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Featured Article

Longitudinal analysis of risk factors for dementia based on Mild Cognitive Impairment Screen results and questionnaire responses from healthy Japanese individuals registered in an online database

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Abstract

Introduction: Despite an urgent need for developing remedial measures against dementia, no disease-modifying drugs have been developed. Efficient protocols for participant recruitment need to be established for conducting clinical trials. To meet this need, a large-scale online registry system, the Integrated Registry of Orange Plan (IROOP®), was created for healthy individuals. Although the risk factors for dementia have been discussed in our previous studies for a short interval of 6 months, some factors remain controversial. The present study aimed to explore factors affecting longitudinal changes in cognitive function for a longer interval of 18 months using the IROOP® data.

Methods: This study assessed the longitudinal changes in the collated data for predicting the risk of dementia and included 473 individuals (175 men and 298 women; mean age 59.6 ± 10.1 years) registered in the IROOP® between July 5, 2016 and January 15, 2018 who completed the initial questionnaire and brief assessment of cognitive function (Mild Cognitive Impairment Screen) at baseline and the regular questionnaire and the Mild Cognitive Impairment Screen at least once after baseline. Statistical analyses were performed using IBM SPSS, version 23.0, for Windows for demographic data and the MIXED procedure in SAS, version 9.4, for the linear mixed-effect model. In each analysis, the statistical significance level was set at $P < .05$.

Results: Mood, sleep, quality of life, and medical histories including cognition were found to influence longitudinal changes in cognitive function.

Discussion: Given the multifactorial etiology of dementia, preventive measures targeting multiple domains are required for maintaining cognitive function, instead of focusing on one lifestyle factor.

Keywords: Online registry; Risk factors; Dementia; Cognitive function; Sleep

1. Introduction

According to the World Health Organization (World Health Organization. Mental health of older adults.2017, https://www.who.int/mental_health/neurology/dementia/en/), the global population is rapidly aging, with a consequent increase

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in the number of people with dementia. Although there is an urgent need for developing treatment modalities against dementia, particularly Alzheimer's disease (AD), no disease-modifying drugs have been developed [1]. The progress in the development and clinical trials of therapeutic drugs against AD is insufficient. A certain participant population is needed for conducting clinical trials and deriving statistically meaningful results. A seamless registration of participants facilitates the recruitment of sufficient numbers. In Japan, registries targeting healthy adults, individuals in the preclinical stage, and patients in the clinical stage are currently under development as part of the New Orange Plan [2].

In Europe, multiple pharmaceutical companies have launched initiatives for secondary prevention of AD through early detection and treatment, called the European Prevention of Alzheimer's Dementia Consortium [3]. Presently, biomedical studies aiming to develop therapeutic strategies for chronic and late-onset diseases focus on early stage interventions [4]. In preventive medicine, the disease course is divided into predisease, early disease, and late disease stages depending on the progression, and the measures taken at these stages are called primary, secondary, and tertiary prevention, respectively (Institute for Work and Health, 2018, https://www.iwh.on.ca/what-researchers-mean-by/primary-secondary-and-tertiary-prevention). Primary prevention refers to the preventive measures aimed at preventing disease onset and accidents and reducing associated morbidity. Ritchie et al. [3] reported that primary prevention is insufficient for achieving improvement based on the existing hypotheses of the risk factors for dementia. Secondary prevention aims at preventing the progression of complications, reducing disease prevalence and mortality, and extending the overall survival through early detection and treatment, and thus, assumes importance. The European Prevention of Alzheimer's Dementia Consortium developed a platform for clinical trials based on secondary prevention, conducted as part of a project on the prevention of dementia typified by AD, and the trials aimed at augmenting the understanding of AD pathogenesis.

