Table 4. Comparison of Serum Isoflabove Groups Between Control and Case Group Restricted to the Equol Producer, the Tsurugaya Project, 2002–2009

		Equol Producer Only			
		Control	Case	OR1(95% CI)	OR2 (95% CI)
Isoflavones	ng/mL	Alive without Disability	Disability or Death	Age–Sex Only	Multiple Adjusted
Daidzein	–36	26	20	1	1
	36.1–76.6	24	23	1.20 (0.53–2.73)	2.67 (0.70–10.16)
	76.7–141.0	25	23	1.17 (0.51–2.67)	2.99 (0.78–11.46)
	141.1–	25	15	0.75 (0.31–1.78)	0.95 (0.26–3.47)
Genistein	–63.5	22	16	1	1
	63.6–145.2	26	29	1.47 (0.64–3.35)	2.53 (0.69–9.28)
	145.3–269.1	23	18	1.03 (0.41–2.57)	1.46 (0.33–6.51)
	269.2–	29	18	0.80 (0.34–1.93)	0.87 (0.24–3.18)
Glycitein	–1.9	21	18	1	1
	2.0–4.6	25	21	0.96 (0.41–2.25)	1.66 (0.44–6.28)
	4.7–9.8	28	23	0.95 (0.41–2.21)	1.40 (0.36–5.40)
	9.9–	26	19	0.81 (0.34–1.93)	0.75 (0.20–2.76)

Notes: 95% CI = 95% confidence interval; diabetes = casual blood glucose ≥ 200 mg/dL or taking antidiabetic drugs; OR = odds ratio; OR1 = age–sex category was used as stratified variables; OR2 = further adjusted for smoking status, drinking status, blood pressure category (home hypertensive, home borderline hypertensive, home normotensive), casual blood glucose (normal glucose, impaired blood glucose, diabetes), total cholesterol (total cholesterol ≥ 240 mg/dL or user of cholesterol lowering drugs, total cholesterol between 200–239 mg/dL, total cholesterol between 160–199 mg/dL, total cholesterol < 160 mg/dL), serum albumin, sex-specific quartile of functional reach, body mass index, depressive symptom (geriatric depression scale ≥ 11 or user of antidepressants), sex-specific quartile of stiffness of calcaneus, history of cardiovascular diseases, history of cancer, and sex-specific quartile of total energy intake, green tea consumption, meat consumption, and physical activity; home hypertensive = home systolic BP ≥ 135 mmHg and/or home diastolic BP ≥ 85 mmHg; and/or user of antihypertensive medication; home borderline hypertensive = not satisfied with home hypertensive critetria and home systolic BP ≥ 125 mmHg and/or home diastolic BP ≥ 80 mmHg; home normotensive = home systolic BP < 125 mmHg and home diastolic BP < 80 mmHg without antihypertensive medication; impaired blood glucose = casual blood glucose ≥ 140 mg/dL and not taking antidiabetic drugs.

higher equol values. However, previous studies in both Japan (28) and Europe (29) failed to find a relationship between smoking and equol levels. Additionally, a higher serum daidzein level predicted higher equol levels in equol producers. Therefore, a greater consumption of soy might increase equol level in equol producers. Thus, additional studies assessing the factors that affect equol levels are warranted.

Higher serum equol levels were found to be associated with a lower risk of disability and death. Initially, it was expected that this inverse association could be explained by superior bone mineral density (30). However, the correlation between equol levels and the bone mineral density of the calcaneus was not significant. Furthermore, adjusting for bone mineral density did not alter the risk of the composite endpoint of death and disability. Therefore, other mechanisms may play a role and should be considered. Unfortunately, the researchers' study did not have any information with respect to the causes of disability or mortality, and consequently, they were not able to clarify the factors associated with reducing risk of the composite endpoint in the higher equol group than the other groups. There are, may be, several explanations for why equol was associated with disability and death. First, as mentioned in previous studies, the benefits of soybean consumption are greater in equol producers (4). Equol is known to have a stronger affinity for the estrogen receptor than any other isoflavone. Although statistical significance was not reached, the other isoflavones were also inversely associated with disability and death. Thus, this observation supports the above hypothesis. Also, it remains possible that rather than contributing to a better health outcome per se, equol may enhance bacterial activity or improve intestinal conditions, which in turn, contribute to better health. However, the researchers were not able to confirm this scenario in their study. Thus, to clarify whether equol per se decreases the risk of disability or mortality, future intervention studies on soybean intake among equol producers are warranted.

In conclusion, it was found that higher serum equol concentrations, and no other isoflavone, are independently associated with a lower risk of the composite endpoint of disability and death. However, whether equol per se has a direct causal effect on disability or mortality remains to be elucidated. Further studies, including randomized controlled trials, which clarify the role of equol in overall health, are warranted.

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AUTHOR CONTRIBUTIONS

Study concept and design (A.H., K.O.-M., S.K., IT).

Acquisition of subjects and/or data (A.H., Y.S., Y.T., M.K,. T.T., K.O.-M., N.N., S.K., I.T.).

Analysis and interpretation of data (A.H., Y.S., Y.T., M.K., T.T., K.O.-M., N.N., S.K., I.T.).

Preparation of manuscript (A.H., A.F.).

Conflicts of Interest

There are no potential conflicts of interest that relate to the manuscript.

