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Original Research Article

Modifiable Factors Associated with Cognitive Impairment in 1,143 Japanese Outpatients: The Project in Sado for Total Health (PROST)

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Key Words

Aged · Body mass index · Cognition · Cross-sectional study · Dementia · Mini-Mental State Examination · Epidemiology

Abstract

Background/Aims: Evidence on modifiable factors associated with cognitive impairment in Japanese patients is scarce. This study aimed to determine modifiable factors for cognitive impairment in a Japanese hospital-based population. ***Methods:*** Subjects of this cross-sectional study were 1,143 patients of Sado General Hospital (Niigata, Japan) registered in the Project in Sado for Total Health (PROST) between June 2008 and September 2014. We assessed disease history, body mass index (BMI), leisure time physical activity, walking time, smoking and drinking habits, and consumption of vegetables, fruits, and green tea as predictors, with cognitive impairment defined by the Mini-Mental State Examination (score <24) as an outcome. Multiple logistic regression analysis was performed to calculate odds ratios (ORs) for cognitive impairment. ***Results:*** The mean subject age was 68.9 years, and the prevalence of cognitive impairment was 21.5%. Multivariate analysis revealed that age ($p < 0.001$), low BMI (<21.1; OR 1.39, 95% CI 1.12–1.72), a history of stroke ($p = 0.003$), a history of myocardial infarction ($p = 0.038$), low fruit consumption (p for trend = 0.012), and low green tea consumption (p for trend = 0.032) were independently associated with a higher prevalence of cognitive impair-

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ment. ***Conclusions:*** Modifiable factors, such as low BMI, low fruit consumption, and low green tea consumption, are associated with cognitive impairment. Longitudinal studies will be needed to confirm these findings.

Introduction

Growing numbers of dementia patients have become an important public health issue worldwide. Currently, approximately 36 million people are affected by dementia globally, and the number is projected to triple by 2050 [1]. An increasing number of dementia patients also represent a major public health burden in Japan, where the elderly population is rapidly growing. The number of dementia patients in Japan was estimated to be 2.8 million in 2010 and is expected to reach 4.7 million in 2025 [2]. Dementia reduces the quality of life of both patients and their families who provide care and causes social and economic loss due to increased medical care costs. As effective treatments for dementia are limited, prevention is a focus of attention.

Modifiable factors associated with cognition and dementia should be determined in view of dementia prevention, and in this context, a number of epidemiological studies have been conducted [3]. A review by Beydoun et al. [3] found lower educational attainment and decreased physical activity to be major predictors, but further studies will be needed to identify other potential modifiable factors in various ethnic groups. Epidemiological studies conducted in Japan have been scarce, with only a few articles mentioned in recent reviews [3, 4], although some studies targeting Japanese populations have recently been published [5, 6].

Cognitive impairment appears in the early or intermediate stage of dementia and is thus targeted in the prevention of this disorder. It is also a meaningful outcome in epidemiological studies, given that cognitive impairment in early stages of dementia is not only a high risk factor for dementia but also an important risk factor for frailty [7], which potentially leads to increased care costs [8]. Against this backdrop, this study aimed to determine modifiable factors for cognitive impairment in a Japanese hospital-based population that underwent a cognitive function examination.

Subjects and Methods

Subjects

The subjects of the present cross-sectional study were those registered in the patient registry of Sado General Hospital in Sado City, Sado Island, Japan (population of 64,310 as of October 1, 2008; working populations of 24% for primary, 21% for secondary, and 54% for tertiary industries, and per capita income of 2.0 million JPY [9]), during the period between June 2008 and September 2014. Sado Island is located 30 km off the coast of Niigata City (population of approximately 800,000; working populations of 5% for primary, 23% for secondary, and 72% for tertiary industries, and per capita income of 2.8 million JPY [9]), the capital of Niigata Prefecture, in mainland Japan. This registry, referred to as the Project in Sado for Total Health (PROST), was initiated in June 2008 in conjunction with the Center for Inter-Organ Communication Research, Niigata University Graduate School of Medical and Dental Sciences, and included all outpatients aged 20 years and older. Details regarding PROST have been described elsewhere [10]. Upon registration, cognitive function and blood pressure were examined, and demographic and lifestyle information was collected. For the present study, the inclusion criterion was patients aged 40 years or older, excluding those

undergoing kidney dialysis, which is considered an independent predictor of cognitive impairment [11]. As of September 11, 2014, a total of 2,161 patients were registered, of whom 1,240 underwent a cognitive function examination. Of these, 97 undergoing dialysis were excluded, and the remaining 1,143 patients were considered the subjects of this study.

