to receive a free evaluation of their physical health, which included a battery of neurological and cognitive tests that examined cognitive function. Recruitment began in May 2007 by distributing flyers to Nakajima residents. Nakajima project was supported by Nanao city, and the information of the residence was used to list target candidates. The baseline survey included questionnaires regarding personal lifestyle, medical conditions, and neuropsychological tests. All participants lived in the community at the time of the baseline survey. Blood samples were also collected, and ascorbic acid (vitamin C) levels and ApoE phenotypes were determined for all participants. The study was conducted by 14 neurologists, two psychologists, seven nurses, one physiotherapist, and one occupational therapist, all of whom were specifically trained for this study.

Baseline survey

Each participant completed a self-administered questionnaire that queried sociodemographic data (including age, sex, and education), past medical history (hypertension, hyperlipidemia, and diabetes mellitus), smoking habits, physical activities/hobbies, and green tea, coffee, and black tea consumption. The trained researchers reviewed the completed questionnaires to identify inconsistent or unanswered items. Green tea, coffee, and black tea consumption was quantified by the frequency of consumption of each beverage using the choice of 0, 1, 2, 3, 4, 5, or 6 times/week or every day. For the present analysis, we further divided this category into three groups: zero (no consumption), 1–6 days/week, and every day.

We assessed participants' cognitive status with the Mini-Mental State Examination (MMSE) [19] and the Clinical Dementia Rating (CDR) [20–22]. Higher MMSE scores indicate higher cognitive function, and the maximum score is 30 points. Standard cut point of <24 out of 30 indicates cognitive impairment [19]. CDR is a dementia-staging device that rates cognitive function from none to maximal along five levels of impairment (rated as 0, 0.5, 1, 2, or 3) in each of the following six domains: memory, orientation, judgment and problem solving, function in community affairs, home and hobbies, and personal care. A global CDR score was calculated using an algorithm that takes into account each of these domain subscores. The possible scores for global CDR were 0 (indicating a normal healthy individual with no cognitive or functional deficits), 0.5 (a normal healthy individual with questionable cognitive and/or functional abilities), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).

High-performance liquid chromatography (HPLC) was used to measure total serum ascorbic acid concentrations [23]. ApoE phenotype was determined using isoelectric electrophoresis as described by Kamboh et al [24].

Diagnosis of dementia was based on the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) [25]. Diagnosis of MCI was established according to the International Working Group on general criteria for MCI [26]. The MCI criteria state that (1) a person should be judged as abnormal using modalities other than those used to fulfill the DSM-III-R dementia criteria, (2) the person's functional activities are mainly preserved or at least impairment is minimal, and (3) the person should have evidence of cognitive decline, either by self-assessment and/or by an informant report in conjunction with deficits in objective cognitive tasks. Among participants without dementia, a CDR score of 0.5 was used as the objective cognitive impairment value to denote cognitive and functional impairment consistent with MCI.

Follow-up survey

During 2011 and 2013, all subjects who could be contacted and who agreed to participate in the follow-up survey were interviewed to determine whether their health status or cognitive functioning had changed. The follow-up survey was conducted in public halls or at the participants' homes. Participants completed the same questionnaires and underwent the same neurological tests that were administered at the initial baseline survey. In addition, we visited seven individuals who were institutionalized in long-term care facilities or hospitals, and administered the same examinations after obtaining written informed consent from their families. Participants who died or who left Nakajima before the follow-up was conducted were excluded from the analysis, and the date they died or moved away were obtained from Nanao city.

Standard protocol approvals and patient consents

This study was conducted with the approval of the medical ethics review board of Kanazawa University (Kanazawa, Japan). All participants provided written informed consent by signing a form that described the purpose and procedures of the study, the potential risks and benefits associated with participation, the strict voluntary nature of participation, the right to withdraw from the research without prejudice or penalty, and a guarantee of confidentiality and security of personal data.

Statistical analyses

Baseline characteristics were evaluated using a one-way ANOVA for continuous variables and the chi-square test for categorical variables. Trend tests were conducted for green tea, coffee, and black tea consumption to test the significance of these variables. Univariate and multivariate logistic regression models were used to analyze the independent effects of green tea, coffee, and black tea consumption on the risk of developing dementia or MCI so that the lowest category served as the reference group. Model 1 was sex- and age- adjusted. Model 2 was further adjusted for history of hypertension, diabetes mellitus, and hyperlipidemia, formal education, and ApoE phenotype status (ApoE E4+ or E4−). Model 3 was fully adjusted and included smoking status, alcohol consumption, green tea, coffee, and/or black tea consumption, physical activities and/or hobbies. A two-sided P-value less than 0.05 was considered statistically significant in all analyses. The SPSS software package (version 12.0J; SPSS Inc., Chicago, IL) was used to perform all statistical analyses.

Results

Of the 2,845 potential candidates, 982 voluntarily participated in the brain-function examination conducted at public town halls in 2007–2008 (participation rate: 34.5%). We excluded 217 subjects from the analysis because of dementia (n = 8), MCI (n = 205), or failure to complete the cognitive tests (n = 4). We further excluded 42 subjects with a MMSE score of <24 at the initial baseline survey. Thus, 723 participants were judged to have normal cognitive function at the initial baseline survey. Of the 723 participants with normal cognitive function, 55 died, 5 moved, 167 did not repeat cognitive testing at follow-up, and 6 incompletely answered the beverage-frequency questionnaire at the initial baseline survey. Thus, data from 490 participants were included in the final analysis. The sociodemographic characteristics between participants included in the final analysis and subjects lost to follow-up did not differ in age, MMSE scores, or formal education years at the time of the baseline survey (Table S1).

With regard to green tea, 195 participants (39.8%) drank moderate amounts (1–6 days per week), 157 (32.0%) drank every

day, and 138 (28.2%) did not drink green tea. With regard to coffee intake, 212 participants (43.3%) drank coffee every day, 180 (36.7%) drank moderate amounts (1–6 days per week), and 98 (20.0%) did not drink coffee. As for black tea consumption, 404 participants (82.4%) did not consume, whereas 86 (17.6%) consumed black tea at least 1 day per week. Because the number of participants drinking black tea for every day was too small (n = 6), we grouped together the participants drinking black tea for 1–6 days/week and every day.

Tables 1–3 show results from the baseline and follow-up surveys according to green tea, coffee, and black tea consumption categories. At baseline, participants who consumed larger amounts of green tea was younger (P<0.001), had more formal education (P<0.001), had higher MMSE scores (P<0.001), and had higher scores for current physical activities and/or hobbies (P = 0.008). More frequent consumption of coffee was associated with lower age (P<0.001) and higher ascorbic acid levels (P = 0.008) at baseline along with higher scores for current physical activities and/or hobbies (P = 0.02). Participants who did not consume black tea had fewer years of formal education (P = 0.005) and tended to have lower MMSE scores (P = 0.083) than those who consumed black tea more than 1 day per week.

During the follow-up survey (follow-up period, 4.9±0.9 years), we documented 26 participants with dementia and 64 participants with MCI. Participants who consumed larger amounts of green tea were younger (P = 0.001), and had higher MMSE scores (P = 0.001). More frequent consumption of coffee was associated with lower age (P<0.001) and higher MMSE scores (P = 0.016). As shown in Tables 1–3, more frequent consumption of green tea was associated with lower incidence of dementia and MCI (P = 0.009 and P = 0.001, respectively). In contrast, no association was found between the frequency of coffee or black tea consumption and the incidence of dementia or MCI.

The relationships between green tea consumption and the incidence of cognitive decline (dementia or MCI) are shown in Table 4. We found that green tea consumption was inversely associated with the incidence of dementia in both age- and sex-adjusted models. With regard to the incidence of dementia, multivariate odds ratios were 1.00 (reference) for not consuming green tea, 0.90 (95% CI: 0.34–2.35) (P = 0.826) for consuming green tea 1–6 days per week, and 0.26 (0.06–1.06) (P = 0.06) for consuming green tea every day. Regarding the incidence of cognitive decline (dementia or MCI), multivariate odds ratios were 1.00 (reference) for not consuming green tea, 0.47 (0.25–0.86) (P = 0.015) for consuming green tea 1–6 days per week, and 0.32 (0.16–0.64) (P = 0.001) for consuming green tea every day (Table 4).

In contrast, we observed no association between coffee or black tea consumption and the incidences of either dementia or cognitive decline (Tables 5 and 6).

Discussion

This prospective longitudinal study demonstrated that daily green tea consumption is significantly associated with a decreased risk of cognitive decline (dementia or MCI), even after controlling for potential confounding factors. In addition, higher green tea consumption was inversely associated with dementia in both age- and sex- adjusted models. To the best of our knowledge, this is the first longitudinal study that examined the association between green tea and the incidence of dementia and cognitive decline. In a cross-sectional study, higher green tea consumption was associated with a lower prevalence of cognitive impairment [16].

