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Associations among smoking, sleep quality, and decline in Mini-Mental State Examination scores based on health check-up data in Japan: a case-control study

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ABSTRACT

The number of individuals with age-related mild cognitive impairment and subsequent dementia has inevitably increased with the rise in population aging. It is important to maintain cognitive function or decelerate declines in cognitive function. However, the evidence on lifestyle-based factors associated with this decline is lacking. Here, we investigated modifiable lifestyle-based factors associated with chronological cognitive decline in cognitively healthy adults aged ≥60 years (Mini-Mental State Examination [MMSE] score ≥27). This case-control study enrolled 363 participants who were divided into two groups based on annual declines in MMSE score: 40 cases with an MMSE score decline of ≥0.5 points/year and 323 controls with maintained MMSE scores. Smoking, lower social functioning scores on the 36-Item Short Form Health Survey version 2, higher Pittsburgh Sleep Quality Index (PSQI) global scores, and sleep disorders were significantly associated with a decline in MMSE scores. Multivariate logistic regression analysis revealed higher age, current smoking status, and either higher PSQI global scores or sleep disorders to be independently associated with MMSE score decline. In conclusion, the present study identified aging, smoking, and sleep quality as factors associated with a greater decline in MMSE scores in cognitively healthy individuals. Our findings highlight the potential importance of lifestyle factors in preventing cognitive decline.

Keywords: cognitive decline, Mini-Mental State Examination, Pittsburgh Sleep Quality Index, sleep, smoking

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Abbreviations:
CI: confidence interval
MCI: mild cognitive impairment
MMSE: Mini-Mental State Examination
OR: odds ratio
PSQI: Pittsburgh Sleep Quality Index
SF: social functioning
SF-36: 36-Item Short Form Health Survey version 2

INTRODUCTION

Cognitive dysfunction, such as dementia, is common among older individuals worldwide and is a major public health concern.[1] Although some dementias are treatable, such as dementia caused by chronic subdural hematoma, almost all cognitive decline results from age-related irreversible neurodegeneration or cerebrovascular lesions. Indeed, the ever-increasing number of people with dementia associated with the global aging of the population has attracted public health attention.[2] Between 1999 and 2014, the estimated prevalence of dementia among individuals aged ≥65 years increased from 681.9 to 2,029.5 per 100,000 population, respectively.[3,4] By 2050, individuals aged ≥60 years are predicted to account for 35% of the European population, 28% of the North American population, and 24% of the Asian population.[5] In Japan, considering its hyper-aged society, individuals aged ≥60 years have been predicted to account for 42% of the total population by 2050.[5] Given this evidence on continued global population aging, the prevalence of age-dependent dementia is expected to increase in the future.

Mild cognitive impairment (MCI) is defined as an intermediate prodromal condition that progresses from normal cognitive function to dementia.[6] Individuals with MCI more closely resemble patients with Alzheimer's disease than healthy individuals in terms of memory. The rate at which patients with MCI develop dementia per year (approximately 12%) is significantly higher, than that at which healthy individuals develop MCI or dementia per year (1–2%).[7] In addition, a meta-analysis of 41 cohort studies supported the difference in the conversion rate to dementia between healthy and MCI individuals.[8] In other words, prevention of MCI would contribute significantly to reducing the incidence of dementia. Patients with MCI are mostly asymptomatic, and the diagnosis of MCI mainly depends on volunteer screening tests, such as the Mini-Mental State Examination (MMSE). For this reason, the factors associated with the development of MCI should be investigated in detail.

Preventive medicine is highly important in terms of individual quality of life and health economic aspects. Prevention against dementia is especially important because it requires social support, and effective pharmacological treatments that dramatically improve MCI or dementia are lacking to date. Currently, abundant evidence has identified risk factors for cognitive decline and the development of dementia, including dietary patterns,[9] excessive alcohol consumption,[10] and sleep problems.[11] However, to date, few studies have focused on the risk factors for the conversion from normal cognitive function to the onset of MCI.

Therefore, we conducted a case-control study to explore modifiable lifestyle factors associated with cognitive function decline in individuals with normal cognitive function.

MATERIALS AND METHODS

Study subjects and design

This case-control study was performed as a part of an ongoing observational study to explore factors associated with cognitive dysfunction. In the original study, residents living in the Iwaki District in Aomori Prefecture were invited to the Iwaki Health Promotion Project annually since 2005.[12,13] Approximately 1,000 subjects attended health check-ups annually. Since the final goal was to extend life expectancy, we measured a comprehensive range of items (approximately 2,000 items in total), including invasive and noninvasive clinical laboratory parameters, body composition parameters, lifestyle, medications, exercise capacity, and cognitive ability, including the MMSE (since 2008). Subjects who underwent a health check-up between 2008 and 2015 and met the definition of a case or control were included. From 2008 to 2015, 2,373 individuals participated in a health check-up at least once. The mean number of times each subject participated in health check-ups was 3.29.

Ethical statement

The study protocol adhered to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of the Hirosaki University School of Medicine (2021-166), Human Genome and Gene Analysis Research Ethics Committee of Nagoya University (2016-0137), and Ethics Committee of Tokyo Medical and Dental University (M2020-186). All subjects provided written informed consent.

Definitions of cases and controls

The case and control groups were defined post hoc based on our dataset. Figure 1 shows the selection process of the study subjects. First, participants <60 years of age were excluded from this observation because the clinical characteristics of younger patients with dementia and individuals with age-dependent cognitive decline are different[14,15] Second, we defined baseline as the time of the first health check-up for each subject. To exclude subjects with MCI at baseline, we excluded those with an initial MMSE score of <27.[16] To consider the learning effect of repeated MMSE administration, only subjects who completed the MMSE at least three times were included (all subjects were followed for at least 2 years). Furthermore, 33 subjects with ≥1 missing value for lifestyle factors were excluded. Finally, 363 subjects (male: 119; female: 244) were included in the study.