Measurements

Cognitive function was assessed using the Mini-Mental State Examination (MMSE) [12], a brief, validated instrument commonly used to screen for dementia. MMSE scores range from 0 to 30, with lower scores indicating greater cognitive impairment. The area under the receiver operating characteristic curve of MMSE for DSM-III-R-diagnosed dementia in a Japanese population was reported to be as high as 0.980 [13]. Cognitive impairment was defined as an MMSE score of <24 (i.e. MMSE cutoff score of 23/24) [13, 14].

Systolic and diastolic blood pressures were measured twice using an automatic sphygmomanometer after an at least 5-min rest. Body weight and height were measured with a digital scale. Height was estimated as twice the value of the arm span [15] for patients whose height was not measured using the scale. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Information on sex, age, disease history, physical activity, smoking and drinking habits, and frequency of vegetable, fruit, and green tea consumption was obtained using a questionnaire. The current history of hypertension and diabetes and the past history of stroke and heart disease were taken. Walking time was indicated as none, 1–29, 30–59, or ≥60 min/day and leisure time physical activity (exercise, brisk walk, etc.) as none, 1–2, 3–4, or ≥5 times/week. For smoking habit, patients were classified as nonsmoker, past smoker, and current smoker and for alcohol intake as nondrinker, chance drinker, and drinker (at least once a week). The frequency of vegetable, fruit, and green tea consumption was each estimated according to subject responses and classified as none, 1–2, 3–6 times/week, or every day for vegetables and fruits, and none, 1–6 times/week, or every day for green tea.

Statistical Analysis

Normality was assessed for continuous variables. The Student t test or the Mann-Whitney U test was used to analyze differences in continuous variables by sex. Simple and multiple logistic regression analyses were performed to calculate odds ratios (ORs) of predictor variables for cognitive impairment (MMSE score <24). Continuous variables were divided into quintiles for OR comparisons, and p for trend was calculated by logistic regression analysis. SAS statistical package (release 9.4, Cary, N.C., USA) was used for all statistical analyses. A p value <0.05 was considered statistically significant.

Statement of Ethics

Written informed consent was obtained from all subjects. The protocol of PROST was approved by the Ethics Committee of Niigata University School of Medicine.

Results

The mean subject age was 68.9 years, and the prevalence of cognitive impairment was 21.5%. Subject characteristics by sex are shown in table 1. There were significant differences in age, height, weight, and BMI, but not in MMSE score, by sex.

Sex- and age-adjusted ORs for cognitive impairment according to levels of predictor variables are shown in table 2. Age was a strong predictor of cognitive impairment. Histories of stroke and myocardial infarction, shorter walking time, less drinking, and lower fruit and

Table 1. Subject characteristics (n = 1,143)

Characteristics	Men		Women		p value[a]
	mean ± SD	n	mean ± SD	n	
Age, years	68.0±10.7	633	70.0±10.3	510	0.002
Body height, cm	164.3±7.3	631	150.6±6.6	503	<0.001
Body weight, kg	66.2±12.0	631	54.5±11.1	501	<0.001
BMI	24.4±3.4	631	23.9±4.4	501	0.037
MMSE score	27[b]	633	27[b]	510	0.314[c]

Data are presented as mean ± SD except for MMSE score. [a] The Student t test was used for MMSE score. [b] Median. [c] Mann-Whitney U test.

green tea consumption were associated with cognitive impairment. Although BMI was not significantly associated with cognitive impairment (p for trend = 0.059), the lowest quintile group had a significantly higher OR relative to the reference group (3rd quintile).

