RESULTS

The baseline demographic, fitness, and interview variables of the participants in the four groups are summarized in Table 1. All of the baseline characteristics were similar between the groups.

The mean attendance rates during the 3-month intervention were 70.3% in the exercise + AAS group, 80.5% in the exercise group, 72.2% in the AAS group, and 71.8% in the HE group. Eleven participants (exercise + AAS = 4, exercise = 3, AAS = 2, HE = 2) were unable to complete the study after randomization because of spouse care (n = 3), admission to nursing home (n = 2), lack of motivation (n = 2), severe knee or back pain (n = 1), death (n = 1), falls and hip fracture (n = 1), and hospitalization (n = 1; Figure 2).

In comparing the pre- and postintervention changes in body composition and functional fitness of the groups (Table 2), there was a significant group × time interaction for leg muscle mass ($F = 4.253$, $P < .007$; exercise + AAS > HE), usual and maximum walking speeds (exercise and exercise + AAS > HE), and knee extension strength ($F = 3.558$, $P = .02$; exercise + AAS > HE).

The within-group analysis showed significant changes in leg muscle mass in the exercise + AAS ($P < .001$) and exercise ($P = .005$) groups and changes in usual walking speed in the exercise + AAS ($P = .001$), exercise ($P < .001$), and AAS groups ($P = .01$). Knee extension strength improved significantly only in the exercise + AAS group ($P = .01$), no improvement was seen in exercise or AAS, and a statistically significant decrease was observed in the HE group ($P = .02$; Figure 1).

Table 3 shows the effects of the type of intervention on changes in combined variables of muscle mass and physical function. Significant increases in leg muscle mass and knee extension strength (odds ratio (OR) = 4.89, 95% confidence interval (CI) = 1.89–11.27) and leg muscle mass and usual walking speed (OR = 4.11, 95% CI = 1.33–13.68) were observed in only the exercise + AAS group.

DISCUSSION

Although many definitions of sarcopenia have been reported,[1–3,24] there has recently been a focus not only on the loss of appendicular skeletal muscle mass, but also on functional decline.[25] In this study, sarcopenic women were operationally defined based on declines in muscle strength or walking ability that accompany the loss of skeletal muscle mass or low BMI. Because defining sarcopenia was beyond the scope of this study, the focus of the discussion will be on the effects of the intervention. To evaluate the intervention effects, the changes observed in the single variables as well as the combined variables will be discussed.

Many studies have focused on exercise or nutrition as interventions to reverse sarcopenia, but the results of these studies have not always been consistent.[8,9,12,26]

This study demonstrated that appendicular muscle mass and walking speed increased with the combination of exercise and essential amino acid ingestion, as well as with the separate exercise and amino acid interventions, but muscle strength improved only with the combination of exercise and amino acid ingestion.

A recently published meta-analysis[9] and a Cochrane review article also confirmed that resistance training two to three times a week can improve physical function and functional limitations and can reduce disability and muscle weakness in older people.[27] Previous studies have demonstrated that resistance training in elderly people produces

Table 1. Selected Variable Characteristics of Participants at Baseline According to Study Group

Characteristic	Exercise + AAS (n = 38)	Exercise (n = 39)	AAS (n = 39)	Health Education (n = 39)	*F*-Value*	*P*-Value*
Age, mean ± SD	79.5 ± 2.9	79.0 ± 2.9	79.2 ± 2.8	78.7 ± 2.8	0.577	.63
Height, cm, mean ± SD	147.1 ± 6.7	147.7 ± 4.4	145.8 ± 4.5	146.5 ± 4.9	0.960	.41
Body weight, kg, mean ± SD	39.5 ± 5.5	41.1 ± 4.7	40.1 ± 3.2	40.4 ± 3.9	0.874	.46
Body mass index, kg/m^2, mean ± SD	18.3 ± 2.5	18.9 ± 2.0	18.9 ± 1.6	18.8 ± 1.7	0.745	.53
Calf girth, cm, mean ± SD	18.3 ± 2.5	18.9 ± 2.0	18.9 ± 1.6	18.8 ± 1.7	0.745	.53
Lean body mass, kg, mean ± SD	29.1 ± 3.4	30.0 ± 2.6	28.8 ± 2.0	29.3 ± 2.4	1.505	.22
Muscle mass, kg, mean ± SD	26.9 ± 3.1	27.7 ± 2.3	26.5 ± 1.8	27.0 ± 2.2	1.538	.21
Appendicular muscle mass, kg, mean ± SD	13.3 ± 1.6	13.7 ± 1.3	13.1 ± 1.0	13.3 ± 1.2	1.502	.22
Legs muscle mass, kg, mean ± SD	9.8 ± 1.2	10.1 ± 1.0	9.7 ± 0.7	9.9 ± 0.9	1.570	.20
Usual walking speed, m/s, mean ± SD	1.26 ± 0.27	1.29 ± 0.28	1.29 ± 0.20	1.18 ± 0.22	1.701	.17
Maximal walking speed, m/s, mean ± SD	1.62 ± 0.37	1.67 ± 0.31	1.67 ± 0.27	1.55 ± 0.32	1.150	.33
Knee extension strength, Nm, mean ± SD	45.9 ± 11.3	46.6 ± 11.1	46.7 ± 7.8	47.4 ± 10.5	0.139	.94
Falls, %	21.1	17.9	15.4	20.5	0.519	.91
Exercise habit, %	26.3	25.6	38.5	33.3	2.029	.57
Urinary incontinence, %	44.7	38.5	41.0	25.6	3.414	.33
Osteoporosis history, %	36.8	43.6	48.7	30.8	2.987	.39
Heart disease history, %	10.5	15.4	12.8	17.9	0.977	.81
Diabetes mellitus history, %	7.9	5.1	5.1	12.8	2.156	.54

