

Development of Alzheimer disease in old major depressive patients based upon their health status

A retrospective study in Taiwan

Ping Tao, MS^{a,b}, Szu-Nian Yang, MD^{c,d,e}, Yu-Chi Tung, PhD^b, Ming-Chin Yang, PhD^{b,*}

Abstract

This study is conducted to investigate the association between major depressive disorder and the subsequent development of Alzheimer disease (AD) in elderly patients with different health statuses using Taiwan's National Health Insurance Research Database (NHIRD).

A retrospective cohort study was performed on subjects over 65 years old from 2002 to 2006 using a random sampling from the 1 million beneficiaries enrolled in the NHI. Patients who were diagnosed with major depressive disorder were selected as the case group. Subjects in the control group were selected from elderly patients who did not have depression during the study period by matching age, sex, and index date of depression with subjects in the case group using a ratio of 1:4 (case:control). Both groups of patients were checked annually over a period of 7 years to observe whether they subsequently developed AD.

A total of 1776 subjects were included in the case group while 7104 subjects were in the control group. After the follow-up period, 59 patients (3.3%) with depression developed AD while 96 patients (1.4%) without depression developed AD. The Kaplan–Meier curves showed that the incidence rate of AD in both groups varied significantly depending on different health statuses (log-rank $P < .001$). Results of the generalized estimating equation model found that patients with depression (hazard ratio [HR] = 1.898; 95% confidence interval [CI] = 1.451–2.438), very severe health status (HR = 1.630; 95% CI = 1.220–2.177), or artery diseases (HR = 1.692; 95% CI = 1.108–2.584) were at a higher risk of developing AD than other groups.

The association between major depressive disorder and the later development of AD varied depending on the health statuses of elderly patients. Clinicians should exercise caution when diagnosing and treating underlying diseases in elderly depressed patients, and then attempt to improve their health status to reduce the incidence rate of subsequent AD development.

Abbreviations: ACG = adjusted clinical groups, AD = Alzheimer disease, GEE = generalized estimating equation, HR = hazard ratio, ICD-9-CM = clinical modification, IRB = Institutional Review Board, MCI = mild cognitive impairment, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute.

Keywords: Alzheimer disease, generalized estimating equation model, health status, major depressive disorder, survival analysis

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^a Department of Medical Affairs and Planning, Taipei Veterans General Hospital,

^b Institute of Health Policy and Management, College of Public Health, National Taiwan University, ^c Superintendent Office, Tri-Service General Hospital Beitou Branch, ^d Institute of Health and Welfare Policy, National Yang-Ming University,

^e Department of Psychiatry, National Defense Medical Center, Taipei, Taiwan.

* Correspondence: Ming-Chin Yang, Institute of Health Policy and Management, College of Public Health, National Taiwan University, Room 637, 6F, No 17, Xuzhou Road, Zhongzheng District, Taipei City 100, Taiwan (e-mail: mcyang637@ntu.edu.tw).

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1. Introduction

The growth of elderly populations worldwide has increased attention to the early detection and treatment of age-related diseases, such as dementia. The number of dementia patients around the world was 47.5 million in 2016 and is expected to exceed 135.5 million by 2050.^[1,2] Alzheimer disease (AD) accounts for approximately 50% to 60% of all dementia patients. As the incidence rate of AD has increased year after year, the welfare and healthcare systems in many countries have incurred high costs.^[3–5] The World Health Organization has urged governments of developed countries to allocate resources to the treatment of patients with AD as a priority in national health policies.

Among elderly patients, depression is common and the prevalence of major depressive disorder in aged adults is approximately 12.9% to 21.7% worldwide. Depression, cancer, and AIDS are 3 major diseases that require particular attention in developed countries due to their high incidence rates and disease burden. In particular, depression results in huge social and economic loss.^[6] Older adults living in cities have 1.4 times the risk of developing depression than those living in rural areas. Moreover, women overall have twice the risk of suffering

depression than men.^[7] Therefore, identifying depressive symptoms and effective treatments in elderly patients is of critical importance.

Precisely diagnosing whether older adults have depression or AD is often difficult because depression and AD share similar clinical symptoms in the early stages, such as poor memory, social withdrawal, apathy, and mild cognitive impairment.^[8] Previous studies have reported that elderly patients who are diagnosed with AD have a higher probability of suffering depression concurrently; however, these studies only showed that depression and AD are correlated and did not further investigate the potential of a causal relationship between these 2 diseases. In recent years, studies have implied that one's health status could be a moderator affecting development of diseases among elderly patients,^[9] especially for those who suffer from single or multiple chronic diseases. Therefore, investigating the influence of health status on the association between depression and AD in elderly patients is crucial. As a number of previous studies on the relationship between depression and AD used small samples from within specific institutions, the translation of these findings to the general population is limited.^[8,10,11] Examining the relationship between depression and AD based on population data sources is therefore necessary.^[10] The current study used subjects drawn from Taiwan's National Health Insurance Research Database (NHIRD) to examine the association between depression and AD among elderly patients with different health statuses. Results are discussed in the light of recommendations for improvements to clinical practice and health policy for geriatric patients with AD.

