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BMI and All-cause Mortality Among Japanese Older Adults: Findings From the Japan Collaborative Cohort Study

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The association between BMI and all-cause mortality may vary with gender, age, and ethnic groups. However, few prospective cohort studies have reported the relationship in older Asian populations. We evaluated the association between BMI and all-cause mortality in a cohort comprised 26,747 Japanese subjects aged 65–79 years at baseline (1988–1990). The study participants were followed for an average of 11.2 years. Proportional-hazards regression models were used to estimate mortality hazard ratios (HRs) and 95% confidence intervals. Until 2003, 9,256 deaths occurred. The underweight group was associated with a statistically higher risk of all-cause mortality compared with the mid-normal-range group (BMI: 20.0–22.9); resulting in a 1.78-fold (95% confidence interval: 1.45–2.20) and 2.55-fold (2.13–3.05) increase in mortality risk among severest thin men and women (BMI: <16.0), respectively. Even within the normal-range group, the lower normal-range group (BMI: 18.5–19.9) showed a statistically elevated risk. In contrast, being neither overweight (BMI: 25.0–29.9) nor obese (BMI: ≥30.0) elevated the risk among men; however among women, HR was slightly elevated in the obese group but not in the overweight group compared with the mid-normal-range group. Among Japanese older adults, a low BMI was associated with increased risk of all-cause mortality, even among those with a lower normal BMI range. The wide range of BMI between 20.0 and 29.9 in both older men and women showed the lowest all-cause mortality risk.

Obesity (2010) **18,** 362–369. doi:10.1038/oby.2009.190

INTRODUCTION

The relationship between high BMI (BMI: weight in kg/height in m^2) and all-cause mortality is well known (1,2). The World Health Organization defines overweight as a BMI of 25.0–29.9 kg/m^2 and obesity as a BMI of ≥30 kg/m^2. These BMI thresholds have been recommended worldwide for all individuals aged ≥18 (3). However, increasing evidence suggests that the association between BMI and mortality varies with age. A 2007 review by Janssen and Mark concluded that BMIs in the overweight range (BMI: 25.0–29.9) were not associated with a significant increase in mortality risk among the older adults (4). Furthermore, some recent studies have revealed that among this age group, being underweight seems to be a better predictor of mortality than obesity (5–7). Thus, it remains to be established whether older adults require different BMI cut-off points from those younger.

Japan has witnessed a rapid growth in its older population in recent years. From a public health perspective, it is important to determine the BMI range associated with a low mortality risk for them. We sought to examine the association between BMI and all-cause mortality among participants in our Japan Collaborative Cohort study.

METHODS AND PROCEDURES

Study subjects and data collection

The study design and methods adopted by the Japan Collaborative Cohort study have been previously described elsewhere (8,9). Briefly, from 1988 to 1990, healthy subjects in 45 areas throughout Japan replied to a self-administered questionnaire. The cohort comprised 110,792 subjects aged 40–79 years old at baseline, among whom those participants aged 65–79 years were enrolled in this study. The ethical board of the Nagoya University School of Medicine, where the central office of the Japan Collaborative Cohort study was located, has approved our complete study design.

Follow-up

The cause and date of death of the study subjects were identified by reviewing all death certificates in each area by each area investigator

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Received 9 January 2009; accepted 11 May 2009; published online 18 June 2009. doi:10.1038/oby.2009.190

with the permission of the Director-General of the Prime Minister's Office (Ministry of Internal Affairs and Communications). Those who had moved out of a study area were treated as censored. Follow-ups were conducted to the end of 2003, except in four areas where they were discontinued at the end of 1999.

BMI

Information on height and weight as well as lifestyle variables was gathered from self-administered questionnaires. BMI at baseline was calculated based on the height and weight reported. We grouped subjects into the following nine detailed categories according to the World Health Organization classification (10): BMIs <16.0, 16.0–16.9, 17.0–18.4, 18.5–19.9, 20.0–22.9, 23.0–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0. These categories incorporated the current definitions of underweight (BMI: <18.5), normal range (18.5–24.9), overweight (25.0–29.9), and obese (≥30.0) (3). There were 26,747 subjects (11,230 men and 15,517 women) aged 65–79 years who provided information on BMI, all of whom were considered to be eligible for this study.

Analysis

To compare the proportions of subject characteristics across BMI categories at baseline, we used the Mantel–Haenszel test. Hazard ratios (HRs) were calculated separately by gender according to Cox's proportional hazard model. Not only in all the subjects combined but also in subcohorts of noncurrent smokers, physically active subjects (engaging in physical exercise ≥1 h per week and/or walking >1 h/day), and those

Table 1 Distribution of some demographic factors according to BMI categories

		BMI category								
		<16.0	16.0–16.9	17.0–18.4	18.5–19.9	20.0–22.9	23.0–24.9	25.0–27.4	27.5–29.9	≥30.0
Men										
Age at baseline										
65–69	%	19.0	31.0	36.5	43.8	47.4	49.5	52.7	51.6	50.6***
70–74	%	34.1	30.6	37.4	32.8	32.1	32.5	32.8	31.2	28.6
75–79	%	46.8	38.4	26.1	23.4	20.5	18.0	14.4	17.2	20.8
Current cigarette smoker	%	50.8	48.7	52.8	47.2	42.6	34.3	34.2	30.8	29.9***
Current alcohol drinker	%	44.4	53.9	56.5	60.7	62.0	61.4	61.8	66.7	50.6***
Sleep 6.5–8.4 h/day	%	49.2	57.3	54.0	57.4	59.8	60.8	57.7	54.8	48.1*
Physically active	%	42.9	47.4	46.7	48.9	49.6	47.6	44.8	40.9	42.9
College or higher education	%	11.1	12.1	11.9	12.6	13.6	14.6	14.8	12.2	9.1
High-mental stress	%	7.9	13.8	9.8	8.7	7.8	8.6	7.7	10.0	11.7*
Married	%	66.7	75.9	70.6	72.6	73.7	76.4	77.3	80.3	75.3*
Eating green vegetables almost daily	%	23.0	31.0	28.1	30.8	29.3	28.8	27.8	23.7	15.6*
No prior disease history (cancer, MI, or stroke)	%	46.0	59.5	59.5	62.7	65.8	63.3	64.8	62.7	66.2***
Number		126	232	871	1,622	4,670	2,217	1,136	279	77
Women										
Age at baseline										
65–69	%	28.1	41.7	43.0	45.4	50.0	54.5	56.7	58.2	53.2***
70–74	%	37.6	32.8	33.4	31.8	31.3	29.8	29.2	28.6	28.4
75–79	%	34.3	25.5	23.5	22.9	18.7	15.7	14.1	13.2	18.4
Current cigarette smoker	%	7.9	9.0	6.0	4.7	3.6	3.5	3.8	5.6	5.1***
Current alcohol drinker	%	11.6	14.2	16.3	16.3	16.3	17.7	15.9	18.1	15.1
Sleep 6.5–8.4 h/day	%	50.0	54.2	55.6	54.7	58.0	56.0	56.6	53.3	54.7*
Physically active	%	29.8	40.9	42.4	43.7	45.4	44.0	42.9	38.9	35.0***
College or higher education	%	9.5	4.9	6.8	6.2	6.2	5.6	5.0	3.8	4.2***
High-mental stress	%	14.5	7.5	10.4	9.4	8.9	10.3	9.6	9.2	11.2*
Married	%	43.8	43.5	54.8	51.8	52.2	53.0	53.4	53.6	51.7**
Eating green vegetables almost daily	%	24.4	33.3	30.9	33.0	32.1	32.2	31.6	30.6	34.4
No prior disease history (cancer, MI, or stroke)	%	61.2	61.4	63.1	64.1	65.4	64.1	66.3	65.4	55.9
Number		242	345	1,062	1,832	5,596	3,107	2,234	768	331

MI, myocardial infarction.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ by Mantel–Haenszel test adjusting for age categories.

without a disease history of cancer, myocardial infarction and/or stroke were analyzed because these factors were known to influence both BMI and mortality (11–14). In addition to age-adjusted HRs, we calculated HRs adjusting for the following potential confounding factors: smoking (current smoker, exsmoker, nonsmoker, or unknown), alcohol consumption (current drinker, exdrinker, nondrinker, or unknown), sleep duration per night (<6.4 h, 6.5–8.4 h, ≥8.5 h, or unknown), physical activity (engaging in physical exercise ≥1 h per week and/or walking >1 h/day, others or unknown), education (attended school up to 15 years of age, 18 years, >18 years or unknown), perceived stress (yes, no, or unknown), marital status (married, single, or unknown), frequency of green vegetables consumed (almost daily, not daily, or unknown), and history of cancer, myocardial infarction or stroke (yes, no, or unknown). Those potential confounding factors were queried in a self-administered questionnaire, and the results of validation studies on the physical activity and food frequency questionnaire were reported previously (15,16). Moreover, additional analyses were conducted to exclude those subjects whose events occurred within 3 years after baseline to avoid reverse-causality bias.

