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Original Research

Association of gamma-glutamyltransferase with incidence of type 2 diabetes in Japan

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Abstract

The aim of this research was to examine the association of gamma-glutamyltransferase (GGT) and its interactions with alcohol consumption (alcohol), body mass index (BMI) and/or alanine aminotransferase (ALT) on the incidence of type 2 diabetes (DM) in Japan. Data from annual health examinations obtained from 1995 to 2005 were analyzed. The total number of subjects in this cohort was 39,563. Hazard ratios (HRs) were calculated by Cox regression analysis. GGT levels were positively associated with the incidence of DM in both men and women, after adjustment for several variables, including alcohol, BMI and ALT. Among women, the association was stronger in non-drinkers than in drinkers due to a significant interaction of GGT and alcohol. In non-drinkers, the HRs of the third and fourth GGT quartiles in women and the fourth GGT quartile in men were significantly higher than those of the first GGT quartile. The association between BMI and the incidence of DM was enhanced by increased GGT levels in women. When GGT levels were in the second to fourth quartiles, the HRs of obese subjects were significantly higher than those of underweight subjects. Conversely, obesity was no longer a significant risk factor for DM when GGT level was in the first quartile. Increased GGT levels were associated with the development of DM after adjustment for several possible confounding factors. The association between GGT and DM in non-drinkers was significantly stronger than that in drinkers. Furthermore, in women, obesity is no longer a risk factor for DM when GGT level is low.

Keywords: incidence of type 2 diabetes, gamma-glytamyltransferase, alcohol consumption, obesity

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Introduction

Serum gamma-glutamyltransferase (GGT) has been widely used as a marker of liver disease and alcohol intake.[1–5] Recent prospective studies reported that increased levels of serum GGT, even within its normal range, showed a dose–response relationship with the incidence of type 2 diabetes (DM).[1,3–6] This association is independent of well-known predictors for diabetes such as age, body mass index (BMI), and also other factors associated with GGT levels such as alcohol consumption (alcohol) and liver damage.[1,3–6] Furthermore, two previous studies showed a significant interaction between GGT and BMI on the risk of DM; one was a cross-sectional study of data from the Third National Health and Nutrition Examination Survey (NHANES) in the USA[7] and the other was a prospective cohort study in Korean men.[3] The authors claimed that BMI was associated with diabetes only when GGT was in its high normal range, and this finding might be useful in the clinical or research setting because the interaction between BMI and GGT may help to define a high-risk target population.[7] However, other prospective studies have failed to show a significant interaction between GGT and BMI on the incidence of DM[4,5] or have found a significant interaction only when the five-year risk was analyzed, and not for the total 15-year risk.[1]

Sato *et al.* reported the association of alcohol and GGT with the risk of DM and showed that non-drinkers or light drinkers with the highest GGT levels had a higher risk of DM than moderate or heavy drinkers with the highest GGT levels.[8] The Hisayama Study, a population-based prospective cohort study in Japan, and a four-year follow-up prospective study performed in the Korean population have evaluated the effects of GGT on the risk of DM among groups stratified by their alcohol intake. They showed significant positive associations between GGT and DM in all of the stratified groups, while the association

appeared to be weaker in drinkers than in non-drinkers, although they did not evaluate the interaction between GGT and alcohol consumption.[3,6]

The aim of this study was to confirm the association between GGT and the risk of DM prospectively using models with or without adjustment for alcohol, BMI and/or alanine aminotransferase (ALT). We also analyzed the interactions of alcohol, BMI or ALT with GGT on the incidence of DM using data from a historical prospective cohort study, with an average eight-year follow-up time, in the Japanese population.