2. Methods

2.1. Data source

This retrospective cohort study used the 2000 to 2013 1 million beneficiary version of the NHIRD as its data source. The NHIRD has collected the demographic data of every beneficiary of the National Health Insurance (NHI) in Taiwan since 1995, including sex, age, diagnoses, and procedural codes in the International Classification of Disease, 9th version, Clinical Modification (ICD-9-CM), and itemized medical expenses for all types of medications, examinations, tests, therapies, and treatments. The ICD-9-CM codes were confirmed by computer programs and medical professionals to ensure satisfactory reliability and validity. Annually, the National Health Research Institute (NHRI) of Taiwan randomly selects 1 million beneficiaries to represent all insured Taiwanese to create the 1 million beneficiary version of the database and releases this to research organizations. This database has been used as the data source for many similar studies and all identifying data of subjects are replaced by encrypted numbers. This study was exempted from the Institutional Review Board (IRB).

2.2. Research samples

Subjects in the case group were selected from patients aged 65 years old and over who were diagnosed for the 1st time with major depressive disorder (ICD-9-CM code 296.2x at least twice in 6 consecutive months) between 2002 and 2006, and prescribed antidepressant medication for 90 days and over within 6 months following the initial diagnosis. Subjects who were diagnosed with major depressive disorder 2 years before reaching 65 years old or who died within the following 7 years were excluded. Subjects in

the control group were randomly selected by matching age, sex, and index date of depression (date when major depressive disorder was confirmed ± 3 months) with the ones in the case group in a ratio of 1:4 (case:control). Subjects in the control group did not die within the 7-year period (Fig. 1).

2.3. Research variables

The major independent variable in this study was whether a patient had major depressive disorder. Another independent variable was health status, which was estimated based on the subject's annual utilization data by applying the adjusted clinical group (ACG) system developed by Johns Hopkins University. The ACG system calculates each subject's burden of morbidity, in terms of ACG's unscaled weights of the year, by analyzing the amount of health resources consumed in association with diagnoses and treatments of each utilization.^[12] The ACG system further divides burden of morbidity into 5 grades from healthy to very severe. This system has been widely adopted in studies on health status and its reliability and validity are widely accepted.

The dependent variable was whether a patient developed AD following diagnosis of major depressive disorder. Control variables included sex, age (while enrolled in the study), and comorbidities of the subjects. Comorbidities included coronary heart disease, ischemic heart disease, artery disease, arrhythmia, hypertension, diabetes, and chronic kidney disease.

2.4. Statistical analysis

The SAS 9.4 was used for statistical analysis. Numbers and percentages were used to describe categorical variables; mean and standard deviation were used to describe continuous variables. A Chi-square test was performed to examine the statistical association between 2 groups and a Fisher exact test was performed if an expected value for any categorical variable was < 5 . For the continuous variables, independent samples *t* tests were conducted to examine whether the mean difference for the 2 groups was significant. Kaplan–Meier curves and log-rank tests were performed to examine significant differences in developing AD between 2 groups. The incidence and hazard ratios of both groups were calculated with different health statuses. A generalized estimating equation (GEE) model was then used to assess the influence of depression on developing AD after controlling for each subject's health status and comorbidities during the 7-year period. Significance level (α) was set at 0.05.

3. Results

3.1. Sample characteristics

A total number of 8880 subjects were included in this study, and 59 out of the 1776 subjects in the case group acquired AD during the study period (Table 1). Subjects in the case group had a higher incidence rate of AD (3.3%) and poorer health status than those in the control group (very severe subjects accounted for 69.0% in the case group and 43.8% in the control group). The case group also had significantly more comorbidities: hypertension (81.0% vs 71.2%), type-2 diabetes (46.2% vs 34.8%), chronic kidney disease (15.6% vs 10.9%), artery disease (62.1% vs 44.1%), arrhythmia (37.7% vs 23.6%), coronary heart disease (7.7% vs