Table 1. Characteristics at baseline survey of the participants according to green tea, coffee, and black tea consumption (part 1).

	Green tea				Coffee				Black tea		
Beverage consumption, days/week	**None**	**1–6 days/week**	**Every day**	**P-value (trend)**	**None**	**1–6 days/week**	**Every day**	**P-value (trend)**	**None**	**1–7 days/week**	**P-value**
Number of subjects	**n = 138**	**n = 195**	**n = 157**		**n = 98**	**n = 180**	**n = 212**		**n = 404**	**n = 86**	
Age at baseline survey, years	73.1 (7.2)	70.0 (5.7)	71.0 (6.1)	<0.001	73.4 (5.8)	71.1 (6.5)	70.2 (6.3)	<0.001	71.4 (6.5)	70.3 (6.0)	0.225
Sex: women, %	70.3	62.1	70.1	0.972	62.2	65.6	70.3	0.140	65.8	72.1	0.264
Education, years	9.1 (2.1)	9.9 (2.0)	10.5 (2.3)	<0.001	9.6 (2.1)	9.9 (2.3)	10.0 (2.2)	0.294	9.6 (2.2)	10.5 (2.4)	0.005
MMSE, points, Median (SE)	27.0 (0.2)	29.0 (0.1)	29.0 (0.1)	<0.001	28.0 (0.2)	28.5 (0.1)	28.0 (0.1)	0.131	28.0 (0.1)	29.0 (0.2)	0.083
ApoE E4 carriers, %	17.5	23.6	23.5	0.227	20.6	19.4	24.4	0.344	21.8	22.1	0.948
HT at baseline, %	39.9	44.1	48.4	0.140	45.9	46.1	42.0	0.439	43.8	46.5	0.648
HL at baseline, %	18.1	16.9	16.6	0.727	17.3	17.8	16.5	0.808	16.8	18.6	0.692
DM at baseline, %	9.4	12.8	15.3	0.132	13.3	11.7	13.2	0.918	12.6	12.8	0.966

Values expressed as mean (SD) unless otherwise indicated.
MMSE: Mini-mental state examination, HT: hypertension, HL: hyperlipidemia, DM: diabetes mellitus.
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Table 2. Characteristics at baseline survey of the participants according to green tea, coffee, and black tea consumption (part 2).

	Green tea				Coffee				Black tea		
Beverage consumption, days/week	**None**	**1–6 days/week**	**Every day**	**P-value (trend)**	**None**	**1–6 days/week**	**Every day**	**P-value (trend)**	**None**	**1–7 days/week**	**P-value**
Number of subjects	**n = 138**	**n = 195**	**n = 157**		**n = 98**	**n = 180**	**n = 212**		**n = 404**	**n = 86**	
Smokers (Current), %	11.6	13.3	7.0	0.186	9.2	8.3	13.7	0.143	11.6	7.0	0.207
Alcohol drinkers (Current), %	34.1	42.1	35.7	0.826	32.7	42.2	36.3	0.810	38.6	33.7	0.396
Physical activities/hobbies (Current), %	67.4	76.9	80.9	0.008	71.4	70.6	81.6	0.02	75.0	77.9	0.570
Green tea consumption,	-	-	-	-	30.6/34.7	43.3/32.2	41.0/30.7	0.965	37.9/30.9	48.8/37.2	0.011
1–6 days/everyday, %											
Coffee consumption,	31.9/43.5	40.0/44.6	36.9/41.4	0.965	-	-	-	-	33.9/44.6	50.0/37.2	0.877
1–6 days/everyday, %											
Black tea consumption,	8.7	21.5	20.4	0.011	11.2	23.9	15.1	0.877	-	-	-
1–7 days/week, %											
Ascorbic acid, μg/mL	6.8 (3.4)	6.8 (3.5)	6.9 (3.2)	0.834	6.0 (3.2)	6.7 (3.2)	7.3 (3.5)	0.008	6.7 (3.3)	7.3 (3.6)	0.147

Values expressed as mean (SD) unless otherwise indicated.

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Table 3. Characteristics at follow-up survey of the participants according to green tea, coffee, and black tea consumption.

	Green tea				Coffee				Black tea			
Beverage consumption, days/week	**None**	**1–6 days/week**	**Every day**	**P-value (trend)**	**None**	**1–6 days/week**	**Every day**	**P-value (trend)**	**None**	**1–7 days/week**	**P-value**
Number of subjects	**n = 138**	**n = 195**	**n = 157**		**n = 98**	**n = 180**	**n = 212**		**n = 404**	**n = 86**	
Age at follow-up survey, years	78.0 (7.1)	75.0 (5.8)	75.8 (6.1)	0.001	78.4 (5.9)	76.1 (6.6)	75.1 (6.3)	<0.001	76.3 (6.5)	75.3 (6.0)	0.251
Follow-up time, years	4.9 (0.8)	5.0 (0.8)	4.8 (1.0)	0.333	4.9 (0.8)	4.9 (0.8)	4.9 (0.9)	0.963	4.9 (0.8)	4.9 (0.9)	0.940
MMSE, points, Median (SE)	27.0 (0.3)	28.5 (0.2)	29.0 (0.2)	0.001	27.0 (0.3)	28.0 (0.3)	29.0 (0.2)	0.016	28.0 (0.2)	29.0 (0.3)	0.543
ΔMMSE (baseline-follow up), points	−0.95 (3.3)	−0.27 (2.7)	−0.46 (2.3)	0.295	−0.77 (2.6)	−0.64 (3.2)	−0.29 (2.4)	0.320	−0.48 (2.8)	−0.67 (2.9)	0.467
Dementia, N (%)	12 (8.7)	11 (5.6)	3 (1.9)	0.009	7 (7.1)	11 (6.1)	8 (3.8)	0.181	20 (5.0)	6 (7.0)	0.430
MCI, N (%)	31 (22.5)	18 (9.2)	15 (9.6)	0.001	13 (13.3)	23 (12.8)	28 (13.2)	0.985	54 (13.4)	10 (11.6)	0.728

Values expressed as mean (SD) unless otherwise indicated.
MMSE: Mini-mental state examination, MCI: mild cognitive impairment.
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In that study, although cognitive function was assessed with MMSE, the incidence of dementia or MCI was not investigated.

In the present study, no relationship was found between coffee consumption and a risk of dementia or cognitive decline. In contrast, higher coffee consumption was reported to decrease the risk of AD over a 5-year period [10] and was associated with a decrease in cognitive decline in a 10-year follow-up [11]. Furthermore, in the Three City Study [12], consuming more than three cups of a caffeinated beverage (coffee or black tea) per day was associated with a lower decline in cognitive tests among elderly women, but there was no relationship between caffeine consumption and dementia risk over a 4-year period, similar to our results. The relatively short follow-up period and the small sample size might be reasons why we did not observe protective effects of coffee against dementia or cognitive decline.

In the present study and in previous longitudinal studies [14,15], no association was found between black tea consumption and the risk of dementia or cognitive decline. Drinking black tea was a relatively uncommon practice in the area of our study, which may have resulted in low statistical power.

Both green and black teas contain polyphenols, caffeine, L-theanine, and other nutrients. The major tea-related polyphenols present in green tea are catechins, especially epigallo catechin 3-gallate (EGCG), whereas black tea mainly contains theaflavins [27]. In addition, green tea contains more myricetin compared with black tea [27]. Other tea-related polyphenols such as quercetin, kaempferol, apigenin, and luteolin, are also present in both green and black tea, but the amounts of these polyphenols are not significantly different between tea types [27]. EGCG is permeable to the blood brain barrier [28] and exerts neuroprotective and neurorescue effects against amyloid β (Aβ) toxicity by inhibiting Aβ aggregation [29] and production [3,29]. Myricetin inhibits Aβ aggregation, especially oligomerization *in vitro* [4,30]. Furthermore, oral administration of EGCG or myricetin prevents the development of AD pathology in AD-model mice [5,6,31]. The positive relationships observed in this study between green tea consumption and both dementia and cognitive decline, and the null relationship between black tea consumption and either dementia or cognitive decline may support previously reported data [1–6,29–31] regarding significant neuroprotective effects of EGCG and myricetin.

The caffeine content is 40–57 mg/100 mL in coffee [32], 25.5 mg/100 mL in black tea, and only 15.3 mg/100 mL in green tea [33]. Caffeine is a nonselective A1 and A2a adenosine receptor antagonist that stimulates cholinergic neurons [8]. Chronic caffeine administration was shown to have neuroprotective effects in a mouse model of AD, indicating that decreased Aβ production is a likely mechanism [8]. Moreover, both caffeine and adenosine A2a receptor antagonists prevent Aβ-induced cognitive deficits in mice [9]. Our study suggests that the contribution of caffeine to cognitive function may be small due to the null relationship observed between coffee consumption and cognitive impairment.

