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Quantitative comorbidity risk assessment of dementia in Taiwan

A population-based cohort study

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Abstract

Dementia is one of the most burdensome illnesses in elderly populations worldwide. However, the literature about multiple risk factors for dementia is scant.

To develop a simple, rapid, and appropriate predictive tool for the clinical quantitative assessment of multiple risk factors for dementia.

A population-based cohort study.

Based on the Taiwan National Health Insurance Research Database, participants first diagnosed with dementia from 2000 to 2009 and aged ≥65 years in 2000 were included.

A logistic regression model with Bayesian supervised learning inference was implemented to evaluate the quantitative effects of 1- to 6-comorbidity risk factors for dementia in the elderly Taiwanese population: depression, vascular disease, severe head injury, hearing loss, diabetes mellitus (DM), and senile cataract, identified from a nationwide longitudinal population-based database.

This study enrolled 4749 (9.5%) patients first diagnosed as having dementia. Aged, female, urban residence, and low income were found as independent sociodemographic risk factors for dementia. Among all odds ratios (ORs) of 2-comorbidity risk factors for dementia, comorbid depression and vascular disease had the highest adjusted OR of 6.726. The 5-comorbidity risk factors, namely depression, vascular disease, severe head injury, hearing loss, and DM, exhibited the highest OR of 8.767. Overall, the quantitative effects of 2 to 6 comorbidities and age difference on dementia gradually increased; hence, their ORs were less than additive. These results indicate that depression is a key comorbidity risk factor for dementia.

The present findings suggest that physicians should pay more attention to the role of depression in dementia development. Depression is a key cormorbidity risk factor for dementia. It is the urgency of evaluating the nature of the link between depression and dementia; and further testing what extent controlling depression could effectively lead to the prevention of dementia.

Abbreviations: ADVI = automatic differentiation variational inference, DM = diabetes mellitus, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, OR = odds ratio.

Keywords: dementia, depression, logistic regression model, vascular disease

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Compliance with Ethical Standards: This study was approved by the Institutional Review Board at Kaohsiung Medical University Hospital (KMUHIRB-SV (II)-20150007). Insurance reimbursement claims from the National Health Insurance Research Database are available for public access. To protect personal privacy, the electronic database with patient identifications was decoded and scrambled for further research access. Although informed consent was not required because of this privacy protection, the study was evaluated and approved by the NHRI.

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1. Introduction

Dementia is one of the most burdensome illnesses in elderly populations worldwide. The global prevalence of dementia was estimated to be 46.8 million in 2015, with a 60% increase to 74.7 million predicted for the year 2030.[1,2] In addition, the global socioeconomic costs for dementia were estimated to be US$818 billion in 2015, with a 144% increase to US$2 trillion by 2030.[1,3] Statistical data estimate an increase in the number of patients with dementia and thus dramatically high costs of care. Several potential risk factors for dementia have been recognized, including sociodemographic (e.g., age, ethnicity, sex, educational level, and family history), lifestyle (e.g., physical activity, dietary habits, and tobacco and alcohol consumption), genetic (e.g., *APOE*, *APP*, *PS-1*, and *PS-2*), environmental, medications, and comorbidities (e.g., depression, vascular disease, severe head injury, hearing loss, diabetes mellitus [DM], and senile cataract).[4–6] Among these risk factors, comorbidity risk factors for dementia can be easily detected and controlled by primary care physicians. Evidence reveals that elderly populations have a higher number of chronic diseases than other populations,[7–11] implying that most elderly patients with dementia have multiple chronic diseases. However, most related studies have only reported ORs of 1- or 2-comorbidity risk factors in patients with dementia,[4,5,12,13] and those reporting ORs of multiple comorbidity risk factors for dementia are scant. The objective of this study was to develop a simple, rapid, and appropriate predictive tool for the clinical quantitative assessment of multiple risk factors for dementia.

