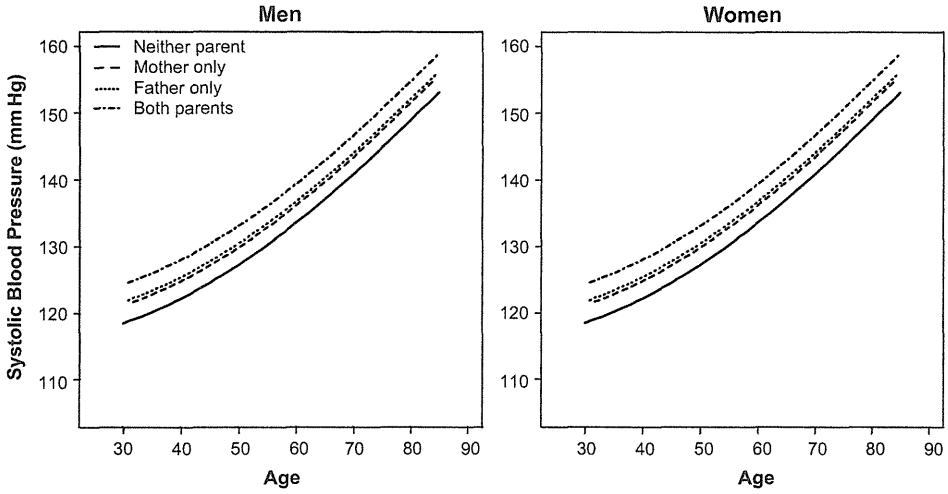

Figure 3. Longitudinal systolic blood pressure changes in subjects with or without maternal and paternal hypertension. Prediction is shown for subjects with body mass index of 22, no drinking or smoking habit, and birth-year category of 1941–1960. Neither parent indicates no parental history of hypertension on both maternal and paternal sides; Mother only, only maternal history of hypertension; Father only, only paternal history of hypertension; Both parents, both maternal and paternal histories of hypertension.

levels independent of age and body mass index (Figures 2), whereas its impact on either low-density lipoprotein cholesterol or high-density lipoprotein cholesterol was not detected. Similar results were obtained when the analysis was conducted by use of data under no medication for dyslipidemia or hyperglycemia (Table S8). The pattern of these changes in metabolic profiles together with modest elevation of BP in subjects with parental hypertension is similar to that in subjects with metabolic syndrome.[19–21] In fact, earlier studies have shown that family history of hypertension is associated with reduction in insulin sensitivity,[22] increased sympathetic activity,[23] and elevation of C-reactive protein level.[24] Furthermore, we observed previously that plasma level of adiponectin, a biomarker correlating with insulin sensitivity, was lower in young men with a parental history of hypertension.[25] These findings support the notion that reduction in insulin sensitivity underlies the effects of parental history of hypertension on metabolic profiles.

We found that parental hypertension induced an upward shift of FBS and TG levels from the third decade to the eighth decade of life. In other words, the effects of parental hypertension on the 3 risk factors do not decay during adult life. Furthermore, increases in BP, FBS, and TG levels by parental hypertension are not trivial. Increase in SBP by 5.3 mm Hg in men with parental hypertension (Figure 1) corresponds with a significant increase in fatal stroke and coronary artery disease.[26] Elevations in FBS and TG levels associated with positive parental history of hypertension were relatively small (eg, ≈0.30 and ≈0.09 mmol/L, respectively, in men), but they also potentially contribute to an increase in cardiovascular events.[27,28] Nevertheless, the present results suggest that parental hypertension should

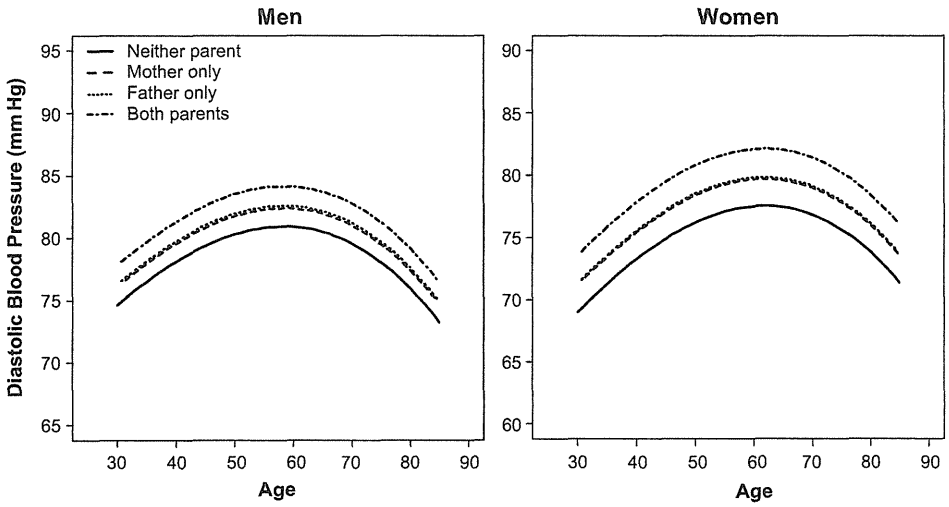

Figure 4. Longitudinal diastolic blood pressure changes in subjects with or without maternal and paternal hypertension. Prediction is shown for subjects with body mass index of 22, no drinking or smoking habit, and birth-year category of 1941–1960. Neither parent indicates no parental history of hypertension on both maternal and paternal sides; Mother only, only maternal history of hypertension; Father only, only paternal history of hypertension; Both parents, both maternal and paternal histories of hypertension.

be recognized as a risk factor upstream of BP, FBS, and TG regardless of age.

There are limitations in the present study. First, presence of parental hypertension relied on self-reports by subjects and was not confirmed by medical documents of their parents. However, awareness of hypertension and its health problems is high in both Tanno and Sobetsu, and accuracy of the information regarding parental hypertension is unlikely to be lower than that in earlier studies[3,7,11] that also used self-reported information. Second, group division into PH^+ and PH^- groups was performed in each study subject at the time of recruitment to the present study, and thus influence of the age of parents on the incidence of parental hypertension was not taken into account in this study. In addition, definition of hypertension by the Japanese Society of Hypertension was revised during the study period (ie, in 2000) from SBP>160 mm Hg and DBP>95 mm Hg to SBP>140 mm Hg and DBP>90 mm Hg. However, 93.7% of the men and 93.9% of the women were recruited during the period from 1977 to 1999 in the present study, and birth-year category (born in 1941–1960) did not significantly interact with parental hypertension in modeling SBP, DBP, FBS, or TG (Tables S2 through S5). Thus, the effect of the inconsistency in criteria of parental hypertension, if any, is unlikely to have misled the conclusion. Finally, we cannot totally rule out the possibility that exclusion of subjects with unknown parental history of hypertension from the analysis resulted in some bias. As shown in Table S1, age, percentage of men, SBP, and TG were slightly higher in the excluded group than in the group used for analysis of the effects of parental hypertension. However, selection bias, if any, would have induced underestimation rather than overestimation of the impact of parental hypertension on SBP.

Perspectives

The present study showed that parental hypertension is associated with significant elevation of background levels of BP, FBS, and TG without effects on the age-dependent changes of these parameters during the third to eighth decades of life. The early onset and no decay appear to be important features of the effects of parental hypertension in both men and women in terms of pathogenesis research and designing therapy. Although insulin resistance is one of the plausible mechanisms, it remains unclear which genetic and environmental factors are responsible for the effects of parental hypertension. It is also unclear whether any therapy can specifically eliminate the effects of parental hypertension on BP, FBS, or TG. These issues may warrant further investigations.

Sources of Funding

This study was supported by research grants from Scientific Research (H19-cardiovascular-common-021 and H20-cardiovascular-common -013) from the Japanese Ministry of Health, Labor, and Welfare.

Disclosures

None.

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Novelty and Significance

What Is New?

- We first examined the effects of parental hypertension on time courses of both blood pressure and metabolic risk factors during the third to eighth decades of life in both men and women.

What Is Relevant?

- Parental hypertension is associated with significant elevation of background levels of BP, FBS, and TG without effects on the age-dependent changes of these parameters during the third to eighth decades of life.

Summary

Parental hypertension has an age-independent impact on elevation of BP, FBS, and TG levels in both men and women, which may underlie the reported increase in cardiovascular events by family history of hypertension.

BMJ open accessible medical research

Impact of obesity, overweight and underweight on life expectancy and lifetime medical expenditures: the Ohsaki Cohort Study

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To cite: Nagai M, Kuriyama S, Kakizaki M, *et al*. Impact of obesity, overweight and underweight on life expectancy and lifetime medical expenditures: the Ohsaki Cohort Study. *BMJ Open* 2012;**2**:e000940. doi:10.1136/bmjopen-2012-000940

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-000940).

Received 25 January 2012
Accepted 12 April 2012

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ABSTRACT

Objectives: People who are obese have higher demands for medical care than those of the normal weight people. However, in view of their shorter life expectancy, it is unclear whether obese people have higher lifetime medical expenditure. We examined the association between body mass index, life expectancy and lifetime medical expenditure.

Design: Prospective cohort study using individual data from the Ohsaki Cohort Study.

Setting: Miyagi Prefecture, northeastern Japan.

Participants: The 41 965 participants aged 40–79 years.

Primary and secondary outcome measures: The life expectancy and lifetime medical expenditure aged from 40 years.

