contribution of FABP4 to development of the early phase of LV hypertrophy and systolic dysfunction.

Similar to our results, a very recent study by Baessler et al. [35] demonstrated that FABP4 level was independently correlated with e' after adjustment of age, sex and adiposity in 96 obese subjects and 24 healthy normal weight control subjects, although the association of FABP4 levels with LV diastolic dysfunction was mainly observed in obese subjects with metabolic complications but not in metabolically healthy obese subjects. However, LV diastolic dysfunction in the previous study was defined by combination of several parameters, such as e', E/e', E/A, E-wave deceleration time and left atrial dimension. This definition may affect the results. Of note, we showed that FABP4 level was an independent predictor of e', which is known as an index of LV relaxation and one of the most sensitive indicator of LV diastolic function compared with other indices, especially in a healthy population [14].

A genetic variant at the FABP4 locus associated with decreased FABP4 expression in adipose tissue has been reported to reduce the risk of cardiovascular disease in a population study [36]. We and others previously showed that serum FABP4 level predicts long-term cardiovascular events [37-39]. Furthermore, a large-scale prospective study showed that concentration of FABP4 predicted the risk of heart failure during a median follow-up of 10.7 years [27]. Accumulating evidence of a causative role of FABP4 in cardiac dysfunction would prove that FABP4 is a novel target for prevention of heart failure.

Since FABP4 is a low-molecular-weight protein and freely filtered at the glomerulus, a decrease in glomerular function was shown to result in an elevation of FABP4 concentration [37]. In the present study, FABP4 was negatively correlated with eGFR but remained as an independent predictor of LV diastolic dysfunction even after adjusting for renal function. Besides eGFR, multivariate regression analysis demonstrated that the association of FABP4 level with LV diastolic dysfunction was independent of blood pressure, LV wall thickness and BNP, a well-known predictor of cardiac damage.

The present study has some limitations. Since it has been reported that several drugs, including statin, angiotensin II receptor blocker and peroxisome proliferator-activated receptor γ agonist, affect FABP4 concentrations [40-42], we excluded subjects who had been treated with any drugs in the present study. Therefore, only a small number of subjects could be enrolled, and the statistical power was not large. Another limitation of this study is its cross-sectional design. Prospective longitudinal studies using larger numbers of subjects with no medication are necessary for determining whether FABP4 level is indeed a major determinant of subsequent development of cardiac dysfunction. In addition, the results of our study rely on correlation analyses. A direct relationship between FABP4 level and progression of LV diastolic dysfunction remains unclear. This issue warrants further investigation using an interventional approach.

Conclusions

The present study is the first study to show an independent association of serum FABP4 level with LV diastolic dysfunction in a general population. The increase in serum FABP4 concentration might precede development of the early phase of cardiac dysfunction. Whether FABP4 can serve as a biomarker for early diagnosis of high-risk individuals with heart disease and a potential therapeutic target for cardiac dysfunction warrants further investigation.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

Collection and analysis of data: TF, MF, SY, AM, MK, MD, TMita, SI, YW, KH, MT, KO, HY. Draft of the manuscript: MF, TMiura. All authors read and approved the final manuscript.

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Original Article

Milk Drinking and Mortality: Findings From the Japan Collaborative Cohort Study

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ABSTRACT

Background: Findings regarding the association between milk consumption and all-cause mortality reported by studies carried out in Western populations have been inconsistent. However, no studies have been conducted in Japan on this issue. The present study aimed to investigate the association of milk drinking with all-cause, cardiovascular, and cancer mortality in Japan.

Methods: The data were obtained from the Japan Collaborative Cohort (JACC) study. A total of 94 980 Japanese adults aged 40–79 years who had no history of cancer, stroke, or chronic cardiovascular diseases were followed between 1988 and 2009. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of mortalities were assessed using a Cox proportional hazard regression model and taking the lowest milk consumption group as the reference.

Results: During a median of 19 years of follow-up, there were 21 775 deaths (28.8% and 35.3% from cardiovascular diseases and cancer, respectively). Drinking milk 1–2 times a month was associated with lower all-cause mortality in men compared to those who never drank milk (multivariable-adjusted HR 0.92; 95% CI, 0.85–0.99). In women, those who drank 3–4 times a week also had a lower mortality risk compared with those who never drank milk (HR 0.91; 95% CI 0.85–0.98). Inverse associations between drinking milk and mortality from cardiovascular diseases and cancer were found only in men.

Conclusions: Drinking milk at least 1–2 times a month was associated with lower all-cause mortality in men compared to never drinking milk. An inverse association was also found between drinking milk and mortality from both cardiovascular diseases and cancer. However, lower all-cause mortality in women was found only in those who drank milk 3–4 times/week.

Key words: milk drinking; all-cause mortality; prospective study

INTRODUCTION

Milk is a widely consumed dairy product, rich in saturated fats, minerals, protein, and vitamins. The relationship of drinking milk or consumption of the nutrients found in milk and health has been often reported. For example, casein has been shown to have potent antimutagenic properties,[1,2] and whey protein has been found to increase glutathione synthesis and suppress the development of tumors in an animal model.[3] Calcium from dairy products suppressed colon tumorigenesis in one study[4] and was associated with reduced mortality from stroke in another.[5]

However, on the contrary, some cohort studies have reported positive associations of milk consumption with stroke,[6] coronary heart disease,[7] endometrial cancer,[8] ovarian cancer,[9] and prostate cancer.[10,11] Likewise, studies examining the association between milk consumption and all-cause mortality have produced inconsistent results. While an inverse association has been observed in a few studies,[12–14] other investigations reported no association.[15–18] In the baseline year of the present cohort study (1990), most "milk and dairy product" consumption (92.1%) was in the form of whole milk. However, the average milk consumption among Japanese at that time was much lower than that in Western countries.[19]

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Therefore, we aimed to examine the association between milk consumption and mortality from all and major causes in a large-scale community-based cohort of Japanese men and women, incorporating a wide range of potential confounding variables.

METHODS

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks, sponsored by the Ministry of Education, Sports, Science, and Technology of Japan, started between 1988 and 1990, enrolling subjects living in 45 areas throughout Japan. A total of 110 585 subjects (46 395 men and 64 190 women) 40–79 years of age completed self-administered questionnaires about their lifestyles and medical histories. Sampling methods and other details of the JACC study have been described elsewhere.[20–22] Subjects with a previous history of any cancer, stroke, or chronic cardiovascular diseases (including myocardial infarction, angina pectoris, and other chronic ischemic heart disease) at baseline were excluded ($n = 5693$; 2493 men and 3200 women). Subjects who did not answer the question regarding milk consumption were also excluded ($n = 9912$; 4263 men and 5649 women). After these exclusions, 94 980 subjects (39 639 men and 55 341 women) were enrolled in the present analysis. The study design and informed consent procedure were approved by the Ethics Review Committee of Nagoya University School of Medicine.

Follow-up and mortality surveillance

In each community, investigators conducted a systematic review of death certificates through 2009 for most communities (follow-up finished at the end of 1999 for 4 communities, 2003 for 4 communities, and 2008 for 2 communities). The date and cause of death were confirmed with the permission of the Director-General of the Prime Minister's Office. Individuals who moved away from the study areas were treated as censored cases because subsequent deaths could not be confirmed. The registration of death is required by the Family Registration Law in Japan and is strictly observed. A few validation studies to date reported the accuracy of causes of death in death certificates.[23,24] The Life Span Study showed that concordance between causes of death in death certificates and those of autopsy were 0.87 to 0.91 for cancer and 0.44 to 0.60 for cardiovascular disease.[23] The Hisayama Study reported that concordance was 0.76 for all-cause mortality, 0.92 for cancer mortality, and 0.68 for cardiovascular mortality.[24] We used the underlying causes of death coded by the *International Statistical Classification of Diseases and Related Health Problems-10th Revision* (ICD-10)[25] to identify mortality endpoints: I00–I99 for mortality from cardiovascular disease (CVD) and C00–C97 for mortality from cancer.