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Green tea consumption and the risk of incident functional disability in elderly Japanese: the Ohsaki Cohort 2006 Study[1–3]

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ABSTRACT

Background: Previous studies have reported that green tea consumption is associated with a lower risk of diseases that cause functional disability, such as stroke, cognitive impairment, and osteoporosis. Although it is expected that green tea consumption would lower the risk of incident functional disability, this has never been investigated directly.

Objective: The objective was to determine the association between green tea consumption and incident functional disability in elderly individuals.

Design: We conducted a prospective cohort study in 13,988 Japanese individuals aged ≥65 y. Information on daily green tea consumption and other lifestyle factors was collected via questionnaire in 2006. Data on functional disability were retrieved from the public Long-term Care Insurance database, in which subjects were followed up for 3 y. We used Cox proportional hazards regression analysis to investigate the association between green tea consumption and functional disability.

Results: The 3-y incidence of functional disability was 9.4% (1316 cases). The multiple-adjusted HR (95% CI) of incident functional disability was 0.90 (0.77, 1.06) among respondents who consumed 1–2 cups green tea/d, 0.75 (0.64, 0.88) for those who consumed 3–4 cups/d, and 0.67 (0.57, 0.79) for those who consumed ≥5 cups/d in comparison with those who consumed <1 cup/d (P-trend < 0.001).

Conclusion: Green tea consumption is significantly associated with a lower risk of incident functional disability, even after adjustment for possible confounding factors. *Am J Clin Nutr* 2012;95:732–9.

INTRODUCTION

Tea is the most frequently consumed beverage in the world. Three billion kilograms of tea are produced worldwide annually. Because of the high rates of tea consumption in the global population, even small effects on an individual could have a large impact on public health.

The health effects of green tea have been extensively investigated by prospective cohort studies. We have found that green tea consumption is significantly associated with a lower risk of mortality due to stroke (1) and pneumonia (2) and a lower risk of cognitive impairment (3), depression (4), and psychological distress (5). These results have been confirmed by other researchers (6–9). In addition, other epidemiologic studies have indicated that green tea consumption is associated with a lower risk of osteoporosis (10, 11), and randomized controlled trials have indicated that green tea is effective for cardiovascular risk factors (12, 13). Because all of the above conditions are major causes of functional disability (14–16), it is expected that green tea consumption would contribute to disability prevention. To our knowledge, however, no study has yet investigated the relation between green tea consumption and the incident risk of functional disability.

We therefore conducted the present analysis to test the hypothesis that green tea consumption is associated with a lower risk of developing functional disability.

SUBJECTS AND METHODS

Study cohort

The design of the Ohsaki Cohort 2006 Study has been described in detail elsewhere (17). In brief, the source population for the baseline survey comprised 31,694 men and women aged ≥65 y who were living in Ohsaki City, northeastern Japan, on 1 December 2006.

The baseline survey was conducted between 1 December and 15 December 2006. A questionnaire was distributed by the heads of individual administrative districts to individual households and then collected by mail. In this analysis, 23,091 persons who provided valid responses formed the study cohort (**Figure 1**). We excluded 6333 persons who did not provide written consent for review of their Long-term Care Insurance (LTCI) information, 1979 persons who had already been certified as having disability by the LTCI at the time of the baseline survey, 5 persons who had died or moved out of the district during the period of the baseline

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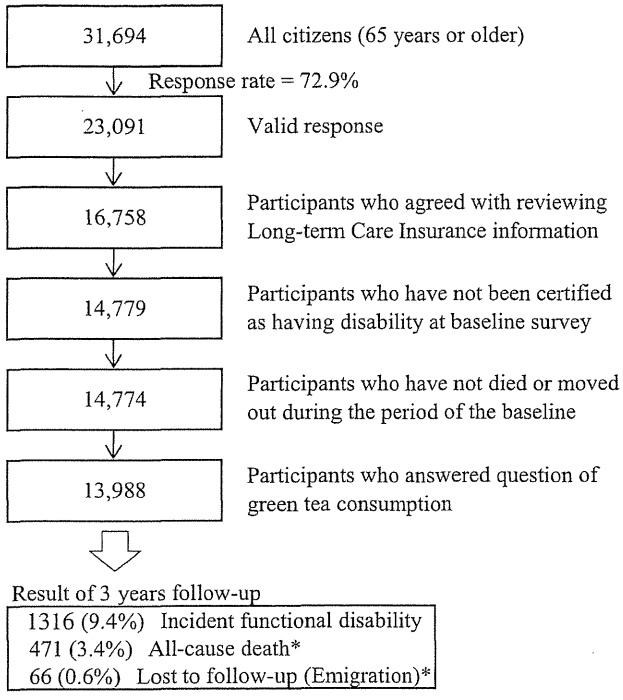

FIGURE 1. Flowchart of study participants: the Ohsaki Cohort 2006 Study. *Without experiencing incident functional disability.

survey, and 786 persons who missed answering the questions on green tea consumption. Thus, 13,988 responses were analyzed for the purposes of this study.

During the 3-y period, only 66 persons were lost to follow-up because of moving from the study area, without developing incident functional disability, which provided a follow-up rate of 99.5%. Among 38,660 person-years, incident functional disability was determined in 1316 persons and the number of all-cause deaths without incident functional disability was 471.

We also analyzed the association between consumption of black tea, oolong tea (Chinese tea), or coffee and incident functional disability. In these analyses, we excluded individuals for whom data on consumption of these beverages were missing (n = 2539 for black tea, n = 2626 for oolong tea, and n = 1105 for coffee).