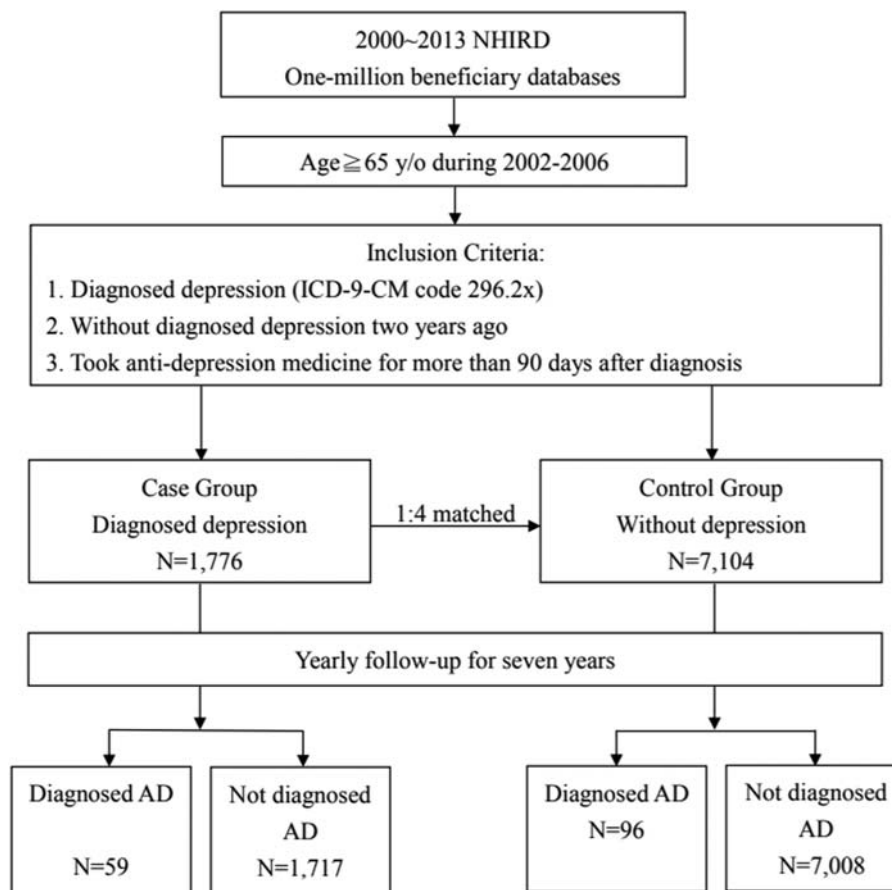


Figure 1. Process of selecting subjects from National Health Insurance Research Database (NHIRD).

Table 1

Baseline characteristics for subjects in study (n = 8880).

		No depression		Depression		Total		P value
		n	(%)	n	(%)	n	(%)	
Alzheimer disease	No	7008	(98.6)	1,717	(96.7)	8725	(98.3)	<.001
	Yes	96	(1.4)	59	(3.3)	155	(1.7)	
Gender	Female	4240	(59.7)	1,060	(59.7)	5300	(59.7)	1.00
	Male	2864	(40.3)	716	(40.3)	3580	(40.3)	
Health status	Mild, moderate, or severe	3992	(56.2)	550	(31.0)	4542	(51.1)	<.001
	Very severe	3112	(43.8)	1,226	(69.0)	4338	(48.9)	
Comorbidity	Hypertension							
	No	2047	(28.8)	338	(19.0)	2385	(26.9)	<.001
Yes	5057	(71.2)	1,438	(81.0)	6495	(73.1)		
Type-2 diabetes	No	4630	(65.2)	955	(53.8)	5585	(62.9)	<.001
	Yes	2474	(34.8)	821	(46.2)	3295	(37.1)	
Chronic kidney disease	No	6332	(89.1)	1,499	(84.4)	7831	(88.2)	<.001
	Yes	772	(10.9)	277	(15.6)	1049	(11.8)	
Artery disease	No	3968	(55.9)	673	(37.9)	4641	(52.3)	<.001
	Yes	3136	(44.1)	1,103	(62.1)	4239	(47.7)	
Arrhythmia	No	5425	(76.4)	1,106	(62.3)	6531	(73.5)	<.001
	Yes	1679	(23.6)	670	(37.7)	2349	(26.5)	
Coronary heart disease	No	6786	(95.5)	1,639	(92.3)	8425	(94.9)	<.001
	Yes	318	(4.5)	137	(7.7)	455	(5.1)	
Ischemic heart disease	No	5231	(73.6)	1,075	(60.5)	6306	(71.0)	<.001
	Yes	1873	(26.4)	701	(39.5)	2574	(29.0)	
		Mean ± SD		Mean ± SD		Mean ± SD		P value
Age, yrs		71.55 ± 5.47		71.55 ± 5.47		71.55 ± 5.47		.999
Survival time, yrs		6.96 ± 0.40		6.87 ± 0.77		6.94 ± 0.50		<.001

