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Association between green tea intake and risk of cognitive decline, considering glycated hemoglobin level, in older Japanese adults: the NILS-LSA study

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ABSTRACT

Positive and negative associations with risk of cognitive decline have been reported for glycated hemoglobin (HbA1c) level and green tea (GT) intake, respectively. This study aimed to assess whether the reduction in the risk of cognitive decline with GT intake depended on HbA1c level. The participants were aged ≥60 years at baseline in the cohort study, wherein examinations were conducted biennially from 2000 to 2012. Subjects (n=1,304) who had no cognitive decline during the first survey and who had participated in the follow-up survey at least once were included. The follow-up end point was the first screening time point for cognitive decline (Mini-Mental State Examination score <27) or the last survey participation. With reference to the Japanese Diabetes Society guideline, the cut-off points for HbA1c level were set at 5.6%, 6.0%, and 6.5%, and lower and higher groups were assigned for each cut-off point. In a multiple Cox proportional hazard model, an interaction between GT intake and HbA1c groups for cognitive decline was observed only at HbA1c 6.0% (*P*-value for interaction [with Bonferroni's correction] <0.05/3). Lower risks of cognitive decline were found for the HbA1c ≥5.6%, ≥6.0%, and <6.5% groups (hazard ratios: 0.59, 0.34, and 0.77; 95% confidence intervals: 0.41–0.88, 0.19–0.61, and 0.56–1.08 for "≥4 times a day" vs. "<once a day" GT intake, respectively; *P*-value for trend: 0.06, <0.01, and 0.09, respectively). With respect to blood glucose level, our cohort study showed non-uniformly reduced risk of cognitive decline with GT intake among older Japanese adults.

Keywords: green tea, HbA1c, blood glucose level, cognitive decline, epidemiology

Abbreviations:
GT: green tea

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HbA1c: glycated hemoglobin
JDS: Japan Diabetes Society
Aβ: amyloid β protein
NILS-LSA: National Institute for Longevity Sciences-Longitudinal Study of Aging
MMSE: Mini-Mental State Examination
BMI: body mass index
HR: hazard ratio
CI: confidence interval
AGEs: advanced glycation endproducts

INTRODUCTION

The International Diabetes Federation reported that the number of adults with diabetes and impaired glucose tolerance was approximately 800 million in 2017, and the number of patients worldwide has been rapidly increasing.[1] For preventing diabetes, the Japan Diabetes Society (JDS) guidelines recommend medical and healthcare staff members to consider the following three levels of glycated hemoglobin (HbA1c)[2,3]: 1) 5.6–5.9%, "a group with a high risk for developing diabetes mellitus in the future"; 2) 6.0–6.4%, "suspected diabetes mellitus cannot be excluded"; and 3) ≥6.5%, "in epidemiological study, for the purpose of estimating the frequency of diabetes mellitus, 'diabetes mellitus' can be submitted for the determination of 'diabetic type' from a single examination. In this case, HbA1c ≥6.5% alone can be defined as 'diabetes mellitus'".

Blood glucose level has been reported to be positively associated with risk of cognitive decline in epidemiological studies,[4-10] and therefore, the Lancet International Commission on Dementia Prevention, Intervention, and Care proposed that diabetes mellitus is a risk factor for dementia,[11] which is caused by progressively decreasing acquired cognitive function. The number of dementia patients in the world has also been increasing and is expected to increase threefold from approximately 35 million people in 2010 within the next 30 years.[12] Since currently there is no cure for dementia, reduced risk of dementia/cognitive decline is considered one of the critical aims of health policy in many countries.[13]