We used the SAS program version 9.1 (SAS Institute, Cary, NC) for analyses conducted at the Aichi Medical University Computation Center.

RESULTS

Mean value of BMI was 21.9 among men and 22.5 among women. Proportions of those underweight (BMI: <18.5), overweight (BMI: 25.0–29.9) and obese (BMI: ≥30.0) were 10.9, 12.6, and 0.7% among men, and 10.6, 19.3, and 2.1% among women at baseline, respectively. Compared to those with normal-range BMI, both underweight and overweight/obese men and women were less likely to be drinkers, to sleep for the normal duration, and to be physically active, while they were more likely to suffer from high levels of mental stress (**Table 1**). Underweight and overweight/obese men were less likely to eat green vegetables, and corresponding women were more likely to be current smokers. However, among men, the proportion of current smokers decreased with increasing BMI. Among both men and women, subjects who were young, married, and free from prior disease history (cancer, myocardial infarction, or stroke) increased according to increasing BMI. Highly educated subjects showed different trends by gender,

Table 2 Cause of mortality according to BMI categories

	BMI category									
	<16.0	16.0–16.9	17.0–18.4	18.5–19.9	20.0–22.9	23.0–24.9	25.0–27.4	27.5–29.9	≥30.0	Total
Men										
Number at baseline	126	232	871	1,622	4,670	2,217	1,136	279	77	11,230
Number of deaths										
All causes	94	157	500	831	2,149	936	473	115	37	5,292
%	74.6	67.7	57.4	51.2	46.0	42.2	41.6	41.2	48.1	47.1
Malignant neoplasms	13	42	139	252	762	320	151	35	11	1,725
%[a]	13.8	26.8	27.8	30.3	35.5	34.2	31.9	30.4	29.7	32.6
Diseases of the circulatory system	23	31	150	244	681	329	179	44	15	1,696
%[a]	24.5	19.7	30.0	29.4	31.7	35.1	37.8	38.3	40.5	32.0
Pneumonia	18	27	63	98	219	73	33	9	5	545
%[a]	19.1	17.2	12.6	11.8	10.2	7.8	7.0	7.8	13.5	10.3
Senility	3	2	17	16	40	10	6	0	1	95
%[a]	3.2	1.3	3.4	1.9	1.9	1.1	1.3	0.0	2.7	1.8
Women										
Number at baseline	242	345	1,062	1,832	5,596	3,107	2,234	768	331	15,517
Number of deaths										
All causes	132	121	362	536	1,322	690	519	179	103	3,964
%	54.5	35.1	34.1	29.3	23.6	22.2	23.2	23.3	31.1	25.5
Malignant neoplasms	21	26	65	132	359	213	161	45	24	1,046
%[a]	15.9	21.5	18.0	24.6	27.2	30.9	31.0	25.1	23.3	26.4
Diseases of the circulatory system	48	42	151	210	488	272	199	87	48	1,545
%[a]	36.4	34.7	41.7	39.2	36.9	39.4	38.3	48.6	46.6	39.0
Pneumonia	17	17	39	54	91	49	30	7	3	307
%[a]	12.9	14.0	10.8	10.1	6.9	7.1	5.8	3.9	2.9	7.7
Senility	3	4	15	15	50	15	16	2	0	120
%[a]	2.3	3.3	4.1	2.8	3.8	2.2	3.1	1.1	0.0	3.0

[a]Percentage of deaths per all causes.

increasing among men and decreasing among women with increasing BMI.

A total of 5,292 (47.1%) and 3,964 (25.5%) deaths occurred prior to 2003 among men and women, respectively. Those who had moved out of the study areas numbered 1,208 (4.5%), and they were more likely to be women and older than those who were successfully followed. The average follow-up period was 11.2 years (10.6 years for men, 11.7 years for women). Deaths from malignant neoplasms (ICD10: C00–C97), diseases of the circulatory system (I00–I99), pneumonia (J12–J18), and senility (R54) accounted for 32.6, 32.0, 10.3, and 1.8% of total deaths among men and 26.4, 39.0, 7.7, and 3.0% among women, respectively (**Table 2**). The proportion of those who died from malignant neoplasms was highest in the normal-range BMI group, but diminished as the BMI fluctuated above or below normal. Mortality from diseases of the circulatory system

Table 3 Hazard ratios and 95% CI of all-cause mortality according to BMI among men aged 65–79

	BMI category								
	<16.0	16.0–16.9	17.0–18.4	18.5–19.9	20.0–22.9	23.0–24.9	25.0–27.4	27.5–29.9	≥30.0
Total									
Person-years at risk	967	1,962	8,565	16,699	50,471	24,168	12,720	3,142	842
Number of deaths	94	157	500	831	2,149	936	473	115	37
Age-adjusted HR	1.99	1.74	1.27	1.16	1.00	0.94	0.91	0.87	1.02
Age-adjusted 95% CI	(1.62–2.45)	(1.48–2.05)	(1.16–1.40)	(1.07–1.25)		(0.87–1.01)	(0.83–1.01)	(0.72–1.05)	(0.74–1.42)
Multivariate HR[a]	1.78	1.66	1.16	1.12	1.00	0.94	0.92	0.89	0.93
Multivariate 95% CI[a]	(1.45–2.20)	(1.41–1.96)	(1.06–1.28)	(1.04–1.22)		(0.87–1.02)	(0.83–1.01)	(0.73–1.07)	(0.67–1.29)
Not current smokers									
Person-years at risk	404	1,024	3,529	7,706	26,355	14,217	7,359	2,050	552
Number of deaths	45	70	203	371	1,008	503	260	66	21
Age-adjusted HR	2.54	1.70	1.41	1.22	1.00	0.98	1.01	0.87	1.04
Age-adjusted 95% CI	(1.88–3.43)	(1.33–2.16)	(1.21–1.64)	(1.08–1.37)		(0.88–1.09)	(0.88–1.16)	(0.67–1.11)	(0.67–1.59)
Multivariate HR[a]	2.24	1.72	1.29	1.20	1.00	0.98	1.01	0.82	0.87
Multivariate 95% CI[a]	(1.66–3.03)	(1.35–2.20)	(1.11–1.50)	(1.07–1.36)		(0.88–1.09)	(0.88–1.16)	(0.64–1.05)	(0.56–1.34)
Physically active									
Person-years at risk	480	992	4,241	8,529	25,511	11,590	5,658	1,303	385
Number of deaths	34	69	201	345	934	399	189	39	11
Age-adjusted HR	1.57	1.84	1.22	1.08	1.00	0.98	0.95	0.83	0.69
Age-adjusted 95% CI	(1.12–2.22)	(1.44–2.35)	(1.04–1.42)	(0.95–1.22)		(0.87–1.10)	(0.81–1.11)	(0.60–1.14)	(0.38–1.25)
Multivariate HR[a]	1.46	1.76	1.11	1.04	1.00	1.00	0.98	0.83	0.65
Multivariate 95% CI[a]	(1.03–2.06)	(1.37–2.25)	(0.95–1.29)	(0.92–1.18)		(0.89–1.13)	(0.84–1.15)	(0.60–1.15)	(0.36–1.19)
No history of cancer, MI or stroke									
Person-years at risk	484	1,236	5,231	10,750	33,931	15,849	8,331	2,069	548
Number of deaths	40	91	282	483	1,323	524	289	64	21
Age-adjusted HR	1.78	1.77	1.29	1.15	1.00	0.87	0.93	0.82	1.04
Age-adjusted 95% CI	(1.30–2.44)	(1.43–2.19)	(1.13–1.47)	(1.04–1.28)		(0.79–0.97)	(0.82–1.06)	(0.63–1.05)	(0.68–1.60)
Multivariate HR[a]	1.68	1.80	1.20	1.14	1.00	0.91	0.93	0.84	0.99
Multivariate 95% CI[a]	(1.22–2.30)	(1.45–2.23)	(1.05–1.36)	(1.03–1.26)		(0.82–1.00)	(0.82–1.06)	(0.66–1.09)	(0.64–1.53)
Excluded those who died within 3 years									
Person-years at risk	920	1,209	8,407	16,472	49,949	23,952	12,612	3,104	840
Number of deaths	65	124	406	708	1,869	818	424	96	36
Age-adjusted HR	1.72	1.68	1.21	1.15	1.00	0.94	0.93	0.83	1.15
Age-adjusted 95% CI	(1.34–2.20)	(1.40–2.01)	(1.09–1.35)	(1.05–1.25)		(0.86–1.02)	(0.84–1.04)	(0.67–1.01)	(0.83–1.60)
Multivariate HR[a]	1.56	1.62	1.11	1.11	1.00	0.95	0.94	0.84	1.07
Multivariate 95% CI[a]	(1.22–2.00)	(1.35–1.94)	(0.99–1.23)	(1.02–1.21)		(0.88–1.03)	(0.84–1.04)	(0.69–1.04)	(0.77–1.49)

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
[a]Adjusted for smoking, drinking, physical activity, sleep duration, stress, education, marital status, green vegetables, stroke, MI, cancer (includes unknown groups).

seemed to increase as the BMI increased, except for a minor increase in the severely thin group. Mortality from pneumonia showed an obvious inverse association with BMI, and senility was rare among overweight/obese groups.