* One-way analysis of variance for continuous variables and chi-square test for categorical variables.
AAS = amino acid supplementation; SD = standard deviation.

Table 2. Comparison of Muscle Mass and Functional Fitness Variables Between Groups After 3-Month Intervention

Variable	Group	Mean ± Standard Deviation		Analysis of Variance (Group × Time), *P*-Value	Post Hoc Analysis*
		Baseline	After 3-Month Intervention		
Muscle mass, kg	Exercise + AAS	26.76 ± 2.77	27.26 ± 3.04	*F* = 1.076, .36	
	Exercise	28.09 ± 1.90	28.51 ± 2.39		
	AAS	26.25 ± 1.81	26.53 ± 2.10		
	HE	27.48 ± 2.04	27.66 ± 2.23		
Appendicular muscle mass, kg	Exercise + AAS	13.25 ± 1.35	13.59 ± 1.53	*F* = 1.354, .26	
	Exercise	13.90 ± 1.06	14.19 ± 1.33		
	AAS	12.86 ± 0.99	13.03 ± 1.10		
	HE	13.57 ± 1.16	13.67 ± 1.05		
Legs muscle mass, kg	Exercise + AAS	9.76 ± 1.01	10.07 ± 1.13	*F* = 4.253, .007	Exercise + AAS > HE
	Exercise	10.28 ± 0.81	10.53 ± 1.05		
	AAS	9.55 ± 0.73	9.65 ± 0.83		
	HE	10.14 ± 0.87	10.11 ± 0.81		
BMI, kg/m^2	Exercise + AAS	18.30 ± 2.64	18.14 ± 2.68	*F* = 0.606, .61	
	Exercise	18.80 ± 1.30	18.50 ± 1.41		
	AAS	18.84 ± 1.43	18.56 ± 1.62		
	HE	18.83 ± 1.75	18.77 ± 1.67		
Usual walking speed, m/s	Exercise + AAS	1.27 ± 0.25	1.43 ± 0.29	*F* = 4.213, .007	Exercise and Exercise + AAS > HE
	Exercise	1.31 ± 0.24	1.50 ± 0.23		
	AAS	1.30 ± 0.18	1.36 ± 0.18		
	HE	1.19 ± 0.21	1.22 ± 0.23		
Maximum walking speed, m/s	Exercise + AAS	1.64 ± 0.34	1.92 ± 0.37	*F* = 9.374, <.001	Exercise and Exercise + AAS > HE
	Exercise	1.72 ± 0.27	2.04 ± 0.27		
	AAS	1.71 ± 0.28	1.92 ± 0.27		
	HE	1.57 ± 0.31	1.64 ± 0.31		
Knee extension strength, Nm/kg	Exercise + AAS	1.15 ± 0.27	1.23 ± 0.29	*F* = 3.558, .02	Exercise + AAS > HE
	Exercise	1.12 ± 0.30	1.14 ± 0.26		
	AAS	1.15 ± 0.25	1.14 ± 0.25		
	HE	1.14 ± 0.26	1.00 ± 0.26		

* A post hoc analysis was performed using the Scheffe method.
AAS = amino acid supplementation; HE = health education; BMI = body mass index.

Table 3. Change in Leg Muscle Mass and Functional Fitness After Intervention According to Study Group

Dependent Variable*	Adjusted Odds Ratio (95% Confidence Interval)		
	AAS	Exercise	Exercise + AAS
Change in leg muscle mass and knee extension strength	1.99 (0.72–5.65)	2.61 (0.88–8.05)	4.89 (1.89–11.27)
Change in leg muscle mass and usual walking speed	1.35 (0.45–4.08)	2.41 (0.79–7.58)	4.11 (1.33–13.68)

Reference: health education.
* 1 = improve, 0 = no change or decrease.
AAS = amino acid supplementation.

9% to 15% increases in strength and approximately 5% in thigh muscle volume.[28,29] Also, many studies have shown that resistance training in elderly people must be conducted at high intensities and volumes to see improvements.[9,27] In contrast, less-intense resistance exercise programs have produced little or no strength gains.