Results: In spite of their shorter life expectancy, obese participants might require higher medical expenditure than normal weight participants. In men aged 40 years, multiadjusted life expectancy for those who were obese participants was 41.4 years (95% CI 38.28 to 44.70), which was 1.7 years non-significantly shorter than that for normal weight participants (p=0.3184). Multiadjusted lifetime medical expenditure for obese participants was £112 858.9 (94 954.1–131 840.9), being 14.7% non-significantly higher than that for normal weight participants (p=0.1141). In women aged 40 years, multiadjusted life expectancy for those who were obese participants was 49.2 years (46.14–52.59), which was 3.1 years non-significantly shorter than for normal weight participants (p=0.0724), and multiadjusted lifetime medical expenditure was £137 765.9 (123 672.9–152 970.2), being 21.6% significantly higher (p=0.0005).

Conclusions: According to the point estimate, lifetime medical expenditure might appear to be higher for obese participants, despite their short life expectancy. With weight control, more people would enjoy their longevity with lower demands for medical care.

ARTICLE SUMMARY

Article focus

- Obese people have higher needs and demands for medical care.
- Obesity is associated with an increased risk of mortality.
- In view of the decreased life expectancy in obese participants, it is unclear whether lifetime medical expenditure increases or decreases as a result.

Key messages

- In spite of their short life expectancy, obese men and women had approximately 14.7% and 21.6% higher lifetime medical expenditure in comparison with normal weight participants, respectively.
- With better weight control, more people would enjoy their longevity with lower needs and demands for medical care.

Strengths and limitations of this study

- This is the first study to have investigated the association between body mass index, life expectancy and lifetime medical expenditure calculated from individual medical expenditure and mortality data over a long period in a general population.
- There was a limit to the accurate estimation of life expectancy and lifetime medical expenditure for obese participants because the Japanese population has a low prevalence of body mass index≥30.0 kg/m^2.

INTRODUCTION

Obesity is closely associated with an increased risk of cardiovascular disease, cancer, hypertension, diabetes mellitus and other medical problems. Previous studies have reported that obese and overweight people have higher needs and demands for medical care than normal weight people.[1–5] However, it is unclear whether obese people have higher lifetime medical expenditure than those of the normal weight people because the former have a comparatively shorter life

expectancy.[6–10] Additionally, underweight people have a higher risk of mortality and thus also tend to have higher medical expenditure per month or per person, based on a 10-year follow-up.[1 4]

Although four previous studies have examined the association between obesity and lifetime medical expenditure,[10–13] the results were inconsistent. One study showed that obese people had lower lifetime medical expenditure than those of the normal weight people,[11] whereas the others indicated that obese people had higher lifetime medical expenditure.[10 12 13] In addition, two of the four studies estimated lifetime medical expenditure from excess risk of cause-specific mortality and mean medical expenditure for the index disease.[10 11] Only the other two studies calculated lifetime medical expenditure on the basis of individual medical expenditure and mortality.[12 13] However, one of those studies followed up the participants for only 2 years[12] and the other calculated lifetime medical expenditure for elderly participants aged 70 years or over.[13] Therefore, the association between body mass index (BMI) and lifetime medical expenditure remains to be fully clarified.

We therefore conducted a 13-year prospective observation of 41 965 Japanese adults aged 40–79 years living in the community, which accrued 392 860 person-years. We examined the association between BMI and lifetime medical expenditure, based on individual medical expenditure and life table analysis.[1 14–17] We collected data for survival and all medical care utilisation and costs, excluding home care services provided home health aides, nursing home care and preventive health services in participants of this cohort study.

MATERIALS AND METHODS

Study cohort

We used data from the Ohsaki National Health Insurance (NHI) Cohort Study.[1 14 16–18] In brief, we sent a self-administered questionnaire on various lifestyle habits between October and December 1994 to all NHI beneficiaries living in the catchment area of Ohsaki Public Health Center, Miyagi Prefecture, northeastern Japan. A survey was conducted of NHI beneficiaries aged 40–79 years. Among 54 996 eligible individuals, 52 029 (95%) responded.

We excluded 776 participants who had withdrawn from the NHI before 1 January 1995, when we started the prospective collection of NHI claim files. Thus, 51 253 participants formed the study cohort. The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine. The participants who had returned the self-administered questionnaires and had signed them were considered to have consented to participate in this study.

For the current analysis, we also excluded participants who did not provide information about body weight and height (n=3543), were at both extremes of the BMI range: lower than the 0.05th percentile for BMI (below 14.41 for men; below 13.67 for women) or higher than the 99.95th percentile for BMI (above 58.46 for men; above 62.00 for women; n=48), those who died within the first year (n=454) or those who had a history of cancer (n=1533), myocardial infarction (n=1233), stroke (n=831) or kidney disease (n=1646). Thus, a total of 41 965 participants (20 066 men and 21 899 women) participated.

Body mass index

The self-administered questionnaire included questions on weight and height, and BMI was calculated as weight divided by the square of height (kilograms per square metre). We divided the participants into groups according to the following BMI categories: <18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight) and ≥30.0 kg/m^2 (obesity). These BMI categories correspond to the cut-off points proposed by the WHO: normal BMI range (18.5–24.9 kg/m^2), grade 1 overweight (25.0–29.9 kg/m^2), grade 2 overweight (30.0–39.9 kg/m^2) and grade 3 overweight (≥40.0 kg/m^2).[19]

The validity of self-reported body weight and height has been reported earlier.[1] Briefly, the weight and height of 14 883 participants, who were a subsample of the cohort, were measured during basic health examinations provided by local governments in 1995. The Pearson correlation coefficient (r) and weighted κ (κ) between the self-reported values and measured values were r=0.96 (p<0.01) for weight, r=0.93 (p<0.01) for height and r=0.88 (p<0.01) and κ=0.72 for BMI categories.

Health insurance system in Japan

The details of the NHI system have been described previously.[1 4 14 16 18] Briefly, everyone living in Japan is required to enrol in one health insurance system. The NHI covers 35% of the Japanese population for almost all medical treatment, including diagnostic tests, medication, surgery, supplies and materials, physicians and other personnel costs and most dental treatment. It also covers home care services provided by physicians and nurses but not those by other professionals such as home health aides. The NHI covers inpatient care but not nursing home care. Also, it does not cover preventive health services such as mass screening and health education. Payment to medical providers is made on a fee-for-service basis, where the price of each service is determined by a uniform national fee schedule.

If a participant withdrew from the NHI system because of death, emigration or employment, the withdrawal date and the reason for withdrawal were coded in the NHI withdrawal history files. We recorded any mortality or migration by reviewing the NHI withdrawal history files and collected data on the death of participants by reviewing the death certificates filed at Ohsaki Public Health Center. We then followed up the participants and prospectively collected data on medical care utilisation and its costs for all participants in the cohort from 1 January 1995 through 31 December 2007.

Statistical analysis

We conducted the same analysis as the previous study about the association between walking, life expectancy and lifetime medical expenditure.[16] Briefly, we divided the age groups (×) from 40 years according to the following categories: 40–44, 45–49, 50–54, 55–59, 60,64, 65–69, 70–74, 75–79, 80–84 and ≥85 years. Based on person-years and the number of deaths from 1996 until 2007, the multiadjusted mortality rates for each age category were estimated from a Poisson regression model. The dependent variable was mortality, and independent variables were age groups, categories of BMI and the following covariates: smoking status (current and past smoker or never smoker), alcohol consumption (current drinker consuming 1–499 g/week, current drinker consuming ≥450 g/week or never and past drinker), sports and physical exercise (≥3 h/week or <3 h/week), time spent walking (≥1 h/week or <1 h/week) and education (junior high school, high school or college/university or higher). We did not adjust for hypertension and diabetes mellitus in the multivariate models because these variables are considered to occupy an intermediate position in the etiologic pathway between BMI and mortality.

We separately calculated medical expenditure for participants who survived through the index year and for those who died because previous study showed that medical expenditure increased before death.[20] The multiadjusted medical expenditure per year was estimated using a linear regression model adjusted for the above covariates in survivors and decedents.

The estimates of multiadjusted mortality and medical expenditure were used for estimating life expectancy and lifetime medical expenditure from 40 years of age. To estimate life expectancy and lifetime medical expenditure, we constructed life tables per 100 000 persons using Chiang's analytical method on the basis of the latest published complete life tables of Japan for the year 2000.[21 22] Then, life expectancy (e_x) and lifetime medical expenditure (M_x) for each age groups (x) were estimated using the numbers of survivors (l_x), deaths (d_x), static population (L_x), multiadjusted medical expenditure for survivors (a_y) and multiadjusted medical expenditure for the deceased (b_y) as follows:

$$\sum \text{is sum of} y = x$$

$$e_x = \frac{\sum L_y}{l_x}$$

$$M_x = \frac{\sum (L_y \cdot a_y + d_y \cdot b_y)}{l_x}$$

The 95% CIs were estimated using a Monte Carlo simulation based on a Poisson regression model and linear regression model. We repeated 100 000 times, and all analysis were used the SAS V.9.1 statistical software package (SAS Institute Inc., 2004). All p values <0.05 were accepted as statistically significant.

We used a purchasing power parity rate of UK£ 1.00= JPN¥140.[16]

RESULTS

After 13 years of follow-up, we observed 5159 deaths (3356 men and 1803 women) among the 41 965 participants (20 066 men and 21 899 women).