High intake of ascorbic acid is associated with lower risk of AD [34]. The content of ascorbic acid is 6 mg/100 mL in green tea, which is the most common source of ascorbic acid in Japan [35,36]. On the other hand, coffee and black tea do not contain ascorbic acid [36]. We cannot exclude the possibility that ascorbic acid in green tea had a positive effect on cognitive function. However, this explanation was not supported by the findings that the serum levels of ascorbic acid were associated with the frequency of coffee consumption, but not green tea consumption, thereby indicating that the effects of ascorbic acid on cognitive function may be small. L-theanine, an amino acid rich in green

Table 4. Association between green tea consumption and the incidence of dementia or cognitive decline (MCI or dementia).

Frequency of green tea consumption	None	1–6 days/week	Every day
Dementia			
Number of cases	12	11	3
Unadjusted Model	1	0.64 (0.27–1.49)	0.21 (0.06–0.76)*
Model 1†	1	0.89 (0.36–2.19)	0.26 (0.07–0.94)*
Model 2§	1	0.89 (0.35–2.28)	0.27 (0.07–1.07)
Model 3¶	1	0.90 (0.34–2.35)	0.26 (0.06–1.06)
Cognitive decline (MCI or dementia)			
Number of cases	43	29	18
Unadjusted Model	1	0.39 (0.23–0.67)**	0.29 (0.16–0.54)***
Model 1†	1	0.53 (0.30–0.93)*	0.34 (0.18–0.64)**
Model 2§	1	0.49 (0.27–0.89)*	0.33(0.17–0.66)**
Model 3¶	1	0.47 (0.25–0.86)*	0.32 (0.16–0.64)**

Values expressed as odds ratios (95% CI) unless otherwise indicated.
*P-value <0.05.
**P-value <0.01.
***P-value <0.001.
†Model 1 was adjusted for age and sex.
§Model 2 was adjusted as for model 1 plus history of hypertension, diabetes mellitus, hyperlipidemia, education, and ApoE E4 carrier status.
¶Model 3 was adjusted as for model 2 plus alcohol drinking, smoking, physical activities and/or hobbies, and coffee and black tea consumption.
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and black teas, but not present in coffee, has antioxidative properties and neuroprotective effects through inhibition of both Aβ-induced oxidative stress and activation of the ERK1/p38 MAPK and NK-kB pathways [37]. Further studies that determine L-theanine levels in participants are required.

We could not fully exclude the possibility that the analyses were confounded by unmeasured factors. For example, green tea consumption is associated a variety of health behavior or social factors, and previous studies have shown that physical activity and hobbies are associated with lower risk of dementia and MCI [38,39]. Hence, the association of more frequent consumption of green tea with more physical activities and hobbies reported here may not be surprising. However, we found that the inverse association between green tea consumption and incidence of dementia and cognitive decline was present even after adjustment for physical activities and hobbies. All participants were free from cognitive impairment and had at least MMSE score of 24 or higher at the time of the baseline survey. However, as lower MMSE scores were associated with smaller amounts of green tea consumption, participants who consumed smaller amounts of green tea might have had very mild cognitive impairment at baseline.

There are some limitations to the present study. First, because the sample size was relatively small, we did not assess the

Table 5. Association between coffee consumption and the incidence of dementia or cognitive decline (MCI or dementia).

Frequency of coffee consumption	None	1–6 days/week	Every day
Dementia			
Number of cases	7	11	8
Unadjusted Model	1	0.86 (0.31–2.30)	0.51 (0.18–1.45)
Model 1†	1	1.06 (0.39–2.90)	0.69 (0.23–2.01)
Model 2§	1	1.13 (0.40–3.21)	0.71 (0.23–2.16)
Model 3¶	1	1.00 (0.34–2.99)	0.70 (0.22–2.17)
Cognitive decline (MCI or dementia)			
Number of cases	20	34	36
Unadjusted Model	1	0.93 (0.50–1.72)	0.80 (0.44–1.47)
Model 1†	1	1.22 (0.63–2.36)	1.19 (0.62–2.28)
Model 2§	1	1.23 (0.63–2.41)	1.09 (0.56–2.14)
Model 3¶	1	1.26 (0.62–2.54)	1.16 (0.58–2.32)

Values expressed as odds ratios (95% CI) unless otherwise indicated.
†Model 1 was adjusted for age and sex.
§Model 2 was adjusted as for model 1 plus history of hypertension, diabetes mellitus, hyperlipidemia, education, and ApoE E4 carrier status.
¶Model 3 was adjusted as for model 2 plus alcohol drinking, smoking, physical activities and/or hobbies, and coffee and black tea consumption.
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Table 6. Association between black tea consumption and the incidence of dementia or cognitive decline (MCI or dementia).

Frequency of black tea consumption	None	1–7 days/week
Dementia		
Number of cases	20	6
Unadjusted Model	1	1.41 (0.55–3.61)
Model 1[†]	1	1.70 (0.64–4.47)
Model 2[§]	1	2.06 (0.76–5.61)
Model 3[¶]	1	2.14 (0.75–6.08)
Cognitive decline (MCI or dementia)		
Number of cases	74	16
Unadjusted Model	1	0.99 (0.54–1.81)
Model 1[†]	1	1.19 (0.64–2.24)
Model 2[§]	1	1.39 (0.72–2.68)
Model 3[¶]	1	1.52 (0.77–3.03)

Values expressed as odds ratios (95% CI) unless otherwise indicated.
[†]Model 1 was adjusted for age and sex.
[§]Model 2 was adjusted as for model 1 plus history of hypertension, diabetes mellitus, hyperlipidemia, education, MMSE score, and ApoE E4 carrier status.
[¶]Model 3 was adjusted as for model 2 plus alcohol drinking, smoking, physical activities and/or hobbies, and coffee and black tea consumption.
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association of the combined frequency of green tea, coffee, and black tea consumption with incidence of dementia or cognitive decline. Second, because we did not include the question about the amounts of cups of beverage consumption at baseline survey, we could not assess the association between amounts of beverage consumption and cognitive decline. Third, we did not evaluate the causes of dementia and MCI with diagnostic tools such as neuroimaging and neuropathology. Further studies involving neuroimaging and neuropathology are required to reveal the cause of dementia and MCI in this population and to evaluate the effects of green tea consumption for each cause of dementia. Furthermore, among the number of subjects at baseline (n = 723), the valid response rate (67.8%, n = 490) was not high. The strengths of the current study are its longitudinal design and the opportunity to adjust for possible confounding factors.

In conclusion, higher green tea consumption was associated with lower incidence of cognitive decline (dementia or MCI) in an elderly Japanese population. Our results suggest that green tea consumption could be beneficial for reducing the risk of cognitive decline.

Supporting Information

Table S1 Characteristics of the participants including the final analysis and subjects lost to follow-up. Values expressed as mean (SD) unless otherwise indicated. MMSE: Mini-mental state examination.
(DOC)

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Author Contributions

Conceived and designed the experiments: MN-S SY CD KI KK HN M. Yamada. Performed the experiments: MN-S SY CD YI MS KI M. Yokogawa KA KK M. Yamada. Analyzed the data: MN-S. Contributed reagents/materials/analysis tools: MN-S SY. Wrote the paper: MN-S M. Yamada.

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Association of cerebral white matter lesions with cognitive function and mood in Japanese elderly people: a population-based study

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Abstract

Background: To determine the relationships between regional white matter lesions (WMLs), lifestyle factors, and cognitive, motor function and mood. **Methods:** A comprehensive evaluation, including brain MRI, blood tests, the Unified Parkinson's Disease Rating Scale, the Mini Mental State Examination, and the Geriatric Depression Scale, was performed for people aged 65 years or older living in Ama-cho on October 1, 2009. Participants were classified by severity of periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) using the Fazekas score. **Results:** Of 900 eligible participants, 688 (76.4%) were enrolled, including 303 men. Significant predictors of severe PVH were older age, lower low-density lipoprotein cholesterol (LDL-C) levels, elevated blood pressure (BP), cerebral infarction, and no current alcohol use. Significant predictors of severe DWMH were older age, lower 1,5-anhydroglucitol (1,5-AG) levels, elevated BP, cerebral infarction, and no current alcohol use. Higher cognitive function was associated with younger age, female sex, mild DWMH, more years of education, and higher high-density lipoprotein cholesterol levels. Depressive symptoms were associated with lower 1,5-AG levels, lower LDL-C levels, moderate to severe PVH, and no current alcohol use. **Conclusions:** White matter lesions in elderly people were related to hypertension and impaired glucose tolerance. The severity of WMLs was associated with cognitive function and mood.