Tables 3 and 4 showed the HRs by gender of all-cause mortality by BMI categories. Compared with the mid-normal-range group (BMI: 20.0–22.9), multiple-adjusted HRs of all-cause mortality for underweight groups were statistically higher among both men and women, with the highest mortality risk found in the severely thin group (BMI: <16.0) as 1.78 (95% confidence interval: 1.45–2.20) in men, and 2.55 (2.13–3.05) in women. Even within the normal-range group, the lower normal range (BMI: 18.5–19.9) showed a statistically elevated risk compared with the mid normal range (HR: 1.12 in men and 1.22 in women). In contrast, overweight subjects showed no relation with risk elevation among either men or women.

Table 4 Hazard ratios and 95% CI of all-cause mortality according to BMI among women aged 65–79

	BMI category								
	<16.0	16.0–16.9	17.0–18.4	18.5–19.9	20.0–22.9	23.0–24.9	25.0–27.4	27.5–29.9	≥30.0
Total									
Person-years at risk	2,301	3,729	11,814	20,849	65,923	37,144	26,483	9,218	3,844
Number of deaths	132	121	362	536	1,322	690	519	179	103
Age-adjusted HR	2.66	1.52	1.45	1.23	1.00	0.98	1.06	1.07	1.37
Age-adjusted 95% CI	(2.22–3.18)	(1.26–1.83)	(1.29–1.63)	(1.11–1.36)		(0.90–1.08)	(0.96–1.17)	(0.91–1.25)	(1.12–1.68)
Multivariate HR[a]	2.55	1.47	1.42	1.22	1.00	0.96	1.01	0.98	1.24
Multivariate 95% CI[a]	(2.13–3.05)	(1.22–1.77)	(1.26–1.59)	(1.11–1.35)		(0.88–1.06)	(0.92–1.12)	(0.84–1.14)	(1.01–1.52)
Not current smokers									
Person-years at risk	1,631	2,678	9,147	16,306	52,259	29,950	21,359	7,410	3,086
Number of deaths	99	88	273	418	1,033	544	406	145	75
Age-adjusted HR	2.89	1.53	1.43	1.23	1.00	0.98	1.06	1.09	1.24
Age-adjusted 95% CI	(2.35–3.55)	(1.23–1.90)	(1.25–1.63)	(1.10–1.38)		(0.89–1.09)	(0.94–1.18)	(0.92–1.30)	(0.98–1.57)
Multivariate HR[a]	2.72	1.48	1.40	1.24	1.00	0.97	1.02	1.00	1.14
Multivariate 95% CI[a]	(2.21–3.35)	(1.19–1.84)	(1.22–1.60)	(1.10–1.39)		(0.87–1.07)	(0.91–1.14)	(0.84–1.19)	(0.90–1.44)
Physically active									
Person-years at risk	726	1,605	5,078	9,141	29,875	16,085	11,503	3,578	1,325
Number of deaths	32	41	126	200	518	253	171	57	30
Age-adjusted HR	2.32	1.45	1.46	1.25	1.00	1.01	1.00	1.10	1.37
Age-adjusted 95% CI	(1.62–3.31)	(1.05–1.99)	(1.21–1.78)	(1.06–1.47)		(0.87–1.17)	(0.84–1.19)	(0.84–1.45)	(0.95–1.99)
Multivariate HR[a]	2.17	1.41	1.42	1.23	1.00	0.99	0.97	1.02	1.37
Multivariate 95% CI[a]	(1.52–3.11)	(1.02–1.94)	(1.17–1.73)	(1.05–1.45)		(0.85–1.15)	(0.82–1.16)	(0.77–1.34)	(0.95–1.98)
No history of cancer, MI or stroke									
Person-years at risk	1,477	2,327	7,659	13,739	43,948	24,071	17,939	6,164	2,233
Number of deaths	77	75	225	327	835	439	322	111	53
Age-adjusted HR	2.53	1.57	1.49	1.22	1.00	1.03	1.05	1.09	1.32
Age-adjusted 95% CI	(2.01–3.20)	(1.24–1.99)	(1.28–1.72)	(1.07–1.38)		(0.92–1.15)	(0.93–1.20)	(0.89–1.33)	(1.00–1.74)
Multivariate HR[a]	2.38	1.52	1.44	1.21	1.00	1.02	1.02	1.01	1.21
Multivariate 95% CI[a]	(1.88–3.01)	(1.20–1.92)	(1.24–1.67)	(1.06–1.37)		(0.90–1.14)	(0.89–1.16)	(0.83–1.23)	(0.92–1.60)
Excluded those who died within 3 years									
Person-years at risk	2,269	3,697	11,722	20,709	65,577	36,995	26,351	9,164	3,825
Number of deaths	111	101	319	465	1,177	626	464	157	94
Age-adjusted HR	2.63	1.45	1.45	1.20	1.00	1.00	1.06	1.05	1.41
Age-adjusted 95% CI	(2.16–3.19)	(1.18–1.77)	(1.28–1.64)	(1.08–1.34)		(0.91–1.10)	(0.95–1.18)	(0.89–1.24)	(1.14–1.74)
Multivariate HR[a]	2.52	1.40	1.42	1.20	1.00	0.98	1.02	0.97	1.28
Multivariate 95% CI[a]	(2.07–3.06)	(1.14–1.72)	(1.25–1.61)	(1.08–1.34)		(0.89–1.08)	(0.92–1.14)	(0.82–1.15)	(1.04–1.59)

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
[a]Adjusted for smoking, drinking, physical activity, sleep duration, stress, education, marital status, green vegetables, stroke, MI, cancer (includes unknown groups).

In addition, obesity (BMI: ≥30.0) did not elevate the all-cause mortality risk among men, though a slight statistically significant risk was observed among women (HR: 1.24) compared with the mid-normal-range group. Subcohort analyses of noncurrent smokers, physically active subjects, and those without major disease at baseline did not alter the risk estimation dramatically. Excluding events occurring within 3 years also produced no change in the effects on all-cause mortality of the underweight and overweight/obese groups.

DISCUSSION

Using a dataset of a large population-based cohort study of older Japanese subjects aged 65–79 who were followed for >10 years on average, we found that a BMI between 20.0 and 29.9 was associated with a minimum risk of all-cause mortality. This wide range was unchanged when our analysis was limited to subjects who could be followed for at least 3 years from baseline. Moreover, the results were essentially unchanged when subcohort analyses were conducted of those who were not currently smoking, were physically active, or were without a history of cancer, cardiovascular disease, or stroke.

The key advantages of our study were its large-scale cohort with subjects from all over Japan, a long follow-up period of >10 years, and adjustments for known confounders. These advantages allowed us to adopt narrow categories of BMI to examine the association with all-cause mortality among older adults. Moreover, subcohort analyses could be performed considering several factors which influence both body composition and all-cause mortality, especially among the older adults, such as (i) heavy and lengthy periods of smoking (14,17), (ii) physical activity (11), and (iii) subclinical diseases (12).