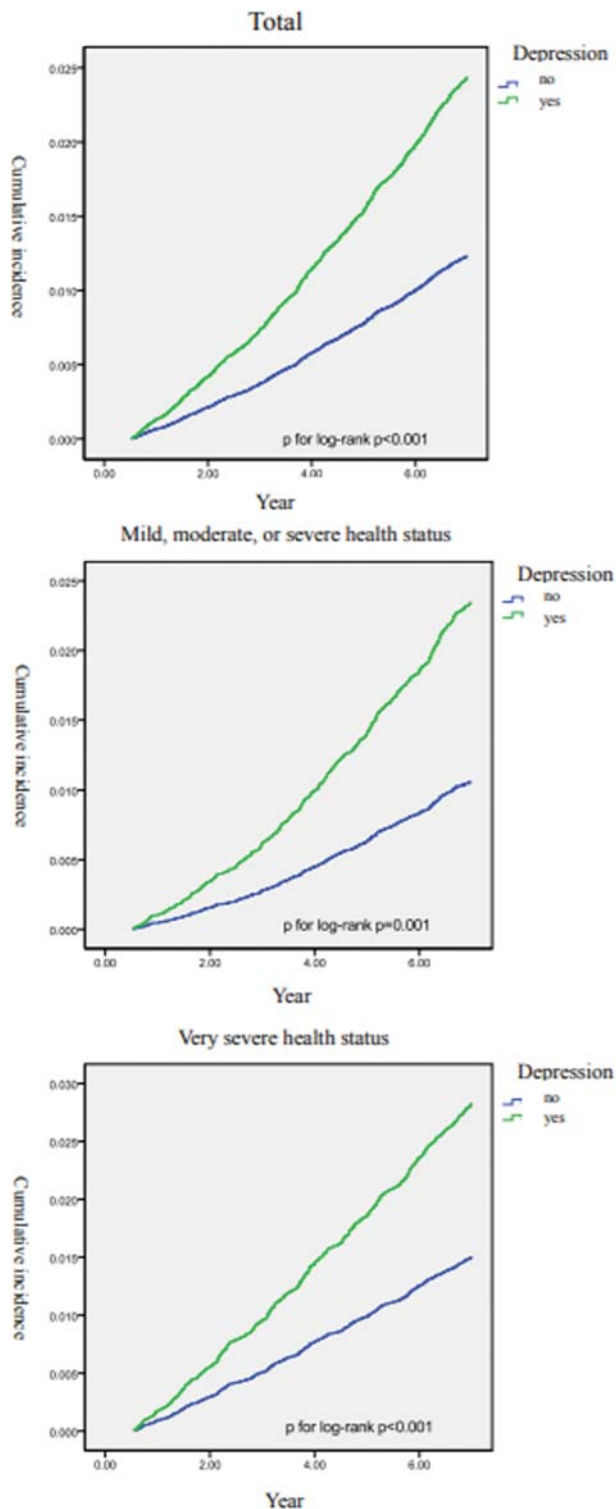


Figure 2. Cumulative incidence curves of Alzheimer disease (AD) from all patients, from patients with mild, moderate, or severe morbidity status, and from very severe morbidity status—log-rank P of all 3 graphs significant at $P < .05$.

4.5%), and ischemic heart disease (39.5% vs 26.4%). Furthermore, subjects in the case group had a shorter survival time following development of AD than subjects in the control group (6.87 vs 6.96 years, $P < .001$).

3.2. Risk of incidence in Alzheimer disease

Table 2 shows the risk of incidence in acquiring AD between the 2 groups. The incidence rate of AD for the case group was 0.96 per 10^3 person-year (95% confidence interval [CI]=0.73–1.22 per 10^3 person-year) and the hazard ratio (HR) was 2.49 (95% CI=1.80–3.45). The adjusted HR was 2.21 (95% CI=1.57–3.11), which was also significantly higher than that of the control group. In addition, the incidence rate of AD for the case group with mild, moderate, or severe health statuses was 0.54 per 10^3 person-year (95% CI=0.32–0.78 per 10^3 person-year), but for the control group, it was 1.39 per 10^3 person-year (95% CI=1.02–1.85 per 10^3 person-year). The HR and adjusted HR for the case group in mild, moderate, or severe health status was 2.84 (95% CI=1.62–4.97) and 2.67 (95% CI=1.50–4.74), respectively. The incidence rate of AD for the case group with very severe health status was 1.40 per 10^3 person-year (95% CI=1.06–1.82 per 10^3 person-year), but for the control group, it was 1.73 per 10^3 person-year (95% CI=1.30–2.24 per 10^3 person-year). The HR and adjusted HR for the case group with very severe health status was 2.08 (95% CI=1.38–3.12) and 2.06 (95% CI=1.36–3.12), respectively.

