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Original Study

Risk of Dementia Among Patients With Asthma: A Nationwide Longitudinal Study



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A B S T R A C T

Keywords:

Asthma
dementia
Alzheimer's disease
comorbidities

Background: Previous studies have suggested an association between asthma and dementia, but the results are still inconsistent.

Methods: Using the Taiwan National Health Insurance Database, we enrolled 11,030 participants aged more than 45 years with asthma and 44,120 (1:4) age-/sex-matched controls between 1998 and 2008, and followed them to the end of 2011. Cases of any dementia or Alzheimer's disease that developed during the follow-up period were identified.

Results: Asthma was associated with an increased risk of developing any dementia [hazard ratio (HR): 2.17, 95% confidence interval (CI): 1.87–2.52] and Alzheimer's disease (HR: 2.62, 95% CI: 1.71–4.02). Stratified by age, both asthma in midlife (>45 years and <65 years) and in late life (≥65 years) was associated with a greater likelihood of any dementia (HR: 2.48, 95% CI: 1.80–3.41; HR: 2.06, 95% CI: 1.74–2.44).

Discussion: Asthma in midlife and in late life increased the risk of developing any dementia and Alzheimer's disease. The underlying mechanisms between asthma and dementia require further investigation.

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Dementia is a neurodegenerative syndrome that causes deterioration in memory and deficits in other cognitive functions including aphasia, apraxia, agnosia, and disturbances in executive functions, and interferes with work and social functioning, and with independence in everyday activities.^{1–4} Both developed and developing countries worldwide are currently facing an aging population, and dementia has become one of the fastest-growing and most important concerns in public health and clinical practice.^{1,2,4,5} The overall global prevalence of dementia among persons ≥60 years was estimated to

be 3.9% (>24 million people) in 2005.⁶ In addition, in some low- and middle-income countries, dementia makes the largest contribution to disability and has a major financial and psychosocial impact on the suffering persons and their family, as well as society in general.^{4,5} However, the definite etiology of dementia is still unknown, though there are different neurodegenerative hypotheses, including depositions of β-amyloid plaques and neurofibrillary tangles, neuroinflammation, and vasculopathy.^{7–9}

In terms of neuroinflammation, little research has been done on the long-term effects of asthma on cognitive functioning or on the risk of dementia, and the findings are inconsistent.^{10–13} A positive association was noted in the Finnish Cardiovascular Risk Factors, Aging, and Dementia study, in which midlife asthma [hazard ratio (HR): 2.40, 95% confidence interval (CI): 1.07–5.40] was found to increase the later risk of cognitive impairment and dementia among 2000 midlife participants who were followed from the 1970s and 1980s to 1998 and the 2000s.¹³ However, Eriksson et al¹⁰ linked the data of self-reported asthma and other atopic diseases in 1963, 1967, and 1973, and data

The authors declare no conflicts of interest.

The study was supported by a grant from Taipei Veterans General Hospital (V103E10-001).

All authors have no financial relationships relevant to this article to disclose.

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from the dementia registry of 22,188 community-dwelling participants between 1974 and 2001, and found that asthma was not associated with the risk of Alzheimer's disease (HR: 0.80, 95% CI: 0.51–1.25) or any dementia (HR: 0.87, 95% CI: 0.61–1.26). Ng et al¹² also found no positive association between asthma and dementia [odds ratio (OR): 2.39, 95% CI: 0.94–6.11] among 1092 elderly aged ≥ 60 years. Furthermore, some evidences suggested the association between the use of inhaled steroid and the cognitive decline.^{14,15} Ancelin et al¹⁴ showed that the elderly, especially women, taking inhaled steroid were at increased risk for cognitive decline in executive functioning (OR: 1.76; 95% CI: 1.14–2.71). However, there were some limitations to the above studies, including the self-reported diagnosis of asthma, which was not confirmed by physicians, not adjusting the regression model for other dementia-related risk factors, and that some studies used a cross-sectional study design.