To determine independent factors associated with cognitive impairment, multiple logistic regression analysis was performed for candidate predictor variables with statistical significance (table 2), including BMI, histories of stroke and myocardial infarction, walking time, drinking habit, fruit consumption, and green tea consumption. Since the association between BMI quintiles and cognitive impairment was U-shaped (table 2), the analysis was performed with BMI as a discrete variable: 1 = BMI 23.2–24.6 (3rd quintile); 2 = BMI 21.1–23.1 (2nd quintile) and BMI 24.7–26.7 (4th quintile), and 3 = BMI <21.1 (1st quintile) and BMI ≥26.8 (5th quintile). Age, BMI (discrete), histories of stroke and myocardial infarction, and consumption of fruit and green tea were found to be independent predictors of cognitive impairment (table 3). The prevalence of cognitive impairment was much higher in the ≥80-year-old age group (45.7%) than in the other groups, and thus, we conducted a subgroup analysis in the <80- and ≥80-year-old age groups (n = 970 and n = 173, respectively). Age (OR 1.08, 95% CI 0.96–1.21, p < 0.001), history of stroke (OR 1.93, 95% CI 1.19–3.13, p = 0.007), and fruit consumption (OR 0.86, 95% CI 0.68–0.97, p = 0.022) were significant predictors in the <80-year-old age group.

Discussion

The present study showed that age, BMI, self-reported history of cerebrovascular and cardiovascular diseases, and consumption of fruits and green tea were independently associated with the prevalence of cognitive impairment as assessed by the MMSE.

In this study, a low BMI was significantly associated with a high prevalence of cognitive impairment. The association between BMI and cognitive impairment has been somewhat contradictory in the literature. A systematic review by Gorospe and Dave [16] found a high BMI to be a risk factor for dementia. Being overweight, a characteristic feature of metabolic syndrome, is associated with insulin resistance and hypertension, both of which are risk factors for cognitive impairment and dementia [17]. Recent reports suggest that the relationship between BMI and cognition is dependent on age (e.g. midlife vs. late life) [18, 19]. Most epidemiological studies [19] have found obesity in midlife to be a risk factor for the development of dementia, whereas a high BMI in late life is a protective factor [19]. According to our data stratified by age groups (table 4), the lowest-BMI group in the older-age group (≥70 years of age) is at high risk of developing cognitive impairment (adjusted OR 2.19), which is in line with the results of previous studies targeting older individuals [19].

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Table 2. ORs for cognitive impairment (MMSE score <24) according to levels of predictor variables (n = 1,143)