Galvin [5] reported that the risk of developing AD could be reduced by preventing lifestyle-related diseases or introducing lifestyle corrections. While the development of disease-modifying drugs is presently awaited, an immediate requirement is the need for identifying risk factors for diagnosing future AD onset. Until the availability of therapeutic or disease-modifying drugs for AD, the pressing issues include investigating risk factors for dementia and performing interventions to correct modifiable risk factors. In Japan, a large-scale registry system had not targeted healthy adults until we created the Integrated Registry of Orange Plan (IROOP®) [6], a large-scale Internet-based registry system, to facilitate the smooth recruitment of participants in clinical trials focused on secondary prevention. The IROOP® is operated for identifying risk factors for dementia that are applicable to primary and secondary prevention.

To date, risk factors for dementia have been identified and discussed previously. We reported that the maintenance of mood, motivation, and basic activities of daily living, and so forth contribute to preventing cognitive decline for a short interval of 6 months [6]. We also advised against the hasty consideration of differences among study results and highlighted the need for further data and continuous monitoring. Following that study, additional longitudinal data have been accumulated from the IROOP® system for a longer interval of 18 months. We hypothesized that the same risk factors as those in the previous study for a short interval also affect the longitudinal changes in cognitive function for a longer interval. This study aimed to verify this hypothesis from the accumulated IROOP® data.

2. Subjects and methods

2.1. Subjects

This study assessed the longitudinal changes for an interval of 18 months in the collated data for predicting the risk of dementia and included 473 individuals (175 men and 298 women; mean age 59.6 ± 10.1 years) registered in the IROOP® between July 5, 2016 and January 15, 2018 who completed the initial questionnaire and brief assessment of cognitive function, hereinafter referred to as the Mild Cognitive Impairment (MCI) Screen [7] at baseline (Table 1) and the regular questionnaire and the MCI Screen at least once after baseline (Table 2). This online registry system comprised healthy Japanese citizens aged ≥40 years without marked cognitive decline who live in Japan and speak Japanese as a mother language. The study

Table 1
Summary of subjects who completed the initial questionnaire and MCI Screen categorized by age groups

	Age groups						
	All	40–49	50–59	60–69	70–79	80–89	
Number of participants	473	92	155	144	71	11	*P* value
Age (mean ± SD)	59.6 ± 10.1	45.9 ± 2.7	55.0 ± 2.8	64.6 ± 2.9	73.9 ± 2.7	81.8 ± 2.2	.000
Male:female	175:298	27:65	28:127	69:75	43:28	8:3	.000
Education years (mean ± SD)	14.9 ± 2.1	14.9 ± 2.2	14.8 ± 2.0	14.7 ± 2.1	14.7 ± 2.2	15.1 ± 2.1	.860
MPI (mean ± SD)	69.7 ± 8.9	77.6 ± 5.9	73.5 ± 6.1	66.3 ± 6.6	60.5 ± 7.5	54.2 ± 4.6	.000

Abbreviations: MCI, Mild Cognitive Impairment Screen; MPI, memory performance index; SD, standard deviation.

excluded individuals diagnosed with AD, MCI, frontotemporal dementia, and dementia with Lewy bodies; individuals with a history of psychiatric disorders (i.e., major depression, bipolar disorder, anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, panic disorder, schizophrenia, and eating disorder); and individuals with a history of oral intake of antidementia drugs, including donepezil. The participants were recruited through advertising media, including television and newspaper. In addition, participants were recruited in lecture meetings at public research institutions and public lectures where our registry was explained.

2.2. Categories of items in the online questionnaire

The questionnaire comprised approximately 220 items (the number of items varied among the registrants), including those selected based on the questionnaire designed for the Brain Health Registry (http://www.brainhealthregistry.org/) operated in the United States, as well as additional items unique to the IROOP®. After consenting and entering registration information as per the IROOP® home page instructions (https://www.iroop.jp/), a "my page" is created. On this page, approximately 220 items of the initial questionnaire are found. The regular questionnaire becomes available on the "my page" every 6 months after answering the initial questionnaire.

- Items required to be entered during registration

  Mail address, birth month, sex, number of years of education, race, prefecture, and whether living alone or with others.