The mean medical expenditure per year for survivors in men was £2393 in underweight, £2055 in normal weight, £2231 in overweight and £2334 in obesity, respectively. In women, it was £2375 in underweight, £1972 in normal weight, £2317 in overweight and £2733 in obesity, respectively. These differences of mean medical expenditure per year for survivors are statistically significant in men and women (ANOVA; p<0.0001). Also, the mean medical expenditure in the year of death for participants in men was £15 445 in underweight, £16 973 in normal weight, £17 811 in overweight and £17 878 in obesity, respectively. In women, it was £12 833 in underweight, £15 584 in normal weight, £17 059 in overweight and £19 635 in obesity, respectively. These differences of mean medical expenditure in the year of death for participants are statistically significant in only women (men, p=0.2241; women, p=0.0059).

Baseline characteristics by BMI category

The baseline characteristics of the study participants according to the BMI categories are shown for men and women (table 1), among whom 3.3% and 3.9% were underweight, 23.6% and 28.4% were overweight and 2.0% and 3.6% were obese, respectively.

Mean age in men decreased linearly with increasing BMI category. In women, mean age was highest in the underweight category. The proportions of men and women who were current and past smokers decreased with increasing BMI, and this tendency was especially marked in men. The proportions of men who had never and past drinker were highest in the underweight category. The proportions of men who did ≥3 h sports and physical exercise per week decreased with increasing BMI. The proportions of men and women who walked ≥1 h/day were the lowest in underweight men and obese women. Educational background increased linearly in men and decreased linearly in women as the BMI category increased. These characteristics showed statistically significant difference.

Mortality in terms of categories for BMI

Figure 1A for men and figure 1B for women show the mortality (per 1000 person-years) in each of the age groups according to the categories of BMI.

In underweight participants, there was a tendency that the mortality was the highest in each age group.

Table 1 Baseline characteristics by BMI categories in 41 965 participants

	Men					Women				
	BMI (kg/m^2)					BMI (kg/m^2)				
	<18.5	18.5–24.9	25.0–29.9	≥30.0	p Value*	<18.5	18.5–24.9	25.0–29.9	≥30.0	p Value
No. of subjects	666	14 278	4730	392	<0.0001	857	14 031	6226	785	<0.0001
Mean age (years)	64.0	59.1	57.4	56.1		63.7	59.8	60.7	61.2	
SD	10.4	10.5	10.2	10.2		10.9	10.1	9.1	9.5	
Smoking status (%)										
Current and past smoker	87.3	82.5	76.6	74.8	<0.0001	18.6	11.2	10.1	10.6	<0.0001
Never smoker	12.7	17.5	23.4	25.2		81.4	88.8	90.0	89.4	
Alcohol consumption (%)										
Current drinker, 1–449 g/week	49.2	61.0	61.4	50.8	<0.0001	18.2	21.8	21.4	19.3	0.0574
Current drinker, ≥450 g/week	9.6	11.7	12.6	15.0		0.6	0.8	0.5	0.9	
Never and past drinker	41.2	27.3	26.0	34.2		81.2	77.4	78.2	79.8	
Sports and physical exercise (%)										
≥3 h/week	17.5	16.1	13.8	10.1	<0.0001	9.8	11.3	11.0	10.8	0.5993
<3 h/week	82.5	83.9	86.2	89.9		90.2	88.7	89.0	89.2	
Time spent walking (%)										
≥1 h/day	41.7	51.4	45.8	42.7	<0.0001	37.9	45.1	41.0	35.6	<0.0001
<1 h/day	58.3	48.7	54.2	57.3		62.1	54.9	59.0	64.4	
Education (%)										
Junior high school	64.2	62.2	58.9	58.8	0.0013	58.3	54.2	62.7	71.3	<0.0001
High school	27.4	30.5	33.4	33.4		34.0	36.9	31.0	24.6	
College/university or higher	8.4	7.3	7.7	7.8		7.7	8.9	6.3	4.1	

*p Values were calculated by χ^2 test (categorical variables) or ANOVA (continuous variables).
BMI, body mass index.

Overweight participants showed similar mortality with normal weight participants, especially women. Overweight men showed slightly lower mortality than normal weight men. In obese participants, the mortality curve was not described smoothly because of small number of participants.

Table 2 shows the mortality ratio with 95% CIs according to the categories of BMI. In underweight participants, the multiadjusted mortality ratio was significantly higher than that in the normal weight participants (men, 1.62, 95% CI 1.41 to 1.86, p<0.0001; women, 1.46, 1.22 to 1.76, p<0.0001). In overweight participants, the multiadjusted mortality ratio was significantly lower in men and non-significantly lower in women than that in normal weight participants (men, 0.91, 0.83 to 0.99, p=0.0260; women, 0.98, 0.88 to 1.10, p=0.7841). In obese participants, the multiadjusted mortality ratio was non-significantly higher than that in normal weight participants (men, 1.14, 0.88 to 1.49, p=0.3177; women, 1.23, 0.98 to 1.55, p=0.0717).

Life expectancy and lifetime medical expenditure by BMI category

Table 3 shows life expectancy and lifetime medical expenditure with 95% CIs according to the BMI categories.

By multiadjusted analysis, obese men and women had approximately 1.7 and 3.1 years non-significantly shorter life expectancy from the age of 40 years in comparison with men and women of normal weight, respectively (men, p=0.3184; women, p=0.0724). Meanwhile, obese men and women had approximately 14.7% non-significantly higher and 21.6% significantly higher lifetime medical expenditure in comparison with normal weight participants, respectively (men, p=0.1141; women, p=0.0005).

In men, multiadjusted life expectancy was greatest for overweight, that is, 44.34 years (95% CI 43.11 to 45.54, p=0.0264), followed by normal weight (43.03 years, 42.22 to 43.73) and obesity (41.36 years, 38.28 to 44.70, p=0.3184) and was shortest for underweight (37.40 years, 35.80 to 38.87, p<0.0001). The multiadjusted lifetime medical expenditure for overweight was the highest, that is, £114 766.9 (95% CI 107 754.1 to 121 966.6, p<0.0001), followed by obesity (£112 858.9, 94 954.1 to 131 840.9, p=0.1141) and normal weight (£98 355.0, 93 615.3 to 103 010.2) and was the lowest for underweight (£93 208.7, 81 704.9 to 104 706.4, p=0.3916).

In women, multiadjusted life expectancy was greatest for overweight, that is, 52.56 years (50.67 to 54.46, p=0.7797), followed by normal weight (52.31 years,

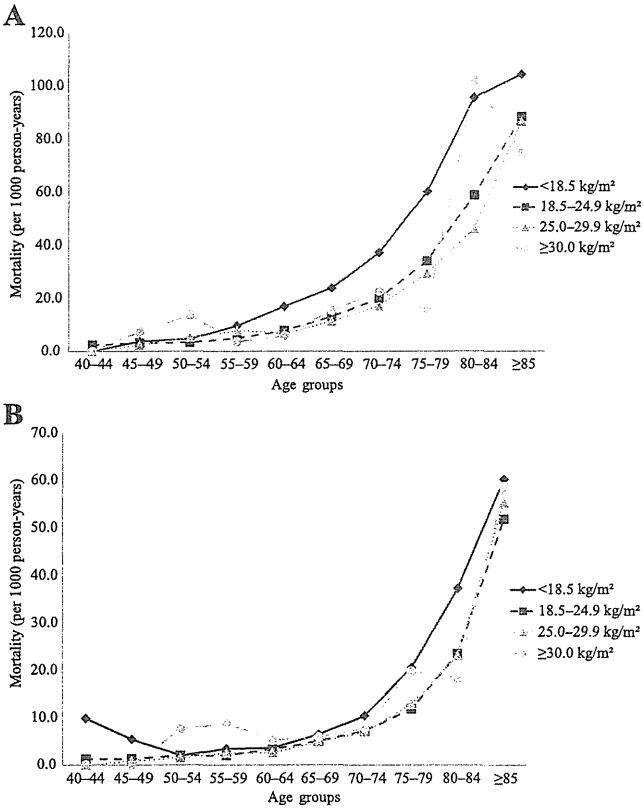

Figure 1 Multiadjusted mortality by BMI categories in each age group in men (A) and women (B).

50.79 to 53.75) and obesity (49.23 years, 46.14 to 52.59, p=0.0724) and was shortest for underweight (46.98 years, 44.63 to 49.29, p<0.0001). The lifetime medical expenditure for obesity was the highest (£137 765.9, 123 672.9 to 152 970.2, p=0.0005), followed by overweight (£129 964.6, 121 845.4 to 138 577.2, p<0.0001) and normal weight (£113 282.9, 106 668.0 to 120 054.6) and was lowest for underweight (£109 382.2, 97 996.6 to 121 008.6, p=0.5174).

DISCUSSION

The present results indicate that (1) obese men and women have 14.7% non-significantly higher and 21.6% significantly higher multiadjusted lifetime medical expenditure than those of the normal weight participants (men, p=0.1141; women, p=0.0005), even though their life expectancy is non-significantly shorter by 1.7 and 3.1 years than those of the normal weight participants, respectively (men, p=0.3184; women, p=0.0724); (2) underweight men and women have 5.2% and 3.4% non-significantly lower lifetime medical expenditure than those of the normal weight participants (men, p=0.5174; women, p=0.3916) because men and women live 5.6 and 5.3 years significantly less than those of the normal weight participants, respectively (men, p<0.0001; women, p<0.0001).