For the remaining 363 subjects, we evaluated the chronological change in MMSE scores as a risk marker for cognitive decline during the observation periods for each subject. The change in MMSE scores was calculated based on the following formula: (baseline MMSE score – last MMSE score)/observation period (point/year). Based on this change, each subject was classified into either the case or control group. Generally, MMSE scores for individuals with normal cognitive function fluctuate only negligibly,[7] and their gradient steepens with increasing risk of cognitive decline by aging. The average slopes of annual decline in MMSE scores at ages 41 years and 84 years were −0.04 points/year (95% confidence interval [CI]: −0.05, −0.03) and −0.53 points/year (95% CI: −0.55, −0.50), respectively.[17] In this study, a decrease in the MMSE score of ≥0.5 points/year was set as the cutoff value for classifying cognitive decline. As such, subjects whose MMSE scores declined by at least 0.5 points/year from baseline were added to the case group, while those who did not meet this criterion were assigned to the control group. Finally, 40 and 323 individuals were classified as cases and controls, respectively.

For sensitivity analysis, we performed an analysis using age- and sex-matched data. Case and control subjects were matched individually according to their sex and age; a total of 37 cases and 37 control subjects were included in the analysis.

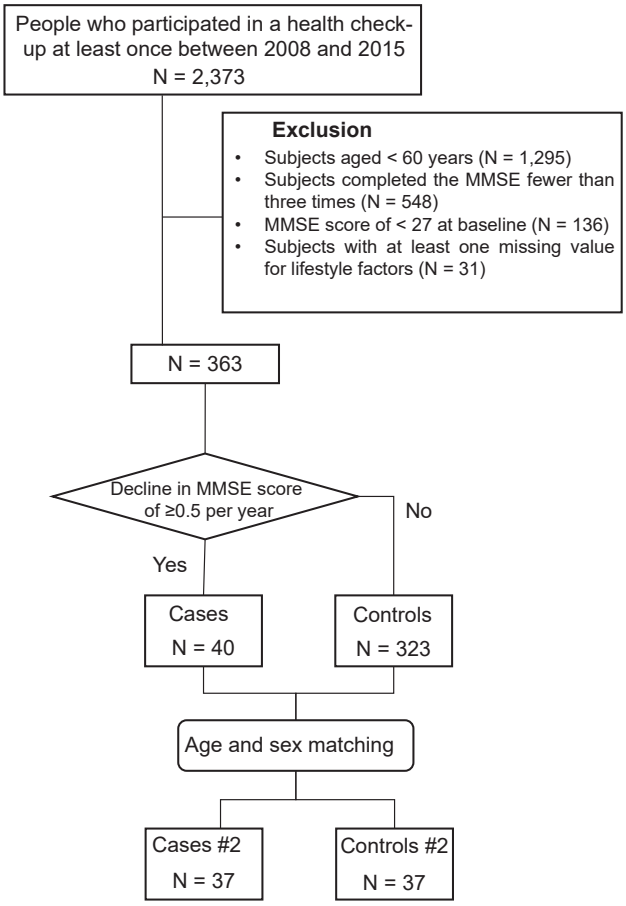

Fig. 1 Participant flowchart
MMSE: Mini-Mental State Examination

Administration of the MMSE

The subjects' global cognitive status was evaluated using the MMSE. This test assesses orientation to place and time, short-term memory, episodic long-term memory, subtraction, sentence construction ability, and oral language ability.[18] The maximum score was 30. The cutoff point for MCI has been generally set to 27.[16] We used the Japanese version of the MMSE, which has been confirmed to be reliable and valid.[19]

Measurement of anthropometric variables and lifestyle factors

All data were obtained from the Iwaki Health Promotion Project. We obtained data on height and weight, which were used to calculate the body mass index. Lifestyle factors, such as smoking status, alcohol consumption, exercise habits, family structure, health-related quality of life, and sleep were included among the items annually assessed between 2008 and 2015. Data on smoking status, alcohol consumption, exercise habits, number of family members living together, and marital status were obtained through self-report questionnaires.

Smoking status was assessed using this question: "Please select the following options regarding

your current smoking status"; the subjects had three choices: current, ever, and never/chance. Regarding alcohol consumption, the question was "Please select from the following options regarding your drinking status throughout the year"; the subjects had three choices: current, ever, and nothing (including several times a month at banquets). Based on this response, the subjects were classified into three categories: current, ever, and never/chance. The subjects were asked about exercise habits in a five-choice format with the questions "Do you exercise or play sports regularly outside?" and "Do you exercise or play sports regularly outside even in winter?" The subjects selected from the following five categories: rarely, once per week, two to three times per week, four to five times per week, or almost every day. The subjects who answered "rarely" were classified as having no exercise habit, whereas the remaining subjects were classified as having an exercise habit.

Measurement of health-related quality of life

Health-related quality of life was assessed using the 36-Item Short Form Health Survey version 2 (SF-36). The SF-36, a self-administered questionnaire used to measure health-related quality of life, comprises 36 items and 8 subscales.[20] We used the Japanese version of the SF-36.[21,22] The score for each subscale is obtained by calculating the mean score for all items in the specific subscale. Each scale is represented by a score ranging from 0 to 100, with a higher score indicating a higher health-related quality of life. The physical subscales include physical functioning, role limitations attributable to physical problems, body pain, and general health. The mental subscales include vitality, social functioning (SF), role limitations attributable to emotional problems, and mental health.

