

# Alcohol Consumption, Serum gamma-Glutamyltransferase Levels, and Coronary Risk Factors in a Middle-Aged Occupational Population

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**Abstract: Alcohol Consumption, Serum gamma-Glutamyltransferase Levels, and Coronary Risk Factors in a Middle-Aged Occupational Population: Yuichi YAMADA, et al. Department of Hygiene, Kanazawa Medical University**—The relationships between alcohol consumption, serum gamma-glutamyltransferase (GGT) levels, and the prevalence of major coronary risk factors were analyzed crosssectionally in 2,399 male and 1,402 female middle-aged workers, to clarify the effects of moderate alcohol consumption on the development of the metabolic syndrome. Male moderate drinkers, consuming less than 60 ml of alcohol per day, had a lower prevalence of upper body obesity and low serum HDL-cholesterolemia (LHDL) in comparison with nondrinkers, but not of hypertension, impaired glucose tolerance or hypertriglyceridemia (HTG). In women, alcohol consumption did not show any significant associations with the coronary risk factors. Men with an elevated serum GGT (EGGT) of 40 U/l or above had a significantly higher odds ratio for all the coronary risk factors as compared with those with normal GGT, even after adjusting for alcohol consumption, together with age, body mass index, cigarette consumption and physical activity. Women with an EGGT of 25 U/l or above had similar findings, although significance was found only in HTG. Nearly 80% and 55% of the appearance of EGGT in men and women were attributable to alcohol consumption, and 20% and 10% of the male and female moderate drinkers had EGGT. These results suggest that even moderate alcohol consumption will increase coronary risk factors characteristic of the metabolic syndrome in drinkers who have an increase in serum GGT. Further studies are required to confirm the causal association between

alcohol consumption, increase in serum GGT and development of the metabolic syndrome.  
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**Key words:** Alcohol consumption, Serum gamma-glutamyltransferase (GGT), Coronary risk factors, The metabolic syndrome, Occupational population

Prevention of the metabolic syndrome<sup>1–3</sup>), a complex of multiple coronary risk factors, such as hypertension (HT), impaired glucose tolerance (IGT) and dyslipidemia, should be targeted by health promotion activities for people living in modern society including occupational fields, where coronary heart disease is a leading cause of death and obesity, the most powerful promoter of the metabolic syndrome, is epidemic<sup>4</sup>).

Meanwhile, moderate alcohol consumption has been shown to protect against the development of coronary heart disease and death<sup>5–7</sup>), and it may even protect against the development of non-insulin dependent diabetes mellitus (NIDDM)<sup>8,9</sup>) although this is still disputed<sup>10</sup>). The protective effects of moderate alcohol consumption on coronary heart disease have been attributed to high serum HDL-cholesterol levels, suppressed coagulation capacity of platelets, or the suspected role of anti-oxidant substances contained in alcoholic beverages<sup>11, 12</sup>). More recently, beneficial effects on insulin resistance, the core pathology of the metabolic syndrome, have been proposed as another possible mechanism<sup>13</sup>), implying that improved insulin resistance in moderate alcohol consumers may suppress the development of the metabolic syndrome, and thus coronary heart disease, but there have also been contradictory studies suggesting increases in insulin resistance after alcohol consumption<sup>14–17</sup>). In addition, high serum gamma-glutamyltransferase (GGT), a well-known biological indicator of alcohol consumption<sup>18, 19</sup>), has been shown to be associated with the metabolic syndrome<sup>20–22</sup>). The aim of the present study is to clarify

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if moderate alcohol consumption protects against the development of the metabolic syndrome, and therefore the associations between alcohol consumption, serum GGT levels and major coronary risk factors characteristic of the metabolic syndrome were analyzed crosssectionally in a middle-aged occupational population.

