might have lower physical function as well as less body fat. A similarly inverse association between adiponectin and bone mineral density has also been reported (34). Because adjusting for physical function and bone mineral density attenuates the relationship between adiponectin and disability or death, lower physical function and lower bone mineral density in individuals with higher adiponectin may play important role in the relationship between adiponectin and disability or death. However, our finding, that is, relatively strong effect of physical activity and bone mineral density on the relationship between adiponectin and composite endpoint, might be due to the outcome consisting predominantly of physical disability (76% of events). Further studies might be required to confirm whether physical function attenuates the relationship between adiponectin and mortality. Another possible candidate mechanism is the effect of NT-pro-BNP on the relationship between adiponectin and mortality. Although Wannamethee and colleagues and Kirstop and colleagues indicated that adjusting for NT-pro-BNP largely attenuates the relationship between adiponectin and mortality (2,19), such adjustment in the present study did not attenuate the relationship between adiponectin and disability or death. The contribution of NT-pro-BNP to the relationship between adiponectin and disability or death might be smaller in our Japanese cohort than in previous reports. Further studies are required to confirm our findings. The present study also clarified that the contribution of renal function or malnutrition to the relationship between adiponectin and disability or death was small. We did not find any positive associations between adiponectin and disability or death after excluding early death or disability that occurred within 3 years. Despite the limited statistical power of this approach, the findings nevertheless suggest that elderly individuals with higher adiponectin levels are likely to develop or already have wasting conditions that are associated with early disability or death. Thus, physical function and subclinical conditions should be assessed among older participants with higher adiponectin levels.

In conclusion, we found that circulating adiponectin levels are positively associated with disability or death. This association was weakened when we adjusted for physical function and excluded early events. Therefore, the positive relationship between higher adiponectin levels and disability or death might be partly explained by lower physical function and physical wasting.

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CONFLICT OF INTEREST

There is no potential conflict of interest that relates to the manuscript.

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Original Article

COACTION PUBLISHING

Randomized controlled trial for an effect of catechin-enriched green tea consumption on adiponectin and cardiovascular disease risk factors

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Abstract

Background: Previous observational studies have indicated that green tea (GT) consumption is associated with reduced mortality from cerebral infarction but not with mortality from cerebral hemorrhage. Therefore, we hypothesized that GT exerts a direct antiatherosclerotic effect without any effect on hypertension. To investigate this hypothesis, we focused on adiponectin that seems to be among the several key players in atherosclerosis.

Objective: The objective of this randomized controlled trial (RCT) was to assess whether the consumption of catechin-enriched GT affects serum adiponectin levels and cardiovascular disease (CVD) risk factors among apparently healthy subjects.

Design: A total of 51 individuals participated in the study. Eligible participants were randomly assigned into GT consumption groups with either high catechin (400 mg/day) or low catechin (100 mg/day). The study participants were asked to stop GT consumption for 2 weeks (washout period), following which they were to start drinking the provided GT beverages everyday for 9 weeks. The outcome measures were changes in the adiponectin levels and CVD risk factors (body weight, body mass index, waist circumference, blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, fasting plasma glucose, as well as aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, uric acid, and high-sensitive C-reactive protein).

Results: After intervention for 9 weeks, we found no significant difference between the high- and low catechin group with respect to changes in the serum adiponectin level: 0.35 μg/ml (95% confidence interval (CI): −1.03, 1.74). Also, no significant difference was observed between the high- and low catechin groups with respect to changes in any of the measured CVD risk factors.

Conclusion: This RCT showed no significant difference between the high-and low catechin groups with respect to changes in the serum adiponectin level and any CVD risk factors.

Keywords: *randomized controlled trial*; *green tea*; *catechin*; *adiponectin*; *cardiovascular disease risk factors*

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Substantial evidence from *in vitro* and animal studies indicates that green tea (GT) preparations inhibit cardiovascular disease (CVD) processes (1–4). In our previous observational study, we showed that GT consumption was associated with a significantly lower risk of mortality due to CVD among middle-aged adults (5). The study also indicated that GT consumption was associated with reduced mortality from cerebral infarction but not with mortality from cerebral hemorrhage. These associations were consistent with those reported in

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another observational study (6). Therefore, we hypothesized that GT exerts a direct antiatherosclerotic effect not mediated via any effect on hypertension. To investigate this hypothesis, we focused on adiponectin that is among the several key players that seem to play a direct role in atherosclerosis. Adiponectin inhibits proliferation of migrated smooth muscle cells (7), monocyte adhesion to endothelial cells, and oxidized low-density lipoprotein (LDL) uptake of macrophages and has been shown to have direct effects on atherosclerotic lesions (8). In addition, some human studies suggested that high plasma adiponectin concentrations are associated with a lower risk of CVD (9–12), and observational studies have indicated an antiatherosclerotic role of adiponectin (13, 14).