Administration of the Pittsburgh Sleep Quality Index

The subjects were assessed using the Pittsburgh Sleep Quality Index (PSQI), a self-report measuring subjective sleep quality over the past 4 weeks that consists of 18 questions.[23] The 18 items of the PSQI consist of 7 components, namely, sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication, and daytime dysfunction, with scores ranging from 0 to 3, which are summed to yield a global score. The higher the score, the worse the quality of sleep. Sleep disorder was defined by a PSQI global score of ≥6. Furthermore, scores for each of the seven PSQI components were calculated. We used the Japanese version of the PSQI.[24]

Statistical analyses

The distributions of continuous and categorical variables at baseline were compared between the case and control groups using Student's *t*-test and Fisher's exact test, respectively.

We defined a decline in the MMSE score as a reduction of at least 0.5 points per year in the MMSE score from baseline to the last visit. We performed univariate logistic regression analysis to assess the association between a decline in the MMSE score and other baseline variables. Continuous variables included age, body mass index, number of family members, SF-36 scores, PSQI global score, and those subscores at baseline. Binary variables included biological sex, the presence of routine smoking habits, routine alcohol habits, exercise habits, exercise habits in winter, having a spouse, and sleep disorders at baseline. We also performed multivariate logistic regression analysis with adjustment for age and sex as typical demographics to assess the association among the decline in the MMSE scores and each of these variables at baseline. Pearson's correlation coefficient was calculated to assess the correlation between SF-36 and PSQI global scores.

Regarding sensitivity analysis, we performed a conditional logistic regression analysis to compare the age- and sex-matched datasets.

All statistical analyses were performed using R version 4.0 (http://www.r-project.org/). A P-value of <0.05 was considered statistically significant. Multiple testing correction was not performed because all hypotheses were considered independently.[25]

RESULTS

Baseline characteristics

Based on the health check-up data from 2008 to 2015, we identified 40 case subjects and 323 control subjects among the 2,373 subjects with at least one check-up during the study period. The baseline characteristics of the study subjects are listed in Table 1. The MMSE scores at baseline were not significantly different between the case and control groups. In the case group, the median MMSE score decline was 0.67 points/year (interquartile [IQR]: 0.50 to 1.00) and 21 (52.5%) subjects were considered to have potential MCI, with an MMSE score of <27, during the observation period. Contrastingly, the median MMSE score decline in the control group was 0 points/year (IQR: −0.14 to 0.14), and only five (1.5%) subjects were considered to have potential MCI during the observation period.

The mean age and PSQI global score values were significantly higher in the case group than in the control group. Subjects with sleep disorders were almost 3 times more likely to show a higher MMSE score decline than those without sleep disorders. As subscales of the PSQI, the mean sleep quality and sleep medication scores significantly differed between the case and control groups.

Table 1 Baseline characteristics of the study subjects

Variable	Control (n = 323)	Case (n = 40)	P value
Age (years)	64.8 ± 5.2	68.3 ± 6.8	<0.001
Male, n (%)	105 (32.5)	14 (35.0)	0.725
MMSE score	29.1 ± 1.0	29.4 ± 0.8	0.111
BMI (kg/m^2)	23.3 ± 2.9	22.9 ± 3.6	0.418
Smoking, n (%)			
Never	257 (79.6)	29 (72.5)	0.163
Current	26 (8.0)	7 (17.5)	
Ever	40 (12.4)	4 (10.0)	
Drinking, n (%)			
Never/Chance	200 (61.9)	26 (65.0)	0.946
Current	113 (35.0)	13 (32.5)	
Ever	10 (3.1)	1 (2.5)	
Exercise habit, n (%)	118 (36.5)	17 (42.5)	0.490
Exercise habit in winter, n (%)	109 (33.7)	18 (45.0)	0.164
Has a spouse, n (%)	247 (76.5)	25 (62.5)	0.080
Number of family members	3.6 ± 1.8	3.4 ± 1.9	0.483
SF-36			
PF	83.3 ± 16.4	83.4 ± 17.6	0.991
RP	89.8 ± 16.5	86.4 ± 20.8	0.237

BP	73.1 ± 21.9	72.4 ± 26.5	0.850
GH	61.6 ± 16.4	61.3 ± 19.7	0.934
VT	68.3 ± 17.6	72.5 ± 19.1	0.161
SF	92.5 ± 14.5	87.5 ± 21.9	0.057
RE	92.3 ± 15.7	89.0 ± 20.0	0.218
MH	78.3 ± 16.7	76.3 ± 19.4	0.480
PSQI global score	2.9 ± 2.2	4.1 ± 3.4	0.004
Components			
Sleep disorder, n (%)	37 (11.5)	12 (30.0)	0.005
1—sleep quality	0.7 ± 0.6	0.9 ± 0.7	0.026
2—sleep latency	0.5 ± 0.8	0.8 ± 0.9	0.032
3—sleep duration	0.7 ± 0.8	0.8 ± 0.9	0.563
4—sleep efficiency	0 ± 0.2	0.1 ± 0.5	0.058
5—sleep disturbances	0.5 ± 0.6	0.6 ± 0.6	0.250
6—sleep medication	0.2 ± 0.6	0.4 ± 1.0	0.023
7—daytime dysfunction	0.3 ± 0.6	0.5 ± 0.7	0.236