Statistical analysis

Information about milk drinking frequency and other lifestyle behaviors was obtained using a self-administered questionnaire. Subjects were divided into five groups by their self-reported milk-drinking frequency: "never," "1–2 times/month," "1–2 times/week," "3–4 times/week," and "almost every day" during the preceding year. The reproducibility and validity of the dietary questionnaire have been reported elsewhere.[26] Specifically, the Spearman rank correlation coefficient between milk-drinking frequency and weighed dietary record for 12 days was 0.65, $P < 0.001$. We compared means using one-way analysis of variance and proportions using the chi-squared test.

Sex-specific age-adjusted all-cause, CVD, and cancer mortality rates were assessed according to the five categories of milk drinking frequency using the Poisson regression model and were expressed as the rate per 1000 person-years. For each subject, the person-years of follow-up were calculated from the date that the baseline questionnaire was completed until the time of death, moving out of the community, or the end of follow-up, whichever occurred first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated separately by sex using the Cox proportional hazard model adjusted for 5-year age groups.

In multivariate analyses, the models were adjusted for potential confounding variables, including smoking status (current, past, or never), alcohol drinking (current, past, or never), sleep duration (<7, 7–7.9, or ≥8 hours/day), body mass index (BMI, continuous), education level (attended school up to age 18), physical activity (exercise more than 1 hour per week), participation in health checkup in the preceding year, green-leafy vegetable intake (almost daily), history of hypertension, history of diabetes mellitus, and history of liver diseases. The number of categories of the covariates adjusted in the multivariate models was dichotomous (yes or no) if not specified. These variables were selected as covariates because they were known or suspected to confound the association.[5,27–30] Missing values were treated as an additional category in the calculations.

Linear trends in mortality risks were assessed by assigning constants of 0, 1.5/30, 1.5/7, 3.5/7, and 1 to the ascending corresponding milk drinking frequency groups, and then treating the categories as numeric variables. Additionally, to address concerns regarding heterogeneity among study areas with different follow-up periods, meta-analysis using individual participant data was conducted. Specifically, three subgroups were defined as different cohorts: cohort 1 included subjects enrolled through 1999 ($n = 12\,944$), cohort 2 included subjects enrolled through 2003 ($n = 4345$), and cohort 3 included subjects enrolled through 2008 or 2009 ($n = 77\,691$). These cohorts were treated as strata in the stratified Cox regression model adjusted for the same covariates as the multivariate model. Heterogeneity between the cohorts was also tested.

Table 1. Demographic characteristics at baseline according to milk intake frequency, 1988–1990, JACC Study

	Men (n = 39639)							Women (n = 55341)						
	Never	1–2 times/ month	1–2 times/ week	3–4 times/ week	Almost everyday	P	Trend P	Never	1–2 times/ month	1–2 times/ week	3–4 times/ week	Almost everyday	P	Trend P
Number of subjects	8551	3534	5962	5597	15995			10481	3666	7627	8146	25421		
Age (years)	56.8 ± 9.9[a]	55.2 ± 10.1	55.5 ± 10.1	55.1 ± 9.9	58.2 ± 10.1	<0.01	<0.01	58.1 ± 10.2	56.6 ± 10.2	55.6 ± 10.1	55.6 ± 9.9	57.9 ± 9.9	<0.01	0.21
Height (cm)	162.6 ± 6.7	163.0 ± 6.7	163.2 ± 6.6	163.3 ± 6.6	163.1 ± 6.4	<0.01	0.03	150.5 ± 6.1	150.8 ± 6.3	151.3 ± 5.9	151.4 ± 5.6	151.4 ± 5.9	<0.01	0.05
Body mass index (kg/m^2)	22.6 ± 3.4	22.8 ± 2.8	22.8 ± 2.8	22.9 ± 5.4	22.6 ± 2.7	0.01	0.51	23.0 ± 3.4	23.0 ± 3.8	23.1 ± 4.4	23.1 ± 3.1	22.8 ± 3.6	<0.01	0.25
Current smoker (%)	60.7	59.3	58.0	53.4	47.3	<0.01	<0.01	7.8	6.8	6.2	4.8	3.9	<0.01	<0.01
Current drinker (%)	75.3	78.7	77.8	79.1	74.0	<0.01	<0.01	22.0	24.3	25.9	27.5	24.7	<0.01	<0.01
Exercise[b] (%)	19.0	26.6	25.1	25.7	29.6	<0.01	<0.01	13.6	17.0	18.5	18.8	22.6	<0.01	<0.01
Sleep duration[c] (%)	30.0	33.5	31.9	32.4	32.0	<0.01	0.02	32.1	34.1	35.8	36.3	36.2	<0.01	<0.01
Green-leafy vegetables intake[d] (%)	21.3	20.1	20.5	20.9	30.1	<0.01	<0.01	24.7	25.0	24.6	24.3	34.9	<0.01	<0.01
Physical checkup participation[e] (%)	54.8	59.2	57.9	54.9	59.2	<0.01	<0.01	54.2	59.1	57.8	54.4	57.6	<0.01	<0.01
College or higher education (%)	9.8	12.4	12.7	11.1	15.9	<0.01	<0.01	4.8	6.5	7.2	6.6	9.4	<0.01	<0.01
History of hypertension (%)	18.5	17.5	17.1	16.9	18.7	0.03	0.45	21.6	20.5	19.1	19.0	20.1	<0.01	0.04
History of diabetes (%)	5.0	4.6	4.2	5.4	7.8	<0.01	<0.01	2.6	3.2	2.7	2.7	4.4	<0.01	<0.01
History of liver diseases (%)	5.8	6.4	6.1	5.4	7.2	<0.01	<0.01	3.5	5.0	3.9	4.0	5.0	<0.01	<0.01

[a]($\bar{X}$) ± SD (all such values).
[b]Defined as regular exercise >1 h per week.
[c]Percentage of subjects reported to sleep 7–8 h per day.
[d]Percentage of subjects reported to consume green-leafy vegetable almost everyday.
[e]Defined as participation in health checkups in the preceding year.

Stratified analysis by sex and age (40–64 and 65–79 years) using the same models was performed because milk-drinking habits may significantly differ with advancing age. Interaction for age groups by milk drinking frequency was tested by adding the interaction term to the Cox models using a likelihood ratio test. In an attempt to avoid possible reverse causation, secondary analysis was also conducted using the same models and excluding deaths that occurred within 5 years of baseline (n = 4922; 2637 men and 2285 women). Statistical analyses were conducted with R version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria),[31] using the Epicalc[32] and survival packages.[33] A P value of less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study sample are shown in Table 1. Subjects who drank milk almost every day (43.6% of the total sample; 40.3% of men, 45.9% of women) tended to be older among men; further, they were more likely to eat green-leafy vegetables every day, had a higher education level, and were less likely to be a current smoker in both men and women.

During the median 19 years of follow-up, 5538 subjects (2038 men and 3500 women) dropped out of the follow-up (5.8%), and 21 775 died (12 203 men and 9572 women). Of these deaths, 28.8% were from CVD (26.1% in men and 32.2% in women), and 35.3% were from cancer (38.5% in men and 31.2% in women). The five most common sites of cancer death were lung, stomach, liver, pancreas, and colon in men (28.9%, 22.8%, 13.5%, 7.4% and 6.5% of cancer deaths, respectively), and stomach, lung, pancreas, liver, and colon in women (19.7%, 13.7%, 12.1% 11.8%, and 11.6% of cancer deaths, respectively).