The data in this study show improvements of 2.4% in leg muscle mass, 2.0% in appendicular muscle mass, and 4.3% in leg strength in the exercise group. The moderate-intensity exercise provided in this trial produced strength gains that were smaller than those seen in previous studies, but the combination of moderate intensity exercise and AAS increased muscle mass 3.1% and muscle strength 9.3%, gains that are comparable with those observed in previous studies of high-intensity exercise.[28]

The results of the current study showed that total muscle mass, appendicular muscle mass, and walking speed significantly increased in the exercise group, suggesting that exercise is effective in the improvement of muscle mass and functional fitness, but increases in muscle

strength were not observed. These results indicate that exercise alone is insufficient for recovery in sarcopenic elderly women.

Previous studies have indicated that declines in muscle mass are related to declines in muscle protein synthesis rates in older adults and that leucine-enriched essential amino acid mixtures are primarily responsible for the amino acid-induced muscle protein anabolism in elderly people.[11,22] These studies investigated the effects of different amino acid dosages (from 6.7 to 20.0 g/d) on protein synthesis, and the 6.0-g/d dosage provided in this study is lower than in previous studies, but the mean weights of the subjects in such studies were from 71.0 to 81.3 kg, making the dosage of amino acid between 0.090 and 0.246 g/kg of body weight. The amino acid dosage in the current study was 0.151 g/kg, which is comparable with the amounts found in the literature.[11,22,26] The results of the current study showed that muscle mass, appendicular muscle mass, and leg muscle mass significantly increased in the AAS group, which is consistent with previous findings.

Many studies have demonstrated an increase in muscle mass from nutritional supplementation, but an increase in muscle strength does not always accompany an increase in muscle mass. A recent study concluded that essential AAS alone was not sufficient to increase muscle strength.[26] Similarly, although the results of the current study showed that AAS alone increased muscle mass, improvement in muscle strength was not observed. The results of the present study showed that muscle mass increased significantly with exercise or essential AAS, although muscle strength, measured according to knee extension strength, improved significantly only in the exercise + AAS group.

Next, the discussion will focus on the changes in the combined variables. One study that investigated the effects of resistance exercise and nutritional supplementation on muscle mass and strength in older adults concluded that high-intensity resistance exercise was beneficial in increasing muscle mass and muscle strength, but the nutritional supplementation, which contained only a small percentage of a soy-based protein within a mixture of mainly carbohydrates, did not contribute to those gains.[8] As illustrated in Figure 2, exercise alone was effective in enhancing single variables such as leg muscle mass or usual walking speed. Similarly, the AAS group improved usual walking speed, but rationally, to treat sarcopenia, improvements in single variables are not sufficient. Improvements observed in the combined variables would presumably lead to the most-efficient reversal of sarcopenia. Significant improvements in the combinations of leg muscle mass, knee extension strength, and walking speed were seen only in the exercise + AAS group. Although whether exercise + AAS was better than either intervention alone remains inconclusive, these results suggest that exercise + AAS may be necessary for benefits in muscle mass and strength.

This study has several limitations. First is the measurement of body composition estimated using BIA. Although magnetic resonance imaging (MRI), computed tomography, and dual-energy X-ray absorptiometry are common, accurate clinical methods of measuring muscle mass,[30,31] they are cost ineffective and are not always appropriate for field studies. BIA is simple, noninvasive, and inexpensive and has been widely used in field studies. The comparison of MRI and BIA measurements has revealed a strong correlation between the two, confirming the validity of the BIA method for muscle mass measurement in older adults.[13,17,18] Therefore, the validity of the data collected using BIA has little influence on the interpretation of the results of this study. Second, it has been reported that AAS enhances muscle protein synthesis,[11,22,32] but the mechanism of the increase in muscle mass from AAS was not explored in the current investigation. Therefore, the results of this study were interpreted based on the assumption that muscle protein synthesis had been enhanced. Third, the effects of the exercise + AAS should have been determined with the use of placebos, but placebo treatments were not provided in this study, so future research should include placebos to observe the effects of exercise and AAS on physical function and muscle strength. Fourth, the total number of dropouts in this study was 11 people, and they were not included in the data analysis. Many studies have used intention-to-treat (ITT) analyses to determine the effects of RCTs, and the use of ITT analyses are increasing, although one previous study found that only approximately 35% of 274 RCTs used ITT analyses.[33] The current study was not an ITT analysis because it confirmed that there were no significant differences between the dropouts and the participants who completed the study, and the exclusion of the 11 dropouts from the analysis did not affect the integrity of the baseline randomization. Finally, previous research has shown that milk contains essential amino acids.[34,35] Because some of the participants took the AAS with milk, the exact essential amino acid dosage in this study could not be determined, and the effect of drinking milk on the results of this study was not confirmed. Future research should avoid the intake of milk with amino acids when investigating the effects of amino acids on muscle strength and mass and physical function.

This study demonstrated that exercise and nutrition may be necessary for the basic treatment of increasing muscle mass and strength to reverse the effects of sarcopenia in community-dwelling sarcopenic women. Exercise and AAS together have significant effects on enhancing not only muscle strength, but also the combined variables of muscle mass and walking speed and of muscle mass and strength in this study population, but further follow-up studies on larger populations are required to confirm these results.

