Table 2
Baseline characteristics according to alcohol drinking category—NIPPON DATA80 in 1980, men aged 30 years and older

	Never	Former	Non-daily	Daily
Normal				
No (total = 3,614)	716	182	980	1,736
Age (year)	52.1 ± 14.1	58.8 ± 14.8**	47.4 ± 12.6**	49.2 ± 12.1**
BMI (kg/m^2)	22.2 ± 3.1	22.1 ± 2.9	22.8 ± 2.9**	22.8 ± 2.6*
Current smoker (%)	56.4	51.1	59.7	69.2**
Hypertension (%)	41.8	53.3	41.5	53.7**
Serum glucose (mg/dL)	97.2 ± 16.6	96.3 ± 17.7	95.3 ± 16.6*	95.0 ± 15.5**
Serum TCH (mg/dL)	184.2 ± 32.9	184.7 ± 33.3	185.7 ± 31.6	185.4 ± 32.3
IGT + DM				
No (total = 404)	85	31	89	199
Age (year)	60.2 ± 13.3	57.4 ± 10.2	51.7 ± 12.3**	55.4 ± 12.3*
BMI (kg/m^2)	22.5 ± 4.0	23.2 ± 3.2	23.2 ± 2.9	22.5 ± 3.1
Current smoker (%)	58.8	64.5	57.3	70.9*
Hypertension (%)	57.7	61.3**	59.6	71.9*
Serum glucose (mg/dL)	161.4 ± 58.7	161.1 ± 57.8	167.2 ± 76.2	156.2 ± 64.9
Serum TCH (mg/dL)	192.5 ± 39.8	200.4 ± 39.4	191.8 ± 38.4	190.7 ± 32.9

BMI = body mass index; DM = diabetes mellitus; IGT = impaired glucose tolerance; TCH = total cholesterol concentration. *$P < .05$; **$P < .01$ never drinker vs. former, non-daily or daily drinker.

similar to that of normal participants (49.3% vs. 48.0%). Despite the fact that alcohol intake in diabetes is often discouraged in current clinical practice, people with glucose intolerance may not comply with these instructions.

Alcohol intake was shown to increase the risk of total strokes in Japanese because of an increase in the risk of hemorrhagic events (WHO, 1999). In Caucasians, however, it was associated with a reduction in the risk of total strokes (MacKay and Mensah, 2004). Furthermore, a study indicated an unfavorable effect of alcohol intake on the incidence of diabetes in Japanese (de Vegt et al., 2002). The other studies in Japanese and Caucasians, however, suggested that alcohol intake reduces the risk of developing type 2 diabetes (Nakamura et al., 2007; Okamura et al., 2003; Waki et al., 2005). Thus, a study of the effect of alcohol intake on cardiovascular mortality among Japanese with diabetes was highly warranted.

Although alcohol may be a surrogate for favorable socioeconomic or lifestyle factors associated with a reduction in coronary risk (Imhof et al., 2001), the anti-inflammatory action and effects of alcohol on lowering low-density lipoprotein cholesterol could contribute to the link between moderate intake and lower cardiovascular mortality (Hart et al., 1999; Imhof et al., 2001). Most of the apparent benefit of alcohol intake on the risk of myocardial infarction has been attributed to an increase in high-density lipoprotein cholesterol (HDL-C) concentrations (De Oliveira et al., 2000; Gaziano et al., 1993). This effect of alcohol may be even more important among diabetics, because low concentrations of HDL-C are a common feature of diabetes.

Strengths and limitations of the study

The strengths of our study include its prospective design and the follow-up of a randomly selected sample from the general population of Japan with a high response rate (73.5%). Because the study includes men with a broad range of ages, findings are likely to be generalizable to middle-aged and elderly Japanese men.

As in any long-term follow-up study, however, there are several weaknesses. First, problems in the self-reporting of drinking may potentially limit the value of the present study, because such a system may underestimate or overestimate true intake, especially in men who actually consume large amounts of alcohol (Bongers et al., 1999). However, it is possible to assume that heavy drinkers in the present population, whether or not under-reported, were scattered in both the non-daily and daily drinking groups. This may have reduced the apparent benefit in both of these groups. Furthermore, self-reporting has been shown to be useful (De Oliveira et al., 2000), and studies using such a system have provided important information (Choudhury et al., 1994; Hines et al., 2001). A second limitation is that we do not have data on the amount of alcohol consumed. Although the beneficial effects of alcohol on mortality were seen in the non-daily drinking category in the normal men, these effects were also seen in the non-daily, as well as in the daily, drinking category in the men with glucose intolerance. It is possible that the men with glucose intolerance might have limited the amount of alcohol intake, because a larger amount of alcohol intake is associated with an increase in cardiovascular disease mortality (Tsugane et al., 1999). A future study using another cohort's data is required. A third limitation is that we used mortality data as end points, which may lead to misclassification of the cause of death. However, it has been reported that the death-certificate diagnosis for stroke in Japan is quite accurate (Ron et al., 1994). It has also been reported that most cases of sudden cardiac death tend to be described on Japanese death certificates as "CHD," "heart failure," or "unknown cause" (Saito et al., 2000). Furthermore,