Several animal experiments have indicated that the intake of GT increases the adiponectin level (15–17). To date, three randomized controlled trials (RCTs) have examined the association between tea catechin consumption and adiponectin levels in humans, but none reported a significant increase in adiponectin by GT catechin consumption (18–20). Because these RCTs recruited patients with diabetes mellitus and obesity, further evidence among healthy subjects is needed to obtain some consensus on this issue. We, therefore, designed this RCT to assess whether consumption of catechin-enriched GT affects serum adiponectin levels and CVD risk factors among apparently healthy subjects.

Subjects and methods

Study participants and intervention program

The study was conducted between June 2007 and September 2007, and between December 2007 and February 2008. The persons included in the present study were those who participated in a weight loss program at Sendai Health Promotion Center (weight loss program participants) and the staff of Sendai Health Promotion Center (weight loss program non-participants) in Japan. The inclusion criteria for the intervention program were (1) both sexes and (2) age between 20 and 70 years. The exclusion criteria were history of diabetes mellitus, cancer, ischemic heart disease, stroke, or renal disease. The weight loss program was based on exercise program (exercise guidance, stretching exercise, and strength training) and nutritional program (nutritional guidance and cooking practice). With a mean $\pm$SD value of 5 ± 7 μg/ml in adiponectin, a minimum sample size of 50 subjects would be required to detect a difference (power = 70%, two-sided $\alpha = 0.05$). We asked 60 subjects to participate in this study and obtained informed consent from 51 subjects. The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine.

We used commercially available catechin-containing beverages (500 ml). According to the data provided by the manufacturer, the high-concentration beverage contained 400 mg catechin and the low-concentration beverage, 100 mg (Table 1). We purchased the beverages and then delivered them to the participants' residences. Adherence to the study protocol was confirmed by asking the subjects to return the bottle caps and by reviewing their consumption records. Eligible participants were stratified by sex (men or women) and the weight loss program (participation or non-participation), and randomization was conducted by permuted block method using a four-person block. A total of 51 participants were randomly assigned by an epidemiologist (NN) to either the high catechin group ($N = 25$) or the low catechin group ($N = 26$) (Fig. 1). The study participants were asked to stop GT consumption for 2 weeks (washout period), following which they were to start drinking the provided GT beverages everyday for 9 weeks. During the intervention period, the participants were asked not to drink any other catechin-containing beverage; other beverages were allowed. The participants and research assistants were blinded to the group allocation. Both the catechin-enriched beverages had similar taste and appearance. At the end of the study, the blinding of the participants was evaluated. (Register No: UMIN000000742).

Outcome measures

The outcome measures were changes in the adiponectin levels and CVD risk factors: body weight, body mass index (BMI), waist circumference, blood pressure (BP), and levels of total cholesterol (TC), LDL cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), fasting plasma glucose, as well as aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), uric acid (UA), and high-sensitive C-reactive protein (CRP). The outcome measures were determined before and after the intervention. We also measured the nutrient intake and energy expenditure.

Table 1. Components of the test beverages

	Intervention beverage	Control beverage
Total catechin (mg)	400	100
Caffeine (mg)	105	80
Total energy (kJ)	0	0
Total protein (g)	0	0
Total fat (g)	0	0
Carbohydrate (g)	0	0
Sodium (mg)	46	53