Regression analysis is a common approach to exploring the relationship between one or more study variables and disease outcomes. The logistic regression model used in this study was fitted using the Bayesian inference approach. Bayesian considerations are widely used in machine learning for prediction and decision-making in new technologies.[14] In addition, Bayesian inference is more direct (e.g., *P* values are not used) and combines data from all relevant sources (e.g., meta-analysis of many studies through Bayesian random-effects hierarchical models) in a straightforward manner. The model represents an integration of prior knowledge and data. Furthermore, the Bayesian statistical method in combination with a logistic regression model is an efficient approach to understanding a problem domain and predicting the outcomes of interventions.[15,16]

In the present study, a logistic regression model with Bayesian supervised learning inference was employed to elucidate quantitative effects of 1- to 6-comorbidity risk factors for dementia, namely depression, vascular disease, severe head injury, hearing loss, DM, and senile cataract, which were identified from a nationwide longitudinal population-based database.

2. Methods

2.1. Data sources and ethical considerations

A detailed description of the Taiwan National Health Insurance Research Database (NHIRD) and procedures has been previously published.[13,17] In brief, we used the 1995 to 2010 NHIRD, a subset containing the data of 1 million randomly selected insurants drawn by the year 2000. The NHIRD includes data on the insurants' demographics, diagnoses, medication types, prescription dates, and dosages and durations of drug supply. Ethical approval was obtained from the affiliated institutions, and informed consent was waived because of the use of previously collected de-identified medical information from the NHIRD.

2.2. Study design

Participants aged ≥65 years in 2000 were included in the study. The patient group comprised patients who received their first diagnosis of dementia from 2000 to 2009. Dementia was identified according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic criteria (ICD-9-CM 290, 294.1–294.2, A210, A213, or A222). To enhance and ensure the diagnostic validity, only the patients with inpatient files for primary or secondary diagnosis of dementia or outpatient files for at least 3 consistent diagnoses of dementia were selected.[13] In addition, the first diagnosis date of dementia was considered the index date.

2.3. Major comorbidity risk factors for dementia

The inpatient and outpatient diagnosis files of patients with dementia before the index date were assessed according to the ICD-9-CM diagnostic criteria to ascertain the history of severe head injury, depression, DM, vascular disease (cardiovascular disease, cerebrovascular disease, and stroke), senile cataract, and hearing loss (S1 Table, http://links.lww.com/MD/C191).[13,18,19] Furthermore, the files of patients without dementia between 1995 and 2010 were identified to ascertain the history of these comorbidities.

2.4. Statistical analysis

In the logistic regression, sex, age, monthly income, urban residence, and comorbidity risk factors for dementia were used as exposure variables to describe or predict the dependent variables (i.e., dementia). Logistic regression model can elucidate effect of each risk factor for dementia.

$$P(Y = 1|X_1 \ldots X_k) = \frac{1}{1 + e^{-[a+b1X1+b2X2+\ldots+bkXk]}} \quad (1)$$

The purpose of this study was to illustrate a quantitative risk assessment for well-known risk factors for dementia. Subsequently, we can predict high-risk and low-risk patients with early dementia and provide appropriate treatment. Given *N* independent observations, to fit the logistic regression model presented in Eq. (1), the values of $a, b_1, b_2, \ldots, b_k$, the unknown parameters, should be estimated. Because only 6 well-known risk factors for dementia were considered in this study, the input feature vectors are clearly relevant and have a low dimension Fig. 1.

3. Results

After the 1,000,000 insurants were screened, 49,747 (5.0%) patients aged ≥65 years in 2000 were selected for this study. Six major comorbidities were investigated in the study population,

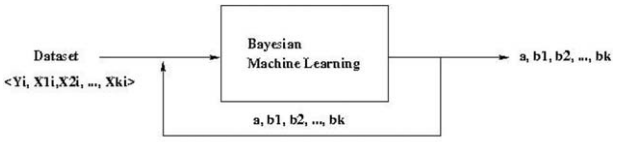

Figure 1. Bayesian machine learning model.

Table 1

Patient characteristics, stratified by presence or absence of dementia from 2000 to 2010 (N = 49,747).