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Author Contributions: H. Kim developed the study concept and design, recruited subjects, developed the intervention program, analyzed and interpreted the data, and prepared the manuscript. S. Takao interpreted the data and reviewed the manuscript for accuracy. K. Saito assisted in AAS and supervised the interview survey. Y. Hideyo assisted in subject recruitment, supervised the

interviewers, and interpreted the data. M. Kobayashi assisted in AAS and subject recruitment and interpreted the data. H. Kato assisted in assisted AAS and body composition assessment. M. Katayama assisted in AAS and interview survey.

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Relationship Between Serum Isoflavone Levels and Disability-Free Survival Among Community-Dwelling Elderly Individuals: Nested Case–Control Study of the Tsurugaya Project

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Background. The longer healthy life expectancy observed in Japan may be partly attributed to the Japanese diet. The researchers sought to examine whether serum isoflavone levels are associated with disability and death.

Methods. The researchers used a nested case–control study to compare serum isoflavones (daidzein, genistein, glycitein, and equol) levels between 165 participants that died or were certificated as disabled (cases) and 177 controls. Disability was defined by certification of long-term care insurance. Conditional logistic regression models were used to calculate the risk of isoflavones for the composite outcome.

Results. The proportion of cases was lower in the group with the highest levels of equol (34/91, 37%) compared with equol nonproducers (84/161, 52%). The risk of disability or death among equol producers remained reduced after adjusting for age and sex (odds ratio: 0.55, 95% confidence interval: 0.33–0.93). In a multivariate model, this *risk was also unchanged* (odds ratio: 0.51, 95% confidence interval: 0.27–0.96). There were no significant associations between daidzein, genistein, and glycitein with the composite endpoint.

Conclusions. Higher serum equol levels, but not any other isoflavones, were inversely associated with the composite endpoint of disability and death. Although it cannot be concluded that equol per se has preventive effects on disability or death, *higher equol levels appear associated with better health.*

Key Words: Isoflavone—Disability—Mortality—Nested case–control study.

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ACCORDING to the Health Report published in 2004 by the World Health Organization, both healthy life expectancy at age 0 and 60 years were the longest in Japan compared with all other countries in the world (1). Therefore, it might be important to explore the determinants of the prolonged healthy life expectancy among Japanese. For instance, this longer healthy life expectancy may be, in part, attributed to the Japanese diet, which is high in foods such as fish, green tea, and soybean. In this study, the researchers focused on the relationship between soy isoflavones and disability-free survival.

A questionnaire survey is frequently used to estimate food consumption. However, in Japan, soybean is frequently used as a raw material in seasonings, such as miso paste and soy sauce. Therefore, it might be difficult to estimate the amount of soybean consumed from food frequency questionnaires. Indeed, the researchers previously found that there was a poor correlation between the assessment of soybean consumption by dietary record and food frequency questionnaire (2). Furthermore, studies on equol, a metabolite of daidzein that is produced by intestinal bacteria in some, but not all, adults have shown that those individuals

who possessed equol-producing intestinal bacteria were more likely to benefit from soyfood consumption than those who did not (3,4). Importantly, equol production can only be assessed from blood or urine samples. Therefore, in the present study, the researchers decided to assess serum isoflavone as markers of soy intake.

Isoflavones, including genistein, daidzein, and glycitein, are found in soy and soy products (3,4). Isoflavones are known to have estrogenic effects, and consequently, may possess an ability to lower cholesterol and inhibit bone loss (3,4). Furthermore, emerging evidence suggests that isoflavones may be associated with lower risk of various cancers, including lung (5–7), prostate (8,9), and breast (10). Therefore, isoflavone levels may be associated with a lower risk of incident disability and mortality.

In the present study, the researchers used a nested case–control study design to investigate the relationship between serum isoflavone levels and risk of composite outcome of disability and death; a good indicator of healthy life expectancy.

Methods

Study Participants

As implemented in 2002 and 2003, the Tsurugaya Project was a comprehensive geriatric assessment of medical status, as well as physical and cognitive functions (11–17). The present study is based on data collected in 2002, as blood samples from that time period were available (16,17).

Of the 2,730 inhabitants aged 70 and older living in the Tsurugaya area of Sendai, Japan, 1,177 provided written informed consent to participate in the study. Because the researchers did not obtain agreement to review information regarding long-term care insurance (LTCI) in 2002, they requested agreement from the participants who underwent a comprehensive geriatric assessment in 2003. Of the 1,177 participants who underwent a comprehensive geriatric assessment in 2002, 671 underwent another comprehensive geriatric assessment in 2003, of which 657 agreed to a review of their LTCI information. The researchers excluded data from participants who were identified as having a disability on their LTCI certificate in 2003 ($n = 55$), participants who did not agree to their blood samples being analyzed or stored ($n = 6$), and participants who moved prior to being certified as disabled ($n = 6$). Of the 590 remaining participants, 208 developed a disability or died by June 30, 2009. The eligible participants were divided into eight strata according to sex and age (every 5 years; Table 1). Specifically, a select 178 cases (ie, participants that developed a disability or died) and 178 controls (ie, participants who lived without disability until June 30, 2009) were stratified. Because 14 serum samples (1 control and 13 cases) did not have sufficient serum to measure isoflavone levels (<1 mL of serum), the researchers assessed a total of 342 participants in the present study (Table 1). The Ethics Committee of the Tohoku University Graduate School of Medicine approved the study protocol.