Age and multivariable-adjusted HRs of all-cause, CVD, and cancer mortality according to the five milk-drinking frequencies are shown in Table 2. Age-adjusted all-cause mortality rates seemed to become lower with increasing frequency of milk drinking in both men and women compared to subjects who never drank milk. In men, this inverse association of milk drinking frequency with all-cause mortality became insignificant after multivariable-adjustment (trend P = 0.09), although HRs for each category were still statistically significant. In women, both the trend and HRs for each category became insignificant after adjustment, except for the "3–4 times/week" category. Total CVD mortality rates were lower in men who drank milk 1–2 times/week or more compared to subjects who never drank milk: multivariable-adjusted HRs for each group compared to subjects who never drank milk were 0.86 (95% CI, 0.77–0.98) for the "1–2 times/week" group, 0.89 (95% CI, 0.79–1.01) for the "3–4 times/week" group, and 0.89 (95% CI, 0.82–0.98) for the "almost every day" group (P for trend = 0.06). Only women who drank milk "3–4 times/week" had a marginally significant lower risk of CVD mortality (HR 0.88; 95% CI, 0.78–1.01) compared to those who never drank milk.

Cancer mortality rates were lower in men who drank milk 1–2 times/month or more compared to those who never drank milk: multivariable-adjusted HRs for each category were 0.88 (95% CI, 0.78–0.99) for the "1–2 times/month" group, 0.90 (95% CI, 0.82–0.99) for the "1–2 times/week" group, 0.85 (95% CI, 0.76–0.94) for the "3–4 times/week" group, and 0.94 (95% CI, 0.87–1.01) for the "almost every day" group. However, we did not observe any linear trend between milk drinking frequency and cancer mortality in men (P for trend = 0.56). In women, milk drinking frequency was not associated with cancer mortality.

Table 2. Hazard ratios for all-cause, cardiovascular, and cancer mortality by milk intake frequency, 1988–2009, JACC study

	Men (n = 39 639)						Women (n = 55 341)					
	Never	1–2 times/ month	1–2 times/ week	3–4 times/ week	Almost everyday	Trend P	Never	1–2 times/ month	1–2 times/ week	3–4 times/ week	Almost everyday	Trend P
Person-years	136 234	56 739	97 564	92 621	254 225		174 369	60 289	129 819	140 478	421 483	
All-cause mortality												
Number of deaths	2813	951	1669	1547	5223		2137	594	1215	1206	4420	
Age-adjusted mortality rate[a]	16.4	14.6	14.7	14.5	14.4		7.2	6.7	6.9	6.4	6.5	
Age-adjusted HR (95% CI)[b]	1	0.89 (0.82–0.95)	0.88 (0.83–0.94)	0.85 (0.79–0.90)	0.86 (0.83–0.91)	<0.01	1	0.97 (0.89–1.06)	0.95 (0.89–1.02)	0.88 (0.82–0.95)	0.91 (0.87–0.96)	<0.01
Multivariable-adjusted HR (95% CI)[c]	1	0.92 (0.86–0.99)	0.91 (0.85–0.96)	0.89 (0.84–0.96)	0.93 (0.89–0.98)	0.09	1	1.00 (0.91–1.05)	0.98 (0.91–1.05)	0.91 (0.85–0.98)	0.96 (0.91–1.01)	0.15
Cardiovascular mortality												
Number of deaths	733	272	423	406	1356		695	210	402	359	1419	
Age-adjusted mortality rate[a]	3.8	3.7	3.4	3.4	3.2		1.8	1.8	1.8	1.6	1.6	
Age-adjusted HR (95% CI)[b]	1	0.97 (0.85–1.12)	0.86 (0.77–0.97)	0.86 (0.76–0.97)	0.84 (0.77–0.92)	<0.01	1	1.09 (0.94–1.27)	1.01 (0.89–1.14)	0.85 (0.75–0.97)	0.92 (0.84–1.02)	0.01
Multivariable-adjusted HR (95% CI)[c]	1	0.98 (0.85–1.13)	0.86 (0.77–0.98)	0.89 (0.79–1.01)	0.89 (0.82–0.98)	0.06	1	1.14 (0.98–1.33)	1.03 (0.91–1.17)	0.88 (0.78–1.01)	0.99 (0.89–1.08)	0.32
Cancer mortality												
Number of deaths	1118	356	659	576	1994		624	159	373	407	1422	
Age-adjusted mortality rate[a]	7.3	6.0	6.4	5.9	6.3		2.9	2.4	2.7	2.7	2.8	
Age-adjusted HR (95% CI)[b]	1	0.84 (0.74–0.94)	0.88 (0.80–0.98)	0.79 (0.72–0.88)	0.86 (0.79–0.93)	<0.01	1	0.83 (0.70–0.99)	0.93 (0.82–1.06)	0.93 (0.82–1.06)	0.97 (0.88–1.06)	0.73
Multivariable-adjusted HR (95% CI)[c]	1	0.88 (0.78–0.99)	0.90 (0.82–0.99)	0.85 (0.76–0.94)	0.94 (0.87–1.01)	0.56	1	0.85 (0.72–1.02)	0.95 (0.83–1.08)	0.95 (0.84–1.08)	1.00 (0.91–1.11)	0.28

CI, confidence interval; HR, hazard ratio.
[a]Age-adjusted mortality was calculated using Poisson regression model and expressed as rate per 1000 person-years.
[b]Age-adjusted HR: adjusted for age categories (5-year age groups).
[c]Multivariable-adjusted HR: adjusted for age categories, smoking status, drinking status, physical activity, sleeping duration, body mass index, education level, participation in health checkups, green-leafy vegetable intake, and history of hypertension, diabetes, and liver disease.

Table 3 shows the results of stratified analysis by subjects' baseline age (40–64 and 65–79 years old). There were more subjects who drank milk every day in the older age group than in the younger age group (46.5% vs. 38.5% in men and 48.2% vs. 42.1% in women; data not shown in tables). Interaction for age groups by milk drinking frequency was marginally significant in men ($P = 0.054$) and significant in women ($P = 0.022$). All-cause mortality was inversely associated with the frequency of milk drinking in older men. Linearity of the association between milk drinking frequency and CVD mortality rates was not significant in either younger or older men, although the multivariable-adjusted HRs of younger men who drank milk "1–2 times/ week" and "almost every day" compared to those who never drank milk were statistically significant: 0.81 (95% CI, 0.67–0.96) and 0.88 (95% CI, 0.77–1.00), respectively. Similarly, although the HRs for cancer mortality were <1 in older men who drank milk 1–2 times/month or more compared to those who never drank milk, the association was not linear.

Although we found lower age-adjusted all-cause and CVD mortality rates in women who drank milk 3–4 times/week compared to those who never drank in younger as well as older subgroups, HRs of milk drinking frequency with all-cause, CVD, and cancer mortality were not statistically significant after multivariate adjustment in any category in either age-group, including the "3–4 times/week" group. Results of the secondary analysis that excluded patients who died within 5 years of baseline were essentially the same (eTables 1 and 2).

DISCUSSION

The present large prospective cohort study showed that men who drank milk at least 1–2 times/month had a significantly decreased risk of all-cause mortality compared to those who never drank milk. Although there was a suggestion of an inverse linear trend ($P = 0.09$), a dose-response relationship was not evident between milk drinking frequency of 1–2 times/month or more and all-cause mortality. The associations were similar between milk drinking and both CVD and cancer mortality in men. In women, the risk of all-cause mortality was lower in those with a milk drinking frequency of 3–4 times/week than those who never drank milk.