Continuous data are presented as the mean ± standard deviation. Differences in characteristics between the case and control groups were evaluated using Student's *t*-test or Fisher's exact test.
BMI: body mass index
BP: bodily pain
GH: general health
MH: mental health
MMSE: Mini-Mental State Examination
PF: physical functioning
PSQI: Pittsburgh Sleep Quality Index
RE: role emotional
RP: role physical
SF: social functioning
SF-36: 36-Item Short Form Health Survey version 2
VT: vitality

Association among lifestyle factors and the decline in MMSE scores

We performed a simple logistic regression analysis to assess the association between a decline in the MMSE score and each baseline variable. Table 2 shows the results of this analysis. Age was most significantly associated with a decline in MMSE scores (odds ratio [OR] 1.11, 95% CI 1.05–1.17, $P < 0.001$). We also found a significant association between the PSQI global score and its subscale scores, such as sleep quality, sleep latency, and sleep medication, and the decline in MMSE scores (Table 2).

Table 2 Results of the logistic regression analysis with the decline in the MMSE score

Variable	Reference	Univariate logistic regression		Multivariate logistic regression	
		OR (95% CI)	P value	OR (95% CI)	P value
Age	–	1.11 (1.05–1.17)	<0.001	–	–
Sex (male)	Female	0.89 (0.45–1.78)	0.752	–	–
BMI	–	0.95 (0.85–1.07)	0.417	0.96 (0.85–1.08)	0.455
Smoking (current)	Never/Ever	2.42 (0.98–6.01)	0.056	3.61 (1.28–10.16)	0.015
Drinking (current)	Never/Chancer/ Ever	0.89 (0.44–1.80)	0.756	0.87 (0.36–2.13)	0.764
Exercise habit (yes)	No	1.28 (0.66–2.50)	0.462	1.30 (0.66–2.57)	0.452
Exercise habit in winter (yes)	No	1.61 (0.83–3.12)	0.162	1.56 (0.79–3.08)	0.200
Has a spouse (yes)	No	1.95 (0.98–3.89)	0.058	1.54 (0.71–3.34)	0.275
Number of family members	–	0.93 (0.77–1.13)	0.483	0.95 (0.79–1.15)	0.623
SF-36					
PF	–	1.00 (0.98–1.02)	0.991	1.01 (0.99–1.04)	0.228
RP	–	0.99 (0.97–1.01)	0.239	0.99 (0.97–1.01)	0.415
BP	–	1.00 (0.98–1.01)	0.850	1.00 (0.99–1.01)	0.996
GH	–	1.00 (0.98–1.02)	0.934	0.99 (0.98–1.01)	0.591
VT	–	1.01 (0.99–1.03)	0.162	1.01 (0.99–1.03)	0.219
SF	–	0.98 (0.97–1.00)	0.063	0.98 (0.96–1.00)	0.048
RE	–	0.99 (0.97–1.01)	0.221	0.99 (0.97–1.01)	0.412
MH	–	0.99 (0.97–1.01)	0.479	0.99 (0.97–1.01)	0.314
PSQI global score	–	1.18 (1.05–1.33)	0.006	1.18 (1.04–1.32)	0.008
Sleep disorder (yes)	No	3.31 (1.55–7.07)	0.002	2.98 (1.35–6.54)	0.007
Components					
1—sleep quality	–	1.78 (1.06–2.98)	0.028	1.97 (1.17–3.32)	0.011

2—sleep latency	–	1.48 (1.03–2.14)	0.035	1.33 (0.91–1.95)	0.135
3—sleep duration	–	1.12 (0.76–1.67)	0.562	1.28 (0.84–1.94)	0.251
4—sleep efficiency	–	2.23 (0.89–5.62)	0.088	1.72 (0.68–4.32)	0.251
5—sleep disturbances	–	1.40 (0.79–2.48)	0.250	1.31 (0.73–2.35)	0.370
6—sleep medication	–	1.48 (1.04–2.12)	0.030	1.44 (1.00–2.08)	0.050
7—daytime dysfunction	–	1.36 (0.82–2.27)	0.238	1.48 (0.88–2.49)	0.141

The odds ratios (ORs), confidence intervals (CIs), and P values were calculated using logistic regression analysis. Multivariate logistic regression was performed with adjustment for age and sex. Abbreviations are explained in the footnote to Table 1.

Next, we performed a multivariate logistic regression analysis with adjustment for age and sex and found that current smoking status was 3.6 times more likely to be associated with a higher MMSE score decline than never- or ever-smoking status (OR 3.61, 95% CI 1.28–10.16, P = 0.015). Regarding the SF-36, a lower SF score was associated with a higher decline in MMSE scores (OR 0.98, 95% CI 0.96–1.00, P = 0.048). A higher PSQI global score was associated with a higher decline in MMSE scores (OR 1.18, 95% CI 1.04–1.32, P = 0.008). Subjects with sleep disorders showed a three-fold higher decline in the MMSE score than that in those without (OR 2.98, 95% CI 1.35–6.54, P = 0.007). Among subscale scores of PSQI, higher scores for sleep quality and sleep medication were associated with a higher decline in MMSE scores.