Table 1. Age and Sex Distribution of the Eligible Participants from the Tsurugaya Project (2002–2009)

		Condition in June 2009	
Age in 2002 (y)	Sex	No Disability and Alive	Disabled or Deceased
70–74	Men	35	32
	Women	36	33
75–79	Men	27	25
	Women	50	47
80–84	Men	9	9
	Women	16	15
85–89	Men	1	1
	Women	3	3

Serum Isoflavone Measurements

Blood samples collected under non-fasting conditions were immediately cooled at 4°C, centrifuged within 4 hours at 3,000*g* at 4°C for 10 minutes, and stored at −80°C. Concentrations of serum isoflavones, namely genistein, daidzein, glycitein, and equol, were measured using triple quadrupole tandem liquid chromatography–mass spectrometry (18). These measurements were determined at a clinical testing laboratory (SRL, Tokyo, Japan). Serum albumin, total cholesterol (TC), and casual glucose levels were also measured.

Other Measurements

Information regarding smoking status, drinking status, food intake, physical activity (PA), and history of disease was surveyed via a questionnaire, and drug information was confirmed by an experienced pharmacist. The participants were instructed to fill out a brief self-administered diet history questionnaire that included 75 food items with specified serving sizes described by natural portions or standard weight and volume measures of the servings commonly consumed in the study population. The mean daily intake of nutrients was calculated by using an ad hoc computer program developed to analyze the questionnaire (14). Participants indicated the mean frequency of consumption of green tea over the previous 1 month in terms of the specified serving size by selecting one of the eight frequency categories: almost never, less than 1 cup/wk, 1 cup/wk, 2–3 cups/wk, 4–6 cups/wk, 1 cup/d, 2–3 cups/d, and greater than or equal to 4 cups/d. Subsequently, the researchers summarized this information into three groups as follows: greater than or equal to 4 cups/d, 2–3 cups/d, and less than 2 cups/d (14). In terms of meat consumption, participants indicated the mean frequency of consuming a specified serving size of (1) chicken, (2) pork or beef, (3) ham, sausage, or bacon, and (4) liver over the previous 1 month by selecting one of the frequency categories: 2 times/d, 1 time/d, 4–6 times/wk, 2–3 times/wk, 1 time/wk, less than 1 time/wk, and none. These four frequencies were summed and a total meat consumption

frequency was calculated. According to the distribution, the researchers classified participants into four groups of meat consumers: greater than or equal to 6.5 times/wk, 4.5–6.4 times/wk, 2.5–4.4 times/wk, and less than 2.5 times/wk. PA was first assessed by a self-reported single question on whether the participant had any PA in the past year. If "yes," further questions were asked about the frequency and duration of walking, brisk walking, and sports. Each PA was classified into three categories on the basis of the frequency and duration of participation: (i) "high" PA (≥3–4 times/wk for ≥30 minutes each time), (ii) "low" PA (some PA in the past year, but not enough), and (iii) "none" (no PA). In this study, the researchers used three categories according to the distribution; participants who did any level of sports or high frequency of brisk walking, participants who did low frequency of brisk walking or any level of walking, and participants who did not have PA. Symptoms of depression were assessed via the Japanese version of the 30-item geriatric depression scale (12,14). The anthropometric variables (height and body weight) were recorded according to standard protocol. Body mass index was calculated as weight in kilograms divided by height in meters squared. Functional reach, which measures how far an individual can reach forward beyond their arm's length while standing without losing balance, was measured and used as an indicator of physical function (13). The researchers used average stiffness of the right and left calcaneus as an indicator of bone mineral density. To assess stiffness, the researchers determined quantitative ultrasound parameters, such as the speed of sound (m/s), broadband ultrasound attenuation (dB/MHz), and the stiffness index (Stiffness), which was derived from speed of sound and broadband ultrasound attenuation. These parameters were measured in the right and left calcaneus using an Achilles Ultrasound Bone Densitometer (A-1000, GE-Lunar Corporation, Madison, WI) (19). Participants self-measured blood pressure at home using an automated device (HEM747IC: Omron Life Science Co. Ltd., Tokyo, Japan) (12). Participants were classified into groups based on the following categories: home hypertension, home borderline hypertension, and home normotension, according to the guidelines for home blood pressure (20). Participants prescribed antihypertensive medication were classified into the home hypertension group. The presence of diabetes was defined as a non-fasting blood glucose greater than or equal to 200 mg/dL (11.1 mmol/L) or use of antidiabetic drugs. Impaired blood glucose was classified as non-fasting blood glucose between 140–199 mg/dL (7.7–11.0 mmol/L). Participants were categorized into four TC groups: TC greater than or equal to 240 mg/dL or use of cholesterol lowering drug, TC between 200–239 mg/dL, TC between 160–199 mg/dL, and TC less than 160 mg/dL.

LTCI Certification

The researchers defined incident disability based on the LTCI certification system, which was launched as a national insurance scheme in April 2000 (21–23), and followed up those with certified incident disability until June 30, 2009.