Consistent with the present finding, a previous meta-analysis reported a statistically significant inverse association between milk and dairy product consumption and all-cause mortality.[34] However, another dose-response meta-analysis published recently reported a null association.[28] Since these meta-analyses only included data from Western countries, the findings may not be readily applicable to East Asians, who tend to consume much less milk or dairy products. In Japan, even though most elementary schools and junior high schools started serving milk in the school meal in 1958 according to the School Lunch Program Act,[35] the average daily consumption of milk per capita is still approximately one third of that in the United States.[36] Therefore, even subjects who drank milk every day in the present study might only be counted as light-to-moderate milk drinkers in those Western studies, and differences in the absolute amount of milk intake may partly account for the inconsistencies. The present study

Table 3. Multivariable-adjusted hazard ratios for all-cause, cardiovascular, and cancer mortality by milk intake frequency, stratified by age, 1988–2009, JACC study

	Men (n = 39 639)						Women (n = 55 341)					
	Never	1–2 times/month	1–2 times/week	3–4 times/week	Almost everyday	Trend P	Never	1–2 times/month	1–2 times/week	3–4 times/week	Almost everyday	Trend P
Person-years												
Age 40–64 years at baseline	112 528	48 023	81 867	78 349	200 197		133 281	48 339	107 514	116 059	325 453	
Age 65–79 years at baseline	23 706	8716	15 6978	14 273	54 028		41 089	11 951	22 305	24 419	96 030	
All-cause mortality												
Age 40–64 years at baseline												
Number of deaths	1473	518	892	851	2506		767	219	531	540	1714	
Age-adjusted mortality rate[a]	10.9	9.8	9.8	9.7	9.7		4.7	3.9	4.4	4.1	4.2	
Multivariable-adjusted HR (95% CI)[b]	1	0.98 (0.88–1.09)	0.93 (0.86–1.01)	0.93 (0.86–1.02)	0.97 (0.91–1.04)	0.76	1	0.89 (0.77–1.04)	0.97 (0.87–1.09)	0.89 (0.81–1.01)	0.95 (0.87–1.04)	0.55
Age 65–79 years at baseline												
Number of deaths	1340	433	777	696	2717		1370	375	684	666	2706	
Age-adjusted mortality rate[a]	57.1	49.9	51.2	50.1	49.1		29.7	29.6	29.1	26.9	27.0	
Multivariable-adjusted HR (95% CI)[b]	1	0.86 (0.77–0.95)	0.88 (0.80–0.96)	0.85 (0.78–0.93)	0.88 (0.83–0.94)	0.02	1	1.07 (0.96–1.21)	0.97 (0.89–1.07)	0.91 (0.83–1.00)	0.97 (0.90–1.03)	0.17
Cardiovascular mortality												
Age 40–64 years at baseline												
Number of deaths	351	122	183	201	551		195	61	137	132	433	
Age-adjusted mortality rate[a]	2.5	2.2	1.9	2.2	2.0		1.1	0.99	1.0	0.93	0.95	
Multivariable-adjusted HR (95% CI)[b]	1	0.97 (0.78–1.19)	0.81 (0.67–0.96)	0.93 (0.78–1.10)	0.88 (0.77–1.00)	0.19	1	0.99 (0.74–1.33)	1.00 (0.81–1.26)	0.89 (0.71–1.11)	0.96 (0.81–1.14)	0.59
Age 65–79 years at baseline												
Number of deaths	382	150	240	205	805		500	149	265	227	986	
Age-adjusted mortality rate[a]	16.2	17.2	15.8	14.7	14.5		10.4	11.4	10.9	9.0	9.6	
Multivariable-adjusted HR (95% CI)[b]	1	1.01 (0.83–1.22)	0.92 (0.78–1.08)	0.87 (0.73–1.03)	0.91 (0.81–1.03)	0.16	1	1.20 (0.99–1.45)	1.04 (0.90–1.21)	0.87 (0.74–1.02)	0.99 (0.89–1.11)	0.36
Cancer mortality												
Age 40–64 years at baseline												
Number of deaths	682	228	428	385	1132		328	84	233	244	760	
Age-adjusted mortality rate[a]	5.1	4.4	4.7	4.4	4.4		2.2	1.6	2.1	2.0	2.0	
Multivariable-adjusted HR (95% CI)[b]	1	0.94 (0.81–1.09)	0.96 (0.85–1.09)	0.91 (0.81–1.04)	0.96 (0.88–1.06)	0.67	1	0.80 (0.63–1.02)	0.98 (0.83–1.17)	0.93 (0.79–1.10)	0.99 (0.87–1.13)	0.55
Age 65–79 years at baseline												
Number of deaths	436	128	231	191	862		296	75	140	163	662	
Age-adjusted mortality rate[a]	18.7	14.9	15.2	13.8	15.9		6.9	6.3	6.3	6.8	6.9	
Multivariable-adjusted HR (95% CI)[b]	1	0.79 (0.65–0.97)	0.81 (0.68–0.95)	0.73 (0.62–0.87)	0.88 (0.79–0.99)	0.60	1	0.93 (0.72–1.19)	0.89 (0.73–1.09)	0.97 (0.80–1.17)	1.02 (0.89–1.17)	0.37

CI, confidence interval; HR, hazard ratio.
[a]Age-adjusted mortality was calculated using Poisson regression model and expressed as rate per 1000 person-years.
[b]Multivariable-adjusted HR: adjusted for age categories, smoking status, drinking status, physical activity, sleeping duration, body mass index, education level, participation in health checkups, green-leafy vegetable intake, and history of hypertension, diabetes, and liver disease.

would be the first to show that light-to-moderate milk consumption was associated with a lower risk of mortality from both CVD and cancer in men.

There are several possible explanations for the gender difference in the association of milk drinking with mortalities. First, women generally had lower-risk lifestyles than men regardless of milk drinking frequency, which might have obscured the potentially risk-lowering effect of milk drinking. Second, women would have received more advice to increase their calcium intake in an attempt to prevent osteoporosis,[37] which might have modified their milk intake and calcium supplement use. This could have distorted the inverse association of milk drinking frequency with mortality in women since supplementation of calcium has been associated with significant lower blood pressure[38] and lower mortality from ischemic heart disease.[39] Third, the absolute numbers of deaths, as well as the age-adjusted mortality rates, were also higher in men than that in women, which may be related to greater statistical power to detect the association between milk drinking and mortality in men.

On the other hand, inverse associations of milk drinking frequency with all-cause mortality were more evident in the older age group in both sexes (P for interaction = 0.054 in men and 0.022 in women, Table 3 and eTable 2). A few explanations were speculated. First, cumulative (lifelong) milk intake would be higher in older subjects with milk drinking habit. Second, the potential risk-lowering effect of milk might be more visible in older individuals. For example, older people often have abnormal antioxidant status, such as lower erythrocyte glutathione reductase activity,[40] and milk, being a rich source of riboflavin (vitamin B2), could function to protect tissues from oxidative injury.