### **Subjects and Methods**

The study subjects were recruited from 2,656 male and 1,460 female workers aged between 35 and 64 yr in an electronic-parts factory who participated in an annual health check-up and comprised 98.3% of the workers in this age range in the factory. 131 men and 24 women were excluded from consideration since they had diseases that might markedly affect the study results, such as myocardial diseases including signs of old infarction, liver disease mainly due to C-type chronic hepatitis or cirrhosis, renal disease or insufficiency due to glomerulonephritis or diabetes mellitus. In addition, 126 men and 34 women were excluded because of incompleteness of the measurements in the check-ups. Finally, 2,399 men and 1,402 women were selected as the study subjects, and written informed consent was obtained from all of them. Nearly half of the male subjects were engaged in shift and night work, and some hundreds of the subjects have handled toxic chemicals, mainly organic solvents, but no excessive exposure or harmful health effects of the shift work and the chemicals have been detected in the workplaces.

The subjects were measured in the morning after fasting 12 h or longer for height (m) and body weight (kg) in light clothes with the shoes removed, and the body mass index (BMI: kg/m<sup>2</sup>) was calculated. A BMI of 25 or above was defined here as obesity. At the same time, waist circumference (cm) was measured at the umbilicus level. The obese subjects with a waist circumference of 95 cm or more in men and 90 cm or more in women were defined as having upper body obesity (UBO)<sup>4)</sup>. Systolic and diastolic blood pressure (BP: mmHg) was measured with a sphygmomanometer in the sitting position after resting on a chair for five minutes or longer. When BP was higher than 140/90 mmHg in the first measurement, it was measured again 10 min later, and the lower value was recorded. The subjects with a BP of 140/90 mmHg or above in the health check-up, together with those under treatment with medicines for hypertension irrespective of the BP levels, were defined as having HYT.

A fasting serum sample was measured for the concentrations of triglycerides (TG: mg/dl) and HDL-cholesterol (HDLc: mg/dl) with an automatic analyzer (HITACH 7450, Hitachi, Japan), as well as hepatic enzymes activities including GGT (U/l) and other biochemical parameters. The serum glucose concentration (mg/dl) was measured by an HK-G6PD method with the automatic analyzer. The glycated

hemoglobin concentration (HbA1c: %) was determined using an automatic analyzer, HA8150, Arkray, Japan. The subjects with a fasting serum glucose level of 110 mg/dl or above, and those with an HbA1c of 5.7% or above, were defined as having IGT as well as 23 men and 6 women who were under treatment for NIDDM. The subjects who showed fasting serum TG of 150 mg/dl or above, and 25 men under treatment for high serum TG were defined as having hypertriglyceridemia (HTG), and men who had a serum HDLc below 38 mg/dl and women below 40 mg/dl were defined as having low HDL-cholesterolemia (LHDLc). The male subjects with a serum GGT of 40 U/l or above and females 25 U/l or above, representing the 95% upper limits of serum GGT observed in the male and female non-obese nondrinkers, were defined as having elevated serum GGT (EGGT).

The data on alcohol and cigarette consumption and physical activity at leisure time were obtained by a questionnaire and confirmed by experienced nurses at the health check-up. The average volume of alcohol consumed per day by the subjects was calculated from the data on usual alcohol consumption during the preceding year. The subjects who consumed alcohol less than once a month were classified as nondrinkers as were abstainers and teetotalers. The subjects who consumed alcohol more than once a month were classified into 4 groups according to the average volume of alcohol consumed per day: less than 30 ml, 30–59 ml, 60–89 ml, and 90 ml or more. Smoking habit was classified into 5 groups as nonsmokers, ex-smokers, current smokers consuming less than 1 pack a day, and those consuming more but less than 2 packs, and those consuming 2 packs or more. The subjects were classified into 4 groups of physical activity at leisure: those who performed any kind of exercise lasting 30 min or longer not more often than once a month, those who performed the exercise once a week or less, 2 to 4 times a week, and 5 times or more a week. All the subjects were scored 1–5 or 1–4 for alcohol and cigarette consumption and physical activity according to those groups. The alcohol consumers were further categorized into moderate drinkers consuming less than 60 ml of alcohol per day and excessive drinkers consuming more. The subjects who performed physical exercise only once a week or less were defined as physically inactive subjects.