Table 3
The effect of alcohol intake on all-cause and cause-specific mortality in 3,614 normal men aged 30 years and older—NIPPON DATA80, 1980–99

	Never	Former	Non-daily	Daily
Number at risk (total = 3,614)	716	182	980	1,736
Person years	11,820	2,596	17,324	30,008
All-cause death (total = 821)	199	88	155	379
/1,000 person years	16.8	33.9	8.9	12.6
Age-adjusted HR	1	1.19 (0.93–1.53)	0.74 (0.60–0.91)	0.98 (0.82–1.16)
Model 1	1	1.20 (0.93–1.54)	0.75 (0.61–0.93)	0.97 (0.81–1.15)
CVD death (total = 264)	72	35	38	119
/1,000 person years	6.1	13.5	2.2	4.0
Age-adjusted HR	1	1.20 (0.80–1.80)	0.53 (0.36–0.79)	0.91 (0.68–1.23)
Model 1	1	1.19 (0.80–1.79)	0.53 (0.36–0.80)	0.90 (0.67–1.21)
Non-CVD death (total = 557)	127	53	117	260
/1,000 person years	10.7	20.4	6.8	8.7
Age-adjusted HR	1	1.18 (0.85–1.63)	0.85 (0.66–1.09)	1.02 (0.82–1.26)
Model 1	1	1.18 (0.86–1.64)	0.87 (0.68–1.12)	1.01 (0.82–1.25)
Cancer death (total = 285)	48	18	64	155
/1,000 person years	4.1	6.9	3.7	5.2
Age-adjusted HR	1	1.13 (0.66–1.95)	1.18 (0.81–1.72)	1.54 (1.11–2.14)
Model 1	1	1.14 (0.66–1.97)	1.21 (0.83–1.76)	1.51 (1.09–2.09)
Stroke death (total = 133)	32	14	20	67
/1,000 person years	2.7	5.4	1.2	2.2
Age-adjusted HR	1	1.05 (0.56–1.98)	0.63 (0.36–1.11)	1.17 (0.76–1.78)
Model 1	1	1.05 (0.56–1.98)	0.65 (0.37–1.13)	1.15 (0.75–1.76)
CerInf death (total = 82)	16	11	12	43
/1,000 person years	1.4	4.2	0.7	1.4
Age-adjusted HR	1	1.59 (0.74–3.43)	0.79 (0.37–1.67)	1.58 (0.89–2.83)
Model 1	1	1.59 (0.73–3.43)	0.80 (0.38–1.69)	1.58 (0.89–2.82)
CerHem death (total = 29)	7	1	3	18
/1,000 person years	0.59	0.39	0.17	0.6
Age-adjusted HR	1	0.34 (0.04–2.75)	0.45 (0.12–1.73)	1.45 (0.60–3.51)
Model 1	1	0.34 (0.04–2.74)	0.45 (0.12–1.76)	1.45 (0.06–3.51)
All-heart death (total = 118)	37	19	15	47
/1,000 person years	3.1	7.3	0.9	1.6
Age-adjusted HR	1	1.29 (0.74–2.25)	0.41 (0.22–0.74)	0.70 (0.45–1.07)
Model 1	1	1.29 (0.74–2.25)	0.41 (0.22–0.75)	0.69 (0.45–1.06)
Non-AMI heart (total = 71)	23	13	7	28
/1,000 person years	1.95	5.01	0.4	0.93
Age-adjusted HR	1	1.37 (0.69–2.72)	0.31 (0.13–0.72)	0.68 (0.39–1.19)
Model 1	1	1.37 (0.69–2.72)	0.31 (0.13–0.73)	0.69 (0.40–1.21)
AMI death (total = 47)	14	6	8	19
/1,000 person years	1.2	2.3	0.5	0.6
Age-adjusted HR	1	1.14 (0.44–2.99)	0.56 (0.23–1.33)	0.72 (0.36–1.44)
Model 1	1	1.14 (0.43–2.97)	0.57 (0.24–1.36)	0.69 (0.35–1.39)

CVD = cardiovascular disease; CerInf = cerebral infarction; CerHem = cerebral hemorrhage; AMI = acute myocardial infarction; HR = hazard ratio. Total person years of follow-up, death case number, mortality per 1,000 person years (/1,000 person years), HR, and 95% confidence intervals (95% CIs) are shown. Model 1 = multivariate-adjusted Cox analysis, adjusted for age, body mass index, and smoking (never and ex-, current smokers <20 cigarettes/day, current smokers 20–40 cigarettes/day, and current smokers ≥41 cigarettes/day).

mortality statistics for CHD may have been underestimated up to the end of 1994 using ICD9, because deaths from coronary events may have been miscoded as "heart failure" (Saito et al., 2000). However, the magnitude of the effects of alcohol intake on all-heart disease and acute myocardial infarction mortality in the present study were comparable in the normal men and men with glucose intolerance, suggesting that the findings in the current report are valid. In conclusion, non-daily to daily alcohol intake were associated with a reduction in cardiovascular and all-heart disease mortality in Japanese men with diabetes, as in men without diabetes.