Epidemiological studies have reported that green tea intake reduces risk of dementia and/or cognitive decline.[14-18] As for the potential underlying mechanisms, polyphenolic catechins contained in green tea have been demonstrated to exert not only anti-oxidative,[19,20] neurogenic anti-inflammatory,[21] and anti-arteriosclerotic effects,[22] but also facilitative effects on normal metabolism of amyloid β (Aβ) precursor protein,[23,24] which is proposed to cause Alzheimer's disease. These effects of green tea may be negatively related to metabolic and vascular changes, such as oxidative stress,[25,26] inflammation,[27,28] atherogenesis,[29] and microvascular disease[30,31] that are caused by an increase in the blood glucose level. These metabolic and vascular changes are considered the underlying mechanisms that promote the onset of dementia in diabetes patients.[32]

Based on the previous studies described above, we hypothesized that the reduction in the risk of cognitive decline with green tea intake is more pronounced in subjects with a high level of blood glucose. Using follow-up data from our cohort study, this prospective cohort study aimed to assess whether the reduction in the risk of cognitive decline with green tea intake depends on the HbA1c level. To achieve this, we examined whether the associations between green tea intake and risk of cognitive decline were different between lower and higher baseline levels of HbA1c by using the cut-off points of HbA1c 5.6%, 6.0%, and 6.5% based on the JDS guideline.[2]

METHODS

Study subjects

The data used in this study are part of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA).[33] The NILS-LSA is a population-based prospective cohort study of normal aging and age-related diseases in Japan. Participants in the NILS-LSA were randomly selected from resident registered in Obu City and Higashiura Town, the National Center for Geriatrics and Gerontology neighborhood areas, in Aichi Prefecture, Japan, using multi-stage stratified sampling according to age decade and sex. The first study wave of the NILS-LSA was conducted from November 1997 to April 2000, with 2,267 participants (1,139 men and 1,128 women; age range, 40–79 years). The NILS-LSA adopted a unique study design, being a dynamic cohort study. The participants were followed up with every 2 years. When participants aged <80 years old dropped out, new age decade- and sex-matched participants were recruited randomly. The details of the same are reported elsewhere.[33]

Mini-Mental State Examination (MMSE) data for cognitive assessment recorded for participants (age, ≥60 years) during all time points, except the first study wave were available in the NILS-LSA. The subjects (n=1,868) selected in the present study were those who participated more than once (≥2) from the second to the seventh study wave (from 2000 to 2012), and whose MMSE data were available. The baseline in this study was defined as the first time point when the MMSE data were obtained. The follow-up time was the number of days that elapsed from baseline to the first detection of cognitive decline or the right-censored data (last participated survey). The exclusion criteria were as follows: 1) MMSE score <27 at baseline; 2) anthropometric measurements, HbA1c measurements, dietary assessments, and/or results for some of the self-reported questionnaires unavailable at baseline; 3) a presence of self-reported history of stroke and/or heart disease at baseline; and 4) no MMSE data in any of the follow-up surveys. Finally, 1,304 subjects (619 men [47.5%] and 685 women [52.5%]; age range, 60–85 years at baseline) were included in the analysis, i.e., n=441 (second study wave), n=366 (third study wave), n=188 (fourth study wave), n=170 (fifth study wave), and n=139 (sixth study wave). The study protocol was approved by the Committee on Ethics of Human Research of the National Center for Geriatrics and Gerontology (No. 899-3). Written informed consent was obtained from all subjects after providing a detailed explanation of the NILS-LSA.

Screening of cognitive decline

Cognitive function was tested at each study wave, using the Japanese version of the MMSE,[34,35] by trained clinical psychologists and graduate psychology students. The MMSE is used as a clinical screening test for dementia, and assesses cognitive performance in the domains of temporal and spatial orientation, registration, attention and calculation, recall, language, and visual construction; MMSE scores are extensively used in epidemiological studies to assess cognitive function. Scores range from 0 to 30, and higher score represent better cognitive function. Based on previous studies[36-42] and a user's guide of the MMSE,[43] cognitive decline was screened as the first time the MMSE score was <27 at a follow-up survey.