The associations between alcohol consumption, serum GGT levels and the major components of the metabolic syndrome, such as UBO, HYT, IGT, HTG and LHDLc, in the male and female subjects were analyzed and tested with a  $\chi^2$ -test and a multiple logistic regression (MLR) analysis adjusting for confounders. All the statistical analyses were performed with an SPSS version 11.0 program package for Windows (SPSS Japan, Tokyo), with  $p < 0.05$  defined as significance,  $p < 0.01$  as high significance, and  $0.05 \leq p < 0.10$  as borderline significance.

**Table 1.** The number (n) and prevalence (%) of upper body obesity (UBO), hypertension (HYT), impaired glucose tolerance (IGT), hypertriglyceridemia (HTG) and low HDL-cholesterolemia (LHDL), and elevated serum GGT (EGGT) in 2,399 middle-aged men and 1,402 women divided by alcohol consumption categories according to the average volume of alcohol consumed per day

Coronary risk factor <sup>c</sup>	Men						Women					
	Nondrinker		Moderate <sup>a</sup>		Excessive <sup>a</sup>		Results of $\chi^2$ -test <sup>d</sup>	Nondrinker		Moderate <sup>b</sup>		Results of $\chi^2$ -test <sup>d</sup>
	n=599		n=1197		n=603			n=1253		n=149		
	n	(%)	n	(%)	n	(%)		n	(%)	n	(%)	
UBO	25	(4.2)	26	(2.2)	19	(3.2)	#	58	(4.6)	9	(6.0)	ns
HYT	82	(13.7)	186	(15.5)	145	(24.0)	**	131	(10.5)	16	(10.7)	ns
IGT	55	(9.2)	135	(11.3)	75	(12.4)	ns	58	(4.6)	10	(6.7)	ns
HTG	133	(22.2)	257	(21.5)	145	(24.0)	ns	82	(6.5)	7	(4.7)	ns
LHDL	79	(13.7)	84	(7.0)	25	(4.1)	**	114	(9.1)	11	(7.4)	ns
EGGT	45	(7.5)	228	(19.0)	256	(42.5)	**	60	(4.8)	14	(9.4)	*

a) For the definitions of the categories of alcohol consumption, refer to text. b) Including 4 women consuming 60 ml or more alcohol per day. c) For the definitions of the risk factors, refer to text. d) ns: not significant ( $p \geq 0.10$ ), #:  $p < 0.10$ , \*:  $p < 0.05$ , \*\*:  $p < 0.01$ .

## Results

Of the 2399 male subjects, 599 (25.0%) were nondrinkers, 536 (22.3%) consumed 29 ml of alcohol or less per day, 661 (27.6%) consumed 30–59 ml, 420 (17.5%) consumed 60–89 ml, and 183 (7.6%) consumed 90 ml or more, so that just half of the present male subjects were considered as moderate drinkers, and a quarter of them excessive drinkers. Of the 1,402 female subjects, drinkers were few, and only 126 (9.0%) of them consumed 29 ml of alcohol or less per day, and 23 (1.6%) consumed 30 ml or more. Those who consumed 60 ml or more of alcohol per day were 4 of the 23 women, and therefore the majority of the female drinkers were considered as moderate drinkers. The major coronary risk factors characteristic of the metabolic syndrome: UBO, HYT, IGT, HTG and LHDL in the male subjects were found in 70 (2.9%), 413 (17.2%), 265 (11.0%), 535 (22.3%) and 188 (7.8%), respectively. In the female subjects, the corresponding figures were 67 (4.8%), 147 (10.5%), 68 (4.9%), 89 (6.3%) and 125 (8.9%), respectively. The prevalence of the coronary risk factors was obtained in the male nondrinkers, moderate drinkers and excessive drinkers, and in the female nondrinkers and drinkers, and the differences were tested by a  $\chi^2$ -test. The results are summarized in Table 1, together with the prevalence of EGGT.