Introduction

Large increases in the number of elderly people with cerebrovascular disorders and dementia in Japan have created significant economic and personal burdens. Dementias, such as Alzheimer's disease and vascular dementia, are the main causes of functional decline in the elderly, and cerebrovascular disorder is a major source of bedridden state (Yoshida et al. 2012). Prevention of these disorders is important for elderly people to maintain their ability to perform activities of daily living and a good quality of life.

Cerebral white matter lesions (WMLs) are associated with declines in cognitive, motor function, and mood (Gouw et al. 2006; Herrmann et al. 2008; Debette and Markus 2010). Risk factors for WMLs include lifestyle factors, hypertension, and renal damage (de Leeuw et al. 2002; Weiner et al. 2009). On the one hand, unlike Western countries, Japan has a relatively higher incidence and mortality caused by stroke than coronary heart disease. In addition, the dominant type of ischemic stroke in Japan differs from it in Western countries (Ueshima et al. 2008). In such the situation, we take an interest in research findings of WMLs in our country. However, there have been few epidemiological studies of these associations in Japan. Therefore, we examined the relationship between these risk factors and WMLs in Japanese elderly inhabitants in a rural island town, with very little population movement in the elderly.

Methods

Study Population

This study was conducted in the municipality of Ama-cho in the northwestern part of Japan (Wada-Isoe et al. 2012). The target population included all persons ages 65 years and older who had been recorded in the Basic Resident Registration of the Ama-cho on October 1, 2009. The subjects knew the recruitment of this study by the appeal of Tottori University and the town office. An exclusion criterion was the usual contraindications to MRI. The study was approved by the Tottori University committee for medical research ethics following the principles outlined in the Declaration of Helsinki, and all participants provided written informed consent.

Data Collection

Hypertension, impaired glucose tolerance, hyperlipidemia, current smoking and alcohol use, and years of education were obtained from a patient-administered questionnaire and review of electronic databases of healthcare system. Blood pressure (BP) at evaluation was assessed during medical examinations. Concurrently with the MRI investigation, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr), and 1,5-anhydroglucitol (1,5-AG) were measured by us for this investigation.

MRI and Measurement of WMLs

Brain MRI scans were performed between March 2010 and May 2010 using 1.5-T scanners (Gyroscan Intera; Philips Electronics Japan, Tokyo, Japan). The scanning protocol included a series of axial proton-density (repetition time [TR], 3000 msec; echo time [TE], 12 msec), T2-weighted (TR, 3000 msec; TE, 96 msec), and sagittal contiguous T1-weighted (TR, 8.6 msec; TE, 4 msec) images.

The Fazecas scale was used to assess periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) (Fazekas et al. 1987). Participants were classified into three severity groups according to their Fazekas score: mild (0–1), moderate (2), and severe (3). The presence of infarcts was assessed visually by a neurologist using a standardized assessment. WMLs were areas of bright, high-signal intensities noted on MRI T2, and proton-density-weighted images. Cerebral infarcts were defined as focal hyperintensities on T2-weighted images ≥3 mm, with corresponding prominent hypointensities on T1-weighted images.

The two neurologists (M.Y. and M.Y.) evaluated 10% of cases for degree of concordance. The inter- and intrarater kappa coefficients for PVH were 0.846 and 0.818, respectively, and for DWMH were 0.660 and 0.867, respectively.

Assessment of Cognitive, Motor Function, and Mood

A standardized neurological examination was conducted by neurologists as previously described, which included an abbreviated (10-item) version of the motor portion of the Unified Parkinson's Disease Rating Scale (mUPDRS) (Uemura et al. 2011, 2013). The 10 items (each rated from 0 to 4) assessed speech, facial expression, tremor at rest, rigidity (rated separately in the neck, right arm, left arm, right leg, and left leg), posture, and body (axial) bradykinesia. As mUPDRS is associated with measures of physical activity obtained using actigraphy, mUPDRS provided a means to assess motor impairment (Uemura et al. 2011). The mini mental state examination (MMSE) was administered to determine global cognitive function (Wada-Isoe et al. 2012). The Japanese version of the Geriatric Depression Scale (GDS) with 15 questions was administered to assess depressive symptoms (Uemura et al. 2011, 2013).

Statistical Analysis

The chi-square tests were used to determine significant differences of the frequencies of categories between the groups. Kruskal–Wallis and Mann-Whitney U tests were used for demographic and clinical comparisons between the groups. Multivariate logistic regressions with stepwise selection and likelihood ratio test were performed to determine the independent predictors of severe PVH and DWMH. In multivariate regression analyses, forward stepwise regression was used to determine the independent predictors of mUPDRS, MMSE and GDS. We chose variables with a P value of less than 0.25 in the univariate analysis as the final candidate variables for the multivariate statistics. We confirmed that predictors were not highly correlated with others. Significance was defined as $P < 0.05$. All analyses were conducted using SPSS (release 20; SPSS, Tokyo, Japan).

Results

Of 900 eligible individuals, 689 (76.6%) were enrolled in the study. The remaining 211 participants did not undergo an MRI scan of the brain despite our eager and repeated appeals prompting their participation. One participant was excluded from analyses because of poor quality MRI due to movement. Thus, this study comprises the remaining 688 participants (76.4%). Compared with participants, nonparticipants were similar in gender, but age of nonparticipants

was significantly increased compared with participants (data not shown). The sample included 303 (44%) males. The sample had a mean ± SD age of 76.5 ± 7.1 (age composition of participants: 69 years of age or younger, 19.6%; 70–79 years of age, 47.2%; 80–89 years of age, 28.9%; 90 years of age or older, 4.2%). The median score of PVH and DWMH were 1 (interquartile range, 1–2) and 1 (interquartile range, 1–2), respectively. There were no significant differences in these variables by sex. Cerebral infarctions were present in 211 participants (30.7%). Most of cerebral infarctions were regarded as small infarctions with a diameter of <15 mm.

Predictors of PVH Severity

Table 1 summarizes participant characteristics by PVH severity. The logistic regression model included age, systolic blood pressure (SBP), Cr, HDL-C, LDL-C, 1,5-AG, current drinker, and cerebral infarction. We revealed that older age, lower LDL-C levels, elevated SBP, presence of cerebral infarction, and no current alcohol use were significant predictors of severe PVH (Table 2).

Predictors of DWMH Severity

Table 3 summarizes participant characteristics by DWMH severity. The logistic regression model included age, SBP, Cr, HDL-C, LDL-C, 1,5-AG, current drinker, and cerebral infarction. We revealed that older age, lower 1,5-AG, elevated SBP, presence of cerebral infarction, and lack of current alcohol use were significant independent predictors of severe DWMH (Table 4).

Predictors of Motor Function

A total of 581 in 688 MRI recorded participants (250 men) were evaluated for motor function by mUPDRS (mean ± SD, 1.0 ± 1.9). There were no significant gender differences. The mUPDRS score was not a significant predictor of severe PVH or DWMH in the multiple regression analyses (data not shown).

Predictors of Cognitive Function

A total of 660 in 688 MRI recorded participants (290 men) were evaluated using the MMSE (mean ± SD, 25.9 ± 3.8), and women had a significantly higher mean score than men (men, 25.6 ± 3.9; women, 26.2 ± 3.7; $P = 0.011$). Multivariate regression model included PVH, DWMH, age, sex, Cr, HDL-C, LDL-C, cerebral infarction, and years of education. Younger age, female sex, mild DWMH, more years of education, and higher HDL-C levels were significant predictors of better cognitive function (Table 5).

Table 1. Characteristics of participants by PVH severity.