Individuals aged 40–64 years and living in Japan, who were diagnosed with aging-related diseases (eg, Alzheimer's disease and stroke), and those aged 65 and older, who were certified as requiring care, are eligible for benefits under the LTCI certification (24). To receive LTCI services, elderly individuals or their caregivers (family or professional) must contact the municipal government to have their care requirements officially certified (22). A trained local government official visits their home to evaluate nursing care needs via a questionnaire that assesses their current physical and mental status, and use of medical services (21). Standardized scores for physical and mental functioning, as well as the estimated amount of time required for care under nine categories (ie, grooming and/or bathing, eating, using the toilet, transferring, eating, assistance with instrumental activities of daily living, behavioral problems, rehabilitation, and medical services), are then calculated using software. Based on the national average values, it is decided whether applicants should be certified to receive LTCI services, and then, the system assigns a care needs level, which is determined by a certification board comprising physicians, nurses, and other experts in health and social services, who were appointed by the local mayor. The minimum standard for LTCI was care support level 1, which requires 25 minutes of total care/d (21,25).

Care needs are assessed according to seven levels, which closely correlate with the Barthel Index (Spearman's coefficient: −0.86) and the Mini-Mental State Examination (Spearman's coefficient: −0.42) (24,26). The outcome represents a comprehensive measure of disability among elderly individuals (26).

The Sendai City Municipal Authority provided annual information regarding LTCI certification, including the care level, date of certification, relocation, and death, between June 30, 2003 and June 30, 2009. The researchers defined incident disability as the certification of an individual by the LTCI to any level of care, and the date of disability as the first date of certification. Six participants were removed from the study due to relocation during the follow-up. The researchers used a composite outcome of disability and death, which can also be considered as an indicator of disability-free survival.

Statistical Analysis

The researchers classified participants into four groups based on quartiles of isoflavone levels. However, with respect to equol, almost half of participants were nonproducers of equol (ie, equol level < 1.0 ng/mL), and consequently, the researchers used three categories, specifically, the nonproducers, lower half of equol producers (ie, equol level ≥ 1.0 ng/mL), and upper half of equol producers.

The characteristics of cases and controls were compared using the χ^2 test or t test, as appropriate. Characteristics

with respect to isoflavone levels were compared using the χ^2 test for categorical variables or ANOVA for continuous variables, as appropriate. A multiple logistic regression analysis was used to determine factors that predict equol production. This model included the following factors: smoking, alcohol drinking, blood pressure (ie, home hypertension, home borderline hypertension, and home normotension), blood glucose (diabetes, impaired blood glucose, and normal range), TC group, albumin, sex-specific quartile of functional reach, depression (geriatric depression scale ≥ 11), body mass index, sex-specific quartile of stiffness of calcaneus, history of cardiovascular disease, history of cancer, sex-specific quartile of total energy intake, green tea consumption, meat consumption, PA group, and serum daidzein concentration. The researchers also determined the factors that predict higher equol values in equol producers via a linear regression model with log-transformed equol and the above-mentioned factors.

A conditional logistic regression model on the age and sex strata was used to calculate the odds ratios (ORs) and 95% confidence intervals of isoflavones and risk of disability or death. The researchers used both crude and multiple adjusted models. In the multivariate model, the researchers adjusted for the potential confounders associated with isoflavone levels or incident disability or death mentioned above excluding serum daidzein level.

The researchers also calculated the risk of disability only (case = 142) or death only (case = 40). Furthermore, the researchers calculated the relationship of daidzein, genistein, and glycitein with composite outcome of disability and death among equol producers. The level of statistical significance was set at $p < .05$. All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Results

The baseline characteristics of control (ie, those that live without disability) and case (ie, those that developed a disability or died by the end of the follow-up period) groups are presented in Table 2. Due to age and sex matching, there were no differences observed in age and proportion of sex. TC levels, functional reach, stiffness, and PA were statistically lower among cases than controls ($p < .05$).

When the researchers compared the baseline characteristics of the participants according to each isoflavone type and their respective levels, there were no apparent age differences across all isoflavone groups. However, the proportions of women were generally lower in the higher ranges of all isoflavone levels. TC levels were also generally lower in the higher ranges of all serum isoflavone levels. The proportion of bone mineral density was significantly different in the glycitein group, but not in the daidzein, genistein, or equol groups. Although the proportion of women was lower at higher serum equol levels, the proportion of current smokers was also lower at the higher serum equol levels. When a multiple logistic regression analysis was performed to determine the predictors of equol producers, male gender was revealed as a significant predictor of higher equol production. Of all equol producers, men, nonsmokers, and participants with diabetes had higher log-transformed equol values. A higher concentration of daidzein also predicted higher log-transformed equol values ($\beta = 0.003$, $p = .002$).