Exposure data

The survey included questions about the frequency of recent average consumption of green tea, oolong tea, black tea, coffee, and 36 food items, as well as items on history of disease, blood pressure, educational level, smoking, alcohol drinking, body weight, height, cognitive activity score (18), psychological distress score (K6) (19, 20), time spent walking per day, and motor function score of the Kihon Checklist (21). The frequency of green tea consumption was categorized as never, occasionally, or 1–2, 3–4, or ≥5 cups/d. Within the study region, the volume of a typical cup of green tea is 100 mL.

We conducted a validation study of the food-frequency questionnaire in which 113 respondents provided four 3-d food records within 1 y and subsequently responded to the questionnaire. The Spearman rank correlation coefficient between green tea consumption according to the questionnaire and that according to the food records was 0.71 for men and 0.53 for women; the correlation between consumption measured by the 2 questionnaires administered 1 y apart was 0.63 for men and 0.64 for women (22).

BMI was calculated as the self-reported body weight (in kg) divided by the square of the self-reported body height (in m). The degree of social support available to each individual was assessed by asking the following questions (23): Do you have someone *1*) with whom you can talk when you are in trouble, *2*) whom you can consult when you do not feel well, *3*) who can help you with your daily housework, *4*) who can take you to a hospital when you feel ill, and *5*) who can take care of you if you become bedridden? This social support questionnaire consisted of 5 questions, each requiring a "yes" or "no" answer. This questionnaire was available only in Japanese. The validity and reliability of the questionnaire had not been evaluated. We also assessed participation in community activities. We asked about how often each respondent participated in the following activities: *1*) neighborhood associations; *2*) sports, exercise, or hobbies; *3*) volunteering for activities related to nonprofit organizations; and *4*) any other type of social gatherings. The frequency of these activities was assessed as never, a few times each year, monthly, 2–3 times/mo, 1 time/wk, 2–3 times/wk, and ≥4 times/wk. The motor function score of the Kihon Checklist has been previously evaluated and has shown predictive validity of functional disability (21).

The LTCI system in Japan

In this study, we defined incident functional disability as certification for LTCI in Japan, which uses a nationally uniform standard of functional disability. LTCI is mandatory social insurance to assist daily activities in the frail and the elderly (24–28). Everyone aged ≥40 y pays premiums, and everyone aged ≥65 y is eligible for formal caregiving services. When a person applies to the municipal governments for benefits, a care manager visits his or her home and assesses the degree of functional disability by using a questionnaire developed by the Ministry of Health, Labor, and Welfare. Then, the municipal governments calculate the standardized scores for physical and mental functions on the basis of the questionnaire and classify whether the applicant is eligible for LTCI benefits (certification). If a person is judged as eligible for benefits, the Municipal Certification Committee decides on 1 of 7 levels of support, ranging from Support Level 1, Support Level 2, and Care Level 1 to Care Level 5. In brief, LTCI certification levels are defined as follows: Support Level 1 is defined as "limited in instrumental activities of daily living but independent in basic activities of daily living (ADLs)", Care Level 2 is defined as "requiring assistance in at least one basic ADL task," and Care Level 5 is defined as "requiring care in all ADL tasks." A community-based study has shown that levels of LTCI certification are well correlated with ability to perform ADLs, and with Mini Mental State Examination scores (29). A prospective study has also indicated that levels of LTCI certification are significantly associated with mortality risk (30). LTCI certification was used as a measure of incident functional disability in the elderly (31–33).

Follow-up and case ascertainment

Incident functional disability was set as our endpoint, which was defined as LTCI certification. The primary outcome was LTCI certification (Support Level 1 or higher), in which deaths without

TABLE 1
Relation between green tea consumption and characteristics of the participants

