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Evaluation of the Influence of Clinical History on the Occurrence of Dementia Using the Database of National Health Insurance in Japan

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Abstract: The global incidence of dementia has been rising for the past several years, posing significant health challenges regarding its management and prevention. Dementia is associated with a substantial burden on patients and their families. Therefore, effective, evidence-based preventive strategies are required for dementia. To achieve this, the predisposing factors for dementia and their relationship with other diseases need to be determined. Japan has a universal health insurance system and these data have been stored in their respective databases since 2008. Herein we explored the influence of clinical history on the occurrence of dementia based on data collected by the National Health Insurance in Japan and Municipal Care Certification Survey over the past 10 years. Multivariate logistic regression analysis was used to determine the factors from clinical history that affect the risk of dementia development. A significant odds ratio was observed for the development of dementia in 5-year data, involving the clinical history of osteoporosis, depression, internal carotid artery occlusion, schizophrenia, and Parkinson's disease. In addition, a significant odds ratio was observed for the development of dementia in 10-year data, involving the clinical history of osteoporosis, cataracts, and schizophrenia.

Keywords: dementia; risk factor; osteoporosis; cataracts; schizophrenia; depression

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1. Introduction

The global incidence of dementia has been rising for the past several years, posing significant health challenges regarding its management and prevention [1]. The World Health Organization estimates that in 2012, 36 million individuals had dementia [2]. The G8 dementia summit stated that the global prevalence of dementia will double in the next two decades between 2030 (66 million) and 2050 (131 million), primarily because of the increasing age of the population [3]. The risk of dementia occurrence rises with age and is the highest among individuals aged >70 years. Dementia is associated with a substantial burden on patients and their families. Therefore, effective, evidence-based preventive strategies are required for dementia. To achieve this, the predisposing factors for dementia and its relationship with other diseases need to be determined.

Preventive strategies for diseases are categorized as primary, secondary, or tertiary. Primary and secondary prevention strategies are essential to reduce the dementia prevalence. These strategies can be developed on the basis of longitudinal cohort studies that evaluate the risk factors of dementia related to lifestyle and health conditions [4].

A previous study demonstrated that nine factors account for 35% of the dementia risk: education up to the age of <11 years, midlife hypertension, midlife obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, and social isolation [5].

Among older individuals, those who exercise regularly are at a higher odds of having normal cognition than those who do not exercise. Few randomized trials have evaluated the effects of exercise on cognitive decline or dementia [6]. However, observational studies have shown that increased exercise is associated with a reduced risk of dementia [7–11]. Observational studies have also demonstrated that physical inactivity is associated with higher risks of diabetes and major cardiovascular disease. Furthermore, patients with the aforementioned health conditions have a higher risk of developing dementia [12–14]. It is unclear whether exercise reduces the risk of developing dementia directly or indirectly by preventing the risk factors of dementia [6].

Previous cohort studies with prolonged follow-up durations demonstrated that a number of depressive episodes were associated with the dementia risk, confirming that depression predisposes an individual to dementia [15]. The underlying mechanisms for this association involve depression-mediated changes in the stress hormones, nerve growth factors, and hippocampal volume, as evidenced by biological studies [16].

Social isolation has comparable effects to physical inactivity. Similarly to depression, social isolation may be a component or prodrome of dementia. Increasing evidence suggests that social isolation predisposes individuals to dementia, hypertension [17], coronary heart disease, [18] depression [19], and consequently cognitive inactivity, leading to rapid cognitive decline and low mood [20]. As a result, to determine the risk of dementia, the physical as well as mental health of individuals should be evaluated.

In 1961, Japan introduced a universal health insurance system. In Japan, there is "social insurance" for office workers and civil servants and national health insurance for self-employed people and freelancers (including "medical care system for the elderly" for elderly people). Deidentified data from the Specified Health Checkups and other medical records were transmitted to and stored at the National Health Insurance databases [21]. Furthermore, Japanese individuals with long-term care needs are provided care services at home and in institutions [22] by municipalities [23]. The Municipal Needs Certification Committee is responsible for evaluating the requests for long-term nursing care by residents based on more than 70 functions, such as activities of daily living, cognitive function, physical function, living function, adaptation to society, and behavioral disorder [4,24]. The Municipal Care Certification Survey collects data related to the cognitive ability and dementia. Data from such these surveys are freely available for use for studies on healthcare cost optimization and the quality improvement of healthcare services.