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Table 4
The effect of alcohol intake on all-cause and cause-specific mortality in 404 men aged 30 years and older with glucose intolerance or diabetes mellitus—NIPPON DATA80, 1980–99

	Never	Former	Non-daily	Daily
Number at risk (total = 404)	85	31	89	199
Person years	1,211	498	1,481	3,140
All-cause death (total = 169)	47	16	22	84
/1,000 person years	38.8	32.1	14.9	26.8
Age-adjusted HR	1	0.91 (0.51–1.60)	0.68 (0.41–1.15)	0.97 (0.68–1.40)
Model 1	1	0.90 (0.51–1.58)	0.69 (0.41–1.17)	0.97 (0.67–1.39)
Model 2	1	1.22 (0.81–1.83)	0.55 (0.37–0.82)	0.93 (0.69–1.25)
CVD death (total = 64)	25	4	10	25
/1,000 person years	20.6	8.0	6.8	8.0
Age-adjusted HR	1	0.44 (0.15–1.27)	0.61 (0.29–1.30)	0.56 (0.32–0.99)
Model 1	1	0.43 (0.15–1.25)	0.62 (0.29–1.33)	0.56 (0.32–0.98)
Model 2	1	0.43 (0.15–1.24)	0.46 (0.21–1.02)	0.49 (0.28–0.86)
Non-CVD death (total = 105)	22	12	12	59
/1,000 person years	18.2	24.1	8.1	18.8
Age-adjusted HR	1	1.42 (0.70–2.88)	0.77 (0.38–1.58)	1.43 (0.87–2.35)
Model 1	1	1.41 (0.70–2.86)	0.78 (0.38–1.61)	1.42 (0.87–2.34)
Model 2	1	1.38 (0.68–2.80)	0.71 (0.34–1.46)	1.34 (0.81–2.21)
Cancer death (total = 52)	10	7	3	32
/1,000 person years	8.3	14.1	2	10.2
Age-adjusted HR	1	1.82 (0.69–4.81)	0.37 (0.10–1.37)	1.57 (0.77–3.23)
Model 1	1	1.83 (0.70–4.84)	0.37 (0.10–1.35)	1.58 (0.77–3.25)
Model 2	1	1.81 (0.69–4.77)	0.36 (0.10–1.35)	1.59 (0.77–3.28)
Stroke death (total = 22)	7	0	4	11
/1,000 person years	5.8	0.0	2.7	3.5
Age-adjusted HR	1	—	1.10 (0.31–3.95)	1.01 (0.38–2.66)
Model 1	1	—	1.22 (0.34–4.46)	1.02 (0.39–2.70)
Model 2	1	—	0.91 (0.23–3.54)	0.88 (0.33–2.35)
CerInf death (total = 13)	5	0	2	6
/1,000 person years	4.1	0	1.4	1.9
Age-adjusted HR	1	—	0.82 (0.15–4.57)	0.80 (0.24–2.72)
Model 1	1	—	1.05 (0.18–6.20)	0.85 (0.24–2.95)
Model 2	1	—	0.53 (0.07–3.91)	0.67 (0.19–2.37)
CerHem death (total = 8)	2	0	1	5
/1,000 person years	1.7	0	0.7	1.6
Age-adjusted HR	1	—	0.89 (0.08–10.3)	1.52 (0.29–8.02)
Model 1	1	—	0.85 (0.07–9.96)	1.51 (0.29–7.96)
Model 2	1	—	0.92 (0.08–11.05)	1.67 (0.31–9.18)
All-heart death (total = 39)	17	3	6	13
/1,000 person years	14.0	6.0	4.1	4.1
Age-adjusted HR	1	0.47 (0.14–1.61)	0.50 (0.19–1.29)	0.41 (0.20–0.85)
Model 1	1	0.47 (0.14–1.61)	0.50 (0.19–1.30)	0.41 (0.20–0.85)
Model 2	1	0.47 (0.14–1.61)	0.36 (0.13–0.99)	0.35 (0.17–0.74)
Non-AMI heart (total = 21)	9	2	4	6
/1,000 person years	7.4	4	2.7	1.9
Age-adjusted HR	1	0.72 (0.15–3.35)	0.90 (0.26–3.11)	0.44 (0.15–1.27)
Model 1	1	0.70 (0.15–3.27)	0.93 (0.27–3.22)	0.44 (0.15–1.26)
Model 2	1	0.70 (0.15–3.30)	0.70 (0.19–2.62)	0.39 (0.13–1.13)
AMI death (total = 18)	8	1	2	7
/1,000 person years	6.6	2.0	1.4	2.2
Age-adjusted HR	1	0.30 (0.04–2.41)	0.25 (0.05–1.22)	0.38 (0.14–1.07)
Model 1	1	0.31 (0.04–2.48)	0.25 (0.05–1.22)	0.39 (0.14–1.11)
Model 2	1	0.30 (0.04–2.44)	0.19 (0.04–0.95)	0.34 (0.12–0.96)