In our study, using the Taiwan National Health Insurance Research Database (NHIRD) with a large sample size and a longitudinal follow-up study design, we attempted to investigate the temporal association between asthma and dementia. We hypothesized that asthma increased the risk of developing dementia during the follow-up.

Methods

Data Source

The Taiwan National Health Insurance (NHI) program was implemented in 1995 and offers comprehensive medical coverage to all residents of Taiwan. The NHI program covered both primary-level and secondary-level health care of all insured participants. National Health Research Institute is in charge of the entire insurance claims database, namely, the NHIRD, which consists of healthcare data from $>97\%$ of the entire Taiwan population (<http://www.nhi.gov.tw/>). The National Health Research Institute audits and releases the NHIRD for use in health service studies. Participants included in the NHIRD are anonymous to maintain individual privacy. Comprehensive information on insured participants is included in the database, including demographic data, dates of clinical visits, disease diagnoses, and prescriptions. The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan.^{16–19}

Inclusion Criteria for Participants With Asthma and the Control Group

Participants aged more than 45 years who were identified with asthma diagnosed (ICD-9-CM code: 493) by pulmonologists or rheumatologists based on the clinical judgment or the pulmonary function test between January 1, 1998 and December 31, 2008, and who had no history of any dementia (ICD-9-CM codes: 290, 294.1–294.2, 331) before enrollment, were included as the asthma cohort. The age- and sex-matched (1:4) control cohort was randomly identified from among the 1,000,000 participants after eliminating the study participants, individuals who had been given a diagnosis of asthma at any time, and individuals who had a diagnosis of any dementia (ICD-9-CM codes: 290, 294.1–294.2, 331) before enrollment. All controls, therefore, had no diagnosis of asthma at any time (before enrollment and the whole follow-up period), and had no diagnosis of any dementia before the enrollment. Diagnoses of any dementia (ICD-9-CM codes: 290.0–290.4, 294.1–294.2, 331.0, 331.1, 331.82) given by psychiatrists or neurologists or Alzheimer's disease (ICD-9-CM code: 331.0) given by psychiatrists or neurologists were identified during the follow-up (to December 31 2011 or to the date of death). Because of the high comorbidity of other allergic diseases with asthma, we assessed the

comorbid effects of different allergic diseases, including allergic rhinitis (ICD-9-CM code: 477) and atopic dermatitis (ICD-9-CM codes: 691 or 691.8), on the risk of developing dementia. Potential dementia-related risk factors were also assessed as confounding factors; these included depressive disorder (ICD-9-CM codes: 296.2, 296.3, 300.4, 311), alcohol-related disorders (ICD-9 codes: 291, 303, 305.0, 357.5, 425.5, 535.3, 571.0, or 571.1–571.3), substance use disorders (ICD-9 codes: 292, 304, 305.1–305.9), hypertension (ICD-9-CM codes: 401–405), dyslipidemia (ICD-9-CM code: 272), diabetes mellitus (ICD-9 code: 250), renal diseases (ICD-9 codes: 580–589), ischemic heart diseases (ICD-9 codes: 410–414), cerebrovascular diseases (ICD-9 codes: 430–438), chronic respiratory diseases (ICD-9 codes: 491, 492, 494, 496, 416.8, 416.9), and head injury (ICD-9 codes: 800–804, 850–854, 959). The use of inhaled steroid and health system utilization (number of medical consultations per year) were also included in the analyses and adjusted for their confounding effect. All diagnoses were given at least twice by corresponding physicians to achieve diagnostic validity. Level of urbanization (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed.²⁰

Statistical Analysis

For between-group comparisons, the independent *t*-test was used for continuous variables and Pearson's χ^2 test for nominal variables, where appropriate. The Cox regression model was used to investigate the HR with 95% CI of developing any dementia and Alzheimer's disease after adjusting for demographic data, medical comorbidities, use of inhaled steroid, and health system utilization. Sensitivity tests were also performed to validate the findings after excluding the first 1-year observation and the first 3-year observation. Subanalysis stratified by age group (age <65 years and age ≥ 65 years) was performed to investigate the risk of developing dementia and Alzheimer's disease in both subgroups. All data processing and statistical analyses were performed with Statistical Package for Social Science v 17 software (SPSS Inc, Chicago, IL) and Statistical Analysis Software v 9.1 (SAS Institute, Cary, NC).