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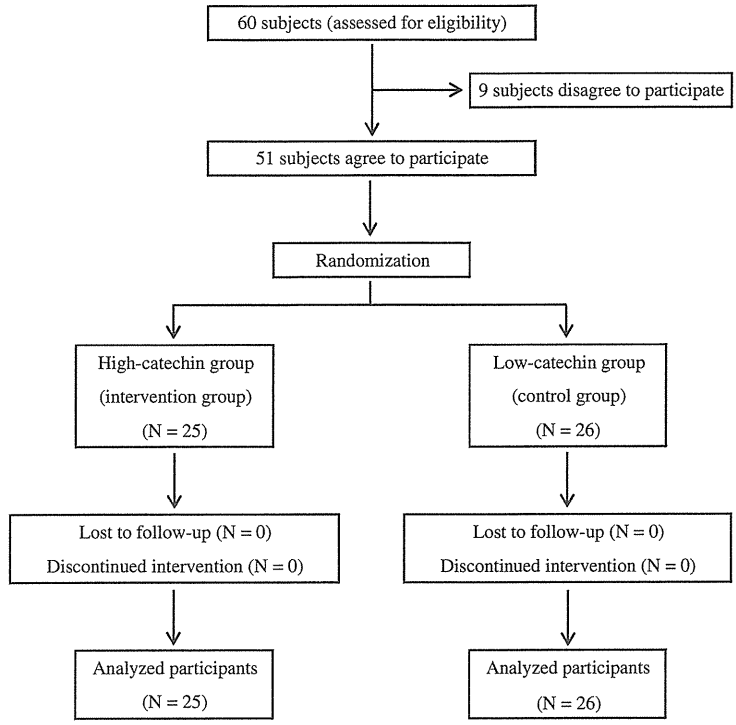

Fig. 1. Trial flow chart.

Venous blood was collected from the antecubital vein after the participants fasted overnight. Blood samples were collected into a tube containing ethylenediaminetetraacetic acid (EDTA)-2Na and a tube containing heparin. Serum and plasma samples were obtained by a 10-min centrifugation at 3,000 rpm within 30 min of obtaining the sample. The samples were then transported frozen to the SRL Laboratory in Hachioji, Tokyo, Japan, and stored at below −20°C until analysis. Serum adiponectin level was determined by enzyme-linked immunosorbent assay (ELISA; Otsuka Pharmaceutical, Tokyo, Japan), serum TC level, CEH-CDH-UV method (Sysmex Corporation, Hyogo, Japan), serum LDL-C level, liquid selective detergent method (Sekisui Medical, Tokyo, Japan), serum HDL-C level, accelerator selective detergent method (Sekisui Medical, Tokyo, Japan), TG level, enzymatic method without endogenous free glycerol (Sekisui Medical, Tokyo, Japan), fasting plasma glucose level, HK-G-6-PDH method (Shino-Test, Tokyo, Japan), AST, ALT, and γ-GTP levels, JSCC transferable method (Kanto Chemical, Tokyo, Japan), UA level, enzymatic method (Sekisui Medical), and the high-sensitive CRP level was assayed by nephelometric immunoassay (Siemens Healthcare Diagnostics, Tokyo, Japan).

BMI was calculated as body weight (kg) divided by squared height (m^2). BP was measured using a cuff placed on the upper arm of each participant in the sitting position. Nutrition surveys were carried out using a food frequency questionnaire (Excel Eiyokun) (21). Energy expenditure was measured using Lifecorder (Suzuken).

Statistical analysis

Comparisons between the two groups were performed by Student's *t*-test to assess the differences in the biochemical and anthropometric parameters at baseline. Sex ratio was compared by a Chi-squared test. Effects of the intervention on serum adiponectin level and other outcome measures were tested using a paired *t*-test in each group before and after the intervention. Analysis of covariance was used to investigate the significance of the differences in the initial values as well as the net changes after the intervention between the two groups. We considered the following variables as potential confounders *a priori*: age at baseline in years (continuous variable), sex, and baseline level of each variable. All statistical analyses were performed using SAS version 9.1 (SAS Inc., Cary, NC, USA). Intention to treat analysis was adopted. Approximate variance formulas were used to calculate the 95% confidence intervals (CIs). Differences were accepted as statistically significant at $p < 0.05$. In addition, stratified analyses according to weight loss program (participation or non-participation) were conducted.

Results

All the study participants completed the study; 95.9% of the tea bottles were consumed in the high catechin

group and 97.6%, in the low catechin group. No apparent harmful effects were observed. At the end of the study, we observed that more than half of the participants were blinded.

Comparisons of baseline variables between the high- and low catechin groups are shown in Table 2. No significant difference in the baseline adiponectin level was observed between the two groups. The proportion of women was approximately 65% in both the groups. With the exception of the baseline mean γ-GTP level, no other variable showed a significant difference between the two groups.

Table 3 shows the changes in nutrient intake and energy expenditure. There were significant reductions in total energy intake and carbohydrate intake in any of the groups. The intake of total fat, total dietary fiber, sodium chloride, and tocopherol was significantly decreased in the low catechin group. However, the net change between the groups was not significant.