Risk elevation among thin older adults with results similar to ours was reported by many other cohort studies (1,18,19). There may be several explanations for this association so commonly observed among older adults. First, because lean mass acts as a nutritional preserve (4), and aging itself results in a decline in immune response, such thin older adults may be less resistant to infection (20). Actually, deaths from pneumonia were more prevalent among underweight subjects compared with normal or overweight subjects in our cohort. Second, preexisting disease may be linked to both thinness and an increased risk of death. As shown in **Table 1**, there were more older adults among low-BMI subjects compared with those in other groups, suggesting that age-related diseases cause weight loss. However, excluding the first 3 years of follow-up did not alter that result. Though the purpose of this article was to examine the association between BMI and all-cause mortality, further investigations into the effects of BMI on cause-specific mortality may help us to better understand the relationship of BMI to lean and/or fat mass, and susceptibility to death among older adults. Third, a confounding influence of smoking may exist, because smokers tend to lose weight more readily than nonsmokers (21), and smoking is known to reduce life expectancy (22). Even if such a confounding effect should exist, subcohort analysis of noncurrent smokers revealed that thin subjects who did not smoke also had a higher risk of all-cause mortality, which suggests that a confounding effect from smoking is not the main explanation. Nevertheless, we cannot rule out the possibility that, even with a careful determination of known confounding variables in the present analysis, other undetected factors related to increased mortality risk among thin older adults might have confounded the association between BMI and mortality.

Overweight/obesity is related to excess mortality among both younger and middle-aged populations (1,23,24), and the cut-off points recommended by World Health Organization (3) are mainly based on them. Though some studies have found that the risk of death among older adults was associated with obesity/overweight (2,12,18), the meta-analysis by Janssen and Mark showed no risk elevation for overweight subjects (estimated risk 1.00 with 95% confidence interval: 0.97–1.03), and a significant though very small risk elevation for obese subjects (1.10, 1.06–1.13) (4). Our study showed no increased risk elevation in overweight/obese subjects (except in obese (BMI: ≥30.0) women), and our results were not altered even among some subcohorts. Although the reason for these inconsistent findings is unclear, explanations of why the weak or absent effect of overweight/obesity on all-cause mortality was observed among the older adults in our study may include the following. First, some individuals who were susceptible to the adverse effects of a high BMI may have already died in youth or middle-age, whereas the older adults with a high BMI who survived may have developed a resistance to the effect of overweight/obesity (4,25). Because obesity in women was found to be associated with increased mortality, it is also possible that severely obese men might have been underrepresented in the present sample (self-selection). Second, the possible protective effects of being overweight reflected by a high BMI (such as nutritional reserve) may have prevailed over its negative effects on all-cause mortality in the elderly population (4). Third, a recent study has shown that the prevalence of a clustering of cardiometabolic risk factors among normal-weight individuals was higher in older age groups compared with that in young and middle-aged subjects (26). Thus, the elevated risk of mortality in the normal-weight group among older adults may have caused a relative risk reduction in the overweight/obese groups. As a result, the BMI in older adults may not be a reliable predictor of mortality risk, especially that from cardiovascular diseases, because the variability of BMI in this age group does not adequately reflect that of other intermediate variables leading to disease.

There are some study limitations we should discuss. First, our data were based on self-reported rather than measured heights and weights. Spencer *et al.* compared self-reported and measured height, weight, and BMI among subjects aged 35–76 years. They found that height was overestimated and weight was underestimated, resulting in underestimation of BMI, especially among heavier men and women (27). Thus, we could not exclude the possibility that overweight/obese older adults underestimated their BMI more often than those with a normal BMI, and consequently, misclassifications leading to an underestimation of overweight/obese risk may have occurred. However, according to the same authors (27), normal BMI category men and women were the least likely to be incorrectly allocated to another BMI category, and underweight participants were also less likely to be misclassified into the normal range than overweight/obese subjects, making it somewhat unlikely that overestimations of underweight risk might occur. Second, we have no information on body fat or its distribution, such as the ratio of waist-to-hip circumferences. Both high-body fat and low fat-free mass are known to be independent predictors of overall mortality (28). Moreover, Simpson *et al.* reported that, among women, central adiposity was a better predictor of mortality than BMI (29). A large-scale cohort study among older adults that includes such information will be required to investigate the relationship between body composition and mortality. Finally, it should be kept in mind that we did not examine any relationships between weight history and mortality. Moreover, a review by Bales and Buhr revealed the benefits of maintaining weight in older persons who become obese after age 65 (30). Therefore, the result of our observational study should not be used to dismiss the necessity of weight reduction among all obese older adults. In addition, we do not recommend that underweight older adults should gain weight based on our results, because ours was not an interventional study.

In conclusion, we found an elevated risk of all-cause mortality among thin Japanese older adults and a wide range of BMI between 20.0 and 29.9 that showed the lowest mortality risk to be among both older men and women.

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ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (Monbusho), and Grants-in-Aid for Scientific Research on Priority Areas of Cancer, as well as Grants-in-Aid for Scientific Research on Priority Areas of Cancer Epidemiology from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Monbu-Kagaku-sho) (nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, and 20390156). We express our sincere appreciation to Kunio Aoki, Professor Emeritus of the Nagoya University School of Medicine and former chairman of the Japan Collaborative Cohort study (JACC Study), to Haruo Sugano, former Director of the Cancer Institute, Tokyo, who greatly contributed to the initiation of the JACC Study, and to Yoshiyuki Ohno, Professor Emeritus of the Nagoya University School of Medicine, who was the ex-chairman of the study. We are also greatly indebted to Tomoyuki Kitagawa of the Cancer Institute of the Japanese Foundation for Cancer Research and former chairman of the Grant-in-Aid for Scientific Research on Priority Area "Cancer" and to Kazao Tajima, Aichi Cancer Center and previous chairman of the Grant-in Aid for Scientific Research on Priority Area of Cancer Epidemiology for their warm encouragement and support of this study.

DISCLOSURE

The authors declared no conflict of interest.

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Dig Dis Sci (2010) 55:176–182
DOI 10.1007/s10620-008-0693-0

ORIGINAL ARTICLE

Alcohol Drinking May Not Be a Major Risk Factor for Fatty Liver in Japanese Undergoing a Health Checkup

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Received: 17 September 2008 / Accepted: 29 December 2008 / Published online: 21 January 2009

Abstract The question of whether alcohol drinking is a risk factor for fatty liver as shown by ultrasonography was investigated by both cross-sectional and longitudinal approaches in Japanese undergoing a health checkup. In this cross-sectional study, 32,438 males (49.0 ± 11.9 years old) and 31,009 females (48.2 ± 11.6 years old) receiving a health checkup from 2000 to 2005 were included. Longitudinally, 5,444 males (49.8 ± 10.7 years old) and 4,980 females (50.4 ± 9.3 years old) participating in both 2000 and 2005 were included. Multiple logistic regression analyses were performed for both sexes, adjusted for age, BMI, and smoking. The prevalence of fatty liver in non-, occasional, daily moderate, and daily heavy drinkers was 28.5, 27.5, 18.7, and 19.1% in men and 12.4, 7.7, 5.4, and 6.7% in women, respectively (inverse association, $P \leq 0.05$ for both). Occasional, daily moderate, and daily heavy drinking in men and occasional and daily moderate drinking in women were inversely associated with fatty liver in the cross-sectional study. Daily moderate and heavy drinking appeared protective in men in the longitudinal study. Alcohol drinking may not be a major risk for fatty liver in Japanese undergoing a health checkup.

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Keywords Alcohol drinking · Fatty liver · Multiple logistic regression analysis · Health checkup · Screening and diagnosis

Abbreviations

BMI Body mass index
OR Odds ratio
FBG Fasting blood glucose

Introduction

Fatty liver due to intrahepatic accumulation of lipids is a widely recognized disease, thought to be linked to obesity and alcohol consumption [1–3]. Non-alcoholic fatty liver is recognized as the hepatic consequence of the metabolic syndrome, characterized by abdominal obesity, hypertriglycemia, hyperglycemia, and hypertension [4–6].

It has been controversial whether alcohol drinking causes obesity, although consumption was associated with a greater waist-to-hip ratio, overweight, and fatty liver [7–12]. Alcohol abuse and obesity were found to be equally strong risk factors for fatty liver in the Guangzhou area of China [13]. On the other hand, alcohol drinking may not increase the risk of obesity among US adults, drinking frequency further being inversely associated with the increase in waist circumference and obesity [9–11].

Low to moderate alcohol drinking may lower the risk of type 2 diabetes as well as the metabolic syndrome and cardiovascular mortality [14–19]. Protective effects of low to moderate alcohol drinking on type 2 diabetes may be related to improved insulin sensitivity [20–23]. It is possible that low to moderate alcohol drinking may therefore reduce the fatty liver, which is closely related to insulin resistance [5, 24]. Moderate alcohol drinking may also be a weaker risk factor for fatty liver than obesity from results for the general population of Northern Italy [25]. Low alcohol drinking, less than 20 g alcohol/day, did not increase the risk for fatty liver in Japanese at a health checkup [26]. Low to moderate alcohol drinking attenuated liver steatosis and non-alcoholic steatohepatitis in severely obese individuals in the USA, possibly by reducing insulin resistance [27]. Moreover, modest wine drinking decreased the prevalence of non-alcoholic fatty liver disease in the Third National Health and Nutrition Survey [28].