Characteristic	Mild (n = 438)	Moderate (n = 176)	Severe (n = 74)	All (n = 688)
Male (%)	45.2	38.6	50.0	44.0
Age, mean ± SD, years	74.4 ± 6.3	79.5 ± 6.6[1]	82.0 ± 6.9[1]	76.5 ± 7.1
SBP, mean ± SD, mmHg	133.3 ± 17.5	136.6 ± 18.6	139.9 ± 19.3[1]	134.7 ± 18.1
DBP, mean ± SD, mmHg	74.8 ± 10.3	75.2 ± 10.9	75.8 ± 9.8	75.0 ± 10.4
Cr, mean ± SD, mg/dL	0.72 ± 0.22	0.77 ± 0.35	0.87 ± 0.42[1]	0.75 ± 0.29
HDL-C, mean ± SD, mg/dL	57.0 ± 14.1	55.1 ± 13.8	53.2 ± 13.1[1]	56.1 ± 14.0
TG, mean ± SD, mg/dL	155.6 ± 107.2	147.3 ± 92.9	130.1 ± 78.0[1]	150.7 ± 101.1
LDL-C, mean ± SD, mg/dL	101.3 ± 28.5	98.9 ± 28.5	88.8 ± 29.9[1]	99.3 ± 28.9
1,5-AG, mean ± SD, μg/mL	21.1 ± 8.8	19.3 ± 9.7	19.1 ± 10.0	20.4 ± 9.2
Cerebral infarction (%)	21.7	44.3[2]	51.4[2]	30.7
Hypertension (%)	60.2	70.5[2]	71.6	64.0
Impaired glucose tolerance (%)	32.9	38.1	36.5	34.6
Hyperlipidemia (%)	34.3	33.0	29.7	33.5
Current smoker (%)	8.0	8.1	10.0	8.3
Current drinker (%)	33.4	24.4[2]	22.9	30.1
mUPDRS, mean ± SD	0.8 ± 1.9	1.3 ± 1.9[1]	1.5 ± 1.8[1]	1.0 ± 1.9
MMSE, mean ± SD	26.6 ± 3.2	25.3 ± 3.8[1]	23.4 ± 5.4[1]	25.9 ± 3.8
GDS, mean ± SD	2.9 ± 2.9	3.8 ± 3.4[1]	4.1 ± 3.7	3.3 ± 3.2
Education, mean ± SD, years	9.8 ± 2.1	9.6 ± 2.2	9.1 ± 2.5	9.7 ± 2.2

Cr, creatinine; DBP, diastolic blood pressure; GDS, Geriatric Depression Scale; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mUPDRS, motor component of Unified Parkinson's Disease Rating Scale; MMSE, mini mental state examination; PVH, periventricular hyperintensities; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides; 1,5-AG, 1,5-anhydroglucitol.

[1]$P < 0.05$, Kruskal–Wallis test with post hoc test versus mild.

[2]$P < 0.05$, chi-square test versus mild.

Table 2. Predictors of severe PVH.[1]

Variable	Regression coefficient	OR (95% CI)	*P*	Predictive accuracy
Intercept	−15.600		<0.001	89.7
Age	0.148	1.160 (1.104–1.218)	<0.001	
Cerebral infarction	1.279	3.595 (1.901–6.797)	<0.001	
SBP	0.026	1.026 (1.008–1.045)	0.005	
LDL-C	−0.016	0.984 (0.972–0.995)	0.006	
Current drinker	−0.931	0.394 (0.175–0.886)	0.024	

CI, confidence interval; Cr, creatinine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PVH, periventricular hyperintensities; SBP, systolic blood pressure; 1,5-AG, 1,5-anhydroglucitol.
Model included age, SBP, Cr, HDL-C, LDL-C, 1,5-AG, current drinker, and cerebral infarction.
[1]Logistic regression model compared severe PVH versus mild PVH (reference group).

Table 3. Characteristics of participants by DWMH severity.

Characteristic	Mild (*n* = 396)	Moderate (*n* = 189)	Severe (*n* = 103)
Male (%)	45.7	42.3	40.8
Age, mean ± SD, years	74.5 ± 6.5	78.8 ± 6.7[1]	80.0 ± 7.3[1]
SBP, mean ± SD, mmHg	134.0 ± 18.1	133.7 ± 17.2	139.9 ± 19.1[1]
DBP, mean ± SD, mmHg	75.0 ± 10.2	74.2 ± 10.8	76.6 ± 10.2
Cr, mean ± SD, mg/dL	0.73 ± 0.22	0.77 ± 0.37	0.82 ± 0.33[1]
HDL-C, mean ± SD, mg/dL	56.4 ± 13.2	57.2 ± 16.1	53.2 ± 12.4[1]
TG, mean ± SD, mg/dL	153.3 ± 103.9	148.7 ± 107.1	144.5 ± 76.4
LDL-C, mean ± SD, mg/dL	101.2 ± 29.4	97.1 ± 27.1	96.3 ± 30.0
1,5-AG, mean ± SD, μg/mL	21.5 ± 9.0	19.0 ± 9.2[1]	18.8 ± 9.2[1]
Cerebral infarction (%)	22.7	37.0[2]	49.5[2]
Hypertension (%)	58.7	70.4[2]	72.8[2]
Impaired glucose tolerance (%)	33.1	34.9	39.8
Hyperlipidemia (%)	32.9	33.9	35.0
Current smoker (%)	9.9	5.7	6.2
Current drinker (%)	35.7	22.3[2]	21.9[2]
mUPDRS, mean ± SD	0.9 ± 2.0	1.1 ± 1.8	1.2 ± 1.6[1]
MMSE, mean ± SD	26.7 ± 3.1	25.1 ± 3.9[1]	24.4 ± 5.0[1]
GDS, mean ± SD	3.0 ± 3.0	3.5 ± 3.4	3.8 ± 3.4
Education, mean ± SD, years	9.8 ± 2.2	9.7 ± 2.3	9.2 ± 2.1

Cr, creatinine; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensities; GDS, Geriatric Depression Scale; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mUPDRS, motor component of Unified Parkinson's Disease Rating Scale; MMSE, mini mental state examination; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides; 1,5-AG, 1,5-anhydroglucitol.
[1]$P < 0.05$, Kruskal–Wallis test with post hoc test versus mild.
[2]$P < 0.05$, chi-square test versus mild.

Predictors of Depressive Symptoms

A total of 631 in 688 MRI recorded participants (278 men) were evaluated using the GDS. The mean ± SD score for all participants was 3.3 ± 3.2, and there were no significant gender differences. Multivariate regression model included PVH, DWMH, age, sex, LDL-C, 1,5-AG, current smoker and drinker, and years of education. Lower 1,5-AG, lower LDL-C levels, moderate to severe PVH, and no current alcohol use were significant predictors of depressive symptoms (Table 6).

Discussion

In this population-based study, we investigated the relationship between WMLs, lifestyle factors, and cognitive and motor function and mood in Japanese elderly people. Our study had a high participant rate and included many very elderly in habitants. Independent predictors of severe PVH were older age, cerebral infarction, lower LDL-C levels, elevated BP, and lack of current alcohol use. Independent predictors of severe DWMH were older age, cerebral infarction, lower 1,5-AG levels, and elevated BP, lack of current alcohol use. Individuals with higher global

Table 4. Predictors of severe DWMH.[1]

Variable	Regression coefficient	OR (95% CI)	*P*	Predictive accuracy
Intercept	−9.685		<0.001	82.7
Age	0.085	1.088 (1.045–1.133)	<0.001	
Cerebral infarction	1.223	3.396 (1.950–5.915)	<0.001	
1,5-AG	−0.042	0.959 (0.931–0.988)	0.006	
Current drinker	−0.852	0.427 (0.220–0.826)	0.012	
SBP	0.017	1.017 (1.003–1.032)	0.020	

CI, confidence interval; Cr, creatinine; DWMH, deep white matter hyperintensities; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; 1,5-AG, 1,5-anhydroglucitol.
Model included age, SBP, Cr, HDL-C, LDL-C, 1,5-AG, current drinker, and cerebral infarction.
[1]Logistic regression model compared severe DWMH versus mild DWMH (reference group).

Table 5. Predictors of MMSE.

Variable	Partial regression coefficient (95%CI)	*P*	Predictor importance	R^2
Intercept	38.105 (34.117 to 42.094)	<0.001		0.235
Age	−0.205 (−0.245 to −0.165)	<0.001	0.754	
DWMH (mild)	0.925 (0.382 to 1.468)	0.001	0.083	
Education	0.219 (0.080 to 0.358)	0.002	0.071	
Sex (men)	−0.739 (−1.257 to −0.222)	0.005	0.058	
HDL-C	0.021 (0.002 to 0.040)	0.034	0.033	

CI, confidence interval; Cr, creatinine; DWMH, deep white matter hyperintensities; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MMSE, mini mental state examination; PVH, periventricular hyperintensities.
Model included age, sex, Cr, HDL-C, LDL-C, cerebral infarction, education, PVH, and DWMH.

Table 6. Predictors of GDS.

Variable	Partial regression coefficient (95% CI)	*P*	Predictor importance	R^2
Intercept	2.646 (−0.609 to 5.901)	0.111		0.043
Current drinker	−0.663 (−1.209 to −0.118)	0.017	0.257	
PVH (mild)	−0.601 (−1.152 to −0.049)	0.033	0.206	
LDL-C	−0.009 (−0.018 to −0.001)	0.034	0.204	
1,5-AG	−0.028 (−0.055 to −0.001)	0.044	0.183	
Age	0.035 (−0.003 to 0.073)	0.069	0.149	

CI, confidence interval; DWMH, deep white matter hyperintensities; GDS, Geriatric Depression Scale; LDL-C, low-density lipoprotein cholesterol; PVH, periventricular hyperintensities; 1,5-AG, 1,5-anhydroglucitol.
Model included age, sex, LDL-C, 1,5-AG, current smoker and drinker, education, PVH, and DWMH.

cognitive function were more likely to be younger, female, and have more years of education, higher HDL-C levels, and mild DWMH. Lower levels of depressive symptoms were associated with higher 1,5-AG levels, higher LDL-C levels, current alcohol use, and mild PVH.