Materials and methods

Subjects

The subjects of this study were residents of Chiba City, Chiba prefecture, Japan. The data from annual health examinations from 1995 to 2005 were collected in accordance with the Health and Medical Service Law for the Aged. The number of participants aged between 40 and 79 years who attended the annual health examinations in 1995 was 58,406 (16,029 men and 42,377 women). We excluded 16,251 participants (5955 men and 10,296 women) with missing data and 2592 participants (1205 men and 1387 women) who had fasting blood glucose levels $\geq$7.0 mmol/L, or non-fasting glucose levels $\geq$11.1 mmol/L, and/or a positive history for DM in 1995. After exclusion, the available number of subjects in this cohort was 39,563 (8869 men and 30,694 women). Of these, 36,873 (8081 men and 28,792 women) were followed up at least once.

Since this cohort was obtained from the annual health examinations conducted in accordance with the Health and Medical Service Law for the Aged, consent was not obtained from the subjects. In order to convert the health examination data into anonymous data, personal information, such as name, date of birth, address and telephone number, were removed from the records at the Health Center in Chiba City. This study was approved by the Institutional Review Board of Chiba University.

Baseline examination

We defined the annual health examinations in 1995 as the baseline. The examinations were performed at the designated clinics or hospitals in Chiba City. Blood samples were drawn during periods of fasting or non-fasting. Plasma glucose, serum ALT and GGT levels were measured at commercial clinical laboratories that had joined the surveys performed by the Japanese Association of Medical Technologists and/or the Japan Medical Association for external quality assessment and had performed internal quality control in their laboratories. Here, 'fasting plasma glucose' is defined as the glucose level from subjects who had not consumed food or drink (except water) for at least eight hours before blood drawing, and 'non-fasting plasma glucose' refers to those who had eaten or drunk fluids other than water. On the basis of the fasting plasma glucose or non-fasting plasma glucose levels at baseline, subjects were categorized into two groups according to the guidelines of the Japanese Diabetes Society:[9] normal type (fasting plasma glucose $<$6.1 mmol/L or non-fasting plasma glucose level $<$7.8 mmol/L) and borderline type (6.1 mmol/L $\leq$fasting plasma glucose $<$7.0 mmol/L or 7.8 mmol/L $\leq$non-fasting plasma glucose $<$11.1 mmol/L). We defined this variable as the 'baseline glucose type'. BMI was calculated as weight divided by the square of height (kg/m^2). On the basis of the baseline BMI, the subjects were categorized into three groups: underweight (BMI $<$ 18.5 kg/m^2), normal weight (18.5 $\leq$ BMI $<$ 25.0 kg/m^2) and obese (BMI $\geq$ 25.0 kg/m^2) according to the guidelines of the Japan Society for the Study of Obesity.[10] We combined the two groups of BMI $\geq$ 30.0 kg/m^2 and BMI $\geq$ 25.0 kg/m^2 because of the small sample size of the former group. A self-reported questionnaire completed by all subjects collected data on age, positive or negative family history of DM in first-degree relatives (parents and sibling[s]), smoking habits (non-smoker, smoker of 1–20 cigarettes/day or smoker of $>$21 cigarettes/day) and alcohol (non-drinker or drinker). The data on alcohol were obtained by asking the number of glasses of Japanese sake (180 mL), beer (633 mL) or whisky (60 mL) that were consumed daily, which are nearly equivalent to 21, 23 and 20 g of ethanol, respectively, according to the Standard Table of Food Composition in Japan. Drinkers were defined as those subjects who drank one or more glasses of sake, beer or whisky per day and non-drinkers as those who did not drink habitually. We did not divide the subjects by alcohol into more than two categories because the number of drinkers was small, especially in women. Subjects were categorized into four groups by age: 40–49, 50–59, 60–69 and 70–79 years. Subjects were also categorized into four groups using the quartiles of serum GGT and ALT levels, which were as follows: $<$16, 16 to $<$24, 24 to $<$41, and $\geq$41 U/L and $<$15, 15 to $<$20, 20 to $<$28, and $\geq$28 U/L for men; and $<$9, 9 to $<$13, 13 to $<$19 and $\geq$19 U/L and $<$12, 12 to $<$16, 16 to $<$21 and $\geq$21 U/L for women, respectively.