Figure 2 is the Kaplan–Meier curves of the 2 groups without accounting for health status. These reveal that the case group had a higher incidence rate of AD than the control group. A similar finding was observed even after accounting for various health statuses. The result of the log-rank test showed that the survival rates for the 2 groups differed significantly ($P < .001$).

3.3. Association between major depressive disorder and Alzheimer disease

The GEE models on patients with major depressive disorder and AD are exhibited in Table 3. Independent variables influencing the development of AD included age, severity of health status, artery disease, and major depressive disorder. For every yearly increase in age, the patients had 1.055 times the risk of developing AD (95% CI=1.035–1.075). Additionally, patients with very severe health statuses had 1.630 times the risk of developing AD than those with mild to severe health statuses (95% CI=1.220–2.177). Subjects suffering from artery disease had 1.692 times the risk of developing AD than those without artery disease (95% CI=1.108–2.584). Finally, the case group diagnosed with major depressive disorder had 1.898 times the risk of developing AD than the control group (95% CI=1.451–2.483) (Table 4).

4. Discussion

4.1. Clinical implications

Although a number of previous studies have found that depressive elderly patients have a higher risk of developing AD than those without depression, the degree of association between depression and AD varied across studies. Our study identified an association between different health statuses of subjects diagnosed with depression, and thereafter the development of AD, irrespective of the age, sex, and comorbidities of these patients. Since this study was a longitudinal and retrospective cohort study with 7 consecutive years of follow-up and defined all subjects with single-episode major depressive disorder, the results of the association between depression and AD must be interpreted with caution. The results showed that depressive elderly patients had a

Table 2
Risk of incidence in Alzheimer disease.

Variables	n	Number of incident cases	Number of person-year	Incidence (per 103 person-year)	Crude hazard ratio (95% confidence interval)	Adjusted hazard ratio* (95% confidence interval)
Total	8880	155	61,663	2.51 (2.14–2.93)		
Without depression	7140	96	49,455	1.56 (1.27–1.89)	1.00	1.00
With depression	1776	59	12,208	0.96 (0.73–1.22)	2.49 (1.80–3.45)	2.21 (1.57–3.11)
Health status – mild, moderate, or severe						
Total	4542	61	31,600	1.93 (1.49–2.46)		
Without depression	3992	44	27,812	1.39 (1.02–1.85)	1.00	1.00
With depression	550	17	3788	0.54 (0.32–0.78)	2.84 (1.62–4.97)	2.67 (1.50–4.74)
Health status – very severe						
Total	4338	94	30,063	3.13 (2.54–3.80)		
Without depression	3112	52	21643	1.73 (1.30–2.24)	1	1
With depression	1226	42	8420	1.40 (1.02–1.86)	2.08 (1.38–3.12)	2.06 (1.36–3.12)

* Adjusted for gender, age, and comorbidities.

higher AD incidence rate (0.96 per 10³ person-year; 95% CI= 0.73–1.22 per 10³ person-year) and an HR of 2.49 (95% CI= 1.80–3.45) relative to those without depression. The adjusted HR to develop subsequent AD was 2.21 (95% CI=1.57–3.11). In addition, this study used the ACG system to quantify health status so that we could investigate the degree of association between depression and subsequent AD, and health status objectively. The variables were often measured by questionnaires in the past. As the health status of all subjects was calculated for 7 years, the significance of our study differs from previous studies because the utilization data used to calculate health status each year and for every subject were complete. The causal relationship between AD and depression in elderly adults could not be determined in previous studies because often the length of observation was too short.^[14,16,17,24]

Many previous studies investigating the relationship between depression in elderly patients and subsequent development of AD used only clinical data including MRI images. However, a lack of longitudinal utilization data for observation prevented the identification of a causal relationship.^[9] According to Saczynski et al, inconsistent results from those studies that investigated the influence of elderly depression on dementia were possibly caused by the short time periods of subsequent follow-up.^[19] Additionally, problems in early studies arose due to the short time between the confirmation of depression and acquisition of AD.^[19] Our study followed its subjects for 7 years and found that there was a higher possibility of developing AD in elderly patients with depression than those without depression; therefore, clinicians

need to pay special attention to this association while treating elderly patients suffering from depression.