Our findings may be interpreted in two ways. First, a milk-drinking habit may simply indicate a generally healthy lifestyle. For example, milk-drinking frequency was negatively associated with the prevalence of smoking habit and positively associated with higher education and the frequency of vegetable intake in the present study. Although these variables were adjusted for in the multivariable models, there is a possibility of residual confounding. Second, nutritional components from milk itself may possibly explain the present results. For example, milk minerals, especially calcium, potassium, magnesium, and phosphorus, were inversely associated with hypertension.[41–43] Bioactive

proteins and tripeptides from milk protein have also exerted beneficial effects in reducing blood pressure,[44] cancer prevention,[2] and enhancement of immune response.[45] Angiotensin-converting enzyme (ACE) inhibition is one of the mechanisms that has been studied most in relation to the antihypertensive effect from milk-derived tripeptides.[46] Results from *in vitro* experiments suggest that tripeptides derived from milk, such as isoleucine-proline-proline and valine-proline-proline,[47] can inhibit ACE activity and potentially lower blood pressure. Furthermore, whey protein is rich in cysteine/cysteine and γ-glutamylcysteine dipeptides, which are efficient substrates for glutathione synthesis. Glutathione is a cellular antioxidant that destroys reactive oxygen species and detoxifies carcinogens.[48] Milk fat also contains the highest level of naturally available conjugated linoleic acid among dietary sources, which could up-regulate the tumor suppressor gene in human breast cells[49] and/or inhibit the expression of certain oncogenes.[50–52] Other components in the milk, such as antioxidant vitamins (β-carotene, vitamin A, and vitamin D), may bind and/or solubilize potentially oxidizing fatty acids or other agents.

There are several limitations in the present study. First, information on milk drinking frequency and other lifestyles was self-reported and collected only at baseline. Second, types of milk (eg, reduced fat or whole milk), as well as the portion size per occasion, were not available from the FFQ used in the JACC study. However, milk drinking frequency was correlated with milk intake from 12-day weighed dietary records ($r = 0.65$, $P < 0.001$).[26] Nevertheless, further studies with more accurate assessments of milk in terms of types and portion size are warranted. Third, end of follow-up differed by area (1999, 2003, 2008, and 2009) in the current study, which might have introduced some biases. However, additional meta-analysis using individual data did not indicate heterogeneity ($P = 0.55$ for men and 0.61 for women); HRs were similar to the original model (data not shown).

In conclusion, the present large-scale prospective study found a significantly decreased risk of all-cause mortality in Japanese men who drank milk at least 1–2 times/month compared to never drinking milk. In contrast, among women, drinking milk 3–4 times/week, not every day, was associated with lower all-cause mortality compared to never drinking milk.

ONLINE ONLY MATERIALS

eTable 1. Hazard ratios for all-cause, cardiovascular, and cancer mortality by milk intake frequency, with exclusion of subjects who died during the 5 years of follow-up, 1988–2009, JACC study.

eTable 2. Multivariable-adjusted hazard ratios for all-cause, cardiovascular, and cancer mortality by milk intake frequency, stratified by age with exclusion of subjects who died during 5 years of follow-up, 1988–2009, JACC study.

Abstract in Japanese.

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ORIGINAL PAPER

Dietary patterns and colorectal cancer risk in Japan: the Ohsaki Cohort Study

Yumi Kumagai · Wan-Ting Chou · Yasutake Tomata · Yumi Sugawara · Masako Kakizaki · Yoshikazu Nishino · Ichiro Tsuji

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Abstract
Purpose To evaluate dietary patterns in relation to colorectal cancer risk in Japanese.
Methods We prospectively assessed the association between dietary patterns among the Japanese and the risk of colorectal cancer. Dietary information was collected from 44,097 Japanese men and women aged 40–79 years without a history of cancer at the baseline in 1994.
Results During 11 years of follow-up, we documented 854 cases of colorectal cancer, which included 554 cases of colon cancer and 323 cases of rectal cancer. Factor analysis (principal component analysis) based on a validated food frequency questionnaire identified three dietary patterns: (1) a Japanese dietary pattern, (2) an "animal food" dietary pattern, and (3) a high-dairy, high-fruit-and-vegetable, low-alcohol (DFA) dietary pattern. After adjustment for potential confounders, the DFA pattern was inversely associated with the risk of colorectal cancer (hazard ratio of the highest quartile vs the lowest, 0.76; 95 % confidence interval 0.60–0.97; p for trend = 0.02). When colon and rectal cancers were separated, the inverse association between the DFA pattern and cancer risk was observed for rectal cancer (p for trend = 0.003), but not for colon cancer (p for trend = 0.43). No apparent association was observed for either the Japanese dietary pattern or the "animal food" dietary pattern.
Conclusions The DFA dietary pattern was found to be inversely associated with the risk of colorectal cancer. This association was observed for rectal cancer, but not for colon cancer.

Keywords Colorectal cancer · Dietary patterns · Japanese · Cohort study

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Introduction

Colorectal cancer is one of the most common cancers worldwide, accounting for approximately 10 % of all incident cases of cancer [1]. In Japan, the colorectal cancer incidence rate has increased markedly over the last few decades and is now one of the highest in the world [2].

Geographic and time-trend analyses, as well as migrant studies, strongly suggest that dietary factors play an important role in the pathogenesis of colorectal cancer [3, 4]. Many case–control and cohort studies have addressed the role of dietary factors in the etiology of colorectal cancer. These studies have suggested that high intakes of red and processed meat [5] and alcohol [6, 7] are related to an increased risk of colorectal cancer, while high intakes of milk and total dairy products [8], calcium [9, 10], vitamin D [10, 11], and foods rich in dietary fiber [12–14] are probably related to a decreased risk.

In addition to specific food items or nutrients, a dietary pattern approach may provide additional insights that take into account the combined effects of foods. In Western countries, several studies have reported a decreased risk of colorectal cancer associated with a prudent dietary pattern characterized by higher intakes of vegetables and fruits

Hypertension. 2014 Jun;63(6):1333-8.

Day-to-day variability in home blood pressure is associated with cognitive decline: the Ohasamastudy.

Matsumoto A[1], Satoh M, Kikuya M, Ohkubo T, Hirano M, Inoue R, Hashimoto T, Hara A, Hirose T, Obara T, Metoki H, Asayama K, Hosokawa A,Totsune K, Hoshi H, Hosokawa T, Sato H, Imai Y.

Abstract

Although an association between high blood pressure and cognitive decline has been reported, no studies have investigated the association between home blood pressure and cognitive decline. Home blood pressure measurements can also provide day-to-dayblood pressure variability calculated as the within-participant SD. The objectives of this prospective study were to clarify whether homeblood pressure has a stronger predictive power for cognitive decline than conventional blood pressure and to compare the predictive power of the averaged home blood pressure with day-to-day home blood pressure variability for cognitive decline. Of 485 participants (mean age, 63 years) who did not have cognitive decline (defined as Mini-Mental State Examination score, <24) initially, 46 developedcognitive decline after a median follow-up of 7.8 years. Each 1-SD increase in the home systolic blood pressure value showed a significant association with cognitive decline (odds ratio, 1.48; P=0.03). However, conventional systolic blood pressure was not significantly associated with cognitive decline (odds ratio, 1.24; P=0.2). The day-to-day variability in systolic blood pressure was significantly associated with cognitive decline after including home systolic blood pressure in the same model (odds ratio, 1.51; P=0.02), whereas the odds ratio of home systolic blood pressure remained positive, but it was not significant. Home blood pressuremeasurements can be useful for predicting future cognitive decline because they can provide information not only on blood pressurevalues but also on day-to-day blood pressure variability.

J Am Geriatr Soc. 2014 Mar;62(3):426-34.

Animal protein intake is associated with higher-level functional capacity in elderly adults: the Ohasama study.

Imai E[1], Tsubota-Utsugi M, Kikuya M, Satoh M, Inoue R, Hosaka M, Metoki H, Fukushima N, Kurimoto A, Hirose T, Asayama K, Imai Y, Ohkubo T.

Abstract

OBJECTIVES:

To determine the association between protein intake and risk of higher-level functional decline in older community-dwelling adults.

DESIGN:

Prospective.

SETTING:

Ohasama Town, Japan.

PARTICIPANTS:

Residents (N = 1,007; mean age 67.4 ± 5.5) free of functional decline at baseline; follow-up was conducted for 7 years.