In previous studies, age and hypertension were reported to be the most common risk factors for WMLs (Liao et al. 1997; de Leeuw et al. 2002). The risk of cerebrovascular disease was found to be increased in individuals with higher BP and BP fluctuations of greater magnitude (Brickman et al. 2010). Some studies have suggested that white matter hyperintensities are associated with diabetes (Murray et al. 2005; van Harten et al. 2007) whereas others found no association (Bogousslavsky et al. 1987). In this study, hypertension and impaired glucose tolerance were related to DWMH severity. In addition, hypertension was related to PVH severity. Associations of PVH and LDL-C levels were in an unanticipated direction. Hyperlipidemia is a risk factor for vascular disorder (Tirschwell et al. 2004) and statin treatment has demonstrated benefits in stroke prevention and prognosis (Amarenco et al. 2006; Alvarez-Sabin et al. 2007). Consistent with previous findings (Jimenez-Conde et al. 2010; Ichikawa et al. 2012), data in this study indicated that

higher LDL-C levels were associated with lower severity of WMLs. The mechanisms of the inverse correlation between LDL-C and PVH are not fully understood, but cholesterol is thought to play important roles in neuron repair and remodeling in the central nervous system (Dietschy and Turley 2001). Mielke et al. indicated that high total cholesterol level in late life is associated with a reduced risk of dementia. Taken together with our result showing higher cholesterol was associated reduction of WMLs, high cholesterol might be associated with better healthy status in late life (Mielke et al. 2005). Moreover, statin treatment may protect the vessels of the brain and increase chances of survival while also being associated with worsening WMLs (Longstreth et al. 2005).

The distinction between PVH and DWMH is of clinical significance as they have been associated with different clinical consequences. DWMH might predominantly disrupt the short association fibers, also known as arcuate U fibers, which connect adjacent cortical areas. PVH probably affects the long association fibers that connect the more distant cortical areas (de Groot et al. 2000). In previous investigations, PVH burden was related to cognitive function (Debette et al. 2007) and a decline in mental processing speed (van den Heuvel et al. 2006). In this study, improved cognitive function was correlated with mild DWMH but was not related to PVH severity. A previous study also found a correlation between DWMH and cognitive function in middle-aged individuals (Soriano-Raya et al. 2012). Differences in study methods and participant races and ages might account for these conflicting findings. Increasing severity of generalized brain atrophy and the presence of cerebral infarcts on MRI are associated with a steeper decline in cognitive function (Prins et al. 2005). Therefore, further investigation is necessary to examine the connections between cognitive function and brain atrophy.

Some authors have found a correlation between depression and WMLs (Iidaka et al. 1996; Jorm et al. 2005; Krishnan et al. 2006; Herrmann et al. 2008). WMLs are caused by cerebrovascular disease and disrupted fiber tracts within frontostriatal circuits. Because of the involvement of frontostriatal circuits in the regulation of mood, disruption of these circuits may lead to a disconnection syndrome (Herrmann et al. 2008). WMLs are believed to be primarily caused by hypoperfusion and arteriosclerosis (Liao et al. 1997). Decline in total cerebral blood flow is associated with an increase in the volume of PVH but not DWMH (ten Dam et al. 2007). PVH may be affected by longer term vascular disorder. Our finding of a relationship between depressive symptoms and PVH supports the vascular hypothesis of depression.

This study has some limitations that should be mentioned. The visual rating scale for assessing WMLs used in this study may differ from quantitative volumetric methods. However, because significant agreement between the Fazekas scale and quantitative volumetric measurement has been shown (Kapeller et al. 2003), the method used to assess WMLs is not expected to affect the findings. The cross-sectional nature of this study precludes conclusions about causality. In addition, this study did not assess the treatments participants received over time, which may have affected results. For example, a previous study found that individuals who used antihypertensive medication and had controlled BP had a reduced risk of severe WMLs (Dufouil et al. 2001; de Leeuw et al. 2002). Both atrophic and ischemic imaging changes are driven by altered glycemic and BP control beginning in midlife (Knopman et al. 2011). We evaluated BP values and clinical biochemistry parameters, but did not include treatment and response to treatment in our models. Although efforts to study regional white matter changes have been initiated, future investigations should seek to define longitudinal relationships between WMLs and other factors.

In conclusion, investigators have begun to take notice of associations between hypertension, glucose intolerance, depression, and cognitive decline. Our population-based study indicated that WMLs in the elderly were related to hypertension and impaired glucose tolerance, and that the severity of WMLs was associated with cognitive function and mood.

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Conflict of Interest

None declared.

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RESEARCH ARTICLE Open Access

Donepezil and life expectancy in Alzheimer's disease: A retrospective analysis in the Tajiri Project

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Abstract

Background: Cholinesterase inhibitors (ChEIs) such as donepezil have the effect of delaying progression of Alzheimer's disease (AD), but their effect on life expectancy is unclear. We analyzed the influence of donepezil on life expectancy after onset of AD, together with the effects of antipsychotic drugs and residency in a nursing home.

Methods: All outpatients at the Tajiri Clinic from 1999–2012 with available medical records and death certificates were included in a retrospective analysis. The entry criteria were a dementia diagnosis based on DSM-IV criteria and diagnosis of AD using NINCDS-ADRDA criteria; medical treatment for more than 3 months; and follow up until less than 1 year before death.

Results: We identified 390 subjects with medical records and death certificates, of whom 275 had a diagnosis of dementia that met the entry criteria. Of 100 patients diagnosed with AD, 52 had taken donepezil and 48 patients had not received the drug due to treatment prior to the introduction of donepezil in 1999 in Japan. The lifetime expectancies after onset were 7.9 years in the donepezil group and 5.3 years in the non-donepezil group. There was a significant drug effect with a significant covariate effect of nursing home residency. Other covariates did not reach a significant level.

Conclusions: Although this report has the limitation of all retrospective analyses: the lack of randomization, we found a positive effect of donepezil on lifetime expectancy after onset of AD. This may be due to a decreased mortality rate caused by reduction of concomitant diseases such as pneumonia. The similar life expectancies in patients taking donepezil at home and those not taking donepezil in a nursing home indicated a positive health economic effect of the drug.

Keywords: Alzheimer's disease, Donepezil, Cholinesterase inhibitors, Life expectancy, Nursing home

Background

Several longitudinal studies have shown that cognitive impairment with advancing age is a negative predictor of subsequent survival [1]. This association remains after adjusting for medical conditions and self-rated health, and thus has been attributed to the effects of decreased biological vitality [2]. However, it has also been suggested that the cognition-mortality link reflects more than just a reduction in biological vitality. Systematic reviews have concluded that the terminal decline is a multifactorial phenomenon, with origins that operate across the entire lifespan [3].

Higher levels of cognition are associated with better health literacy and higher socioeconomic status, and lead to better health management and reduced mortality. Education is positively associated with access to health services, increased likelihood of correctly following instructions for use of medication, and better chronic disease management [4]. Health literacy may, therefore, result in earlier diagnosis and earlier intervention, thus reducing disease impact on cognitive development over the lifespan. Alternatively, possible positive effects of psychosocial activities such as exercise and mental activities may be decreased by cognitive impairment. In addition to

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these effects, dementia itself is a risk factor for decreased life expectancy.

Life expectancy for patients with dementia directly influences prevalence and service needs and is a common question posed by families and patients. A recent [5] systematic review compared mortality and survival in dementia with estimated life expectancies in the general population. Survival after diagnosis of dementia varies considerably and depends on numerous factors and complex interactions among these factors. Relative loss of life expectancy decreases with age at diagnosis and also depends on gender, dementia subtype, and severity stage. A definitive meta-analysis of survival in dementia is precluded by deficiencies in primary studies.

Alzheimer's disease (AD) is the main cause of dementia. At present, there are no curative drugs for AD; however, symptomatic drugs such as cholinesterase inhibitors (ChEIs) or memantine may delay progression of the disease. This effect combined with psychosocial interventions may increase quality of life (QOL) [6]. Beyond delayed progression and increased QOL, the ultimate outcome of drug treatment should be measured in terms of life expectancy.

ChEIs such as donepezil are used for symptomatic treatment of AD. Treatment with these drugs can delay nursing home placement [7], reduce the caregiver burden and the time spent caring [8], and possibly reduce mortality for patients living in nursing homes [9] and in the community [10]. However, the effect on mortality is uncertain: Lopez et al. [10] found that ChEIs can delay a move to a nursing home, but have no effect on life expectancy, whereas a recent cohort study [11] in 7,073 AD patients in the Swedish Dementia Registry suggested that ChEIs were associated with a lower risk of death and myocardial infarction. These associations were stronger with increasing ChEI dose, which may be due to the vagotonic and antiinflammatory effects of these drugs on atherosclerosis.