	Patients with dementia (N = 4749)	Patients without dementia (N = 44,998)	*P*
Age (≥65 y)*, mean (SD)	73.3 (5.3)	70.9 (4.8)	<.001
Sex, n (%)			<.001
Male	2070 (43.6)	22,231 (49.4)	
Female	2679 (56.4)	22,767 (50.6)	
Urban level, n (%)			.003
Urban	3113 (66.0)	28,506 (63.0)	
Suburban and rural	1636 (34.0)	16,492 (37.0)	
Monthly income, NT$, n (%)			<.001
Low (0–15,000)	3457 (72.8)	27,924 (62.1)	
High (>15,000)	1292 (27.2)	17,074 (37.9)	
Number of chronic diseases†, n (%)			<.001
0	366 (7.7)	4,014 (8.9)	
1	911 (19.2)	9,783 (21.7)	
2	1521 (32.0)	15,310 (34.0)	
3	1335 (28.1)	11,719 (26.0)	
4	515 (10.8)	3586 (8.0)	
5	96 (2.0)	515 (1.2)	
6	5 (0.1)	51 (0.1)	

NT$ = New Taiwan dollar, SD = standard deviation.

* Study population was sampled in 2000.

† Six major comorbidities or chronic diseases include severe head injury, depression, diabetes mellitus, vascular diseases, senile cataract, and hearing loss.

namely severe head injury, depression, DM, vascular disease, senile cataract, and hearing loss. The mean number of comorbidities in the selected patients was 2.1 ± 1.1, which accounted for approximately one-third of the sample. The numbers of patients with 2, 3, and 1 comorbidities were 16,831 (33.8%), 13,054 (26.2%), and 10,694 (21.5%), respectively. Table 1 shows the distribution of sociodemographic characteristics of the study population. A total of 4749 individuals (9.5%) had a diagnosis of dementia. Furthermore, the logistic regression analysis revealed that older age, female sex, urban residence, and low monthly income were independent sociodemographic risk factors for dementia (Table 1).

After adjustment for age, sex, urban residence, and income level, the ORs of patients with only 1 comorbidity were as follows: 4.938 for depression, 3.261 for vascular disease, 3.165 for severe head injury, 2.435 for hearing loss, 2.321 for DM, and 1.674 for senile cataract (S2 Table, http://links.lww.com/MD/C191). For an age difference of 1 to 10 years, the 2 highest adjusted ORs were 4.934 to 10.612 for depression and 3.261 to 7.008 for vascular disease (S2 Table, http://links.lww.com/MD/C191). We obtained the ORs of 2- to 6-comorbidity risk factors for dementia after adjustment for sociodemographic factors (Tables S2–S5, http://links.lww.com/MD/C191). The 2 highest ORs of dementia for 2-comorbidity risk factors for dementia were 6.726 (comorbid with depression and vascular disease) and 6.527 (depression and severe head injury). For the age factor, the 2 highest adjusted ORs of dementia were 6.726 to 14.454 (depression and vascular disease) and 6.527 to 14.027 (depression and severe head injury) (Table 2). Among all ORs of dementia for 3-comorbidity risk factors, the 5 highest ORs were

Table 2

All ORs of 2 comorbidity risk factors for dementia.

	ORs for age difference (y/o)									
Comorbidity risk factors	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
DEP+VD	6.726	7.323	7.973	8.680	9.450	10.288	11.201	12.195	13.277	14.454
DEP+SHI	6.527	7.106	7.737	8.423	9.171	9.984	10.870	11.834	12.884	14.027
DEP+HL	5.023	5.468	5.954	6.482	7.057	7.683	8.365	9.107	9.915	10.794
DEP+DM	4.787	5.212	5.675	6.178	6.726	7.323	7.973	8.680	9.450	10.288
SHI+VD	4.310	4.693	5.109	5.562	6.056	6.593	7.178	7.815	8.508	9.263
DEP+SC	3.452	3.758	4.092	4.455	4.850	5.280	5.749	6.259	6.814	7.419
HL+VD	3.317	3.611	3.931	4.280	4.660	5.073	5.523	6.013	6.547	7.128
HL+SHI	3.219	3.504	3.815	4.154	4.522	4.923	5.360	5.836	6.353	6.917
DM+VD	3.161	3.442	3.747	4.080	4.442	4.836	5.265	5.732	6.240	6.794
DM+SHI	3.068	3.340	3.636	3.959	4.310	4.693	5.109	5.562	6.056	6.593
DM+HL	2.361	2.570	2.798	3.047	3.317	3.611	3.931	4.280	4.660	5.073
SC+VD	2.280	2.482	2.702	2.942	3.203	3.487	3.796	4.133	4.500	4.899
SC+SHI	2.212	2.408	2.622	2.855	3.108	3.384	3.684	4.011	4.367	4.754
HL+SC	1.702	1.853	2.018	2.197	2.392	2.604	2.835	3.086	3.360	3.658
DM+SC	1.623	1.766	1.923	2.094	2.280	2.482	2.702	2.942	3.203	3.487

These results are adjusted for sex, income, and urban levels. DEP = depression, DM = diabetes mellitus, HL = hearing loss, ORs = odds ratios, SC = senile cataract, SHI = severe head injury, VD = vascular diseases, y/o = years old.