- Items of the initial questionnaire

  Mood: Are you basically satisfied with your life?,
  Quality of life: Compared to one year ago, how would you rate your health in general now?
  Sleep: During the past month, when have you usually gone to bed at night?
  Diet: How many meals do you eat each day? Medication history: Please indicate whether you currently have or had any of the following conditions in the past [Stroke/Parkinson's disease/Movement disorder, and so on]?
  Family history: Do you have a family member who is known to carry a genetic mutation that causes early onset Alzheimer's disease? History of trauma and cerebral concussion: In your lifetime, have you ever been hospitalized or treated in an emergency room following an injury to your head or neck?

- Items required to be entered in the regular questionnaire (every 6 months)

  Health status: Compared to six months ago, how would you rate your memory in general?

Others are the same as the first questionnaire.

2.3. Methods to answer the questionnaires

To answer the question "Do you feel that your life is empty?," the option "1 yes" is selected when the participants feel so, and the option "2 no" is selected when they do not. Besides the questions answered by selecting either "1 yes" or "2 no," the questionnaires administered in the present study included questions answered by selecting from >2 options (e.g., 1: yes, limited a lot; 2: yes, limited a little, and 3: no, not limited at all) and questions with free-descriptive answer pattern. Depending on the questions, the patterns of answers vary.

2.4. MCI Screen

The MCI Screen is a brief, telephonic assessment of cognitive function approved by the United States Food and Drug Administration. After answering all the questions in either the initial or regular questionnaires, a number is displayed on the examinee's "my page." When this number is entered at the toll-free number displayed on the same "my page," the Japanese version of the MCI Screen [8] can be taken for free. Each questionnaire takes approximately 15 minutes to complete and is composed of different questions. A scoring algorithm is then used to calculate a memory performance index (MPI) score based on the patient's test results, age, educational background, and race [7]. The index is categorized as follows: ≥50.2, no problem; 49.8–50.2, borderline, and <49.8, suspected MCI.

2.5. Statistical analyses

In this study, the questions of free-description answer pattern were excluded from analyses. Statistical analyses

Table 2
Summary of subjects who completed the questionnaire and MCI Screen from the baseline to one and half years later

	Time point			
	Baseline	Half a year later	One year later	One and half years later
Number of participants	473	362	344	176
Age (mean ± SD)	59.6 ± 10.1	59.9 ± 10.0	61.4 ± 10.3	62.2 ± 9.0
Male:female	175:298	142:220	132:212	76:100
Education years (mean ± SD)	14.9 ± 2.1	14.9 ± 2.1	14.7 ± 2.1	14.7 ± 2.1
MPI (mean ± SD)	69.7 ± 8.9	70.0 ± 9.2	69.8 ± 9.6	69.0 ± 8.4

Abbreviations: MCI, Mild Cognitive Impairment Screen; MPI, memory performance index; SD, standard deviation.

Table 3
Average values for MPI changes at each time point from baseline

Time	Estimate	Lower CL	Upper CL	*T* value	*P* value
A half year later	−0.27	−0.8	0.26	−0.99	.321
One year later	−0.96	−1.51	−0.41	−3.42	.001
One and half years later	−0.71	−1.47	0.06	−1.82	.069

Abbreviations: CL, 95% of confidence limit; MPI, memory performance index.

were performed using IBM SPSS, version 23.0, for Windows (SPSS Inc. Tokyo, Japan) for demographic data and the MIXED procedure in SAS, version 9.4, for the linear mixed-effect model. In each analysis, the statistical significance level was set at $P = .05$. The linear mixed-effect model consisted of 3 parameters as follows:

Response variable, the changes in the results of the second, third, and fourth MCI Screen from the initial results; random effect, the number of examinees, and the fixed effect being the time point, were simultaneously fitted to the model. Other fixed effects were selected based on stepwise analysis with the exclusion criteria with $P = .05$.

2.6. Ethical consideration

The IROOP® is a longitudinal registry based on the New Orange Plan and has been approved by the ethics committee of the National Center of Neurology and Psychiatry. On the home page of the IROOP®, the participants gave voluntary consent by accepting the terms of consent after examining the contents of the present study displayed therein (UMIN000022795).