Criteria for DM incidence during the follow-up period

Participants were defined as having diabetes according to the guidelines of the Japanese Diabetes Society;[9] a fasting plasma glucose level $\geq$7.0 mmol/L, or a non-fasting plasma glucose level $\geq$11.1 mmol/L; and/or being newly diagnosed as having diabetes by a physician during the follow-up period (according to the self-reported questionnaire).

Statistical analysis

The distributions of age, BMI, GGT and ALT between men and women were compared by the Mann-Whitney *U* test. Frequencies of alcohol consumption, family history of diabetes, smoking habits and baseline glucose type between men and women were compared using the chi-square test. Hazard ratio (HR) was estimated by Cox regression analysis. The association between GGT and the incidence of DM in each sex were evaluated by five models: model 1, with adjustments for age, family history of DM, smoking habits and

baseline glucose type; models 2–4, with adjustments for the same variables in model 1 plus alcohol, BMI or ALT, respectively; and model 5, with adjustments for the same variables in model 1 plus alcohol consumption, BMI and ALT. Interactions between GGT levels and alcohol consumption, BMI or ALT on the incidence of DM were estimated for all potential confounding factors such as age, family history of diabetes mellitus, smoking habits, baseline glucose type, alcohol consumption, BMI and ALT. Results were considered significant when the two-tailed alpha value was <0.05. All data were analyzed using the SPSS version 17.0 software package (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of the subjects are shown in Table 1. Age, BMI, GGT and ALT were higher in men than in women. The proportions of drinkers, smokers and borderline types of DM were significantly higher in men than in women. Subjects were followed for 8.0 ± 2.8 years (7.4 ± 3.0 years for men and 8.2 ± 2.7 years for women). During the follow-up period, 2969 (1119 men and 1850 women) developed DM. Elevated serum GGT levels were associated with the increased incidence of DM in several models, as shown in Table 2. When HRs of model 1 without the adjustment for alcohol were compared with those of model 2 with the adjustment, the HRs of model 2 appeared to be slightly higher than those of model 1 in men; the HRs between models 1 and 2 were similar in women. When HRs were compared between models with and without adjustments for BMI (model 3 versus model 1) and ALT (model 4 versus model 1), HRs in models 3 and 4 appeared to be lower than those in model 1 in both sexes. Even though all potential confounding factors including alcohol, BMI and ALT were adjusted, elevated GGT levels increased the risk of the incidence of DM, as shown in model 5. HRs for the incidence of DM in relation to GGT quartiles among drinkers and non-drinkers are shown in Figure 1. HRs of the third and fourth GGT quartiles in women and the fourth GGT quartile in men were significantly higher than those of the first GGT quartile, although only in non-drinkers. A significant interaction between GGT and alcohol was shown in women (P value for interaction $= 0.035$), but not in men (P value for interaction $= 0.316$).

The associations between BMI and the risk of DM among each of the GGT quartiles are shown in Figure 2. In women, HRs of obesity (BMI $\geq 25.0\ kg/m^2$) for the incidence of DM were significantly higher than those of underweight subjects (BMI $< 18.5\ kg/m^2$) in the second to fourth GGT quartiles ($P = 0.011$, 0.001 and <0.001, respectively). However, obesity was not a significant risk factor for DM in the first quartile of GGT. A borderline significant interaction beween GGT and BMI was shown in women (P value for interaction $= 0.070$), but not in men (P value for interaction $= 0.978$). There was no significant interaction between ALT and GGT in both sexes.

