72	0.97	1.41	1.13	0.380
Model 2	1	0.76	0.96	1.35	1.16	0.440
Model 3	1	0.77	0.98	1.40	1.23	0.398
Model 4	1	0.75	0.91	1.26	1.02	0.642
Ischemic stroke death						
No.	24		13	4	1	42
Crude rate (per 1000 person-years)	1.20		1.20	0.62	0.24	1.01
						P for trend
Model 1	1		1.47	1.16	0.59	0.839
Model 2	1		1.45	0.97	0.52	0.616
Model 3	1		1.59	1.15	0.65	0.845
Model 4	1		1.64	1.19	0.65	0.794

Model 1 was adjusted for age. Model 2 further included systolic blood pressure, BMI, smoking, exercise, total cholesterol, HDL-cholesterol, ln-TG, and diabetes mellitus. Model 3 further included alcohol intake (never, past, current). Model 4 further included ln-GOT and ln-GPT.

Abbreviations: CHD, coronary heart disease; GGT, γ-glutamyltransferase; BMI, body mass index; HDL, high-density lipoprotein; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

The results were virtually unchanged when detailed categorization for alcohol intake was used in the models (data not shown). For subgroup analysis on never-drinker, observed number of death from HD and from stroke were 79 and 68 in women ($n = 4064$), and 41 and 24 in men ($n = 1074$), respectively. Estimated patterns of association were similar to the main analysis except that no J-shaped trend was observed between GGT and HD in men. The adjusted HRs for HD death of 25th, 50th, 75th, 90th GGT strata were 1.56, 2.36, 2.36, and 5.46 in women (P for trend < 0.001), 0.56, 0.79, 0.30, and 0.77 in men (P for trend = 0.564); the corresponding HRs for stroke death were 1.54, 0.98, 1.24, and 1.45 in women (P for trend = 0.679), 1.00, 0.70, 1.58, and 0.00 in men (P for trend = 0.815. No events in the highest group) (data not tabulated).

Discussion

In this 15-year follow-up study, we examined whether baseline GGT is independently associated with both HD and stroke deaths in Japanese men and women. We observed positive associations of GGT with the risk of total HD mortality and of CHD mortality in women. For men, there seemed to be a non-significant J-shaped trend of HD, especially CHD. In contrast, we did not observe a clear association between GGT and stroke mortality in either sexes.

Previous studies indicated that elevated GGT is associated with increased risk for CVD, but less is clear whether GGT is independently associated with both HD and stroke mortality. For example, Fraser and colleagues conducted a

meta-analysis pooling prospective cohorts, and showed that GGT was associated with both incident CHD and incident stroke [4]. However, many studies including those in the meta-analysis did not adjust for alcohol intake [2,3,5,6,14], which left a possibility of confounding by alcohol effect. We dealt with this issue by both statistical adjustment and by restriction to never-drinkers, and the results from both approaches seemed similar. Another uncertainty is regarding a potential ethnic difference. Current evidence on association between GGT and CVD risk is largely based on US/European population, and Asians are far less studied. Since stroke is more common in east-Asia [15] compared to the US/European population, it is important to examine disease-specific association of GGT.

In our study population, stroke death rate was higher than that of CHD. Thus, it is unlikely that the observed null association with stroke risk is attributable to fewer deaths in light of positive association with CHD risk in women. However, the null association with stroke is not consistent with some studies including one from Japan that reported a positive association with incident stroke [7]. Although the exact reason for this inconsistency is unclear, we speculate followings reasons. First, stroke includes etiologically heterogenous conditions with different fatality risk [16,17]. Therefore, factors that affect stroke incidence may be different from those of stroke death. Second, prevalence of stroke subtype can be different between Asians and Caucasians [18], which could lead to difference in association.

We observed sex-difference in association of GGT with HD and CHD; not significant in men, whereas significant and monotonic in women. Similar sex-difference in association of GGT with incident stroke was reported from a Japanese population [7]. Such difference might be explained by the fact that GGT level is affected not only by alcohol consumption, but also obesity (through visceral and hepatic fat [19]), as well as smoking in the presence of alcohol [20]. Most women in our study were never-drinker, never-smoker, and young female tended to have lower BMI. In contrast, among our male group, both alcohol intake and smoking habit were common especially in the young who tended to have greater BMI. In a population such as our male group, the association of GGT may be obscured despite the attempt to deconfound. A larger sample size for never-drinking men is needed to examine this issue.

GGT has other potentially important determinants that can be even stronger than liver function or alcohol consumption [21]. Biological mechanism in explaining the link between elevated GGT and CVD mortalities is not fully understood. Serum GGT is considered to be a marker for insulin resistance [22], as well as for oxidative stress and inflammation which may lead to cardiovascular diseases [23,24]. Another mechanism has been suggested by histochemical analyses showing GGT activity expressed by macrophage-derived foam cells within human atheromas [25] co-localizing with oxidized LDL [26]. Furthermore, GGT is shown to mediate LDL oxidation [27], indicating that GGT is a potential marker for the preclinical atherosclerosis.