The prevalence of UBO was somewhat lower in the male moderate drinkers in comparison with nondrinkers and excessive drinkers, although the differences in the three categories remained at a borderline significant level ( $p=0.06$ ). The prevalence of HYT in men was increased with increases in alcohol consumption, and the differences

were highly significant. On the other hand, LHDL was lower in alcohol consumers than in non-consumers, and lower in heavier alcohol consumers. The differences in the three categories were highly significant. The prevalence of IGT and HTG in men was, however, not significantly different in the three categories of alcohol consumption, although both were slightly higher in the excessive drinkers. No significant association of alcohol consumption with the prevalence of the coronary risk factors was found in women, probably because of the low volume of alcohol consumed in the few drinkers.

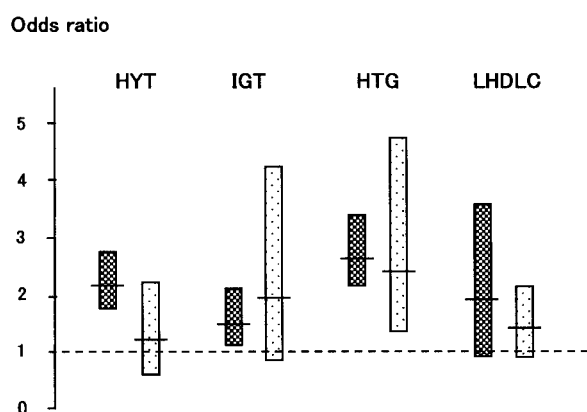
Although not shown in the table, when adjusting for age and the scores for cigarette consumption and physical activity at leisure by a multiple logistic regression analysis, the odds ratios in the male moderate drinkers and excessive drinkers for UBO as compared with nondrinkers were determined to be 0.54 and 0.78, respectively, and the low odds ratio in the moderate drinkers was significant ( $p=0.03$ ). Multiple logistic regression analyses adjusting for BMI, as well as age and the scores for cigarette consumption and physical activity, showed that the odds ratios in the moderate and excessive drinkers for HYT were 1.2 and 2.0, respectively, and those for LHDL were 0.53 and 0.25, respectively, as compared with nondrinkers. Those were all significant except for the odds ratio in moderate drinkers for HYT. No significant high or low odds ratios were found for IGT and HTG in the male moderate and excessive drinkers. None of the odds ratios for the coronary risk factors were significant in the female drinkers.

When the threshold was set at 40 U/l in men and 25 U/l in women, EGGT was found in 529 (22.1%) of the male subjects and 74 (5.3%) of the female subjects. As shown

**Table 2.** The results of multiple logistic regression analyses on possible contributors to the appearance of elevated serum GGT in 2,399 middle-aged men and 1,402 women

Contributor	Men			Women		
	Odds ratio	95% C.I. <sup>a</sup>	<i>p</i> <sup>b</sup>	Odds ratio	95% C.I. <sup>a</sup>	<i>p</i> <sup>b</sup>
Age (yr)	1.02	1.01–1.03	*	1.07	1.03–1.11	**
Alcohol consumption	4.92	3.55–6.83	**	2.30	1.21–4.36	*
Obesity	2.72	2.19–3.39	**	2.19	1.32–3.62	**
Current smoking	1.54	1.25–1.91	**	1.70	0.49–5.95	ns
Physical inactivity	1.41	1.02–1.95	*	0.73	0.33–1.59	ns

a) 95% confidence interval. b) ns: not significant ( $p \geq 0.10$ ), \*:  $p < 0.05$ , \*\*:  $p < 0.01$ .



**Fig. 1.** Odds ratios in middle-aged men and women with elevated serum GGT ( $\geq 40$  U/l for men and  $\geq 25$  U/l for women) for hypertension (HYT), impaired glucose tolerance (IGT), hypertriglyceridemia (HTG) and low HDL-cholesterolemia (LHDLC) as compared with those with normal GGT, adjusted for age, body mass index, alcohol and cigarette consumption, and physical activity at leisure. Bars and boxes represent odds ratios and the 95% confidence intervals, respectively. Dark boxes represent men and light boxes represent women.

in Table 1, the prevalence of EGGT was higher in both male and female drinkers than in nondrinkers, and higher in heavier alcohol consumers. The differences were significant in both men and women. Meanwhile, EGGT was found in less than half (42.5%) of the male excessive drinkers consuming 60 ml or more of alcohol per day, showing a considerable individual difference in the serum GGT elevations even after large volume alcohol consumption.