The vast majority of AD cases have a late onset (usually ≥ 65 years of age). This disease is rare among younger individuals.^[25] Age is recognized as one of the major risk factors for the development of AD. Our study also demonstrated the same result by both univariate analysis and the GEE model. This suggests that older age is symbolic of an indicator for AD. From the clinical viewpoint, age at onset of AD is often a very difficult parameter to record with precision when assessed retrospectively. The ability to delay the age at onset of this disease through preventive or therapeutic approaches would have significant benefits. However, few therapies have been successful in achieving this important goal.^[26]

It was strongly linked to the health status of the elderly and development of AD after adjustment for confounding factors in this study. Previous study indicated that elderly people's need to adopt lifestyle modifications for their health. However, lifestyle changes are not made easily.^[27] Functional status and health status are both highly related to the quality of life, and especially so for the elderly.^[28] To decrease the progression of AD, it is essential that healthcare services be easily accessible and address the elderly population's increasing needs for health management, risk reduction, help adopting healthy lifestyles, and improving personal quality of life.

Another association found in this study was the influence of artery diseases on elderly patients with depression and subsequent AD. Artery diseases have been identified as a comorbidity

Table 3
Generalized estimating equation (GEE) models for patients with depression and Alzheimer disease (n=8880).

Variable	β	SE	Hazard ratio	95% confidence interval	P value
Age, yrs	0.054	0.010	1.055	1.035–1.075	<.001
Gender (male vs female)	−0.245	0.130	0.783	0.607–1.009	.059
Health status (very severe vs others)	0.488	0.148	1.630	1.220–2.177	.001
Depression (yes vs no)	0.641	0.137	1.898	1.451–2.483	<.001
Coronary heart disease (yes vs no)	−0.214	0.468	0.808	0.323–2.020	.648
Type 2 diabetes (yes vs no)	0.228	0.145	1.256	0.946–1.668	.114
Hypertension (yes vs no)	−0.214	0.128	0.808	0.628–1.038	.096
Arrhythmia (yes vs no)	0.070	0.199	1.073	0.726–1.586	.724
Artery disease (yes vs no)	0.526	0.216	1.692	1.108–2.584	.015
Ischemic heart disease (yes vs no)	−0.297	0.206	0.743	0.496–1.113	.150
Chronic kidney disease (yes vs no)	0.172	0.205	1.187	0.794–1.775	.403

Table 4**Study results of development of Alzheimer disease form major depression patients in various populations.**