Results

In all, 11,030 patients with asthma and 44,120 age-/sex-matched controls were included in our study, with an average age of 60.88 ± 10.39 years and a female predominance (58.3%), and with a mean follow-up of 8.00 ± 3.04 years. Patients with asthma had higher incidence rates of developing any dementia (6.79 vs 3.08/1000 person-years, $P < .001$) and Alzheimer's disease (0.87 vs 0.33/1000 person-years), with an earlier age of diagnoses of dementia (75.63 ± 8.30 vs 78.94 ± 7.64 years, $P < .001$) and Alzheimer's disease (77.61 ± 6.42 vs 79.27 ± 6.77 years, $P = .090$), compared with the control group (Table 1). Those with asthma had an elevated prevalence of psychiatric and medical comorbidities, including depressive disorder (7.6% vs 4.2%, $P < .001$), alcohol-related disorders (0.8% vs 0.6%, $P = .074$), hypertension (57.3% vs 48.4%, $P < .001$), dyslipidemia (32.7% vs 27.3%, $P < .001$), diabetes mellitus (26.3% vs 21.8%, $P < .001$), renal diseases (6.1% vs 4.9%, $P < .001$), ischemic heart diseases (16.5% vs 10.1%, $P < .001$), cerebrovascular diseases (16.2% vs 11.9%, $P < .001$), chronic respiratory diseases (42.6% vs 6.1%, $P < .001$), and head injury (5.1% vs 3.7%, $P < .001$), compared with the controls (Table 1). Use of inhaled steroid (64.1% vs 1.8%, $P < .001$) and health system utilization (13.14 ± 15.26 vs 9.01 ± 12.75 times per year, $P < .001$) were also higher among patients with asthma than in the control group (Table 1). Patients with asthma resided in more urbanized areas ($P = .001$) and had higher income ($P = .001$) than the control group (Table 1).

After adjusting demographic data, use of inhaled steroid, health system utilization, and medical comorbidities, Cox regression models

Table 1
Demographic Data of Patients With Asthma and the Control Group

	Patients With Asthma (n = 11,030)	Controls (n = 44,120)	P Value
Age at diagnosis of asthma/enrollment (years, SD, n, %)	60.88 (10.39)	60.88 (10.39)	
<65 years	7038 (63.8)	28152 (63.8)	
≥65 years	3992 (36.2)	15968 (36.2)	
Sex (M, %)	4599 (41.7)	18396 (41.7)	
Any dementia (n, 1000 person-year)	590 (6.79)	1091 (3.08)	<.001
Age at diagnosis (years, SD)	75.63 (8.30)	78.94 (7.64)	<.001
Duration between asthma/enrollment and diagnosis (years, SD; n, %)	5.50 (3.18)	6.87 (3.02)	<.001
<1 year	43 (7.3)	18 (1.6)	
1–3 years	111 (18.8)	120 (11.0)	
>3 years	436 (73.9)	953 (87.4)	
Alzheimer's disease (n, 1000 person-year)	77 (0.87)	118 (0.33)	<.001
Age at diagnosis (years, SD)	77.61 (6.42)	79.27 (6.77)	.090
Duration between asthma/enrollment and diagnosis (years, SD; n, %)	6.21 (2.75)	7.08 (3.07)	.045
<1 year	3 (3.9)	1 (0.8)	
1–3 years	9 (11.7)	10 (8.5)	
>3 years	65 (84.4)	107 (90.7)	
Comorbidities during the whole follow-up (n, %)			
Atopic dermatitis	141 (1.3)	379 (0.9)	<.001
Allergic rhinitis	3396 (30.8)	4209 (9.5)	<.001
Depressive disorder	838 (7.6)	1864 (4.2)	<.001
Alcohol-related disorders	87 (0.8)	279 (0.6)	.074
Substance use disorders	14 (0.1)	48 (0.1)	.633
Hypertension	6325 (57.3)	21355 (48.4)	<.001
Dyslipidemia	3608 (32.7)	12043 (27.3)	<.001
Diabetes mellitus	2901 (26.3)	9623 (21.8)	<.001
Renal diseases	672 (6.1)	2178 (4.9)	<.001
Ischemic heart diseases	1818 (16.5)	4467 (10.1)	<.001
Cerebrovascular diseases	1792 (16.2)	5255 (11.9)	<.001
Chronic respiratory diseases	4699 (42.6)	2698 (6.1)	<.001
Head injury	560 (5.1)	1630 (3.7)	<.001
Use of inhaled steroid (n, %)	7066 (64.1)	814 (1.8)	<.001
Level of urbanization (n, %)			.001
1 (most urbanized)	3216 (29.2)	12641 (28.7)	
2	3312 (30.0)	12833 (29.1)	
3	1710 (15.5)	6579 (14.9)	
4	1585 (14.4)	6798 (15.4)	
5 (most rural)	1207 (10.9)	5269 (11.9)	
Income-related insured amount			.001
≤15,840 NTD/month	6005 (54.4)	23611 (53.5)	
15,841–25,000 NTD/month	3163 (28.7)	13411 (30.4)	
≥25,001 NTD/month	1862 (16.9)	7098 (16.1)	
Health system utilization (number of consultations/year)	13.14 (15.26)	9.01 (12.75)	<.001