	Green tea consumption				
	<1 cup/d	1–2 cups/d	3–4 cups/d	≥5 cups/d	*P* value[1]
n	2318	3141	3978	4551	
Male sex (%)	57.0	48.9	42.5	36.0	<0.001
Age (y)	73.7 ± 6.2[2]	73.9 ± 6.1	73.9 ± 5.9	74.0 ± 5.8	0.152
BMI (kg/m^2)	23.7 ± 3.8	23.6 ± 3.4	23.5 ± 3.2	23.6 ± 3.3	0.319
Psychological distress (%)[3]	6.8	4.6	4.4	4.1	<0.001
Educational level <16 y (%)	35.1	31.1	26.4	28.0	<0.001
Past history of (%)					
Stroke	4.1	3.4	2.4	2.0	<0.001
Myocardial infarction	6.3	5.2	5.1	4.2	0.003
Hypertension	43.3	44.3	44.0	43.0	0.662
Dyslipidemia	6.6	8.8	9.4	8.6	0.002
Diabetes	12.5	12.0	12.0	11.5	0.646
Arthritis	14.1	15.1	16.0	17.3	0.003
Osteoporosis	9.8	10.2	11.4	11.4	0.091
Fracture	16.1	16.7	15.9	15.3	0.404
Cancer	8.8	8.1	9.2	8.6	0.437
Hepatic disease	7.3	6.0	4.5	4.6	<0.001
Gastric and duodenal ulcer	16.7	15.2	15.7	15.1	0.323
Body pain ≥moderate (%)	31.1	28.6	28.9	26.7	<0.001
Been in bed for >1 wk (%)	5.9	3.7	3.2	2.9	<0.001
Weight reduction of ≥2 kg compared with 1 y ago (%)	14.0	13.5	12.2	12.0	0.001
Current smoker (%)	18.4	14.1	11.4	11.4	<0.001
Current alcohol drinker (%)	43.9	39.9	36.8	32.8	<0.001
Frequent cognitive activity (%)[4]	34.2	40.2	45.1	44.8	<0.001
Social support (%)					
To consult when you are in trouble	85.5	89.3	91.5	92.7	<0.001
To consult when you are in poor physical condition	91.3	93.9	94.1	95.1	<0.001
To help with your daily housework	82.8	85.2	86.2	86.9	<0.001
To take you to a hospital	90.3	92.8	93.2	93.7	<0.001
To take care of you	84.9	88.2	87.0	86.8	<0.001
Participation in community activities (%)					
Activities in neighborhood association	41.4	49.1	51.0	50.8	<0.001
Sports or exercise	39.7	47.9	49.4	50.3	<0.001
Volunteering	28.4	32.4	33.7	34.0	0.001
Social gathering	40.9	49.3	52.4	53.0	<0.001
Time spent walking ≥1 h/d (%)	39.0	36.9	35.4	32.5	<0.001
Better motor function (%)[5]	75.4	76.1	78.5	79.2	<0.001
Intake of (g/d)					
Rice	434 ± 220	429 ± 228	425 ± 197	421 ± 186	0.078
Miso soup	19.7 ± 9.7	20.2 ± 10.3	20.4 ± 8.6	21.7 ± 74.3	0.233
Meat	21.2 ± 15.7	22.4 ± 16.7	23.0 ± 16.2	23.6 ± 16.4	<0.001
Fish	57.0 ± 32.5	59.1 ± 31.5	62.2 ± 30.8	65.7 ± 31.2	<0.001
Green and yellow vegetables	79.8 ± 46.6	89.5 ± 47.5	96.2 ± 45.9	105.4 ± 47.5	<0.001
Potatoes	21.2 ± 16.4	23.1 ± 16.2	25.4 ± 16.1	28.3 ± 16.6	<0.001
Soy products	57.6 ± 29.9	62.7 ± 28.3	66.0 ± 26.5	68.8 ± 25.5	<0.001
Fruit	113.6 ± 89.8	132.1 ± 92.0	145.8 ± 91.0	160.6 ± 92.0	<0.001
Sweets	14.6 ± 15.7	16.6 ± 15.9	18.2 ± 16.2	20.3 ± 17.3	<0.001
Black tea consumption of <1 cup/d (%)	95.5	86.6	91.6	90.7	<0.001
Oolong tea consumption of <1 cup/d (%)	95.0	89.2	93.2	92.1	<0.001
Coffee consumption of <1 cup/d (%)	50.4	40.2	48.2	55.2	<0.001
Energy intake (kcal/d)[6]	1355 ± 423	1402 ± 417	1445 ± 394	1495 ± 374	<0.001
Protein intake (g/d)	48.9 ± 14.8	51.3 ± 14.5	53.9 ± 13.8	56.8 ± 13.7	<0.001

[1] Obtained by using chi-square test for variables of proportion and 1-factor ANOVA for continuous variables.
[2] Mean ± SD (all such values).
[3] Kessler 6-item psychological distress scale score ≥13.
[4] Cognitive activity score ≥23.
[5] Motor function score of the Kihon Checklist <3.
[6] Excluding alcohol.

TABLE 2
Relation between green tea consumption and incident functional disability[1]

	Green tea consumption					
Incident functional disability	<1 cup/d	1–2 cups/d	3–4 cups/d	≥5 cups/d	*P*-trend	*P*-interaction
All (n = 13,988)						
No. of participants	2318	3141	3978	4551		
Primary outcome events [no. (%)]	296 (12.8)	343 (10.9)	339 (8.5)	338 (7.4)		
Model 1	1.00 (reference)[2]	0.79 (0.68, 0.93)	0.60 (0.51, 0.70)	0.51 (0.44, 0.60)	<0.001	
Model 2	1.00 (reference)	0.86 (0.74, 1.01)	0.70 (0.60, 0.82)	0.61 (0.52, 0.72)	<0.001	
Model 3	1.00 (reference)	0.88 (0.75, 1.03)	0.72 (0.61, 0.85)	0.63 (0.54, 0.75)	<0.001	
Model 4	1.00 (reference)	0.90 (0.77, 1.06)	0.75 (0.64, 0.88)	0.67 (0.57, 0.79)	<0.001	
Men (n = 6186)						
No. of participants	1320	1536	1691	1639		
Primary outcome events [no. (%)]	140 (10.6)	138 (9.0)	140 (8.3)	108 (6.6)		
Model 1	1.00 (reference)	0.80 (0.63, 1.01)	0.71 (0.56, 0.89)	0.55 (0.42, 0.70)	<0.001	
Model 2	1.00 (reference)	0.90 (0.71, 1.15)	0.87 (0.68, 1.10)	0.64 (0.50, 0.83)	<0.001	
Model 3	1.00 (reference)	0.90 (0.70, 1.14)	0.85 (0.66, 1.08)	0.64 (0.49, 0.83)	0.001	
Model 4	1.00 (reference)	0.88 (0.69, 1.13)	0.86 (0.68, 1.10)	0.67 (0.52, 0.88)	0.005	0.384
Women (n = 7802)						
No. of participants	998	1605	2287	2912		
Primary outcome events [no. (%)]	156 (15.6)	205 (12.8)	199 (8.7)	230 (7.9)		
Model 1	1.00 (reference)	0.78 (0.64, 0.96)	0.53 (0.43, 0.66)	0.49 (0.40, 0.60)	<0.001	
Model 2	1.00 (reference)	0.83 (0.67, 1.02)	0.61 (0.50, 0.76)	0.58 (0.47, 0.71)	<0.001	
Model 3	1.00 (reference)	0.84 (0.68, 1.04)	0.64 (0.52, 0.80)	0.62 (0.50, 0.77)	<0.001	
Model 4	1.00 (reference)	0.87 (0.70, 1.07)	0.67 (0.54, 0.83)	0.65 (0.53, 0.81)	<0.001	