Herein, we explored the relationship between the clinical history and occurrence of dementia based on data collected by the National Health Insurance and Municipal Care Certification Survey over the past 10 years. Although many studies have investigated the relationship between the onset of dementia and one other specific disease, there are few studies that have investigated the relationship between the onset of dementia and multiple other diseases using multivariate analysis. Furthermore, we evaluated the relationship between dementia onset and clinical history over the past 10 years to facilitate the development of primary prevention strategies.

2. Materials and Methods

2.1. Participants

At present, it is not possible to completely match National Health Insurance data and long-term care certification data across the country. Therefore, this study focused on one city (Mishima City), where National Health Insurance data and long-term care certification had already been completely matched. This study targeted 34,756 residents aged 18 years and older in Mishima City, Japan, who were enrolled in the National Health Insurance System (including medical insurance for the elderly). To examine the long-term and short-term effects of medical history, we examined the 5-year and 10-year effects. In total, 24,371 individuals (10,289 men and 14,082 women; mean age: 73.91 $\pm$ 13.79 years; 18–107 years) received medical treatment at a medical institution using the National Health Insurance both in 2022 as well as 5 years ago, in 2017 (Analysis 1). Furthermore, we se-

lected 20,488 individuals (8408 men and 12,080 women; mean age: 75.19 ± 13.83 years; 18–107 years) who underwent medical treatment using the National Health Insurance in 2022 as well as 10 years ago, in 2012 (Analysis 2). Individuals diagnosed with dementia (Alzheimer's disease, Lewy body dementia, frontotemporal dementia, and vascular dementia) in 2017 or 2012 were excluded from this study.

2.2. Classification of Cognitive Ability

Dementia was defined as "residents receiving treatment for dementia (Alzheimer disease, Lewy body dementia, frontotemporal dementia, vascular dementia) in 2022" or "residents with a level of cognitive decline level 4 or higher on 7-point scale in 2022 Municipal Care Certification Survey." In the Municipal Care Certification Survey, physicians assessed the core and peripheral symptoms of dementia. For instance, short-term memory was evaluated by pointing out three familiar objects to the patients. After removing the objects from the patients' vision, the physician asks the patients to recall the three objects. Furthermore, the long-term care specialist records the patient's cognitive function (9 items), mental/behavioral disorders (15 items), and adaptation to social life (6 items) to classify the cognitive level of patients (I: can live independently; II: monitoring needed only outside the home; III: monitoring needed inside and outside the home; IV: need support during the day; V: need support during the night; VI: need support during day and night; and VII: need support in a nursing home).

2.3. Statistical Analysis

Logistic regression analysis was used to determine the factors from the clinical history that affect the risk of dementia development. The results of the logistic regression analysis are reported as the adjusted odds ratio (OR), and the potential effects of confounders were excluded. The residents were classified into two groups, Group A (residents at levels I–III or not receiving medical treatment) and Group B (residents at levels IV–VII or receiving medical treatment), using their cognitive level and whether they were treated for dementia in 2022. Multivariate logistic regression analysis was performed with (A/B) as the objective variable and clinical history in the past 5 or 10 years as the explanatory variables. The clinical history was recorded in 2017 or 2012 and covered the top 35 most frequently reported diseases in the National Health Insurance. In addition to these diseases, age and sex were entered into the multivariate logistic regression analysis as independent variables. SPSS (version 27) and Modeler (version 18.3) (IBM Japan Ltd., Tokyo, Japan) were used to conduct data analyses.

The research protocol was approved by the ethics committee of the National Institute of Public Health (NIPH-IBRA #12386) and the municipal assembly of Mishima. The study was performed in accordance with the International Ethical Guidelines for Epidemiology [25], Guidelines for the Utilization of the Database for National Health Insurance Claim, Specific Medical Checkup/Health Guidance [26], and Guidelines of Security for Health Information Systems [27]. The local administration deidentified the data before analysis.