Table 1 Baseline characteristics of the subjects

	Men (n = 8081)	Women (n = 28,792)	P value
Age†	65 (55–69)	55 (48–62)	<0.001‡
BMI†	23.3 (21.5–25.1)	22.3 (20.6–24.3)	<0.001‡
GGT†	24 (16–41)	13 (9–19)	<0.001‡
ALT†	20 (15–28)	16 (12–21)	<0.001‡
Alcohol consumption			
Non-drinkers	42.1%	93.6%	<0.001§
Drinkers	57.9%	6.4%	
Family history of diabetes			
Negative	87.1%	83.1%	<0.001§
Positive	12.9%	16.9%	
Smoking habits			
Non-smokers	63.4%	92.4%	<0.001§
Smokers of 1–20 cigarettes/day	27.6%	7.1%	
Smokers of >20 cigarettes/day	8.9%	0.5%	
Baseline glucose type			
Normal type	90.6%	94.9%	<0.001§
Borderline type	9.4%	5.1%	

BMI, body mass index; GGT, gamma-glutamyltransferase; ALT, alanine aminotransferase
†Data are median (25 percentile and 75 percentile)
‡Mann-Whitney *U* test
§Chi-square test

Discussion

This study showed that serum GGT levels were positively associated with the incidence of DM in the Japanese population. Similar results have been previously reported in prospective[1,3–6,8] and cross-sectional studies.[7] GGT is a well-known marker for liver damage and alcohol consumption[1–5] and its levels increase concomitantly with BMI.[1,3–5] HRs for the incidence of DM associated with GGT quartiles were found to decrease after adjustment with BMI categories or ALT quartiles, but not to decrease by adjustment with alcohol in both sexes. An increase in ALT usually indicates liver damage more specifically than for other enzymes such as aspartate aminotransferase (AST) and GGT.[2] Thus, we can assume that part of the positive significant association between serum GGT levels and the incidence of DM can be explained by BMI and liver damage, which were represented by serum ALT levels, but not by alcohol. Furthermore, we clarified that elevated serum GGT levels increased the incidence of DM in both sexes after adjustment for several confounding factors including alcohol, BMI and ALT. This result agrees with previous studies indicating that alcohol, obesity, or liver disease cannot completely explain the association of serum GGT levels with DM.[1,3,6] At present, although the mechanism remains largely unknown, the Coronary Artery Risk Development in Young Adults (CARDIA) studies suggested that oxidative stress might explain this association because serum GGT levels, even within the normal range, had a dose–response relationship with serum and/or dietary antioxidant vitamins and markers of oxidative stress such as F2-isoprostanes.[1,11,12] Furthermore, GGT has a positive association with nitrotyrosine, an oxidative stress marker, but not ALT or AST in healthy subjects.[13] Oxidative stress appears to be a key component of chronic inflammation.[14,15] Significant associations

Table 2 Hazard ratio of incidence of type 2 diabetes associated with GGT quartiles for several models in Japanese men and women

Men	First GGT quartile (<16 U/L)	Second GGT quartile (16 to <24 U/L)	Third GGT quartile (24 to <41 U/L)	Fourth GGT quartile (≥41 U/L)
Number of subjects	1958	1993	2066	2064
Number of incidents	205	212	308	394
Person-years (PY)	14,743	15,197	15,411	14,718
Incident per 1000 PY	13.9	14.0	20.0	26.8
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1	1.00 (reference)	1.00 (0.82–1.21)	1.37 (1.15–1.64)	1.83 (1.54–2.17)
Model 2	1.00 (reference)	1.02 (0.84–1.24)	1.43 (1.20–1.72)	1.95 (1.63–2.33)
Model 3	1.00 (reference)	0.98 (0.80–1.18)	1.30 (1.09–1.55)	1.69 (1.42–2.01)
Model 4	1.00 (reference)	0.95 (0.78–1.15)	1.19 (0.99–1.43)	1.43 (1.19–1.73)
Model 5	1.00 (reference)	0.95 (0.78–1.16)	1.12 (0.99–1.45)	1.47 (1.21–1.79)
Women	**First GGT quartile (<9 U/L)**	**Second GGT quartile (9 to <13 U/L)**	**Third GGT quartile (13 to <19 U/L)**	**Fourth GGT quartile (≥19 U/L)**
Number of subjects	5553	8341	7206	7692
Number of incidents	200	372	463	815
Person-years (PY)	45,778	69,241	59,018	61,020
Incident per 1000 PY	4.4	5.4	7.8	13.4
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1	1.00 (reference)	1.20 (1.01–1.43)	1.58 (1.34–1.87)	2.50 (2.14–2.92)
Model 2	1.00 (reference)	1.20 (1.01–1.43)	1.58 (1.34–1.86)	2.49 (2.13–2.91)
Model 3	1.00 (reference)	1.17 (0.99–1.39)	1.45 (1.23–1.72)	2.17 (1.85–2.54)
Model 4	1.00 (reference)	1.16 (0.97–1.37)	1.40 (1.18–1.67)	1.92 (1.62–2.27)
Model 5	1.00 (reference)	1.13 (0.95–1.35)	1.33 (1.12–1.57)	1.77 (1.49–2.09)