Most earlier studies excluded subjects with regular alcohol consumption of more than 20 g/day. Some 54–70% of men and 13% of women in Japan consume more than 23 g alcohol/day [29, 30], drinking behavior being to some extent determined by genetic polymorphisms of alcohol metabolism genes and alcohol-induced liver damage being influenced by the genetic variation of cytochrome P4502EI and alcohol dehydrogenase [31–33]. Therefore, exclusion and selection of categories of drinkers may give rise to misleading results.

In the present cross-sectional and longitudinal investigation, we therefore included all alcohol drinkers in an assessment of risk factors including alcohol drinking for fatty liver assessed by ultrasonography. Adjustment was made for age, body mass index (BMI), and smoking in Japanese undergoing a health checkup.

Methods

Design of Study

This study included both cross-sectional and retrospective longitudinal analyses to investigate whether alcohol consumption, determined by questionnaire, is associated with fatty liver, assessed by ultrasonography, in apparently healthy Japanese undergoing a health checkup. Informed consent was obtained from all participants.

Subjects of the Cross-Sectional Study

A total of 179,646 participants (men: 95,977, 51.7 ± 11.6 years old; women: 83,669, 51.4 ± 11.1 years old) underwent medical examinations including ultrasonography at Okazaki City Medical Association, Public Health Center, between April 2000 and March 2006. Since more than half of the participants repeatedly underwent medical checkups, the participants undergoing a checkup for the first time during this period were included. These comprised 34,593 men and 32,743 women. After exclusion of participants who had past or present histories of hepatic diseases induced by drugs, autoimmune conditions, or unknown etiology based on questionnaire and positive results for hepatitis virus, a total of 63,447 participants (men: 32,438, 49.0 ± 11.9 years old; women: 31,009, 48.2 ± 11.6 years old) were included.

Subjects of the Longitudinal Study

The numbers of participants undergoing medical checkups including ultrasonograpy in 2000 and 2005 were 26,247 (men: 14,627; women: 11,620) and 32,548 (men: 17,207; women: 15,341), respectively. After exclusion of participants who had past or present histories of hepatic diseases induced by drugs, autoimmune conditions, or unknown etiology based on questionnaire and positive results of hepatitis virus, a total of 12,453 participants in both 2000 and 2005 (men: 6,924, 49.5 ± 10.5 years old; women: 5,529, 50.7 ± 9.3 years old) were included. Since 2,029 cases (men: 1,480, 21.4%; women: 549, 9.9%) were assessed as having fatty liver in 2000 on ultrasonography, a total of 10,424 participants (men: 5,444, 49.8 ± 10.7 years old; women: 4,980, 50.4 ± 9.3 years old) without fatty liver in 2000 were longitudinally analyzed to determine risk factors for newly developed fatty liver on ultrasonography in 2005.

Questionnaire

Subjects provided data for alcohol consumption and smoking status in a self-administered questionnaire that was then checked during individual interview by expert nurses in the center. Alcohol consumption was recorded using questions on both frequency and quantity. Frequency of drinking was classified into occasional (1–6 days/week) and daily (7 days/week). One drink was defined as one bottle (500 ml) of beer containing 4–5% alcohol or 1 gou (180 ml) of Japanese sake containing 14% alcohol, which is equivalent to 23 g alcohol [29, 30]. Quantities of drinks were recorded as one, two, or three and more than three drinks per day. Amounts of alcohol consumed per week were estimated by assessing both frequency and numbers of drinks only in the daily drinkers since it was difficult to accurately determine amounts of alcohol in the occasional drinkers. The amounts of alcohol in the participants having daily one, two, and three or more than three drinks were estimated to be 161 g/week, 322 g/week, and 483 g or more than 483 g/week, respectively.

The drinkers were divided into three categories: occasional drinkers, daily moderate drinkers who have one drink (23 g alcohol) per day, and daily heavy drinkers who have two and three or more than three drinks (46 g and 69 g or more than 69 g alcohol, respectively) per day. These categories were determined according to the previous reports demonstrating that less than 30 g alcohol/day prevented cardiovascular diseases and the risk threshold for alcohol-induced liver disease was more than 30 g alcohol/day [34, 35].

Measurements

Body weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. BMI was categorized into three categories: <25, 25–29.9, and ≤30 according to the criteria determined by the Japan Society for the Study of Obesity. Age was categorized into four categories: <40, 40–49, 50–59, and <60.

Blood samples were taken from each participant after overnight fasting. Fasting blood glucose (FBG) was measured by Hitachi autoanalyzer models 7600 and 7700 (Hitachi Medical, Co., Tokyo, Japan).

Fasting hyperglycemia was defined if serum FBG was ≤110 mg/dl. Elevated blood pressure or hypertension was diagnosed if resting blood pressures was ≤130/85 mmHg or if the participants had either a history of hypertension or antihypertensive medication, respectively.

Abdominal ultrasonographic examination was performed using convex-type real-time electronic scanners (SSA 250 and 300, Toshiba Medical, Co., Tokyo, Japan) by ten technicians lacking any information about the subjects, including alcohol history. All images were printed on sonograph paper and reviewed by other technicians and physicians. Fatty liver was assessed according to the modified criteria reported previously [36, 37]. These include a comparative assessment of liver brightness (diagnosed by a difference of more than 10 in the average liver and renal cortical echo amplitudes), attenuation of echo penetration, and decreased visualization of veins.

Statistical Analyses

Multiple logistic regression analyses were performed to determine the influence of drinking as a risk factor for fatty liver in both men and women, both adjusted for age and for age, BMI, and smoking in the cross-sectional and longitudinal studies. Adjustment was also made for age, BMI, smoking, and either FBG or elevated blood pressure and hypertension. The analyses were further performed after excluding daily heavy drinkers.

Statistical differences among groups were identified using one-way analysis of variance, followed by multiple comparisons using Bonferroni method. The $m \times n$ chi-square test and Fisher's test were used for comparison of prevalence of fatty liver. Logistic regression analyses were performed using computer software (SPSS version 13.0 for Windows). P values less than 0.05 were considered significant.

Results

Cross-Sectional Study

The percentages of occasional, daily moderate, and daily heavy drinkers were 32.9, 17.7, and 9.3% overall, 33.8, 27.6, and 16.5% for men, and 32.1, 7.4 and 1.8% for women, respectively. Age was significantly lower in occasional and daily drinkers than in non-drinkers in both sexes (Table 1). BMI was significantly higher in occasional drinkers and lower in daily drinkers than in non-drinkers in men and was significantly lower in occasional and daily drinkers than in non-drinkers in women. In addition, the overall prevalence of fatty liver was 23.9% in men and 10.3% in women, and the prevalence of fatty liver in daily

Table 1 Age, BMI, prevalence of fatty liver, and ever smoking rates due to drinking habits in the cross-sectional study

	Non-drinkers	Occasional drinkers	Daily moderate drinkers	Daily heavy drinkers
Men				
%	21.7	33.8	27.6	16.5
Age	50.9 ± 12.6	46.4 ± 12.1*	50.7 ± 11.2	49.1 ± 10.7*
BMI	23.1 ± 3.2	23.4 ± 3.1*	22.9 ± 2.8	23.0 ± 2.8
Fatty liver (%)	28.5	27.5	18.7	19.1
Ever smoking rates (%)	41.1	41.3	44.4	59.6
Women				
Number (%)	58.5	32.1	7.4	1.8
Age	50.6 ± 11.4	44.3 ± 11.2*	47.5 ± 10.0*	42.7 ± 10.1*
BMI	22.2 ± 3.3	21.7 ± 3.1*	21.4 ± 2.8*	21.2 ± 3.0*
Fatty liver (%)	12.4	7.7	5.4	6.7
Ever smoking rates (%)	5.9	11.6	17.3	52.4

* $P < 0.05$ compared with non-drinkers

drinkers was significantly lower than in non-drinkers in both sexes.

Multiple logistic regression analysis revealed that occasional and daily moderate drinking both adjusted for age and for age, BMI, and smoking was inversely associated with fatty liver in both sexes (Table 2). Daily heavy drinking fully adjusted for other factors was inversely associated with fatty liver in men, while this relation did not reach statistical significance in women.

Adding FBG or elevated blood pressure and hypertension, the ORs were not changed in both sexes. After removing the daily heavy drinkers (5,370 men and 563 women), the results were not essentially changed (data not shown).