Comparison with other studies

Obese participants had shorter life expectancy than normal weight participants, as has been observed in previous studies.[6–10] Overweight participants had longer life expectancy than normal weight participants. Two of the four previous studies have reported that overweight participants had longer life expectancy than normal weight participants.[7 9] These results support our finding of an association between being overweight and life expectancy. Additionally, an association between BMI and all-cause mortality in the Japanese population has been reported by other data sets.[23–29] All seven previous studies showed that among the BMI categories, the lowest one had the highest mortality risk. These results are consistent with the fact that underweight participants have significantly the shortest life expectancy, as was observed in our study.

Thus, the association between BMI and life expectancy showed same trend with the pooled analyses of the association between BMI and all-cause mortality in Asia and Japan.[30 31]

Our present results support three of the four previous studies of lifetime medical expenditure for obese

Table 2 Mortality ratio for BMI categories in 41 965 participants

	Univariate		Multiadjusted*	
BMI (kg/m²)	Mortality ratio (95% CI)	p Value	Mortality ratio (95% CI)	p Value
Men				
<18.5	1.69 (1.47 to 1.93)	<0.0001	1.62 (1.41 to 1.86)	<0.0001
18.5–24.9	1.00 (Reference)		1.00 (Reference)	
25.0–29.9	0.90 (0.82 to 0.98)	0.0163	0.91 (0.83 to 0.99)	0.0260
≥30.0	1.13 (0.87 to 1.47)	0.3712	1.14 (0.88 to 1.49)	0.3177
Women				
<18.5	1.50 (1.25 to 1.81)	<0.0001	1.46 (1.22 to 1.76)	<0.0001
18.5–24.9	1.00 (Reference)		1.00 (Reference)	
25.0–29.9	1.00 (0.89 to 1.11)	0.9613	0.98 (0.88 to 1.10)	0.7841
≥30.0	1.29 (1.03 to 1.62)	0.0273	1.23 (0.98 to 1.55)	0.0717

*Adjusted for age groups, smoking status, alcohol drinking, sports and physical exercise, time spent walking and education.
BMI, body mass index.

Table 3 Life expectancy and lifetime medical expenditure at age 40 years for BMI categories in 41 965 participants

	Univariate			Multiadjusted*		
BMI (kg/m^2)	Estimate	95% CI	p Value	Estimate	95% CI	p Value
Men						
Life expectancy at age 40 years (years)						
<18.5	36.72	35.10 to 38.17	<0.0001	37.40	35.80 to 38.87	<0.0001
18.5–24.9	42.70	41.91 to 43.37	Reference	43.03	42.22 to 43.73	Reference
25.0–29.9	44.09	42.89 to 45.25	0.0157	44.34	43.11 to 45.54	0.0264
≥30.0	41.23	38.16 to 44.54	0.3733	41.36	38.28 to 44.70	0.3184
Lifetime medical expenditure at age 40 years (£)						
<18.5	94 877.5	83 411.4 to 106 275.7	0.6846	93 208.7	81 704.9 to 104 706.4	0.3916
18.5–24.9	97 244.1	92 662.5 to 101 774.0	Reference	98 355.0	93 165.3 to 103 010.2	Reference
25.0–29.9	114 398.2	107 490.1 to 121 505.3	<0.0001	114 766.9	107 754.1 to 121 966.6	<0.0001
≥30.3	115 362.6	97 361.8 to 134 555.0	0.0501	112 858.9	94 954.1 to 131 840.9	0.01141
Women						
Life expectancy at age 40 years (years)						
<18.5	46.26	43.98 to 48.43	<0.0001	46.98	44.63 to 49.29	<0.0001
18.5–24.9	51.70	50.28 to 53.02	Reference	52.31	50.79 to 53.75	Reference
25.0–29.9	51.74	49.98 to 53.48	0.9582	52.56	50.67 to 54.46	0.7797
≥30.0	48.13	45.23 to 51.22	0.0272	49.23	46.14 to 52.59	0.0724
Lifetime medical expenditure at age 40 years (£)						
<18.5	108 278.3	97 142.8 to 119 593.7	0.5816	109 382.2	97 996.6 to 121 008.6	0.5174
18.5–24.9	111 512.8	105 303.4 to 117 910.4	Reference	113 282.9	106 668.0 to 120 054.6	Reference
25.0–29.9	127 869.3	120 236.3 to 135 932.3	<0.0001	129 964.6	121 845.4 to 138 577.2	<0.0001
≥30.0	134 887.1	121 318.4 to 149 383.6	0.0007	137 765.9	123 672.9 to 152 970.2	0.0005

*Adjusted for age groups, smoking status, alcohol drinking, sports and physical exercise, time spent walking and education.
BMI, body mass index.

participants.[10 12 13] In comparison to previous studies, we calculated lifetime medical expenditure from individual medical expenditure and survival data covering longest follow-up period to date. Meanwhile, one study has shown that obese participants have lower lifetime medical expenditure than normal weight participants.[11] However, that study limited the participants to non-smokers and calculated lifetime medical expenditure from the mortality of a hypothetical cohort and estimated medical expenditure from other cohort. In the present study, overweight participants were found to have higher lifetime medical expenditure than normal weight participants, as had been reported previously.[10 12 13] We consider that this was attributable to the higher medical expenditure per month or per person from the 10-year or 9-year follow-up than for normal weight participants.[1 3 4] On the other hand, with regard to underweight participants, our present findings were inconsistent with those of a previous study that examined the association between being underweight and lifetime medical expenditure.[13] However, that study calculated lifetime medical expenditure for elderly participants aged over 70 years. Elderly underweight participants have high mortality,[32] and medical expenditure increases in the 1 year prior to death.[20] Thus, lifetime medical expenditure from 70 years for underweight participants becomes higher than for participants of normal weight. Our study results are thus inconsistent with those reported previously.

We previously calculated life expectancy and lifetime medical expenditure for smokers and non-smokers from age 40 years by using the same data set as that for the present study.[17] The results indicated that lifetime medical expenditure was non-significantly lower in smokers than in non-smokers, reflecting the 3.5 years shorter life expectancy of smokers. On the other hand, the present study indicated that lifetime medical expenditure was higher for obese participants in spite of their shorter life expectancy. This difference would result from the difference in which obesity and smoking affect one's health and longevity. Previous studies of healthy and disability free life expectancy have agreed that smoking shortens life expectancy without affecting the years of life spent with ill-health or disability, while obesity shortens life expectancy and extends the years of life with ill-health or disability.[33] On the basis of these differences, Reuser *et al* summarised the situation as 'smoking kills and obesity disables'.[7] Extended years with ill-health and/or disability must result in increased lifetime medical expenditure. All these findings suggest that weight control would bring about longer life expectancy and long-term enhancement of the quality of life and a cost saving.

Strengths and limitations

A major strength of our present study is that it is the first in the world to have clarified the association between BMI and lifetime medical expenditure calculated from individual medical expenditure and mortality data over

a long period in a general population from the age of 40 years.[1 14 16–18] The NHI covers almost all medical care utilisation.[1 4 14 16 18] Additionally, in order to reduce bias, we adjusted confounders by including various covariates in our Poisson regression model and linear regression mode.[16] On the other hand, several limitations of our study should also be considered. First, we used self-reported BMI which in a source of error.[34 35] We consider this error to be a non-differential misclassification. This misclassification would lead to attenuation of the true association towards the null. To address this problem, van Dam *et al*[36] studied the association between BMI and mortality using lower BMI cut-off points: 24.5 kg/m^2 to reflect a measured BMI of 25.0 kg/m^2 and 29.0 kg/m^2 to reflect a measured BMI of 30.0 kg/m^2. The association showed similar with original cut-off points. Second, the 95% CI was wide, and there was a limit to the accurate estimation of life expectancy and lifetime medical expenditure for obese participants. Additionally, we did not observe significant association in obese participants without lifetime medical expenditure in women. However, our results are consistent with those of the previous studies.[6–8 10 12 13] In Japan, prevalence of obesity is only 3%.[37] Thus, the reason for non-significant association might be β error because of the lack of statistical power due to small number of obese participants.

Conclusions and policy implication

In summary, even though we observed non-significant association between obesity, life expectancy and lifetime medical expenditure without lifetime medical expenditure in women, lifetime medical expenditure might appear to be higher for obese participants, despite their short life expectancy. With better weight control, more people would enjoy their longevity with lower needs and demands for medical care.

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Contributors All authors contributed to the design of the study. MN, SK, MK, KO-M, TS and IT participated in data collection. MN, SK, AH, MK and SH participated in data analysis. MN, MK, KO-M, TS, AH, MK and SH participated in the writing of the report. SK and IT participated in critical revision of the manuscript. All authors approved the final version of the report for submission.

Funding This study was supported by a Health Sciences Research Grant for Health Services (H21-Choju-Ippan-001, H20-Junkankitou (Seisyu)-Ippan-013, H22-Junkankitou (Seisyu)-Ippan-012), Ministry of Health, Labour and Welfare, Japan. MN is a recipient of a Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

Competing interests None.