NTD, New Taiwan Dollar; SD, standard deviation.

Table 2
Risk of Developing Any Dementia of Patients With Asthma and the Control Group

	<65 Years HR (95% CI)	≥65 Years HR (95% CI)	Total HR (95% CI)
	Any Dementia*		
Asthma, presence vs absence	2.48 (1.80–3.41)	2.06 (1.74–2.44)	2.17 (1.87–2.52)
Comorbidities, presence vs absence			
Atopic dermatitis	1.06 (0.44–2.58)	0.88 (0.53–1.46)	0.92 (0.59–1.44)
Allergic rhinitis	1.06 (0.80–1.40)	0.90 (0.78–1.05)	0.94 (0.82–1.07)
Depressive disorder	3.74 (2.84–4.92)	2.79 (2.36–3.30)	3.12 (2.71–3.60)
Alcohol-related disorders	0.65 (0.16–2.64)	2.03 (1.08–3.81)	1.56 (0.88–2.77)
Substance use disorders	NA	0.56 (0.08–3.98)	0.38 (0.05–2.74)
Hypertension	0.92 (0.71–1.18)	1.02 (0.89–1.12)	1.04 (0.92–1.16)
Dyslipidemia	0.74 (0.58–1.94)	0.88 (0.78–2.01)	0.87 (0.78–1.97)
Diabetes mellitus	1.31 (1.03–1.68)	1.13 (1.00–1.28)	1.18 (1.05–1.31)
Renal diseases	1.16 (0.79–1.71)	0.95 (0.78–1.15)	0.99 (1.83–1.18)
Ischemic heart diseases	1.11 (0.83–1.49)	0.94 (0.82–1.07)	0.97 (0.86–1.10)
Cerebrovascular diseases	2.39 (1.85–3.08)	1.50 (1.33–1.68)	1.63 (1.46–1.82)
Chronic respiratory diseases	0.75 (0.54–1.92)	0.87 (0.75–2.00)	0.84 (0.73–1.96)
Head injury	1.73 (1.16–2.56)	1.12 (0.92–1.36)	1.18 (0.99–1.41)
Use of inhaled steroid, presence vs absence	1.11 (0.79–1.57)	0.96 (0.81–1.15)	0.98 (0.84–1.15)

NA, not available.

Bold type indicates the statistical significance.

*Adjusted by demographic data, health system utilization, medical comorbidities, and use of inhaled steroid and asthma as a binary variable.

only depressive disorder was associated with the risk of Alzheimer's disease (HR: 1.71, 95% CI: 1.03–2.85) (Table 3).