Table 4 shows the changes in the serum adiponectin level and CVD risk factors. After 9 weeks of catechin consumption, the mean ± SD changes from baseline in the adiponectin level were 1.29 ± 2.77 μg/ml in the high catechin group and 1.00 ± 1.87 μg/ml in the low catechin group. We found no significant difference between the high- and low catechin group with respect to changes in the serum adiponectin level: 0.35 μg/ml (95% CI: −1.03, 1.74). There were significant decreases in the body weight, BMI, and waist circumference in both the groups, but the net change was not significant for any of these variables. Furthermore, there were no significant differences in the net change in other variables as well.

As for the net change in serum adiponectin, stratified analyses according to weight loss program (participation or non-participation) were conducted (Table 5). Among weight loss program participants and weight loss program non-participants, there were no significant differences in the net change: 0.15 μg/ml (95% CI: −1.54, 1.85) among weight loss program participants, and 1.49 μg/ml (95% CI: −0.46, 3.43) among weight loss program non-participants.

Discussion

In this RCT, we tested a hypothesis that consumption of catechin-enriched GT would affect the serum adiponectin level and CVD risk factors in apparently healthy subjects.

Table 2. Baseline characteristics of participants according to high-catechin group and low-catechin group[a]

Variables	High-catechin group (N = 25)	Low-catechin group (N = 26)	P-values[b]
Serum adiponectin (μg/mL)	8.2 ± 4.7	8.8 ± 3.2	0.06
Age (years)	43.2 ± 14.8	48.2 ± 12.4	0.38
Women (%)	64.0	65.4	0.92
Body weight (kg)	66.4 ± 13.7	64.8 ± 13.7	0.97
Body mass index (kg/m^2)	24.6 ± 4.3	24.5 ± 4.2	0.92
Waist circumference (cm)	85.0 ± 12.7	85.7 ± 12.0	0.78
Systolic blood pressure (mmHg)	123 ± 15	123 ± 16	0.81
Diastolic blood pressure (mmHg)	75 ± 10	76 ± 10	0.71
Total cholesterol (mmol/L)	4.66 ± 0.82	4.96 ± 0.67	0.31
LDL cholesterol (mmol/L)	2.70 ± 0.68	2.98 ± 0.75	0.61
HDL cholesterol (mmol/L)	1.37 ± 0.36	1.46 ± 0.37	0.93
Triglyceride (mmol/L)	1.20 ± 1.15	1.31 ± 1.63	0.09
Fasting plasma glucose (mmol/L)	5.30 ± 0.68	5.48 ± 0.53	0.25
Aspartate aminotransferase (U/L)	21.9 ± 7.2	19.9 ± 6.0	0.37
Alanine aminotransferase (U/L)	19.2 ± 11.3	17.4 ± 8.0	0.09
Gamma-glutamyl transpeptidase (U/L)	28.4 ± 28.0	31.9 ± 44.7	0.03
Uric acid (μmol/L)	308 ± 70	329 ± 76	0.70
High-sensitive C-reactive protein (ng/mL)	511 ± 573	521 ± 534	0.73
Energy intake (MJ/day)	7.82 ± 2.12	8.01 ± 1.77	0.39
Protein intake (g/day)	62.1 ± 20.4	69.5 ± 20.0	0.91
Fat intake (g/day)	55.8 ± 21.2	60.9 ± 18.6	0.52
Carbohydrate intake (g/day)	251 ± 63	252 ± 50	0.24
Energy expenditure (MJ/day)	8.75 ± 1.33	8.49 ± 1.60	0.56

[a]Values were expressed as mean ± SD.

[b]P-values with chi-squared test for female ratio and for biochemical parameters, anthropometric parameters, nutrient intake, and energy expenditure, with Student's t-test.

