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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

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.

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 al[10] linked the data of self-reported asthma and other atopic diseases in 1963, 1967, and 1973, and data

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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 al[12] 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 al[14] 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