3. Results

The significant crude ORs in 2017 were determined based on the results of the univariate logistic analysis, with significant results for all items except for six (Table 1).

Table 1. Multivariate logistic regression analysis of clinical history in 2017.

History of Past Illnesses	Crude Odds Ratio	95% CI		*p*-Value	Multivariate Adjusted Odds Ratio	95% CI		*p*-Value
		Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Age	1.148	1.140	1.157	<0.001	1.143	1.132	1.154	<0.001
Sex	1.398	1.253	1.560	<0.001	0.995	0.852	1.161	0.948
Hypertension	2.130	1.861	2.437	<0.001	0.980	0.841	1.142	0.797

Table 1. *Cont.*

History of Past Illnesses	Crude Odds Ratio	95% CI		*p*-Value	Multivariate Adjusted Odds Ratio	95% CI		*p*-Value
		Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Hyperlipidemia	1.247	0.996	1.560	0.054	0.954	0.827	1.100	0.516
Diabetes	1.549	1.364	1.758	<0.001	1.018	0.883	1.173	0.809
Low back pain	1.569	1.361	1.809	<0.001	0.929	0.796	1.084	0.351
Hypercholesterolemia	1.225	1.061	1.413	0.006	0.890	0.761	1.041	0.145
Osteoporosis	2.280	1.988	2.615	<0.001	1.198	1.016	1.413	0.032
Angina pectoris	1.939	1.661	2.263	<0.001	1.030	0.866	1.225	0.737
Knee osteoarthritis	1.805	1.564	2.084	<0.001	0.890	0.757	1.046	0.156
Cataract	1.448	1.232	1.701	<0.001	0.919	0.775	1.090	0.333
Hearing loss	1.002	0.723	1.389	0.990	0.740	0.527	1.040	0.083
Cerebral infarction	2.057	1.747	2.423	<0.001	1.126	0.944	1.345	0.188
Hyperuricemia	1.460	1.206	1.768	<0.001	1.169	0.941	1.451	0.158
Arteriosclerosis	0.939	0.526	1.678	0.832	0.781	0.428	1.424	0.420
Lumbar spinal stenosis	1.822	1.532	2.168	<0.001	0.991	0.814	1.208	0.933
Acute heart failure	2.278	1.917	2.707	<0.001	1.213	0.997	1.476	0.054
Peripheral neuropathy	1.532	1.263	1.859	<0.001	0.944	0.763	1.167	0.593
Hepatic dysfunction	1.471	1.242	1.741	<0.001	1.048	0.870	1.263	0.621
Depression	1.830	1.421	2.357	<0.001	1.634	1.239	2.154	<0.001
Arrhythmia	1.648	1.306	2.081	<0.001	1.049	0.816	1.348	0.709
Internal carotid artery occlusion	2.576	1.769	3.750	<0.001	1.544	1.033	2.308	0.034
Glaucoma	1.553	1.283	1.881	<0.001	1.028	0.839	1.260	0.787
Stomach cancer	1.051	0.820	1.347	0.695	0.933	0.717	1.214	0.605
Chronic renal failure	1.905	1.290	2.814	0.001	1.172	0.762	1.803	0.471
Colon cancer	1.198	0.960	1.495	0.111	0.994	0.784	1.260	0.960
Lung cancer	1.562	1.119	2.183	0.009	1.052	0.739	1.499	0.778
Schizophrenia	1.495	1.046	2.137	0.027	3.190	2.129	4.781	<0.001
Cerebral thrombosis	2.318	1.208	4.449	0.012	1.369	0.679	2.756	0.380
Stroke sequelae	1.875	1.532	2.294	<0.001	1.091	0.872	1.365	0.444
Chronic heart failure	2.209	1.683	2.900	<0.001	1.288	0.957	1.735	0.095
Decreased renal function	1.402	1.092	1.800	0.008	1.056	0.803	1.389	0.694
Rheumatoid arthritis	1.201	0.884	1.631	0.241	1.031	0.747	1.423	0.851
Psychosomatic disorder	1.274	0.826	1.965	0.274	0.976	0.622	1.533	0.917
Parkinson's disease	4.031	2.556	6.358	<0.001	2.551	1.565	4.157	<0.001
Atrial fibrillation	1.864	1.396	2.490	<0.001	0.987	0.720	1.353	0.936
Arteriosclerosis obliterans	1.472	1.200	1.806	<0.001	0.944	0.757	1.177	0.607
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"Cerebral infarction" in this study does not include "cerebral hemorrhage".