GGT, gamma-glutamyltransferase; HR, hazard ratio; BMI, body mass index; ALT, alanine aminotransferase
Model 1: adjusted for age, family history of diabetes, smoking habits and baseline glucose type
Model 2: adjusted for the same variables in model 1 + alcohol consumption
Model 3: adjusted for the same variables in model 1 + BMI
Model 4: adjusted for the same variables in model 1 + ALT
Model 5: adjusted for the same variables in model 1 + alcohol consumption + BMI + ALT

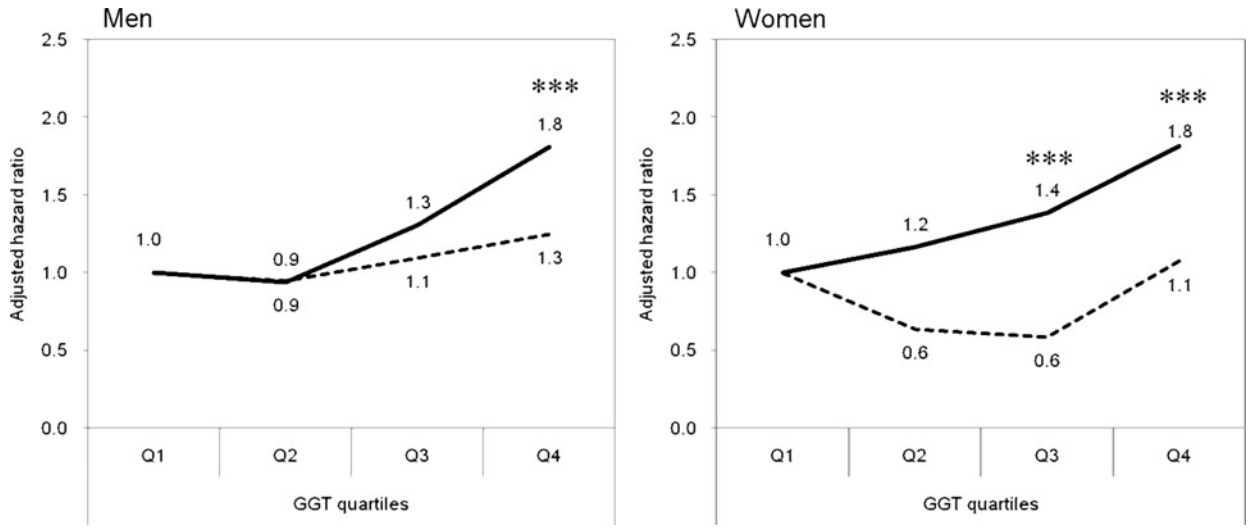

Figure 1 Relation between GGT quartiles and the risk of DM among drinkers and non-drinkers. HRs were calculated and adjusted for age, family history of diabetes, smoking habits, baseline glucose type, BMI and ALT. Q1, Q2, Q3 and Q4 express the first, second, third and fourth quartiles of GGT which were <16, 16 to <24, 24 to <41 and ≥41 U/L for men and <9, 9 to <13, 13 to <19 and ≥19 U/L for women, respectively. Drinkers and non-drinkers are expressed as dotted line and solid line, respectively. $^{***}P < 0.001$; compared with the first quartile of GGT using Cox regression analysis. Interaction between GGT and alcohol on the incidence of DM is significant in women (*P* value for interaction = 0.035), but not in men (*P* value for interaction = 0.316). GGT, gamma-glutamyltransferase; DM, type 2 diabetes; HR, hazard ratio; ALT, alanine aminotransferase

between serum GGT levels and inflammatory makers such as *C*-reactive protein have been reported.[1,16] From these data, we hypothesize that elevated GGT levels could be a risk marker for the development of DM through accelerated oxidative stress, which accompanies inflammation.

We also demonstrated a significant interaction between GGT levels and alcohol on the risk of DM in women. Analysis of the associations between GGT and the incidence of DM in each stratified group by alcohol showed that HRs of the third and fourth GGT quartiles were significantly higher than that of the first GGT quartile in non-drinkers, but not in drinkers, among women. Although the interaction between alcohol and GGT levels was not significant in men, a similar tendency was observed; the HR of the fourth GGT quartile was significantly higher than that of the first GGT quartile only in non-drinkers. We assume that this interaction did not reach a significant level in men because of their relatively smaller sample size than women. In general, GGT levels increase along with the amount of alcohol consumption.[1–4,13] Many studies have shown that moderate alcohol consumption reduced the risk of DM,[8,17,18] although a consistent result was not obtained regarding the effects of high alcohol consumption on DM.[17,18] In drinkers, because variation in GGT levels