We performed an additional multivariate logistic regression analysis, including the aforementioned variables, to confirm those independently associated with a significant decline in MMSE scores. Table 3 shows the results of a multivariate logistic regression analysis of age, smoking, the SF score of the SF-36, and the PSQI global score. We found that age, smoking, and the PSQI global score were independently associated with a decline in the MMSE score; however,

Table 3 Multivariate logistic regression analysis of the association between a decline in the MMSE score and age, smoking status, social functioning score on the SF-36, and the PSQI global score

Variable	OR (95% CI)	P value
Age	1.12 (1.06–1.19)	<0.001
Current smoking (vs never/ever smoking)	3.93 (1.48–10.45)	0.006
SF-36 SF	0.99 (0.97–1.00)	0.145
PSQI global score	1.16 (1.03–1.31)	0.018

CI: confidence interval
MMSE: Mini-Mental State Examination
OR: odds ratio
PSQI: Pittsburgh Sleep Quality Index
SF: social functioning
SF-36: 36-Item Short Form Health Survey version 2

Table 4 Multivariate logistic regression analysis of the association between a decline in the MMSE score and age, smoking status, social functioning score on the SF-36, and sleep disorder

Variable	OR (95% CI)	P value
Age	1.12 (1.05–1.18)	<0.001
Current smoking (vs never/ever smoking)	3.79 (1.43–10.06)	0.007
SF-36 SF	0.99 (0.97–1.00)	0.127
Sleep disorder	2.66 (1.18–5.96)	0.018

CI: confidence interval
MMSE: Mini-Mental State Examination
OR: odds ratio
SF: social functioning
SF-36: 36-Item Short Form Health Survey version 2

the SF score showed no such association. Table 4 shows the results of a multivariate logistic regression analysis that included age, smoking, the SF score of SF-36, and sleep disorders. This result also indicated that age, smoking, and sleep disorders, but not the SF score, were independently associated with a decline in the MMSE score. We assessed the correlation between the PSQI global score and SF score and found a significant negative correlation between these variables ($r = -0.262$, $P < 0.001$).

Results of analyses using age- and sex-matched datasets

For the sensitivity analysis, we created age- and sex-matched datasets from the original dataset (Fig. 1). After individual matching (1:1), we obtained 37 cases and 37 control subjects. The baseline characteristics of the matched datasets are listed in Table 5. The age and sex distributions perfectly matched between the case and control groups. The MMSE scores at baseline were not significantly different between the case and control groups. The mean values of the PSQI global scores were significantly higher in the case groups than in the control group. The proportion of subjects with a sleep disorder in the case group was significantly higher than that in the control group.

We performed conditional logistic regression analysis to assess the association between a decline in MMSE scores and each baseline variable using the matched dataset (Table 6). For the SF-36, a lower SF score was associated with a higher decline in the MMSE score (OR 0.95, 95% CI 0.91–1.00, P = 0.034). A higher PSQI global score was associated with a higher decline in the MMSE score (OR 1.40, 95% CI 1.06–1.83, P = 0.017). This assessment could not be performed for smoking status due to the low number of current smokers.

Table 5 Baseline characteristics of the age- and sex-matched dataset

Variable	Control (n = 37)	Case (n = 37)	P value
Age (years)	67.5 ± 6.5	67.5 ± 6.5	1.000
Male, n (%)	11 (29.7)	11 (29.7)	1.000
MMSE score	29.1 ± 1.1	29.5 ± 0.7	0.051
BMI (kg/m^2)	23 ± 2.4	23 ± 3.7	0.938
Smoking, n (%)			
Never	31 (83.8)	28 (75.7)	0.045
Current	1 (2.7)	7 (18.9)	
Ever	5 (13.5)	2 (5.4)	
Drinking, n (%)			
Never/Chance	22 (59.5)	25 (67.6)	0.712
Current	13 (35.1)	11 (29.7)	
Ever	2 (5.4)	1 (2.7)	
Exercise habit, n (%)	9 (24.3)	15 (40.5)	0.214
Exercise habit in winter, n (%)	7 (18.9)	15 (40.5)	0.074
Has a spouse, n (%)	23 (62.2)	22 (59.5)	1.000
Number of family members	3.5 ± 1.7	3.4 ± 1.9	0.697
SF-36			
PF	83 ± 14.4	82.7 ± 18.1	0.944
RP	90.5 ± 14.9	85.3 ± 21.3	0.225
BP	74.4 ± 20.8	71.6 ± 27.2	0.629
GH	63 ± 16	59.8 ± 19.1	0.438
VT	68.8 ± 15.9	70.6 ± 18.6	0.646
SF	95.6 ± 11.5	86.5 ± 22.5	0.031
RE	89.6 ± 17.3	88.1 ± 20.6	0.722
MH	79.5 ± 14.9	75.7 ± 19.5	0.352
PSQI global score	2.5 ± 1.9	4.2 ± 3.5	0.010
Components			
Sleep disorder, n (%)	5 (13.5)	12 (32.4)	0.096
1—sleep quality	0.4 ± 0.6	0.9 ± 0.7	0.001
2—sleep latency	0.4 ± 0.7	0.8 ± 0.9	0.021
3—sleep duration	0.5 ± 0.6	0.8 ± 1.0	0.123
4—sleep efficiency	0.1 ± 0.2	0.1 ± 0.5	0.400
5—sleep disturbances	0.6 ± 0.5	0.6 ± 0.6	0.840
6—sleep medication	0.2 ± 0.7	0.5 ± 1.0	0.187
7—daytime dysfunction	0.3 ± 0.5	0.5 ± 0.7	0.262

Abbreviations are explained in the footnote to Table 1.