Discussion

Our results supported the study hypothesis that asthma in both midlife and late life was an independent risk factor for developing dementia after adjusting for demographic data, other allergic diseases, medical comorbidities, use of inhaled steroid, and health system utilization. Only asthma in late life, however, was associated with the increased risk of Alzheimer's disorder.

From the clinical perspective, Jelicic et al¹¹ assessed the cognitive function of a sample of community-dwelling elderly participants (n = 4528) and demonstrated that those who had received treatment for asthma/chronic bronchitis during the last 12 months had slightly lower Mini Mental State Examination scores than their counterparts without these diseases. In the Finnish Cardiovascular Risk Factors, Aging, and Dementia study, a population-based study investigating cardiovascular and lifestyle-related risk factors for dementia and cognitive functioning, Rusanen et al¹³ followed 2000 participants for more than 20 years, from their midlife to their geriatric period, and found that asthma in midlife was associated with an increased risk of developing any dementia (HR: 2.40, 95% CI: 1.07–5.40) after adjusting for age, sex, and education; however, this significance disappeared (HR: 1.88, 95% CI: 0.77–4.63) when additionally adjusting for cardiovascular risk factors, including dyslipidemia, hypertension, and other vascular diseases. The researchers further concluded that asthma is associated with an increased risk of cardiovascular diseases and stroke, which are also known to increase the risk of dementia.¹³ In our study, patients with asthma indeed had higher prevalence rates of cardiovascular risk factors and related diseases than the control group, but our results still showed that asthma in both midlife and late life was an independent risk factor for developing any

showed that patients with asthma had a greater likelihood of developing any dementia (HR: 2.17, 95% CI: 1.87–2.52) and Alzheimer's disease (HR: 2.62, 95% CI: 1.71–4.02) during the follow-up than the controls (Tables 2 and 3). Sensitivity tests after excluding the first 1-year and first 3-year observation revealed consistent findings for the development any dementia (HR: 1.99, 95%CI: 1.70–2.31; HR: 1.84, 95% CI: 1.55–2.18) and Alzheimer's disease (HR: 2.40, 95% CI: 1.55–3.71; HR: 2.32, 95% CI: 1.46–3.69) (Table 4). Subgroup analyses stratified by age group also found that both subgroups of patients (midlife: <65 years and late life: ≥65 years) with asthma had an increased risk of developing dementia (HR: 2.48, 95% CI: 1.80–3.41; HR: 2.06, 95% CI: 1.74–2.44), but only those aged ≥65 years with asthma had an increased risk of developing Alzheimer's disease (HR: 2.95, 95% CI: 1.87–4.65) (Tables 2 and 3). Furthermore, depressive disorder (HR: 3.12, 95% CI: 2.71–3.60), diabetes mellitus (HR: 1.18, 95% CI: 1.05–1.31), and cerebrovascular diseases (HR: 1.63, 95% CI: 1.46–1.82) were associated with the risk of dementia (Table 2), and

Table 3
Risk of Developing Alzheimer's Disease of Patients With Asthma and the Control Group

	<65 Years	≥65 Years	Total
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Alzheimer's Disease*			
Asthma, presence vs absence	1.20 (0.32–4.54)	2.95 (1.87–4.65)	2.62 (1.71–4.02)
Comorbidities, presence vs absence			
Atopic dermatitis	NA	1.31 (0.40–4.31)	1.12 (0.34–3.68)
Allergic rhinitis	0.99 (0.35–2.80)	0.96 (0.63–1.46)	0.95 (0.65–1.40)
Depressive disorder	1.31 (0.30–5.67)	1.74 (1.01–3.01)	1.71 (1.03–2.85)
Alcohol-related disorders	NA	NA	NA
Substance use disorders	NA	NA	NA
Hypertension	0.67 (0.30–1.51)	0.54 (0.38–1.76)	0.59 (0.43–1.80)
Dyslipidemia	1.50 (0.66–3.43)	1.20 (0.84–1.71)	1.32 (0.95–1.82)
Diabetes mellitus	1.05 (0.45–2.49)	0.94 (0.65–1.35)	0.98 (0.70–1.37)
Renal diseases	0.44 (0.06–3.36)	1.07 (0.62–1.86)	0.98 (0.58–1.67)
Ischemic heart diseases	1.36 (0.49–3.77)	0.85 (0.57–1.27)	0.90 (0.61–1.31)
Cerebrovascular diseases	0.63 (0.18–2.17)	0.97 (0.67–1.41)	0.93 (0.65–1.34)
Chronic respiratory diseases	0.44 (0.13–1.51)	0.96 (0.64–1.44)	0.91 (0.62–1.34)
Head injury	NA	0.54 (0.24–1.23)	0.49 (0.21–1.10)
Use of inhaled steroid, presence vs absence	3.01 (0.76–11.91)	0.86 (0.53–1.38)	1.01 (0.65–1.57)