3. Results

3.1. Categorization of the registered participants

There were 473 registered participants who completed the initial questionnaire and the MCI Screen at baseline and the regular questionnaire and the MCI Screen at least once after baseline. Table 1 presents the categorization of these participants and baseline MPI data by age groups. The registered participants, aged between 40 and 60 years, included more women than men, whereas more men were in their 70s and 80s than women. No significant differences in years of education were observed in the older age groups; this may be attributed to the features of an online registry system. Participants in the 80s received long education equivalent to that in other age groups. MPI significantly decreased with advancing age.

Table 2 presents the demographic and MPI data of participants at each time point at baseline, half a year later, one year later, and one and half years later.

Table 3 shows average values for MPI changes at each time point from baseline. Chronologically, MPI demonstrated an overall decrease.

3.2. Factors influencing longitudinal changes of MPI

Table 4 shows the results of the linear mixed-effect model analysis for selected factors significantly influencing the longitudinal change of the MPI score. Answers to questionnaires for selected factors are listed in the Supplementary Material. The estimates are the regression coefficients for each fixed effect. The positive and negative values indicate that as the fixed effect level increases by 1 unit, the average change from the baseline increases and decreases, respectively.

Among those selected as candidate factors, longitudinal changes in MPI were positively associated with "baseline MPI," "duration of watching television per day," "serving times of fruit," "duration of nap," "trouble in remembering what you said and to whom," "chronic pain," "awaking time," "decline in language understanding over the past 10 years," "use of a cardiac pacemaker," and "sleeping trouble because of pain over the past month," whereas longitudinal changes in MPI were negatively associated with "health problem that limits daily activities," "smoking history," "having a friend to call," "delay in motor development," "bedtime over the past month," "emotional problem that limits daily activities," "decline in executive function over the past 10 years," and "satisfaction with life".

4. Discussion

Here, we investigated factors influencing longitudinal changes in MPI. Based on statistical analysis using a linear mixed-effect model, 18 factors were identified with significance (Table 4). Interestingly, among the factors identified, 3 were associated with sleeping hours, namely "bedtime," "duration of nap," and "awaking time." Based on these findings, MPI appears to remain longitudinally high in individuals who go to bed earlier, wake up later, and nap for a longer time. To summarize, we newly demonstrated that good sleep is beneficial for maintaining cognitive functions in the present longitudinal studies for 18 months. The association between old age and sleeping hours was previously discussed. Irwin and Vitiello [9] reported that sleep disorder is a risk factor for dementia. Similarly, studies have attempted at finding possible associations between dementia and changes in sleep structures with age, use of hypnotics, and so forth [10,11]. Wennberg et al. [12] reported that 60%–70% of patients with neurodegenerative disease or dementia have sleep disorder and poor prognosis. These findings highlight the importance of sleep control and establishment of good sleeping habits as primary prevention measures of dementia. Although the precise role of appropriate sleeping hours is controversial owing to negative genetic factors and differences in the body constitution, Pocnet et al. [13] reported that the quality of sleep starts deteriorating at MCI stage. A pathological model for hypothesis was recently proposed, wherein sleep disorder reduced the

Table 4
Results of the linear mixed-effect model analysis for each factor influencing the longitudinal change of the MPI score