Predictor variables	Subjects, n	Cognitive impairment, n (prevalence, %)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Sex			p = 0.858	p = 0.359
Women	510	111 (21.8)	1 (ref.)	1 (ref.)
Men	633	135 (21.3)	0.97 (0.73–1.29)	1.15 (0.85–1.56)
Age			p for trend <0.001	p for trend <0.001
<60 years	210	10 (4.8)	1 (ref.)	1 (ref.)
60–69 years	319	39 (12.2)	2.79 (1.36–5.71)	2.83 (1.38–5.82)
70–79 years	441	118 (26.8)	7.31 (3.74–14.27)	7.31 (3.74–14.27)
≥80 years	173	79 (45.7)	16.81 (8.33–33.91)	16.63 (8.22–33.61)
BMI			p for trend = 0.734	p for trend = 0.059
1st quintile (<21.1)	227	68 (30.0)	1.71 (1.11–2.64)	1.75 (1.09–2.81)
2nd quintile (21.1–23.1)	226	45 (19.9)	1.06 (0.67–1.70)	1.16 (0.72–1.89)
3rd quintile (23.2–24.6)	227	43 (18.9)	1 (ref.)	1 (ref.)
4th quintile (24.7–26.7)	227	43 (18.9)	1.00 (0.63–1.60)	1.25 (0.76–2.06)
5th quintile (≥26.8)	225	47 (20.9)	1.13 (0.71–1.79)	1.50 (0.92–2.45)
	11 missing values			
Self-reported history of hypertension			p for trend = 0.686	p for trend = 0.065
No	433	96 (22.2)	1 (ref.)	1 (ref.)
Yes	709	150 (21.2)	0.94 (0.71–1.26)	0.75 (0.55–1.02)
	1 missing value			
Self-reported history of diabetes			p for trend = 0.078	p for trend = 0.771
No	816	187 (22.9)	1 (ref.)	1 (ref.)
Yes	325	59 (18.2)	0.75 (0.54–1.03)	0.95 (0.67–1.35)
	2 missing values			
Self-reported history of stroke			p < 0.001	p = 0.005
No	992	195 (19.7)	1 (ref.)	1 (ref.)
Yes	149	51 (34.2)	2.13 (1.47–3.09)	1.80 (1.20–2.71)
	2 missing values			
Self-reported history of myocardial infarction			p = 0.002	p = 0.032
No	1,089	225 (20.7)	1 (ref.)	1 (ref.)
Yes	53	21 (39.6)	2.52 (1.43–4.45)	1.97 (1.06–3.66)
	1 missing value			
Systolic blood pressure			p for trend = 0.840	p for trend = 0.362
1st quintile (<117 mm Hg)	207	50 (24.2)	1 (ref.)	1 (ref.)
2nd quintile (117–127 mm Hg)	236	52 (22.0)	0.93 (0.60–1.44)	0.96 (0.59–1.54)
3rd quintile (128–139 mm Hg)	235	42 (17.9)	0.72 (0.45–1.13)	0.70 (0.43–1.15)
4th quintile (140–150 mm Hg)	223	50 (22.4)	0.95 (0.61–1.48)	0.92 (0.57–1.48)
5th quintile (≥151 mm Hg)	230	51 (22.2)	0.94 (0.60–1.46)	0.79 (0.49–1.27)
	12 missing values			
Diastolic blood pressure			p for trend = 0.011	p for trend = 0.755
1st quintile (<63 mm Hg)	205	59 (28.8)	1 (ref.)	1 (ref.)
2nd quintile (63–69 mm Hg)	236	50 (21.2)	0.70 (0.46–1.08)	0.89 (0.55–1.42)
3rd quintile (70–76 mm Hg)	234	54 (23.1)	0.79 (0.51–1.20)	1.11 (0.70–1.77)
4th quintile (77–84 mm Hg)	224	40 (17.9)	0.57 (0.36–0.90)	0.84 (0.51–1.39)
5th quintile (≥85 mm Hg)	232	42 (18.1)	0.58 (0.37–0.91)	1.03 (0.61–1.74)
	12 missing values			
Leisure-time physical activity			p for trend = 0.478	p for trend = 0.500
None	680	156 (22.9)	1.03 (0.71–1.49)	1.04 (0.70–1.53)
1–2 times/week	123	20 (16.3)	0.67 (0.38–1.20)	0.72 (0.39–1.33)
3–4 times/week	73	10 (13.7)	0.55 (0.26–1.15)	0.54 (0.25–1.18)
≥5 times/week	214	48 (22.4)	1 (ref.)	1 (ref.)
	53 missing values			

Table 2 (continued)