Ethics approval The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine. Participants who had returned the self-administered questionnaires and signed them were considered to have consented to participate.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

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J Sleep Res. (2012) Regular Research Paper

Long sleep duration and cause-specific mortality according to physical function and self-rated health: the Ohsaki Cohort Study

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Keywords
Japanese, mortality, sleep duration

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Accepted in revised form 4 August 2012;
received 19 April 2012

DOI: 10.1111/j.1365-2869.2012.01053.x

Summary
Although several studies have examined the association between sleep duration and all-cause or cause-specific mortality, it is unclear whether long sleep duration might merely reflect decreased physical strength and poorer health status. We therefore examined the association between sleep duration and all-cause and cause-specific mortality, and conducted stratified analysis based on physical function and self-rated health. This study used prospective data from the Ohsaki Cohort Study, conducted in Miyagi Prefecture, in northern Japan. This study population comprised 49 256 subjects aged 40–79 years at the baseline survey. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and cause-specific mortality according to the five categories of sleep duration ($\leq$6, 7, 8, 9, $\geq$10 h day^{-1}), treating 7 h as the reference group, employing Cox's proportional hazard regression analysis. We found that long sleep duration was associated with mortality. The HRs (95% CIs) of subjects who slept more than 10 h were 1.37 (1.27–1.47), 1.49 (1.30–1.71) and 1.53 (1.36–1.73) for mortality due to all causes, total cardiovascular disease and other causes of death mortality, respectively. The association between long sleep duration and stroke mortality was especially marked among subjects with limited physical function and poorer health status. However, we did not observe such a trend for mortality due to all causes, total cardiovascular disease, ischaemic heart disease, cancer or other causes of death. We conclude that, with the exception of stroke mortality, the association between long sleep duration and mortality is not modified by physical function or health status.

INTRODUCTION

Sleep duration and mortality risk have been indicated in several previous studies (Cappuccio *et al.*, 2010, 2011; Gallicchio and Kalesan, 2009). Although three meta-analyses have concluded that both long and short sleep duration were associated with an increased risk of mortality, the effect was larger among those who slept longer (long sleeper) than among short sleepers (Cappuccio *et al.*, 2010, 2011; Gallicchio and Kalesan, 2009). The meta-analysis by Cappuccio *et al.*, 2011 also reported that the hazard ratio (HR) of long sleep duration was higher than of short sleep with regard to mortality due to total cardiovascular disease (CVD) and stroke. The results of previous studies conducted in East Asia, predominantly Japan, have tended to indicate stronger HRs for both short and long sleep duration than those of studies conducted in Europe or the United States (Cappuccio *et al.*, 2010). This difference might be attributable to `differences in average sleep duration among countries, or to the longer life

expectancy in Japan (Cappuccio *et al.*, 2010; Steptoe *et al.*, 2006).

However, it remains unclear whether long sleep duration directly increases the risk, or whether it merely reflects the presence of comorbidity or unhealthy status. In a cross-sectional study, Stranges *et al.*, 2008 reported that long sleepers had lower physical activity and lower scores on the Short Form-36 physical scale. They suggested that long sleep duration was a reflection of comorbidity or poor health status. Conversely, Mesas *et al.*, 2010 conducted a stratified analysis based on health status and physical function in a prospective cohort study. They found that long sleep duration was associated with greater mortality, irrespective of health status, and considered that the association between long sleep duration and mortality would not be explained by poorer health status among long sleepers. However, their sample size was small and they did not examine causes of death, even though some studies have suggested that the association between sleep duration and mortality risk differs according to cause of death (Amagai *et al.*, 2004; Burazeri *et al.*, 2003; Ferrie *et al.*, 2007; Ikehara *et al.*, 2009; Lan *et al.*, 2007; Patel *et al.*, 2004; Qureshi *et al.*, 1997).

We therefore examined the association between sleep duration and all-cause and cause-specific mortality, and conducted stratified analysis by physical function and self-rated health.

METHODS

Study cohort

We used data obtained from the Ohsaki National Health Insurance (NHI) Cohort Study, details of which have been described elsewhere (Kuriyama *et al.*, 2006; Tsuji *et al.*, 1998). Briefly, we delivered a self-administered questionnaire, including items on sleep duration, between October and December 1994 to all NHI beneficiaries aged 40–79 years living in the catchment area of Ohsaki Public Health Center, a local government agency that provides preventive health services for residents of 14 municipalities in Miyagi Prefecture, northern Japan. Of 54 996 eligible men (26 481) and women (28 515), 52 029 (94.6%) responded (men: 24 895, women: 27 134).

To ascertain the date of, and reason for, withdrawal from the NHI, we began prospective collection of NHI withdrawal history files on 1 January 1995. We excluded 776 participants who had withdrawn from the NHI before the baseline questionnaire survey. Thus, 51 253 participants (men: 24 573, women: 26 680) ultimately formed the study cohort.

Exposure measurement

The questionnaire included items about sleep duration, as well as alcohol drinking and smoking habits, a 40-item food frequency questionnaire (FFQ), personal and family history of diseases, job status, level of education, marital status, body weight, height, time spent walking, physical function, self-rated health and perceived mental stress.

For items related to sleep duration, participants entered the mean integer number of hours of sleep they had taken per day during the last year. We categorized sleep duration into five groups: ≤ 6, 7, 8, 9 and ≥ 10 h day^{-1}. We rounded-off sleep duration to the closest whole number.

The physical function status of each subject was assessed using the self-completed questionnaires returned at the baseline survey in 1994 using the six-item physical function measure of the Medical Outcomes Study (MOS) Short-form General Health Survey (Stewart *et al.*, 1988, 1989; Tsuji *et al.*, 1999; Ware *et al.*, 1996). This measure examines the extent to which health affects a variety of physical activities, ranging from strenuous exercise to basic self-care. The validity and reliability of the MOS questionnaire have been fully established (Stewart *et al.*, 1988, 1989; Ware *et al.*, 1996). The Japanese version of the MOS scale has been reported to predict all-cause mortality, hospitalization risk and medical costs (Tsuji *et al.*, 1999). In the analysis, we classified the subjects into the following seven groups according to their self-response, which was referred to as the MOS score: level 6, able to perform vigorous activities such as lifting heavy objects, running or participating in strenuous sports; level 5, able to perform moderate activities such as moving a table, carrying groceries or bowling; level 4, able to walk uphill or climb a few flights of stairs; level 3, able to bend, lift or stoop; level 2, able to walk one block; level 1, able to perform self-care activities such as eating, dressing, bathing or using the toilet; level 0, unable to do anything unaided (Tsuji *et al.*, 1999). This classification was ordered hierarchically in terms of difficulty in performing physical tasks, and we scored the levels of each subject according to the highest physical task he/she answered as being not limited at all. For each item measured, we classified the subjects into two groups: 'limited' (levels 0–4) and 'unlimited' (levels 5 and 6).

Self-rated health was assessed through the subject's response to the question: 'How is your overall health status?'. The subjects were asked to choose one of five answers: 'bad', 'poor', 'moderate', 'good' or 'excellent', and on the basis of their responses, we classified them into two groups: 'worse' (poor or bad) and 'better' (excellent, good or moderate).

Follow-up

The end-points were mortality due to all causes, CVD [ischaemic heart disease (IHD) and stroke], cancer and other causes. We followed-up the subjects for mortality and emigration by reviewing the NHI withdrawal history files from 1 January 1995 to 31 March 2008. When a subject withdrew from the NHI system because of death, emigration or employment, the date of withdrawal and the reason were coded on the NHI withdrawal history files. Because we were unable to obtain subsequent information for subjects who

withdrew from the NHI, we discontinued their follow-up. For deaths thus identified, we investigated the causes by reviewing the death certificates filed at Ohsaki Public Health Center. Cause of death was coded by trained physicians according to the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) (WHO, 1992). We identified deaths due to CVD as codes I00–I99 (including IHD as codes I20–I25 and strokes as codes I60–I69), and those due to cancer as codes C00–C97.

After exclusion of subjects who had not entered responses for sleep duration (n = 1 783), and who had reported a sleep duration of <4 h or more than 12 h (n = 214), 49 256 participants (men: 23 749, women: 25 507) remained, including 8447 participants who had died due to all causes (CVD 2549; cancer 2764; other causes 3134). In order to improve the reliability of our questionnaire, we excluded participants who had reported sleep durations of <4 h or more than 14 h, because these durations were considered to be extremely long or short. Also, these subjects were less likely to have answered the question items (data not shown).

Ethical permissions

The study protocol was reviewed and approved by the ethics committee of Tohoku University School of Medicine. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.

Statistical analysis

We counted person-years of follow-up for each of the subjects from 1 January 1995 until the date of death, the date of withdrawal from the NHI or the end of follow-up (31 March 2008), whichever occurred first. The average follow-up time was 10.8 years. The validity of the proportional hazards assumption was verified by adding a time-dependent variable to each model to confirm that the HR for each covariate did not increase or decrease over time.