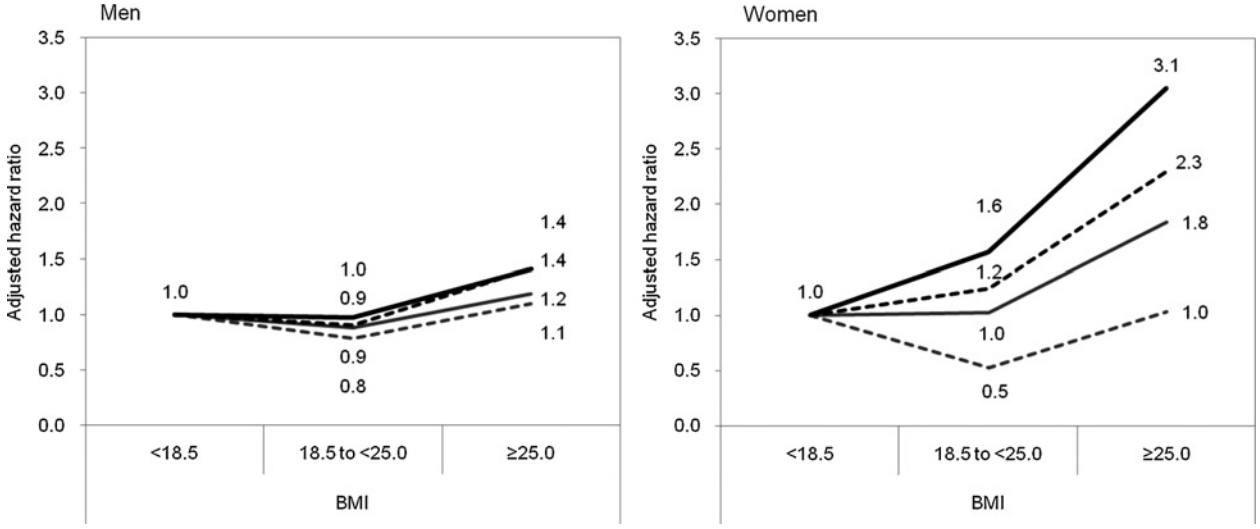

Figure 2 Relation between BMI and the risk of DM among GGT categories. HRs were calculated and adjusted for age, family history of diabetes, smoking habits, baseline glucose type, alcohol consumption and ALT. The first, second, third and fourth quartiles of GGT which were <16, 16 to <24, 24 to <41 and ≥41 U/L for men and <9, 9 to <13, 13 to <19 and ≥19 U/L for women are expressed as gray dotted line, gray solid line, black dotted line and black solid line, respectively. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; compared with underweight subject by using Cox regression analysis. Interaction between GGT and BMI on the incidence of DM is borderline significant in women (*P* value for interaction = 0.070), but not in men (*P* value for interaction = 0.978). BMI, body mass index; DM, type 2 diabetes; GGT, gamma-glutamyltransferase; HR, hazard ratio; ALT, alanine aminotransferase

among subjects was thought to reflect both oxidative stress and alcohol consumption, it is suggested that the effects of elevated GGT levels by oxidative stress on DM were obscured by the effects of moderate or high alcohol consumption on DM. Conversely, GGT levels may reflect oxidative stress more genuinely in non-drinkers.

In the current study, a borderline significant interaction between GGT levels and BMI on the incidence of DM was observed only in women. A cross-sectional study[7] and a prospective study[3] both indicated a significant interaction between GGT and BMI on the risk of DM. The authors of these studies suggested that obesity may not be a sufficient risk factor for DM because obese subjects with low-normal GGT levels would no longer be considered at high risk of DM and that the interaction between BMI and serum GGT levels may be clinically useful for detecting a high-risk subpopulation of DM.[7] Our results agreed with this suggestion for women. The CARDIA study groups described a possible interpretation of this interaction, in which obese individuals with high-normal GGT levels have already suffered subclinical pathological changes as a result of obesity, whereas obese individuals with low-normal GGT levels are at an earlier stage of pathogenesis.[1] Recently, Lee *et al.* suggested that the interaction between GGT and BMI on the risk of DM might be related to environmental pollutants such as persistent organic pollutants (POPs).