All items were entered into the multivariate logistic regression analysis, regardless of their results in the univariate analysis, to exclude potential confounders and determine the risk factors of dementia incidence. Significant ORs were found for dementia occurrence in six items, including "Age", "Osteoporosis", "Depression", "Internal carotid artery thrombosis", "Schizophrenia", and "Parkinson's disease" (Table 1).

Next, a similar analysis was conducted for the clinical history since 2012. In the univariate analysis, significant crude ORs were found for all diseases except for eleven (Table 2).

Table 2. Multivariate logistic regression analysis of clinical history in 2012.

History of Past Illnesses	Crude Odds Ratio	95% CI		*p*-Value	Multivariate Adjusted Odds Ratio	95% CI		*p*-Value
		Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Age	1.398	1.253	1.560	<0.001	1.140	1.129	1.151	<0.001
Sex	1.148	1.140	1.157	<0.001	0.959	0.825	1.114	0.582
Hypertension	2.200	1.935	2.502	<0.001	1.126	0.973	1.302	0.112
Hyperlipidemia	1.436	1.267	1.627	<0.001	0.990	0.862	1.138	0.891
Diabetes	1.488	1.314	1.685	<0.001	1.073	0.932	1.235	0.330
Low back pain	1.444	1.246	1.674	<0.001	0.868	0.740	1.018	0.081
Hypercholesterolemia	1.256	1.088	1.450	0.002	0.881	0.753	1.030	0.112
Osteoporosis	2.429	2.115	2.790	<0.001	1.211	1.024	1.431	0.025
Angina pectoris	1.918	1.638	2.246	<0.001	1.062	0.890	1.267	0.504
Knee osteoarthritis	2.115	1.839	2.433	<0.001	1.023	0.874	1.198	0.774
Cataract	2.172	1.882	2.506	<0.001	1.220	1.046	1.424	0.012
Hearing loss	1.321	0.987	1.766	0.061	0.870	0.640	1.182	0.372
Cerebral infarction	2.029	1.740	2.367	<0.001	1.145	0.969	1.353	0.111
Hyperuricemia	1.209	0.970	1.508	0.091	0.965	0.757	1.229	0.771
Arteriosclerosis	1.273	0.738	2.195	0.386	0.830	0.470	1.467	0.521
Lumbar spinal stenosis	2.068	1.731	2.471	<0.001	1.005	0.821	1.231	0.959
Acute heart failure	1.811	1.478	2.219	<0.001	0.954	0.758	1.200	0.688
Peripheral neuropathy	1.798	1.494	2.163	<0.001	1.124	0.915	1.380	0.265
Hepatic dysfunction	1.016	0.836	1.235	0.871	0.839	0.680	1.036	0.102
Depression	1.353	1.029	1.780	0.030	1.100	0.816	1.484	0.532
Arrhythmia	1.398	1.086	1.800	0.009	0.916	0.697	1.204	0.530
Internal carotid artery occlusion	2.378	1.638	3.453	<0.001	1.324	0.890	1.970	0.166
Glaucoma	1.589	1.289	1.958	<0.001	0.942	0.754	1.177	0.597
Stomach cancer	1.392	1.102	1.757	0.005	1.161	0.906	1.487	0.238
Chronic renal failure	1.367	0.758	2.466	0.298	1.104	0.587	2.078	0.759
Colon cancer	1.281	1.015	1.617	0.037	0.910	0.711	1.164	0.452
Lung cancer	1.806	1.281	2.545	0.001	1.235	0.859	1.774	0.255
Schizophrenia	1.176	0.775	1.784	0.447	4.356	2.725	6.962	<0.001
Cerebral thrombosis	1.528	0.823	2.834	0.179	1.050	0.549	2.006	0.883
Stroke sequelae	1.608	1.295	1.998	<0.001	0.907	0.717	1.147	0.414
Chronic heart failure	1.875	1.204	2.920	0.005	1.037	0.643	1.671	0.883
Decreased renal function	1.044	0.757	1.439	0.793	0.778	0.553	1.096	0.151
Rheumatoid arthritis	1.297	0.962	1.750	0.088	1.097	0.799	1.506	0.567
Psychosomatic disorder	0.800	0.467	1.371	0.417	0.595	0.341	1.039	0.068
Parkinson's disease	2.485	1.236	4.996	0.011	1.478	0.703	3.107	0.303
Atrial fibrillation	1.724	1.258	2.362	0.001	1.106	0.788	1.552	0.560
Arteriosclerosis obliterans	2.190	1.806	2.655	<0.001	1.231	0.992	1.528	0.059
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"Cerebral infarction" in this study does not include "cerebral hemorrhage".