First author	Study year	Screened number	Following period	Setting	Results	Reference
Chong et al	2001	1500 subjects	Mid-1996 and the end of 1998	Taiwan	1-month prevalence of psychiatric disorder was 33.7%, with 15.3% depressive neurosis and 59% major depression	[5]
Green et al	2003	4046 individuals	10 yrs	United States	There was a significant association between depression symptoms and AD (adjusted OR, 2.13; 95% CI=1.71–2.67). In families where depression symptoms 1st occurred within 1 yr before the onset of AD, the association was higher (OR, 4.57; 95% CI=2.87–7.31), while in the families where the depression symptoms 1st occurred more than 1 yr before the onset of AD, the association was lower (OR, 1.38; 95% CI=1.03–1.85). In families where depression symptoms 1st occurred more than 25 yrs before the onset of AD, there was still a modest association (OR, 1.71; 95% CI=1.03–2.82).	[13]
Modrego and Ferrández	2004	114 patients	Mean period of 3 yrs (June 1999 to June 2001)	Spain	Of the depressed patients, 35 (85%) developed dementia in comparison with 24 (32%) of the nondepressed patients (RR 2.6; 95% CI=1.8–3.6). The survival analysis also showed that depressed patients developed dementia earlier than the nondepressed. Most patients with depression at baseline exhibited a poor response to antidepressants.	[14]
Pérès et al	2006	1517 patients	Visited at 8–10 yr follow-ups	France	In multivariate analyses, the OR for dementia was 7.4 (CI=3.3–16.5) in the IADL-restricted MCI and 2.8 (CI=1.3–6.0) in the non-IADL-restricted MCI compared with the non-IADL-restricted controls.	[15]
Ravaglia et al	2007	1016 subjects	4 yrs (1999/2000–2003/2004)	Italy	Overall prevalence of MCI was 7.7% (95% CI=6.1–9.7%) and was greater with older age and poor education. During 4 yrs of follow-up, 155 incident MCI cases were diagnosed, with an incidence rate of 76.8 (95% CI=66.8–88.4) per 1000 person-years. Approximately half of prevalent and incident MCI cases had memory impairment. Compared with normal cognition, multivariable-adjusted risk for progression from MCI with memory impairment to dementia was 4.78 (95% CI=2.78–8.07) for any dementia, 5.92 (95% CI=3.20–10.91) for AD, and 1.61 (95% CI=0.37–7.00) for VaD. No association with dementia risk was found for MCI without memory impairment.	[16]
Palmer et al	2007	232 patients	3 yrs	Stockholm, Sweden	Among persons with MCI, the 3-yr risk of progressing to AD almost doubled with each anxiety symptom (RR=1.8 [1.2–2.7] per symptom). Conversely, among cognitively intact subjects, only symptoms of depressive mood were related to AD development (RR=1.9 [1.0–3.6] per symptom).	[9]
Ravaglia et al	2008	667 subjects	4-yr follow-up (1999/2000–2003/2004)	Italy	Baseline depressive symptoms (GDS ≥ 10) were more frequent in prevalent MCI cases (44.4%) than in MCI participants (18.3%). The association was independent of MCI subtype, antidepressant use, and sociodemographic and vascular risk factors. In MCI subjects, baseline depressive symptoms were also associated with increased risk of MCI at follow-up, but only for subjects on antidepressant drugs at baseline (incident cases=72.7%) compared with those without depressive symptoms and not on antidepressant therapy (incident cases=24.0%). The association was independent of other confounders and stronger for <i>m</i> – MCI (incident cases=45.4%) with respect to <i>m</i> + MCI (incident cases=27.3%).	[17]
Grünblatt et al	2009	606 patients	30 mos	Austria	AD and depression were significant associated.	[18]
Saczynski et al	2010	949 participants	17-yr follow-up period	Framingham, United States	Depressed participants (CES-D ≥ 16) had more than a 50% increased risk for dementia (HR 1.72, 95% CI=1.04–2.84, <i>P</i> =.035) and AD (HR 1.76, 95% CI 1.03–3.01, <i>P</i> =.039). Results were similar when we included subjects taking antidepressant medications as depressed. For each 10-point increase on the CES-D, there was significant increase in the risk of dementia (HR 1.46, 95% CI=1.18–1.79, <i>P</i> < .001) and AD (HR 1.39, 95% CI 1.11–1.75, <i>P</i> =.005). Results were similar when we excluded persons with possible mild cognitive impairment.	[19]
Barnes et al	2012	3535 long-term Kaiser permanente members	6 yrs in midlife (1964–1973) and late life (1994–2000)	Northern California, United States	The adjusted hazard of dementia was increased by approximately 20% for midlife depressive symptoms only (HR 1.19, 95% CI=1.07–1.32), 70% for late-life symptoms only (HR 1.72, CI=1.54–1.92).	[8]
Lee et al	2012	243 MCI subjects	2 yrs (before June 1, 2010, and reflect the status of the database at that point)	United States	Depressive symptoms subjects had more frontal (<i>P</i> =.024), parietal (<i>P</i> =.030), and temporal (<i>P</i> =.038) white matter atrophy than no-symptom subjects.	[10]
Gorska-Ciebiada et al	2014	276 diabetics elders	1 yr	Poland	The prevalence of MCI was 31.5%, depressive syndrome was 29.7%, and MCI with coexisting depressive mood was 9.1%.	[20]
Polyakova et al	2014	23 original research articles	Last date July 15, 2013	Germany.	Point prevalence for MinD is higher in medical settings (median 14.4%) than in the community-based settings (median 10.4%) and primary care patients (median 7.7%).	[21]
Singh et al	2014	5 studies	At least 1 yr (November 2012)	United States	The subjects in the highest MeDi tertile had 33% less risk (adjusted HR 0.67; 95% CI=0.55–0.81; <i>P</i> < .0001) of cognitive impairment (MCI or AD) as compared to the lowest MeDi score tertile. Among cognitively normal individuals, higher adherence to the MeDi was associated with a reduced risk of MCI (HR 0.73; 95% CI=0.56–0.96; <i>P</i> =.02) and AD (HR 0.64; 95% CI=0.46–0.89; <i>P</i> =.007). There was no significant heterogeneity in the analyses.	[11]
Bae et al	2015	460 subjects	3.5 yrs	Korea	MCI was associated with a 6-fold increased risk of AD	[22]
Diniz et al	2013	23 studies	Median follow-up interval for 5 yrs	United States	Late-life depression was associated with a significant risk of all-cause dementia (1.85, 95% CI=1.67–2.04, <i>P</i> =.001), Alzheimer disease (1.65, 95% CI=1.42–1.92, <i>P</i> =.001) and vascular dementia (2.52, 95% CI=1.77–3.59, <i>P</i> =.001). Subgroup analysis, based on 5 studies, showed that the risk of vascular dementia was significantly higher than for Alzheimer disease (<i>P</i> =.03).	[23]

AD = Alzheimer disease, CES-D = center for epidemiologic studies depression scale, CI = confidence interval, GDS = geriatric depression scale, HR = hazard ratio, IADL = instrumental activities of daily living, MCI = mild cognitive impairment, RR = relative risk, VaD = criteria for diagnosis of vascular dementia.

or risk factor causing AD and were well-documented in previous studies. A subtype of late-onset depression is vascular depression. Some vascular risk factors (e.g., hypertension, diabetes, and heart disease) cause neural pathways responsible for regulating emotion to exhibit vascular lesions. This leads to the destruction of emotional regulation and results in vascular depression.^[29] Despite this, we found that only artery disease had a significant impact on AD. Therefore, clinicians must be careful to distinguish between depression and vascular depression because the latter can cause cognitive dysfunction similar to AD. In particular, patients with prominent executive dysfunction have a relatively high possibility of being diagnosed with dementia.^[30] As a result, artery disease could be treated as a comorbidity which moderates depression but not vascular depression or AD.