Table 2 shows the results of multiple logistic regression analyses on possible contributors to the appearance of EGGT in the male and female subjects. The possible contributors defined here were age, obesity ( $\text{BMI} \geq 25$ ),

alcohol and cigarette consumption, and physical inactivity at leisure time. In men, alcohol consumption was the strongest contributor. Drinkers had an odds ratio of 4.92 in comparison with nondrinkers, with the next strongest being obesity of 2.72. In addition, both current smoking and physical inactivity showed a small but significant contribution to the appearance of EGGT. In women, both alcohol consumption and obesity had strong effects on the appearance of EGGT, and the odds ratios were 2.30 and 2.19, respectively. Smoking and physical inactivity were, however, not significant in women. From these figures, the attributable risk percent of alcohol consumption to the appearance of EGGT was calculated as 79.7% in men and 56.5% in women.

Figure 1 illustrates the odds ratios and the 95% confidence intervals for the appearance of HYT, IGT, HTG and LHDLC in the male and female subjects showing EGGT as compared with those with normal serum GGT, after adjusting for age, BMI and the scores for alcohol and cigarette consumption and physical activity. In men, the subjects with EGGT had the odds ratios (the confidence intervals) of 2.14 (1.65–2.78), 1.43 (1.04–1.96), 2.70 (2.13–3.40) and 1.91 (0.99–3.67), respectively, in HYT, IGT, HTG and LHDLC. Except for a borderline significance in LHDLC ( $p=0.05$ ), all the odds ratios in the risk factors were significant. Women had similar findings, and the odds ratios (the confidence intervals) were 1.13 (0.58–2.19), 1.91 (0.87–4.18), 2.33 (1.18–4.62) and 1.44 (0.98–2.13), respectively, for HYT, IGT, HTG and LHDLC, although statistical significance was detected only for HTG and a borderline significance in LHDLC ( $p=0.07$ ).

It is not shown in the figure, but the odds ratios (the confidence intervals) for UBO in the male and female subjects with EGGT as compared with those with a normal GGT were calculated as 5.25 (3.11–8.85) and 1.63 (0.67–3.96), respectively, when adjustments were done for age, alcohol and cigarette consumption, and physical activity. The odds ratio in men was highly significant.

## Discussion

Upper body obesity (UBO) is a characteristic feature of the metabolic syndrome<sup>2)</sup>. The definitions of UBO adopted in the present study, i.e., men and women having a BMI of 25 or above and a waist circumference of 95 cm or more in men and 90 cm or more in women at the umbilicus level, are not established criteria<sup>4)</sup>. But, the criteria for UBO used in the U.S.<sup>23)</sup>, a waist circumference of 102 cm in men and 88 cm in women, were measured at the top of the iliac bone but not at the umbilicus level, and must be excessive particularly for Japanese men with smaller body height. On the other hand, the criteria proposed by the Japan Society for the Study of Obesity (JSSO)<sup>24)</sup>, 85 cm in men and 90 cm in women measured at the umbilicus level, the unusual lower setting in men than in women, were determined by a principle different from the U.S. criteria, i.e., the waist circumference corresponding to a visceral fat area of 100 cm<sup>2</sup> in the abdominal cavity measured by a CT technique. The validity of JSSO criteria thus remains to be evaluated in further studies with regard to the associations with coronary risk factors. The waist circumferences of 95 cm in men and 90 cm in women adopted here corresponded to the mean waist circumference in men and women having a BMI of 30<sup>4)</sup>, and thus imply a larger waist size relative to the BMI in most of the obese subjects in the present study. The prevalence of UBO was significantly lower in the male moderate drinkers than in the nondrinkers. This lower risk of UBO was not found in female drinkers, and the reasons for the gender difference remain unknown.