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Table 3. Change in nutrient intake and energy expenditure of participants according to high-catechin group and low-catechin group

Variables	Baseline Mean±SD	After 9 weeks Mean±SD	P-values[a]	Net change[b] (95% CI)	P-values[b]
Energy intake (MJ/day)					
High-catechin group	7.82±2.12	7.00±1.17	0.03	−0.14 (−0.83, 0.55)	0.68
Low-catechin group	8.01±1.77	7.22±1.63	0.009		
Protein intake (g/day)					
High-catechin group	62.1±20.4	60.8±16.5	0.75	−0.91 (−8.62, 6.80)	0.81
Low-catechin group	69.5±20.0	66.5±16.9	0.24		
Fat intake (g/day)					
High-catechin group	55.8±21.2	50.8±12.4	0.15	−0.01 (−6.12, 6.10)	0.99
Low-catechin group	60.9±18.6	53.3±14.9	0.006		
Carbohydrate intake (g/day)					
High-catechin group	251±63	219±34	0.01	−7.82 (−30.94, 15.29)	0.50
Low-catechin group	252±50	227±51	0.03		
Total dietary fiber intake (g/day)					
High-catechin group	12.1±4.5	11.7±4.9	0.64	0.33 (−1.45, 2.10)	0.71
Low-catechin group	13.8±4.4	12.7±3.6	0.03		
Sodium chloride intake (g/day)					
High-catechin group	8.9±2.9	8.6±3.1	0.64	1.16 (−0.52, 2.83)	0.17
Low-catechin group	10.8±4.3	8.7±3.9	0.01		
Potassium intake (g/day)					
High-catechin group	2.16±0.78	2.06±0.74	0.49	−0.02 (−0.30, 0.26)	0.89
Low-catechin group	2.44±0.75	2.29±0.61	0.07		
Calcium intake (mg/day)					
High-catechin group	575±230	545±213	0.48	12.29 (−67.27, 91.86)	0.76
Low-catechin group	581±170	556±173	0.19		
Magnesium intake (mg/day)					
High-catechin group	236±75	224±79	0.53	−0.98 (−33.86, 31.90)	0.95
Low-catechin group	258±78	244±64	0.14		
Iron intake (mg/day)					
High-catechin group	6.73±2.19	6.90±2.32	0.74	0.44 (−0.53, 1.41)	0.37
Low-catechin group	7.80±2.56	7.18±1.94	0.07		
Zinc intake (mg/day)					
High-catechin group	7.62±2.23	7.24±1.69	0.40	−0.15 (−0.93, 0.62)	0.69
Low-catechin group	8.28±2.14	7.81±1.74	0.09		
Copper intake (mg/day)					
High-catechin group	1.02±0.29	0.95±0.26	0.29	−0.02 (−0.14, 0.09)	0.68
Low-catechin group	1.11±0.32	1.04±0.25	0.10		
Tocopherol intake (mg/day)					
High-catechin group	6.90±2.21	6.36±1.64	0.18	−0.08 (−0.79, 0.62)	0.81
Low-catechin group	7.93±2.53	7.04±1.73	0.006		
Vitamin K intake (μg/day)					
High-catechin group	200±81	201±105	0.94	8.99 (−28.20, 46.19)	0.63
Low-catechin group	231±89	218±66	0.19		
Vitamin C intake (mg/day)					
High-catechin group	80±45	82±44	0.73	4.08 (−9.05, 17.21)	0.54
Low-catechin group	100±44	95±38	0.22		
Energy expenditure (MJ/day)					
High-catechin group	8.75±1.33	8.51±1.27	0.06	−0.09 (−0.38, 0.19)	0.51
Low-catechin group	8.49±1.50	8.38±1.29	0.28		

[a]Paired t test.

[b]The change in high-catechin group minus the change in low-catechin group. The net differences were calculated by analysis of covariance. Adjusted for age (in years), sex, and individual baseline variables.

Table 4. Change in serum adiponectin and cardiovascular risk factors of participants according to high-catechin group and low-catechin group