Table 6 Results of the conditional logistic regression analysis with the decline in MMSE score using the age- and sex-matched datasets

Variable	Reference	OR (95% CI)	P value
BMI	–	1.01 (0.87–1.16)	0.939
Smoking (current)	Never/ever	NC	NC
Drinking (current)	Never/chance/ever	0.71 (0.23–2.25)	0.566
Exercise habit (yes)	No	2.20 (0.76–6.33)	0.144
Exercise habit in winter (yes)	No	3.00 (0.97–9.30)	0.057
Has a spouse (yes)	No	1.10 (0.47–2.59)	0.827
Number of family members	–	0.96 (0.77–1.20)	0.734
SF-36			
PF	–	1.00 (0.97–1.03)	0.937
RP	–	0.98 (0.95–1.01)	0.197
BP	–	0.99 (0.97–1.02)	0.557
GH	–	0.99 (0.96–1.02)	0.438
VT	–	1.01 (0.98–1.04)	0.608
SF	–	0.95 (0.91–1.00)	0.034
RE	–	0.99 (0.97–1.02)	0.684
MH	–	0.98 (0.95–1.01)	0.295
PSQI global score	–	1.40 (1.06–1.83)	0.017
Sleep disorder (yes)	No	3.33 (0.92–12.11)	0.067
Components			
1—sleep quality	–	2.95 (1.29–6.76)	0.011
2—sleep latency	–	2.63 (1.12–6.19)	0.027
3—sleep duration	–	1.65 (0.88–3.13)	0.121
4—sleep efficiency	–	1.69 (0.45–6.32)	0.434

5—sleep disturbances	–	0.92 (0.42–2.02)	0.842
6—sleep medication	–	1.54 (0.81–2.94)	0.192
7—daytime dysfunction	–	1.66 (0.69–3.97)	0.259

BMI: body mass index
BP: bodily pain
CI: confidence interval
GH: general health
MH: mental health
MMSE: Mini-Mental State Examination
NC: not calculated
OR: odds ratio
PF: physical functioning
PSQI: Pittsburgh Sleep Quality Index
RE: role emotional
RP: role physical
SF: social functioning
SF-36: 36-Item Short Form Health Survey version 2
VT: vitality

DISCUSSION

Identifying modifiable risk factors for pre-MCI stages holds promise for earlier intervention for dementia and MCI. This case-control study used longitudinal health check-up data from Japanese community residents to explore lifestyle-related risk factors that contribute to cognitive decline, as reflected by the MMSE score. Our present results demonstrated that the decline in the MMSE score was independently associated with age, smoking status, the SF score of the SF-36, the PSQI global score, and sleep disorder status. Given that the subjects in this study had normal cognitive function at baseline, our results show that in addition to age, SF scores, and sleep disorders, lifestyle factors with modifiable aspects, such as smoking habits and sleep quality, may also be associated with the maintenance of cognitive function or deceleration of cognitive decline.

Many observational studies have demonstrated the negative effects of smoking on cognitive function. Ohara et al reported that the risk of all-cause dementia was significantly greater in current smokers than in never-smokers (hazard ratio [HR] 2.28, 95% CI 1.49–3.49) in late or mid-life in a Japanese population residing in the southern part of Japan.[10] Kawakami et al reported that higher smoking levels were dose-dependently associated with a higher HR (adjusted P for trend = 0.0105), with the ≥20 cigarettes/day group having a significantly higher adjusted HR (1.80) in middle-aged and older Japanese individuals.[26] A meta-analysis that incorporated 37 studies also supported the results of our study, demonstrating that smoking is associated with the risk of all-cause dementia.[27] In contrast, epidemiological evidence suggests that smoking has a protective effect on cognitive function.[28] Additionally, nicotine could enhance neurotransmission and improve performance on certain cognitive tests.[29] Thus, no clear consensus has yet been reached on the association between smoking habits and cognitive function. In this study, we

confirmed that current smoking was significantly associated with a higher decline in the MMSE score. Our results suggest that smoking habits may accelerate cognitive decline, at least in the very early stages of cognitive decline during the conversion from normal cognitive function to MCI. However, we could not elucidate the detailed mechanism of the association between smoking and cognitive decline, since this was a non-interventional observational study. It is possible that smoking contributes to cerebrovascular disease, which in turn is associated with dementia, although smoking may not directly contribute to the development of the amyloid plaques and tau tangles that characterize Alzheimer's disease.[30] Further research is necessary to investigate whether quitting smoking can prevent cognitive decline.

We found that a higher PSQI global score was associated with a higher decline in the MMSE score. Moreover, subjects with a sleep disorder had a higher decline in the MMSE score than those without. Among the component scores of the PSQI, higher scores in sleep quality and sleep medication were associated with a decline in the MMSE score. Consistently, higher scores for other components were also linked to a higher decline in the MMSE score, although not significantly. Overall poor sleep quality is likely to be associated with cognitive decline. Sleep problems have been reportedly associated with dementia for over 50 years.[31] Ohara et al reported that short sleeping hours (<5.0 h) and long sleeping hours (>10 h) were significantly associated with the incidence rate of dementia (short: HR 2.64, 95% CI 1.38–5.05, long: HR 1.67, 95% CI 1.07–2.60)[32] in an older Japanese population. Nakakubo et al reported that the incidence of cognitive decline differed among groups with varied sleeping hours (short, 15.9%; medium, 11.9%; long, 20.1%; P = 0.001) among 3,151 community-dwelling older Japanese individuals.[33] Recently, a meta-analysis, including 51 eligible cohorts, revealed that 10 different sleep-related exposures, including insomnia, fragmentation, daytime dysfunction, prolonged latency, rapid eye movement sleep behavior disorder, and excessive time in bed, were associated with a higher risk of all-cause cognitive disorders.[11] Poor sleep quality increases brain amyloid β deposition in older adults without evidence of dementia[34] These results support the validity of our findings. Therefore, poor sleep quality is a risk factor for the early stages of cognitive dysfunction, MCI, and dementia.