Table 3

All ORs of 3 comorbidity risk factors for dementia.

Comorbidity risk factors	ORs for age difference (y/o)									
	1	2	3	4	5	6	7	8	9	10
DEP+HL+VD	6.841	7.448	8.109	8.829	9.612	10.465	11.393	12.404	13.504	14.702
DEP+SHI+VD	6.787	7.389	8.045	8.758	9.535	10.381	11.302	12.305	13.397	14.585
DEP+HL+SHI	6.639	7.228	7.870	8.568	9.328	10.155	11.056	12.037	13.105	14.268
DEP+DM+VD	6.521	7.099	7.729	8.415	9.161	9.974	10.859	11.822	12.871	14.013
DEP+DM+SHI	6.328	6.890	7.501	8.166	8.891	9.679	10.538	11.473	12.491	13.599
DEP+DM+HL	4.870	5.302	5.772	6.284	6.841	7.448	8.109	8.829	9.612	10.465
DEP+VD+SC	4.702	5.119	5.573	6.068	6.606	7.192	7.830	8.525	9.281	10.105
DM+HL+SHI	5.103	5.371	5.679	6.034	6.446	6.927	7.491	8.157	8.951	9.902
DEP+SC+SHI	4.563	4.968	5.409	5.888	6.411	6.980	7.599	8.273	9.007	9.806
HL+SHI+VD	4.384	4.773	5.197	5.658	6.160	6.706	7.301	7.949	8.654	9.422
DM+ SHI+VD	4.179	4.549	4.953	5.392	5.871	6.392	6.959	7.576	8.248	8.980
DEP+SC+HL	3.511	3.823	4.162	4.531	4.933	5.371	5.847	6.366	6.931	7.546
DEP+DM+SC	3.347	3.644	3.967	4.319	4.702	5.119	5.573	6.068	6.606	7.192
DM+HL+VD	3.216	3.501	3.811	4.150	4.518	4.918	5.355	5.830	6.347	6.910
SC+SHI+VD	3.013	3.281	3.572	3.888	4.233	4.609	5.018	5.463	5.948	6.475
DM+SC+SHI	3.373	3.538	3.727	3.944	4.194	4.485	4.825	5.224	5.696	6.258
HL+SC+VD	2.319	2.524	2.748	2.992	3.258	3.547	3.861	4.204	4.577	4.983
HL+SHI+SC	2.250	2.450	2.667	2.904	3.161	3.442	3.747	4.080	4.442	4.836
DM+SC+VD	2.210	2.406	2.620	2.852	3.105	3.380	3.680	4.007	4.362	4.749
DM+HL+SC	1.650	1.797	1.956	2.130	2.319	2.524	2.748	2.992	3.258	3.547

These results are adjusted for sex, income, and urban levels. DEP = depression, DM = diabetes mellitus, HL = hearing loss, ORs = odds ratios, SC = senile cataract, SHI = severe head injury, VD = vascular diseases, y/o = years old.

all >6, and the ORs for the interaction effects of these risk factors and an age difference of 10 years were >13. The 3 highest ORs of dementia for 3-comorbidity risk factors were 6.841 (comorbid with depression, vascular disease, and hearing loss), 6.787 (depression, vascular disease, and severe head injury), and 6.527 (depression, severe head injury, hearing loss) (Table 3).