MEASUREMENTS:

Nutrient and food intakes were determined using a validated 141-item food frequency questionnaire. Participants were divided into quartiles according to intake levels of total, animal, and plant protein. Subscales of the Tokyo Metropolitan Institute of Gerontology Index of Competence subscales were used to assess higher-level functional decline. Logistic regression analysis was used to examine the future risk of higher-level functional decline in relation to protein intake, with lowest protein intake as reference.

RESULTS:

During the study period, 24.4% of eligible participants reported declines in higher-level functional capacity. After adjustment for putative confounding factors, men in the highest quartile of animal protein intake had significantly lower risk of higher-level functionaldecline than those in the lowest quartile (odds ratio (OR) = 0.41, 95% confidence interval (CI) = 0.20-0.83; P for trend .01). These associations were not seen in women (OR = 0.76, 95% CI = 0.41-1.34; P for trend .37). No consistent association was observed between plant protein intake and future higher-level functional decline in either sex.

CONCLUSION:

Higher protein, particularly animal protein, was associated with lower risk of decline in higher-level functional capacity in older men. Animal protein intake may be a modifiable indicator for early detection and prevention of higher-level functional decline inelderly adults

Clin Exp Hypertens. 2014;36(2):108-14.

Aldosterone-to-renin ratio and nocturnal blood pressure decline assessed by self-measurement ofblood pressure at home: the Ohasama Study.

Satoh M[1], Hosaka M, Asayama K, Kikuya M, Inoue R, Metoki H, Utsugi MT, Hara A, Hirose T, Obara T, Mori T, Totsune K, Hoshi H, Mano N, Imai Y,Ohkubo T.

Abstract

Based on ambulatory blood pressure (BP) monitoring, the aldosterone-to-renin ratio (ARR) has been reported to be associated with a diminished nocturnal decline in BP, generally referred to as a "non-dipping" pattern. The objective of this cross-sectional study was to investigate the association between ARR and the non-dipping pattern based on home BP measurements. This study included 177 participants≥55 years from the general population of Ohasama (mean age: 67.2 years; 74.6% women); no patient was receiving antihypertensive treatment. The median plasma renin activity (PRA), plasma aldosterone concentration (PAC) and ARR were 0.8 ng/mL/h, 8.1 ng/dL and 9.7 ng/dL per ng/mL/h, respectively. Each 1 SD increase in log-transformed (ln) ARR was significantly associated with the prevalence of the non-dipping pattern after adjustments for possible confounding factors including home morning systolic BP (odds ratio, 1.45; p=0.049). However, no significant associations of PRA or PAC with the non-dipping pattern were observed (p≥0.2). When participants were divided into four groups according to median levels of home morning and night-time systolic BPs, the group with a higher home morning systolic BP (≥128.4 mmHg) with a higher home night-time systolic BP (≥114.4 mmHg) had the greatest ARR levels (ANCOVA p=0.01). These results support the hypothesis that relative aldosterone excess may be related to a non-dipping pattern in a general population and suggest that a non-dipping pattern can be accurately observed by home BP measurements.

Tohoku J Exp Med. 2014;234(3):197-207.

Personality traits as predictors of decline in higher-level functional capacity over a 7-year follow-up in older adults: the Ohasama study.

Tsubota-Utsugi M[1], Satoh M, Hosaka M, Inoue R, Asayama K, Hirose T, Metoki H, Kikuya M, Imai Y, Ohkubo T.

Abstract

Numerous factors that affect functional decline have been identified, and personality traits are considered to be an important factor in functional decline risk. The Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG) was developed to measure three higher-level functional capacities, instrumental activities of daily living, intellectual activity, and social roles, in Japanese elderly, which were previously not assessed adequately with existing scales of functional decline. The objective of this study was to explore the effect of personality traits as predictors of higher-level functional decline over a 7-year follow-up in a rural Japanese community. Data on 676 participants (mean 67.1 years) who were free of functional decline and had completed questionnaires at baseline and 7 years later, were analyzed. Demographic characteristics, lifestyle and personality characteristics were obtained from a self-administered questionnaire at baseline. Higher-level functional decline was examined using the subscales of the TMIG at baseline and at a 7-year follow-up examination. Over the 7-year study period, 21.7% of eligible participants reported decline in higher-level functional capacity. After adjustment for putative confounding factors, the traits that were significant predictors of decline in higher-level functional capacity at the 7-year follow-up had higher psychoticism scores [odds ratio (95% confidence interval) 2.12 (1.23-3.66)] and lower extraversion scores [1.89 (1.01-3.56)]. The personality traits of higher psychoticism and lower extraversion were significantly associated with a risk of future functional decline. A better understanding of these personality traits may help identify of at-risk individuals and could help reduce functional decline in older adults.

Yakugaku Zasshi. 2014;134(12):1347-55.

[A survey of self-medication practices and related factors in the general population: the Ohasamastudy].

[Article in Japanese]

Satoh M[1], Matsumoto A, Hara A, Iwamori S, Obara T, Kikuya M, Metoki H, Hosaka M, Asayama K, Takahashi N, Sato H, Mano N, Imai Y, Ohkubo T.

Abstract

Encouraging self-medication is expected to reduce healthcare costs. To assess the current situation of self-medication practices in thegeneral population, we conducted a questionnaire survey regarding the use of over-the-counter (OTC) medications or dietary supplements in 1008 participants (37% men; mean age, 64±13 years) from Ohasama, a rural Japanese community. A total of 519 (52%) participants used OTC medications or dietary supplements, with common cold medication (36%) and supplements (28%) such as shark cartilage products representing the most common choices. Stepwise logistic regression showed female gender, a higher frequency of visits from a household medicine kit distributor, dyslipidemia, and lower home systolic blood pressure levels as predictors for the use of such materials (chi-square values: 25.3, 12.6, 7.0, and 4.6, respectively; all $p<0.03$). Stratifying the participants according to the use of antihypertensive treatment showed a negative association between systolic blood pressure and the use of OTC medications or supplements only in participants being treated for hypertension. These results suggest that although the adoption rate ofself-medication in Japan can be increased in rural areas, it may remain lower in urban areas. The present study clarifies the factorsassociated with the use of OTC medications or dietary supplements and indicates that appropriate self-medication practices might improve the control of hypertension, particularly in patients undergoing antihypertensive treatment.

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Association between a Serum Thyroid-stimulating Hormone Concentration within the Normal Range and Indices of Obesity in Japanese Men and Women

Masaru Sakurai[1,2], Koshi Nakamura[1], Katsuyuki Miura[3], Katsushi Yoshita[4], Toshinari Takamura[5], Shin-ya Nagasawa[1], Yuko Morikawa[1], Masao Ishizaki[6], Teruhiko Kido[7], Yuchi Naruse[8], Motoko Nakashima[9], Kazuhiro Nogawa[10], Yasushi Suwazono[10] and Hideaki Nakagawa[1]

Abstract

Objective This cross-sectional study investigated the associations between the serum thyroid-stimulating hormone (TSH) concentration and indices of obesity in middle-aged Japanese men and women.

Methods The participants were 2,037 employees (1,044 men and 993 women; age, 36-55 yr) of a metal products factory in Japan. Clinical examinations were conducted in 2009. We obtained a medical history and anthropometric measurements (body weight, body mass index [BMI] and waist circumference) and measured the serum TSH concentrations. The anthropometric indices were compared across serum TSH quartiles. The associations were evaluated separately according to the smoking status in men.

Results The mean body weight (kg), BMI (kg/m^2) and waist circumference (cm) were 69.2, 23.7 and 83.2 in men and 55.3, 22.3 and 74.3 in women, respectively. Men with a higher TSH concentration had higher body weight and BMI values (p for trend=0.016 and 0.019, respectively), and these significant associations were observed even after adjusting for age, smoking status and other potential confounders. The TSH level was not associated with waist circumference. We found a significant interaction between the TSH level and the smoking status on body weight (p for interaction=0.013) and a significant association between the TSH level and body weight in nonsmokers, but not in current smokers. No significant associations were observed between the TSH level and the anthropometric indices in women.