The relationship between levels of different isoflavones and the composite endpoint of disability or death are presented in Table 3. There were no significant associations between daidzein, genistein, and glycitein with the composite outcome of disability or death after adjusting for age and sex. However, in the equol group, the risk of composite endpoint was lower with higher levels of equol, after control for age and sex (OR = 0.55; 95% confidence interval = 0.33–0.93). These associations remained unchanged when additional potential confounders were added to the model (OR = 0.51; 95% confidence interval = 0.27–0.96). Similarly, the relationship was unchanged when the researchers excluded participants who died without disability. Although participants with the highest isoflavone quartiles consistently showed lower risk of death (OR ≤ 0.46), this observation did not reach statistical significant due to the small number of deaths. The relationships between daidzein, genistein, and glycitein levels with the composite endpoint were also assessed among equol producers only (Table 4). The highest quartiles of the daidzein, genistein, and glycitein groups showed a nonsignificant trend for a lower risk of the composite endpoint (OR ≤ 0.86).

Discussion

The present nested case–control study is the first to show that higher levels of equol are associated with lower risk of disability or mortality. This inverse relation was also observed when the researchers compared participants with disability with controls. However, whether equol per se plays a causal role in increasing healthy life expectancy remains to be determined in future research.

There are several advantages of the present study. First, this study assessed comprehensive geriatric parameters, including physical function and depressive symptoms, which have been previously associated with incident disability or mortality. Second, the researchers used a nested case–control design, in which the measurement precedes the onset of the outcome, thus establishing the temporal relationship between the putative cause and the hypothesized effect. Third, the researchers used LTCI certification to assess disability, which is based on strictly established and uniform rules throughout Japan. This methodology enabled us to achieve higher follow-up rates, and eliminated potential selection bias in both the case and control groups. Nevertheless, this system is not perfect, as

Table 2. Comparison of Baseline Characteristics Between Control and Case Groups, the Tsurugaya Project 2002–2009.

		Condition at June 2009		
		Control	Case	
		Alive without Disability	Disability or Death	*p* Value
Numbers of participants		177	165	
Age	y, mean (*SD*)	75.9 (3.8)	76.5 (4.2)	.14
Sex	Women	59%	59%	
Smoking	Current	10%	13%	
	Past	27%	29%	
	Never	63%	55%	
Drinking	≥46 g of alcohol/d	8%	8%	.15
	23–45.9 g of alcohol/d	8%	3%	
	0–22.9 g of alcohol/d	15%	21%	
	0 g	69%	68%	
Blood pressure	Normotension	19%	16%	.76
	Borderline hypertension	12%	9%	
	Hypertension	65%	70%	
	Home BP not measured	5%	5%	
Blood glucose	Diabetes	7%	8%	.09
	Impaired blood glucose	4%	10%	
	Normoal blood glucose	89%	82%	
Cholesterol	TC ≥ 240 mg/dL or cholesterol lowering drug	34%	26%	.32
	TC 200–239 mg/dL	36%	36%	
	TC 160–199 mg/dL	24%	30%	
	TC < 160 mg/dL	6%	8%	
Albumin	g/dL, mean (*SD*)	4.4 (0.3)	4.3 (0.3)	.32
Functional reach	Could not measure	1%	1%	<.01
	Men 0–28.8 cm, women 0–25.6 cm	15%	35%	
	Men 28.9–32.1 cm, women 25.7–28.6 cm	21%	28%	
	Men 32.2–36.3 cm, women 28.7–32.2 cm	31%	18%	
	Men 36.4 cm–, women 32.3 cm–	33%	19%	
Depression	GDS ≥ 11 point	25%	35%	.0497
Body mass index	kg/m^2 (SD)	23.7 (3.0)	23.6 (3.6)	.76
Stiffness of calcaneus	Men 0%–60.4%, women 0%–49.4%	19%	30%	<.01
	Men 60.5%–71.4%, women 49.5%–56.9%	23%	25%	
	Men 71.5%–81.9%, women 58.5%–65.9%	31%	20%	
	Men 82.0%–, women 66.0%–	28%	25%	
History of CVD	Present	11%	18%	.10
History of cancer	Present	5%	10%	.06
Total energy intake	kcal/d (SD)	1616 (398)	1654 (468)	.41
Green tea consumption	≥4 cups/d	50%	45%	.43
Meat consumption	6.5 times/wk	29%	28%	.71
Physical activity	Sports or higher amount of brisk walking	27%	16%	.02
	Lower amount of brisk walking or any amount of walking	42%	56%	

Notes: CVD = cardiovascular diseases; diabetes = casual blood glucose ≥ 200 mg/dL or taking antidiabetic drugs; GDS = geriatric depression scale; 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; *SD* = standard deviation; TC = total cholesterol.

elderly individuals or their caregivers must initiate contact with the municipal government to receive LTCI services, and thus, some elderly individuals with disability may not be certified. However, this confounder would attenuate the relationship between equol levels and the composite outcome of disability and death. Therefore, the researchers' conclusion that higher serum equol was associated with lower risk of composite endpoint of incident disability and death, should remain true. Another limitation of this study was that blood samples were collected in non-fasting conditions, potentially affecting serum isoflavone levels. Similarly, because equol production has been found to vary over time within individuals (27), the misclassification of equol status is a possibility. However, these limitations would only attenuate the relationship between equol levels and the composite outcome of disability and death.