CVD = cardiovascular disease; CerInf = cerebral infarction; CerHem = cerebral hemorrhage; AMI = acute myocardial infarction; HR = hazard ratio. Total person years of follow-up, death case number, mortality per 1,000 person years (/1,000 person years), HR, and 95% confidence intervals (95% CI) are shown. Model 1 = multivariate-adjusted Cox analysis, adjusted for age, body mass index, and smoking (never and ex-, current smokers <20 cigarettes/day, current smokers 20–40 cigarettes/day, and current smokers ≥41 cigarettes/day); Model 2 = Model 1 + glucose, postprandial hours.

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Original Article

Relationship between 5-Year Decline in Instrumental Activity of Daily Living and Accumulation of Cardiovascular Risk Factors: NIPPON DATA90

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Aim: To clarify the relationship between the accumulation of cardiovascular risk factors and the 5-year decline in instrumental activity of daily living (IADL) among a cohort representative of the Japanese population aged 65 years and over.
Methods: An IADL survey was performed by public health centers throughout Japan. Study subjects were elderly men and women living in districts under the jurisdiction of collaborating health centers. Subjects were invited to participate in the IADL survey assessed by the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence twice in 1995 and in 2000; 1222 participants were eligible for the analysis. The relationship between the number of cardiovascular risk factors, such as hypertension, hypercholesterolemia, hypertriglycemia, low serum high-density lipoprotein cholesterol, diabetes, obesity and smoking, at baseline and the 5-year difference in IADL scores was examined by linear regression analysis and logistic regression analysis.
Results: Decrease in IADL scores was larger in those with cardiovascular risk factors than in those without. The multivariable odds ratio (OR) for decreased IADL after adding one CVD risk factor was 1.16 (95% confidence interval (CI), 1.04–1.29) after adjusting for age, sex, alcohol consumption and TMIG score at baseline. Among participants who were regarded as physically independent with respect to basic ADL in the baseline survey, the odds ratio was also similar and significant.
Conclusion: Preventive interventions directed against cardiovascular risk factors, especially against their accumulation, may contribute to maintaining IADL in the Japanese elderly.

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Key words; Accumulation of cardiovascular risk factors, Instrumental activity of daily living, Cohort study, General population

Objectives

It is very important to create a society in which the elderly can live a healthy and active life for as long as possible. To minimize disability in elderly people in Japan, where the numbers of those aged 65 and older are increasing each year, we need to clarify modifiable risk factors that predict the future decline in activity of daily living (ADL)[1, 2]. ADL is often used to evaluate the disabled elderly, for example, those requiring rehabilitation or nursing home admission; however, as ADL is not suitable for screening elderly residents who are not disabled but have a potential need for home health-care services[3], another indicator is needed to evaluate the ability to live independently in the community. Instrumental activity of daily living (IADL) has been used in this manner[4]; however, most previ-

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ous studies to clarify the determinants of IADL have been cross-sectional in design.

Cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes, are often clustered[5-7]. The presence of multiple risk factors, recently termed metabolic syndrome, has been reported to increase the risk of developing or dying from cardiovascular disease such as myocardial infarction and stroke[8, 9]. However, to our knowledge, few studies have examined the relationship between the accumulation of cardiovascular risk factors and a future decline in IADL in a community setting.

Accordingly, we attempted to followup a cohort thought to be representative of the Japanese population to evaluate the relationship between the 5-year decline in IADL and the accumulation of cardiovascular risk factors measured in the National Survey of Circulatory Disorders, 1990.

Methods

A cohort study of the participants in the 4th National Survey on Circulatory Disorders, Japan was performed in 1990, NIPPON DATA90 (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1990). The details of this cohort have been previously reported[1, 2, 5, 10-14]. A total of 8,384 community residents (3,504 men and 4,880 women, ≥30 years old) from 300 randomly selected districts participated in the survey and were followed until November 15, 2000. The overall population aged 30 years and older in all districts was 10,956, and the participation rate was 76.5%. Accordingly, these participants were thought to be representative of the Japanese population.

We performed a survey of basic ADL and IADL in 1995 (baseline) and 2000 of the elderly (≥65 years in 1995) members of this cohort. This survey was performed by the public health centers whose jurisdiction included cohort districts of NIPPON DATA90. Of 284 health centers, 245 collaborated with the present study; 1945 participants were living in districts under the jurisdiction of collaborating health centers in 1995, and 301 had died or moved to different districts by 2000. Accordingly, 1644 participants were included in the present study. Of these, 36 declined to participate, 89 could not be contacted, and 297 had missing information at 2000; therefore, 1222 subjects (492 men, 730 women) were eligible for analysis.