Factor	Estimate	Lower	Upper	*T* value	*P* value
Time: a half year later	0.44	−0.41	1.29	1.01	.312
Time: 1 year later	−0.26	−1.12	0.6	−0.59	.557
Time: one and half years later	0	-	-	-	-
Baseline MPI	0.25	0.2	0.3	9.85	.001*
How many hours of television do you watch every day?	0.3	0.11	0.49	3.16	.002*
Does your health now limit you in these activities?—moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf. (1: yes limited a lot, 2: yes, limited a little, 3: no, not limited at all)	−2	−2.97	−1.03	−4.06	.000†
Do you currently smoke tobacco or have smoked tobacco in the past? (1: yes, 2: no)	−1.87	−2.77	−0.97	−4.09	.000†
Do you have a friend to call? (1: yes, 2: no)	−1.75	−2.67	−0.83	−3.73	.000†
On average, how many servings of fruit do you eat each day?	0.58	0.22	0.93	3.18	.002*
Were you diagnosed with motor development delay (e.g. late walking or difficulties with fine movements/ learning to use tools)?	−14.44	−24.7	−4.18	−2.76	.006*
How many hours do you spent napping in a typical day?	0.94	0.37	1.51	3.26	.001*
During the past month, when have you usually gone to bed at night?	−0.29	−0.48	−0.11	−3.07	.002*
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? Cut down the amount of time you spent on work or other activities- (1: yes, 2: no)	−2.84	−4.81	−0.88	−2.84	.005*
Do you have trouble remembering if you have already told someone something? (1: yes, 2: no)	1.12	0.25	1.99	2.54	.011*
Is chronic pain a problem for you? (1: yes, 2: no)	1.15	0.15	2.16	2.25	.025*
During the past month, when have you usually gotten up in the morning?	0.23	0.03	0.43	2.25	.025*
Compared to 10 years ago, has there been any change in…Language—Understanding the point of what other people are trying to say. (1: better or no change, 2: questionable/occasionally worse, 3: consistently a little worse, 4: consistently much worse, 5: I don't know)	1.45	0.63	2.27	3.48	.001*
Compared to 10 years ago, has there been any change in…Executive functioning Organization.—Keeping mail and papers organized. (1: better or no change, 2: questionable/occasionally worse, 3: consistently a little worse, 4: consistently much worse, 5: I don't know)	−1.32	−2.16	−0.48	−3.09	.002*
Do you have a cardiac pacemaker/defibrillator? (1: yes, 2: no)	7.39	1.32	13.46	2.39	.017*
During the past month, how often have you had trouble sleeping because you have pain? (1: not during the past month, 2: less than once a week, 3: once or twice a week, 4: three or more times a week)	0.74	0.06	1.41	2.14	.033*
Are you basically satisfied with your life? (1: yes, 2: no)	−1.25	−2.5	0	−1.97	.049*

*$P < .05$.
†$P < .001$.
Abbreviation: MPI, memory performance index.

clearance of amyloid β (Aβ), thereby promoting AD development [14]. A study conducted at Washington University in St. Louis revealed that following division of the study participants into 3 groups based on sleep efficiency, Aβ deposition was higher in cases reporting lower sleep efficiency. The study additionally reported that the preclinical AD group, compared with healthy controls, showed a lower sleep efficiency, longer duration of each nocturnal awakening, and higher proportion of nap, ≥3 days per week [15].

Sleep in the elderly is characterized by short sleeping hours, lack of continuous sleep, and early wakefulness, that is, the elderly wake up earlier than young people [16]. As reported by Yo-El et al. [15]; changes in either the quality and amount of sleep or both are associated with amyloid deposition, and short sleeping hours and reduced sleep efficiency pathologically inhibit Aβ clearance, leading to its deposition. Because Aβ deposition starts decades before dementia onset [17], sleep control and good sleeping habits may be essential throughout all age groups. To prevent cognitive decline in old age, studies must not restrict itself to older age groups; conversely, the need for establishing a good overall lifestyle must be widely advocated in younger ages. Although the IROOP® targets people aged >40 years, comparative cohort studies including adolescents need to be conducted, or large-scale registry systems need to be developed for conducting new studies providing conclusive results for the identification and screening of risk factors for dementia.

Based on analysis using the linear mixed-effect model, for the question "Do you have a friend to call?," the mean change was smaller by 1.75 in participants answering "no" than in those answering "yes." This question aimed at identifying whether the registrants had friends they could reach out to such that they were socially connected and not isolated. Previous reports on the association between loneliness and cognitive function identified both transient and chronic loneliness as a risk factor for cognitive decline in elderly people [18]. The same analysis using linear mixed-effect model identified a question "Are you basically satisfied with your life?" as a contributing factor. The question belonged to the category of "mood." A cross-sectional study using registry data from the IROOP® [6] identified mood as one of the contributing factors toward cognitive functions. Because social involvement inhibits the development of depression [19], social engagements and presence of friends to call, in the present study,

indicate the presence of social connections, inhibiting the development of depression and acting as a protective factor against cognitive decline.