Longitudinal Study

The percentages of occasional, daily moderate, and daily heavy drinkers were 30.6, 20.3, and 9.5% overall, 31.3, 32.3, and 17.0% for men, and 29.9, 7.0, and 1.2% for women, respectively. Age was significantly lower in occasional and daily heavy drinkers in men and in three groups of drinkers in women than in non-drinkers (Table 3). Fatty liver newly developed in 10.2, 12.1, 11.7, and 12.0% of non-, occasional, daily moderate, and daily heavy drinkers, respectively, overall within the 5-year period. Fatty liver was found in 16.4, 16.7, 12.9, and 12.4% of non-, occasional, daily moderate, and daily heavy drinkers in men, respectively, and in 8.2, 6.8, 5.7, and 6.7% of the women, respectively. The risk of newly developed fatty liver was significantly lower in daily moderate and heavy drinkers than non-drinkers in men.

In the multiple logistic regression analysis, daily moderate and heavy drinking was inversely associated with fatty liver adjusted for age, BMI, and smoking in men. Although similar inverse association was observed in women, this did not reach statistical significance (Table 4). Adding FBG or elevated blood pressure and hypertension did not alter the ORs (data not shown). After removing the daily heavy drinkers (928 men and 60 women), daily moderate drinking was the inverse risk factor for fatty liver (ORs 0.72, 95% CI 0.58–0.89) in men, while the results were not changed in women.

Table 2 Multiple logistic regression analysis for fatty liver in the cross-sectional study

	Age-adjusted OR	95% CI	Multivariate OR*	95% CI
Men				
Non-drinkers	1.00	References	1.00	References
Occasional drinkers	0.93	0.87–0.99	0.89	0.83–0.96
Daily moderate drinkers	0.56	0.52–0.60	0.58	0.53–0.63
Daily heavy drinkers	0.56	0.51–0.61	0.57	0.52–0.63
Women				
Non-drinkers	1.00	References	1.00	References
Occasional drinkers	0.74	0.68–0.81	0.77	0.70–0.85
Daily moderate drinkers	0.44	0.37–0.53	0.53	0.43–0.64
Daily heavy drinkers	0.70	0.50–0.98	0.85	0.60–1.23

* Adjusted by age, BMI, and smoking status

Table 3 Age, BMI, and ever smoking rates due to drinking habits in the longitudinal study

	Non-drinkers	Occasional drinkers	Daily moderate drinkers	Daily heavy drinkers
Men				
Number (%)	19.1	31.3	32.3	17.0
Age	51.4 ± 11.2	48.7 ± 11.1*	50.3 ± 10.5	49.0 ± 9.5*
BMI	22.2 ± 2.6	22.5 ± 2.5*	22.4 ± 2.4	22.4 ± 2.4
Ever smoking rates (%)	39.0	41.8	44.6	63.9
Women				
Number (%)	61.5	29.9	7.0	1.2
Age	51.8 ± 9.2	47.9 ± 9.2*	49.6 ± 8.6*	46.8 ± 9.0*
BMI	21.8 ± 2.6	21.8 ± 2.6	21.5 ± 2.5	21.5 ± 2.7
Ever smoking rates (%)	4.3	9.2	17.7	53.5

* $P < 0.05$ compared with non-drinkers

Table 4 Multiple logistic regression analysis for fatty liver in the longitudinal study

	Age-adjusted OR	95% CI	Multivariate OR*	95% CI
Men				
Non-drinkers	1.00	References	1.00	References
Occasional drinkers	0.97	0.78–1.19	0.95	0.77–1.17
Daily moderate drinkers	0.73	0.59–0.90	0.72	0.58–0.89
Daily heavy drinkers	0.67	0.52–0.87	0.65	0.50–0.85
Women				
Non-drinkers	1.00	References	1.00	References
Occasional drinkers	0.83	0.65–1.05	0.81	0.63–1.04
Daily moderate drinkers	0.67	0.42–1.07	0.71	0.44–1.16
Daily heavy drinkers	0.08	0.29–2.26	0.74	0.25–2.17

* Adjusted by age, BMI, and smoking status

Discussion

The present study demonstrated that alcohol drinking may not be a major risk factor for fatty liver as assessed by ultrasonography in Japanese undergoing a health checkup. Thus, the prevalence of fatty liver in both sexes was significantly lower in daily drinkers than in non-drinkers. Occasional, daily moderate, and daily heavy drinking in men and occasional and daily moderate drinking in women fully adjusted for other factors were inversely associated with fatty liver in the cross-sectional study. Daily moderate and heavy drinking exerted protective effects against the development of fatty liver in men in the longitudinal study.

The low to moderate amounts of alcohol found to reduce type 2 diabetes, metabolic syndrome, and cardiovascular diseases have ranged widely [14–23]. However, low to moderate amounts of alcohol were usually defined as less than 30 g alcohol/day [34, 35, 38]. Further, the risk for cardiovascular diseases is lower when alcohol consumption is low to moderate, and the risk is higher when alcohol consumption is high, resulting in a dose-response curve that is J- or U-shaped [38]. It was also demonstrated that the threshold for non-cirrhotic and cirrhotic liver damage was reported to be less than 30 g alcohol/day, and risk increased with increasing daily intake [35, 39]. We estimated that alcohol consumption of daily heavy drinkers ranged from 46 g alcohol/day to 69 g or more than 69 g alcohol/day in the present study. We also demonstrated that even daily heavy drinking was inversely associated with fatty liver and that exclusion of daily heavy drinkers did not essentially alter the trend in both cross-sectional and longitudinal studies. However, we do not encourage heavy alcohol drinking since we focused the effect on fatty liver, but not on liver injury, and more than 30 g alcohol/day has been reported to be injurious to the liver [35, 39].

Ethanol is known to impair fat oxidation and stimulate lipogenesis in the liver [2, 3]. Although there is conflicting evidence, alcohol intake is reported to be associated with fatty liver in apparently healthy adult men in Spain, with alcohol abuse and obesity being equally strong risk factors for fatty liver in the Guangzhou area of China [12, 13]. Alcohol drinking was found to be a weaker risk factor for fatty liver than obesity in another study [25].

Although our results appear paradoxical on the surface, we speculate that the discrepancy may be related to the different proportion of heavy alcohol drinkers. Our results are in line with other reports that low alcohol drinking did not increase the risk for fatty liver in health checkup participants in Japan and that low to moderate alcohol drinking reduced liver steatosis and non-alcoholic steatohepatitis found in the severely obese in the USA [26, 27]. Further, it was recently demonstrated that modest wine consumption was associated with a reduced prevalence of non-alcoholic fatty liver disease [28].

Adding FBG or elevated blood pressure and hypertension did not alter the ORs in both cross-sectional and longitudinal studies, suggesting that the relationship between alcohol drinking and fatty liver was not confounded by these factors and the effect of alcohol drinking on fatty liver may be independent of improved glucose metabolism and endothelial function. The mechanism by which low to moderate alcohol drinking reduces type 2 diabetes, cardiac ischemic diseases, and the metabolic syndrome may be, in part, related to increased insulin sensitivity [20–23]. Insulin resistance causes accumulation of fat in the hepatocytes through lipolysis and hyperinsulinemia [4, 40]. Although we did not measure insulin sensitivity in the present study, we speculate that this may be increased in our population by alcohol drinking, thereby attenuating fatty liver.

A major limitation of the present study was the cross-sectional and retrospective longitudinal design. The subjects were limited to the Japanese participants undergoing a health checkup. Although it would have been preferable to follow up all participants in 2000 to investigate the risk factor for fatty liver in 2005 in a cohort manner, only 42.5% of the participants in 2000 received the medical checkup in 2005. In addition, alcohol consumption was self-reported, and the drinkers were roughly divided into four groups according to the frequency of drinking for logistic regression analyses, which may result in inaccuracies. Finally, although histological diagnosis is more accurate, we had to rely on ultrasonography for the purposes of the present study. Ultrasonography cannot distinguish steatosis and steatohepatitis, with the result that it may be unclear if the participants drinking alcohol have liver damage. However, it has been widely used to assess fatty liver since it is a non-invasive procedure with relatively high sensitivity and specificity for screening purposes [1, 12, 13, 25, 26, 36, 37]. The prevalence of fatty liver, 23.9% in men and 10.3% in women in the present study, is consistent with values in a previous Japanese report [41].

In conclusion, alcohol drinking may not be a major risk factor for fatty liver on ultrasonography in Japanese undergoing a health checkup. However, we should be prudent, and the available data do not yet provide a rationale for encouragement of alcohol consumption. Future cohort studies assessing the influence of differing amounts of alcohol are necessary to confirm whether alcohol drinking may indeed not be a risk for fatty liver.