Blood sampling and laboratory analysis for HbA1c level

Venous blood was sampled using tubes containing ethylenediaminetetraacetic acid (disodium salt, 50 mM) in the morning after fasting for at least 12 hours to obtain the baseline. The HbA1c level (JDS units) was measured from non-frozen blood using the latex agglutination method at a clinical laboratory (SRL, Tokyo, Japan). The measured values were translated to global standard (National Glycohemoglobin Standardization Program) values by adding 0.4%.[44]

Green tea intake

The frequency of green tea intake in the previous year, used as the baseline, was determined by trained dietitians using a food frequency questionnaire,[45] which was scientifically validated. The categories of intake frequency in the questionnaire used in the second to the fourth study waves were based on nine levels (never or rarely, once a month, 2–3 times a month, once a week, 2–3 times a week, 4–6 times a week, once a day, 2–3 times a day, and ≥4 times a day), and those used in the fifth and sixth study waves were based on seven levels (never or <once a month, once a month, 2–3 times a month, once a week, 2–3 times a week, 4–6 times a week, and ≥once a day), in response to a question on how many times the beverage was consumed in a day. We categorized intake frequency into <once a day, once a day, 2–3 times a day, and ≥4 times a day.

Covariates

Baseline data of the following variables were used: body mass index (BMI, kg/m^2) based on measured height (m) and body weight (kg); intake of total energy (kcal/day), alcohol (ethanol equivalent, g/day), green and yellow vegetables (g/1000kcal/day), and fish (g/1000kcal/day) based on a dietary record that was completed over three continuous days (two weekdays and one weekend day) with photographs acquired before and after meals[46]; self-reported medical history (yes or no) of hypertension and dyslipidemia; smoking status (current smoker or non-smoker); self-reported education level (years); total physical activity (metabolic equivalents×hour/day) based on a scientifically validated questionnaire modified from the Minnesota Leisure-Time Physical Activity Questionnaire.[47]

Statistical analysis

As described above, lower or higher groups of HbA1c levels were assigned for each of the three cut-off points (5.6%, 6.0%, and 6.5%) based on the JDS guideline,[2] and then statistical analyses were executed at each cut-off point. Baseline characteristics and endpoint parameters of the HbA1c groups were assessed using t-test and χ^2 test for continuous and categorical variables, respectively. Using a Cox proportional hazards model, first, multivariate-adjusted hazard ratio (HR) and 95% confidence interval (CI) for cognitive decline were estimated in the higher HbA1c groups, compared with the lower groups. Second, a multivariate-adjusted interaction for cognitive decline was assessed between green tea intake and HbA1c groups. Third, multivariate-adjusted HR and 95% CI for cognitive decline in the lower and higher HbA1c groups were estimated according to green tea intake with reference to "<once a day," and then the corresponding linear trend was tested across the categories of green tea intake. The baseline data of the following variables were appropriately used for multivariate-adjustment controlling for confounding factors: age, sex, BMI, smoking, total physical activity, education, medical history of hypertension and dyslipidemia (considered separately), total energy intake, alcohol intake, intake of green and yellow vegetables, fish intake, the green tea intake frequency category (which is not an independent variable), and MMSE scores.

Statistical analyses were performed using Statistical Analysis System (SAS) version 9.3 (SAS Institute, Cary, NC, USA). The *P*-values were calculated using two-tailed analyses, and statistical significance was defined as $P<0.05$ (i.e., $\alpha=0.05$), excepting $P<0.017$ (i.e., considering Bonferroni's correction: $\alpha=0.05/3$) for the three repeated interaction analyses.

RESULTS

The follow-up time and number of follow-up surveys were 6,896 total person-years and 2.5±1.4 times per participant (mean±standard deviation), respectively. During the follow-up period, screening revealed that 431 subjects exhibited cognitive decline. Among them, 224 (52.0%), 120 (27.8%), 48 (11.1%), 22 (5.1%), 13 (3.0%), and 4 (0.9%) had MMSE scores of 26, 25, 24, 23, 22, and 21, respectively.