Variables	Baseline Mean±SD	After 9 weeks Mean±SD	P-values[a]	Net change[b] (95% CI)	P-values[b]
Serum adiponectin (μg/mL)					
High-catechin group	8.2±4.7	9.5±5.7	0.03	0.35 (−1.03, 1.74)	0.61
Low-catechin group	8.8±3.2	9.8±4.1	0.01		
Body weight (kg)					
High-catechin group	66.4±13.7	64.9±13.7	0.002	−0.35 (−1.44, 0.74)	0.52
Low-catechin group	64.8±13.7	63.5±13.1	0.001		
Body mass index (kg/m^2)					
High-catechin group	24.6±4.3	24.0±4.1	0.002	−0.18 (−0.58, 0.23)	0.39
Low-catechin group	24.5±4.2	24.1±3.9	0.003		
Waist circumference (cm)					
High-catechin group	85.0±12.7	82.7±12.2	0.007	−0.73 (−2.76, 1.29)	0.47
Low-catechin group	85.7±12.0	83.9±11.4	0.009		
Systolic blood pressure (mmHg)					
High-catechin group	123±15	123±19	0.96	−0.14 (−6.89, 6.61)	0.97
Low-catechin group	123±16	123±13	0.73		
Diastolic blood pressure (mmHg)					
High-catechin group	75±10	74±12	0.82	−0.74 (−4.34, 2.86)	0.68
Low-catechin group	76±10	76±10	0.92		
Total cholesterol (mmol/L)					
High-catechin group	4.66±0.82	4.75±0.77	0.27	0.10 (−0.10, 0.31)	0.32
Low-catechin group	4.96±0.67	4.93±0.70	0.59		
LDL cholesterol (mmol/L)					
High-catechin group	2.70±0.68	2.76±0.73	0.41	0.07 (−0.14, 0.28)	0.50
Low-catechin group	2.98±0.75	2.97±0.75	0.91		
HDL cholesterol (mmol/L)					
High-catechin group	1.37±0.36	1.42±0.37	0.13	0.04 (−0.06, 0.15)	0.39
Low-catechin group	1.46±0.37	1.47±0.37	0.82		
Triglyceride (mmol/L)					
High-catechin group	1.20±1.15	1.14±1.06	0.40	0.25 (−0.11, 0.62)	0.17
Low-catechin group	1.31±1.63	0.93±0.47	0.22		
Fasting plasma glucose (mmol/L)					
High-catechin group	5.30±0.68	5.34±0.75	0.65	0.12 (−0.13, 0.38)	0.34
Low-catechin group	5.48±0.53	5.35±0.45	0.20		
Aspartate aminotransferase (U/L)					
High-catechin group	21.9±7.2	22.0±8.5	0.90	1.99 (−1.06, 5.05)	0.20
Low-catechin group	19.9±6.0	19.2±5.7	0.38		
Alanine aminotransferase (U/L)					
High-catechin group	19.2±11.3	20.2±9.8	0.52	1.93 (−1.78, 5.63)	0.30
Low-catechin group	17.4±8.0	17.7±7.8	0.85		
Gamma-glutamyl transpeptidase (U/L)					
High-catechin group	28.4±28.0	31.5±32.0	0.07	4.61 (−0.98, 10.19)	0.10
Low-catechin group	31.9±44.7	29.4±30.7	0.41		
Uric acid (μmol/L)					
High-catechin group	308±70	315±71	0.31	15.46 (−4.16, 35.09)	0.12
Low-catechin group	329±76	318±78	0.16		
High-sensitive C-reactive protein (ng/mL)					
High-catechin group	511±573	513±496	0.99	−85.92 (−387.89, 216.06)	0.57
Low-catechin group	521±534	627±692	0.35		

[a]Paired t test.

[b]The change in high-catechin group minus the change in low-catechin group. The net differences were calculated by analysis of covariance. Adjusted for age (in years), sex, and individual baseline variables.

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Table 5. Change in serum adiponectin of participants according to high-catechin group and low-catechin group stratified by weight-loss program

Variables	Baseline Mean ± SD	After 9 weeks Mean ± SD	P-values[a]	Net change[b] (95% CI)	P-values[b]
Serum adiponectin (μg/mL)					
Weight-loss program participants					
High-catechin group (N = 15)	7.4 ± 5.2	8.6 ± 6.1	0.13	0.15 (−1.54, 1.85)	0.86
Low-catechin group (N = 16)	8.1 ± 3.1	9.0 ± 3.8	0.10		
Weight-loss program non-participants					
High-catechin group (N = 10)	9.5 ± 3.6	10.9 ± 5.0	0.15	1.49 (−0.46, 3.43)	0.12
Low-catechin group (N = 10)	9.9 ± 3.1	11.1 ± 4.3	0.06		

[a]Paired t test.

[b]The change in high-catechin group minus the change in low-catechin group. The net differences were calculated by analysis of covariance. Adjusted for age (in years), sex, and baseline serum adiponectin.

After 9 weeks of catechin consumption, the mean ± SD changes from baseline in the adiponectin level were significantly increased in the both groups. However, we found no significant difference between the high- and low catechin group with respect to changes in the serum adiponectin level: 0.35 μg/ml (95% CI: −1.03, 1.74). The CVD risk factors, namely, body weight, BMI, and waist circumference, were significantly decreased in both the groups, but the net change was not significant for any of these variables.