NA, not available.

Bold type indicates the statistical significance.

*Adjusted by demographic data, health system utilization, medical comorbidities, and use of inhaled steroid and asthma as a binary variable.

dementia and Alzheimer's disease, even after adjusting for demographic data, medical comorbidities, and use of inhaled steroid. Our findings suggested that other factors in addition to cardiovascular diseases and stroke may contribute to the risk of developing any dementia or Alzheimer's disease.

From the neurobiological perspective, asthma-related immunologic dysregulation and disturbance may explain the comorbid association between asthma and dementia, as well as Alzheimer's disease.^{21–26} A growing body of evidence has shown that the proinflammatory cytokines released during the allergic responses of asthma play an important role in the pathophysiology of dementia and Alzheimer's disease, and suggests that dysregulation of the inflammatory pathway may affect the central nervous system and be involved in the pathophysiological mechanisms of neurodegenerative disorder.^{21–26} Elevated levels of interleukin (IL)-1 α , IL-1 β , IL-6, tumor necrosis

factor α , and interferon- α are noted in brain tissue of Alzheimer's disease patients.^{21,25} Ringheim et al²⁷ found that IL-6 promotes expression of amyloid- β precursor protein, and Quintanilla et al²⁸ demonstrated that IL-6 could also contribute to neurofibrillary tangles formation by inducing Tau phosphorylation. Griffin et al^{23,29} proposed the increase in IL-1 and astrocyte-derived neurotogenic cytokine S100B expression prior to the detection of either β -amyloid plaques or neurofibrillary tangles, and indicated that dysregulated neuroinflammation may precede the development of dementia. Takeda et al³⁰ reported that the increased level of IL-6 in the brain was significantly higher in Alzheimer amyloid precursor protein-transgenic mice than in wild-type mice, and further suggested the increased blood-brain barrier vulnerability to systemic inflammation in Alzheimer's disease. Some evidence has indicated that the over-secreted proinflammatory cytokines during an allergic response would penetrate the blood-brain barrier and activate abnormal neuroimmune mechanisms involving some specific neural circuits related to cognitive and emotional modulation.^{31–33} Asthma-related neuroimmune changes, as in a vicious cycle, take time to impair the specific brain function and neural circuitry involved in memory and cognition, which may explain the sequential phenomenon of asthma developing first and dementia following. Further studies would be required to investigate the definite underlying mechanisms between asthma and dementia, as well as Alzheimer's disease.

Consistent with previous studies investigating the association between depressive disorder and dementia, as well as Alzheimer's disease, our results also showed that depressive disorder was associated with an increased risk of developing dementia and Alzheimer's disease.^{34,35} A recent meta-analysis study demonstrated that depression was associated with a significant risk of all-cause dementia (OR: 1.85, 95% CI: 1.67–2.04), Alzheimer's disease (OR: 1.65, 95% CI: 1.42–1.92) and vascular dementia (OR: 2.52, 95% CI: 1.77–3.59).³⁵ da Silva also indicated that greater frequency and severity of depressive episodes increased this risk further.³⁴ In our study, patients with asthma had a higher prevalence of depressive disorder, but asthma was still an independent risk factor for developing dementia and Alzheimer's disease after adjusting for depressive disorder and other confounding factors. The association among asthma, depressive disorder, and dementia, as well as Alzheimer's disease, requires further investigation.