In this study, we examined whether donepezil has an effect on life expectancy in AD. We hypothesized that 1) the drug has a positive effect on life expectancy in AD, 2) that nursing home residency also has a positive effect, and 3) that use of antipsychotic drugs has a negative effect. We analyzed donepezil alone because in Japan this drug has been used since 1999, whereas other drugs such as galantamine or memantine have only been used since 2011. The combined effect of donepezil and nursing home residency was also analyzed. Although the retrospective design, this is the long-term study of the possible effect of donepezil on life expectancy of patients with AD.

Methods

Patients

All patients were outpatients at the memory clinic at the Osaki-Tajiri SKIP Center or residents at the Kagobo-no-sato nursing home, which is associated with the Osaki-Tajiri SKIP Center. All nursing home patients received medical services at the memory clinic. Outpatients and nursing home patients all underwent magnetic resonance imaging (MRI) to confirm the medical diagnosis of dementia. Chest X-ray, electrocardiogram, and blood tests were performed to exclude possible systemic diseases that could affect cognitive functions. The entry criteria were 1) a dementia diagnosis based on DSM-IV criteria, a Clinical Dementia Rating (CDR) [12] of 1+, and diagnosis of dementing diseases using the established criteria described below; 2) medical treatment for more than 3 months; and 3) follow up until less than 1 year before death.

Dementia diagnosis

Diagnoses of the following diseases were made at a meeting of two neurologists, a psychiatrist, and a physician.

1) Pure AD without cerebrovascular diseases (CVD) was diagnosed in patients who met NINCDS-ADRDA criteria for probable AD [13] and had no CVD on MRI. On MRI, low signal intensity on T_1-weighted images, high signal intensity on T_2-weighted images, and high signal intensity surrounding the low signal intensity areas on FLAIR images were considered to show CVD.
2) AD with CVD was diagnosed based on NINCDS-ADRDA criteria for probable AD and on evidence for the presence of CVD on MRI; however, CVD lesions were judged to be concomitant with AD and not responsible for cognitive deterioration.
3) VaD was diagnosed based on NINDS-AIREN criteria for probable VaD [14].
4) Dementia with Lewy bodies (DLB)/ Parkinson disease with dementia (PDD) and frontotemporal lobar degeneration (FTLD) were diagnosed based on the respective consensus criteria [15,16].
5) Others conditions were diagnosed in 20 patients with head trauma (n = 3), hydrocephalus (n = 3), diabetic dementia (n = 2), vitamin B_{12} deficiency (n = 2), thyroid dysfunction (n = 2), progressive supranuclear palsy (n = 1), alcoholic dementia (n = 1), chronic subdural hematoma (n = 1), hepatic encephalopathy (n = 1), renal encephalopathy (n = 1), hypoxic encephalopathy (n = 1), syphilis (n = 1), and brain tumor (n = 1).

Analyses

The main outcome was the time (months) between onset of AD and death. Age at the first clinic visit, gender, presence of concomitant CVDs, use of antipsychotic drugs

(typical and atypical), and nursing home residency were analyzed as covariates.

One-way Analysis of Variance (ANOVA) was performed to analyze the drug effect with the covariate effects. A Spearman correlation was calculated between the period of donepezil administration and life expectancy.

Written informed consent was obtained from each of the patients and from the family of those with dementia at entry according to the Declaration of Helsinki (BMJ 1991; 302: 1194). The study was approved by the ethical committee of Tohoku University Graduate School of Medicine, as well as those of the Osaki-Tajiri SKIP Center.

Results

Dementing diseases

A total of 390 medical records and death certificates were available for the period 1999–2012, including 275 patients with diagnoses of dementia that met the entry criteria. The number of patients with each dementing disease is shown in Figure 1. The most common disease was VaD, followed by AD and AD with CVD. Of the 100 patients with AD and AD with CVD (both of which are diseases that can be treated with donepezil), 52 received donepezil and 48 patients did not receive the drug due to treatment prior to the introduction of donepezil in 1999 in Japan.

Demographics and causes of deaths

The patients who received donepezil (DNP group, n = 52) included 18 men and 34 women, and had a mean (SD) age of 80.5 (6.9) years old and a mean score on the Mini-Mental State Examination (MMSE) of 14.1 (6.3). The patients who did not receive donepezil (non-DNP group, n = 48) included 10 men and 38 women, and had a mean age of 82.9 (6.7) years old and a mean MMSE score of 14.1 (6.8). Thus, there was no significant difference in the male-to-female ratio, age or MMSE score between the two groups. The two groups also had a similar distribution of causes of death (Table 1), with pneumonia and respiratory failure being the main causes in each group.

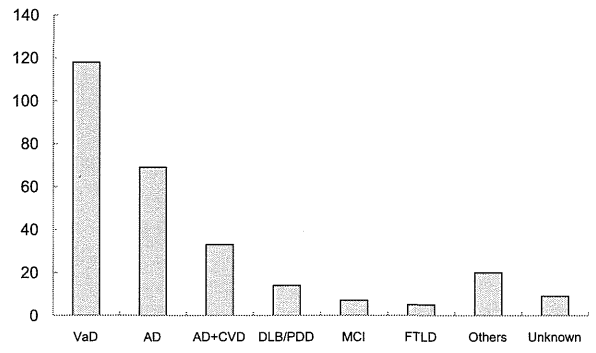

Figure 1 Numbers of patients with different dementing diseases. VaD = vascular dementia, AD = Alzheimer's disease, CVD = cerebrovascular diseases, DLB = dementia with Lewy bodies, PDD = Parkinson disease with dementia, MCI = mild cognitive impairment, FTLD = frontotemporal lobar degeneration. The vertical line indicates the numbers.

Effect on life expectancy

The life expectancies after onset were 7.9 years in the DNP group and 5.3 years in the non-DNP group (Figure 2). There was a significant drug effect with a significant covariate effect of nursing home residency. Other covariates did not reach a significant level.

Spearman analysis showed a significant positive correlation between the period of donepezil use and life expectancy in AD (Figure 3).

Since there was a significant effect of nursing home residency on life expectancy, the patients were classified into 4 groups: those taking donepezil and living in a nursing home (DNP + NH group) or at home (DNP + non-NH group), and those not taking donepezil and living in a nursing home (non-DNP + NH group) or at home (non-DNP + non-NH group). The demographics of these groups are shown in Table 2. There were no group differences for men/women ratio and mean age.

As shown in Figure 4, life expectancy was increased by nursing home residency, in addition to the donepezil treatment effect.

Discussion

This report demonstrates the possible effect of donepezil on life expectancy after onset of AD. This possible effect was found to be independent of age, gender, and the use of antipsychotic drugs. Before discussing the results, we should note methodological limitations.

Table 1 Demographics and causes of death for DNP and non-DNP groups

	DNP group	Non-DNP group
n (men/women)	52 (18/34)	48 (10/38)
Mean age (SD), years	80.5 (6.9)	82.9 (6.7)
Causes of death		
Pneumonia and/or respiratory failure	19	21
Cancer	1	4
Stroke	3	3
Heart diseases	5	5
Others	13	10
Unknown	11	5

DNP = donepezil.
There were no group differences for men/women ratio, causes of deaths (chi-square tests) and mean age (t-test).

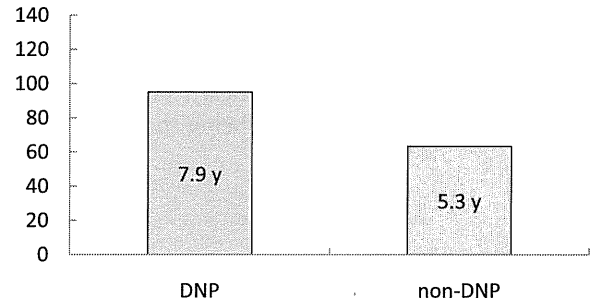

Figure 2 Donepezil effect on life expectancy in AD. DNP = donepezil, AD = Alzheimer's disease. The vertical line indicates life expectancy (months). There was a significant drug effect ($F = 14.497$; $p < 0.001$) with a significant covariate effect of nursing home residency ($F = 18.167$. $p < 0.001$). No other covariates reached a significant level (age: $F = 0.075$, $p = 0.785$; gender: $F = 0.171$, $p = 0.680$; CVD: $F = 3.827$, $p = 0.054$; typical antipsychotic drugs: $F = 0.353$, $p = 0.554$; atypical antipsychotic drugs: $F = 0.583$, $p = 0.447$).