We used Cox's proportional hazard regression analysis to estimate hazard ratios (HRs) and the 95% confidence intervals (CIs) of mortality according to the five categories of sleep duration ($\leq$6, 7, 8, 9 and $\geq$10 h day^{-1}), treating 7 h as the reference group. We chose 7 h as a reference group because this category had been used as a reference group in most previous studies, and we had predicted that this group would have the lowest mortality risk (Cappuccio *et al.*, 2010, 2011; Gallicchio and Kalesan, 2009). In these analyses, we considered the following parameters as covariates: age (continuous variable); sex; total caloric intake (continuous variable, calculated from the 40-item FFQ); body mass index (BMI) in kg m^{-2} (<18.5, 18.5–24.9, $\geq$25.0); marital status (married or unmarried); level of education (junior high school or less, high school or college/university or higher); job status (employed or unemployed); history of myocardial infarction; history of cancer; history of stroke; history of hypertension; history of diabetes mellitus; smoking status (never smoker, ex-smoker, current smoker one to 19 cigarettes day^{-1}, or current smoker $\geq$ 20 cigarettes day^{-1}); alcohol drinking (never drinkers, ex-drinkers, current drinkers < 27.8 g day^{-1}, current drinkers 27.8–45.59 day^{-1}, current drinkers 45.6–68.39 day^{-1} or current drinkers $\geq$ 68.4 day^{-1} ethanol); time spent walking (<1 h day^{-1}, 1 h day^{-1} or longer); perceived mental stress (low, moderate or high); self-rated health (worse or better); physical function (limited or unlimited). All the covariates we selected had been suggested to show an association with all-cause mortality or cause-specific mortality in the previous studies. We did not use a stepwise procedure. In addition, we conducted analyses stratified by physical function and self-rated health. In the stratified analyses, we excluded subjects for whom answers about health status and/or physical function were missing. Interactions between the five categories of sleep duration and physical function and self-rated health were tested for using the likelihood ratio test, which compared the models with and without cross-product interaction terms.

All statistical analyses were performed using the SAS statistical software package, version 9.2 (SAS Institute Inc., Cary, NC, USA). All the statistical tests reported were two-sided. Differences at $P < 0.05$ were accepted as statistically significant.

RESULTS

Table 1 shows the baseline characteristics, according to sleep duration, separately for both sexes. For both men and women subjects, those who slept for 10 h or more per day were more likely to be older, to have a lower daily total caloric intake, to have a history of myocardial infarction, cancer, stroke, hypertension or diabetes mellitus, to have lower perceived mental stress, to have worse self-rated health and more limited physical function and were less likely to be employed or married (P-values < 0.0001). For both men and women, subjects those who slept 6 h or less per day were younger, less likely to have a history of myocardial infarction, cancer, stroke and hypertension and less limited physical function, and were more likely to have a higher education level and perceived mental stress (P-values < 0.0001).

Table 2 shows the age- and sex-adjusted and multivariate adjusted HRs for all-cause and cause-specific mortality according to sleep duration. Among subjects who slept 10 h or more per day, there was a significantly increased risk of mortality due to all causes, total CVD, IHD, stroke and other causes, respectively. Among subjects who slept 6 h or less per day, there was a significantly increased IHD mortality, but no significant association with risk of mortality due to all causes, total CVD, stroke or other causes. In addition, all-cause, total CVD and IHD mortality risk were increased significantly among subjects who slept for 8 h

Table 1 Baseline characteristics of the subjects according to sleep duration exclude extreme sleep duration

	Sleep duration (hours per day)					
	≤6	*7*	*8*	*9*	*≥10*	P *values**
Men						
Number of subjects	2 837	6 160	9 848	2 723	2 181	
Mean age (years), SD	58.2 (11.0)	56.8 (10.5)	59.5 (10.3)	62.9 (9.4)	66.0 (8.7)	<0.0001
Mean Body Mass Index (kg m^{-2}), SD	23.6 (3.2)	23.4 (2.9)	23.3 (3.0)	23.1 (3.2)	22.9 (3.7)	<0.0001
Mean total caloric intake (kcal day^{-1}), SD	1 735.1 (647.8)	1 829.2 (629.4)	1 806.3 (640.8)	1 765.7 (641.9)	1 649.9 (651.2)	<0.0001
Having history of MI	3.7	2.6	3.2	3.2	5.5	<0.0001
Having history of cancer	3.3	2.5	2.7	3.1	4.6	<0.0001
Having hisotry of stroke	2.4	1.4	2.6	3.9	8.6	<0.0001
Having history of hypertension (%)	23.6	20.8	24.7	29.1	31.2	<0.0001
Having history of DM (%)	9.0	6.6	7.2	7.5	9.5	<0.0001
Employed (%)	58.1	62.7	58.1	51.4	41.2	<0.0001
Married (%)	86.8	89.7	89.3	90.4	86.5	<0.0001
Junior high school graduated or less	50.0	52.1	60.0	69.7	72.5	<0.0001
Never drinkers (%)	15.2	16.3	16.3	14.6	15.4	<0.0001
Never smokers	19.0	18.6	17.3	15.6	15.9	<0.0001
Time spent walking 1 h day^{-1} or longer (%)	42.2	45.4	45.2	45.0	40.2	<0.0001
High perceived mental stress (%)	20.7	15.3	11.7	11.2	11.7	<0.0001
Poor or bad self-rated health (%)	20.4	14.7	17.2	18.2	31.6	<0.0001
Limited physical function (%)	18.0	12.6	16.5	21.0	36.8	<0.0001
Women						
Number of subjects	4 840	7 486	9 199	2 259	1 723	
Mean age (years), SD	59.1 (10.5)	58.5 (10.0)	61.6 (9.3)	65.0 (8.4)	68.5 (8.6)	<0.0001
Mean Body Mass Index (kg m^{-2}), SD	23.6 (3.4)	23.7 (3.3)	23.8 (3.4)	24.0 (3.5)	23.9 (4.4)	<0.0001
Mean total caloric intake (kcal day^{-1}), SD	1 216.6 (378.6)	1 260.9 (367.5)	1 238.5 (380.5)	1 197.3 (402.2)	1 127.4 (419.9)	<0.0001
Having history of MI	2.4	1.8	2.2	3.1	4.4	<0.0001
Having history of cancer	4.0	3.1	3.8	4.1	6.2	<0.0001
Having hisotry of stroke	1.2	0.9	1.6	2.5	6.2	<0.0001
Having history of hypertension (%)	25.3	25.2	29.6	35.2	39.3	<0.0001
Having history of DM (%)	5.5	4.8	5.7	7.4	10.4	<0.0001
Employed (%)	34.4	38.2	32.1	26.4	18.3	<0.0001
Married (%)	73.1	78.6	76.9	70.6	60.3	<0.0001
Junior high school graduated orless	47.1	47.1	57.8	65.9	66.3	<0.0001
Never drinkers (%)	54.8	60.2	60.4	60.8	58.7	<0.0001
Never smokers	69.0	71.9	68.8	66.8	63.0	<0.0001
Time spent walking 1 h day^{-1} or longer (%)	37.8	39.5	38.5	38.0	31.4	<0.0001
High perceived mental stress (%)	25.3	18.7	13.5	12.2	11.1	<0.0001
Poor or bad self-rated health (%)	24.3	18.7	22.2	26.9	38.8	<0.0001
Limited physical function (%)	29.2	25.2	32.9	43.4	56.0	<0.0001

*Continuous variables were analyzed by ANOVA, and categorical variables were analyzed by chi-square test.
SD, standard deviation. MI, myocardial infarction; DM, diabetes mellitus.

and 9 h day^{-1}. Mortality risk due to stroke and other causes of death was increased significantly among subjects who slept 9 h day^{-1}.

A significant interaction between sleep duration and physical function was observed only for stroke mortality (Table 3, Fig. 1). The association between long sleep duration and risk of stroke mortality was stronger among subjects who had limited physical function than among those who had unlimited physical function. Otherwise, there were no differences in the risk of mortality due to all causes, total

Table 2 Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality according to sleep duration

	Sleep duration (hours per day)				
	≤6	*7*	*8*	*9*	*≥10*
Person-years	83 530	150 684	206 537	52 157	37 066
All-cause					
No. of deaths	1 074	1 671	3 206	1 117	1 379
Age- and sex-adjusted HR (95% CI)	1.09 (1.01–1.17)	1.00 (reference)	1.10 (1.04–1.17)	1.18 (1.09–1.27)	1.63 (1.52–1.75)
Multivariable HR1 (95% CI)*	1.01 (0.93–1.09)	1.00 (reference)	1.07 (1.01–1.14)	1.14 (1.06–1.24)	1.37 (1.27–1.47)
All CVD					
No. of deaths	325	439	972	361	452
Age- and sex-adjusted HR (95% CI)	1.20 (1.04–1.39)	1.00 (reference)	1.26 (1.12–1.41)	1.39 (1.21–1.60)	1.88 (1.64–2.15)
Multivariable HR1 (95% CI)*	1.10 (0.96–1.28)	1.00 (reference)	1.21 (1.08–1.36)	1.32 (1.15–1.52)	1.49 (1.30–1.71)
IHD					
No. of deaths	81	91	224	82	83
Age- and sex-adjusted HR (95% CI)	1.49 (1.10–2.01)	1.00 (reference)	1.40 (1.10–1.79)	1.55 (1.15–2.10)	1.73 (1.28–2.35)
Multivariable HR1 (95% CI)*	1.38 (1.02–1.86)	1.00 (reference)	1.36 (1.06–1.73)	1.49 (1.10–2.02)	1.41 (1.04–1.92)
Stroke					
No. of deaths	143	203	435	166	218
Age- and sex-adjusted HR (95% CI)	1.14 (0.92–1.41)	1.00 (reference)	1.23 (1.04–1.45)	1.40 (1.14–1.73)	1.99 (1.63–2.42)
Multivariable HR1 (95% CI)*	1.05 (0.84–1.30)	1.00 (reference)	1.17 (0.99–1.39)	1.30 (1.06–1.60)	1.51 (1.24–1.85)
Cancer					
No. of deaths	366	637	1,071	335	355
Age- and sex-adjusted HR (95% CI)	1.01 (0.89–1.15)	1.00 (reference)	0.99 (0.89–1.09)	0.98 (0.85–1.12)	1.20 (1.05–1.37)
Multivariable HR1 (95% CI)*	0.97 (0.85–1.11)	1.00 (reference)	0.97 (0.88–1.07)	0.96 (0.84–1.10)	1.10 (0.96–1.25)
Other					
No. of deaths	383	595	1,163	421	572
Age- and sex-adjusted HR (95% CI)	1.08 (0.95–1.23)	1.00 (reference)	1.11 (1.01–1.23)	1.22 (1.08–1.38)	1.86 (1.66–2.09)
Multivariable HR1 (95% CI)*	0.98 (0.86–1.11)	1.00 (reference)	1.09 (0.99–1.20)	1.20 (1.06–1.36)	1.53 (1.36–1.73)