We used the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence, a widely used scale for measuring IADL with demonstrated reliability and validity[3, 15]. The first five questions (No. 1–5) inquire about instrumental independence, the subsequent four (No. 6–9) about intellectual activity, and the final four (No. 10–13) about social roles. The respondent selects either "yes" (one point) or "no" (zero points), for a maximum score of 13 points[3, 15]. Participants were also asked about five basic (physical) ADL items (Feeding, Dressing, Bathing, Toileting, and Transfer: walking indoors) and whether each of these could be accomplished without help, with partial help, or with full help. "Physical ADL decline" was defined as partial or full support needed to perform any of the five basic ADL items[1, 2].

We used home-visit interviews to assess subjects; if this was impractical, the questions were asked over the phone or the questionnaire was mailed.

Risk factors for cardiovascular disease were defined as the following seven items in 1990: hypertension (systolic blood pressure, SBP ≥140 mmHg and/or diastolic blood pressure, DBP ≥90 mmHg), diabetes (casual blood glucose ≥200 mg/dL and/or HbA1c ≥6.0), hypercholesterolemia (total cholesterol, TCH ≥240 mg/dL), low serum high-density lipoprotein (HDL) cholesterol (HDLC <40 mg/dL), high serum triglyceride (TG) (TG >150 mg/dL), obesity (BMI ≥25 kg/m^2), and current smoking.

We examined whether the difference in IADL scores differs depending on the presence or absence of each risk factor. A *t*-test or one-way analysis of variance was conducted for continuous variables and a chi-square test for proportions, and linear regression analysis to evaluate the relationship between the number of risk factors and the 5-year difference in IADL scores. The individual 5-year difference in IADL scores was calculated by subtracting the score in 1995 from that in 2000. We also performed logistic regression analysis to evaluate the relationship between the number of risk factors and IADL decline. In logistic regression analysis, we defined IADL decline as a 2-point decline in the TMIG score between 1995 and 2000, as a previous study reported that a difference of ±1 point in the TMIG score was within the error range[16]. In both regression analyses, we adjusted for age, sex and alcohol consumption as confounding factors (Model 1). Further adjustment of the TMIG score at baseline (in 1995) was also performed (Model 2). A p value of <0.05 was considered significant.

The Statistical Package for the Social Sciences (SPSS Japan Inc. version 14.0J, Tokyo, Japan) was used for analyses.

The present study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 12–18, 2000).

Table 1. Mean scores of instrumental activities of daily living (IADL) assessed by the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence

	N	1995		2000		Mean IADL	p value*
		Mean	SD	Mean	SD		
Men							
65-69	204	12.0	1.9	11.4	2.9	-0.412	
70-74	164	11.9	1.8	10.7	3.3	-1.134	
75-79	81	11.8	2.0	9.4	3.9	-2.222	<0.001
80-84	37	10.7	3.3	7.9	3.8	-2.568	
85+	6	7.6	2.6	3.2	1.9	-3.167	
Women							
65-69	290	12.2	1.6	11.6	2.2	-0.476	
70-74	208	11.9	2.0	10.8	3.1	-1.154	
75-79	142	11.2	2.2	9.4	3.6	-1.634	<0.001
80-84	69	9.8	3.0	6.8	3.8	-2.855	
85+	21	7.4	3.9	4.4	3.6	-3.143	

Maximum score is 13.
Mean IADL was calculated by substracting the score in 1995 from than in 2000.
*Comparison between age groups by chi-square test.

Results

The mean age of subjects in 1995 was 71.9 (standard deviation, SD=5.0) years for men and 72.8 (SD=5.7) years for women. The difference in IADL scores rated by the TMIG Index of Competence is shown by sex and age group in **Table 1**. Between the two surveys, mean IADL scores decreased significantly in the older age groups in both men and women. The absolute value of decrease in the IADL scores was also large in the older age groups in both men and women. In men aged 65 to 69, the decrease in the IADL score was 0.412 points, while in those aged 85 years and older, it was 3.167. In women aged 65 to 69, the decrease in IADL score was 0.476 points, while in those aged 85 and older it was 3.143.

Participants were classified into "risk status categories" according to the number of cardiovascular risk factors (obesity, hypertension, hypercholesterolemia, diabetes, low serum HDLC, high serum TG, and current smoking). **Table 2** shows the means and prevalence of each risk factor. There was no difference in mean age between the risk status categories. Hypertension was the most prevalent risk factor in all categories except for the 4+ risk factor category in women. In the 4+ risk factor category, obesity was observed in 63.4% of men and 80.0% of women. In this category, diabetes was also detected in 66.2% of men and 79.5% of women. The mean decreases in IADL scores according to the number of CVD risk factors (0, 1, 2, 3, 4) were -0.90, -1.03, -1.05, -1.67 and -1.25, respectively.