In the present study, half of the participants were classified as equol producers, which corroborate the findings of previous reports from Asia (4,17). In the researchers' attempt to determine the predictors of equol production, they were able to only identify sex. Interestingly, among all equol producers, men, nonsmokers, and participants with diabetes had

Table 3. Serum Isoflavone Levels in the Control and Case Groups from the Tsurugaya Project (2002–2009)

		All Samples				Control vs Disabled			Control vs Death		
		Control	Case	OR1 (95% CI)	OR2 (95% CI)	Control	Case	OR2 (95% CI)	Control	Case	OR2 (95% CI)
Isoflavones	ng/mL	No Disability and Alive	Disabled or Deceased	Age and Sex Only	Multiple Adjusted	No Disability and Alive	Disabled*	Multiple Adjusted	No Disability and Alive	Deceased	Multiple Adjusted
Daidzein	–36	48	38	1	1	48	36	1	48	6	1
	36.1–76.6	43	41	1.21 (0.66–2.21)	1.42 (0.68–2.97)	43	31	1.22 (0.55–2.67)	43	15	9.31 (1.50–57.94)
	76.7–141.0	42	44	1.32 (0.73–2.41)	1.64 (0.77–3.50)	42	35	1.63 (0.73–3.66)	42	16	9.53 (1.28–71.20)
	141.1–	44	42	1.21 (0.66–2.21)	1.52 (0.73–3.19)	44	40	1.56 (0.72–3.36)	44	3	0.24 (0.02–2.95)
Genistein	–63.5	47	39	1	1	47	37	1	47	7	1
	63.6–145.2	41	44	1.30 (0.71–2.38)	1.42 (0.68–2.95)	41	35	1.21 (0.55–2.66)	41	13	4.89 (0.90–26.52)
	145.3–269.1	41	44	1.30 (0.71–2.37)	1.31 (0.63–2.71)	41	33	1.09 (0.50–2.39)	41	15	2.04 (0.43–9.71)
	269.2–	48	38	0.96 (0.52–1.75)	0.99 (0.47–2.07)	48	37	1.05 (0.49–2.28)	48	5	0.37 (0.05–2.49)
Glycitein	–1.9	43	37	1	1	43	31	1	43	10	1
	2.0–4.6	46	43	1.09 (0.60–2.01)	1.06 (0.51–2.22)	46	37	1.09 (0.49–2.43)	46	10	1.26 (0.31–5.08)
	4.7–9.8	46	41	1.04 (0.57–1.91)	1.12 (0.53–2.35)	46	36	1.27 (0.57–2.84)	46	11	0.98 (0.25–3.82)
	9.9–	42	44	1.22 (0.66–2.27)	1.31 (0.62–2.74)	42	38	1.52 (0.68–3.37)	42	9	0.46 (0.10–2.08)
Equol	–0.9	77	84	1	1	77	75	1	77	16	1
	1.0–23.5	43	47	1.00 (0.60–1.68)	1.10 (0.59–2.05)	43	38	1.01 (0.52–1.98)	43	14	1.90 (0.55–6.62)
	23.6–	57	34	0.55 (0.33–0.93)	0.51 (0.27–0.96)	57	29	0.52 (0.27–1.02)	57	10	0.45 (0.12–1.68)

Notes: 95% CI = 95% confidence interval; diabetes = casual blood glucose ≥ 200 mg/dL or taking antidiabetic drugs; OR = odds ratio; OR1 = stratified for age and sex; 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 = does not satisfy the 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.

*Participants died without incident disability was not included in this analysis.

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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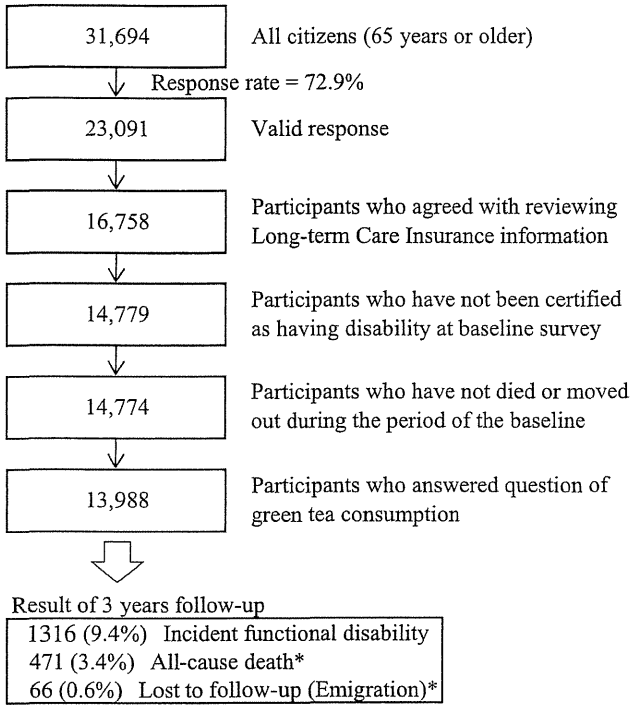

FIGURE 1. Flowchart of study participants: the Ohsaki Cohort 2006 Study. *Without experiencing incident functional disability.

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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