Next, all items were entered into the multivariate logistic regression analysis to exclude potential confounders and determine the risk factors of dementia occurrence. The ORs of developing dementia were significant with four items, including "Age", "Osteoporosis", "Cataract", and "Schizophrenia" (Table 2).

4. Discussion

In 2019, the estimated worldwide cost of dementia was USD 1313.4 billion for the 55.2 million individuals with dementia, which translated into USD 23,796 per person with dementia. Among these costs, USD 213.2 billion (16%) were direct medical costs, USD 448.7 billion (34%) were direct social sector costs (including long-term care), and USD 651.4 billion (50%) were the costs of informal care [28]. The Ministry of Health, Labor, and Welfare (MHLW) in Japan estimates that 4.62 million individuals had dementia in 2013, which is predicted to rise to 6.75 million in 2025 and 8.2 million in 2030 [29]. Data collected by long-term care services and National Health Insurance in Japan are accumulated, analyzed, and stored in databases at the national level, which enables the identification of predisposing factors for dementia to facilitate the development of preventive strategies. We have reported on the relationship between past health checkup results and the onset of dementia using these databases, but in this study, we focused our analysis on the relationship with past clinical history [4]. In this study, only the most common diseases were used as explanatory variables; however, even if the number is small, there may be other diseases that may influence the onset of dementia or serve as confounding factors.

In this study, multivariate adjusted OR demonstrated that a clinical history of osteoporosis 5 and 10 years ago was related to an increased incidence of dementia (OR: 1.211, 95% confidence interval [CI]: 1.024–1.431 in 2012). Systematic reviews and meta-analyses indicate that individuals with osteoporosis have higher risks of cognitive impairment, and its treatment can prevent or delay the onset of cognitive impairment in high-risk patients [30]. Certain studies have identified an independent association between bone mineral density and cognition, with higher values of the former correlating with lower cognitive dysfunction [31]. Furthermore, the bone formation marker osteocalcin indicates the degree of bone transformation in osteoporosis and the degree of cognitive impairment. Indeed, the loss of osteocalcin predisposes individuals to the dysfunction of spatial learning and memory dysfunction [32]. In addition, since osteoporosis leads to movement disorders, lack of exercise may indirectly increase the risk of dementia [5–11].

The multivariate analysis demonstrated that a history of cataract within the past 10 years ago was associated with a higher OR of developing dementia (OR: 1.220, 95% CI: 1.045–1.424 in 2012). A recent systematic review and meta-analysis demonstrated an association between cataracts and higher risks of all-cause dementia, Alzheimer's disease, vascular dementia, and mild cognitive impairment in older adults [33]. Cataracts are characterized by lens opacities that compromise visual acuity, contrast sensitivity, visual function, and quality of life, thereby predisposing individuals to the development of cognitive impairment. There are numerous explanations for these findings, such as reduced sensory stimulation, social isolation, depression, physical inactivity, and vascular risk factors. In particular, vision impairment inhibits social participation and contributes to the patient's social engagement [34]. Visual impairment contributes to social isolation and may indirectly contribute to dementia [5].