[7,19] They showed a dose–response relationship between POPs and the prevalence of DM, a POPs dose-dependent increase of association between obesity and DM,[20] and a dose–response relationship between serum POPs and GGT.[19] We propose a possible explanation as follows. The levels of biomarkers of oxidative damage, in general, are known to be decreased by a high intake of fruit, and to be increased by smoking[21] and a high intake of iron, mainly supplied by red meat.[22] Furthermore, serum GGT levels reportedly decrease in association with a high intake of fruit and dietary constituents of vegetables such as vitamin C, beta-carotene and fiber, and increase with consumption of animal meat and iron[12] With a lifestyle for low oxidative damage, and thus with low levels of biomarkers, even obese individuals are considered to have a relatively low risk of developing DM. However, several prospective studies have failed to show a significant interaction between GGT and BMI on the incidence of DM.[4,5] As a borderline significant interaction between GGT and BMI was shown only in women, we considered that the inconsistent results could be due to a sex difference. Even though statistically significant relations between GGT and the incidence of DM were observed in both sexes, the association was weaker in men than in women. This sex difference might derive from the distribution difference of serum GGT, where the distribution was significantly higher in men than that in women, as shown in Table 1. In order to clarify the controversial interaction between BMI and GGT on the incidence of DM, further study is warranted.

In conclusion, elevated serum GGT levels were associated with a high risk of DM. Significant interactions between GGT and alcohol on the incidence of DM revealed that the association between GGT and the incidence of DM in non-drinkers was significantly stronger than that in drinkers. Furthermore, in women, obesity was not a risk factor for DM when they had low GGT levels.

Author contributions: The work was carried out in collaboration between all authors. MS, KU and AH defined the research theme. MS and AH designed methods. MS analyzed the data, MS, KU and AH interpreted the results and MS and AH co-wrote the paper. All authors have contributed to, seen and approved the manuscript.

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