Table 3 shows the difference in IADL scores between 1995 and 2000, focusing on the presence/absence of cardiovascular risk factors. The decrease in IADL scores was larger in both men and women with any cardiovascular risk factors (with the exception of hypercholesterolemia and high serum TG) than in those without. In this comparison, however, no significant difference was observed other than for low serum HDLC in women.

Table 4 shows the relationship between the 5-year difference in IADL scores and the number of cardiovascular risk factors at the baseline survey. As the number of cardiovascular risk factors increased, IADL scores decreased significantly. Among subjects who were regarded as independent with respect to basic (physical) ADL in the first IADL survey in 1995, IADL scores also decreased significantly as the number of cardiovascular risk factors increased.

The multivariable odds ratio (OR) for decreased IADL after adding one CVD risk factors in model 1 was 1.15 (95% confidence interval (CI), 1.04-1.28). When we performed further adjustment for the TMIG score at baseline (Model 2), the odds ratio was almost the same (OR, 1.16; 95%CI, 1.04-1.29). Among participants who were regarded as physically independent with respect to basic ADL in the baseline survey, the odds ratio was also similar and significant.

Although the TMIG score indicated a broader

Table 2. Means and prevalences of baseline characteristics stratified by the number of risk factors at the baseline survey, NIPPON DATA90

	Number of risk factors					*p* value
	None	One	Two	Three	Four or more	
Men						
Number of participants (%)	48 (10.1)	134 (28.1)	144 (30.2)	86 (18.0)	65 (13.6)	
Age (years)	72.6±6.0	72.9±5.4	71.5±4.7	71.5±4.4	71.3±4.7	0.093
Body mass index >25 (%)	0.0	4.2	12.8	27.5	63.4	<0.001
Smoking habit						
Ex-smoker (%)	60.4	53.7	20.8	25.6	26.2	<0.001
Current smoker (%)	0.0	23.1	66.0	58.1	64.6	
Drinking habit						
Ex-drinker (%)	10.4	7.5	8.3	10.5	16.9	0.285
Daily drinker (%)	45.8	56.7	56.9	44.2	46.2	
Hypertension (%)	0.0	56.0	75.7	72.1	89.2	<0.001
Hypercholesterolemia (%)	0.0	2.2	6.3	17.4	43.1	<0.001
Low HDL (%)	0.0	6.0	18.1	47.7	75.4	<0.001
High TG (%)	0.0	7.5	16.0	69.8	83.1	<0.001
Diabetes (%)	0.0	4.5	13.2	27.9	66.2	<0.001
Women						
Number of participants (%)	80 (11.9)	207 (30.7)	193 (28.6)	121 (18.0)	73 (10.8)	
Age (yr)	72.0±5.7	72.3±5.6	72.7±5.6	73.2±5.8	73.2±5.1	0.465
Body mass index >25 (%)	0.0	10.7	31.1	49.2	80.0	<0.001
Smoking habit						
Ex-smoker (%)	2.5	1.4	1.6	4.1	2.7	<0.001
Current smoker (%)	0.0	3.4	4.7	8.3	21.9	
Drinking habit						
Ex-drinker (%)	0.0	0.0	0.0	0.8	4.1	0.008
Daily drinker (%)	5.0	1.9	4.1	3.3	4.1	
Hypertension (%)	0.0	59.9	76.7	83.5	91.8	<0.001
Hypercholesterolemia (%)	0.0	10.6	32.1	44.6	49.3	<0.001
Low HDL (%)	0.0	5.8	12.4	38.0	60.3	<0.001
High TG (%)	0.0	8.2	38.3	66.9	94.5	<0.001
Diabetes (%)	0.0	11.1	31.6	47.9	79.5	<0.001

HDL, high density lipoprotein. TG, triglyceride.
The number of risk factors was the sum of the following seven items: hypertension, diabetes, hypercholesterolemia, low serum HDL cholestrol, high serum TG, obesity, and current smoking.

range of activity in daily life for the elderly than the narrowly defined IADL, the above results were substantially similar when we only used the subscale of IADL in the TMIG score.

Discussion

The present study found a significant inverse relationship between the number of cardiovascular risk factors and the decrease in IADL scores during a 5-year period in this representative sample of elderly Japanese people. Even though the effect of each individual risk factor did not reach statistical significance, the accumulation of cardiovascular risks resulted in a significant decrease in IADL scores. These results suggest that appropriate management of the cardiovascular risk factors might prevent a decline in IADL in elderly residents.