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INTERNATIONAL JOURNAL OF
UROLOGY

International Journal of Urology (2011) 18, 131–140 doi: 10.1111/j.1442-2042.2010.02690.x, 10.1111/j.1442-2042.2010.02702.x

Original Article: Clinical Investigation

Impact of insulin resistance, insulin and adiponectin on kidney stones in the Japanese population

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Objectives: It has been reported that kidney stones are linked to metabolic syndrome (MetS), which is characterized by insulin resistance. The aim of the present study was to examine the association of insulin resistance, insulin and adiponectin with kidney stones in a Japanese population.
Methods: From February 2007 to March 2008, 1036 (529 men and 507 women) apparently healthy Japanese subjects, aged 35–79 years, were analyzed. Weight, height, waist circumference and blood pressure were measured. Overnight fasting blood was collected to measure insulin and adiponectin levels. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated to assess insulin resistance. Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence intervals for a self-reported history of kidney stones across tertiles of HOMA-IR, insulin and adiponectin.
Results: Of the participants, 84 men (15.6%) and 35 women (6.9%) had a history of kidney stones. Age, body mass index, waist circumference, systolic and diastolic blood pressures, HOMA-IR and insulin were significantly higher in women with than in women without kidney stones. There was no difference in adiponectin level between subjects with and without a history of kidney stones in either sex. Furthermore, a significant positive trend was observed in the age-adjusted OR for a history of kidney stones across insulin tertiles (*P*-value for trend = 0.04) in women.
Conclusions: For Japanese women, HOMA-IR and insulin are associated with a history of kidney stones. The findings suggest that MetS components could increase the risk of kidney stones through subclinical hyperinsulinemia and insulin resistance.

Key words: adiponectin, insulin, insulin resistance, kidney stone, metabolic syndrome.

Introduction

Kidney stones are a common urological problem with a lifetime prevalence of approximately 10% in men and 5–6% in women, and their prevalence has been increasing in many developed countries.[1–3] In Japan, as in other countries, the age-standardized annual incidence of first-episode upper urinary tract stones was 81.3 per 100 000 men and 29.5 per 100 000 women in 1965, and it rose steadily to reach 165.1 per 100 000 men and 65.1 per 100 000 women in 2005.[4] Around the same period, a rapid increase in the prevalence of obesity in Asian countries – including Japan, where obesity traditionally had not been common – was reported.[5] Furthermore, 24.4% of middle-aged Japanese men and 12.1% of middle-aged Japanese women appeared to have metabolic syndrome (MetS) in 2006.[6]

Kidney stone disease has been linked to the major MetS components, including obesity, hypertension and diabetes mellitus (DM), in several epidemiological studies.[7–10] A positive relationship between a self-reported history of kidney stones and the number of MetS components has also been observed in a cross-sectional analysis.[11] MetS is characterized by high insulin resistance and compensatory hyperinsulinemia.[12] Based on this evidence, high insulin resistance and hyperinsulinemia might raise the risk for kidney stone formation. In contrast, adiponectin might protect against the development of kidney stones, because it is the most abundantly circulating adipokine showing an inverse association with adiposity and body mass index (BMI).[13]

Given the rapid increase in the prevalence or incidence of kidney stones and the prevalence of MetS in many nations, it is important to clarify the relationships between kidney stones and MetS. However, the associations of insulin resistance, insulin and adiponectin with kidney stones have not

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Received 15 August 2010; accepted 16 November 2010.
Online publication 22 December 2010

been reported. In the present study, associations of MetS components, insulin resistance assessed by homeostasis model assessment of insulin resistance (HOMA-IR), insulin and adiponectin with a self-reported history of kidney stones were investigated in an apparently healthy Japanese population.

Methods

Study population

All procedures of the present study were approved by the Nagoya City University Institutional Review Board. Okazaki City, which is located in the central area of Japan, had a population of 374 358 (189 200 men and 185 158 women) on 1 January 2008. From February 2007 to March 2008, 38 920 people (21 717 men and 17 203 women) visited the Okazaki City Medical Association Public Health Center for a comprehensive health examination. A consent form and a questionnaire for the present study were randomly sent to 3852 inhabitants aged 35–79 years before their medical check-up. An answer to the questionnaire survey was received from 1112 respondents (566 men and 546 women). Participants who did not complete the questions on medical history of kidney stone disease (4 men and 2 women) and those who did not undergo blood examinations (33 men and 37 women) were excluded. The remaining 1036 participants (529 men and 507 women) were analyzed in the present study. Written informed consent was obtained from all participants.

Anthropometrics and biochemistry

Bodyweight (kg), height (cm) and waist circumference (cm) were measured to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated as the weight in kilograms/height in meters squared. Blood pressure (BP; mmHg) was measured in the morning after 10 min of rest in the sitting position. Overnight fasting venous blood samples were collected in the morning. After serum was separated, glucose, triglyceride, total cholesterol, high-density lipoprotein (HDL) cholesterol and uric acid levels were immediately measured with a Hitachi autoanalyzer model 7700 (Hitachi Medical, Tokyo, Japan). Serum insulin was measured by a chemiluminescence enzyme immunoassay kit (FUJIREBIO, Tokyo, Japan). Blood was collected in plasma tubes and stored at −80°C until analysis of adiponectin levels. The concentrations of plasma adiponectin were measured using commercially available ELISA kits (Otsuka Pharmaceutical, Tokyo, Japan). HOMA-IR[14] was used to assess insulin resistance. The HOMA-IR value was calculated as fasting insulin (μU/mL) × fasting glucose (mmol/L) / 405.[14]

Components of MetS were diagnosed using the Evaluate Diagnostic Standards for MetS in Japan,[15] and participants were classified as patients with MetS if they had central obesity (waist circumference ≥85 cm in men, ≥90 cm in women) and two or more of the three following components: (i) high BP (≥130 mmHg systolic and/or ≥85 mmHg diastolic or self-reported antihypertensive medication use); (ii) high triglyceride level (≥150 mg/dL or self-reported anti-high triglyceride medication use) or low HDL-cholesterol (<40 mg/dL or self-reported anti-low HDL-cholesterol medication use); and (iii) fasting hyperglycemia (≥110 mg/dL or self-reported diabetic medication use).

Questionnaire

The subjects' medical histories were obtained by a self-administered questionnaire that was partially supported and reconfirmed by a personal interview with a trained examiner. Participants who responded "yes" to the question "Have you ever had kidney stone disease?" were defined as having had an episode of kidney stones. Age at first kidney stone or family history of kidney stones was not ascertained. History of and medication for hypertension, DM and dyslipidemia were also self-reported. In women, menopausal status was also checked.

Statistical analysis

All data were analyzed by sex. The demographic variables were calculated and tabulated between subjects with and without a self-reported history of kidney stones. Categorical variables were compared using the χ^2-test or Fisher's exact test, and mean values of continuous variables were compared between groups using Student's *t*-test. Pearson's correlation coefficients were calculated between two variables. Based on HOMA-IR, insulin and adiponectin, participants were grouped into tertiles. The Mantel–Haenszel χ^2-test was used to check trends in the prevalence of self-reported history of kidney stones across HOMA-IR, insulin and adiponectin tertiles. Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) for a self-reported history of kidney stones across HOMA-IR, insulin and adiponectin tertiles were estimated using logistic regression analysis. To test linear trends across HOMA-IR, insulin and adiponectin tertiles, the median of each tertile was used as a continuous variable. Because the distributions of HOMA-IR, insulin and adiponectin were skewed, log-transformed HOMA-IR, insulin and adiponectin were used and subsequently back-transformed for interpretation of the results. All statistical analyses were carried out using the Statistical Analysis System, version 9.1 (SAS Institute, Cary, NC, USA), and significance was defined as $P < 0.05$.