Some study limitations should be addressed here. First, the incidence of dementia and Alzheimer's disease and the prevalence of medical comorbidities may be underestimated because only those participants who sought medical help were enrolled. Therefore, a bias of identification of the participants may be existent. However, the participants enrolled in our study had board-certified physician diagnoses, yielding a better diagnostic validity. Furthermore, we also used the sensitivity test to re-confirm this association between asthma and the risk of dementia. However, the clinical population-based study may be required in the future to validate this association between asthma and the risk of dementia. Second, in our study, we only analyzed the use of inhaled steroid as the confounding factors with the risk of dementia because the previous studies suggested the possible impact of inhaled steroid in the risk of cognitive decline. However, the dosage and treatment duration of asthma medications were difficultly analyzed because it would be very complicated during such a long follow-up period. The difference in the risk of dementia on patients who were on short acting beta agonist versus who were on inhaled steroids or any anticholinergic may require the clinical case-control study in the future. Third, the NHI database did not provide some information, such as the disease severity (ie, the severity of dementia), the medication adherence, family history, personal lifestyle, smoking status, and environmental factors. Without this information, we were unable to examine their influence.

Table 4
Sensitivity Test for the Risk of Developing Any Dementia and Alzheimer's Disease of Patients With Asthma and the Control Group

	Total	>1 Year	>3 Years
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Any dementia*			
Asthma, presence vs absence	2.17 (1.87–2.52)	1.99 (1.70–2.31)	1.84 (1.55–2.18)
Alzheimer's disease*			
Asthma, presence vs absence	2.62 (1.71–4.02)	2.40 (1.55–3.71)	2.32 (1.46–3.69)

Bold type indicates the statistical significance.

*Adjusted by demographic data, health system utilization, medical comorbidities, and use of inhaled steroid and asthma as a binary variable.

In conclusion, our results supported the hypothesis that patients with asthma had an increased risk of developing dementia and Alzheimer's disease during the follow-up, after adjusting for demographic data, medical comorbidities, use of inhaled steroid, and health system utilization. Further studies are required to investigate the underlying pathophysiology between asthma and dementia, as well as Alzheimer's disease.

Acknowledgments

The authors thank Mr I-Fan Hu for his friendship and support. The authors also thank Dr MHC, Dr TPS, and Dr YMB, who designed the study, and wrote the protocol and manuscripts, Dr YMB, Dr TPS, Dr CTL, Dr CFT, Dr WCL, and Prof TLP who assisted with the preparation and proof-reading of the manuscript, and Dr YMB, Dr TJC, and Ms WHC, who provided the advices on statistical analysis.