Limitation of the study

This report has the limitation of all retrospective analyses: the lack of randomization. The evaluation of a drug effect is essentially dependent on how patients are ascertained to the drug or to non-drug groups. However, observational studies can help understanding associated effects of drugs, since main bias is carefully considered. We considered that there were no remarkable differences between DNP group and Non-DNP group for social status, such as economic status, or family supports. Actually the patients were all residents in Tajiri, a typical agricultural town, where they were born, grew up, and got married in the same area. All men analyzed were farmers and all women analyzed were house wives, having similar life styles. This unique "pure" social status can exclude possible confounding effects of social factors on life expectancy.

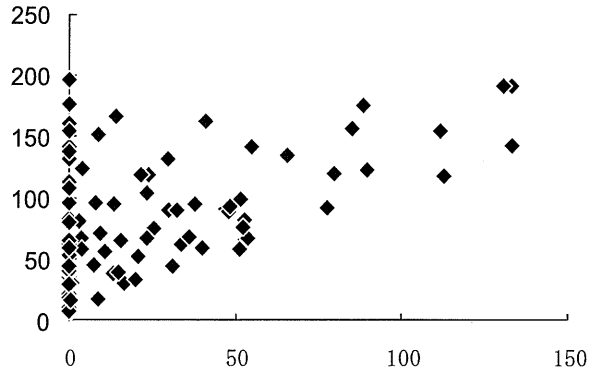

Figure 3 Period of donepezil use and life expectancy in AD. AD = Alzheimer's disease. There was a significant Spearman correlation ($Rs = 0.439$, $p < 0.0001$) between the period of donepezil administration (months, horizontal line) and life expectancy (months, vertical line).

Table 2 Demographics for four groups

	DNP & NH group	DNP & non-NH group	Non-DNP & NH group	Non-DNP & non-NH group
N	10	42	14	34
Men/Women	1/9	17/25	2/12	8/26
Age (mean)	80.2	80.6	82.9	82.9
(SD)	8.8	6.5	6.4	6.8

DNP = donepezil, NH = nursing home.
There were no group differences for men/women ratio (chi-square tests) and mean age (one-way ANOVA).

Regarding health status, two groups' distribution of vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, cardiac diseases) were not statistically different (chi-square tests, data not shown). Also, we previously reported the Quality-Adjusted Life-Year (QUALY) for various degrees of daily activities of AD [17]; we herein analyzed the QUALY for the DNP and Non-DNP groups, and the same results were obtained (data not shown). Thus we think that although the study has the limitation, the results can provide useful information on the life expectancy in AD. The possible reasons for the positive finding were discussed below.

Cause of death

Knowledge of the causes of death is of value in terminal care of patients with dementia. Cancer, heart disease, and stroke are the main causes of death in the whole Japanese population (the Ministry of Health, Labour and Welfare 2011 < http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suikei10/index.html >), but not in patients with AD. Stroke and heart diseases are vascular diseases that are commonly accompanied by VaD, but not by AD. In

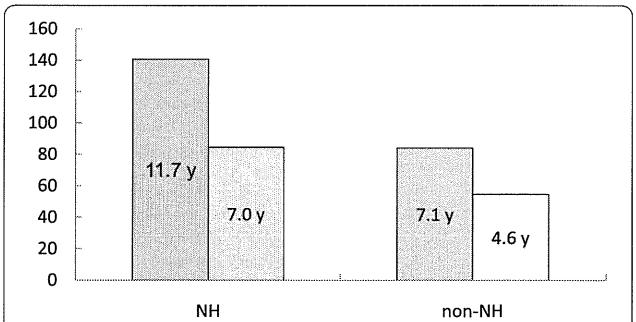

Figure 4 Donepezil and nursing home effects on life expectancy in AD. NH = nursing home, AD = AD = Alzheimer's disease. The vertical line indicates life expectancy (months). From the left to right, DNP + NH group, non-DNP + NH group, DNP + non-NH group, and non-DNP + non-NH group. There were significant effects of the drug ($F = 14.105$; $p < 0.001$) and nursing home residency ($F = 17.326$, $p < 0.001$) without significant interactions ($F = 0.894$, $p = 0.347$). No other covariates reached a significant level (age: $F = 0.206$, $p = 0.651$; gender: $F = 0.796$, $p = 0.375$; CVD: $F = 2.911$, $p = 0.091$; typical antipsychotic drugs: $F = 0.035$, $p = 0.852$; atypical antipsychotic drugs: $F = 0.362$, $p = 0.549$).

contrast, respiratory failure or pneumonia is common in patients with AD. In cases with clinical and pathological diagnoses of dementia and a complete autopsy, Brunnström et al. [18] found that the two most common causes of death were bronchopneumonia and ischemic heart disease, while cancer was uncommon. Pneumonia as an immediate cause of death in dementia may reflect a terminal stage in which patient care and feeding is difficult to manage effectively.

Wada et al. [19] found that use of antipsychotics, presence of CVD in the basal ganglia, severity of dementia, and male gender were associated with aspiration pneumonia in AD. However, our investigation of these factors did not show these relationships in patients who did and did not take donepezil (data not shown). Drugs such as angiotensin-converting enzyme inhibitors improve the swallowing reflex, thus preventing exacerbation of pneumonia [20], but we also found no effect of these drugs (data not shown). Thus the longer life expectancy in the DNP group was considered to be due to donepezil itself.

Why does donepezil prolong life expectancy?

As described above, the possible effect of donepezil on mortality is uncertain. A recent cohort study [19] showed that donepezil use was associated with a lower risk of death and myocardial infarction, probably because of the vagotonic and anti-inflammatory properties of the drug on atherosclerosis. Given the important actions of ChEIs on the heart, Sato et al. [21] undertook a retrospective cohort investigation to assess the effects of donepezil on cardiovascular mortality. Contrary to the drug action and the higher risk for sinus node dysfunction or cardiac conduction impairment, this analysis showed better cardiovascular and overall survival in donepezil-treated patients. This finding is supported by an animal study showing that oral donepezil improved survival in a mouse congestive heart failure model through prevention of pumping failure and cardiac remodeling [22]. However, in our AD patents, there was no difference in heart disease between the DNP and non-DNP groups.

Donepezil may have a negative effect on aspiration pneumonia due to a side effect of nausea. An increased gastro-esophageal reflex may induce pneumonia. This and the absence of an effect on heart disease in our patients suggest that the effect of donepezil on life expectancy was not purely pharmacological. Single photon emission CT studies have shown increased psychomotor speed or attention function after administration of donepezil, associated with frontal, limbic, lower temporal lobes in the cingulate cortex [23] or frontal and parietal lobes in the basal ganglia [24]. Stimulation of psychomotor speed and attention by donepezil is consistent with the higher mortality in older adults with lower perceptual speed [1].

The effect of donepezil of delaying progression of AD may also maintain the "energy level" of life. Patients with moderate to severe AD show instrumental and basic activities of daily living (ADL) benefits after donepezil administration. In a study of the long-term effects of donepezil on the use of community-based home help service, Wattmo et al. [25] found that the drug reduced the use of the service, i.e., maintained higher self-supported levels of instrumental ADL. Psychosocial activities may occur more smoothly with maintenance of ADL, as well as with increased psychomotor speed and attention. Rehabilitation also has a long-term effect in decreasing mortality, and especially improves motor disability and ADL [26] and prevents aspiration pneumonia [27]. Based on these observations, a prospective longitudinal study is needed to clarify the effects of donepezil in patients with AD.

Effect of antipsychotics on life expectancy

In recent years, atypical antipsychotic drugs such as risperidone have largely replaced conventional medications such as haloperidol due to equal efficacy and better tolerance [28]. In particular, physicians prefer to prescribe atypical antipsychotics to patients with dementia. However, atypical antipsychotics were found to have efficacy limitations for treatment of BPSD in a double-blind randomized placebo-controlled trial [29].

Such limitations are not the only problem with antipsychotics, since these drugs have a negative effect on life expectancy [30] and this has led to a discussion of the appropriateness of their use. A large retrospective cohort study (n = 4,369) [31] showed twofold and fivefold increases in mortality in users of atypical and conventional antipsychotics, respectively, compared to non-users. Our results were in contrast to these findings, but this was probably because the AD patients took only small doses of antipsychotic drugs (risperidone 1 mg/day, levomepromadine 5 mg/day) for less than 3 months.

Nursing home effect

The effect of nursing home residency should also be considered. Compared with living at home, better management of therapy (better drug compliance) and a better general environment (good temperature and nutrition) in a nursing home may have a positive effect on life expectancy. However, the similar life expectancies of patients taking donepezil at home and those who did not receive donepezil and lived in a nursing home suggests a positive health economics effect of the drug. In the Long-Term Care Insurance (LTCI) system in Japan, nursing home residency costs about 100,000 Yen/month, whereas donepezil treatment costs 500 Yen/day, i.e., 15,000 Yen/month. Thus, use of donepezil at home can significantly reduce the cost of management of patients with AD.