Predictor variables	Subjects, n	Cognitive impairment, n (prevalence, %)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Walking time			p for trend = 0.009	p for trend = 0.052
0 min/week	37	15 (40.5)	2.75 (1.39–5.42)	2.41 (1.13–5.14)
1–29 min/week	149	36 (24.2)	1.28 (0.85–1.94)	1.23 (0.79–1.92)
30–59 min/week	135	30 (22.2)	1.15 (0.74–1.79)	1.06 (0.66–1.69)
≥60 min/week	769	153 (19.9)	1 (ref.)	1 (ref.)
	53 missing values			
Smoking			p = 0.247	p = 0.098
Nonsmoker	616	135 (21.9)	1 (ref.)	1 (ref.)
Past smoker	377	88 (23.3)	1.09 (0.80–1.47)	1.40 (0.90–2.17)
Current smoker	149	23 (15.4)	0.65 (0.40–1.06)	1.68 (0.91–3.09)
	1 missing value			
Alcohol intake			p < 0.001	p = 0.024
Nondrinker	471	129 (27.4)	1 (ref.)	1 (ref.)
Chance drinker	304	61 (20.1)	0.67 (0.47–0.94)	0.73 (0.50–1.09)
Drinker at least once/week	367	56 (15.3)	0.48 (0.34–0.68)	0.66 (0.42–1.02)
	1 missing value			
Vegetable consumption			p for trend = 0.100	p for trend =0. 616
None	18	2 (11.1)	0.44 (0.10–1.91)	0.76 (0.16–3.66)
1–2 times/week	39	7 (18.0)	0.76 (0.33–1.75)	1.54 (0.62–3.83)
3–6 times/week	52	7 (13.5)	0.54 (0.24–1.22)	1.26 (0.52–30.5)
Every day	1,033	230 (22.3)	1 (ref.)	1 (ref.)
	1 missing value			
Fruit consumption			p for trend = 0.757	p for trend = 0.001
None	120	29 (24.2)	1.10 (0.70–1.75)	2.24 (1.31–3.81)
1–2 times/week	207	48 (23.2)	1.04 (0.72–1.52)	1.59 (1.04–2.43)
3–6 times/week	231	38 (16.5)	0.68 (0.46–1.01)	0.86 (0.56–1.32)
Every day	584	131 (22.4)	1 (ref.)	1 (ref.)
	1 missing value			
Green tea consumption			p for trend = 0.034	p for trend = 0.007
None	539	133 (24.7)	1 (ref.)	1 (ref.)
1–6 times/week	134	21 (15.7)	0.57 (0.34–0.94)	0.72 (0.42–1.24)
Every day	467	90 (19.3)	0.73 (0.54–0.99)	0.65 (0.47–0.89)
	3 missing values			

[a] Adjusted for age and sex (except for the variables sex and age); sex was adjusted for age, and age was adjusted for sex.

According to a meta-analysis by Anstey et al. [18], a U-shaped relationship was found between midlife BMI and later risk of dementia, i.e. both underweight and overweight individuals are at risk. Moreover, a recent large cohort study showed that underweight individuals are at an increased risk of dementia in all age groups [20]. Our findings are consistent with these reports in that the observed association was nearly U-shaped, although risk in the 5th quintile of BMI was marginal. Taken together, a low BMI appears to be a risk factor for cognitive impairment.

It remains unclear why a lower BMI is associated with a higher prevalence of cognitive impairment, but this could be related to low levels of dementia-related molecules, such as leptin and adiponectin, which are protective of cognitive function [19]. Moreover, a lower BMI is associated with in vivo biomarkers of cerebral amyloid and tau, suggesting that neuropathologic changes may occur in areas including the hypothalamus that play regulatory roles in energy metabolism and food intake [21]. It should be noted, however, that there may be a

Table 3. Results of multiple logistic regression analysis with cognitive impairment (MMSE score <24) as an outcome (n = 1,143)

Predictor variables[a]	Adjusted OR (95% CI)	p value
Age (years)	1.11 (1.08–1.13)	<0.001
Body mass index[b]	1.39 (1.12–1.72)	0.003
History of stroke (0 = absent; 1 = present)	1.88 (1.24–2.85)	0.003
History of myocardial infarction (0 = absent; 1 = present)	1.95 (1.04–3.66)	0.038
Walking time (0 = none; 1 = 1–29; 2 = 30–59; 4 = ≥60 min/week)	0.87 (0.73–1.04)	0.132
Alcohol intake (0 = nondrinker; 1 = chance drinker; 3 = drinker)	0.86 (0.70–1.04)	0.119
Fruit consumption (0 = none; 1 = 1–2; 2 = 3–6; 3 = 7 times/week)	0.82 (0.70–0.96)	0.012
Green tea consumption (0 = none; 1 = 1–6; 2 = 7 times/week)	0.83 (0.70–0.98)	0.032

[a] All variables are included in the multivariate model. [b] BMI is categorized as 1 = 23.2–24.6 (3rd quintile); 2 = 21.1–23.1 (2nd quintile) and 24.7–26.7 (4th quintile), and 3 = <21.1 (1st quintile) and ≥26.8 (5th quintile) given the U-shaped association between BMI and cognitive impairment as shown in table 2.