Conclusion Significant positive associations between the serum TSH concentration, body weight and BMI were detected in men only, and an interaction with the smoking status was observed for this association.

Key words: thyroid-stimulating hormone, body weight, obesity, smoking, epidemiology

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Introduction

Thyroid dysfunction is associated with body weight and adiposity (1, 2). In previous studies, the potential impact of minor changes in the thyroid function on body weight and other anthropometric indices in euthyroid participants was investigated (3-6). A recent review of population-based studies indicated that seven of 12 studies found positive associations (7); however, the two studies conducted in Asian populations did not (8, 9).

Gender is associated with the thyroid-stimulating hormone (TSH) concentration (10) and may also affect the relationship between the TSH level and body mass index (BMI) (11). The smoking status is also associated with the thyroid function (12) and body weight (13). The smoking rates in East Asian men, such as those living in Japan and South Korea, are relatively high compared to those observed in Western countries (14). However, of the four studies that evaluated the association between the TSH level and obesity in Asian populations, two were based solely on clinical samples and included only women (15, 16), while the other two population-based studies evaluated the associations in men and women simultaneously without considering the smoking status as a confounding factor (8, 9). Hence, no studies have evaluated the interaction between the TSH level and the smoking status in Asian men.

We therefore investigated the relationship between the serum TSH concentration and anthropometric indices of obesity (body weight, BMI and waist circumference) in this cross-sectional study of middle-aged Japanese men and women. The objectives were: (i) to investigate whether the serum TSH concentration is associated with indices of obesity; (ii) to determine whether a gender difference is observed in the relationship; and (iii) to investigate how this relationship is influenced by the smoking status.

Materials and Methods

Participants

The participants of this study included 36- to 55-year-old employees of a zipper and aluminum sash-producing factory in Toyama Prefecture, Japan. In the spring of 2009, 2,362 (1,219 men and 1,143 women) employees received health examinations. Of these potential participants, 325 (14%) were excluded, including 122 patients with missing baseline data, such as those for body weight, waist circumference and smoking status, 182 patients with a serum TSH concentration outside the normal range (<0.4 or >4.0 μU/mL) and 21 patients with a present/past history of thyroid disease, such as chronic thyroiditis or Graves' disease. Therefore, a total of 2,037 participants (1,044 men and 993 women) were included in this study.

Data collection

The annual health examinations included a medical history, physical examination, anthropometric measurements and measurements of the fasting plasma glucose and serum lipid levels. Height, weight and waist circumference were measured in all subjects, except women who were pregnant, during the routine annual medical checkups. Height was measured to the nearest 0.1 cm without shoes using a stadiometer. Weight was measured in light clothing without shoes using a standard scale and recorded to the nearest 0.1 kg. BMI was calculated as weight/height^2 (kg/m^2). Waist circumference was measured to the nearest 0.1 cm above the iliac crest and below the lowest rib margin at minimal respiration in a standing position. Blood pressure was measured using an automatic manometer (BP 103i, Nippon Colin, Komaki, Japan) after the subjects had rested for five minutes in a seated position. Trained staff obtained the measurements.

The blood samples were obtained in the morning after overnight fasting. The plasma glucose levels were measured enzymatically using an Abbott glucose UV test (Abbott Laboratories, Chicago, USA). The total cholesterol and triglyceride levels were measured using an enzymatic assay. The LDL-cholesterol concentration was calculated using the Friedewald formula (17). Serum was separated immediately after blood collection and stored at -80℃. The stored samples were used to measure the TSH concentrations using a chemiluminescent immunoassay (Chemilumi ACS-TSH, Siemens Healthcare Diagnostics K.K., Tokyo, Japan).

A self-administered questionnaire was used to collect information regarding medical treatment for hypertension, dyslipidemia and diabetes. Metabolic abnormalities were defined according to the Japanese guidelines for metabolic syndrome (18). High blood pressure was defined as a systolic blood pressure of at least 130 mmHg, a diastolic blood pressure of at least 85 mmHg or the current use of antihypertensive medications. Dyslipidemia was defined as a serum triglyceride level of at least 150 mg/dL, an HDL-cholesterol level not exceeding 40 mg/dL or the current use of antihyperlipidemic medications. High fasting plasma glucose was defined as a fasting plasma glucose level of at least 110 mg/dL or the use of antidiabetic medications. Hypercholesterolemia was defined as a serum LDL-cholesterol level of at least 160 mg/dL or the current use of antihyperlipidemic medications.

Statistical analysis

The characteristics of the study participants were compared according to quartiles of the serum TSH concentration. The percentage or prevalence among TSH quartiles was compared using the chi-square test. Linear trends with increasing levels of TSH were tested by assigning each participant a median value for the category and modeling this value as a continuous variable. Multivariate-adjusted p values for the trend were calculated using multiple linear re-

Table 1. Characteristics of the Male Participants according to Thyroid-stimulating Hormone Quartiles

		TSH quartile				
	All	Q1 (lowest)	Q2	Q3	Q4 (highest)	p[a]
TSH (range, μU/mL)		0.4-1.0	1.1-1.3	1.4-1.9	2.0-4.0	
n	1,044	332	202	265	245	
Age (y)	44.1±6.1	44.7±6.1	43.2±5.8	44.6±6.2	43.5±6.0	0.077
Current smokers (%)	39.8	46.4	45.5	38.5	27.3	<0.001
Alcohol drinking						0.433
Nondrinker (%)	16.5	16.9	19.3	16.2	13.9	
Occasional drinker (%)	18.1	15.7	18.3	17.4	22.0	
≥ 1 time/week (%)	65.4	67.5	62.4	66.4	64.1	
Habitual exercise_yes (%)	50.1	49.1	51.0	49.8	51.0	0.962
High blood pressure (%)[b]	31.6	29.2	32.2	35.1	30.6	0.473
Dyslipidemia (%)[b]	30.2	30.7	30.7	27.5	31.8	0.738
Hypercholesterolemia (%)[b]	18.5	17.8	20.3	19.6	16.7	0.734
High plasma glucose (%)[b]	11.3	12.0	8.4	11.7	12.2	0.548

The data are presented as n, mean ± standard deviation or %.
TSH: thyroid-stimulating hormone
[a] p for the trend analyses or *chi*-square tests.
[b] Metabolic abnormalities were defined as follows: high blood pressure, a systolic blood pressure of ≥ 130 mmHg, a diastolic blood pressure of ≥ 85 mmHg or the current use of antihypertensive medications; dyslipidemia, a serum triglyceride level of ≥ 150 mg/dL, an HDL cholesterol level of ≤ 40 mg/dL or the current use of antihyperlipidemic medications; high fasting plasma glucose, a fasting plasma glucose level of ≥ 110 mg/dL or the use of antidiabetic medications; hypercholesterolemia, a serum LDL cholesterol level of ≥160 mg/dL or the current use of antihyperlipidemic medications.