There are at least three reasons that the changes from baseline in the adiponectin level were significantly increased in both groups. First, more than half of the study participants participated in a weight loss program. Second, lifestyle of the study participants may have been changed by this study. Third, catechin was contained not only in high-concentration beverage (high catechin group; 400 mg) but also in low-concentration beverage (low catechin group; 100 mg). Therefore, if the low concentration of the catechins might be enough to increase the adiponectin levels, an increase would be observed in the both groups.

In addition, we conducted stratified analyses according to weight loss program (participation or non-participation) because the change in adiponectin levels in both the groups may be related to the significant weight loss program. We also found that there were no significant differences in the net change among weight loss program participants and non-participants. Because the net change among weight loss program non-participants was greater than that among weight loss program participants, the change in adiponectin levels would be less affected by the weight loss program.

To date, three RCTs have examined the association between tea catechin consumption and adiponectin levels in humans (18–20). These RCTs recruited patients with diabetes mellitus and obesity. Because these patients might have had atherosclerosis before the study, the effect of tea catechin consumption on serum adiponectin level might not be well detected. Ryu et al. observed a change in the adiponectin level after the consumption of 900 ml of water containing 9 g of GT daily for 4 weeks in patients with type 2 diabetes mellitus (18). After 4 weeks, the mean ± SD change in the adiponectin level from the baseline value was 6.03 ± 3.71 μg/ml in intervention group and 6.01 ± 3.16 μg/ml in control group, although the net change between the groups was not significant. Hsu et al. observed a significant increase in the adiponectin level in obese women who consumed one capsule containing 491 mg of total catechin daily (19). After 12 weeks, the mean ± SD change in the adiponectin level from the baseline value was 2.5 ± 4.2 μg/ml in intervention group and 2.0 ± 5.4 μg/ml in control group, although the net change was not significantly different. Nagao et al. observed a significant increase in the adiponectin level after the consumption of 582.8 mg of catechin daily in patients with type 2 diabetes mellitus (20). After 12 weeks, the mean ± SD change in the adiponectin level from the baseline value was 1.32 ± 0.61 μg/ml in intervention group and 0.34 ± 0.48 μg/ml in control group, although the net change was not significantly different. Thus, all the three RCTs showed that the increase in the serum adiponectin level in the intervention group was greater than that in the control group, although the net change between the groups was not significant. Although we recruited healthy participants who did not have a history of diabetes mellitus, cancer, ischemic heart disease, stroke, or renal disease, our findings were consistent with those of the above reports.

Although we found no significant difference in the net change in adiponectin level, several reasons should be considered in the interpretation of our results. First,

it may be necessary to consider the difference in the catechin dose between the high- and low catechin groups and the intervention period. In the present study, the difference in the catechin dose between the high- and low catechin groups was only 300 mg/day and the intervention period was 9 weeks. Hsu et al. adopted the difference in the catechin dose of 491 mg/day and intervention period of 12 weeks, but the net change in adiponectin level was not significant (19). Also, Nagao et al. adopted the difference in the catechin dose of 486.5 mg/day and intervention period of 12 weeks, but the net change in adiponectin level was not significant (20). Therefore, the difference in the catechin dose and the intervention period could not explain our observation.

Second, because GT is consumed primarily in Japan and China (22), habitual GT consumption may have the potential to affect study results. Although we adopted the washout period for 2 weeks, we did not find any apparent association between catechin-enriched GT consumption and adiponectin. Similarly, previous studies adopted the washout period for 2 weeks (19) and 4 weeks (20), but the net change in adiponectin level was not significant. Ryu et al. also excluded subjects who had consumed GT regularly for over a month, but the net change in adiponectin level was not significant (18). Therefore, the washout period could not explain our observation.

Third, the compounds such as caffeine found in GT may have been responsible for the association between GT consumption and CVD risk factors. A previous observational study indicated the association between consumption of caffeine-containing coffee and adiponectin. No association between consumption of caffeine-containing coffee and adiponectin was indicated in either group (quartile 1: 0–100 mg, quartile 2: 101–237 mg, quartile 3: 237–378 mg, quartile 4: 379–967 mg) among non-diabetic subjects (23). Because the difference in the caffeine dose between the high- and low catechin groups was small (25 mg/day) in our study, caffeine could not explain our observation.