In this study, the association between depression and AD was the way in which the diagnosis of AD was also confirmed. Since medication for AD is expensive compared with those used in other chronic diseases, the NHI bureau requests that physicians exclude depression before confirming a diagnosis of AD. Nonetheless, previous studies have found that many patients exhibit mild cognitive impairment (MCI) before the confirmation of AD; therefore, the evidence of AD warrants discussion.^[31] Panza et al found that the incidence and prevalence of depression varied considerably in some MCI studies mainly because the diagnostic conditions, sampling, and assessment methods for MCI and AD were similar, but the prevalence of MCI and AD also differed substantially.^[24] Some studies considered symptoms of MCI as evidence of early-stage AD; that is, confirmation of AD included preexisting MCI.^[24] Polyakova et al agreed that inconsistent research methods not only resulted in considerably different prevalence rates of depression among patients with AD but also led to difficulties interpreting the results due to the confirmation of AD.^[21] The diagnosis of MCI, though, is rare in the NHIRD, and for this reason, we did not include MCI as a variable.

There was no evidence that sex had any influence on the development of AD in our study. The risk of developing AD in depressed patients increased by 1.055 times compared to those without depression for every year older. The relationship between depression and AD confirmed the findings of previous studies.^[15,16,20,22] Our study confirmed that health status, as derived by applying the ACG software to utilization data for 7 years, was a significant moderator of the correlation between depression and AD. Although comorbidities could be multicollinear in correlation to health status, a high level of multicollinearity for the derived data of health status was not necessary because the results of the ACG calculation of health status have been proven useful in studies of this kind.

4.2. Methodologic considerations

Our study has several potential limitations. Firstly, because we used a more conservative method to select subjects who had depression and/or AD by diagnosis and medication instead of by questionnaire, some subjects with depression or AD diagnosis/medication could have been excluded due to a lack of information. However, since the NHI in Taiwan is a compulsory insurance covering 99% of the total population of Taiwan, we believe that unidentified cases of elderly patients with both diseases are rare. Secondly, because the treatment of both depression and AD in Taiwan is expensive, the NHI bureau requests that physicians go through complex processes to confirm the incidence of both diseases. Therefore, the influence of

depression on AD might be underestimated because of the high stringency in selecting subjects. Since over 99% of total population is insured by the NHI, the impact of uninsured subjects on our findings should be minimal. Thirdly, the data source of this study was the NHIRD which lacked relevant clinical variables such as laboratory data and pathology findings. A misclassification bias might have been present. Finally, due to the sex effect in this study was viewed as one of confounding factors when explore the association between major depressive disorder and the later development of AD, further studies should be conducted to analyses the potential for condition-related sex difference, because it was considered that such difference might underscore important implications for the understanding of the overall pathogenesis of the development of AD among the old major depressive patients.

5. Conclusion

In conclusion, the onset of AD is found in approximately one-third of the elderly patients with AD also suffering from depression. Symptoms related to cognitive functions are unclear; therefore, accurate diagnosis relies on the reliability of information provided by families or care-givers. Unfortunately, some patients' families or care-givers also suffer from depression or other emotional problems while taking care of the patients. This may influence the information provided. Therefore, hospitalization often proves to be a more reliable method of diagnosis. Thus, different diagnostic codes should be devised for geriatric patients with depression and other depressive symptoms.

Author contributions

Ping Tao, Szu-Nian Yang, Yu-Chi Tung, Ming-Chin Yang conducted the study and drafted the manuscript. Szu-Nian Yang and Yu-Chi Tung participated in the design of the study and performed statistical analyses. Ping Tao and Ming-Chin Yang conceived the study, and participated in its design and coordination. All of the authors read and approved the final manuscript.

Conceptualization: Yu-Chi Tung, Ming-Chin Yang.

Formal analysis: Szu-Nian Yang.

Methodology: Szu-Nian Yang.

Supervision: Ming-Chin Yang.

Writing – original draft: Ping Tao, Szu-Nian Yang, Yu-Chi Tung.

Writing – review & editing: Ping Tao, Ming-Chin Yang.

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