Table 2. Characteristics of the Female Participants according to Thyroid-stimulating Hormone Quartiles

		TSH quartile				
	All	Q1 (lowest)	Q2	Q3	Q4 (highest)	p[a]
TSH (range, μU/mL)		0.4-1.2	1.3-1.7	1.8-2.3	2.4-4.0	
n	993	285	245	217	246	
Age (y)	45.0±6.0	44.8±5.9	44.4±6.0	45.1±6.2	45.9±5.9	0.013
Current smokers (%)	6.0	8.4	6.9	4.6	3.7	0.092
Alcohol drinking						0.936
Nondrinker (%)	9.1	9.8	7.8	8.3	10.2	
Occasional drinker (%)	46.1	47.4	45.3	46.1	45.5	
≥ 1 time/week (%)	44.8	42.8	46.9	45.6	44.3	
Habitual exercise_yes (%)	61.5	61.1	61.2	62.7	61.4	0.984
High blood pressure (%)[b]	17.6	18.2	16.3	16.6	19.1	0.827
Dyslipidemia (%)[b]	7.0	7.4	6.1	7.4	7.3	0.935
Hypercholesterolemia (%)[b]	13.0	13.3	10.6	14.3	13.8	0.631
High plasma glucose (%)[b]	4.1	4.9	2.9	5.1	3.7	0.559

The data are presented as n, mean ± standard deviation or %.
TSH: thyroid-stimulating hormone
[a] p for the trend analyses or *chi*-square tests.
[b] Metabolic abnormalities were defined as follows: high blood pressure, a systolic blood pressure of at least 130 mmHg, a diastolic blood pressure of at least 85 mmHg or the current use of antihypertensive medications; dyslipidemia, a serum triglyceride level of at least 150 mg/dL, an HDL-cholesterol level not exceeding 40 mg/dL or the current use of antihyperlipidemic medications; high fasting plasma glucose, a fasting plasma glucose level of at least 110 mg/dL or the use of antidiabetic medications; hypercholesterolemia, a serum LDL-cholesterol level of at least 160 mg/dL or the current use of antihyperlipidemic medications.

gression analyses of the obesity variables. Adjustment for possible confounders was performed sequentially for age (model 2), plus current smoking status (yes, no) (model 3), plus alcohol drinking (nondrinker, occasional, drinking one time or more/week), habitual exercise (no, yes), presence of hypertension (no, yes), presence of dyslipidemia (no, yes) and presence of high fasting plasma glucose (no, yes) (model 4). Because both the TSH level and anthropometric indices are associated with the smoking status in men, the associations between the TSH levels and the obesity indices in men were evaluated according to the smoking status ("nonsmokers/ex-smokers" versus "current smokers"). We were unable to evaluate these associations in women because the number of female smokers was too small. The statistical analyses were conducted using the Statistical Package for the Social Sciences version 12.0J (SPSS, Tokyo, Japan). A p value of <0.05 was considered to be statistically significant.

The present study was approved by the Institutional Review Committee for Ethical Issues at Kanazawa Medical University.

Results

The participants had a mean serum TSH concentration of 1.5 (standard deviation 0.8) μU/mL for men and 1.8 (0.8) μU/mL for women, which was significantly higher in women than in men (p<0.001). The characteristics of the study participants are shown in Tables 1 (men) and 2 (women). Men had a mean age of 44.1 years and women

Table 3. **Associations between the Anthropometric Indices for Obesity and Serum Thyroid-stimulating Hormone Concentrations in Men and Women**

	TSH quartile				p for trend[a]			
	Q1 (lowest)	Q2	Q3	Q4 (highest)	Model 1	Model 2	Model 3	Model 4
Men								
Body weight (kg)	68.1±0.5	69.8±0.7	69.2±0.6	70.4±0.7	0.016	0.010	0.021	0.035
Body mass index (kg/m^2)	23.4±0.2	23.8±0.2	23.7±0.2	24.1±0.2	0.019	0.007	0.023	0.044
Waist circumference (cm)	82.4±0.5	83.7±0.6	83.6±0.6	83.5±0.6	0.175	0.075	0.128	0.280
Women								
Body weight (kg)	54.5±0.5	55.6±0.6	57.0±0.8	54.8±0.6	0.665	0.684	0.700	0.563
Body mass index (kg/m^2)	21.9±0.2	22.2±0.2	23.1±0.3	22.1±0.2	0.377	0.572	0.568	0.422
Waist circumference (cm)	73.4±0.6	74.1±0.6	76.0±0.8	74.0±0.6	0.358	0.594	0.584	0.422

The data are presented as the mean ± standard error.
TSH: thyroid-stimulating hormone
[a]Model 1, univariate model; Model 2, adjusted for age; Model 3, adjusted for age and smoking; Model 4, adjusted for age, smoking, alcohol drinking, habitual exercise and the presence of high blood pressure, dyslipidemia and high fasting plasma glucose.

Table 4. **Associations between the Anthropometric Indices for Obesity and Serum Thyroid-stimulating Hormone Concentrations according to the Smoking Status in Men**

	TSH quartile				p for trend	p for interaction
	Q1 (lowest)	Q2	Q3	Q4 (highest)		
n (nonsmokers, ex-smokers / current smokers)	178/154	110/92	163/102	178/67		
Body weight (kg)						
Nonsmokers, ex-smokers	68.0±0.7	70.1±0.9	69.7±0.7	71.6±0.7	0.001	0.013
Current smokers	68.3±0.7	69.0±1.0	68.8±0.9	67.0±1.1	0.400	
Body mass index (kg/m^2)						
Nonsmokers, ex-smokers	23.5±0.2	23.9±0.3	24.0±0.2	24.4±0.2	0.005	0.068
Current smokers	23.2±0.2	23.7±0.3	23.4±0.3	23.1±0.3	0.639	
Waist circumference (cm)						
Nonsmokers, ex-smokers	82.4±0.6	83.9±0.8	83.7±0.7	84.5±0.6	0.031	0.057
Current smokers	82.3±0.6	83.5±0.8	83.5±0.8	80.8±1.0	0.295	

The data are presented as the mean ± standard error.
TSH: thyroid-stimulating hormone
The means and standard errors of the anthropometric indices were calculated in each TSH quartile adjusted for age, alcohol drinking, habitual exercise and the presence of high blood pressure, dyslipidemia and high fasting plasma glucose.

had a mean age of 45.0 years. Higher TSH concentrations were associated with a lower percentage of current smokers in men and an older age in women. No associations were observed between the serum TSH concentrations and alcohol drinking, habitual exercise or the prevalence of metabolic abnormalities.

The participants had a mean body weight of 69.2 kg in men and 55.3 kg in women, a mean BMI of 23.7 kg/m^2 in men and 22.3 kg/m^2 in women and a mean waist circumference of 83.2 cm in men and 74.3 cm in women. Table 3 shows the anthropometric obesity indices according to the TSH concentration quartiles. Men with higher TSH concentrations had higher body weight and BMI values. These significant associations were observed even after adjusting for age (model 2), smoking status (model 3) and other potential confounders (model 4). The TSH concentration was not associated with waist circumference. No significant associations were observed in women between the serum TSH concentrations and the anthropometric indices of obesity.

We evaluated the association between the TSH concentration and obesity in men according to the smoking status. Compared to the nonsmoker/past smokers, the current smokers had lower serum TSH concentrations (1.4±0.6 μU/mL for current smokers vs. 1.6±0.8 μU/mL for nonsmokers/ex-smokers, p<0.001), body weight values (68.3±9.9 vs. 69.8± 10.3 kg, p=0.02) and BMI measurements (23.3±3.0 vs. 24.0±3.4 kg/m^2, p=0.002). The waist circumference values did not differ between the two groups (83.4±8.5 vs. 84.1± 9.1 cm, p=0.169). We found a significant interaction between the serum TSH concentration and the smoking status on the relationship with body weight, and the nonsmoking participants with a higher TSH concentration had a significantly higher body weight (Table 4). Similarly, higher TSH concentrations were significantly associated with higher BMI and waist circumference values in nonsmokers only; however, the p values for the interaction were 0.068 and 0.057, respectively, and we found no significant interactions between the TSH concentration and the smoking status (Table 4).