*Multivariable HR was adjusted for age (continuous variable); sex; total caloric intake (continuous variable); body mass index in kg m^{-2} (<18.5, 18.5–24.9, ≥25.0); marital status (married or unmarried); level of education (junior high school or less, high school, or college/university or higher); job status (employed or unemployed); history of myocardial infarction; history of cancer; history of stroke; history of hypertension; history of diabetes mellitus; smoking status (never smoker, ex-smoker, current smoker 1–19 cigarettes day^{-1}, or current smoker ≥ 20 cigarettes day^{-1}); alcohol drinking (never drinkers, ex-drinkers, current drinkers < 27.8 g day^{-1}, current drinkers 27.8–45.59 g day^{-1}, current drinkers 45.6–68.39, current drinkers ≥ 68.4 g day^{-1} ethanol); time spent walking (<1 h day^{-1} or 1 h day^{-1} or longer); perceived mental stress (low, moderate, or high); self-rated health (worse or better), physical function (limited or unlimited).
CVD, cardiovascular disease; IHD, ischaemic heart disease.

CVD, IHD, cancer or other causes, irrespective of whether or not subjects had limited physical function.

Table 4 shows the analysis stratified by self-rated health (worse or better). The association between long sleep duration and stroke mortality was stronger among subjects who reported worse health status than among subjects who reported better health status. In addition, the HR for short sleep duration among subjects who reported worse health status was higher than that for subjects who reported better health status. Otherwise, the risk of mortality due to all causes, total CVD, IHD, cancer and other causes showed no differences among the subjects, irrespective of health status.

DISCUSSION

In this study, we found that long sleep duration was associated with an increased risk of mortality due to all causes, total CVD, IHD, stroke and other causes, and that short sleep duration was associated with an increased risk of IHD mortality. Significant interactions were observed only

Table 3 Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality stratified by physical function status

	Number of deaths	*Sleep duration (hours per day)*					P *for interaction*
		≤6	*7*	*8*	*9*	*≥10*	
All-cause							
Limited	3 362	1.08 (0.96–1.22)	1.00 (reference)	1.10 (1.00–1.21)	1.24 (1.10–1.39)	1.41 (1.26–1.57)	0.15
Unlimited	4 317	0.94 (0.85–1.05)	1.00 (reference)	1.04 (0.96–1.12)	1.04 (0.93–1.15)	1.23 (1.10–1.38)	
All-CVD							
Limited	1 278	1.06 (0.86–1.32)	1.00 (reference)	1.20 (1.01–1.42)	1.43 (1.17–1.75)	1.58 (1.31–1.91)	0.20
Unlimited	1 131	1.15 (0.93–1.41)	1.00 (reference)	1.24 (1.06–1.46)	1.24 (1.00–1.52)	1.21 (0.96–1.52)	
IHD							
Limited	263	1.31 (0.83–2.06)	1.00 (reference)	1.16 (0.79–1.69)	1.70 (1.10–2.61)	1.48 (0.97–2.26)	0.19
Unlimited	269	1.52 (0.99–2.32)	1.00 (reference)	1.63 (1.16–2.29)	1.25 (0.78–1.99)	1.38 (0.83–2.28)	
Stroke							
Limited	594	1.20 (0.87–1.65)	1.00 (reference)	1.30 (1.00–1.69)	1.57 (1.16–2.14)	1.88 (1.42–2.49)	0.04
Unlimited	501	0.93 (0.68–1.28)	1.00 (reference)	1.12 (0.89–1.41)	1.15 (0.85–1.56)	0.93 (0.65–1.34)	
Cancer							
Limited	911	1.11 (0.89–1.38)	1.00 (reference)	0.95 (0.79–1.14)	0.96 (0.76–1.22)	1.00 (0.80–1.25)	0.07
Unlimited	1 718	0.86 (0.73–1.02)	1.00 (reference)	0.95 (0.84–1.07)	0.92 (0.77–1.09)	1.15 (0.96–1.38)	
Other							
Limited	1 476	1.08 (0.89–1.31)	1.00 (reference)	1.14 (0.97–1.33)	1.29 (1.07–1.57)	1.56 (1.32–1.86)	0.41
Unlimited	1 468	0.90 (0.75–1.08)	1.00 (reference)	1.03 (0.90–1.17)	1.06 (0.88–1.27)	1.37 (1.13–1.66)	

Adjusted for age (continuous variable); sex; total caloric intake (continuous variable); body mass index in kg m^{-2}(<18.5, 18.5–24.9, ≥25.0); marital status (married or unmarried); level of education (junior high school or less, high school, or college/university or higher); job status (employed or unemployed); history of myocardial infarction; history of cancer; history of stroke; history of hypertension; history of diabetes mellitus; smoking status (never smoker, ex-smoker, current smoker 1–19 cigarettes day^{-1} or current smoker ≥ 20 cigarettes day^{-1}); alcohol drinking (never drinkers, ex-drinkers, current drinkers < 27.8 g day^{-1}, current drinkers 27.8–45.59 g day^{-1}, current drinkers 45.6–68.39, current drinkers ≥ 68.4 g day^{-1} ethanol); time spent walking (<1 h day^{-1}, or 1 h day^{-1} or longer); perceived mental stress (low, moderate, or high); self-rated health (worse or better).
CVD, cardiovascular disease; IHD, ischaemic heart disease.

for stroke mortality, the risk of which was elevated among subjects who had limited physical function or worse health status. Otherwise, the risk of mortality due to all causes, total CVD, IHD, cancer and other causes was not increased among subjects who had limited physical function or worse health status.

The present results are consistent with most previous studies, including three meta-analyses of the association between longer sleep duration and all-cause mortality, CVD mortality or CVD incidence (Cappuccio *et al.*, 2010, 2011; Gallicchio and Kalesan, 2009). In this study we have demonstrated no significant interaction between sleep duration and physical function or health status in terms of all-cause mortality, consistent with the results of Mesas *et al.*, 2010, who found that long sleepers had an increased risk of mortality irrespective of health status. We also demonstrated that stroke mortality was increased significantly among subjects who had limited physical function, but not among subjects whose physical function was not restricted. We also found that mortality due to causes other than stroke, such as total CVD, IHD, cancer and other causes, showed no significant interaction with sleep duration, physical function or health status. In the present study, interactions between long sleep duration and physical function or health status were elevated only for stroke mortality, suggesting that the mechanism responsible for the association between long sleep duration and mortality differed among causes of death. However, Mesas *et al.* did not conduct any analysis of cause-specific mortality.

Several researchers have hypothesized that long sleep duration might reflect sleep need, reflecting in turn decreased physical strength, poor health status or accompanying comorbidity (Chen *et al.*, 2008; Ikehara *et al.*, 2009; Patel, 2009; Patel *et al.*, 2004). Because long sleepers are more likely to have low physical activity and low scores on the Short Form-36 physical score scale (Stranges *et al.*, 2008), it has been hypothesized that long sleep duration might be a consequence of unrecognized chronic comorbidity. We also conducted analysis stratified by history of diseases (cancer, myocardial infarction or stroke) that would provide an objective measure of health; however, this made no appreciable difference to the result (data not shown). Therefore, with the exception of stroke mortality, our results did not support this hypothesis in terms of mortality due to all causes, total CVD, IHD, cancer and other causes.