Results

Of the participants, 84 men (15.6%) and 35 women (6.9%) had a history of kidney stones. In men, there were no

Table 1 Subjects' characteristics between men with/without self-reported history of kidney stones

Men (n = 529)	Self-reported history of kidney stones		P*
	With (n = 84)	Without (n = 445)	
Age, mean ± SD (year)	61.2 ± 9.5	60.2 ± 10.4	0.44
Height, mean ± SD (cm)	165.4 ± 5.8	166.0 ± 6.2	0.47
Weight, mean ± SD (kg)	63.7 ± 9.1	64.1 ± 9.8	0.70
BMI, mean ± SD (kg/m^2)	23.2 ± 2.9	23.2 ± 3.0	0.99
Waist circumference, mean ± SD (cm)	84.5 ± 7.6	84.4 ± 7.8	0.91
Systolic BP, mean ± SD (mmHg)	129.8 ± 15.1	128.2 ± 15.2	0.38
Diastolic BP, mean ± SD (mmHg)	81.4 ± 9.5	80.3 ± 9.1	0.32
Total cholesterol, mean ± SD (mg/dL)	202.8 ± 32.2	206.0 ± 30.8	0.39
Triglycerides, mean ± SD (mg/dL)	115.7 ± 69.2	122.3 ± 85.5	0.44
HDL-cholesterol, mean ± SD (mg/dL)	61.4 ± 15.0	64.1 ± 16.9	0.16
Uric acid, mean ± SD (mg/dL)	6.1 ± 1.1	5.9 ± 1.2	0.41
Glucose, mean ± SD (mg/dL)	99.5 ± 16.5	100.3 ± 20.8	0.70
HOMA-IR†	1.14	1.12	0.86
Insulin (μU/mL)†	4.69	4.61	0.79
Adiponectin (μg/mL)†	5.69	5.87	0.62
Overweight (25 ≤ BMI < 30), n (%)	18 (21.4)	88 (19.8)	0.73
Obese (30 ≤ BMI), n (%)	1 (1.2)	7 (1.6)	1.00
Hypertension, n (%)	25 (29.8)	99 (22.3)	0.14
Diabetes mellitus, n (%)	9 (10.7)	31 (7.0)	0.23
Dyslipidemia, n (%)	14 (16.7)	51 (11.5)	0.18
Metabolic syndrome, n (%)	15 (17.9)	69 (15.5)	0.59

*P-value for t-test, χ^2-test or Fisher's exact test. †Geometric mean. BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; SD, standard deviation.

significant differences between subjects with and without a history of kidney stones (Table 1). In contrast to men, age, BMI, waist circumference, systolic and diastolic BP, HOMA-IR and insulin were significantly higher in women with than in women without a history of kidney stones (Table 2). On the other hand, adiponectin was no different between the two groups of either sex (Tables 1,2). The prevalence of overweight, obese, hypertension, DM, dyslipidemia or MetS was no different between the two groups in men (Table 1). In contrast to men, the prevalence of obesity and MetS in women tended to be higher in the kidney stone group ($P = 0.06$ and 0.07, respectively: Table 2). Postmenopausal status was significantly more frequent in women with a history of kidney stones ($P = 0.02$: Table 2).

Figure 1 shows scatter plots with the r-value for correlation coefficients between natural logarithm (ln) HOMA-IR, ln (insulin), ln (adiponectin) and age (Fig. 1a–c), BMI (Fig. 1d–f), waist circumference (Fig. 1g–i) and systolic BP (Fig. 1j–l) by sex. In both sexes, HOMA-IR and insulin were correlated positively with BMI, waist circumference and systolic BP. In contrast, adiponectin was correlated negatively with BMI and waist circumference in both sexes. The r-values for correlation coefficients between ln (HOMA-IR), ln (insulin), ln (adiponectin), and age (Fig. 1a–c), ln (adiponectin) and systolic BP (Fig. 1l) were low.

In each of the HOMA-IR tertiles, the prevalence of self-reported history of kidney stones and age-adjusted OR (95% CI) are shown in Table 3. In men, the prevalence and age-adjusted OR for history of kidney stones were not different across HOMA-IR tertiles. Although upper HOMA-IR tertiles had the highest prevalence of self-reported history of kidney stones and the highest age-adjusted OR in women, no significant trend was found (P-value for trend = 0.09 and 0.14, respectively: Table 3 & Fig. 2a). Table 4 shows the prevalence of self-reported history of kidney stones and age-adjusted OR (95% CI) across insulin tertiles. In women, significant positive trends were observed for the prevalence of self-reported history of kidney stones and age-adjusted OR across insulin tertiles (P-value for trend = 0.03 and 0.04, respectively: Table 4 & Fig. 2b). In each of the adiponectin tertiles, no significant trends were observed for the prevalence and age-adjusted OR for a history of kidney stones in either sex (Table 5 & Fig. 2c).

Table 2 Subjects' characteristics between women with/without self-reported history of kidney stones

Women (*n* = 507)	Self-reported history of kidney stones		*P**
	with (*n* = 35)	without (*n* = 472)	
Age, mean ± SD (year)	59.3 ± 6.9	56.0 ± 9.5	0.01
Height, mean ± SD (cm)	154.4 ± 5.3	154.2 ± 5.3	0.83
Weight, mean ± SD (kg)	56.4 ± 11.2	52.7 ± 7.3	0.06
BMI, mean ± SD (kg/m^2)	23.6 ± 3.8	22.1 ± 2.8	0.04
Waist circumference, mean ± SD (cm)	85.6 ± 10.8	81.4 ± 8.0	0.03
Systolic BP, mean ± SD (mmHg)	131.3 ± 16.3	122.7 ± 15.6	0.002
Diastolic BP, mean ± SD (mmHg)	80.0 ± 9.0	76.4 ± 9.3	0.03
Total cholesterol, mean ± SD (mg/dL)	221.0 ± 30.6	215.6 ± 33.6	0.36
Triglyceride, mean ± SD (mg/dL)	102.6 ± 49.0	92.7 ± 51.8	0.27
HDL cholesterol, mean ± SD (mg/dL)	74.5 ± 19.8	76.9 ± 17.4	0.44
Uric acid , mean ± SD (mg/dL)	4.7 ± 1.0	4.4 ± 0.9	0.13
Glucose, mean ± SD (mg/dL)	95.7 ± 13.6	93.9 ± 12.7	0.42
HOMA-IR†	1.31	1.08	0.04
Insulin (μU/mL)†	5.60	4.71	0.04
Adiponectin (μg/mL)†	8.57	9.43	0.23
Overweight (25 ≤ BMI < 30), *n* (%)	8 (22.9)	65 (13.8)	0.14
Obese (30 ≤ BMI), *n* (%)	2 (5.7)	4 (0.8)	0.06
Hypertension, *n* (%)	7 (20.0)	76 (16.1)	0.55
Diabetes mellitus, *n* (%)	2 (5.7)	18 (3.8)	0.64
Dyslipidemia, *n* (%)	7 (20.0)	76 (16.1)	0.55
Metabolic syndrome, *n* (%)	4 (11.4)	19 (4.0)	0.07
Menopause, *n* (%)‡	28 (93.3)	327 (73.2)	0.02

**P*-value for *t*-test, χ^2-test or Fisher's exact test. †Geometric mean. ‡Missing values (*n* = 30 in menopausal status) were excluded in the calculation of percentage (%). BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; SD, standard deviation.

Discussion

The present study was carried out to explore associations between MetS components and a history of kidney stones in an apparently healthy Japanese population with a smaller BMI than Caucasians and Africans. Positive associations of obesity estimated by BMI and waist circumference, systolic BP and diastolic BP with a history of kidney stones were found in Japanese women.

Previous epidemiological studies also showed that the effect of obesity, hypertension and DM on kidney stones was present predominantly in women.[8,10,16,17] The Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS) I and II showed that the relative risk for a patient with kidney stones who weighs more than 100.0 kg *vs* a patient with kidney stones who weighs less than 68.2 kg was 1.44 (95% CI, 1.11–1.86) in men, 1.89 (95% CI, 1.52–2.36) in older women and 1.92 (95% CI, 1.59–2.31) in younger women.[8] BMI and waist circumference were also associated with stone formation, predominantly in women rather than in men in the prospective studies.[8] Another study involving approximately 6000 patients with urinary stone disease showed that obesity (men > 120 kg, women > 100 kg) was more prevalent among female patients than male patients (3.8% of men and 12.6% of women); furthermore, the mean number of stone episodes was significantly higher in women over 100 kg than in women under 85 kg (2.93 *vs* 3.38), but not in men.[17] The Third National Health and Nutrition Examination Survey showed that stone formers had a 69% increase in self-reported hypertension compared with non-stone formers among women, but not among men.[16] Diabetes was associated with prevalent stone disease in both sexes and an increased risk of incident kidney stone formation in women in the HPFS and the NHS.[10]

The mechanism of sex differences for the effect of obesity, hypertension and DM on kidney stone disease is uncertain. BMI was associated positively with urinary oxalate excretion in both sexes, but this relationship persisted only in women after adjusting for urinary phosphate and uric acid excretion.[18] In fact, the urinary excretion of lithogenic factors depending on body size was also different in the two sexes. In the present study, MetS components did not differ between male subjects with or without kidney