Major strengths of the study include prospective study design with longitudinal ascertainment of deaths, length of follow-up, and enrollment of both sexes with a broad age range based on the National Survey on randomly sampled areas nationwide, which made our cohort representative of the Japanese population. Several limitations should be mentioned. First, we did not have incidence data for CHD and stroke. Thus we were unable to examine potential difference between incidence and mortality. Second, we did not have information pertinent to hepatic conditions, such as chronic viral hepatitis, although we believe this limitation is less likely to distort our inference because our main outcomes are CVD mortalities, not hepatic/gastrointestinal or total mortalities.

Conclusion

We found that baseline GGT level was independently associated with long-term risk of HD mortality, especially in women, but not with stroke mortality in a representative sample of Japanese population.

Conflict of interest statement

None declared.

Role of funding source

This study was supported by a grant-in-aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebro-Cardiovascular Disease Control, a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labour and Welfare and a Health and Labour Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-Chouju-046, H14-Chouju-003, H17-Chouju-012, and H19-Chouju-014), and by the Korea Research Foundation Grant funded by the Korean Government (MEST) (KRF-2009-220-E00023). These sponsores had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Acknowledgments

The authors thank all members of Japanese Association of Public Health Center Directors and all staff members of the public health centers that cooperated with our study. Investigators and members of the research group are listed in Ref. [11].

References

[1] Lee DH, Silventoinen K, Hu G, 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 2006;27:2170—6.

[2] Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. Stroke 2000;31:1851—5.

[3] Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation 2005;112:2130—7.

[4] Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA. 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 2007;27:2729—35.
[5] Bots ML, Salonen JT, Elwood PC, et al. Gamma-glutamyltransferase and risk of stroke: the EUROSTROKE project. J Epidemiol Community Health 2002;56 Suppl 1:i25—9.
[6] Ebrahim S, Sung J, Song YM, Ferrer RL, Lawlor DA, Davey Smith G. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. BMJ 2006;333:22.
[7] Shimizu Y, Imano H, Ohira T, et al. γ-Glutamyltranspeptidase and incident stroke among Japanese men and women. The Circulatory Risk in Communities Study (CIRCS). Stroke 2010;41:385—8.
[8] Hozawa A, Okamura T, Kadowaki T, et al. gamma-Glutamyltransferase predicts cardiovascular death among Japanese women. Atherosclerosis 2007;194:498—504.
[9] Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H. What cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med 2003;253:169—80.
[10] Nakamura K, Okamura T, Hayakawa T, et al. Electrocardiogram screening for left high R-wave predicts cardiovascular death in a Japanese community-based population: NIPPON DATA90. Hypertens Res 2006;29:353—60.
[11] Okuda N, Miura K, Yoshita K, et al. Integration of data from NIPPON DATA80/90 and National Nutrition Survey in Japan: For Cohort Studies of Representative Japanese on Nutrition. J Epidemio 2010;20(Suppl 3):S506—14.
[12] Lee DH, Jacobs Jr DR, Gross M, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 2003;49:1358—66.
[13] Lee DH, Silventoinen K, Jacobs Jr DR, Jousilahti P, Tuomileto J. gamma-Glutamyltransferase, obesity, and the risk of type 2 diabetes: observational cohort study among 20,158 middle-aged men and women. J Clin Endocrinol Metab 2004;89:5410—4.
[14] Strasak AM, Kelleher CC, Klenk J, 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 2008;28:1857—65.
[15] Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. Circulation 2008;118:2702—9.
[16] Wang X, Jiang G, Choi BC, et al. Surveillance of trend and distribution of stroke mortality by subtype, age, gender, and geographic areas in Tianjin, China, 1999—2006. Int J Stroke 2009;4:169—74.
[17] de Jong G, van Raak L, Kessels F, Lodder J. Stroke subtype and mortality: a follow-up study in 998 patients with a first cerebral infarct. J Clin Epidemiol 2003;56:262—8.
[18] Ng WK, Goh KJ, George J, Tan CT, Biard A, Donnan GA. A comparative study of stroke subtypes between Asians and Caucasians in two hospital-based stroke registries. Neurol J Southeast Asia 1998;3:19—26.
[19] Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. Diabetes Care 1998;21:732—7.
[20] Breitling LP, Raum E, Muller H, Rothenbacher D, Brenner H. Synergism between smoking and alcohol consumption with respect to serum gamma-glutamyltransferase. Hepatology 2009;49:802—8.
[21] Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001;38:263—355.
[22] Shin JY, Chang SJ, Shin YG, Seo KS, Chung CH. Elevated serum gamma-glutamyltransferase levels are independently associated with insulin resistance in non-diabetic subjects. Diabetes Res Clin Pract 2009;84:152—7.
[23] Lee DH, Blomhoff R, Jacobs Jr DR, Is serum gamma glutamyltransferase a marker of oxidative stress?. Free Radic Res 2004;38:535—9.
[24] Yamada J, Tomiyama H, Yambe M, et al. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. Atherosclerosis 2006;189:198—205.
[25] Paolicchi A, Emdin M, Ghliozeni E, et al. Images in cardiovascular medicine. Human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. Circulation 2004;109:1440.
[26] Paolicchi A, Minotti G, Tonarelli P, et al. Gamma-glutamyl transpeptidase-dependent iron reduction and LDL oxidation — a potential mechanism in atherosclerosis. J Invest Med 1999;47:151—60.
[27] Emdin M, Pompella A, Paolicchi A. Gamma-glutamyltransferase, atherosclerosis, and cardiovascular disease: triggering oxidative stress within the plaque. Circulation 2005;112:2078—80.