In this study, a lower SF score was associated with a higher decline in the MMSE score after adjustment for age and sex. The SF score of the SF-36 indicates the degree of social interaction, with a higher score corresponding to having more social interaction. Individuals living alone and those without any close social ties have a high relative risk of developing dementia.[35] These results are consistent with our findings. However, in a multivariate logistic regression analysis that included other significant variables, the association between the SF score and a decline in the MMSE score was no longer significant. This may be attributed to a decrease in the quality of sleep, which in turn decreases quality of life according to the SF score as a significant negative correlation between the SF scores and PSQI scores was confirmed in the correlation analysis. A number of epidemiological studies have reported that insomnia affects all aspects of social functioning,[36-38] and it is also associated with depression and chronic pain.[39,40] Sleep problems may be related to an individual's social quality of life due to multifaceted factors that encompass physical and mental health.

We identified significant differences in age between the case and control groups. Aging is a risk factor for cognitive decline; therefore, we performed the same analysis using both the age- and sex-matched datasets. Sensitivity analyses using small samples adjusted for age and sex also showed that the PSQI global score and SF score of the SF-36 questionnaire were associated with the annual decline in the MMSE score as well as the unadjusted analysis, implying that poor social behavior and sleep quality may be robust predictors of very early cognitive decline. Conversely, smoking status was not confirmed, possibly because matching reduced the sample

size of current smokers.

However, some limitations of the present study should be acknowledged. The study was exploratory in nature, and our findings were not validated in independent cohorts. The sample size for this study was small, especially the number of current smokers in the case group (only 11 subjects with smoking habits). Therefore, future independent multi-center observational studies are warranted to validate our findings; in particular, the contribution of smoking to the decline in MMSE scores must be verified by independent studies. The cognitive function assessment in this study was simplified based solely on the MMSE. To strengthen the findings obtained in the present study, future validation studies should also comprehensively use other measures of cognitive decline (eg, amyloid imaging). Furthermore, the study had a case-control design and therefore cannot establish a cause-and-effect relationship between sleep and a slight decline in the MMSE score. Therefore, future studies must evaluate such associations in prospective cohorts. According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, dementia and MCI can be divided into multiple types, according to etiology, such as that associated with Alzheimer's disease, Lewy body dementia, and frontotemporal dementia.[41] In this study, cognitive decline was assessed only using MMSE score decline; hence, further studies are warranted to determine the specific type of dementia associated with the identified factors.

CONCLUSIONS

The current findings among residents living in Japan demonstrated associations between a higher decline in MMSE score and higher age, current smoking status, lower social functioning scores on the SF-36, higher PSQI global scores, or sleep disorders. These variables associated with a decline in the MMSE score include modifiable lifestyle factors, such as smoking habits, social functioning, and sleep disorders, which may be important in preventing cognitive decline.

AUTHORS' CONTRIBUTIONS

MN and AH conceptualized the study. YT and KM curated the data. MN, KY, MF, FK, YK, HS, and AH performed the formal data analysis. MN and AH acquired the funding. YT and KM were responsible for the resources. MN and AH supervised the study. MN and AH wrote the original draft. KY, MF, YO, FK, YK, HS, YT, and KM reviewed and edited the document.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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REFERENCES

1 Zhao C, Noble JM, Marder K, Hartman JS, Gu Y, Scarmeas N. Dietary Patterns, Physical Activity, Sleep, and Risk for Dementia and Cognitive Decline. *Curr Nutr Rep.* 2018;7(4):335–345. doi:10.1007/s13668-018-0247-9
2 World Health Organization. Dementia: A public health priority. Accessed March 8, 2021. https://www.who.int/mental_health/publications/dementia_report_2012/en/
3 Ministry of Health, Labour and Welfare. Patient survey. Accessed March 8, 2021. https://www.mhlw.go.jp/english/database/db-hss/ps.html
4 Koyama T, Sasaki M, Hagiya H, et al. Place of death trends among patients with dementia in Japan: a population-based observational study. *Sci Rep.* 2019;9(1):20235. doi:10.1038/s41598-019-56388-w
5 United Nations Department of Economic and Social Affairs. World Population Ageing. Accessed March 8, 2021. https://www.un.org/en/development/desa/population/theme/ageing/WPA2017.asp
6 Flicker C, Ferris SH, Reisberg B. Mild cognitive impairment in the elderly: predictors of dementia. *Neurology.* 1991;41(7):1006–1009. doi:10.1212/wnl.41.7.1006
7 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol.* 1999;56(3):303–308. doi:10.1001/archneur.56.3.303
8 Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand.* 2009;119(4):252–265. doi:10.1111/j.1600-0447.2008.01326.x
9 Ozawa M, Ninomiya T, Ohara T, et al. Dietary patterns and risk of dementia in an elderly Japanese population: the Hisayama Study. *Am J Clin Nutr.* 2013;97(5):1076–1082. doi:10.3945/ajcn.112.045575
10 Ohara T, Ninomiya T, Hata J, et al. Midlife and Late-Life Smoking and Risk of Dementia in the Community: The Hisayama Study. *J Am Geriatr Soc.* 2015;63(11):2332–2339. doi:10.1111/jgs.13794
11 Xu W, Tan CC, Zou JJ, Cao XP, Tan L. Sleep problems and risk of all-cause cognitive decline or dementia: an updated systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2020;91(3):236–244. doi:10.1136/jnnp-2019-321896
12 Kinoshita F, Yoshida K, Fujitani M, et al. Lifestyle parameters of Japanese agricultural and non-agricultural workers aged 60 years or older and less than 60 years: A cross-sectional observational study. *PLoS One.* 2023;18(10):e0290662. doi:10.1371/journal.pone.0290662
13 Nakaji S, Ihara K, Sawada K, et al. Social innovation for life expectancy extension utilizing a platform-centered system used in the Iwaki health promotion project: A protocol paper. *SAGE Open Med.* 2021;9:20503121211002606. doi:10.1177/20503121211002606
14 Pawlowski M, Johnen A, Duning T. Young onset dementia. Article in German. *Nervenarzt.* 2020;91(10):936–945. doi:10.1007/s00115-020-00967-0
15 Li R, Li R, Xie J, et al. Associations of socioeconomic status and healthy lifestyle with incident early-onset and late-onset dementia: a prospective cohort study. *Lancet Healthy Longev.* 2023;4(12):e693-e702. doi:10.1016/S2666-7568(23)00211-8
16 Kaufer DI, Williams CS, Braaten AJ, Gill K, Zimmerman S, Sloane PD. Cognitive screening for dementia and mild cognitive impairment in assisted living: comparison of 3 tests. *J Am Med Dir Assoc.* 2008;9(8):586–593. doi:10.1016/j.jamda.2008.05.006
17 Nagaratnam JM, Sharmin S, Diker A, Lim WK, Maier AB. Trajectories of Mini-Mental State Examination Scores over the Lifespan in General Populations: A Systematic Review and Meta-Regression Analysis. *Clin Gerontol.* 2022;45(3):467–476. doi:10.1080/07317115.2020.1756021
18 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189–198. doi:10.1016/0022-3956(75)90026-6
19 Mori E, Mitani Y, Yamadori A. Usefulness of a Japanese Version of the Mini-Mental State Test in Neurological Patients. Article in Japanese. *Jpn J Neuropsychol.* 1985;1(2):82–90.
20 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework

and item selection. *Med Care.* 1992;30(6):473–483.
21 Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol.* 1998;51(11):1037–1044. doi:10.1016/s0895-4356(98)00095-x
22 Fukuhara S, Ware JE Jr, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. *J Clin Epidemiol.* 1998;51(11):1045–1053. doi:10.1016/s0895-4356(98)00096-1
23 Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193–213. doi:10.1016/0165-1781(89)90047-4
24 Doi Y, Minowa M, Uchiyama M, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. *Psychiatry Res.* 2000;97(2–3):165–172. doi:10.1016/s0165-1781(00)00232-8
25 Rubin M. When to adjust alpha during multiple testing: a consideration of disjunction, conjunction, and individual testing. *Synthese.* 2021;199(3–4):10969-11000. doi:10.1007/s11229-021-03276-4
26 Kawakami S, Yamato R, Kitamura K, et al. Alcohol consumption, smoking, and risk of dementia in community-dwelling Japanese people aged 40–74 years: The Murakami cohort study. *Maturitas.* 2023;176:107788. doi:10.1016/j.maturitas.2023.107788
27 Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. *PLoS One.* 2015;10(3):e0118333. doi:10.1371/journal.pone.0118333
28 Wang CC, Lu TH, Liao WC, et al. Cigarette smoking and cognitive impairment: a 10-year cohort study in Taiwan. *Arch Gerontol Geriatr.* 2010;51(2):143–148. doi:10.1016/j.archger.2009.09.041
29 Levin ED. Nicotinic systems and cognitive function. *Psychopharmacology (Berl).* 1992;108(4):417–431. doi:10.1007/BF02247415
30 The Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):700–789. doi:10.1002/alz.12638
31 Krassoievitch M, Weber K, Junod JP. Disintegration of the sleep cycle in senile dementia. Article in French. *Schweiz Arch Neurol Neurochir Psychiatr.* 1965;96(1):170–179.
32 Ohara T, Honda T, Hata J, et al. Association Between Daily Sleep Duration and Risk of Dementia and Mortality in a Japanese Community. *J Am Geriatr Soc.* 2018;66(10):1911–1918. doi:10.1111/jgs.15446
33 Nakakubo S, Doi T, Makizako H, et al. Sleep condition and cognitive decline in Japanese community-dwelling older people: Data from a 4-year longitudinal study. *J Sleep Res.* 2019;28(4):e12803. doi:10.1111/jsr.12803
34 Lucey BP, Hicks TJ, McLeland JS, et al. Effect of sleep on overnight cerebrospinal fluid amyloid beta kinetics. *Ann Neurol.* 2018;83(1):197–204. doi:10.1002/ana.25117
35 Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet.* 2000;355(9212):1315–1319. doi:10.1016/S0140-6736(00)02113-9
36 Roth T, Ancoli-Israel S. Daytime consequences and correlates of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. II. *Sleep.* 1999;22 Suppl 2:S354-S358.
37 Léger D. Public health and insomnia: economic impact. *Sleep.* 2000;23 Suppl 3:S69-S76.
38 Katz DA, McHorney CA. The relationship between insomnia and health-related quality of life in patients with chronic illness. *J Fam Pract.* 2002;51(3):229–235.
39 Scott AJ, Webb TL, Martyn-St James M, Rowse G, Weich S. Improving sleep quality leads to better mental health: A meta-analysis of randomised controlled trials. *Sleep Med Rev.* 2021;60:101556. doi:10.1016/j.smrv.2021.101556
40 Karimi R, Mallah N, Scherer R, Rodríguez-Cano R, Takkouche B. Sleep quality as a mediator of the relation between depression and chronic pain: a systematic review and meta-analysis. *Br J Anaesth.* 2023;130(6):747–762. doi:10.1016/j.bja.2023.02.036
41 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders : DSM-5.* 5th ed. American Psychiatric Publishing; 2013.