Baseline characteristics and end-point parameters of the subjects according to the HbA1c groups for the 6.0% cut-off point are shown in Table 1. Higher BMI and percentage of presence of medical history of diabetes mellitus and hypertension were observed in the HbA1c ≥6.0% group than in the HbA1c <6.0% group (P<0.05 for all).

Table 1 Baseline characteristics and end-point parameters of the subjects according to the HbA1c groups for the 6.0% cut-off point among 1,304 older Japanese adults

	<6.0% group (n=979)	**≥6.0% group (n=325)**	***P* value[a]**
Baseline characteristics			
Age, years, mean (SD)	66.8 (6.2)	66.6 (6.1)	0.70
Men, n (%)	450 (46.0)	169 (52.0)	0.06
BMI, kg/m^2, mean (SD)	22.7 (2.7)	23.6 (2.9)	<0.001
HbA1c, %, mean (SD)	5.5 (0.3)	6.7 (1.1)	<0.001
Current smokers, n (%)	136 (13.9)	52 (16.0)	0.35
Education, years, mean (SD)	11.6 (2.7)	11.5 (2.7)	0.61
Total physical activity, METs × hour/day, mean (SD)	32.0 (3.3)	32.1 (3.4)	0.53
MMSE score, mean (SD)	28.6 (1.1)	28.5 (1.1)	0.44
Dietary intake			
Frequencies of green tea intake, n (%)			
< once a day, n (%)	103 (10.5)	43 (13.2)	0.16
once a day, n (%)	85 (8.7)	33 (10.2)	
2–3 times a day, n (%)	353 (36.1)	97 (29.9)	
≥4 times a day, n (%)	438 (44.7)	152 (46.8)	
Total energy, kcal/day, mean (SD)	2,039 (426)	2,013 (400)	0.33
Alcohol, g/day, mean (SD)	9.0 (16.5)	9.0 (15.6)	0.95
Green and yellow vegetables, g/1000kcal/day, mean (SD)	63.2 (39.2)	64.8 (38.6)	0.53
Fish[c], g/day, mean (SD)	50.2 (25.5)	50.0 (24.2)	0.94
Medical history			
Diabetes mellitus, n (%)	9 (0.9)	108 (33.2)	<0.001
Hypertension, n (%)	309 (31.6)	127 (39.1)	<0.05
Dyslipidemia, n (%)	233 (23.8)	84 (25.9)	0.46
Endpoint parameters			
Follow-up, years, mean (SD)	5.4 (2.9)	5.1 (2.8)	0.10
Case of cognitive decline, n (%)	314 (32.1)	117 (36.0)	0.19

Abbreviations: HbA1c; glycosylated hemoglobin A1c (National Glycohemoglobin Standardization Program value), n; number, SD; standard deviation, BMI; body mass index, METs; metabolic equivalents, MMSE; Mini-Mental State Examination.

[a] Differences of mean and percentage between the HbA1c levels were tested by t-test and χ^2 test, respectively.

In Table 2, with higher cut-off points, higher percentages of subjects with cognitive decline were observed in the groups with a high level of HbA1c. The risk of cognitive decline in the HbA1c ≥5.6% group was significantly higher than that in the reference HbA1c <5.6% group. However, the high risks of cognitive decline in the HbA1c ≥6.0% and ≥6.5% groups were not significant with respect to those in the reference HbA1c <6.0% and <6.5% groups, respectively.