[1] Model 1 was adjusted for age (65–69, 70–74, 75–79, 80–84, or ≥85 y) and sex (among all participants). Model 2 was adjusted as for model 1 plus history of disease [stroke, myocardial infarction, hypertension, arthritis, osteoporosis, or fracture (yes, no)], educational level (age at last school graduation: <16 y, 16–18 y, ≥19 y, or missing), smoking (never, former, current, or missing), alcohol drinking (never, former, current, or missing), BMI (in kg/m^2; <18.5, 18.5–24.9, ≥25.0, or missing), cognitive activity score (<19, 19–23, ≥23, or missing), psychological distress score (<13, ≥13, or missing), and time spent walking (<30 min/d, 30 min to 1 h/d, ≥1 h/d, or missing). Model 3 was adjusted as for model 2 plus 3 tertile groups of consumption volume of rice, miso soup, meat, fish, green and yellow vegetables, potatoes, soy products, fruit, and sweets. Model 4 was adjusted as for model 3 plus social support (whether subject perceived that he or she was supported for all 5 categories), participation in community activities (whether subject participated in any of 4 categories), and motor function score(<3, ≥3, or missing).
[2] HR; 95% CI in parentheses (all such values).

LTCI certification were treated as censored. In the subanalysis, we set the criteria of disability toward a more severe level, ie, Care Level 2 (requiring assistance with one basic ADL task) or higher.

We obtained information on the date of LTCI certification, death, or moving from Ohsaki City. With regard to LTCI certification, information on care level was also provided. All data were transferred from the Ohsaki City Government under the agreement related to Epidemiologic Research and Privacy Protection yearly each December.

Ethical issues

We considered the return of completed questionnaires to imply consent to participate in the study involving the baseline survey data and subsequent follow-up of death and emigration. We also confirmed information regarding LTCI certification status after obtaining written consent from the subjects. The Ethics Committee of Tohoku University Graduate School of Medicine (Sendai, Japan) reviewed and approved the study protocol.

Statistical analysis

We counted the person-years of follow-up for each subject from 16 December 2006 until the date of incident functional disability, date of moving from Ohsaki City, date of death, or the end of the study period (30 November 2009), whichever occurred first.

Baseline characteristics were evaluated by using ANOVA for continuous variables and the chi-square test for categorical variables. We used the multiple adjusted Cox proportional hazards model to calculate HRs and 95% CIs for incidence of functional disability according to amounts of green tea consumption.

We defined respondents who consumed <1 cup green tea/d as the reference category, and examined the relation between green tea consumption and incident functional disability by using the following models. Model 1 was sex- and age-adjusted. To examine whether the association between green tea consumption and incident functional disability could be explained as resulting from healthy physical status or other lifestyle factors, model 2 was further adjusted for history of stroke, myocardial infarction, hypertension (individuals with self-measured systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg were also defined as hypertensive), arthritis, osteoporosis and fracture, educational level, smoking status, alcohol consumption, BMI, tertile categories of cognitive activity score, psychological distress score, and time spent walking per day. Because green tea consumption was thought to be especially related to a healthy dietary pattern, model 3 was further adjusted for 3 tertile groups of consumption volume of rice, miso soup, meat, fish, green and yellow vegetables, potatoes, soy products, fruit, and sweets. Model 4 was fully adjusted and included answers to questions about social support, participation in community activities, and motor function score.

Because green tea is the beverage most frequently served at social activities in Japan, its consumption might be merely a surrogate marker of social support or participation in community

TABLE 3
Relation between green tea consumption and incident functional disability stratified by social support and community activity subgroup[1]