The present study is the first large-scale epidemiological study to have examined whether or not physical function or self-rated health modifies the association between sleep duration and all-cause and cause-specific mortality. Furthermore, we recruited subjects from a large general population, allowing possible generalization of our results. We followed a large number of participants over a 14-year period; as the

Table 4 Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality stratified by self-rated health

	Number of deaths	*Sleep duration (hours per day)*					P *for interaction*
		≤6	*7*	*8*	*9*	*≥10*	
All-cause							
Worse (poor or bad)	3 011	1.00 (0.88–1.14)	1.00 (reference)	1.05 (0.95–1.17)	1.18 (1.03–1.35)	1.39 (1.23–1.57)	0.61
Better (excellent to fair)	5 148	0.99 (0.90–1.09)	1.00 (reference)	1.06 (0.99–1.14)	1.07 (0.97–1.18)	1.26 (1.14–1.40)	
All-CVD							
Worse (poor or bad)	996	1.18 (0.93–1.48)	1.00 (reference)	1.23 (1.02–1.50)	1.32 (1.04–1.68)	1.59 (1.28–1.97)	0.86
Better (excellent to fair)	1 463	1.05 (0.87–1.27)	1.00 (reference)	1.21 (1.05–1.40)	1.30 (1.08–1.55)	1.33 (1.10–1.61)	
IHD							
Worse (poor or bad)	212	1.04 (0.65–1.68)	1.00 (reference)	1.10 (0.75–1.63)	1.29 (0.79–2.10)	1.11 (0.70–1.78)	0.77
Better (excellent to fair)	333	1.70 (1.14–2.53)	1.00 (reference)	1.64 (1.18–2.26)	1.57 (1.05–2.34)	1.76 (1.15–2.68)	
Stroke							
Worse (poor or bad)	452	1.45 (1.02–2.06)	1.00 (reference)	1.27 (0.94–1.73)	1.49 (1.03–2.16)	2.04 (1.48–2.82)	0.046
Better (excellent to fair)	669	0.81 (0.60–1.08)	1.00 (reference)	1.12 (0.91–1.38)	1.21 (0.93–1.56)	1.06 (0.79–1.41)	
Cancer							
Worse (poor or bad)	784	0.93 (0.73–1.18)	1.00 (reference)	0.88 (0.72–1.07)	1.02 (0.79–1.32)	1.10 (0.87–1.39)	0.60
Better (excellent to fair)	1 889	0.96 (0.82–1.12)	1.00 (reference)	0.97 (0.86–1.09)	0.88 (0.75–1.03)	1.06 (0.89–1.25)	
Other							
Worse (poor or bad)	1 231	0.94 (0.77–1.16)	1.00 (reference)	1.06 (0.90–1.26)	1.21 (0.98–1.49)	1.47 (1.22–1.77)	0.34
Better (excellent to fair)	1 796	0.99 (0.83–1.17)	1.00 (reference)	1.07 (0.94–1.21)	1.12 (0.95–1.31)	1.46 (1.23–1.72)	

Adjusted for age (continuous variable); sex; total caloric intake (continuous variable); body mass index (BMI) in kg m^{-2} (<18.5, 18.5–24.9, ≥25.0); marital status (married or unmarried); level of education (junior high school or less, high school, or college/university or higher); job status (employed, or unemployed); history of myocardial infarction; history of cancer; history of stroke; history of hypertension; history of diabetes mellitus; smoking status (never smoker, ex-smoker, current smoker 1–19 cigarettes day^{-1} or current smoker ≥ 20 cigarettes day^{-1}); alcohol drinking (never drinkers, ex-drinkers, current drinkers < 27.8 g day^{-1}, current drinkers 27.8–45.59 g day^{-1}, current drinkers 45.6–68.39 or current drinkers ≥ 68.4 g day^{-1} ethanol); time spent walking (<1 h day^{-1}, or 1 h day^{-1}, or longer); perceived mental stress (low, moderate or high); physical function (limited or unlimited).
CVD, cardiovascular disease; IHD, ischaemic heart disease.

response rate was 94.6%, the subjects were highly representative of the target population.

Our study also had several limitations. First, sleep duration was determined on the basis of a self-reported questionnaire, and the assessment was conducted only once. Lauderdale *et al.*, 2008 reported that the correlation between self-reported sleep duration and that measured objectively by wrist actigraphy was moderate and systematically biased. There is a possibility that some misclassification occurred in our analysis; therefore, some misclassification of sleep duration could have arisen, and this might have affected its perceived association with mortality. However, any such misclassification would have been non-differential, and thus might have led to underestimation of the impact of sleep duration. Secondly, we had no information about sleep quality, the timing of sleep, presence of sleeping disorders, the use of sleep medication or other types of medication, such as antidepressants or benzodiazepines Such factors would have an influence on sleep duration, and thereby might affect the association between long sleep duration and mortality (Suzuki *et al.*, 2009). Thus, considering the influence of such factors, our results might have been overestimated. Finally, we had no information about rotating shift work or night work, even though shift work might affect the association between sleep duration and CVD (Fujino, 2007). However, as about 15% of our study subjects were housewives, 30% were farmers and 20% were retirees, we consider that very few would have been involved in rotating or night shift work.

In conclusion, our study indicates that longer sleep duration appears to be associated with mortality due to all causes, total

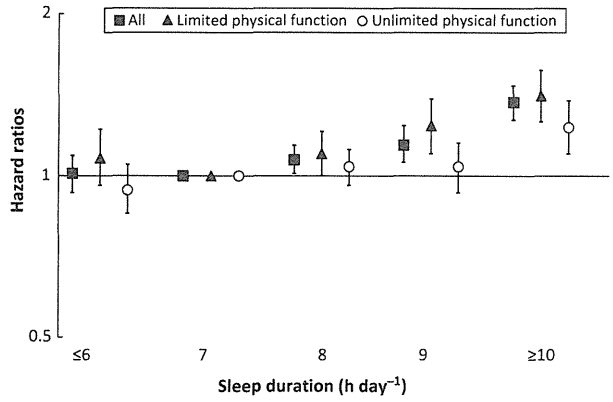

Figure 1. Sleep duration and all-cause mortality. Hazard ratio and 95% confidence intervals according to sleep duration by all subjects, subjects who had limited physical function or subjects who had unlimited physical function.

CVD, IHD and other causes, except for stroke mortality. Such an association was observed irrespective of physical function or self-rated health. The HR for stroke mortality in particular was markedly higher in subjects whose physical function was limited, or in those who had worse health status. Future studies of the association between longer sleep duration and cause-specific mortality may need to consider the effect of physical function and self-rated health.

ACKNOWLEDGEMENTS

This study was supported by a Health Sciences Research Grant for Health Services (H21-Choju-Ippan-001, H20-Junkankitou (Seisyu)-Ippan-013), H23-Junkankitou (Seisyu)-Ippan-005, Ministry of Health, Labour and Welfare, Japan.

DISCLOSURE STATEMENT

All authors have no conflicts of interest.

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Serum Gamma-Glutamyltransferase and the Risk of Hyperuricemia: A 6-Year Prospective Study in Japanese Men

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Key words
- gamma-glutamyltransferase
- aspartate aminotransferase
- alanine aminotransferase
- hyperuricemia
- epidemiology

Abstract

We conducted a longitudinal study to investigate whether increased serum gamma-glutamyltransferase independently predicts subsequent development of hyperuricemia. The study participants included 3310 Japanese men without hyperuricemia, aged 20–54 years. The participants had annual heath examinations for 6 years to assess incident hyperuricemia (defined as serum uric acid > 416.4 μmol/l and/or taking medication for hyperuricemia). The risk of incident hyperuricemia was compared in participants grouped according to their baseline serum gamma-glutamyltransferase level. During follow-up, there were 529 incident cases of hyperuricemia. A positive, dose-response relationship was observed between serum gamma-glutamyltransferase and the risk of incident hyperuricemia. The hazard ratios (95% confidence intervals) for hyperuricemia, compared with a serum gamma-glutamyltransferase level ≤ 19 U/l, were 1.32 (1.05–1.67) for 20–39 U/l, 1.28 (0.90–1.83) for 40–59 U/l, 1.56 (0.98–2.47) for 60–79 U/l, and 1.57 (1.02–2.41) for ≥ 80 U/l after adjustment for baseline serum uric acid, creatinine, total cholesterol, and glycated hemoglobin levels, ln(serum alanine aminotransferase), age, systolic blood pressure, medications for hypertension, hypercholesterolemia, and diabetes, body mass index, and smoking and exercise habits. A similar positive relationship was observed regardless of the presence or absence of alcohol drinking, obesity, metabolic disorders (any combination of hypertension, hypercholesterolemia and/or diabetes), or clinically high serum aminotransferases, without evidence of a significant interaction between increased serum gamma-glutamyltransferase and risk factors for incident hyperuricemia. These findings indicate that increased serum gamma-glutamyltransferase is an independent predictor of subsequent development of hyperuricemia.

received 15.03.2012
accepted 13.06.2012

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DOI http://dx.doi.org/10.1055/s-0032-1321788
Published online: July 20, 2012
Horm Metab Res 2012; 44: 966–974

ISSN 0018-5043

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Introduction

Serum gamma-glutamyltransferase (GGT) has been traditionally used as a marker of excessive alcohol intake and as a screening tool for hepatobiliary disease [1], despite its wide presence throughout the body [2]. However, epidemiological studies suggest that elevated levels of GGT predict subsequent development of several metabolic disorders such as hypertension, diabetes, and the metabolic syndrome, independently of potential confounding factors such as alcohol intake and obesity status [3–8].

A number of cross-sectional studies have shown that GGT is correlated positively with serum uric acid even after alcohol intake and obesity status are taken into account [9–13]. However, only a small number of prospective studies have investigated whether or not increased GGT is an independent predictor of subsequent development of hyperuricemia [5], a condition closely linked with various disorders including gouty arthritis [14, 15], urolithiasis [16, 17], and kidney disease [18, 19]. The present study collected 6-year longitudinal follow-up data to determine the nature of the relationship between GGT and the risk of incident hyperuricemia in Japanese men. Because of the strong correlation between GGT and serum aminotransferases [i.e., aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] [9, 10], the study also examined the relationship between serum aminotransferases and the risk of incident hyperuricemia.