Table 2 Hazard ratio and 95% confidence interval for cognitive decline according to HbA1c groups at each cut-off point of HbA1c level among 1,304 older Japanese adults

Cut-off point of HbA1c 5.6%	**<5.6% group**		**≥5.6% group**	
n (%)	514	(39.4)	790	(60.6)
Subjects with cognitive decline, n (%)	169	(32.9)	262	(33.2)
Multivariate-adjusted HR (95% CI)[a]	1.00	(reference)	1.29	(1.06–1.58)
Cut-off point of HbA1c 6.0%	**<6.0% group**		**≥6.0% group**	
n (%)	979	(75.1)	325	(24.9)
Subjects with cognitive decline, n (%)	314	(32.1)	117	(36.0)
Multivariate-adjusted HR (95% CI)[a]	1.00	(reference)	1.14	(0.91–1.41)
Cut-off point of HbA1c 6.5%	**<6.5% group**		**≥6.5% group**	
n (%)	1,171	(89.8)	133	(10.2)
Subjects with cognitive decline, n (%)	379	(32.4)	52	(39.1)
Multivariate-adjusted HR (95% CI)[a]	1.00	(reference)	1.26	(0.93–1.68)

Abbreviations: HbA1c; glycosylated hemoglobin A1c (National Glycohemoglobin Standardization Program value), HR; hazard ratio, CI; confidence interval, n; number.

[a] Adjusted for age, sex, body mass index, smoking, total physical activity, education, medical history of hypertension and dyslipidemia (considered separately), total energy intake, alcohol intake, intake of green and yellow vegetables, fish intake, green tea intake, and MMSE scores at baseline.

As shown in Table 3, an interaction effect between green tea intake and HbA1c groups was observed for cognitive decline at the HbA1c level cut-off point 6.0% (*P* for interaction <0.017, lower than Bonferroni's correction: α=0.05/3), but not 5.6% and 6.5%.

Table 4 shows multivariate-adjusted HRs and corresponding 95% CIs for cognitive decline according to green tea intake by HbA1c groups at each cut-off point of HbA1c level. Lower HRs with green tea intake were observed in the HbA1c ≥5.6% and ≥6.0% groups (*P* for trend =0.06 and <0.01, respectively), and even in the HbA1c <6.5% (*P* for trend =0.09); however, the dose-response relationships of the numbers of these HRs were not clear.

Data for subjects with no history of diabetes mellitus (n=1,187) were also analyzed. A similar interaction effect for risk of cognitive decline was observed between green tea intake and HbA1c groups at the HbA1c level cut-off point 6.0% (*P* for interaction =0.034, higher than Bonferroni's correction: α=0.05/3). Lower HRs with green tea intake were observed only in the HbA1c ≥6.0% group (*P* for trend =0.07).

Table 3 Type 3 test of multivariate-adjusted interaction effects for cognitive decline between green tea intake and HbA1c groups at each cut-off point of HbA1c level among 1,304 older Japanese adults[a]

	Wald χ^2	*P* value[b]
Cut-off point of HbA1c 5.6%		
Green tea intake[c] × HbA1c groups[d]	0.355	0.551
Green tea intake[c]	2.625	0.105
HbA1c groups[d]	1.803	0.179
Cut-off point of HbA1c 6.0%		
Green tea intake[c] × HbA1c groups[d]	6.237	0.013
Green tea intake[c]	7.593	<0.01
HbA1c groups[d]	7.733	<0.01
Cut-off point of HbA1c 6.5%		
Green tea intake[c] × HbA1c groups[d]	0.655	0.418
Green tea intake[c]	3.042	0.081
HbA1c groups[d]	1.609	0.205

Abbreviations: HbA1c; glycosylated hemoglobin A1c (National Glycohemoglobin Standardization Program value).

[a] Cox proportional hazard model was used with adjusting for age, sex, body mass index, smoking, total physical activity, education, medical history of hypertension and dyslipidemia (considered separately), total energy intake, alcohol intake, intake of green and yellow vegetables, fish intake, and MMSE scores at baseline.

[b] Significance level adjusted by Bonferroni's correction: $P<0.017$.

[c] Categories: < once a day, once a day, 2–3 times a day, and ≥4 times a day.

[d] Lower or higher groups of HbA1c levels were assigned for each of the three cut-off points.