	Green tea consumption					
	<1 cup/d	1–2 cups/d	3–4 cups/d	≥5 cups/d	*P*-trend	*P*-interaction
Social support						
No lack						
No. of participants	1570	2252	2947	3392		
Primary outcome events [no. (%)]	208 (13.3)	248 (11.0)	235 (8.0)	239 (7.1)		
Age-and sex-adjusted HR (95% CI)[2]	1.00 (reference)	0.75 (0.63, 0.90)	0.54 (0.45, 0.65)	0.46 (0.38, 0.56)	<0.001	
Multiple-adjusted HR (95% CI)[3]	1.00 (reference)	0.89 (0.73, 1.07)	0.68 (0.56, 0.83)	0.61 (0.50, 0.75)	<0.001	0.103
Any lack						
No. of participants	624	710	867	979		
Primary outcome events [no. (%)]	74 (11.9)	75 (10.6)	81 (9.3)	83 (8.5)		
Age-and sex-adjusted HR (95% CI)[2]	1.00 (reference)	0.86 (0.62, 1.19)	0.65 (0.48, 0.90)	0.59 (0.43, 0.81)	<0.001	
Multiple-adjusted HR (95% CI)[3]	1.00 (reference)	0.95 (0.68, 1.33)	0.78 (0.56, 1.09)	0.74 (0.53, 1.04)	0.047	
Participation in community activities						
Participated						
No. of participants	1114	1669	2297	2542		
Primary outcome events [no. (%)]	80 (7.2)	106 (6.4)	122 (5.3)	115 (4.5)		
Age-and sex-adjusted HR (95% CI)[2]	1.00 (reference)	0.80 (0.60, 1.08)	0.61 (0.46, 0.82)	0.52 (0.39, 0.70)	<0.001	
Multiple-adjusted HR (95% CI)[3]	1.00 (reference)	0.84 (0.62, 1.13)	0.73 (0.54, 0.97)	0.65 (0.48, 0.88)	0.003	0.585
Did not participate						
No. of participants	781	802	951	1066		
Primary outcome events [no. (%)]	162 (20.7)	164 (20.5)	139 (14.6)	142 (13.3)		
Age-and sex-adjusted HR (95% CI)[2]	1.00 (reference)	0.86 (0.69, 1.07)	0.62 (0.49, 0.78)	0.55 (0.44, 0.70)	<0.001	
Multiple-adjusted HR (95% CI)[3]	1.00 (reference)	0.90 (0.72, 1.13)	0.69 (0.55, 0.88)	0.64 (0.50, 0.81)	<0.001	

[1] Any lack, participants who perceived that they were not supported for at least one social support category; Did not participate, participants who did not participate in any community activities; No lack, participants who perceived that they were supported for all 5 social support categories; Participated, participants who participated in at least one community activity.
[2] Adjusted as for model 1 in Table 2.
[3] Adjusted as for model 4 in Table 2.

activity (5, 34). Therefore, we further stratified the responses according to social support and community activity. Those who did not answer any questions about social support or participation in community activities were excluded from these stratified analyses. For analysis of social support and participation in community activities, neither of these was used as the respective covariate.

We also analyzed the consumption of black tea, oolong tea, and coffee as independent variables by using the fully adjusted model (model 4). In the analyses for black tea, oolong tea, or coffee as a main exposure, persons with missing data were excluded (n = 11,449 for black tea, n = 12,883 for oolong tea, and n = 11,362 for coffee).

All data were analyzed by using SAS version 9.1 (SAS Institute Inc). All statistical tests described here were 2-sided, and differences at $P < 0.05$ were accepted as significant.

RESULTS

The baseline characteristics of the participants according to green tea consumption category are shown in **Table 1**. Subjects who consumed larger amounts of green tea were less likely to be men, to suffer from psychological distress, to have <16 y of education, to have shown a weight reduction of >2 kg compared with 1 y ago, to be current smokers, to be current alcohol drinkers, and to have a history of stroke, myocardial infarction, or hepatic disease. More frequent consumption of green tea was associated with significantly higher consumption of meat, fish, green and yellow vegetables, soy products, fruits, and sweets; greater intake of energy and protein; better cognitive activity; better perception of support for all 5 social support categories; and greater participation in the 4 community activities categories. Conversely, subjects who more frequently consumed green tea included a higher proportion of individuals with arthritis and a lower proportion of individuals who walked ≥1 h/d.

The relation between green tea consumption and incident functional disability with HRs and associated 95% CIs are shown in **Table 2**. We found that green tea consumption was inversely associated with incident functional disability in model 1 (P-trend < 0.001). Even with the addition of the several adjustment items, these associations remained significant. In model 4, the multivariate HRs were 1.00 (reference) for <1 cup/d, 0.90 (95% CI: 0.77, 1.06) for 1–2 cups/d, 0.75 (95% CI: 0.64, 0.88) for 3–4 cups/d, and 0.67 (95% CI: 0.57, 0.79) for ≥5 cups/d. This inverse association was significant for both sexes (P = 0.384 for interaction with sex).

Even if we set stricter criteria for disability (LTCI certification for Care Level 2 or higher), the results did not change. The multivariate HRs (model 4) were 1.00 (reference) for <1 cup/d, 0.92 (95% CI: 0.72, 1.17) for 1–2 cups/d, 0.71 (95% CI: 0.55, 0.91) for 3–4 cups/d, and 0.68 (95% CI: 0.53, 0.88) for ≥5 cups/d (data not shown).

To examine possible reverse causality, we analyzed whether the association would be different by excluding participants whose event of disability occurred in the first year of follow-up. When we excluded 577 such participants, the results did not change substantially. The multivariate HRs (model 4) were 1.00 (reference) for <1 cup/d, 0.91 (95% CI: 0.75, 1.10) for 1–2 cups/d, 0.81 (95% CI: 0.66, 0.98) for 3–4 cups/d, and 0.71 (95% CI: 0.58, 0.87) for ≥5 cups/d (data not shown). In addition, when we excluded participants with any history of diseases that cause functional disability (stroke, myocardial infarction, hypertension, arthritis, osteoporosis, or fracture), the results also did not change

TABLE 4
Relation between consumption of other beverages and incident functional disability