Table 4. ORs for cognitive impairment (MMSE score <24) according to levels of BMI stratified by age groups

Predictor variables	Subjects, n	Cognitive impairment, n (prevalence, %)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
BMI; ≤69 years of age (n = 523)				
<21.1	90	8 (8.9)	0.71 (0.27–1.89)	0.76 (0.30–2.09)
21.1–23.1	105	9 (8.6)	0.73 (0.28–1.89)	0.70 (0.27–1.83)
23.2–24.6	88	10 (11.4)	1 (ref.)	1 (ref.)
24.7–26.7	114	8 (7.0)	0.59 (0.22–1.56)	0.61 (0.23–1.64)
≥26.8	126	14 (11.1)	0.98 (0.41–2.31)	1.06 (0.44–2.55)
BMI; ≥70 years of age (n = 609)				
<21.1	137	60 (43.8)	2.35 (1.41–3.93)	2.19 (1.27–3.78)
21.1–23.1	121	36 (29.8)	1.36 (0.78–2.36)	1.36 (0.77–2.41)
23.2–24.6	139	33 (23.7)	1 (ref.)	1 (ref.)
24.7–26.7	113	35 (31.0)	1.44 (0.83–2.52)	1.61 (0.90–2.88)
≥26.8	99	33 (33.3)	1.62 (0.91–2.85)	1.67 (0.93–3.02)

[a] Adjusted for age and sex.

reverse causal relationship, i.e. changes in eating habits of patients with cognitive impairment (e.g. appetite loss) might have led to a low BMI.

In the present study, lower fruit consumption was associated with a higher prevalence of cognitive impairment. Although limited epidemiological evidence exists regarding fruit consumption [22, 23], associations between greater fruit and vegetable intake and better cognitive performance have been suggested [24, 25]. High levels of antioxidants and/or macronutrients from fruits and vegetables reportedly have favorable effects on cognitive function [22]. However, the present study did not detect an association between vegetable consumption and the prevalence of cognitive impairment. This may be due to subjects' responses to the question of vegetable consumption being clustered in the 'every day' group.

Green tea consumption was also a protective factor against cognitive impairment. Consistent with this, previous cross-sectional [26] and longitudinal [6] studies also reported

that consumption of green tea, but not black tea or coffee, protects against cognitive impairment, suggesting that the effects of green tea consumption may be independent of caffeine intake, which is a possible factor for improved cognitive function [3]. Since green tea is widely consumed in Japan, further studies to accumulate evidence are warranted.

In agreement with our study, recent review articles showed with sufficient evidence that cognitively stimulating activities, including physical and social activities, are modifiable protective factors [3, 27], and that moderate alcohol consumption may also be protective against cognitive impairment [27]. However, conflicting results have been reported on the putative protective role of healthy dietary habits and other lifestyle factors [3, 27]. Further well-designed longitudinal studies are needed, especially in Asian populations.

As described in the Subjects section, Sado is considered rural in comparison to urban cities such as Niigata City in Japan. The rural aspect of the study location is also characterized by the fact that Sado Island is within uneasy access of mainland Japan. Although the way of living is not different from that on the mainland, findings of the present study may not be generalizable to urban populations.

This study has several limitations. First, our subjects were outpatients of a general hospital and may not represent the general population of the same age group. In addition, outpatients have various health problems, which may have confounded predictor-outcome associations in this study. Second, we did not assess subject education level, an important factor associated with cognitive impairment [3]. This may also have confounded the observed associations. Third, self-reported variables are prone to misclassification bias due, in part, to errors of recall. Finally, our study used a cross-sectional design that does not necessarily imply causal relationships and did not assess all modifiable factors associated with cognitive impairment. Further studies will be needed to confirm our results.

In conclusion, the present study demonstrated that some modifiable factors, such as low BMI, low fruit consumption, and low green tea consumption, as well as a history of vascular disease, are associated with a high prevalence of cognitive impairment in a Japanese population. Longitudinal studies should be performed to confirm these findings.

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Disclosure Statement

The authors report no conflicts of interest.

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