Table 4 Hazard ratio and 95% confidence interval for cognitive decline according to green tea intake by HbA1c groups at each cut-off point of HbA1c level among 1,304 older Japanese adults

Green tea intake	Multivariate-adjusted HR (95% CI)[a]	
Cut-off point of HbA1c 5.6%	**<5.6% group (n=514)**	**≥5.6% group (n=790)**
< once a day	1.00 (reference)	1.00 (reference)
once a day	1.07 (0.54–2.08)	0.44 (0.24–0.78)
2–3 times a day	0.77 (0.47–1.29)	0.62 (0.42–0.94)
≥4 times a day	0.86 (0.53–1.43)	0.59 (0.41–0.88)
P for trend	*P*=0.32	*P*=0.06
Cut-off point of HbA1c 6.0%	**<6.0% group (n=979)**	**≥6.0% group (n=325)**
< once a day	1.00 (reference)	1.00 (reference)
once a day	0.86 (0.56–1.19)	0.29 (0.12–0.66)
2–3 times a day	0.81 (0.56–1.18)	0.42 (0.24–0.78)
≥4 times a day	0.90 (0.63–1.30)	0.34 (0.19–0.61)
P for trend	*P*=0.52	*P*<0.01
Cut-off point of HbA1c 6.5%	**<6.5% group (n=1,171)**	**≥6.5% group (n=133)**
< once a day	1.00 (reference)	1.00 (reference)
once a day	0.83 (0.53–1.30)	0.04 (0.01–0.30)

2–3 times a day	0.73	(	0.53–1.03	)	0.51	(	0.21–1.28	)
≥4 times a day	0.77	(	0.56–1.08	)	0.37	(	0.15–0.97	)
P for trend	*P*=0.09				*P*=0.77			

Abbreviations: HbA1c; glycosylated hemoglobin A1c (National Glycohemoglobin Standardization Program value), HR; hazard ratio, CI; confidence interval, n; number.

[a] Adjusted for age, sex, body mass index, smoking, total physical activity, education, medical history of hypertension and dyslipidemia (considered separately), total energy intake, alcohol intake, intake of green and yellow vegetables, fish intake, and MMSE scores at baseline.

DISCUSSION

In the present study, the results on the risk of cognitive decline in subjects with a baseline high level of HbA1c suggested that those with HbA1c level of ≥5.6% had higher risk of cognitive decline. According to the limitations (e.g., sample size and selection bias of study subjects) of this study, we could not show appropriate threshold of HbA1c level for the risk. The significant interaction at the cut-off point of 6.0% indicates that the risk of cognitive decline with green tea intake is significantly different between subjects with HbA1c <6.0% and those with HbA1c ≥6.0%. In addition, green tea intake is significantly associated with lower risks of cognitive decline when the HbA1c level is ≥6.0% but not <6.0%. This prospective cohort study shows that baseline blood glucose level was associated with the risk of cognitive decline with green tea intake for followed-up periods among the community-dwelling older Japanese adults. The reduction in the risk of cognitive decline with green tea intake was greater in the HbA1c ≥6.0% groups than in the HbA1c <6.0% group.

This study showed that the reduction in risk of cognitive decline with green tea intake differed depending on blood glucose level and has the following strengths: 1) using follow-up data, temporality of the effect of blood glucose level on risk of cognitive decline was demonstrated, and then, protective effect of green tea against risk of cognitive decline was observed, considering blood glucose level; 2) based on the JDS guideline,[2,3] three cut-off points for HbA1c level were defined keeping in mind the scope for primary prevention and clinical advice; 3) prospective study design, with a long follow-up period of up to 10.8 years (mean±standard deviation, 5.3±2.9 years); 4) stratified random sampling, in which similar numbers of participants were assigned to each age range (decade) and sex group to reduce potential age- and sex-related bias; and 5) comprehensive investigation of lifestyle, clinical, and sociodemographic data by specialists in various areas.