References

- Chan KY, Wang W, Wu JJ, et al. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990–2010: A systematic review and analysis. *Lancet* 2013;381:2016–2023.
- Larson EB, Yaffe K, Langa KM. New insights into the dementia epidemic. *N Engl J Med* 2013;369:2295–2297.
- Okie S. Confronting Alzheimer's disease. *N Engl J Med* 2011;365:1069–1072.
- Sousa RM, Ferri CP, Acosta D, et al. Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: A 10/66 Dementia Research Group population-based survey. *Lancet* 2009;374:1821–1830.
- Sabat SR. Dementia in developing countries: A tidal wave on the horizon. *Lancet* 2009;374:1805–1806.
- Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: A Delphi consensus study. *Lancet* 2005;366:2112–2117.
- Iadecola C. The pathobiology of vascular dementia. *Neuron* 2013;80:844–866.
- Loy CT, Schofield PR, Turner AM, Kwok JB. Genetics of dementia. *Lancet* 2014;383:828–840.
- Song IU, Kim YD, Cho HJ, Chung SW. Is neuroinflammation involved in the development of dementia in patients with Parkinson's disease? *Intern Med* 2013;52:1787–1792.
- Eriksson UK, Gatz M, Dickman PW, et al. Asthma, eczema, rhinitis and the risk for dementia. *Dementia Geriatr Cogn Disord* 2008;25:148–156.
- Jelicic M, Kempen GL. Cognitive function in community-dwelling elderly with chronic medical conditions. *Int J Geriatr Psychiatry* 1997;12:1039–1041.
- Ng TP, Chiam PC, Kua EH. Mental disorders and asthma in the elderly: A population-based study. *Int J Geriatr Psychiatry* 2007;22:668–674.
- Rusanen M, Ngandu T, Laatikainen T, et al. Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: A population based CAIDE study. *Curr Alzheimer Res* 2013;10:549–555.
- Ancelin ML, Carriere I, Helmer C, et al. Steroid and nonsteroidal anti-inflammatory drugs, cognitive decline, and dementia. *Neurobiol Aging* 2012;33:2082–2090.
- McEwen BS, de Leon MJ, Lupien SJ, Meaney MJ. Corticosteroids, the aging brain and cognition. *Trends Endocrinol Metab* 1999;10:92–96.
- Chen MH, Su TP, Chen YS, et al. Higher risk of mood disorders among adolescents with ADHD and asthma: A nationwide prospective study. *J Affect Disord* 2014;156:232–235.
- Chen MH, Su TP, Chen YS, et al. Asthma and attention-deficit/hyperactivity disorder: A nationwide population-based prospective cohort study. *J Child Psychol Psychiatry* 2013;54:1208–1214.
- Shen CC, Tsai SJ, Perng CL, et al. Risk of Parkinson disease after depression: A nationwide population-based study. *Neurology* 2013;81:1538–1544.
- Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. *JAMA* 2012;308:1906–1914.
- Liu CY, Hung YT, Chuang YL, et al. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. *J Health Manage (Chin)* 2006;4:1–22.
- Ferretti MT, Cuervo AC. Does a pro-inflammatory process precede Alzheimer's disease and mild cognitive impairment? *Curr Alzheimer Res* 2011;8:164–174.
- Griffin WS. Neuroinflammatory cytokine signaling and Alzheimer's disease. *N Engl J Med* 2013;368:770–771.
- Griffin WS, Barger SW. Neuroinflammatory cytokines—The common thread in Alzheimer's pathogenesis. *US Neurol* 2010;6:19–27.
- Meraz-Rios MA, Toral-Rios D, Franco-Bocanegra D, et al. Inflammatory process in Alzheimer's Disease. *Front Integr Neurosci* 2013;7:59.
- Rubio-Perez JM, Morillas-Ruiz JM. A review: Inflammatory process in Alzheimer's disease, role of cytokines. *Sci World J* 2012;2012:756357.
- Michaud M, Balardy L, Moulis G, et al. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc* 2013;14:877–882.
- Ringheim GE, Szczepanik AM, Petko W, et al. Enhancement of beta-amyloid precursor protein transcription and expression by the soluble interleukin-6 receptor/interleukin-6 complex. *Brain Res Mol Brain Res* 1998;55:35–44.
- Quintanilla RA, Orellana DI, Gonzalez-Billault C, Maccioni RB. Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway. *Exp Cell Res* 2004;295:245–257.
- Griffin WS, Stanley LC, Ling C, et al. Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc Natl Acad Sci USA* 1989;86:7611–7615.
- Takeda S, Sato N, Ikimura K, et al. Increased blood-brain barrier vulnerability to systemic inflammation in an Alzheimer disease mouse model. *Neurobiol Aging* 2013;34:2064–2070.
- Raison CL, Miller AH. Do cytokines really sing the blues? *Cerebrum* 2013;2013:10.
- Rosenkranz MA, Busse WW, Johnstone T, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proc Natl Acad Sci USA* 2005;102:13319–13324.
- Yarlagadda A, Alfson E, Clayton AH. The blood brain barrier and the role of cytokines in neuropsychiatry. *Psychiatry (Edmont)* 2009;6:18–22.
- da Silva J, Goncalves-Pereira M, Xavier M, et al. Affective disorders and risk of developing dementia: Systematic review. *Br J Psychiatry* 2013;202:177–186.
- Diniz BS, Butters MA, Albert SM, et al. Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry* 2013;202:329–335.