Okamura *et al.* reported that elderly residents with systolic hypertension (≥160 mmHg) in two communities located in Akita and Kochi Prefectures showed a 3.41 times higher odds ratio for having low IADL scores than those with normal blood pressure[17]; however, they surveyed the TMIG Index of Compe-

Table 3. Decrease in IADL scores from 1995 to 2000 by the presence/absence of risk factors, NIPPON DATA90

Age (years)	Men 71.9 (±5.0)			Women 72.8 (±5.7)		
	N	mean ΔIADL	*p* value	N	mean ΔIADL	*p* value
BMI						
BMI <25	400	−1.11	0.545	513	−1.11	0.211
BMI ≥25	92	−1.32		217	−1.40	
Smoking						
Non-smoker	92	−0.87		664	−1.16	
Ex-smoker	173	−1.43	0.268	19	−2.47	0.142
Current smoker	227	−1.04		47	−1.26	
Hypertension						
SBP <140 and DBP <90	180	−1.09	0.768	258	−1.11	0.544
SBP ≥140 or DBP ≥90	312	−1.18		472	−1.24	
Hypercholesterolemia						
TCH <240	422	−1.17	0.890	500	−1.14	0.804
TCH ≥240	55	−1.11		174	−1.21	
HDL						
HDL ≥40	353	−1.10	0.483	548	−1.03	0.016
HDL <40	124	−1.32		126	−1.71	
TG						
TG <150	330	−1.24	0.410	433	−1.09	0.396
TG ≥150	147	−0.99		241	−1.29	
Diabetes						
Glucose <200 and HbA1c <6.0	443	−1.11	0.178	633	−1.12	0.209
Glucose ≧200 or HbA1c ≧6.0	34	−1.82		41	−1.71	

IADL, instrumental activities of daily living.
HDL, high density lipoprotein. TG, triglyceride.

tence only at the end of follow-up. In the Framingham Disability Study, Pinsky *et al.* reported that hypertension, obesity, and diabetes adversely affected ADL in women after 27 years, while only hypertension adversely affected ADL in men[18]; however, IADL was not evaluated in that study. We reported the impact of serum albumin and total cholesterol (TC) on ADL in NIPPON DATA80[19]. Serum albumin was inversely associated with a composite outcome of death or impaired ADL in the group below the median of TC in both sexes; however, in that study, IADL was not evaluated and ADL was assessed only at the end of follow-up.

The above-mentioned previous studies focused only on the relationship between the respective risk factors and ADL or IADL. As previously reported, individual risk factors, such as hypertension, dyslipidemia, and diabetes, are associated with the development of cardiovascular disease; however, even though each of these cardiovascular risk factors may elevate the risk only slightly, the risk becomes more powerful when they are combined[20, 21]. Metabolic syndrome is a cluster of risk factors comprising insulin resistance, increased abdominal fat, dyslipidemia, and hypertension[22]. To our knowledge, the present study is the first to show the relationship between the accumulation of cardiovascular risk factors and IADL in community-dwelling elderly using a cohort design.

The present study suggests that the presence of multiple risk factors might contribute to the decline in IADL in the future. Cerebral infarction associated with impaired cognition without a clinical symptom is common, even in older men and women[23]. Bokura *et al.* suggested that the clustering of metabolic risk factors tended to increase the prevalence of silent cerebral ischemic lesions in 1,151 healthy Japanese subjects[24]. Furthermore, Elias *et al.* indicated that the risk factor profile for stroke was associated with low cognitive performance in a cross-sectional analysis of the Framingham Offspring Study[25]. These findings were consistent with those of the present study.

There are several limitations to our study. First,

Table 4. Relationship between the 5-year decline in scores of instrumental activity of daily living (IADL) and the number of cardiovascular risk factors

Five- year decrease in IADL scores assessed by the TMIG Index of Competence			
Baseline risk factors	Regression coefficient (β)	95%CI	p
Total participants (n=1,222)			
Model 1	−0.149	(−0.278, −0.020)	0.029
Model 2	−0.161	(−0.285, −0.036)	0.011
Participants without physical ADL decline at baseline (n=1,155)			
Model 1	−0.146	(−0.277, −0.015)	0.028
Model 2	−0.171	(−0.297, −0.046)	0.008
Odds ratio for IADL decline* during 5-year period			
	Odds Ratio	95%CI	p
Total participants (n=1,222)			
Model 1	1.15	(1.04, 1.28)	<0.001
Model 2	1.16	(1.04, 1.29)	0.008
Participants without physical ADL decline at baseline (n=1,155)			
Model 1	1.15	(1.03, 1.28)	0.015
Model 2	1.15	(1.03, 1.29)	0.013

*The number of risk factors was the sum of the following seven items: hypertension, diabetes, hypercholesterolemia, low serum HDL cholestrol, high serum TG, obesity, and current smoking.
Model 1, include age, sex, number of risk factors, daily alcohol consumption, ex-drinker and ex-smoker;
Model 2, model 1+TMIG at baseline (1995).
Sex was defined as Male=0 and Female=1.
Daily drinking means drinking at least 1 drink per day.
Ex-drinker means having discontinued alcohol consumption.
Ex-smoker means having discontinued smoking.

the risk factors selected were examined not in the initial IADL survey but in the survey conducted 5 years earlier. However, the accuracy of cardiovascular risk factor definition was assured because risk factors were based on medical examinations rather than on respondents' self-reports. Moreover, participants with severe disease at the time of the risk factor survey might have found it difficult to attend the first IADL survey, which was held 5 years later. This might have allowed us to avoid "reverse-causality"; in other words, participants with subclinical severe disease that was not detected by the risk factor survey were less likely to be included in the first IADL survey.