Our multivariate analysis showed that a clinical history of internal carotid artery occlusion 5 years ago was associated with an increased risk of dementia. Previous systematic reviews have reported that individuals with the complete occlusion of the internal carotid artery are at risk of cerebral hypoperfusion, which in turn can lead to accelerated cognitive decline [35].

Furthermore, our findings of multivariate adjusted ORs showed that a clinical history of schizophrenia 5 and 10 years ago was related to an increased incidence of dementia. Recent studies have demonstrated rapid cognitive decline and brain changes in middle-aged and older individuals with schizophrenia compared to healthy individuals [36].

Dementia is hypothesized to have a complex relationship with schizophrenia. Calcium signaling dysregulation, e.g., increased intracellular calcium level, and the cAMP signaling pathways can cause both diseases [37].

A significant OR was obtained for a 5-year history of depression, whereas the OR was not significant for a 10-year history of depression. A cohort study followed individuals for almost 28 years prior to dementia onset and showed an increased prevalence of depressive symptoms among individuals who developed dementia than the healthy population within the 10 years before dementia onset [38]. Additionally, a cohort of adults aged $\geq$ 65 years were followed for 14 years to determine the prodromal manifestations of Alzheimer's disease, and depressive symptoms were found 8 years before the diagnosis [39]. These results are consistent with those of our study.

Our study also yielded a significant multivariate adjusted OR for a 5-year history of Parkinson's disease. A significant number of individuals with Parkinson's disease develop dementia, with a prevalence of nearly 30% [40]. It is unclear whether Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies are separate disease entities or part of the same family of diseases [41]. Further detailed studies on the association between Parkinson's disease and dementia are required.

Hearing loss is linked to cognitive decline, dementia [5], and the atrophy of the frontotemporal brain regions due to the blockage of afferent pathways and dysregulated cognitive control networks due to the increased listening effort. It also leads to social disengagement, loneliness, and depression, which are independent risk factors of cognitive decline [5,42]. Recent research suggests that the use of hearing aids may slow dementia progression [42]. In our study, a history of hearing loss did not yield significant multivariate adjusted ORs. However, our study only considered a clinical history and did not consider variables related to hearing aid use or treatment, which may have affected our results. A more detailed analysis is needed that takes into account variables related to treatment methods.

As a limitation of the research, this study focuses on one city rather than the data for the whole of Japan. At present, national health insurance data and long-term care certification data cannot be completely matched across the country. Additionally, in this study, only the most common diseases were used as explanatory variables, but it is possible that there are diseases that are small in number and may influence the onset of dementia or serve as confounding factors. Furthermore, as the impact of the COVID-19 pandemic on the onset of dementia is currently unknown, this study was unable to consider the impact of the COVID-19 pandemic on dementia. Future long-term, large-scale prospective studies that include a therapeutic approach are needed to identify historical factors associated with an increased risk of dementia.

5. Conclusions

Our analysis of the 5-year data from the National Health Insurance database showed that clinical history of osteoporosis, depression, internal carotid artery occlusion, schizophrenia, and Parkinson's disease were associated with the dementia risk. In addition, a 10-year history of osteoporosis, cataracts, and schizophrenia was associated with the dementia risk. Future long-term, large-scale prospective studies that include a therapeutic approach are needed to identify historical factors associated with an increased risk of dementia.

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Institutional Review Board Statement: The study protocol was approved by the Institutional Review Board (NIPH-IBRA #12386) of the National Institute of Public Health in Japan and the Mishima City Council.

Informed Consent Statement: The data used in this study were anonymized and deidentified by the city. In Japan, data such as receipt data can be used without residents' consent only for academic research of public interest other than the original purpose (24 December 2010 Minister of Health, Labor and Welfare Notification No. 424).

Data Availability Statement: To protect the anonymity of participants, data will not be shared unless they apply to the municipality for administrative procedures.

Conflicts of Interest: All authors have reported no conflict of interest related to this study.

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