The 2 highest ORs of dementia for 4-comorbidity risk factors were for dementia comorbid with depression, vascular disease, severe head injury, and hearing loss (adjusted OR = 8.741); and for that comorbid with depression, vascular disease, severe head injury, and DM (adjusted OR = 8.619). The ORs for quantitative effects of these comorbidity risk factors and an age difference of 10 years were >18.5 (Table S4, http://links.lww.com/MD/C191). The highest ORs of dementia for 5-comorbidity risk factors was for that comorbid with depression, vascular disease, severe head injury, hearing loss, and DM (adjusted OR = 8.767). Moreover, the ORs of dementia for the quantitative effect of these risk factors and an age difference of 10 years was also the highest (adjusted ORs = 18.840; Table S5, http://links.lww.com/MD/C191). The OR for all 6-comorbidity risk factors was 5.954 after adjustment for sociodemographic factors; the OR for the interaction effect with an age difference of 10 years was 13.027 (Table S3, http://links.lww.com/MD/C191). Accordingly, the quantitative effects of 2- to 6-comorbidities and age difference on dementia gradually increased. Obviously, the ORs were less than additive when multiple risk factors were considered together. The results indicate that depression is a key comorbidity risk factors for dementia.

4. Discussion

This is the first nationwide study to identify multiple comorbidity risk factors for dementia by using a logistic regression model with Bayesian supervised learning inference. Old age, female sex, urban residence, and low income level were identified as independent sociodemographic risk factors for dementia. After adjustment for the sociodemographic risk factors, the highest OR for 1-comorbidity risk factors was 4.938 (depression). Furthermore, the highest adjusted OR for 2- to 6-comorbidity risk factors was 8.767, which was for 5 comorbidities, namely depression, vascular disease, severe head injury, hearing loss, and DM. Overall, the quantitative effects of 2 to 6 comorbidities and age difference on dementia gradually increased; hence, the corresponding ORs were less than additive. Notably, depression was a key comorbidity risk factor for dementia in this study.

The global prevalence of dementia has been reported to be higher among older people, women, and those with a low socioeconomic status.[4–6,13] These results are similar to the present findings. Therefore, the risk factors for dementia can vary with urbanization level, as is the case with any sociodemographic risk factors that can be altered (exceptions include age, sex, and educational level). Several studies have reported that the prevalence of dementia is inconsistent among urban, rural, and other areas in China.[20–23] Our results demonstrate that the prevalence of dementia in urban areas in Taiwan is higher than that in suburban and rural areas. This situation might be because in Taiwan, elderly people with a low socioeconomic status desire and require convenient medical care and therefore migrate to cities to live with their children. In addition, the prevalence of dementia in suburban and rural areas of Taiwan may be underdiagnosed because there is limited access to health care facilities, particularly in rural areas. Increasing evidence indicates that elderly people with dementia have at least 1 comorbid chronic disease. Zhang et al[24] reported that the mean number of comorbidities in elderly people with dementia at 19 Spanish primary care centers was 3.7. However, the number of comorbidities in patients with dementia is higher than that in the present study; the mean number of comorbidities was 2.2. A possible reason for these inconsistent findings is the different study populations; participants in the present study were from the general population and those in the study by Zhang et al[24] were from primary care centers. Of the patients with

2 dementia-related comorbidities in the present study, the highest adjusted OR for the study population was 6.726, and the highest risk factor was dementia comorbid with depression and vascular disease. This finding suggests that clinicians should focus on these 2 comorbidity risk factors for dementia. This is because depression and vascular disease are 2 of the most common diseases in middle-aged and elderly people in the general population.