Comparing our results from the present study with those of previous studies, one of the affecting factors identified in the present study was the question "Are you basically satisfied with your life?" and that in the previous study was "Do you usually feel happy?". Hypotheses were proven regarding the item "mood." Mood, satisfaction, and happiness in life prevent the feeling of depression. Old age depression induces the destructive nature of confining oneself to the home in old age [20]. This further leads to a decrease in physical activity. Because the questions belonging to the category of "mood" were selected in both studies, being satisfied with life was suggested to be a key point. Data on these factors need to be longitudinally accumulated and analyzed. Zhong et al. [21] in a meta-analysis reported smokers to be at high risk for developing dementia. Conversely, this study showed that the mean change in MPI in participants without smoking history was smaller by 1.87 than that in participants with smoking history, indicating that MPI longitudinally remained constant in participants with smoking history. According to several preceding studies, smoking is considered a risk factor for AD [22–24]. Owing to the lack of consensus in results between the present and previous reports, future studies are warranted investigating the involvement of other factors conferring protection against dementia in the participants with smoking history. In addition, the aforementioned study conducted at Washington University in St. Louis reported that the proportion of participants who napped for $\geq$3 days/week was higher in the preclinical AD group than in the healthy group. Our results showed that MPI was higher in participants with longer nap durations, which is not strictly consistent with the results of a former study. This factor appears to be contentious, warranting continuous investigation. The short follow-up period and a small sample size of our study may limit the universal applicability of the results. Although data were collected at 4 different time points for analyzing the longitudinal changes in MPI, the changes were monitored for 1.5 years from the baseline data collection and therefore are far from a long-term analysis. In this research, it is the self-report of subjects via Internet about diagnosis such as mental disease. Therefore, the limit exists in the reliability of the data. In addition, the registrants in this study tended to have a long educational history. This represents another potential limitation in that our findings may not be generalizable to older adults with lower levels of education.

Secondary prevention refers to the measures aimed at 3-preventing the progression of health problems, reducing the prevalence and mortality, and extending the overall survival period through early detection and treatment. Registering with the IROOP® and self-examining temporal changes every 6 months are the primary steps to early detection of dementia. Although this registry system allowed the registrants to take a questionnaire and undergo the MCI Screen every 6 months, only about 37% of the initial participants remained registered through the fourth assessment point. In the IROOP®, the materials explaining the new clinical trials utilizing data from this registry system can be sent to interested registrants, and the contracted academia contacts the eligible registrants for recruitment. The contacted registrants participated in the clinical trials at a high rate of 25%. Registration with the IROOP® allows the registrants to self-examine changes in their cognitive function and permits those interested to participate in a new clinical trial on meeting the inclusion criteria.

The items identified as potential risk factors in our study should be widely publicized such that individuals can be conscious of them in their daily lives. Given the multifactorial etiology of dementia, preventive measures targeting multiple domains are required, rather than the sole focus on lifestyle factors. We identified sleeping hours, mood, and social connection as affecting factors, and interventions addressing these factors appear vital in preventing a cognitive decline. We envisage the continuous operation and accumulation of data through the IROOP®. With these data, investigations on the identification of modifiable risk factors for developing dementia will be undertaken to contribute to reducing the incidence of dementia for primary prevention and early detection for secondary prevention.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2019.06.003.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using academic databases (such as PubMed) and investigated risk factors for cognitive decline in a large-scale registration system. Extracted factors were discussed in comparison with those in previous studies. These relevant literatures are properly cited.
2. Interpretation: Our analyses showed that factors such as "the presence of friends to make a phone call" and "sleeping time" affected the longitudinal changes of cognitive function. Given the multifactorial etiology of dementia, multidomain prevention is required rather than focusing on one lifestyle factor.
3. Future directions: This article proposes a framework for the generation of new hypotheses and the conduct of additional studies. Future work should move toward continuous data collection to register more new data for further exploration.

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