	Beverage consumption				
	<1 cup/d	1–2 cups/d	3–4 cups/d	≥5 cups/d	*P*-trend
Oolong tea (Chinese tea)					
No. of participants	10,482	502	225	153	
Primary outcome events [no. (%)]	925 (8.8)	45 (9.0)	11 (4.9)	13 (8.5)	
Age- and sex-adjusted HR (95% CI)[1]	1.00 (reference)	1.12 (0.83, 1.52)	0.58 (0.32, 1.05)	0.94 (0.54, 1.63)	0.387
Multiple-adjusted HR (95% CI)[2]	1.00 (reference)	1.47 (1.07, 2.03)	0.77 (0.42, 1.40)	1.25 (0.71, 2.18)	0.354
Black tea					
No. of participants	10,408	785	190	66	
Primary outcome events [no. (%)]	914 (8.8)	73 (9.3)	11 (5.8)	4 (6.1)	
Age- and sex-adjusted HR (95% CI)[1]	1.00 (reference)	1.11 (0.87, 1.41)	0.61 (0.34, 1.11)	0.65 (0.24, 1.74)	0.323
Multiple-adjusted HR (95% CI)[2]	1.00 (reference)	1.23 (0.96, 1.59)	0.82 (0.45, 1.51)	1.01 (0.37, 2.75)	0.567
Coffee					
No. of participants	6317	4997	1031	538	
Primary outcome events [no. (%)]	701 (11.1)	357 (7.1)	62 (6.0)	41 (7.6)	
Age- and sex-adjusted HR (95% CI)[1]	1.00 (reference)	0.83 (0.73, 0.94)	0.82 (0.63, 1.07)	0.92 (0.67, 1.27)	0.023
Multiple-adjusted HR (95% CI)[2]	1.00 (reference)	0.90 (0.79, 1.03)	0.93 (0.72, 1.22)	1.02 (0.74, 1.41)	0.408

[1] Adjusted as for model 1 in Table 2.
[2] Adjusted as for model 4 in Table 2.

substantially. The multivariate HRs (model 4) were 1.00 (reference) for <1 cup/d, 0.89 (95% CI: 0.66, 1.20) for 1–2 cups/d, 0.69 (95% CI: 0.51, 0.94) for 3–4 cups/d, and 0.72 (95% CI: 0.53, 0.98) for ≥5 cups/d (n = 4954; data not shown).

To confirm whether there was a relation between green tea consumption and incident functional disability, irrespective of social support or participation in community activities, we also conducted stratified analyses for these 2 factors (*see* **Table 3**). The inverse association was observed irrespective of social support or participation in community activities (P = 0.103 for interaction with social support, P = 0.585 for interaction with community activities).

The multiple-adjusted HRs for the primary outcome event according to frequency of consumption of oolong tea, black tea, and coffee are compared in **Table 4**. We observed a weak association between coffee consumption and incident functional disability in age- and sex-adjusted models (P-trend= 0.023). However, there were null associations for consumption of oolong tea, black tea, or coffee in multiple-adjusted models.

DISCUSSION

In this study, we found significant inverse dose-response associations between green tea consumption and incident functional disability. To our knowledge, this is the first reported study to have proved the relation between green tea consumption and incident risk of functional disability.

Our study had a number of strengths: *1*) it was a large population-based cohort study in 13,988 persons, *2*) it had a follow-up rate of almost 100%, *3*) the study subjects lived in an area in which green tea is widely consumed, and *4*) many confounding factors were taken into account.

Because green tea consumption is associated a variety of health behavior or social factors, we used several approaches to control for these effects. First, we adjusted the effect of dietary habit, because green tea is usually consumed with a Japanese-style diet such as fish and soy bean products (Table 1). Consumption of fish and soy products has been reported to reduce the risk of stroke, fracture, and dementia (35–40). However, our results indicated that the association between green tea consumption and incident functional disability did not alter, even when dietary covariates were adjusted for.

Second, we also considered the confounding effect of social support or community activities. Previous studies have shown that these factors are associated with a lower risk of functional disability (41, 42). However, we found that the inverse association between green tea consumption and incident functional disability persisted even after adjustment for social support and participation in community activities.

Because our follow-up period was only 3 y, the effects of reverse causality could not be fully avoided. However, the strong inverse relation between green tea consumption and incident functional disability persisted even after excluding individuals who experienced incident functional disability in the first year of follow-up. The above findings suggest that the present results are unlikely to be explained by reverse causality.

We thus considered that the inverse relation between green tea consumption and functional disability risk would be attributable to the preventive effect of green tea consumption on disabling diseases such as stroke, cognitive impairment, and osteoporosis. These diseases are major causes of functional disability in Japanese elderly individuals, with prevalence as follows: 23.3% for stroke, 14.0% for dementia, 12.2% for articular disease, and 9.3% for bone fracture (43). As we noted before, green tea consumption was associated with lower risks of stroke, dementia, and bone fracture. This survey reported that the third most common cause of functional disability was "frailty" (13.6%), which is mostly associated with sarcopenia and lower muscle strength. More recently, green tea polyphenols have been reported to improve leg strength (44). Furthermore, depression is also known to pose a risk of functional disability in the elderly (45). Our previous study indicated that green tea consumption was associated with a lower risk of depression. All of these findings provide a biological basis for the effect of green tea in preventing or postponing the onset of functional disability in the elderly.

In contrast to green tea, we observed no association between black tea, oolong tea, or coffee consumption and incident functional

disability, which is consistent with previous epidemiologic studies (1, 3–5). This discrepancy among beverages suggests that the effect of green tea cannot be explained by fluid intake but rather by some component in the beverage. As compared with black tea and oolong tea, green tea contains a large amount of polyphenols such as epigallocatechin gallate, which reduce oxidative damage to DNA and lipid concentrations (46–48). Randomized controlled trials of green tea polyphenol have indicated that it exerts antiatherosclerotic effects by reducing the level of oxidative stress (49).