Some comorbidity risk factors for dementia in this study may be intermediate or confounding factors, such as senile cataract and DM. For example, DM and vascular disease have been identified as 2 comorbid risk factors for dementia[4–5,13]; meanwhile, DM is also a major risk factor for vascular disease. Overadjustment bias and unnecessary adjustment in this study may have reduced the effect of these comorbidities on dementia.[25] Consequently, the effect of 6 comorbidities (adjusted OR = 5.954) on dementia was not greater than that of 2 to 6 comorbidities, with 5-comorbidity risk factors exhibiting the highest OR (adjusted OR = 8.767). This result may be because the sample size decreased as the number of comorbidities increased. Clinical observations revealed that many patients with dementia have a history of depression,[26] which is consistent with our findings. The study results indicate that depression is a key comorbidity risk factor for dementia; but it is not surprising that depression is a key risk factor of dementia.[27] Also, depression and depressive symptoms are commonly presented in patients with various disorders.[28] However, the role of depression in dementia development remains controversial or overlooked in some studies. Several studies have proposed hypotheses explaining the association between dementia and depression. First, depression may be an early prodromal sign of dementia. A clinical trial study involving an elderly population reported that the incidence of new cases with dementia declined by 10% over 7 years when depression was controlled.[27] Second, depression is an independent risk factor for dementia. A study demonstrated that treatment for depression, even at early stages, might not prevent the onset of dementia; however, its elimination may reduce the rate of disability.[6] A systematic meta-analysis and meta-regression analysis revealed that patients with a history of depression were at a higher risk of subsequent Alzheimer disease in later life.[28] Furthermore, depression may cause damage to the hippocampus through the glucocorticoid cascade.[26] Although the treatment of depression may eliminate the onset of dementia or reduce the risk by alleviating depression symptoms, patients experience the underlying negative biological effects associated with depression, such as inflammation, increased blood–brain barrier permeability, white matter damage, and increased cortisol concentrations, which may be linked to the etiology of dementia.[6] Our statistical analyses do not provide sufficient information on the association between dementia and depression; however, the data indicate that depression is common and frequently precedes the onset of dementia. Compared with other potential risk factors, depression can be easily treated after it is screened relatively easily by using complete assessment tools.[6]

Risk assessment of 2-comorbidity risk factors for some diseases may be essential in some situations. Logistic regression models assess the interactions between 2 independent variables. The product terms in regression, such as X_1*X_2, can be included in a logistic model. The terms X_1 and X_2 are the main effect variables, and the product term, X_1*X_2, is called an interaction effect variable. Subsequently, a test is performed to verify the significance of the product term. Furthermore, the no-interaction hypothesis can be verified by evaluating the significance of the coefficient of the product term in the model. If the test is nonsignificant, the model would be reduced to a simpler one including only the main effects. By contrast, if the test is significant, it indicates a particular interaction on a multiplicative scale.

The major strength of this study is the execution of a probabilistic risk assessment of individual risk factors and multiple-comorbidity risk factors for dementia. This study was based on a large nationwide population-based sample, and the results may accurately represent the ethnic Chinese population with dementia. The diagnoses of dementia and its comorbidities are reliable, because the health insurance claims are scrutinized by medical reimbursement specialists and are peer reviewed. The quantitative risk assessment model used in this study was logistic regression with Bayesian inference, in which a logistic regression analysis was performed within the context of Bayesian inference. One of the main advantages of using Bayesian inference to fit the logistic regression model is that it allows for the inclusion of prior information.[29,30] Although other risk factor assessment methods use prior information by providing the levels or ranges of individual parameters in sensitivity analyses, the Bayesian method analyzes historical data sets or refers to expert domain knowledge to determine what is known about the biological parameters and processes.[31,32] Most conventional risk factor assessment methods do not use any quantitative information that can be obtained from historical data on other risk factors; therefore, these methods consider each risk factor assessment as a new and independent problem. Bayesian inference can effectively assist clinicians and researchers in examining the effect of multiple comorbidity risk factors for diseases (e.g., dementia), which can be explored by analyzing big data such as data obtained from the Taiwan NHIRD.

Nevertheless, this study had some limitations. First, detailed information on other potential risk factors for dementia, such as biochemical data (e.g., *APOE*), clinical severity of disease, body mass index, educational level, family history, and lifestyle factors, are unavailable in the database. Lifestyle-related risk factors for dementia, including physical activity, dietary habits, and tobacco and alcohol consumption, are also unavailable. Second, this retrospective study was more susceptible to bias than it would have been under a prospective design[33]; therefore, we avoided 2 possible major biases related to sample population (selecting random patients from nationwide data) and patient recall (analyzing national health care records). Third, all administrative databases are subject to possible coding errors or undercoding; therefore, these errors may have limited effects on the study results. Finally, probabilistic relationships with multiple risk factors of interest were neglected.

5. Conclusions

The quantitative effects of 2 to 6 comorbidities on dementia gradually increased; however, the corresponding ORs were less than additive. In addition, depression was determined to be a key comorbidity risk factor for dementia; and depression can be treated in clinics after screening for it, which is comparably easier than screening for other risk factors. The logistic regression model with Bayesian inference could aid clinicians in exploring the multiple risk factors for dementia and facilitate the development of simple, rapid, and appropriate risk assessment tools and treatment strategies for patients with dementia.

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