In the present subjects, the proportions of those with HbA1c 6.0–6.4% and ≥6.5% at the baseline (April 2000–July 2010) were 14.7% and 10.2%, respectively. These proportions were lower than those of the National Health and Nutrition Survey in Japan.[48] This implies that the proportion of men and women aged ≥60 years with HbA1c 6.0–6.4% was approximately 15.6% in 2002, 19.4% in 2007 (peak), and 16.7% in 2016, and that the proportion of those with HbA1c ≥6.5% had increased from 13.7% in 2002 to 18.5% in 2016. Higher proportions of HbA1c 6.0–6.4% and ≥6.5% were reported in older people, and healthcare promotion is needed to maintain the appropriate level of HbA1c in the aged population because aging rate is continuously increasing in Japan.[49]

Blood glucose level is related to blood insulin level, and insulin resistance is caused if high blood glucose level is maintained for a long time. Decreased brain level of insulin due to increase in the peripheral level of insulin is thought to be a cause of impaired Aβ clearance.[50]

In addition, glycated proteins, such as HbA1c, are converted to advanced glycation end products (AGEs) as the reaction progresses. The association of Alzheimer's disease pathology with AGEs has been pointed out,[51,52] and AGEs are thought to possibly promote Aβ aggregation while decreasing Aβ clearance. These physiological abnormalities may increase the risk of cognitive decline synergistically.

The potential mechanisms underlying the phenomenon investigated in this study are: green tea intake could suppress the increase in risk of cognitive decline due to a high level of HbA1c, consequence of polyphenolic catechins contained in green tea, which have been reported to improve insulin resistance[53,54]; exert anti-arteriosclerotic,[22] anti-oxidative,[19,20] and anti-hyperglycemic,[55,56] effects; prevent elevation of blood pressure[57]; and improve lipid metabolism.[58] These effects may be independently and/or synergistically related to suppression of increase in risk of cognitive decline.

Regarding factors for reducing risk of cognitive decline, some epidemiological studies have reported that the diet pattern of traditional Japanese style and participation in social activities are associated with prevention of dementia and improvement of cognitive function, respectively.[59,60] Green tea is usually consumed with meals of the diet pattern of traditional Japanese style and served at social events and meetings. A variety of healthy lifestyles followed by people with higher intake of green tea may also be associated with the reduced risk of cognitive decline, and therefore, lifestyle modification would help synergistically reduce risk of cognitive decline.

The present study has some limitations. First, the present study did not determine an optimal cut-off point or range of HbA1c level at which green tea intake reduces risk of cognitive decline because of the sample size being relatively small. Based on the JDS guideline, however, we showed a representative HbA1c level cut-off point of 6.0% because a significant interaction was observed between green tea intake and HbA1c groups for risk of cognitive decline. Second, cognitive decline was assessed only using a cut-off MMSE score. In this study, neuroimage data and neuropathology were not assessed. However, MMSE has been reported to be a reliable screening test that can quantitatively assess the severity of cognitive decline.[43,61] Third, we did not consider assessing improvement in impaired cognitive function over a long follow-up period. Finally, green tea was not distinguished based on the type of tea leaves.

Regarding implications, the present study showed that the risk of cognitive decline is significantly lower with green tea intake among the subjects with HbA1c ≥6.0%, who require healthcare advice at a health check-up to prevent diabetes, than in those with HbA1c <6.0%. Because green tea is also believed to prevent diabetes,[62] the results of this study are expected to be useful for giving effective dietary advice, including advice on consumption of green tea to reduce the risk of cognitive decline in people with a high blood glucose level. Further large-scale studies are required to determine an appropriate cut-off point or range of HbA1c level for optimal reduction in risk of cognitive decline due to green tea intake.

In conclusion, this prospective cohort study shows the association between baseline blood glucose level and the reduced risk of cognitive decline with green tea intake for followed-up periods, and that the reduction in risk of cognitive decline with green tea intake differed depending on baseline blood glucose status due to HbA1c level among community-dwelling older Japanese adults.

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CONFLICT OF INTEREST

The authors declare no conflict of interest for the present study.

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