Fourth, chocolate, red wine, apples, and berries are known as good source of catechin (24, 25). Although we asked participants not to drink any other catechin-containing beverage, we had no information on the intake of these food items during the 9 weeks. In addition, we had no data on the levels of the major dietary catechins (gallocatechin, epicatechin, epigallocatechin, etc.) and the total blood antioxidant levels. However, these factors may be divided equally between the high- and low catechin groups by successful randomization. Also, a previous study indicated that the half-lives of epigallocatechin-3-gallate, epigallocatechin, and epicatechin once ingested were 3.4, 1.7, and 2.0 h, respectively (26). Therefore, it is difficult to interpret the results of all-night fasting plasma levels of catechins, if measured.

Finally, our RCT design might yield a relatively small number of participants, although we made a power calculation regarding sample size. We found no significant difference between the high- and low catechin groups with respect to changes in the serum adiponectin level. Our study had a similar sample size to previous RCTs, and our results were consistent with results of previous RCTs (19, 20). Therefore, a larger sample size may be necessary to detect any effect of tea catechin consumption on serum adiponectin level.

The present study also aimed to explore the changes in CVD risk factors. We found no significant differences in CVD risk factors between the high- and low catechin groups. Many studies have assessed the relation between GT consumption and CVD risk factors. In previous studies, the GT consumption showed statistically significant reductions in body weight, BMI, and waist circumference (27–29). Our study showed that decrease in the anthropometric parameters in the high catechin group was greater than that in the low catechin group, although the net change between groups was not significant. The previous studies that suggested statistically significant changes had a larger sample size (28, 29). Therefore, a larger sample size may be necessary to detect the effect of tea catechin consumption on the anthropometric parameters.

The effect of GT consumption on BP has been investigated in meta-analysis of previous studies. These data suggested that GT consumption did not show significant effects on systolic and diastolic BP (30). Our results on BP were consistent with the previous studies.

Among previous studies that have examined the association between GT and blood cholesterol (TC, LDL-C, and HDL-C), GT consumption significantly lowered the TC and LDL-C level, but no effect on HDL-C was observed (20, 28, 30, 31). Our results on HDL-C were consistent with previous studies, but the inconsistent findings on the effect of GT consumption on TC and LDL-C were observed. There are several possible reasons for the discrepancy between our study and previous studies on TC and LDL-C. First, the subjects of the previous studies were not a healthy population (20). Therefore, one of the reasons for discrepancy might be explained by the difference in the study subjects. Second, the sample size in the previous studies was large (28). Therefore, another reason for discrepancy might be explained by sample size.

Conclusions

This RCT showed that increase in serum adiponectin level in the high catechin group was greater than that

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in the low catechin group, although the net change between groups was not significant. Also, no significant difference was observed between the high- and low catechin groups with respect to changes in any CVD risk factors.

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Conflict of interest and funding

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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* doi: 10.3945/ajcn.111.023200.

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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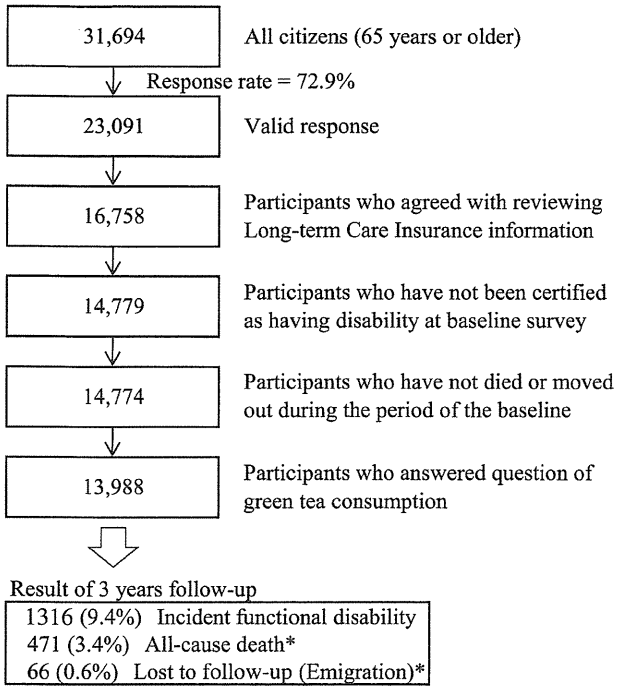

FIGURE 1. Flowchart of study participants: the Ohsaki Cohort 2006 Study. *Without experiencing incident functional disability.

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 any 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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