The associations of alcohol consumption and coronary risk factors found in the male subjects were in accordance with the previous findings<sup>11, 12)</sup>, i.e., increases in alcohol consumption were significantly related to increases in hypertension (HYT) whereas the prevalence of low HDL-cholesterolemia (LHDL) was decreased with an increase in alcohol consumption. The odds ratio for HYT in the male moderate drinkers relative to nondrinkers was estimated as 1.2 but was not significant, but that for LHDL was nearly half and highly significant. The odds ratios in the male moderate drinkers were not significant for impaired glucose tolerance (IGT) and hypertriglyceridemia (HTG). And the odds ratios for all the coronary risk factors in the female drinkers relative to nondrinkers were not significant. These results showed that moderate alcohol consumption, less than 60 ml/ of alcohol consumed per day, had neither a positive nor negative association with the appearance of coronary risk factors except for the low risk of LHDL. Moderate alcohol consumption may thus be beneficial for the suppression of the risks of UBO and LHDL, particularly in men, but not so for the other coronary risk factors of HYT, IGT and HTG, and therefore not so for the

development of the metabolic syndrome.

On the other hand, even after adjusting for alcohol consumption, together with age, BMI, cigarette consumption and physical activity, the odds ratios for HYP, IGT and HTG in the male subjects showing EGGT were significantly higher than in those with normal GGT. Even the high odds ratio for LHDL in men with EGGT was borderline significant. Women with EGGT had a significantly high odds ratio in HTG and a borderline significant one in LHDL, although the odds ratios for HYT and IGT were above 1.0 but not significant in the women. The odds ratio for UBO in men with EGGT was as high as 5.25 after adjusting for age, alcohol and cigarette consumption, and physical activity. These results strongly suggested an association between elevations of serum GGT and the appearance of coronary risk factors characteristic of the metabolic syndrome.

These results, as well as those obtained in previous studies in Japanese and Finnish populations<sup>20-22)</sup>, showed that the association between serum GGT and the coronary risk factors was independent of alcohol consumption. Nevertheless, it should be noted that nearly 80% and 55% of EGGT in the male and female subjects was attributable to alcohol consumption. Therefore, although a considerable individual difference exists in serum GGT elevations after alcohol consumption, and obesity is also a strong contributor to the elevations of serum GGT, and even smoking<sup>25)</sup> and physical inactivity<sup>26)</sup> contributes to it, alcohol consumption is undoubtedly the major cause of serum GGT increase<sup>27, 28)</sup> in this population, particularly in men. EGGT was found in nearly half of the male excessive drinkers consuming 60 ml/ or more of alcohol per day, but was found even in 20% of the male and 10% of the female moderate drinkers consuming less alcohol.

Summing up these study results, it can be said that moderate alcohol consumption is not beneficial for the suppression of the metabolic syndrome, but that it will increase the risk of the development of the metabolic syndrome in drinkers who show elevations of serum GGT, although considerable limitations exist in interpreting the study results. First, crosssectional observations cannot provide any evidence of causal associations. Second, the effects of possible alcohol moderation in the subjects who had been detected by physicians or nurses to have coronary risk factors were not evaluated in the present study, and which might have blurred the association between alcohol consumption and the prevalence of coronary risk factors. Third, the appearance of coronary risk factors but not that of the metabolic syndrome itself was analyzed in this study, because of some technical difficulties in confirming the definition of the metabolic syndrome in the present subjects. All those limitations require further studies on the association between alcohol consumption, serum GGT elevations and the development of metabolic syndrome, particularly in follow-up or

interventional designs.

Furthermore, details of the biological link between increase in serum GGT and the development of multiple coronary risk factors also remain unclear. High serum GGT was often found in both alcohol consumers and obese people, and thus it may reflect the progression of hepatic manifestation common in them, probably hepatic steatosis<sup>29,30</sup>. Hepatic steatosis has been suggested to play an important role in the development of insulin resistance<sup>31</sup>, and thus the metabolic syndrome related to upper body obesity<sup>32</sup>. Further studies are also required to clarify the biological link between elevations of serum GGT, the progression of hepatic steatosis, and increase in insulin resistance in alcohol consumers and obese people.

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