This study had several limitations. First, we did not investigate the causes of functional disability in subjects who received LTCI certification. Thus, the mechanism responsible for functional disability reduction by green tea remained unidentified.

Second, among the source population of 31,694, the valid response rate (72.9%, $n = 23,091$) in the present study was not high. In addition, among the number of valid responses ($n = 23,091$), the number of subjects included in the present study was 13,988 (60.6%) and the number of those who were not included was 9103 (39.4%). Three-year follow-up indicated that mortality was higher in the nonstudy subjects (13%) than in the study subjects (5%). Thus, the present study would have been biased toward the healthier people in the community. However, this bias did not explain to affect the internal validity of association between green tea consumption and incident functional disability.

Third, not all potential confounding factors were considered, because we used only indirect measures of physical and cognitive function for adjustment. Furthermore, addition of income to the multivariate analysis might have been an appropriate indicator of socioeconomic status.

Fourth, because not all candidates applied for LTCI certification, this study may not have been completely free from detection bias. The degree of this bias remains to be verified.

In conclusion, this cohort study indicates that green tea consumption is inversely associated with incident functional disability. Clinical trials are ultimately be necessary to confirm the protective effect of green tea against functional disability.

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

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ABSTRACT

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

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

Setting: Miyagi Prefecture, northeastern Japan.

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

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

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

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

ARTICLE SUMMARY

Article focus

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

Key messages

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

Strengths and limitations of this study

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

INTRODUCTION

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

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

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

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

MATERIALS AND METHODS

Study cohort

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

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

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

Body mass index

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

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

Health insurance system in Japan

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

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

Statistical analysis

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

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

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

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

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

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

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

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

RESULTS

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

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

Baseline characteristics by BMI category

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

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

Mortality in terms of categories for BMI

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

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

Table 1 Baseline characteristics by BMI categories in 41 965 participants

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

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

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

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

Life expectancy and lifetime medical expenditure by BMI category

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

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

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

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

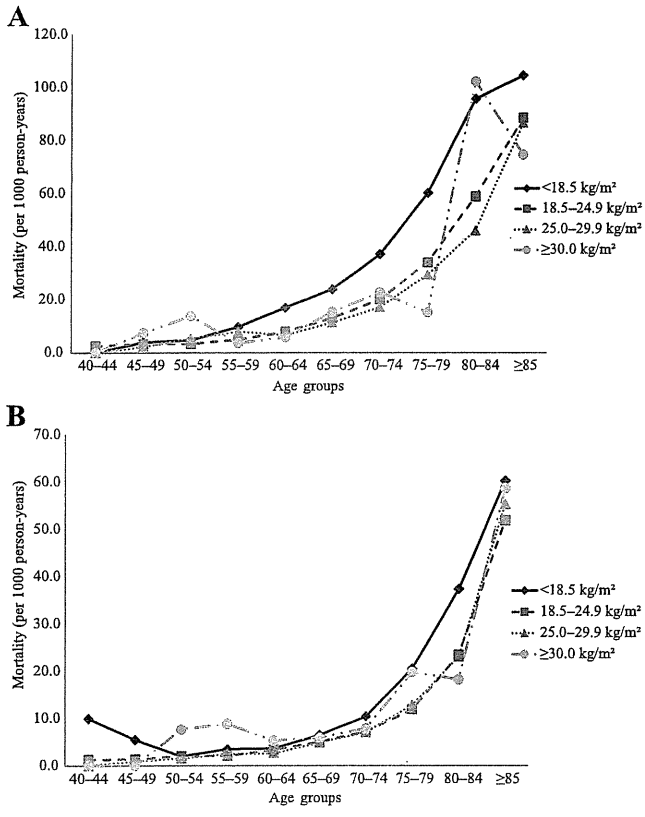

Figure 1 Multiadjusted mortality by BMI categories in each age group in men (A) and women (B).

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

DISCUSSION

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

Comparison with other studies

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

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

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

Table 2 Mortality ratio for BMI categories in 41 965 participants

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

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

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

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

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

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

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

Strengths and limitations

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

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

Conclusions and policy implication

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

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

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Competing interests None.

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

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

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Correlation Between High-Sensitivity C-Reactive Protein and Brain Gray Matter Volume in Healthy Elderly Subjects

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Abstract: Although elevated serum high-sensitivity C-reactive protein (hsCRP) is related to atherosclerosis, brain infarction, and cognitive decline, it has not been clarified whether increased hsCRP is associated with the decline in brain gray matter volume. Therefore, the purpose of this study was to determine the relationship between hsCRP levels and brain regional gray matter volume using brain magnetic resonance imaging (MRI) data from 109 community-dwelling healthy elderly subjects. Brain MRIs were processed with voxel-based morphometry using a custom template by applying diffeomorphic anatomical registration using the exponentiated lie algebra (DARTEL) procedure. We found a significant negative correlation between regional gray matter volume of the posterior and lateral aspects of the left temporal cortex and hsCRP level after adjusting for age, gender, and intracranial volume. Our results suggest that subjects who have mild inflammation related to arteriosclerosis have decreased regional gray matter volume in the posterior and lateral aspects of the left

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