As previously reported, NIPPON DATA90 was a cohort study of a representative sample of Japanese, as participants of this cohort were randomly selected from the Japanese population; however, in the present study, as subgroup analysis of elderly participants of NIPPON DATA90, participants were limited to those living in districts under the jurisdiction of collaborating health centers, although we believe that there was no systematic bias in the regions whese public health centers did not collaborated with the present study. Non-surveyed districts were distributed uniforml throughout Japan. Furthermore, there was no difference in substantial health status between surveyed and non-surveyed districts due to the incorporation of health centers. For example, there was not significant difference in all-cause mortality between two districts during follow-up periods. Second, because the IADL survey was conducted only every 5 years, we could not pinpoint exactly when and why IADL declined during the 5-year period.

In conclusion, we found a significant relationship between the number of cardiovascular risk factors and the decrease in IADL scores among this cohort, which is thought to be representative of the Japanese population. Interventions aimed at preventing cardiovascular risk factors, especially the accumulation of such risk factors, may therefore be effective to prevent a future decline in IADL for the Japanese elderly, allowing them to live a healthy and active life.

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Appendix 1. NIPPON DATA90 Research groups

NIPPON DATA90	"National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged"
Chairman	Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga)
Consultant	Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido), Teruo Omae (Health C&C Center, Hisayama, Kasuya, Fukuoka), Kazuo Ueda (Murakami Memorial Hospital, Nakatsu, Oita), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya, Saitama), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi)
Research Members	Akira Okayama (The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Chiyoda-ku, Tokyo), Kazunori Kodama, Fumiyoshi Kasagi (Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Hiroshima), Tomonori Okamura (Department of Preventive Cardiology, National Cardiovascular Center, Suita, Osaka), Yoshikuni Kita (Department of Heath Science, Shiga University of Medical Science, Otsu, Shiga), Takehito Hayakawa (Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Fukushima), Shinichi Tanihara (Department of Hygiene and Preventive, Fukuoka university, Fukuoka, Fukuoka), Shigeyuki Saito (Second Department of Internal Medicine School of Medicine, Sapporo Medical University, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University School of Medicine, Morioka, Iwate), Yoshikazu Nakamura (Department of Health Science Division of Epidemiology and Community Health, Jichi Medical School, Minami Kawachi, Tochigi), Fumihiko Kakuno (Higashi-Oumi Public Health Center, Higashi-Oumi, Shiga),
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Appendix 2. Questions on the multidimensional 13-item index of competence

(1) Can you use public transportation (bus or train) by yourself?	Yes / No
(2) Are you able to shop for daily necessities?	Yes / No
(3) Are you able to prepare meals by yourself?	Yes / No
(4) Are you able to pay bills?	Yes / No
(5) Can you handle your own banking?	Yes / No
(6) Are you able to fill out forms for your pension?	Yes / No
(7) Do you read newspapers?	Yes / No
(8) Do you read books or magazines?	Yes / No
(9) Are you interested in news stories or programs dealing with health?	Yes / No
(10) Do you visit the homes of friends?	Yes / No
(11) Are you sometimes called on for advice?	Yes / No
(12) Are you able to visit sick friends?	Yes / No
(13) Do you sometimes initiate conversations with young people?	Yes / No

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Title:

Gamma-Glutamyltransferase and Mortality Risk from Heart Disease and Stroke in Japanese Men and Women: NIPPON DATA 90

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ABSTRACT

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.

Methods: From 1990 to 2005, we followed 7,488 adults (3,089 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.

Keywords: γ-glutamyltransferase; heart disease; stroke; mortality; Asia

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 potential 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 8,383 community residents (3,504 men and 4,879 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 8,383 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 7,488 individuals

for analysis (3,089 men, 4,399 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 (ICD-9) was used for deaths occurring up to the end of 1994, and the 10th International Classification for Disease (ICD-10) 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 to 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 minute-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* (180mL) of *sake* contains 23 gram of alcohol) of consumption for those who responded as "current". Based on these questions, we used 3 categories (never, past, current) in main analysis, and 6 categories (never, past, current <23g of alcohol/day, current 23g to <46g/day, current 46g to <69g/day, and current ≥69g/day) in sensitive 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≥200mg/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 were 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 the absolute sense 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 were shown in **Table 2** for women and in **Table 3** for men.

In women, crude mortality rates (per 1,000 person-years) were similar between HD and total stroke; 1.34, and 1.13 respectively (Table2). 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 1,000 person-years) were 2.00 for HD, and 1.59 for stroke, respectively (Table3). 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 were 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.

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=4,064), and 41 and 24 in men (n=1,074), 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, Fraiser 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